QUALITY OF MEDICATION USE IN HIGH-COST HEALTHCARE USERS

THE QUALITY OF PRESCRIBING AND MEDICATION USE AND ITS IMPACT ON OLDER ADULT HIGH-COST HEALTHCARE USERS

BY

JUSTIN YUSEN LEE, BScPhm, ACPR, MD

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy

McMaster University DOCTOR OF PHILOSOPHY (2021) Hamilton, Ontario (Department of Health Research Methods, Evidence, and Impact, Health Research Methodology)

TITLE: The Quality of Prescribing and Medication Use and Its Impact on Older Adult High-Cost Healthcare Users

AUTHOR: Justin Yusen Lee, BScPhm (University of Toronto), MD (McMaster University)

SUPERVISOR: Professor Anne Holbrook

NUMBER OF PAGES: xx, 121

To Joan, Violet, Beatrice, Cora and Percy

This thesis was only possible because of your patience, love and support

LAY ABSTRACT

High-cost healthcare users (HCUs) are patients who use disproportionate healthcare resources compared to their peers. More research is needed to better understand HCUs to design interventions to improve their health outcomes and costs. In this thesis, we evaluated what previous studies have discovered about HCUs and we used Ontario's health system data to explore whether the quality of prescribing and medication use in older adults influences their risk of becoming a HCU. We found that current interventions for HCUs have had inconsistent effects on improving health outcomes and costs. We also found two medication-related factors contributing to the risk of becoming an older adult HCU: (1) use of very expensive medications, and (2) use of potentially inappropriate medications where the risk of harm may outweigh potential benefits. Interventions and health policies to optimize the appropriate and cost-effective use of medications are needed to manage high-cost healthcare and prevent HCU development.

ABSTRACT

Background: High-cost healthcare users (HCUs) are patients who use disproportionate healthcare resources compared to their peers. A better understanding of their co-morbidity status, medication use, and healthcare utilization is needed to improve health interventions and policies.

Objectives: We aimed to: (1) synthesize what is known about HCUs and interventions for managing them, (2) characterize how HCUs differ from non-HCUs, and (3) explore the impact of medications and whether prescribing quality contributes to differences in healthcare costs and HCU status development.

Methods: We synthesized what is known about HCUs and used the GRADE framework to evaluate the evidence for interventions designed to improve their health. We conducted retrospective population-based matched cohort and case-control studies of incident older adult HCUs using health administrative data. We examined prescribing and medication costs over the non-HCU to HCU transition period and compared them to non-HCUs. We conducted logistic regression to evaluate associations between HCU status development and the use of high-cost drugs and potentially inappropriate medications.

Results: HCU interventions to date have shown inconsistent effects on clinical outcomes and healthcare costs and the overall quality of evidence supporting their efficacy is low. Compared to non-HCUs, HCUs have higher rates of polypharmacy, hospitalization, and mortality. Medications are the highest healthcare cost category in the pre-HCU year and these costs rise nearly 1.7-fold in the HCU year. High-cost drug use increases significantly

during the HCU transition period and 3.6% achieve HCU status based on drug costs alone. Use of several potentially inappropriate medications and high-cost drugs significantly increase the odds of HCU development.

Conclusions: Medications can contribute to high-cost healthcare directly through drug costs alone or indirectly through adverse effects on health. Medication optimization interventions and policies to reduce inappropriate medication use and ensure cost-effective medication use are needed to manage high-cost healthcare and prevent HCU development.

ACKNOWLEDGEMENTS

First, I would like to express my deep and sincere appreciation to my supervisor, Dr. Anne Holbrook. I am extremely grateful for the guidance, support and critical feedback that you have provided me for so many years. Several years ago, by serendipity, I met you on CTU Central at SJH and we somehow got talking about research and the rest is history. You helped me sow and cultivate my ideas, and you have opened so many doors of opportunity for me. I will forever be indebted to you.

To my thesis committee, Hsien Seow and Lehana Thabane - thank you for your support, patience, and pragmatic advice throughout this journey. You have always been willing to make time for me and I will never forget that.

To my collaborators and mentors at ICES, ODPRN and DSECT, especially Michael Paterson, Lisa Dolovich, Tara Gomes, Wayne Khuu – I am very appreciative of the opportunity and feedback you provided me as a trainee. I learned so much from all of you. It was truly a pleasure to work with you.

To the many other collaborators and friends that I have made during this journey, including Jean-Eric Tarride, Sergei Muratov, and Courtney Kennedy – Each one of you has had a special impact on me and I am privileged to have met you. Thank you for your always being there to help, listen and encourage. I appreciate it more than you know.

To Drs. Sharon Marr and Dr. Papaioannou - thank you for your mentorship and unwavering support through all the ups and downs of this journey. I've learned so much about what it truly means to be a successful geriatrician, academic, colleague and parent

through your actions and words. You were both there for me during some of the most challenging times of my life and I will never forget it.

To my parents – thank you for always supporting me no matter what. Throughout my life, you have always made sacrifices to do whatever you could to help me and my family. I hope that I will be able to return the same unconditional love and kindness to you.

To Violet, Beatrice, Cora and Percy - thank you for bringing me so much joy to my life. Through all the ups and downs of life, you can make me forget about life's challenges in an instant and remind me of what is most important.

And lastly to my wife, Joan - thank you for being my companion and walking with me every step of the way. Whether it be proofreading emails, abstracts and manuscripts or getting through the challenges of life, we have gone through so much together and you have made so many sacrifices for me. I know the pandemic has been especially challenging for both of us, but I know we will get through it in the end. You have been there for me during my brightest and my darkest hours and I could not have survived without you. I share this PhD with you and I cannot wait to celebrate closing this chapter of being a "professional student."

TABLE OF CONTENTS

LIST OF TABLES

Chapter 5

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ADGs	Aggregated Diagnosis Groups
ACGs	Adjusted Clinical Groups
ACO	Accountable care organization
AHFS	American Hospital Formulary Service
AOR	Adjusted odds ratio
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
BENZO	Benzodiazepine
CAD	Canadian dollar
CAPE	Client Agency Program Enrolment
CCRS	Continuing Care Reporting System
CHF	Congestive heart failure
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CIHR	Canadian Institutes of Health Research
CMS	Centers for Medicare
COPD	Chronic obstructive pulmonary disease
DAD	Discharge Abstract Database
DiD	Difference-in-difference

DOAC	Direct oral anticoagulant
DSECT	Drug Safety and Effectiveness Cross-Disciplinary Training
ED	Emergency department
EDCs	Expanded Diagnosis Clusters
FY	Fiscal year
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCD	Home Care Database
HCU	High-cost healthcare user
HiCOSTT	HIgh-cost user Characterization of Ontario's Seniors' MedicaTion use and healthcare UTilization
ICD	International Classification of Diseases
ICES	Institute for Clinical Evaluative Sciences
IPDB	ICES Physician Database
IQR	Interquartile range
IRCC-PR	Immigration, Refugees and Citizenship Canada Permanent Resident
LCL	95% lower confidence interval limit
LHIN	Local Health Integration Network
NACRS	National Ambulatory Care Reporting System
NRS	National Rehabilitation Reporting System
NSAID	Nonsteroidal anti-inflammatory drug
OCCD	Ontario Crohn's and Colitis Cohort Database

ODB	Ontario Drug Benefit
ODD	Ontario Diabetes Database
ODPRN	Ontario Drug Policy Research Network
OHIP	Ontario Health Insurance Plan
OMHRS	Ontario Mental Health Reporting System
OMID	Ontario Myocardial Infarction Database
OPHRDC	Ontario Physician Human Resource Data Centre
OR	Odds ratio
ORAD	Ontario Rheumatoid Arthritis Database
PIM	Potentially inappropriate medication
PPI	Proton pump inhibitor
RECORD-PE	Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement for Pharmacoepidemiology
RCT	Randomized controlled trial
RIO	Rurality Index for Ontario
RPDB	Registered Persons Database
RR	Relative risk
SD	Standardized difference
SDS	Same Day Surgery
SPOR	Strategy for Patient-Oriented Research
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions

UCL	95% upper confidence interval limit

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich" thesis 6 chapters that includes four individual manuscripts that are either published or have been submitted to peer-reviewed journals. All of the papers included in this document were part of Justin Lee's research program on improving medication prescribing for older adult high-cost healthcare users funded by the Fellowship Program of the Canadian Institutes of Health Research (CIHR).

Chapter 1 (Introduction) is unpublished. Justin Lee is the sole author.

Chapter 2 is published in the Journal of the American Geriatrics Society (JAGS). All authors contributed to the original concept and design of the manuscript. Justin Lee and Sergei Muratov conducted comprehensive, systematic searches of the literature independently. Justin Lee reviewed and interpreted the data and drafted the initial manuscript. All authors provided critical input and approved the final version of the manuscript.

Chapter 3 is published in CMAJ Open. Justin Lee, Anne Holbrook, Sergei Muratov, Jean-Eric Tarride, Michael J. Paterson and Kednapa Thavorn conceptualized the study and all authors contributed to its design. Justin Lee developed the research questions, drafted the

study protocol and wrote the initial manuscript. All authors provided critical input and approved the final version of the manuscript.

Chapters 4 and 5 have been submitted for publication in peer-reviewed journals. Justin Lee developed the research questions, drafted the study protocol, and wrote the initial manuscript. Justin Lee and Wayne Khuu performed the statistical data analysis. All authors provided critical input and approved the final version of the manuscript.

Chapter 6 (Conclusions and Discussion) is unpublished. Justin Lee is the sole author.

CHAPTER 1: INTRODUCTION

Global spending on healthcare is rising and the costs of providing healthcare are challenging health systems internationally. Healthcare expenditures exceed 10% of gross domestic product in almost every developed country and they are expanding faster than the economy.[1] Between 2000 to 2017, global health spending grew at a rate of 3.9% a year, while the global economy grew 3.0% a year.[2] Many health systems internationally, as a result, have been focused on trying to achieve the "Triple Aim" goal of improving the quality of care and population health, while reducing healthcare costs.[3,4] Since the majority of healthcare utilization and expenditure is concentrated and attributable to a small group of individuals in the population, health systems have directed their attention and "Triple Aim" efforts towards improving the management of a small patient cohort commonly referred to as "super utilizers" or "high-cost healthcare users" (HCUs).

HCUs are a small proportion of the population who use a disproportionate amount of healthcare resources compared to the average patient. This HCU phenomenon is neither new nor unique to any specific jurisdiction. As early as 1956, researchers noted that healthcare expenditures were concentrated in a small segment of the population.[5] Although there is no universally accepted definition of a HCU, criteria have ranged from heavy use of specific services [e.g. hospitalizations or emergency department (ED) visits] to a fiscal threshold (e.g. top 1% or 5% of overall healthcare expenditures) or some combination of the above.

Although HCUs receive substantial and/or frequent health services from multiple areas of the healthcare system, many health experts and studies have suggested that critical healthcare needs are not being met and that many HCUs may be receiving care that is neither necessary or cost-effective.[6–10] Intervention programs developed for these high-need, high-cost patients, for example, have had mixed and inconsistent success across studies in achieving the "Triple Aim" goal when evaluated using randomized controlled trial methodology despite promising initial observational studies.[11,12] These observations suggest that the epidemiology of HCUs is still not well understood. HCUs are a heterogenous group with multifactorial contributors and complex healthcare needs. It is not only unclear how best to improve the care for these patients, but also unclear which patients in this group are most likely to benefit from such interventions. In order to develop effective interventional programs or policy, further research is needed to understand the variations and determinants of their healthcare utilization and expenditures including their demographics, co-morbidities, medications, healthcare providers, and health service needs compared to non-HCUs.

Thesis Aims and Rationale

In this thesis, we aimed to bridge some of these HCU knowledge gaps by focusing on older adult HCUs during their transition period from non-HCU to HCU and exploring what may be contributing to their differences in health compared to older adult non-HCUs (e.g. sociodemographic and clinical characteristics, medication use). Our overall goal was

to identify potential opportunities to improve the quality of care and prevent HCU development. Using a population segmentation framework and incident HCU observational study design, we employed a strategic method to better understand their health issues as older adults and improve our ability to inform targeted HCU interventions that would be better suited and more specific to their age and context.

We also planned this thesis to specifically explore the need for a medication optimization intervention for older adults HCUs. The results have directly informed the design of an intervention and contributed to the successful funding of a pilot randomized controlled trial that is currently underway. This evaluation will provide preliminary info regarding the potential impact of medication optimization and test the feasibility of a larger, definitive trial.

Overview of the Thesis Papers

This "sandwich" thesis consists of four distinct manuscripts that advance our understanding of older adult HCUs and the impact of prescribing quality and medication use. Each manuscript builds on the findings of the previous in a sequential fashion and mirrors our thought process and understanding of older adult HCUs over time. The following overview puts each of these papers into context.

In **Chapter 2,** "*Managing High-Cost Healthcare Users – The International Search for Effective Evidence-Supported Strategies*", we present the results of a comprehensive and structured review of the scientific literature to delineate what is already known about

HCUs, how they are defined, what are their general characteristics, what interventions have been tried to prevent or manage their high-cost healthcare use, and what is the quality of the evidence supporting their efficacy using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

In **Chapter 3**, "*Medication Use and Its Impact on High-Cost Healthcare Users Among Older Adults: Protocol for the Population-Based Matching Cohort HiCOSTT Study*", we describe the protocol for the creation of a retrospective population-based matched cohort and research program of incident older adult HCUs that was conceived after reflection on the HCU knowledge gaps identified in our review in Chapter 2. The manuscript provides a comprehensive outline of the specific research questions, hypotheses, methods, data sources, and analytical plan for the sequential studies presented in Chapters 4 and 5 of this thesis.

In **Chapter 4**, "*Contribution of Medications to High-Cost Healthcare User Status: A Population-Based Matched Cohort Study of Older Adults*", we present the results of an observational matched cohort study that characterizes the difference in clinical profiles, medication use, outcomes, and prognoses of incident older adult HCUs to matched non-HCU peers. This manuscript also outlines the direct financial contributions of prescription medication costs to HCU expenditures and their impact as a whole on incident HCU status.

In **Chapter 5**, "*The Association of Potentially Inappropriate and High-Cost Drug Use with Becoming a High-Cost Healthcare User: A Population-Based Matched Case-Control Study*", we explore the impact of prescribing quality on the development of HCU

status using a population-based case-control study design. We treat incident HCU status as an outcome and evaluate the impact of exposure to several medication classes within two distinct categories: (1) potentially inappropriate medication use, where risks of harm and costs of adverse health outcomes often outweigh potential benefits, and (2) use of expensive higher-cost (per unit) medications (e.g. biologics), where the financial costs of the medications alone could be sufficient to achieve HCU status.

Since the large study cohorts (as described in Chapter 3) were created to form a common database for the studies in Chapters 4-5, there is some overlap in the Introduction, Methods, and Results sections of these manuscripts (e.g. setting, definitions and baseline characteristics of study cohorts).

Methodological Considerations and Advancements

There were many methodological considerations to take into account in designing the studies included in this thesis. The following provides an overview of the rationale for some of the major study design choices.

Study Population – Older Adults

We choose to focus on the older adult HCU because older adults aged 65 years and older represent the largest subgroup of HCUs and incur the greatest median healthcare expenditures amongst HCUs.[13,14] In Ontario, for example, 60% of all HCUs are older adults

with median healthcare expenditures of $45,203 CAD (vs. $7961 CAD for all HCUs).[14,15] Furthermore, studies focused specifically on older adult HCUs are limited. In the Canadian context, for example, there are no studies that we are aware of (outside of our research team and our older adult HCU database) that have focused on older adults. Most have focused on HCUs in general as a collective cohort or on specific subpopulations of interests including those with mental illness or those in their last year of life.[14–21]

Study Population – Incident vs. Prevalent High-Cost Healthcare Users

Unlike most studies to date which have looked at HCUs as a collective group (i.e. prevalent HCUs who meet HCU criteria), we focused on incident (i.e. new) HCUs and explored changes occurring during the period of transition from non-HCU to HCU. The incident HCUs is a significant subpopulation to target as studies have reported that they account for more than 50% of all HCU cases annually.[14,22] This method of population segmentation provided two major advantages: (1) it eliminated the inclusion of persistent HCUs or "recovering" transient HCUs, who may be distinct populations with different characteristics and needs, and (2) it facilitated a pro-active, preventative "lens" and allowed for better identification of factors that may be contributing to the development of HCU status.

Study Cohort Creation - Matched Non-HCU Comparator Cohort

Research focused on HCUs has been predominantly cross-sectional in nature with many studies not having a comparator group or controlling for confounding.[10,18] In those with a comparator group, the usual comparison are unmatched patients within the 50-95th percentiles of healthcare expenditure. This cross-sectional approach makes many of these studies at higher risk of bias for accurately delineating distinguishing HCU features. Their lack of longitudinal design at an individual level also limits their ability to study potential precipitants of high-cost healthcare use and their temporal association (i.e. those that may be modified before significant costs begin to accrue). In those that repeated analyses at different times to assess trends over time, many were conducted at the individual level. As a result, it is difficult to ascertain whether changes in prevalence reflect a true trend or differences between different groups of participants sampled from the population. There are few recent examples of HCU studies that have employed longitudinal cohort designs with analysis at the individual level, but they have focusing primarily on cost trajectories and social determinants of health in general HCU population.[14,17]

In the observational studies included in this thesis, we employed a longitudinal matched cohort design. Older adult HCUs were matched to non-HCUs in a 1:3 ratio based on age, sex and geographic location. This reduced confounding due to these factors and created more comparable HCU and non-HCU cohort groups. The 1:3 also significantly improved the statistical efficiency of our analyses while balancing the excess loss of individuals due to matching. Only marginal improvements in statistical efficiency would have been achieved with higher ratios (e.g. 1:4 or 1:5).[23]

Study Design and Analysis - Matched Cohort with Unconditional Analysis

Although matching was also used in our case-control study design to create matched cohorts, we elected not to conduct a conditional matched analysis that is often assumed to be required to control for the matched factors (i.e. age and sex). Since we did not anticipate expect sparse data with this population-based study, we used a standard unconditional analysis. This provided valid and similar findings to a matched (conditional) analysis, but additionally simplified the analysis, increased its statistical precision, and enhanced the clarity and dissemination of the findings.[24,25]

Study Design and Analysis – Logistic Regression versus Propensity Score Method

In our case-control study designed to evaluate the associations between medication classes of interest and the risk of becoming a HCU, we used traditional logistic regression modeling to control for imbalances in important confounders between the matched HCU and non-HCU cohorts. We elected to use this method over propensity score methodology for several reasons. First, given the broad exploratory scope of our study and its multiple research questions, the use of traditional regression modeling was pragmatic. It facilitated the scoping evaluation of several medication classes in a single study using a common, parsimonious methodology and avoided the loss of individuals due to propensity score matching. Second, this approach provided adequate precision for the exploratory nature of study and did not compromise our ability to achieve our study objectives. Evidence syntheses have suggested that observational studies have had similar results regardless of

whether traditional regression or propensity scores are used to adjust for confounding (i.e. they did not usually differ in the strength or statistical significance of associations between exposures and outcomes).[26] Propensity score methods have potential benefits in the scenario of rare outcomes and multiple confounders, but we did not anticipate HCU status to be a rare outcome in our study. In fact, some studies suggest that logistic regression may be the preferred method to control for confounding when outcomes are not rare (e.g. >8 events per confounder expected). In these scenarios, Monte Carlo simulation studies show that resultant estimates from logistic regression are precise, but less biased than those derived using propensity scores.[27]

CHAPTER 2: Managing High-Cost Healthcare Users – The International Search for Effective Evidence-Supported Strategies

This chapter describes what is known about high-cost healthcare users (HCUs) and reviews the available evidence for the effectiveness of interventions to manage their high and costly healthcare use. The analysis includes: (1) a scoping review that used a comprehensive and structured search strategy to identify studies that evaluated interventions designed to prevent or reduce healthcare costs and/or utilization amongst HCUs, and (2) an evaluation of the quality of evidence supporting the efficacy of current care management interventions being employed for HCUs using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Citation:

Lee J, Muratov S, Tarride JE, Holbrook A. Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies. J Am Geriatr Soc. 2018; 66(5): 1002-1008.

INTERNATIONAL HEALTH AFFAIRS

Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies

Justin Y. Lee, BScPhm, MD,[*†‡§] *Sergei Muratov, MD, MPH,*[‡¶] *Jean-Eric Tarride, PhD,*[‡¶] *and Anne M. Holbrook, MD, PharmD, MSc*[†‡]

High-cost healthcare users (HCUs) are a small proportion of the population who use a disproportionate amount of healthcare resources. Although the phenomenon occurs across the entire age spectrum, older adults represent the majority of HCUs. HCUs have drawn increasing attention internationally from clinicians, health policy-makers, and government administrators. Many experts have suggested that the short- and long-term sustainability of the healthcare system is threatened unless current approaches to the care and healthcare costs of this population are modified. Complex case management and care coordination models are being implemented internationally to address HCUs despite a lack of strong evidence to support their effectiveness in improving clinical outcomes or savings in costs of care. We review what is known about HCUs and the available evidence for the effectiveness of interventions designed to manage their high and costly healthcare use. **J Am Geriatr Soc 66:1002–1008, 2018.**

Key words: high-cost healthcare users; older adults; health service use; healthcare delivery; interventions

A small proportion of the population uses a disproportionate amount of healthcare resources. In Canada, for example, 5% of residents in Ontario, Canada's largest province (population 12.9 million; 38.4% of Canadian population), accounted for 65% ($19.8 billion) of the province's total measurable healthcare expenditures in 2011 with annual mean expenditures of CAD7,961.[1,2] Similarly, 5% of the noninstitutionalized population in the United States accounted for 48.7% (~$700 billion) of healthcare expenditures in 2013, with annual mean expenditures of USD43,253.[3] The majority of these patients are older adults, with those aged 65 and older accounting for 60% of the top 5% of healthcare expenditure users and 80% of the top 1%.[4] In Canada, these individuals are often identified as high-cost healthcare users (HCUs), but different names have been used internationally, including high-cost beneficiaries, super-utilizers, frequent users, and high-need patients. Given growing international concerns about health system sustainability, efforts to improve management of this small cohort have substantially increased, but the Institute for Healthcare Improvement's "Triple Aim" goal of improving the quality of care and population health while reducing healthcare costs has proved to be complex and challenging. Some interventions have demonstrated effectiveness in their local context, but many questions remain unanswered. In the following analysis, we summarize what is known about HCUs and the evidence for the effectiveness of interventions to manage high and costly healthcare use.

CHARACTERISTICS OF HCUS

The HCU phenomenon is neither new nor unique to any specific jurisdiction, but it is not consistently defined or described. Criteria range from heavy use of specific services to exceeding a fiscal threshold to some combination of these (Table 1).

Common drivers include frequent healthcare use, use of expensive healthcare services, and individuals with complex needs or high vulnerability. Centers for Medicare and Medicaid Services (CMS) analyses of Medicare expenditures suggest that healthcare expenditures grow in an exponential, nonlinear way with increasing number of comorbidities.[5] Expenditures can also be intense at the end of life. Data from U.S. Medicare and national datasets suggest that 13% to 25% of annual healthcare expenditures are consistently attributable to the costs of expensive care for people in the last year of their life.[6,7]

In contrast to pediatric HCUs characterized by preterm birth, cancer, and mental illness, adult HCUs are

From the *Divisions of Geriatric Medicine; †Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University; ‡Department of Health Research Methods, Evidence, and Impact, McMaster University; §Geriatric Education and Research in Aging Sciences Centre, Hamilton Health Sciences; and ¶Programs for Assessment of Technology in Health, Research Institute of St. Joseph's Hamilton, Hamilton, Ontario, Canada.

Address correspondence to Justin Lee, Geriatric Education and Research in Aging Sciences Centre, 88 Maplewood Avenue, Room 158, Hamilton, Ontario, Canada L8M 1W9. E-mail: justin.lee@medportal.ca

See related editorial by Allen R. Huang et al.

DOI: 10.1111/jgs.15257

0002-8614/18/$15.00

Table 1. High-Cost Healthcare User (HCU) Definitions

Patient Characteristic	Terminology Used in Literature	Example Definitions
High-cost healthcare technology or service use	High-cost healthcare user High-cost beneficiary High user High spender Super-utilizer	Overall healthcare use, prescription medication expenditure, or inpatient hospitalization costs meet prespecified fiscal threshold (e.g., top 1%/5%/10%)
Frequent healthcare service use	High user High utilizer Frequent user Super-utilizer Multiple-admission patient	Number of emergency department visits, inpatient hospitalizations, or ambulatory physician visits meet prespecified frequency or rate
High risk for healthcare service use	High-risk patient High utilizer	High risk of future inpatient hospitalization in pre-specified period
High or complex needs	High-need patient	Complex medical and socioeconomic needs (e.g., multiple chronic conditions, mental health and addiction, poverty, homelessness, institutionalization) with or without associated high healthcare resource use

characterized by older age (≥65), multimorbidity, polypharmacy and annual mortality as high as 20%.[2,8] Comorbid mental illness and psychosocial challenges, including depression, substance abuse, unemployment, and homelessness, are common.[2,8,9] Sector-specific analyses suggest that acute hospitalization is the predominant cost driver.[4,10] Similar findings have been reported internationally, including in the United States, Australia, and Germany.[11–13]

Jurisdictional differences in healthcare financing and insurance may influence observed HCU characteristics. In the United States, for example, one's capacity to pay for care (based on insurance coverage or income status) appears to increase the likelihood of incurring high costs even after controlling for health status.[11,14]

INTERVENTIONS TO PREVENT AND MANAGE HIGH-COST HEALTHCARE USE

Using a common search strategy developed with an experienced librarian, two authors (JL and SM) conducted a comprehensive scoping review and independently searched MEDLINE, EMBASE, and grey literature for studies evaluating interventions designed to prevent or reduce healthcare costs or use amongst HCUs. Our strategy used all identified HCU key words (e.g. high, super, frequent, cost, needs, utilizer) in varying combinations. We focused our search using the Medical Subject Heading terms "delivery of health care," "health services," and "health care costs." We did not find any randomized controlled trials (RCTs) that defined their study population using a HCU definition, but we identified and reviewed several relevant reviews, RCTs, and observational studies of initiatives designed to manage high-risk or high-need individuals in populations that probably included a large proportion of HCUs. It is difficult to make definitive conclusions about their effect on healthcare costs and use because of heterogeneous metrics and methodologies, as well as potential confounding of results.

The analysis identified two distinct approaches: a conceptual (prospective) approach focused on predicting HCUs with the goal of prevention and an operational (reactive) approach focused on identifying HCUs with the goal of management and reduction.[9] These approaches typically identify HCUs or "at-risk" individuals in multiple ways, including high-risk comorbidity profiles, health service use history, predictive modelling, population segmentation, and risk scores for poor outcomes. HCU operational interventions (Table 2) are more plentiful than prospective predictive ones, but are more heterogeneous and at high risk of bias. There are many small, single-center studies using before-and-after analyses with short follow-up periods. Often lacking randomization or adequately controlled and matched contemporaneous comparison groups, many are susceptible to misleading conclusions because of regression to the mean, selection bias, and other unmeasured confounders. They do not account for the fact that high costs and health service use tend to decline naturally over time independent of interventions, or that test sites and HCUs that program administrators select and who agree to participate may be more likely to respond than those who do not. Studies also rarely measure the quality and consistency of implementation. Given the complexity of interventions, this makes it difficult to understand why programs were or were not successful.

Methods of Identifying High-Risk Individuals for Targeted Intervention

The United Kingdom pioneered a virtual ward model that used predictive modeling tools to identify community-dwelling individuals at risk of future hospitalization and provided them with multidisciplinary case management of a hospital ward at home.[15] Although variations of this model have been adopted internationally, its efficacy and cost-effectiveness have not been rigorously evaluated. In a recent Canadian RCT of 1,928 individuals at high risk of readmission or death, a virtual ward model of care coordination and multidisciplinary care did not reduce readmissions, mortality, nursing home admissions, or emergency department (ED) visits after hospital discharge.[16] Similarly, a retrospective propensity-matched cohort study of individuals on a virtual ward in England demonstrated no significant reductions in hospitalizations (difference in difference (DiD) −0.07 per person, $P = .37$) or hospital costs (DiD

Table 2. High-Cost Healthcare User (HCU) Operational Care Management Models[44]

Care Management Model	Description
Ambulatory intensive caring unit (aICU)	Complex HCUs receive all care from a separate high-risk clinic or team instead of their primary care provider
Community based	Engagement by care management team wherever individual is located
Emergency department based	ED-related team provides care management to HCUs or at-risk individuals recruited in ED
Health plan	Care management team operates from health plan
Home based	All care management takes place in individual's home
Hospital discharge	Intensive care management during transition from inpatient setting to home and management by primary care practice
Housing first	Stable housing provided to HCUs who are homeless or living in unstable housing situations; no specific medical care component provided
Primary care	Care management team embedded in one or more primary care practices

ED = emergency department.

–£114.11 per person, $P = .60$) over 6 months after the intervention.[17]

In the United States, the Camden Coalition used a "hot-spotting" approach with claims data to identify neighborhoods with high healthcare costs and use to create an automatic data-driven referral process for complex care management of high-risk individuals. A before-and-after analysis showed that this intervention decreased hospitalizations by 57%, ED visits by 33%, and care costs by 56% in "super-users."[18] A RCT evaluation is currently underway.

The Canadian provinces of British Columbia and Alberta have used population segmentation according to healthcare status and need to better target HCUs and identify potential areas of improvement (e.g., care coordination, chronic disease prevention, community services).[19] The resultant interventions have yet to be fully implemented and evaluated.

Methods of Case Management, Disease Management and Care Coordination

Because the largest component of HCU spending is acute care, most interventions have focused on a high-risk care-management strategy (directing additional resources and services to people experiencing poor outcomes and high healthcare costs) with the aim of minimizing further ED visits and hospitalizations. This strategy has typically used an integrated care approach, with varying levels of case management, care coordination, and disease management.

The current body of evidence suggests that programs using this strategy have had mixed effects on health service use and costs. A systematic review of 36 RCTs of care coordination aimed at frequent users showed that patients randomized to the intervention had a lower risk of hospitalization (relative risk (RR) = 0.81, 95% confidence interval (CI) = 0.72–0.91) but not ED visits (RR = 1.11, 95% CI = 0.65–1.90) compared to those in the control group.[20] In subgroup analyses, this effect applied to individuals with chronic diseases but not mental illness. There was no difference in mean number of hospitalizations or ED visits per person per month. Subgroup analyses suggested that older adults in the intervention group had fewer ED visits (RR = 0.69, 95% CI = 0.54–0.89) than those in the control group, but this was based on data from fewer than 500 participants in 2 studies. More than half of studies excluded older adults or targeted individuals who were at risk of frequent use but were not necessarily current frequent users.

In contrast, a systematic review of 36 studies (including 28 RCTs, of which the majority were of high methodological quality) conducted internationally in Canada, the United States, Europe, or Australia evaluated the effectiveness of case management for high-risk individuals in primary care. Despite a small improvement in patient satisfaction (standardized mean difference 0.26, 95% CI = 0.16–0.36), meta-analyses showed no significant difference in total healthcare costs, mortality, or use of primary or secondary care within or beyond 12 months.[21] Sensitivity analyses that excluded studies at high risk of bias did not change the results.

A review of CMS's Medicare Coordinated Care Demonstration (which included 15 RCTs of care coordination programs for high-need Medicare beneficiaries of 4 to 8 years duration) found that 13 programs showed no significant differences in hospitalizations and that none demonstrated statistically significant cost savings (even without including the additional expenditures required for program administration).[22] Targeted extension of one program with the most favorable results to "high risk" individuals most likely to benefit based on subgroup analysis resulted in no significant difference in hospitalizations, ED visits, mortality, or healthcare expenditures.[23] Similarly, an independent review of 34 CMS disease management and care coordination programs in the United States (of which 30 were RCTs) revealed that, on average, they had little or no effect on hospitalizations or healthcare expenditures[24] and that effects varied considerably from program to program, with more than 40% showing increases in hospitalizations (some in excess of 15%).[24]

Qualitative analyses of the subset of successful programs in both of the aforementioned reviews reveal some key learning points.[22,24] Reductions in hospitalizations and expenditures were more likely in programs characterized by targeting of high-risk individuals with moderate to severe chronic conditions; team-based, multidisciplinary approaches; greater frequency of in-person contact; greater focus on patient and caregiver self-care education and management, including medications; frequent interaction and information sharing between care coordinators, hospitals, and physicians; use of real-time data on individuals'

health service use to promote timely intervention; and a focus on transitional care (coordination and continuity of healthcare as individuals transfer between locations or levels of care).[25] For example, hospitalizations were reduced by 7% in programs in which care managers had frequent in-person interaction with physicians or patients (compared with no effect in programs without these characteristics).[24] For these reasons, experts have recommended these features (summarized in Table 3) for inclusion in HCU interventional programs.[24,26]

The effects of these complex care management and integrated care coordination strategies on patient-reported outcomes also appear to be inconclusive. Although several studies report greater patient satisfaction, limited RCT evidence suggests that their effect on health-related quality of life using validated scales (e.g., Medical Outcomes Study 36-item Short-Form Survey), physical health, and activities of daily living have been mixed and inconsistent.[22,26–28] In the studies that have shown improvement in these outcomes, the magnitude of difference has been sufficiently low to question its clinical significance.[22,27]

Despite this lack of high-quality evidence to support their effectiveness, these strategies are being implemented internationally to address the HCU phenomenon.[9] In the United States, networks of hospitals and clinicians, known as accountable care organizations (ACOs), have been developed to provide coordinated care along the healthcare continuum to Medicare beneficiaries in a shared savings incentive model to improve healthcare quality and reduce costs. Through a variety of models with different expenditure benchmarks, advance payments, and infrastructure investments, ACO providers can choose to assume higher levels of financial risk for higher potential rewards. In Australia, patient-centered medical homes concentrated on team- and system-based coordinated care are the focus of health system reforms despite insufficient RCT evidence in a recent systematic review that they significantly reduce hospitalizations (RR = 0.96, 95% CI = 0.84–1.10) or reduce overall costs in older adults.[29]

In Canada, an ACO-like model has been adopted in the Ontario Health Links initiative. Interdisciplinary coordinated care plans are being implemented for individuals with complex needs by networks of family physicians, specialists, hospitals, and home healthcare organizations.[30] Concurrently, based on pilot data suggesting shorter hospital stay and fewer rehospitalizations, bundled care services are being provided to select high-risk individuals.[31] These include care coordinators for hospital and home, constant care team access and availability (24/7), and shared health records to enhance team and patient communication.

Overall, the quality of evidence supporting the efficacy of HCU care management interventions using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria is low based on methodological quality, indirectness of patient populations, and inconsistency and imprecision of results.[32] The common notion that care management and care coordination improve outcomes and lower costs is not evidence based because the conclusive clinical effect and cost-effectiveness of these initiatives have yet to be determined.

Interventions Addressing Clinical and Social Needs

Addressing the theory that medical care for problems arising from social needs may be more expensive than addressing the underlying social needs themselves, a RCT compared a housing first with a treatment then housing approach in more than 2,000 homeless individuals with severe mental illness in 5 Canadian cities.[33] Every $10 invested in supportive housing resulted in average savings of $21.72 in healthcare use and community support services.[33] Improvements were seen in mental health and substance-related problems as assessed using validated symptom and severity scales, but the changes were similar between intervention and control groups. As a result, interventions customized for "patient archetypes" of unmet clinical or psychosocial needs have been proposed for future HCU initiatives.[34]

Table 3. Common Features Observed in Successful High-Cost Healthcare User Interventions and Models[44,45]

Feature	Comments
Frequent in-person contact	Personal contact with specified care coordinator or case manager is more effective and important than remote monitoring, telephone-based support, or high-tech health information systems or devices.
Team-based, multidisciplinary approach with clearly defined roles	No standard care management team composition has been shown to be universally effective. Most teams include a nurse and social worker, but needs typically determine members in local context.
Trained personnel with frequent interaction with local hospitals and physicians	Care coordinators or case managers build rapport and facilitate timely communication between individual and care team.
Real-time healthcare use information sharing between all members of care team	Knowledge of health service utilization (e.g., emergency department visits) can facilitate timely intervention by care teams to potentially prevent hospitalization or facilitate postdischarge continuity of care.
Focus and targeting of high-risk individuals	Limited randomized controlled trial evidence suggests that individuals with moderate to severe disease severity benefit most from care management.
Individual and caregiver education and coaching, including medication management	Successful programs have generally incorporated teaching about disease self-management (e.g., early warning signs) and facilitated navigation of health and social service systems. Accurate medication histories and mechanisms to manage suspected drug-related problems are important.
Facilitation of transitional care between hospital to post-acute community care	Programs with hospital-to-home care management programs have generally had greater success than in-hospital discharge planning alone.

CHALLENGES, UNANSWERED QUESTIONS, AND FUTURE DIRECTIONS

There is no "one size fits all" approach. HCUs are heterogeneous, with complex, unique care needs depending on their socioeconomic, multimorbidity, and frailty status (level of vulnerability based on cumulative deficits or phenotype).[35,36] It is likely that a diversified approach in which interventions are customized to specific HCU subgroups and their providers is necessary. Although the use of nursing staff to coordinate care and engage individuals in disease management may be useful in multimorbid individuals, regions with significant mental health and socioeconomic disparities may have greater success by improving access to mental health and social services. Interventions need to be piloted properly to elucidate the most effective and feasible components, which then need to be evaluated in an appropriately powered RCT to validate their efficacy and cost-effectiveness.

Recent studies have demonstrated that the commonly assumed stereotype that individuals with chronic diseases with high inpatient or ED use account for less than half of HCUs.[37,38] There are many HCU subgroups, including those characterized by surgical and critical care patients with infrequent admissions, ambulatory individuals with high outpatient treatment costs (e.g., chemotherapy), and individuals with low socioeconomic status and high mental illness burden.[35,37,38] Thus, focusing solely on care management interventions that aim to prevent hospitalizations with intensive outpatient follow-up may have limited potential to reduce overall health system costs.

In addition to increasing services to those in need, initiatives focused on encouraging evidence-based decision-making and elimination of low-value services are also important. Choosing Wisely and other agencies such as the Canadian Agency for Drugs and Technologies in Health and the United Kingdom's National Institute for Health and Clinical Excellence provide many case examples of prevalent and often costly interventions that persist despite evidence of limited clinical benefit, questionable cost-effectiveness, or patient harm. Arthroscopy for osteoarthritis, percutaneous coronary intervention for stable coronary disease, and diagnostic imaging for nonspecific low back pain are a few examples in which quality improvement initiatives need to focus on encouraging providers to do less.[39]

The design of an effective intervention also needs to take into account appropriate versus inappropriate healthcare use, avoidable versus unavoidable healthcare costs, and episodic versus persistent HCUs. High-cost healthcare may be appropriate and unavoidable because of expensive required services (e.g., intensive care due to trauma, long-term care, high-cost but essential medications). Because HCU status may be episodic, it may be more cost-effective to focus on the estimated 23.8% to 57.9% of HCUs who maintain their HCU status in the following year.[2,40,41]

Successful interventions are likely to focus on avoidable inappropriate healthcare use of persistent HCUs, but what is avoidable is not always clear. A retrospective analysis of inpatient and outpatient services between 2009 and 2010 for more than 1 million individuals in the top 10% of spending amongst Medicare beneficiaries estimated that only 10% of costs were potentially preventable.[42] Although it overlooks other potential areas of cost containment, this analysis challenges the widely held assumption that preventable HCU expenses can be found in ED visits and hospitalizations.

It may be that the time frame needed to reap significant cost savings is years rather than months. Super-utilizer programs in the United States have generally found that the effect of interventions begin to become apparent only after 18 to 24 months, for several reasons, including the time needed to enroll and engage people and then to change behavior and healthcare use.[43] Healthcare use and costs often increase in the early stages as individuals receive treatment for previously unmet needs.

Current methods of costing healthcare use and defining HCUs based on these data are incomplete. *Ad hoc* HCU definitions have been developed given local technology and available health administrative data. Thus, there may be contributing factors to high-cost healthcare that are not well understood and have been overlooked for intervention (e.g., high-cost drug use, including chemotherapy, particularly in younger populations and ambulatory settings).

Moreover, disproportionate healthcare use will always exist given the natural history of aging and illness. The goal of HCU interventions should not be to modify this skewed distribution. Instead, they should prioritize and concentrate on improving the most important clinical health outcomes. It is hoped that, in doing so, this will lead to more cost-effective care and system-level cost containment while improving the quality of care.

MOVING FORWARD AND ADVANCING HCU RESEARCH

The heterogeneity, complexity, and multifactorial nature of HCUs states speak to the need for a strategic approach to HCU research. Accounting for the largest proportion of HCUs, older adults arguably represent the most important HCU subpopulation to target. Moreover, any of the following would help us deepen our understanding of HCUs and move closer to developing an effective intervention: agreement on a common definition for HCUs and creation of a Medical Subject Heading term for article indexing to improve our ability to synthesize evidence; in-depth characterization of HCU predictors, attributes, and outcomes to enhance intervention design; research prioritizing a few HCU subgroups most amenable to an intervention; higher quality studies (RCTs) of HCU interventions; and development of standardized core outcome sets to promote evidence syntheses. Ideally, this would involve international expert collaboration and agreement through a valid consensus approach.

CONCLUSION

HCUs are a small but important group of individuals who have a significant effect on the sustainability and delivery of healthcare. Although focusing on them is an attractive and seemingly simple means of improving cost-effective care and healthcare sustainability, more rigorous research is required to better characterize the determinants of their healthcare use and properly design interventions that address their clinical and social needs. Given the heterogeneity and dynamic reality of HCU states, standard

definitions and focus on cost-effective care rather than just costs is likely to be of utmost importance.

KEY MESSAGES

HCUs are a small, complex, heterogeneous group of people who are generally older adults and use disproportionate levels of healthcare resources.

Most HCU interventions focus on outpatient case management and care coordination, but evidence syntheses incorporating results of more than 30 RCTs of reasonable quality show no significant effect on clinical outcomes or savings in care costs.

Interventions with favorable results tend to incorporate a targeted focus on high-risk individuals; frequent in-person contact; multidisciplinary team-based care; close collaborations between care coordinators, physicians, and hospitals; sharing of real-time healthcare usage information, patient coaching, and transitional care.

Future directions require better characterization of HCUs and better ability of interventions to meet clinical and social needs, followed by a more systematic approach to intervention development and evaluation.

ACKNOWLEDGMENTS

Conflict of Interest: The authors have no potential conflicts of interest to declare.

Authors Contributions: All authors contributed to the original concept and design of the manuscript. Drs. Lee and Muratov conducted an independent comprehensive literature review. Dr. Lee drafted the initial manuscript, and all authors contributed to data analysis, interpretation, and final approval of the manuscript.

Sponsor's Role: None.

REFERENCES

1. Statistics Canada. Population and Dwelling Counts, for Canada, Provinces and Territories, 2011 and 2006 Censuses, 2016 [on-line]. Available at http://www12.statcan.gc.ca/census-recensement/2011/dp-pd/hlt-fst/pd-pl/Table-tableau.cfm?LANG=Eng&T=101&S=50&O=A Accessed December 5, 2016.
2. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. Can Med Assoc J 2016;188:182–188.
3. Cohen SB. Differentials in the Concentration of Health Expenditures across Population Subgroups in the U.S., 2013. Statistical Brief #480. Agency for Health Care Policy and Research [on-line]. Available at https://meps.ahrq.gov/mepsweb/data_files/publications/st480/stat480.pdf Accessed October 31, 2017.
4. Wodchis WP. The Concentration of Health Care Spending: Little Ado (yet) About Much (money). 2012 Canadian Association for Health Services and Policy Research Conference [on-line]. Available at https://www.cahspr.ca/web/uploads/presentations/C6.1_Walter_P._Wodchis.pdf Accessed October 1, 2015.
5. MaCurdy T, Bhattacharya J. Challenges in Controlling Medicare Spending: Treating Highly Complex Patients [on-line]. Available at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/HighCostComplexPatients.pdf Accessed October 31, 2017.
6. Riley GF, Lubitz JD. Long-term trends in Medicare payments in the last year of life. Health Serv Res 2010;45:565–576.
7. Aldridge MD, Kelley AS. The myth regarding the high cost of end-of-life care. Am J Public Health 2015;105:2411–2415.
8. Rosella LC, Fitzpatrick T, Wodchis WP et al. High-cost health care users in Ontario, Canada: Demographic, socio-economic, and health status characteristics. BMC Health Serv Res 2014;14:532.
9. Canadian Institute for Health Information. Pan-Canadian Forum on High Users of Health Care—Summary Report, 2014 [on-line]. Available at https://secure.cihi.ca/free_products/highusers_summary_report_revised_FR_web (1).pdf Accessed October 1, 2015.
10. Pritchard D, Petrilla A, Hallinan S et al. What contributes most to high health care costs? Health care spending in high resource patients J Manag Care Spec Pharm 2016;22:102–109.
11. Hayes SL, Salzberg CA, McCarthy D et al. High-need, high-cost patients: Who are they and how do they use health care? A population-based comparison of demographics, health care use, and expenditures Issue Brief (Commonw Fund) 2016;26:1–14.
12. Calver J, Brameld KJ, Preen DB. High-cost users of hospital beds in Western Australia. Med J Aust 2006;184:647.
13. Hartmann J, Jacobs S, Eberhard S et al. Analysing predictors for future high-cost patients using German SHI data to identify starting points for prevention. Eur J Public Health 2016;26:549–555.
14. Garfinkel SA, Riley GF, Iannacchione VG. High-cost users of medical care. Health Care Financ Rev 1988;9:41–52.
15. Bardsley M, Lewis G. Reflections from the NHS in England. Healthc Pap 2014;14:26–30.
16. Dhalla IA, O'Brien T, Morra D et al. Effect of a postdischarge virtual ward on readmission or death for high-risk patients: A randomized clinical trial. JAMA 2014;312:1305–1312.
17. Lewis GH, Georghiou T, Steventon A et al. Impact of "Virtual Wards" on Hospital Use: A Research Study Using Propensity Matched Controls and a Cost Analysis. Final Report. National Institute for Health Research (NIHR) Service Delivery and Organisation Programme [on-line]. Available at http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0011/87923/FR-09–1816–1021.pdf Accessed October 1, 2015.
18. Green SR, Singh V, O'Byrne W. Hope for New Jersey's city hospitals: The Camden Initiative. Perspect Health Inf Manag 2010;7:1d.
19. Briggs T, Burd M, Fransoo R. Identifying high users of healthcare in British Columbia, Alberta and Manitoba. Healthc Pap 2014;14:31–36.
20. Tricco AC, Antony J, Ivers NM et al. Effectiveness of quality improvement strategies for coordination of care to reduce use of health care services: A systematic review and meta-analysis. Can Med Assoc J 2014;186:E568–E578.
21. Stokes J, Panagioti M, Alam R et al. Effectiveness of case management for "at risk" patients in primary care: A systematic review and meta-analysis. PLoS ONE 2015;10:e0132340.
22. Peikes D, Chen A, Schore J et al. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. JAMA 2009;301:603–618.
23. Peterson G, Zurovac J, Mutti A et al. Evaluation of the Medicare Coordinated Care Demonstration: Final Report for the Health Quality Partner's Program [on-line]. Available at https://innovation.cms.gov/Files/reports/mccd-hqp-finaleval.pdf. Accessed October 31, 2017.
24. Nelson L. Lessons from Medicare's Demonstration Projects on Disease Management and Care Coordination [on-line]. Available at https://www.cbo.gov/publication/42860 Accessed October 1, 2015.
25. Coleman EA. Falling through the cracks: Challenges and opportunities for improving transitional care for persons with continuous complex care needs. J Am Geriatr Soc 2003;51:549–555.
26. Hong CS, Siegal AL, Ferris TG et al. Caring for high-need, high-cost patients: What makes for a successful care management program? Issue Brief (Commonw Fund) 2014;19:1–19.
27. Counsell SR, Callahan CM, Clark DO et al. Geriatric care management for low-income seniors: A randomized controlled trial. JAMA 2007;298:2623–2633.
28. Boyd CM, Reider L, Frey K et al. The effects of guided care on the perceived quality of health care for multi-morbid older persons: 18-month outcomes from a cluster-randomized controlled trial. J Gen Intern Med 2010;25:235–242.
29. Jackson GL, Powers BJ, Chatterjee R et al. Improving patient care. The patient centered medical home. A systematic review. Ann Intern Med 2013;158:169–178.
30. Robertson M. Health Links: Meeting the needs of Ontario's high-needs users. Canadian Institute of Health Information (CIHI) High User Web Conference Series: From Definitions to Action: Meeting the Needs of Health Care's Highest Users [on-line]. Available at http://www.cihiconferences.ca/highusers/downloads/Michael_Robertson_EN.pdf Accessed January 27, 2016.
31. Gosse C, Johnson D. Integrated comprehensive care. HealthAchieve 2014 [on-line]. Available at http://www.healthachieve.com/2014/Presentations 2014/Integrated Comprehensive Care_Winnie Doyle_Carolyn Gosse and Donna Johnson.pdf. Accessed December 5, 2016.

32. Guyatt G, Oxman AD, Akl EA et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–394.
33. Goering PS, Veldhuizen A, Watson C et al. National At Home/Chez Soi Final Report. Calgary, AB: Mental Health Commission of Canada, 2014.
34. Vaillancourt S, Shahin I, Aggarwal P et al. Using archetypes to design services for high users of healthcare. Healthc Pap 2014;14:37–41.
35. Powers BW, Chaguturu SK. ACOs and high-cost patients. N Engl J Med 2016;374:203–205.
36. Clegg A, Young J, Iliffe S et al. Frailty in elderly people. Lancet 2013;381:752–762.
37. Nguyen OK, Tang N, Hillman JM et al. What's cost got to do with it? Association between hospital costs and frequency of admissions among "high users" of hospital care J Hosp Med 2013;8:665–671.
38. Lee NS, Whitman N, Vakharia N et al. High-cost patients: Hot-Spotters don't explain the half of it. J Gen Intern Med 2017;32:28–34.
39. Schwartz AL, Landon BE, Elshaug AG et al. Measuring low-value care in Medicare. JAMA Intern Med 2014;174:1067.
40. Coughlin TA, Long SK. Health care spending and service use among high-cost Medicaid beneficiaries, 2002–2004. Inquiry 2009;46:405–417.
41. Riley GF. Long-term trends in the concentration of Medicare spending. Health Aff (Millwood) 2007;26:808–816.
42. Joynt KE, Gawande AA, Orav EJ et al. Contribution of preventable acute care spending to total spending for high-cost. JAMA 2013;309:2572–2578.
43. Hasselman D. Super-Utilizer Summit: Common Themes From Innovative Complex Care Management Programs. Princeton, NJ: Robert Wood Johnson Foundation, 2013.
44. Bodenheimer T. Strategies to Reduce Costs and Improve Care for High-Utilizing Medicaid Patients: Reflections on Pioneering Programs. Trenton, NJ: Center for Health Care Strategies, 2013.
45. Goodell S, Bodenheimer T, Berry-Millet R. Policy Brief No. 19: Care Management of Patients With Complex Health Needs. Princeton, NJ: Robert Wood Johnson Foundation, 2009.

CHAPTER 3: Medication Use and Its Impact on High-Cost Healthcare Users Among Older Adults: Protocol for the Population-Based Matched Cohort HiCOSTT Study

This chapter describes the protocol for a retrospective population-based matched cohort study of incident older adult high-cost healthcare users (HCUs). This research program consists of a series of sequential analyses designed to: (1) determine the relative financial contributions of prescription medications to incident HCU expenditures, (2) explore the hypothesis that medications and the quality of their prescribing may be important contributors to HCU status, and (3) characterize how the clinical profiles and prognoses of older adult HCUs differ from non-HCUs.

Citation:

Lee J, Muratov S, Tarride JE, Paterson M, Gomes T, Thavorn K, Mbuagbaw L, Gomes T, Khuu W, Seow H, Thabane L, Holbrook A. Medication Use and Its Impact on Older Adult High Cost Healthcare Users: Protocol for the Population-Based Matched Cohort HiCOSTT Study. CMAJ Open 2020. DOI:10.9778/cmajo.20190196.

cmajOPEN

Research

Medication use and its impact on high-cost health care users among older adults: protocol for the population-based matched cohort HiCOSTT study

Justin Lee MD BScPhm, Sergei Muratov MD PhD, Jean-Eric Tarride PhD, J. Michael Paterson MSc, Kednapa Thavorn PhD, Lawrence Mbuagbaw MD PhD, Tara Gomes PhD, Wayne Khuu MPH, Hsien Seow PhD, Lehana Thabane PhD, Anne Holbrook MD PharmD

Abstract

Background: Health interventions and policies for high-cost health care users (HCUs) who are older adults need to be informed by a better understanding of their multimorbidity and medication use. This study aims to determine the financial contribution of medications to HCU expenditures and explore whether potentially inappropriate prescribing is associated with incident HCU development.

Methods: This is a protocol for a retrospective population-based matched cohort analysis of incident older adult HCUs (those with the highest 5% of costs and 66 years of age or older) in Ontario during fiscal year 2013. We will obtain person-level data for the index year and year before HCU status from health administrative databases and match each HCU to 3 non-HCUs based on age, sex and geographic location. Average annual medication costs (per patient) and the ratio of medication to total health care costs (at population level) will be examined over the HCU transition period and compared with non-HCUs. We will explore potential quality improvement areas for prescribing by analyzing chronic conditions and the use of medications with a strong evidence base for either clinical benefit or risk of harms outweighing benefits in older adults with these diagnoses. The relation between these medication classes and incident HCU status will be explored using logistic regression.

Interpretation: Using a matched cohort design and focusing on incident rather than prevalent HCUs, this protocol will explore our hypotheses that medications and the quality of their prescribing may be important triggers of HCU status and facilitate the identification of potential preventive clinical interventions or policies. Dissemination of results will occur via publications in peer-reviewed journals, presentations at conferences and academic settings, and knowledge translation activities with relevant health system and patient stakeholder groups. **Study registration:** Clinicaltrials.gov, no. NCT02815930

High-cost health care users (HCUs) are a small segment of the population that use disproportionate health care resources. In 2011, 5% of individuals in Ontario, Canada, accounted for 65% ($19.8 billion) of the province's total measurable health care expenditures.[1] These individuals are often characterized by frequent admission to hospital, comorbid mental illness, socioeconomic challenges and increased mortality risk.[2] With health care costs expected to double in 20 years, the current approach to providing and financing health care for HCUs has been deemed unsustainable without major reforms.[3,4] Similar findings have been reported internationally including those from the United States, United Kingdom and Australia.[5–7]

Despite increasing international scrutiny, the clinical epidemiology and economic impact of HCUs are not well understood. Most interventional studies have focused on case management, care coordination and disease management of high-risk or high-needs patients to prevent emergency department visits and admissions to hospital.[2] However, it is unclear whether these interventions substantially improve clinical outcomes, decrease use of health care or reduce health care expenditures; studies of these interventions have had mixed and inconsistent results, and the overall quality of

Competing interests: Justin Lee reports a fellowship award from the Canadian Institutes of Health Research (CIHR) and studentship awards from the Ontario Drug Policy Research Network, the CIHR Drug Safety and Effectiveness Cross-Disciplinary Training Program, The Research Institute of St. Joe's Hamilton and St. Peter's/McMaster Chair in Aging, during the conduct of the study. No other competing interests were declared.

This article has been peer reviewed.

Correspondence to: Justin Lee, justin.lee@medportal.ca

***CMAJ Open* 2021. DOI:10.9778/cmajo.20190196**

cmajOPEN
Research

evidence is low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[2,8]

Studies have also described the presence of both transient HCUs and persistent HCUs. Although there are transient HCUs who experience a time-limited acute health event and recover, an estimated 45% become persistent HCUs.[9] The event may result in a transition to a new state of frailty or health management requirement that is challenging to reverse or stop. In both cases, the initial HCU transition might be preventable or delayed with earlier intervention.

Some of the primary challenges have been determining which patients, comorbidities, medications and health care services are most likely to benefit from intervention and identifying the key elements of a successful strategy. A recent analysis suggested that improved HCU management would require different tactics for different HCU subpopulations because of causes and solutions that vary by age and context.[9]

Older adults aged 65 years and older arguably represent the most important HCU subpopulation that needs to be targeted. They account for the largest proportion of HCUs, and this age group incurs the greatest median health care expenditures among HCUs.[9,10] Among older adults in Ontario, HCUs with the top 5% of costs account for 44% of total health care expenditures in that age group. We have previously described their unplanned admissions to hospital and the incremental and regional variation of their health care costs.[11–13] However, the impact of medication costs and the quality of prescribing on HCU development remains unclear. The prevalence of potentially inappropriate prescribing is reported to be 21%–79% in the general older adult population, and it is likely higher in the older adult HCU population given higher rates of polypharmacy.[14,15]

Planning interventions and developing effective health policy for older adult HCUs requires a deeper understanding of their demographic characteristics, comorbidities, medications, health care providers, and health service use and associated costs compared with those of non-HCUs. To address these knowledge gaps, we will conduct the High-cost User Characterization of Ontario's Seniors' Medication Use and Health care Utilization (HiCOSTT) study.

By exploring the patterns of health service and medication use during the transition period from non-HCU to HCU, we seek to identify opportunities to improve the quality of care and prevent HCU development. This may include the development of new health-related policies or targets for intervention, such as specific high-risk patients suited for more intensive transitional care programs or high-cost drugs suited for reference-based drug pricing reimbursement.

This study's primary objectives are to determine the relative financial contribution of prescription medications to total health care expenditures in incident older adult HCUs, and to explore whether suboptimal or potentially inappropriate prescribing is associated with increased health care expenditures and incident HCU development in older adults. The secondary objective is to characterize how the clinical profiles and prognoses of older adult HCUs differ from non-HCUs by describing their sociodemographic characteristics, comorbidities, health service use, medication use, clinical outcomes and health care expenditures.

Methods

Study design

This is a retrospective population-based matched cohort study protocol that is registered with clinicaltrials.gov (NCT02815930). We are concurrently using a case–control study design to discriminate the impact of specific medication classes on the development of HCU status. We report this protocol with guidance from the Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement for Pharmacoepidemiology (RECORD-PE) checklist.[16] Table 1 describes the main research questions, hypotheses and outcome measures.

Observational periods

The observational study period will run from Apr. 1, 2010, to Mar. 31, 2014. The accrual period to ascertain exposure (i.e., HCU status) will extend from the index date of Apr. 1, 2013, to the maximum follow-up date of Mar. 31, 2014. This will allow for a 1-year look-back period to determine incident HCU, baseline demographic information, and medication and health services use data before HCU status as well as a 3-year look-back period to determine comorbidities.

Participants

This study will examine a population-based cohort of incident older adult HCUs aged 66 years or older with annual total health care expenditures within the top 5% threshold of all residents in Ontario.[9] The top 5% financial threshold will be determined using costing algorithms of ICES person-level health care use, which have previously been described in detail.[17] Total health care use expenditures for each eligible Ontario resident in the fiscal year will be calculated. We will then sort individuals by expenditures to identify the top 5% of HCUs.

We will include patients if they were Ontarians registered in the Ontario Health Insurance Plan (OHIP) Registered Persons Database during the accrual period and aged 66 years or older on the index date of Apr. 1, 2013. Patients will be excluded if they do not have a valid OHIP number or died on or before the index date.

Study cohort selection is shown in Figure 1. The prevalent HCU cohort will be defined as those patients who had annual total health care expenditures equal to or greater than the top 5% financial threshold for fiscal year 2013. The incident HCU cohort will be defined as those patients in the prevalent HCU cohort whose annual total health care expenditures in fiscal year 2012 did not meet the top aforementioned 5% financial threshold. The non-HCU cohort will be defined as those patients whose annual total health care expenditures were less than the top 5% financial threshold in both fiscal year 2012 and fiscal year 2013.

cmajOPEN
Research

Table 1: Main research questions, hypotheses and outcome measures

Main research questions	Hypotheses	Study design	Main outcome measures
Primary			
1. What is the relative financial contribution of prescription medications to incident HCU expenditures and how do they compare with non-HCUs?	• Prescription medication costs will rank within the top 3 cost categories of HCU expenditures • Average medication costs (on an individual level) and the proportion of costs attributable to medications (at a population level relative to total costs) are different in HCUs and non-HCUs • In a subset of incident HCUs, prescription medication costs alone will be greater than the financial threshold for HCU status	Retrospective matched cohort analysis (HCU status treated as an "exposure")	• Annual total prescription medication costs (co–primary outcome) • Annual drug cost to total health care expenditure ratio (co–primary outcome) • Frequency of patient cases in which annual drug costs alone exceeds health expenditure threshold for HCU status
2. What is the relative clinical contribution of prescription medications to incident HCU status? (i.e., Does the quality of medications prescribed and used contribute to differences in health care costs and HCU development?)	• The use of "high quality" medication classes (i.e., those with a strong evidence base for primary or secondary prevention selected a priori for analysis) will be associated with a decreased odds of incident HCU status • The use of "potentially inappropriate or high risk" medications selected a priori for analysis will be associated with an increased odds of incident HCU status • The use of "high cost (per unit)" medications for recognized indications will be associated with an increased odds of incident HCU status	Case–control analysis (HCU status treated as an outcome)	• Odds ratio of incident HCU status
Secondary			
3. What is the relative difference in clinical profiles of newly incident HCUs v. non-HCUs including diagnoses, medications and prognosis?	• Incident HCUs will have a significantly higher prevalence and baseline burden of chronic condition diagnoses and prescription drug use compared with non-HCUs • Incident HCUs will have a significantly higher annual risk of mortality and hospital admissions compared with non-HCUs	Retrospective matched cohort analysis (HCU status treated as an "exposure")	• Number of Johns Hopkins Adjusted Diagnosis Groups and Expanded Diagnosis Clusters • Number of unique prescription drug classes dispensed • All-cause mortality rate • All-cause hospital admission rate
4. What is the prevalent use of prescription medication classes with a strong evidence base for primary or secondary prevention of complications associated with the most common chronic conditions?	• In the pre-HCU year, the prevalent use of "high quality" prescription medication classes will be lower in HCUs compared with non-HCUs with the relevant associated indications	Retrospective matched cohort analysis (HCU status treated as an "exposure")	• Prevalent use of "high quality" medication classes selected a priori for analysis • Prevalence of relevant chronic condition based on John Hopkins Expanded Diagnosis Clusters and chart-validated ICES chronic disease cohorts

Note: HCU = high-cost health care user.

cmajOPEN
Research

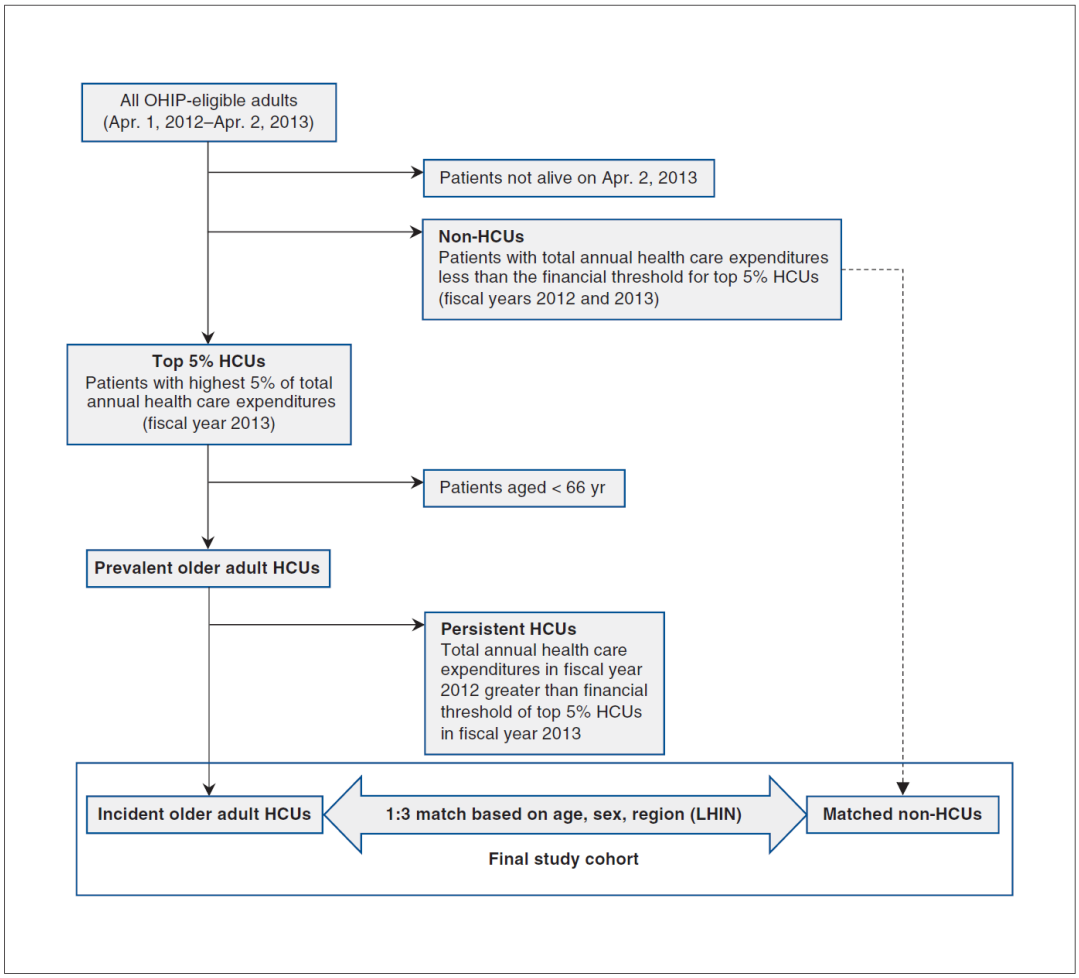


Figure 1: Study cohort selection. Note: HCUs = high-cost health care users, LHIN = Local Health Integration Network, OHIP = Ontario Health Insurance Plan.

We will match the incident HCU cohort without replacement to a cohort of non-HCUs using a 3:1 matching ratio (non-HCU to HCU) based on age at cohort entry (± 1 mo), sex and geographic location for comparative analysis. The geographic location will be based on Local Health Integration Networks, which are the health authorities responsible for regional administration of public health care services in Ontario.

We will create the cohorts in this fashion to focus on incident HCUs (rather than those persisting or transitioning out of HCU status), to include as many incident HCUs as possible to look for important cohort and subgroup characteristics (i.e., comorbidities, medication use and health care use, and to minimize confounding because of age, gender and geography). The 3:1 matching ratio was selected to increase our statistical efficiency.[18]

Databases used

We will obtain patient-level data from ICES, which holds linked health administrative databases for Ontario's publicly funded health care services using patient-specific, coded identifiers. This study will use 19 health administrative databases (described in Table 2) to track all health service encounters such as physician billings, hospital admissions and prescription drugs. More detailed descriptions of the individual variables contained in these databases can be found in the ICES data dictionary.[23] All of these data sets are held securely at ICES and analyzed in linked, coded form using a patient-

cmajOPEN
Research

Table 2 (part 1 of 2): Health administrative databases

Health administrative database	Description	Database variables or data used
Ontario Registered Persons Database (RPDB)	The RPDB records vital statistics, including date of death.	• Date of death • Rurality Index Ontario Score • Age • Sex
Immigration, Refugees and Citizenship Canada Permanent Resident Database	The CIC database contains landing records for every permanent legal immigrant to Canada who arrived from 1985 onward.	• Date of landing or immigration
Local Health Integration Network (LHIN) database	The LHIN database contains records of the health authorities responsible for the regional administration of public health care services in the province.	• Geographic location of residence of included patients
Ontario Drug Benefit (ODB) database	The ODB database contains highly accurate records for outpatient prescriptions dispensed to patients aged 65 yr or older (with error rates reported to be < 1%).[19]	• Prescription drug fill dates and costs • Long-term care indicator
Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD contains validated patient-level demographic, diagnostic, procedural and treatment information on all acute- and long-term–care hospital admissions.	• ICD-10 codes for hospital discharge diagnoses and Johns Hopkins ACGs and EDCs • Hospital admissions (elective and urgent) and costs
CIHI — National Ambulatory Care Reporting System (NACRS) database	The CIHI-NACRS database contains patient-level demographic, diagnostic, procedural and treatment information for all hospital-and community-based ambulatory care including day surgery, outpatient and community-based clinics and emergency departments.	• ICD-10 codes for hospital discharge diagnoses and Johns Hopkins ACGs and EDCs • Visits and costs
CIHI — Same Day Surgery (SDS)	The CIHI-SDS contains patient-level demographic, diagnostic, procedural and treatment information for all day surgeries.	• ICD-10 codes for hospital discharge diagnoses and Johns Hopkins ACGs and EDCs • Visits and costs
CIHI — National Rehabilitation Reporting System (NRS)	The CIHI-NRS contains patient-level demographic, diagnostic, procedural and treatment information from participating adult inpatient rehabilitation facilities and programs.	• Visits and costs
Ontario Home Care Database (HCD)	The Ontario HCD contains patient-level demographic, diagnostic, procedural and treatment information or all home care visits.	• Home care visits • Type of home care service provided • Visits and costs
Ontario Continuing Care Reporting System (CCRS)	The Ontario CCRS contains demographic, clinical, functional and resource use information or patients receiving continuing care services in hospitals or long-term care homes in Canada.	• Visits and costs
Ontario Mental Health Reporting System (OMHRS) database	The OMHRS database contains patient-level demographic, diagnostic, procedural and treatment information for all psychiatric facility visits.	• Visits and costs
ICES Physician Database (IPDB)	The IPDB reports prescriber and specialist referral and billing data in Ontario. The physician demographic data are validated against the Ontario Physician Human Resource Data Centre database.	• Visits to primary care and specialists
Ontario Health Insurance Plan database (OHIP)	The OHIP database includes health claims for physician services.	• ICD-10 codes for hospital discharge diagnoses and Johns Hopkins ACGs and EDCs • All health service visits and costs
Client Agency Program Enrolment (CAPE) database	The CAPE database contains enrolment information of an individual in a program with a specific practitioner and group.	• Primary care practitioner reimbursement model of included patients

cmajOPEN
Research

Table 2 (part 2 of 2): Health administrative databases

Health administrative database	Description	Database variables or data used
ICES-derived cohorts: • Congestive Heart Failure database • Chronic Obstructive Pulmonary Disease database • Ontario Crohn's and Colitis Cohort dataset • Ontario Diabetes Dataset • Ontario Myocardial Infarction Database Dataset • Ontario Rheumatoid Arthritis Dataset	The ICES-derived cohorts are chart-validated cohorts of patients with specific diseases and conditions. These cohorts are created using health administrative case definitions that link hospital inpatient and outpatient care, physician claims and drug benefits data over time using an anonymous unique identifier.[20] The case definitions are validated by clinical scientists at ICES using data collected directly from reviews of medical charts in the community. For example, the diabetes and hypertension definitions have a positive predictive value of 80% and 87%, respectively.[21,22]	• Comorbidities of included patients

Note: ACG = Adjusted Clinical Group, EDC = Expanded Diagnosis Cluster, ICD-10 = *International Statistical Classification of Diseases and Related Health Problems,* 10th Revision.

specific identifier. ICES is permitted to receive and use personal health information through a special designation under Ontario's *Personal Health Information Protection Act* (PHIPA). This designation is maintained through a tri-annual review and approval process undertaken by the Office of the Information and Privacy Commissioner of Ontario, which is described at https://www.ices.on.ca/Data-and-Privacy/Privacy-at-ICES.

Study outcomes

Study outcomes are summarized in Table 1. This study's co–primary outcomes are the between-group (incident HCU versus non-HCU) differences of the following in the 1-year period after the index date: the annual total prescription medication expenditures per patient and the annual drug cost to total health care expenditure ratio. The study's secondary clinical outcomes are the between-group differences in the 1-year mortality and rates of hospital admission.

We will determine mortality using records from the OHIP Registered Persons Database. The rate of hospital admissions will be determined by dividing the frequency of hospital admissions by the total number of days for which the patients were not admitted (i.e., days at risk) during the given year. A "hospital admission" will be defined as each unique "episode of care." An episode of care links a series of hospital admissions to prevent interhospital transfers being counted as a readmission.

Statistical analysis

We will present descriptive statistics for baseline clinical and demographic characteristics of both cohorts and for study outcomes. Standardized differences will be used to compare the distribution of baseline covariates between groups for the matched cohort. We will interpret a standardized difference greater than 0.1 as a meaningful difference.[24] Missing data for any covariates will be reported as separate categories. Since our sample size is expected to be large, we will use pairwise deletion unless the proportion of missing data for any variable is greater than 5% and an independent statistician suggests multiple imputation.[25]

Baseline patient characteristics will be obtained for the index date including sociodemographic characteristics (e.g., age, gender, income quintile, social assistance recipient and immigration status), geographic distribution (e.g., health region and rurality) and primary care exposure. The Rurality Index of Ontario score will be used to define urban, suburban and rural residence using the Rurality Index of Ontario scores of less than 10, 10–39 and ≥ 40, respectively. Patients will be considered recent immigrants if they landed in Canada less than 15 years from the index date according to the Immigration, Refugees and Citizenship Canada Permanent Resident database. We will characterize patients' primary care exposure based on whether they have an identified provider in the Client Agency Enrolment Program database and the type of payment model for that provider (e.g., fee-for-service v. capitation).

The baseline comorbidity burden of each cohort on the index date will be summarized by using John Hopkins Adjusted Clinical Groups (ACGs) derived from the Johns Hopkins ACG System version 10, using hospital admission and ambulatory care encounter data over 3 years preceding the index date. The ACG system assigns *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) diagnosis codes from inpatient and ambulatory health administrative data to 1 of 32 diagnosis clusters known as Aggregated Diagnosis Groups (ADGs). A previous retrospective cohort study in Ontario found that ADGs accurately predict 1-year mortality in a general population cohort.[26] Comorbidities will be profiled by focusing on the most prevalent, clinically important or economically important disease states identified by John Hopkins Expanded Diagnosis Clusters (EDCs). Based on the ACG System, EDCs are groupings of diagnostic codes that describe the same or related condition. When available, the chart-validated chronic disease indicators (e.g., chronic obstructive pulmonary disease and congestive heart failure) developed by ICES will be preferentially used for any diagnoses that have complementary EDCs.

In the incident year and year before becoming an HCU, we will delineate drug and health care use of both cohorts to

cmajOPEN
Research

compare how health care resources are being used by older adult HCUs and non-HCUs. This will include annual usage rates of emergency departments, hospitals, physician visits and home care. We will determine reasons for hospital admission using discharge abstract ICD codes. Health care expenditures will also be broken down into key components (e.g., hospital admission, long-term care, home care and drugs) as per the ICES costing algorithm.[17] Similar analyses will be conducted in the year of incident HCU designation and for non-HCUs.

Identification of the most commonly used therapeutic medication classes and the most common reasons for hospital admissions will be used to hypothesize care management issues that may be contributing to HCU development. Previous studies have highlighted the existence of important prescribing practice gaps, and the use of potential prescribing omissions and inappropriate medication use as quality indicators of pharmacologic care in older adults.[27–29] Two such examples include suboptimal prescribing and use of statins (< 30%) and bisphosphonates (< 50%) in those with a history of cerebrovascular disease and osteoporosis, respectively.[27,28] In a similar fashion, we will compare the prevalent use of specific medication classes with the relevant diagnoses of patients within these cohorts to explore potential quality improvement areas for prescribing and the financial implications of current drug use by HCUs v. non-HCUs and health care usage prev. post-HCU designation.

We have selected medication classes a priori for analysis based on 3 considerations: those with a strong evidence base for the prevention of complications in common, high-priority disease states in older adults ("high-quality" medications); those with a strong evidence base for harms outweighing potential benefits or those commonly targeted for deprescribing in older adults because of potential inappropriateness (e.g., sedative-hypnotics, antipsychotics and opioids; "high-risk" medications); and those known to be high-cost (per unit) medications (Table 3). We chose these classes as high-priority medications based on review of expert consensus guidelines on potentially inappropriate prescribing in older adults (i.e., START/STOPP and Beers Criteria), Canadian deprescribing guidelines and previous studies of potentially inappropriate prescribing and high-cost medication use in Ontario.[30–35] Medication use will be defined as the occurrence of at least 1 prescription claim during the study period.

Using a case–control study design with HCU development as the outcome (i.e., incident HCUs are the cases and the matched non-HCUs are the controls), we will conduct logistic regression to explore the relation between the use of these medications and incident HCU status. Each medication class will be analyzed independently in a series of analyses. To minimize potential bias from confounding by indication and severity of illness, we will adjust estimates for age, sex, number of comorbidities, number of major John Hopkins ADGs and the most common conditions for which the drugs are indicated. As a variation of the traditional dose–response relation in the Bradford–Hill criteria for potential causal association, we will incorporate duration of medication use (within the study window) into the analysis to explore any associations with HCU transition based on increasing exposure to the drugs.[36]

We will use these data to explore whether more in-depth analysis is required (i.e., are there signals that potential drug-related interventions before HCU designation could be implemented to avoid critical health care events, minimize drug-related expenditures or prevent HCU status?)

Table 3: Medication classes of interest for patient-level analysis

High-quality medication use	Potentially inappropriate or high-risk medication use	High-cost drug use
• Statins • β-blockers • ACE inhibitors • Angiotensin receptor blockers • Antiplatelet agents (e.g., ASA, adenosine diphosphate inhibitors, platelet aggregation inhibitors) • Anticoagulants - Vitamin K antagonists - DOACs — factor Xa inhibitors - DOACs — direct thrombin inhibitors • Bisphosphonates • Bone calcium regulators (e.g., denosumab) • Bronchodilator and anti-inflammatory combination inhalers • Long-acting anti-cholinergic inhalers (e.g., tiotropium)	• Proton pump inhibitors • Benzodiazepines • Narcotics (opiate agonists) • Antipsychotics • NSAIDs (non-ASA) • Digitalis preparations (digoxin)	• Immunosuppressive agents (e.g., mycophenolic acid, natalizumab, sirolimus, tacrolimus, thalidomide) • Antineoplastic agents (e.g., tocilizumab, imatinib, dasatinib) • Ophthalmologics (e.g., ranibizumab) • Biologic response modifying agents (e.g., adalimumab, aldesleukin, certolizumab, etanercept, glatiramer, golimumab, infliximab, interferons, levamisole)

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, ASA = acetylsalicylic acid, DOAC = direct oral anticoagulant, NSAID = nonsteroidal anti-inflammatory drug.

cmajOPEN
Research

Ethics approval

This study has been approved by the Hamilton Integrated Research Ethics Board (No. 1715-C).

Interpretation

Comparative analysis of drug and health care use and expenditures during the HCU transition period will help identify key contributors to HCU development. We expect to find common groups of diagnoses, medications and clinical outcomes among older adult HCUs. Some of these conditions may be amenable to cost-effective preventive management strategies or less expensive but equally effective medication therapies. In particular, data from this study will describe the degree to which drugs costs contribute to overall health care costs in HCUs, confirm whether or not prescription drug costs rank within the top 3 cost categories of HCU expenditures, describe how medication and health care expenditures change with HCU status, and explore whether there are possible quality improvement areas for prescribing among older adult HCUs. This may facilitate the identification of potential high-yield areas for targeted clinical or medication management interventions to prevent HCU development, provision of data to support health policies for HCUs in Ontario and areas requiring further study.

This population-based matched cohort analysis will provide important data about older adult HCUs and their medication use. Use of linked health data in a large population of older adults (n = 5 352 983) provides a unique opportunity to compare and contrast the characteristics of HCUs to their non-HCU counterparts.[37] The focus on incident rather than prevalent HCUs allows for the identification of potential triggers of HCU status and exploration of potential preventative interventions. The large estimated cohort size makes it possible to study predictors of high-cost health care use with statistical efficiency and examine their impact on clinical outcomes in a way that transcends differences in local practice patterns. Medication records from the provincial drug plan provide data that is generally more accurate than self-recorded information on drug use.

The results of this study will be shared via peer-reviewed publications and presentations at provincial, national and international conferences. Knowledge translation activities will include information exchange and policy recommendations to local and national health system and patient stakeholder groups.

Limitations

This study is subject to the limitations and residual confounding inherent in observational data from health administrative databases. It is not possible to guarantee that patients were adherent to dispensed medications nor that they were used as prescribed. Our ability to account for the duration of medication exposure is limited to 2 years of available prescription data. This may affect our ability to detect associations related to the timing of medication initiation and HCU transition.

Comorbidity and disease data are reliant on the use of hospital discharge diagnosis data using ICD and billing codes. Although the quality of discharge coding is generally good, we do not know the accuracy of every diagnosis listed on a discharge abstract.[38] In addition, physicians are permitted only 1 diagnosis code for each office encounter. This means that acute problems often take precedence over long-term ones, which can serve to underrepresent the prevalence of chronic disease.

High-cost health care users and non-HCUs are being identified based on costs of health care use accrued during a fiscal year. Some patients (including those in their last year of life) may be classified differently using an alternative method depending on when they accrued costs or died.

Conclusion

This study will determine the relative contribution of medications to HCU expenditures and explore whether the quality of prescribing and medication use may be contributing to suboptimal clinical outcomes and their high-cost use. By identifying key contributors to HCU status, we will help clinicians, administrators and policy-makers determine which patients, diseases, drugs and expenses could benefit from intervention. If modest improvements in prescribing and medication use can be achieved, then there will likely be substantial health care savings that could be reinvested to fund better care for these high-risk, high-cost older adults.

References

1. Blair A, Baigent L. High cost users. Toronto: Ministry of Health and Long-Term Care; 2013.
2. Lee JY, Muratov S, Tarride J-E, et al. Managing high-cost healthcare users: the international search for effective evidence-supported strategies. *J Am Geriatr Soc* 2018;66:1002-8.
3. Ontario population projections update, 2012–2036. Queen's Printer for Ontario; updated 2019 Oct. 1. Available: www.fin.gov.on.ca/en/economy/demographics/projections/ (accessed 2014 Oct. 12).
4. *Fiscal sustainability of health systems: bridging health and finance perspectives*. Paris: Organisation for Economic Co-operation and Development; 2015.
5. Calver J, Brameld KJ, Preen DB, et al. High-cost users of hospital beds in Western Australia: a population-based record linkage study. *Med J Aust* 2006;184:393-7.
6. The concentration of health care spending [NIHCM Foundation data brief]. Washington (DC): National Institute for Health Care Management; 2012.
7. Bardsley M, Lewis G. Reflections from the NHS in England. *Healthc Pap* 2014;14:26-30, discussion 58-60.
8. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction — GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383-94.
9. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ* 2016;188:182-8.
10. Wodchis WP. The concentration of health care spending: little ado (yet) about much (money). In: Proceedings of the Canadian Association for Health Services and Policy Research conference; Montreal; 2012 May 30. Available: www.longwoods.com/blog/the-concentration-of-health-care-spending-little-ado-yet-about-much-money/ (accessed 2015 Oct. 1).
11. Muratov S, Lee J, Holbrook A, et al. Unplanned index hospital admissions among new older high-cost health care users in Ontario: a population-based matched cohort study. *CMAJ Open* 2019;7:E537-45.
12. Muratov S, Lee J, Holbrook A, et al. Incremental healthcare utilisation and costs among new senior high-cost users in Ontario, Canada: a retrospective matched cohort study. *BMJ Open* 2019;9:e028637.
13. Muratov S, Lee J, Holbrook A, et al. Regional variation in healthcare spending and mortality among senior high-cost healthcare users in Ontario, Canada: a retrospective matched cohort study. *BMC Geriatr* 2018;18:262.
14. Hill-Taylor B, Sketris I, Hayden J, et al. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther* 2013;38:360-72.

cmajOPEN

Research

15. Weng M-C, Tsai C-F, Sheu K-L, et al. The impact of number of drugs prescribed on the risk of potentially inappropriate medication among outpatient older adults with chronic diseases. *QJM* 2013;106:1009-15.
16. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ* 2018;363:k3532.
17. Wodchis WP, Bushmeneva K, Nikitovic M, et al. Guidelines on person-level costing using administrative databases in Ontario. Working Paper Series Vol. 1. Toronto: Health System Performance Research Network; 2013:1-71.
18. Breslow NE, Day NE. *Statistical Methods in Cancer Research: Volume I — The Analysis of Case-Control Studies*. IARC Scientific Publication No. 32. Lyon (France): International Agency for Research on Cancer; 1980. p. 169.
19. Levy AR, O'Brien BJ, Sellors C, et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003;10:67-71.
20. Iron K, Lu H, Manuel D, et al. Using linked health administrative data to assess the clinical and healthcare system impact of chronic diseases in Ontario. *Healthc Q* 2011;14:23-7.
21. Hux JE, Ivis F, Flintoft V, et al. Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512-6.
22. Tu K, Campbell NR, Chen Z-L, et al. Accuracy of administrative databases in identifying patients with hypertension. *Open Med* 2007;1:e18-26.
23. ICES Data Dictionary. Available: https://datadictionary.ices.on.ca/ (accessed 2020 Apr. 1).
24. Austin P. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;38:1228-34.
25. Cheema JR. Some general guidelines for choosing missing data handling methods in educational research. *J Mod Appl Stat Methods* 2014;13.
26. Austin PC, van Walraven C, Wodchis WP, et al. Using the Johns Hopkins Aggregated Diagnosis Groups (ADGs) to predict mortality in a general adult population cohort in Ontario, Canada. *Med Care* 2011;49:932-9.
27. Brown F, Singer A, Katz A, et al. Statin-prescribing trends for primary and secondary prevention of cardiovascular disease. *Can Fam Physician* 2017; 63:e495-503.
28. Burden AM, Paterson JM, Solomon DH, et al. Bisphosphonate prescribing, persistence and cumulative exposure in Ontario, Canada. *Osteoporos Int* 2012;23:1075-82.
29. Higashi T, Shekelle PG, Solomon DH, et al. The quality of pharmacologic care for vulnerable older patients. *Ann Intern Med* 2004;140:714-20.
30. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2 [published erratum in *Age Ageing* 2018;47:489]. *Age Ageing* 2015;44:213-8.
31. Deprescribing guidelines and algorithms. Bruyère Research Institute and Centre de recherche (Ottawa) and Institut universitaire de gériatrie de Montréal (Montréal). Available: https://deprescribing.org/resources/deprescribing-guidelines-algorithms (accessed 2019 Mar. 3).
32. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019;67:674-94.
33. Morgan SG, Hunt J, Rioux J, et al. Frequency and cost of potentially inappropriate prescribing for older adults: a cross-sectional study. *CMAJ Open* 2016;4:E346-51.
34. Black CD, Thavorn K, Coyle D, et al. The health system costs of potentially inappropriate prescribing: a population-based, retrospective cohort study using linked health administrative databases in Ontario, Canada. *Pharmacoeconon Open* 2020;4:27-36.
35. Tadrous M, Martins D, Mamdani MM, et al. Characteristics of high–drug-cost beneficiaries of public drug plans in 9 Canadian provinces: a cross-sectional analysis. *CMAJ Open* 2020;8:E297-303.
36. Hill AB. The Environment and Disease: Association or Causation? *J R Soc Med.* 1965;58(5):295-300. doi:10.1177/003591576505800503
37. Table 17-10-0005-01: Population estimates on July 1st, by age and sex. Ottawa: Statistics Canada; modified 2020 Sept. 14. Available: www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501 (accessed 2019 Sept. 15).
38. Juurlink D, Preyra C, Croxford R, et al. Canadian Institute for Health Information Discharge Abstract Database: a validation study [ICES investigative report]. Toronto; ICES: 2006. Available: www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information (accessed 2019 Oct. 1).

Affiliations: Division of Geriatric Medicine (Lee), Department of Medicine, and Department of Health Research Methods, Evidence, and Impact (Lee, Muratov, Tarride, Mbuagbaw, Seow, Thabane, Holbrook), and Centre for Health Economics and Policy Analysis (CHEPA) (Tarride), McMaster University, Hamilton, Ont.; ICES (Paterson, Gomes, Khuu, Seow, Thavorn); Institute of Health Policy, Management and Evaluation (Paterson, Thavorn), University of Toronto, Toronto, Ont.; Ottawa Hospital Research Institute (Thavorn), The Ottawa Hospital, Ottawa, Ont.; Li Ka Shing Knowledge Institute (Gomes), St. Michael's Hospital, Toronto, Ont.; Department of Oncology (Seow), Faculty of Health Sciences, and Division of Clinical Pharmacology and Toxicology (Holbrook), Department of Medicine, McMaster University, Hamilton, Ont.

Contributors: Justin Lee, Anne Holbrook, Sergei Muratov, Jean-Eric Tarride, J. Paterson and Kednapa Thavorn conceptualized the study. All authors contributed to its design. Justin Lee drafted the initial protocol manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: This work is supported by the Ontario Drug Policy Research Network which is funded by grants from the Ontario Ministry of Health and Long-Term Care, and the Ontario Strategy for Patient-Oriented Research Support Unit, which is supported by CIHR and the Province of Ontario. This study will also be supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care, and by personnel funding from the Canadian Institutes of Health Research (CIHR) Fellowship Program, the CIHR Drug Safety and Effectiveness Cross-Disciplinary Training Program, The Research Institute of St. Joe's Hamilton and the St. Peter's/McMaster Chair in Aging.

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

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/9/1/E44/suppl/DC1.

Disclaimer: This study is supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

CHAPTER 4: Contribution of Medications to High-Cost Healthcare User Status: A Population-Based Matched Cohort Study of Older Adults

This chapter describes the results of the first set analyses for the research program described in Chapter 3. In this study, we evaluate whether prescription medication costs are important contributors to incident high-cost healthcare user (HCU) expenditures and we characterize the difference in clinical profiles, medication use, outcomes, and prognoses of these older adult HCUs to their matched non-HCU peers during their non-HCU to HCU transition period.

Publication Status:

This manuscript has been submitted to JAMA Internal Medicine for peer review and publication consideration.

Contribution of Medications to High-Cost Healthcare User Status: A Population-Based Matched Cohort Study of Older Adults

AUTHORS:

Justin Lee, MD1,2

Sergei Muratov, PhD2

Jean-Eric Tarride, PhD2,3

J. Michael Paterson, MSc4,5

Kednapa Thavorn, PhD4,6,7

Lawrence Mbuagbaw, PhD2

Tara Gomes, PhD4,8

Wayne Khuu, MPH4

Hsien Seow, PhD2,4,9

Lehana Thabane, PhD2

Anne Holbrook, MD2,10

1Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

2Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

3Center for Health Economics and Policy Analysis (CHEPA), McMaster University, Hamilton, Ontario, Canada

4ICES, Toronto, Ontario, Canada

5Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

6Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada

7School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada

8Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

9Department of Oncology, Faculty of Health Sciences, McMaster University

10Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

CORRESPONDING AUTHOR:

Justin Lee

Geriatric Education and Research in Aging Sciences (GERAS) Centre

88 Maplewood Avenue, Room 158

Hamilton, Ontario, Canada, L8M 1W9

Email: justin.lee@medportal.ca

Telephone: (905) 521-2100

WORD COUNT: 3000 (excluding title page, abstract, references, tables, and figures)

KEY POINTS:

Question: How much do medications contribute to healthcare expenditures and high-cost healthcare user (HCU) development?

Findings: In this matched cohort study of 704,793 older adults, HCUs had significantly higher polypharmacy rates (55.1% vs. 14.5%) and mean annual medication costs ($2456 vs. $854) compared to non-HCUs. Drug expenditures increased nearly two-fold during the HCU transitional period and many HCUs achieved high-cost status based on annual drug expenditures alone.

Meaning: Medications are important contributors to HCU expenditures and status, but the adverse consequences of severe polypharmacy and suboptimal medication use in pre-HCU years may be even more costly and require further investigation.

ABSTRACT

Importance: The management of high-cost healthcare users (HCUs) is a priority of health systems internationally. Improved understanding of their multi-morbidity, medication use, and costs is needed to inform interventions and policy.

Objectives: We sought to compare newly incident older adult HCUs (those with the highest 5% of healthcare costs) to their non-HCU peers to (1) determine the financial contribution of medications to HCU status and (2) characterize the differences between HCUs and non-HCUs in clinical characteristics and prognosis.

Design: Population-based matched cohort study of administrative healthcare data.

Setting: Ontario, Canada

Participants: Incident older adult HCUs (those with the highest 5% of costs) identified between April 1, 2013 to March 31, 2014. HCUs were matched to non-HCUs (1:3) based on age, sex, and geographic location.

Main Outcomes and Measures: Primary outcomes were the differences in annual prescription medication expenditures per patient and the ratio of annual drug costs to total healthcare expenditures. Secondary outcomes were the rate differences in one-year mortality and hospitalization.

Results: Incident older adult HCUs (n=175,847) accounted for $5.2 billion and $431 million CAD in annual healthcare and medication costs respectively. Compared to non-HCUs (n=527,541), HCUs had higher mean annual medication costs ($2456 vs. $854 CAD, p<0.001), prevalence of polypharmacy (55.1% vs. 14.5%, p < 0.001), 1-year mortality (10.39% vs. 0.72%, p<0.001), and hospitalization rates (3.20 vs. 0.06 hospitalizations per 1000 person-years, p<0.001). Although drug expenditures were the highest healthcare cost category in the pre-HCU year and increased nearly 1.7-fold in the incident HCU year, the ratio of drug-to-total health expenditures decreased from 35.9% of $0.74 billion to 8.3% of $5.24 billion CAD over this time due to increased hospitalizations. Use of high unit-cost medications increased dramatically amongst HCUs contributing to 6,358 HCUs (3.6%) achieving incident HCU status based on annual drug expenditures alone.

Conclusions and Relevance: Medication costs are an important contributor to HCU expenditures. The high prevalence of polypharmacy, rising use of high unit-cost drugs, and higher mortality and hospital admission rates among HCUs suggest that further study of the appropriateness and cost-effectiveness of medications is required.

INTRODUCTION

High-cost healthcare users (HCUs), also known as super-utilizers, have drawn attention internationally because their healthcare utilization comes at a cost that many believe is not sustainable nor always appropriate for their health needs.[1–3] In 2009, for example, the National Institute for Health Care Management reported that 1% of the United States population accounted for more than 20% of healthcare expenditures ($275 billion), while 5% of the population accounted for nearly 50% of healthcare expenditures ($623 billion).[4] Using a disproportionate healthcare resources compared to the average patient, HCUs have become the focus of initiatives addressing healthcare sustainability, utilization, and cost-effectiveness.[5]

Older adults, in particular, are a priority population. Although they account for the largest proportion of HCUs and incur the greatest median healthcare expenditures amongst HCUs, studies focused specifically on older adult HCUs are limited.[6,7] Their characteristics and economic impact is complex and not well understood. We have previously shown that unplanned, prolonged hospitalizations are the primary driver of HCU expenditures and regional variation in their healthcare costs is low.[8–10] However, the impact of medications on HCU status and development, both directly through their prescription costs and indirectly through their effect on health outcomes, is not well delineated.

Developing effective interventions and policies for older adult HCUs requires a deeper understanding of the determinants of their healthcare utilization and expenditures including their demographics, co-morbidities, medications, healthcare providers, and health service needs compared to non-HCUs. To address some of these knowledge gaps,

we conducted the HIgh-cost user Characterization of Ontario's Seniors' medicaTion use and healthcare uTilization (HiCOSTT) study. In this study, our objectives were to: (1) determine the relative financial contribution of prescription medications to total healthcare expenditures in incident older adult HCUs, and (2) compare the clinical profiles, medication use, outcomes, and prognoses of these HCUs to their matched non-HCU peers during their non-HCU to HCU transition period.

METHODS

The study protocol is described in detail in a previous publication.[11] We report this study using the REporting of studies Conducted using Observational Routinely collected health Data statement for PharmacoEpidemiology (RECORD-PE) checklist.[12] All costs reported are expressed in 2013 Canadian dollars.

Design and Setting

We conducted a population-based matched cohort study of incident older adult HCUs aged ≥66 years in the province of Ontario (population, 14.7 million) using the linked health administrative databases housed at ICES.[13] The accrual period to ascertain HCU status ran from April 1, 2013 to March 31, 2014 (fiscal year 2013 [FY2013]).

Population

We established a cohort of incident older adult HCUs with annual total healthcare expenditures within the top 5% threshold of all residents in Ontario, Canada. This financial

threshold was determined by calculating total annual expenditures associated with healthcare utilization for each resident using person-level health utilization costing algorithms.[11]

Cohort selection is shown in Figure 1. Patients were included in the "incident HCU" cohort if they: (1) were Ontario residents registered in the Ontario Health Insurance Plan (OHIP) Registered Persons Database during the accrual period; (2) were aged 66 years or older on the first day of the accrual period; and (3) had total healthcare expenditures in the top 5% of Ontarians in FY2013, but not FY2012. Patients were excluded if they did not have a valid OHIP number or died on or before the accrual start date.

The incident HCU cohort was matched without replacement to non-HCUs using a 3:1 matching ratio (non-HCU to HCU) based on age at cohort entry (+/- 1 month), sex, and geographic location. The "non-HCU" cohort consisted of patients whose annual healthcare expenditures were less than the top 5% financial threshold in both FY2012 and FY2013. Geographic location was based on the Local Health Integration Network (LHIN) of residence. LHINs were the health authorities responsible for regional administration of public healthcare services at the time of study.

Data Sources

Individual patient-level data for all health service encounters and medications were obtained from the province's health administrative databases. This includes demographic and socioeconomic data, physician service claims, prescription drug claims, and records

for inpatient and outpatient hospital services. In total, 19 health administrative databases were used. Their contents are described in detail in our protocol.[11]

We assessed the baseline co-morbidity burden of individuals using a combination of Aggregated Diagnosis Groups (ADGs) and Expanded Diagnosis Clusters (EDCs) derived from the Johns Hopkins ACG® System, version 10, and chart-validated chronic disease cohorts (e.g., for chronic obstructive pulmonary disease, congestive heart failure, etc.) developed by ICES. We defined medication use as the occurrence of ≥1 prescription claim during the study period and polypharmacy as the use of >10 unique medications (based on generic drug name) during the year. We determined the main reason for hospitalizations using the "most responsible" International Classification of Diseases (ICD) 10th revision diagnosis code recorded on each hospitalization discharge abstract. All-cause mortality was determined using the OHIP Registered Persons Database.

Main Outcomes

The co-primary outcomes were the between-group differences in the following measures during the 365 days after cohort entry: (1) total prescription medication expenditures per patient; and (2) the ratio of total prescription medication expenditures to total healthcare expenditures. Secondary clinical outcomes were the between-group differences in one-year mortality and all-cause hospitalization rates.

Statistical Analysis

We summarized baseline characteristics and compared the matched cohorts using descriptive statistics and standardized differences (SD). We interpreted a SD> 0.1 as representing a meaningful difference and used a type I error rate of 0.05 as the threshold for statistical significance.[14] Data cells representing <6 individuals were suppressed to protect patient privacy.

For the incident year and year prior to becoming a HCU, the frequency and costs associated with drug and healthcare utilization were calculated to compare and contrast how healthcare resources were used by HCUs and non-HCUs. Healthcare expenditures were subsequently expressed according to 12 cost categories: inpatient care, long-term care, home care, prescription drugs, etc.

Hospitalization rates were determined by dividing the number of individuals admitted to hospital by the total number of days cohort members were at risk for hospitalization (i.e. not hospitalized and alive) during the study year. A "hospitalization" was defined as each unique "episode of care." An episode of care linked a series of admissions to acute care hospitals when a patient was transferred from one hospital to another. This prevented transfers from being counted as a hospital readmission. Mortality and hospitalization rate differences between cohorts were analyzed using conditional logistic regression and Poisson regression respectively.

All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, North Carolina).

RESULTS

The annual healthcare expenditure threshold for the top 1% and top 5% of individuals in the province of Ontario was $48,801 and $10,192 respectively. We identified 383,257 older adult HCUs meeting our top 5% threshold definition. Of these, 177,252 were incident HCUs. After matching, our sample included a cohort of 175,847 HCUs and 527,541 non-HCUs. Our incident HCU cohort included 53,490 (30.1%) individuals who also met the Top 1% expenditure threshold.

Baseline Characteristics

Baseline characteristics of the HCU and non-HCU cohorts in the pre-HCU year are shown in Table 1. The median age was 77 years (IQR 71-83) and distribution based on sex was similar (53% female). The majority of HCUs lived in the community in a non-institutionalized urban setting (65.6% urban, 0.4% long-term care). No meaningful differences were observed based on income status or social assistance (i.e. low-income individual who qualify for reduced prescription deductibles and co-payments).

Compared to non-HCUs, HCUs had more physicians involved in their care (7 vs 5, SD 0.56), but no differences were observed among primary care physician reimbursement models (e.g. fee-for-service, capitation). They were more likely to have seen a geriatrician, but the overall prevalence was low (2.8% vs 1.1%, SD 0.12). HCUs had a higher burden of co-morbidities (as measured by Johns Hopkins ADGs and EDCs) with a greater proportion affected by several common chronic conditions (i.e. ischemic heart disease,

heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease, diabetes, degenerative joint disease, and cognitive impairment).

Healthcare and Prescription Drug Expenditures

During the incident year of achieving HCU status, older adult HCUs accrued $5.2 billion in total healthcare expenditures. Prescription drug costs accounted for more than $431 million (8.25%) of these costs. Compared to non-HCUs, this represented average prescription drug and healthcare expenditures of $2456 (vs $854) and $29,784 (vs. $2471) respectively ($p<0.001$ for both).

The breakdown of HCU expenditures by healthcare sector is shown in Figure 2. In the pre-HCU year, prescription drugs were the most expensive category accounting for 35.9% ($263 million of $0.74 billion) of total healthcare expenditures. In the incident HCU year, this relative proportion attributable to prescription drugs fell to 8.3% ($431 million of $5.24 billion) due to a dramatic rise in acute hospitalization expenditures. However, HCUs incurred higher mean annual prescription drug costs compared to non-HCUs both before and after they became HCUs (Figure 3). Although mean prescription drug costs remained stable for non-HCUs in the incident HCU year ($823 vs $853), they increased nearly 1.7-fold for HCUs ($1496 vs. $2456).

Mortality, Hospitalization and Other Clinical Outcomes in Incident HCU Year

In the incident HCU year, HCUs were more likely than non-HCUs to have at least one hospitalization (77.7% vs. 2.1%, $p<0.001$). In contrast to those for non-HCUs, the most

common reasons for hospitalization among HCUs were predominantly those with sudden catastrophic or chronic organ failure illness trajectories [e.g. myocardial or cerebral infarction, heart failure or chronic obstructive pulmonary disease exacerbations, fracture, joint arthroplasty for osteoarthritis] (eTable1).

Overall, HCUs had higher annual mortality (RR 14.4, 10.39% vs. 0.72%, $p<0.001$) and hospitalization rates (RR 53.3, 3.20 vs. 0.06 hospitalizations per 1000 person-years, $p<0.001$) compared to non-HCUs. As expected, HCUs also had more visits to primary care (mean 16.07 vs. 5.47 per year, SD 0.95) and specialist physicians (mean 29.55 vs. 4.55 per year, SD 2.29) as well as annual visits by home care workers (mean 33.27 vs. 2.47 per year, SD 0.52).

Patterns of Prescription Drug Utilization and Impact on HCU Status

HCUs were more likely to meet our definition of polypharmacy (>10 medications) compared to non-HCUs (55.1% vs. 14.5%, $p < 0.0001$, Table 2). Statins, proton pump inhibitors, and beta-blockers were the most commonly used prescription medications. The top 10 drug classes used by HCUs arranged by claim frequency is shown in eTable2. The most common drug classes used were similar in the pre-HCU and incident HCU years.

Claims for high-cost drugs rose dramatically in the incident year for HCUs. For example, compared to the year preceding HCU status, claims for biologic response modifying agents and monoclonal antibodies increased 60-fold and 120-fold respectively ($p<0.001$ for both).

In a small subset of the HCU cohort, prescription drug costs were the primary healthcare-related expense with 6358 HCUs (3.6%) achieving their incident HCU status based on annual drug expenditures alone. Of these, 5216 HCUs (82.0%) achieved their incident HCU status based solely on the use of one of the following higher unit cost drug classes: immunosuppressive agents (e.g. sirolimus), anti-neoplastics (e.g. imatinib), ophthalmologicals (e.g. ranibizumab), or biologic response modifying agents (e.g. infliximab, adalimumab, interferons).

DISCUSSION

This study provides a comprehensive overview of older adult HCUs, their prescription medication use, clinical outcomes, and associated costs compared to their non-HCU peers. Unlike most HCU studies that examine prevalent HCUs without comparison to non-HCUs, we utilized a population-based matched cohort design to compare characteristics of HCUs to non-HCUs and focused on incident HCUs to identify potential triggers of HCU status during this HCU transition period. We also describe HCU medication use in more depth than previous studies which have only reported their aggregate cost contributions.

Our results show that older adult HCUs have significant differences in multi-morbidity, healthcare utilization, and acute hospitalization expenditures compared to non-HCUs. They represent a vulnerable and high-risk cohort where risk differences for death and hospitalization are very large over a short one-year period. This is not surprising given that healthcare costs are directly associated with hospitalizations and hospitalizations are

associated with an increased risk of death. These results are consistent with other observational studies internationally that report an increased likelihood of multiple chronic conditions, multiple and longer hospitalizations, and increased physician and home care needs.[2]

This study provides new information about HCU medication use and related costs. Some studies have reported their cumulative cost as a cost category, but they have not examined how they are being used.[2] Others have focused on a different population of high-drug-cost beneficiaries (e.g. those with the top 5% of drug costs rather than the top 5% healthcare expenditures).[2,15,16] Our analyses demonstrate that prescription medications are important contributors to both HCU expenditures and incident HCU status. Medications represent the highest category of expenditures in the year prior to becoming a HCU and these costs nearly double in the following year.

HCUs use more medications and incur higher medication costs compared to non-HCUs both before and after they become HCUs. However, the degree of polypharmacy is noteworthy. With more than half of HCUs taking >10 medications and nearly one quarter > 15 medications, polypharmacy in this population may be reaching levels identified in the literature as “hyper”, “excessive” and “severe”.[17] Even at much lower threshold levels, there is a strong well-established relationship between polypharmacy and adverse outcomes.[18] Although this may be partially explained by confounding by indication and illness severity, there is likely an independent effect due to cumulative exposure to medication adverse effects.[19,20] Since prescription drugs represent the highest category of

healthcare expenditures in the year prior to becoming a HCU, thoughtful deprescribing may be an important part of any HCU management or prevention strategy.

Our results also suggest that the quality of prescribing and medication use require further investigation. Several medications with a strong evidence base for prevention are available for the most common reasons for hospitalization in HCUs observed in our study (e.g. bisphosphonates for osteoporosis and fracture prevention, ACE inhibitors for heart failure). HCUs in our study had higher mortality and rates of hospitalization, but it is unclear whether HCUs are being prescribed and adhering to optimal medication regimens that might have prevented these outcomes. A significant gap in medication best practices may be occurring. Previous studies have shown that only half of patients receive recommended medical care and treatment and that a significant proportion of medication that is prescribed is inappropriate or unnecessary.[21,22] If this gap is confirmed, pro-active medication optimization may represent an opportunity to improve the health of otherwise would-be HCUs.

The need for controlled and rational use of high unit-cost drugs is another area highlighted by our study. Our results demonstrate that there is an important subgroup of patients becoming new HCUs each year based on prescription drug costs alone, and the majority is the result of a small number of high-cost medication classes (e.g. biologics). Although some of this drug utilization may be temporary treatment of acute conditions or malignancies, there is also a significant component that will be long-term treatment of chronic conditions (e.g. ranibizumab for diabetic macular edema and age-related macular

degeneration). This results in long-term HCUs regardless of improving, stable, or deteriorating health.

Although many international initiatives are underway to decrease the high cost of drugs from a pricing perspective, more work is needed to contain these drug costs at a prescriber level without compromising patient health.[23–27] Examples of potential strategies with emerging evidence to support them are therapeutic substitution with bevacizumab or a 'watchful waiting' approach rather than ranibizumab prescription in age-related macular degeneration.[28,29] Developing and implementing smart drug policies (such as indication-based, reference-based, or biosimilar substitution policies) to ensure that the use of high unit-cost drugs is evidence-based and avoided when there is minimal or unproven benefit over less-expensive therapies is an important potential starting point.[24]

Strengths and Limitations

This study has several strengths. Utilization of population-level health administrative databases allowed for inclusion of all older adult HCUs in Canada's most populous province and a large sample size compared to previous studies. This enhanced statistical efficiency, minimized selection bias, and provided results that transcend local practice and utilization patterns. The matched cohort design focused on incident HCUs allowed for comparisons to non-HCUs and exploration of potential HCU triggers. A prevalent HCU design, for example, would have otherwise hidden the important and growing contribution of prescription drug costs to HCU status.

Our study has limitations that merit discussion. First, our study provides a comprehensive, but incomplete delineation of healthcare spending. Our data do not include expenditures paid by private insurers (e.g. private home-care) and out-of-pocket by individuals or their caregivers (e.g. long-term care accommodation costs not subsidized by the government). It has been estimated that our cost capture methods account for ~92% of government costs associated with healthcare services provided to individual patients.[7] Second, prescription drug data was limited to those reimbursed on an outpatient basis (including long-term care) through the provincial drug benefit program. We did not have access to prescription drug data covered by private insurance plans or medications dispensed to hospital inpatients (whose costs are embedded within hospitalization expenditures). For these reasons, the impact and importance of prescription drugs on HCU expenditures and status suggested is likely even greater than estimated by our study. Third, medication counts were derived based on unique generic drug names and may differ from those using alternative methods (e.g. Anatomical Therapeutic Chemical classification system). Fourth, HCUs and non-HCUs were identified based on healthcare utilization costs accrued during a fixed one-year period (i.e. fiscal year). Some individuals (including those in their last year of life) may be classified differently using an alternative method (e.g. calendar year) depending on exactly when they accrued costs and/or died.

CONCLUSION

Older adult HCUs are characterized by significant multi-morbidity, hospital readmission, and risk of mortality compared to non-HCUs. Medication costs alone are

important contributors to HCU expenditures, but the adverse consequences of suboptimal medication use in previous years may be even more costly. The high rates of severe polypharmacy, rising use of high unit-cost drugs, and inferior clinical outcomes compared to non-HCUs suggest that more attention on the appropriateness and cost-effectiveness of medications may be needed in this high cost, high needs population.

ACKNOWLEDGEMENTS

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information and IQVIA Solutions Canada Inc. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding and data sources; no endorsement is intended or should be inferred.

Author Contributions:

JL, AH, SM, JET, JMP, and KT conceptualized the study. All authors contributed to its design. WK and JL conducted the statistical analysis. All authors contributed to the interpretation of the data. JL drafted the initial manuscript and all authors contributed to revision and final approval.

Conflicts of Interest:

None declared.

Funding:

This work was supported by the Ontario Drug Policy Research Network (ODPRN) which is funded by grants from the Ontario Ministry of Health and Long-Term Care, and the Ontario Strategy for Patient-Orientated Research (SPOR) Support Unit, which is supported by the Canadian Institutes of Health Research (CIHR) and the Province of Ontario. This study also was supported by personnel funding from the CIHR Fellowship Program, the CIHR Drug Safety and Effectiveness Cross-Disciplinary Training (DSECT) Program, the Research Institute of St. Joe's Hamilton, and the St. Peter's/McMaster Chair of Aging.

Role of the Funder:

The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data. They were not involved in the preparation of the manuscript or the decision to submit the manuscript for publication.

REFERENCES

1. *Fiscal Sustainability of Health Systems*. Organisation for Economic Co-operation and Development (OECD); 2015. doi:10.1787/9789264233386-en
2. Wammes JJG, Van Der Wees PJ, Tanke MAC, Westert GP, Jeurissen PPT. Systematic review of high-cost patients' characteristics and healthcare utilisation. *BMJ Open*. 2018;8(9):23113. doi:10.1136/bmjopen-2018-023113
3. Shrank WH, Rogstad TL, Parekh N. Waste in the US Health Care System: Estimated Costs and Potential for Savings. *JAMA - J Am Med Assoc*. 2019;322(15):1501-1509. doi:10.1001/jama.2019.13978
4. National Institute for Health Care Management. *The Concentration of Health Care Spending*. Washington, DC; 2012.
5. Lee J, Muratov S, Tarride J-E, Holbrook A. Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies. *J Am Geriatr Soc*. 2018;66(5):1002-1008.
6. Wodchis WP. The Concentration of Health Care Spending: Little Ado (yet) About Much (money). 2012 Canadian Association for Health Services and Policy Research Conference. https://www.cahspr.ca/web/uploads/presentations/C6.1_Walter_P._Wodchis.pdf. Published 2012. Accessed October 1, 2015.
7. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ*. 2016;188(3):182–188. doi:10.1503/cmaj.150064
8. Muratov S, Lee J, Holbrook A, et al. Unplanned index hospital admissions among

new older high-cost health care users in Ontario: a population-based matched cohort study. *C Open*. 2019;7(3):E537-E545. doi:10.9778/cmajo.20180185

9. Muratov S, Lee J, Holbrook A, et al. Incremental healthcare utilisation and costs among new senior high-cost users in Ontario, Canada: a retrospective matched cohort study. *BMJ Open*. 2019;9(10):e028637. doi:10.1136/bmjopen-2018-028637
10. Muratov S, Lee J, Holbrook A, et al. Regional variation in healthcare spending and mortality among senior high-cost healthcare users in Ontario, Canada: a retrospective matched cohort study. *BMC Geriatr*. 2018;18(1):262. doi:10.1186/s12877-018-0952-7
11. Lee J, Muratov S, Tarride J-E, et al. Medication use and its impact on high-cost health care users among older adults: protocol for the population-based matched cohort HiCOSTT study. *C Open*. 2021;9(1):E44-E52. doi:10.9778/cmajo.20190196
12. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532. doi:10.1136/bmj.k3532
13. Statistics Canada. Table 17-10-0009-01 Population estimates, quarterly. 2020. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901. Accessed November 25, 2020.
14. Austin P. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Comm Stat Simul Comput*. 2009;38(6):1228-1234.
15. Tadrous M, Martins D, Mamdani MM, Gomes T. Characteristics of high–drug-cost

beneficiaries of public drug plans in 9 Canadian provinces: a cross-sectional analysis. *C Open*. 2020;8(2):E297-E303. doi:10.9778/cmajo.20190231

16. Weymann D, Smolina K, Gladstone EJ, Morgan SG. High-Cost Users of Prescription Drugs: A Population-Based Analysis from British Columbia, Canada. *Health Serv Res*. 2017;52(2):697-719. doi:10.1111/1475-6773.12492
17. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17(1):230. doi:10.1186/s12877-017-0621-2
18. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57-65. doi:10.1517/14740338.2013.827660
19. Dhalwani NN, Fahami R, Sathanapally H, Seidu S, Davies MJ, Khunti K. Association between polypharmacy and falls in older adults: a longitudinal study from England. *BMJ Open*. 2017;7(10):e016358. doi:10.1136/bmjopen-2017-016358
20. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia. *JAMA Intern Med*. June 2019. doi:10.1001/jamainternmed.2019.0677
21. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348(26):2635-2645. doi:10.1056/NEJMsa022615
22. Levine DM, Linder JA, Landon BE. The quality of outpatient care delivered to adults in the United States, 2002 to 2013. *JAMA Intern Med*. 2016;176(12):1778-

1790. doi:10.1001/jamainternmed.2016.6217

23. Humphries B, Xie F. Canada's Amendment to Patented Drug Price Regulation. *JAMA*. March 2019. doi:10.1001/jama.2019.2280

24. Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States. *JAMA*. 2016;316(8):858. doi:10.1001/jama.2016.11237

25. Pearson SD, Dreitlein WB, Henshall C, Towse A. Indication-specific pricing of pharmaceuticals in the US healthcare system. *J Comp Eff Res*. 2017;6(5):397-404. doi:10.2217/cer-2017-0018

26. Robinson JC, Whaley CM, Brown TT. Association of Reference Pricing with Drug Selection and Spending. *N Engl J Med*. 2017;377(7):658-665. doi:10.1056/NEJMsa1700087

27. Lee JLY, Fischer MA, Shrank WH, Polinski JM, Choudhry NK. A systematic review of reference pricing: Implications for us prescription drug spending. *Am J Manag Care*. 2012;18(11):429-437.

28. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration. *Ophthalmology*. 2012;119(7):1388-1398. doi:10.1016/j.ophtha.2012.03.053

29. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of Initial Management With Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss Among Patients With Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity. *JAMA*. 2019;321(19):1880. doi:10.1001/jama.2019.5790

Figure 1: Cohort Selection

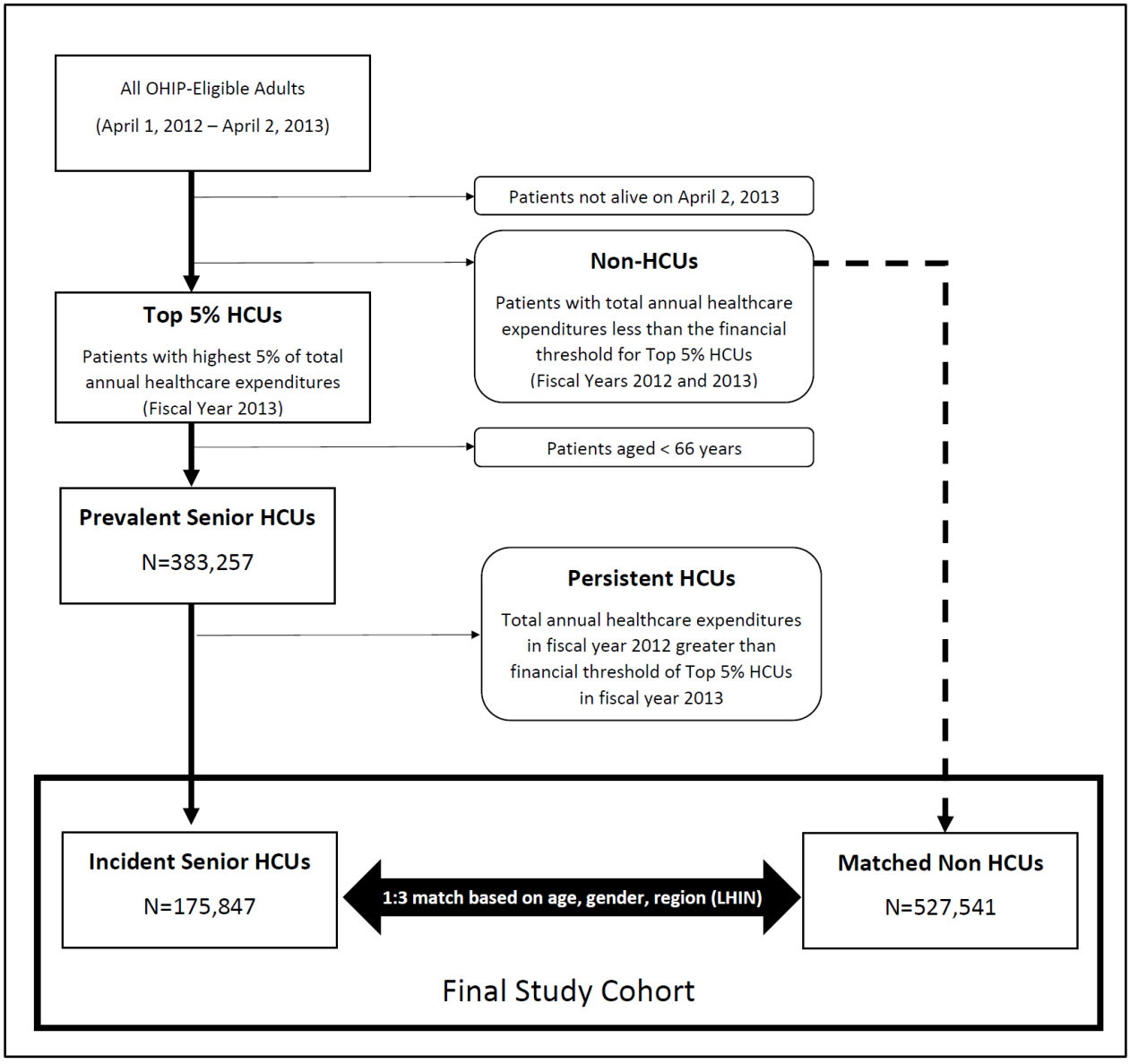
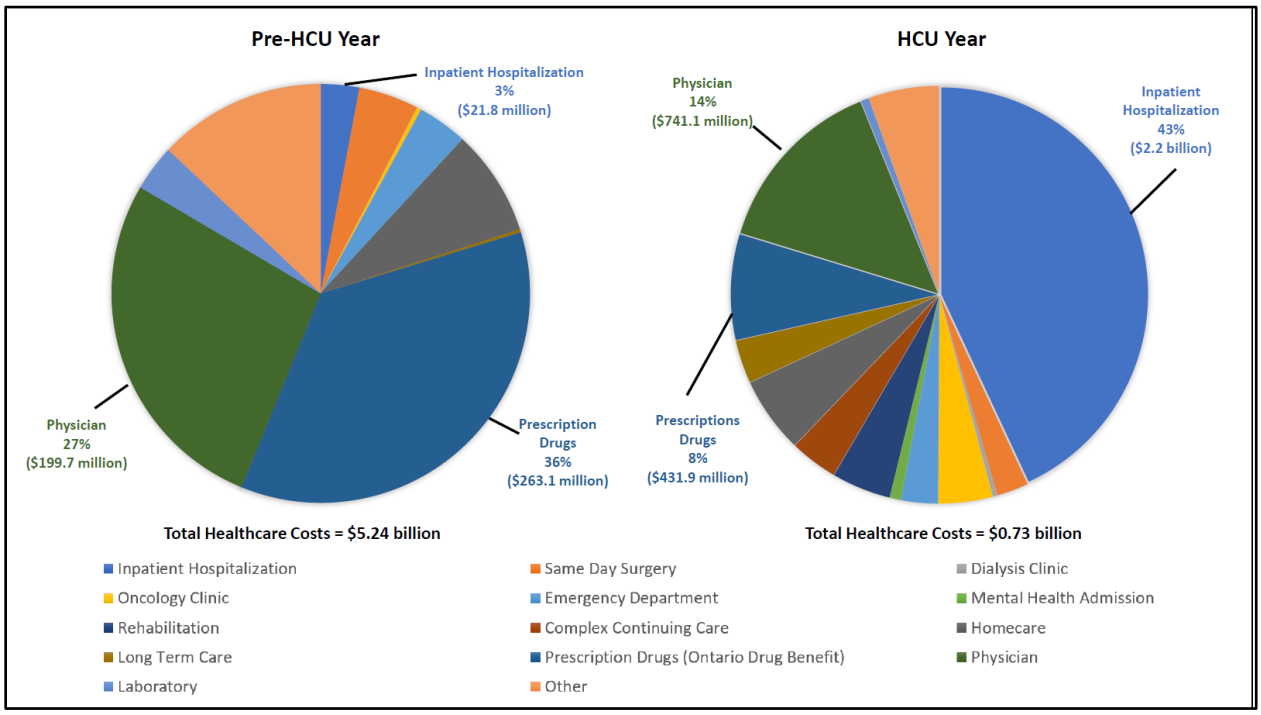
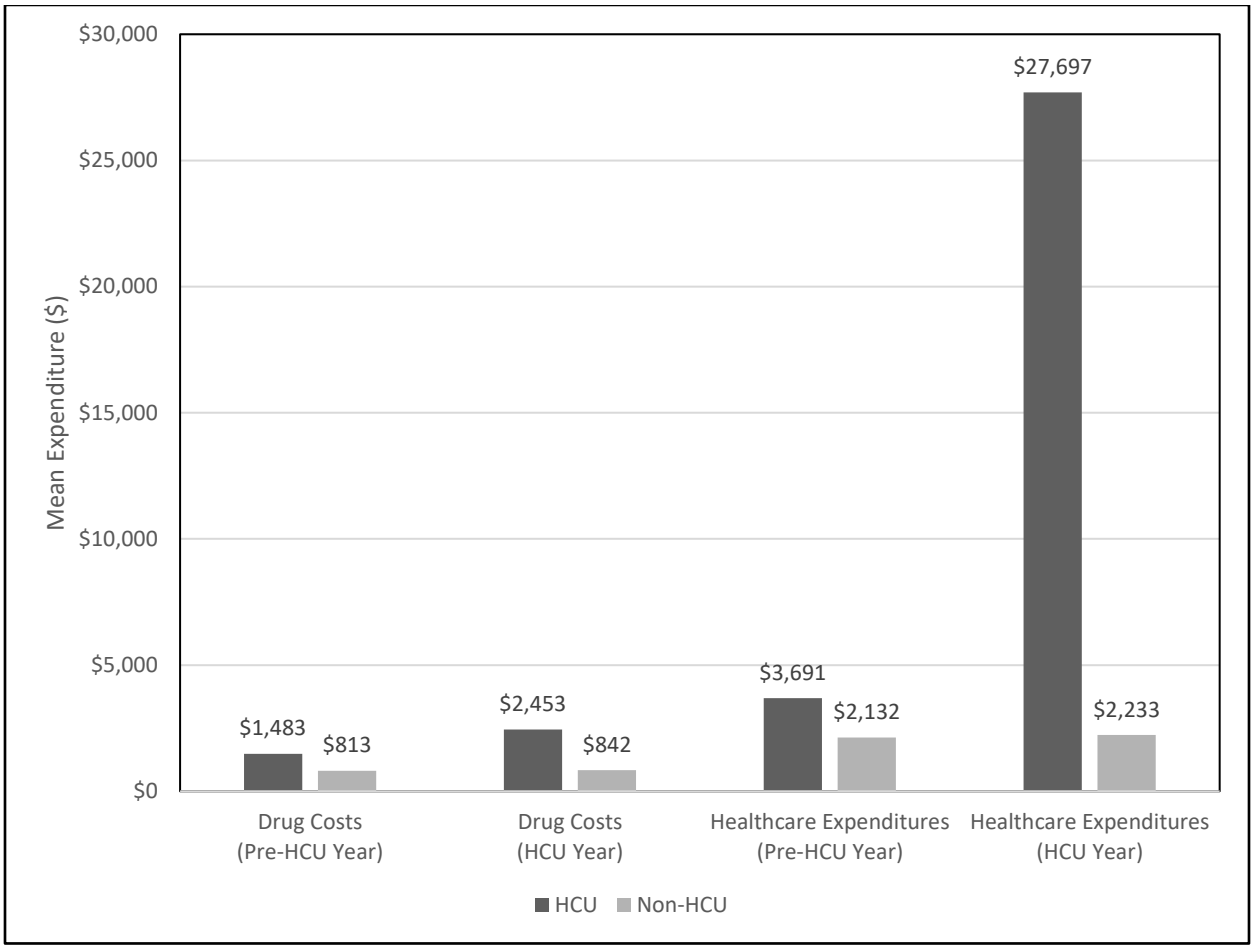


Figure 2: Distribution of Total Healthcare Expenditures Amongst Incident High-Cost Healthcare Users (HCUs)



Costs are expressed in 2013 Canadian dollars
Abbreviations: HCU, high-cost healthcare user

Figure 3: Mean Annual Drug and Healthcare Expenditures in High-Cost Healthcare Users (HCUs) and Non-High-Cost Healthcare Users (non-HCUs)



Costs are expressed in 2013 Canadian dollars
Abbreviations: HCU, high-cost healthcare user

Table 1: Baseline Characteristics of Matched HCU and Non-HCU Cohorts

Baseline Characteristics	Incident HCUs N=175,847	Non-HCUs N=527,541	Standardized Difference[a]
SOCIODEMOGRAPHICS			
Age (years): n (%)[b]			
66-74	68,644 (39.0%)	205,932 (39.0%)	N/A
75-84	70,156 (39.9%)	210,465 (39.9%)	N/A
85-94	34,665 (19.7%)	104,011 (19.7%)	N/A
95+	2,382 (1.4%)	7,133 (1.4%)	N/A
Female, n (%)	93,167 (53.0%)	279,501 (53.0%)	N/A
Residence in Long-Term Care: n (%)	632 (0.4%)	199 (0.0%)	0.07
Geographic Location Based on Rurality Index for Ontario (RIO)[b,c], n (%)			
Urban (RIO < 10)	115,305 (65.6%)	354,536 (67.2%)	0.03
Suburban (RIO 10-39)	41,551 (23.6%)	117,353 (22.2%)	0.03
Rural (RIO ≥ 40)	17,645 (10.0%)	51,403 (9.7%)	0.01
Income Quintile, n (%)			
Q1	34,417 (19.6%)	98,036 (18.6%)	0.03
Q5	35,094 (20.0%)	110,427 (20.9%)	0.02
Social Assistance Recipient, n (%)	30,686 (17.5%)	74,527 (14.1%)	0.09
PHYSICIAN CARE			
Circle of Medical Care			
Number of unique physicians, median (IQR)	7 (5-11)	5 (3-8)	0.56
Geriatric Medicine specialist, n (%)	4,974 (2.8%)	5,935 (1.1%)	0.12
CO-MORBIDITY BURDEN			
John Hopkin EDCs[d]			
Total number, mean (SD)	15.19 (7.72)	11.05 (7.32)	0.55
Specific Comorbidities			
Heart Failure	25,203 (14.3%)	36,877 (7.0%)	0.24
Cardiac Arrhythmia	34,960 (19.9%)	62,215 (11.8%)	0.22
Ischemic Heart Disease	46,678 (26.5%)	90,135 (17.1%)	0.23
Chronic Obstructive Pulmonary Disease	48,761 (27.7%)	96,513 (18.3%)	0.23
Diabetes	62,031 (35.3%)	138,794 (26.3%)	0.20
Degenerative Joint Disease	67,487 (38.4%)	136,031 (25.8%)	0.27
Cognitive Impairment	21,462 (12.2%)	28,264 (5.4%)	0.24

Abbreviations: EDC, Expanded Diagnosis Cluster; HCU, high-cost healthcare user; IQR, interquartile range; N/A, not applicable; RIO, rurality index for Ontario; SD, standardized difference

[a] SD greater than 0.1 represents a meaningful difference

[b] Cumulative total may not equal to N (100%) due to missing values (<1%)

[c] RIO determines rurality based on community population size, population density, and travel times to the nearest basic and advanced referral centres

[d] Higher number of EDCs indicates a greater number of conditions/comorbidities

Table 2: Clinical Outcomes and Healthcare Utilization During Incident HCU Year for Matched HCUs and non-HCUs

	Incident HCUs N=175,847	**Non-HCUs N=527,541**	
			P-value
All-Cause Mortality	18,382 (10.45%)	4,017 (0.76%)	<0.001
All-Cause Hospitalization Rate (1000 Person-Years at Risk)	3.21	0.06	<0.001
			Standardized Difference[a]
All-Cause Hospitalizations (Episodes of Care)			
No Hospitalization	39,162 (22.3%)	516,491 (97.9%)	2.43
1-2 Hospitalization	126,622 (72.0%)	11,050 (2.1%)	2.10
≥ 3 Hospitalizations	10,063 (5.7%)	0 (0.0%)	0.35
Length of Stay ≥ 30 days	12,215 (6.9%)	<=5 (0.0%)	0.39
ED Visits			
Annual Total, Mean (SD)	1.87 (2.19)	0.32 (0.81)	0.94
MD Visits			
Annual Total, Mean (SD)	45.62 (32.54)	10.02 (8.97)	1.49
Primary Care, Mean (SD	16.07 (14.73)	5.47 (5.56)	0.95
Specialist, Mean (SD)	29.55 (25.96)	4.55 (5.24)	1.33
Home Care Visits			
Annual Total, Mean (SD)	33.27 (82.16)	2.47 (17.33)	0.52
Number of Medications Used			
<6	21,589 (12.3%)	275,938 (52.3%)	0.95
6-10	56,940 (32.4%)	174,645 (33.1%)	0.02
11-15	54,964 (31.3%)	61,080 (11.6%)	0.49
16-20	28,578 (16.3%)	13,226 (2.5%)	0.49
21-25	10,096 (5.7%)	2,227 (0.4%)	0.31
>25	3,680 (2.1%)	425 (0.1%)	0.20

Abbreviations: ED, emergency department; HCU, high-cost healthcare user; IQR, interquartile range; SD, standardized difference

[a] Standardized difference (SD) greater than 0.1 represents a meaningful difference

eTable 1: Most Common Reasons for Hospitalization Based on Frequency

Top 10 Most Responsible Reasons for Hospitalization (Rank Based on Frequency	Incident HCUs With Hospitalizations N=136685 individuals	Non-HCUs With Hospitalizations N=11050 individuals
1	Knee Arthrosis 10,065 (7.4%)	Hyperplasia of prostate 462 (4.2%)
2	Acute myocardial infarction 7,455 (5.5%)	Pneumonia 442 (4.0%)
3	Heart failure 6,422 (4.7%)	Syncope 436 (3.9%)
4	Hip fracture 6101 (4.5%)	Pain in throat and chest 387 (3.5%)
5	Chronic obstructive pulmonary disease 5,168 (3.8%)	Atrial fibrillation and flutter 333 (3.0%)
6	Hip arthrosis 5.562 (4.1%)	Inguinal hernia 320 (2.9%)
7	Chronic ischemic heart disease 4,919 (3.6%)	Chronic obstructive pulmonary disease 312 (2.8%)
8	Cerebral infarction 4,676 (3.4%)	Other disorders of the urinary system 291 (2.6%)
9	Pneumonia 3,889 (2.8%)	Other medical care 295 (2.7%)
10	Other medical care 3,518 (2.6%)	Paralytic ileus and intestinal obstructions without hernia 269 (2.4%)

Abbreviations: HCU, high-cost healthcare user

eTable 2: Most Common Drug Classes Used by Incident HCUs Based on Claim Frequency

Pre-HCU Year	HCU Year
1. Statins	1. Statins
2. Proton pump inhibitors	2. Proton pump inhibitors
3. Oral hypoglycemics	3. Beta-blockers
4. Diuretics	4. Diuretics
5. Beta-blockers	5. Oral hypoglycemics
6. Calcium channel blockers	6. Calcium channel blockers
7. Angiotensin-converting enzyme inhibitors	7. ACE inhibitors
8. Hypothyroidism therapy	8. Hypothyroidism therapy
9. Angiotensin II antagonists	9. Opioids
10. Benzodiazepines	10. Selective serotonin reuptake inhibitors

Abbreviations: HCU, high-cost healthcare user

Chapter 5: The Association of Potentially Inappropriate and High-Cost Drug Use with Becoming a High-Cost Healthcare User: A Population-Based Matched Case-Control Study

This chapter describes the results of the second set analyses for the research program described in Chapter 3. In this study, we evaluate whether the quality of prescribing and medication use in older adults may be contributing to the development of high-cost healthcare user status. We examine whether exposure to specific medication classes may increase utilization and costs to the highest tiers within a population (i.e. HCU status) and which may be more problematic.

Publication Status:

This manuscript has been submitted to the Journal of the American Geriatrics Society (JAGS) for peer review and publication consideration.

Association of Potentially Inappropriate and High-Cost Drug Use with Becoming a High-Cost Healthcare User: A Population-Based Matched Case-Control Study

AUTHORS:

Justin Lee, MD, BScPhm[1,2]

Sergei Muratov, MD, PhD[2]

Jean-Eric Tarride, PhD[2,3]

J. Michael Paterson, MSc[4,5]

Kednapa Thavorn, PhD[5,6]

Lawrence Mbuagbaw, MD, PhD[2]

Tara Gomes, PhD[4,7]

Wayne Khuu, MPH[4]

Hsien Seow, PhD[2,8]

Lehana Thabane, PhD[2]

Anne Holbrook, MD, PharmD[2,9]

[1]Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[3]Center for Health Economics and Policy Analysis (CHEPA), McMaster University, Hamilton, Ontario, Canada

[4]ICES, Toronto, Ontario, Canada

[5]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

[6]Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada

[7]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

[8]Department of Oncology, Faculty of Health Sciences, McMaster University

[9]Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

CORRESPONDING AUTHOR:

Justin Lee

Geriatric Education and Research in Aging Sciences (GERAS) Centre

88 Maplewood Avenue, Room 158

Hamilton, Ontario, Canada, L8M 1W9

Email: justin.lee@medportal.ca

Twitter: @JustinLeeMD

WORD COUNT: 3059 (excluding title page, abstract, references, tables and figures)

IMPACT STATEMENT:

We certify that this work is novel. In this population-based matched case-control study involving 704,793 older adults, we demonstrate that there are two distinct medication-related factors contributing to the risk of becoming an older adult high-cost healthcare user (HCUs): (1) use of potentially inappropriate high-risk medications where risks of harm and costs of adverse health outcomes often outweigh potential benefits, and (2) use of expensive higher-cost (per unit) medications (e.g. biologics) where the financial costs of the medications alone are sufficient to achieve HCU status. We are not aware of previous studies that show that this exposure may increase utilization and costs to the highest tiers within a population (i.e., HCU status) or have examined these associations for specific medication classes (rather than potentially inappropriate medications [i.e., PIMs] as a collective category) to explore which may be more problematic. These results suggest that, in order to manage high-cost healthcare and prevent high-cost user development in older adults, medication optimization interventions and policies to reduce inappropriate medication use and ensure cost-effective use of expensive medications (especially when cheaper, equally effective alternatives may be available) are needed at the health system and individual level.

KEY POINTS

- Use of potentially inappropriate medications is associated with an increased risk of becoming a high-cost healthcare user

- Medications can contribute to high-cost healthcare directly through drug costs alone or indirectly through adverse effects on health and subsequent healthcare utilization

WHY DOES THIS MATTER?

Medication optimization interventions and policies to reduce inappropriate medication use and ensure cost-effective use of expensive medications are needed at the health system and individual level to manage high-cost healthcare and prevent high-cost user development.

ABSTRACT

Background/Objectives: High-cost healthcare users (HCUs) use disproportionate healthcare resources compared to their peers. The extent to which suboptimal medication use may be contributing to their adverse health outcomes and HCU status is unclear. We sought to determine whether the quality of prescribing contributes to differences in healthcare utilization costs and HCU status development.

DESIGN: Population-based case-control study

SETTING: Ontario, Canada

PARTICIPANTS: Incident HCUs (those with the highest 5% of healthcare costs) aged ≥66 years identified between April 1, 2013 to March 31, 2014 using linked health administrative databases. HCUs were matched to non-HCUs (1:3) based on age, sex and geographic location.

MEASUREMENTS: Healthcare and drug utilization data were analyzed over the 2-year period of transition from non-HCU to HCU. Descriptive and logistic regression analyses were conducted to evaluate the association between the development of HCU status and the use of high-cost drugs and potentially inappropriate medications (selected a priori due to evidence for harms outweighing potential benefits), adjusting for potentially important confounders.

RESULTS: Incident older adult HCUs (n=175,847) accounted for $5.2 billion in annual healthcare costs, of which $431 million (8.25%) was medication costs. Potentially

inappropriate medication use increased the odds of HCU status including benzodiazepines (aOR 1.62, 95% CI 1.60-1.64), opioids (aOR 3.56, 95% CI 3.52-3.60, and antipsychotics (aOR 4.45, 95% CI 4.34-4.58). Benzodiazepines, opioids, antipsychotics and digoxin also significantly increased the odds of one-year mortality. Use of high-cost drugs increased significantly amongst HCUs and increased the odds of HCU status: immunomodulators (aOR 2.84, 95% CI 2.64-3.06), ophthalmologicals (aOR 11.87, 95% CI 11.27-12.5), biologics (aOR 30.85, 95% CI 20.97-45.39) and antineoplastics (aOR 53.46, 95% CI 36.75-77.77).

CONCLUSION: Use of potentially inappropriate medications and high-cost drugs increase the likelihood of becoming a HCU. Interventions focused on improving medication appropriateness and cost-effectiveness may prevent HCU status and contain expenditures.

WORD COUNT: 299

KEY WORDS: high-cost healthcare users; potentially inappropriate medications; older adults; healthcare utilization; healthcare costs

INTRODUCTION

Health systems internationally are focused on the "Triple Aim" goal of improving the quality of care and population health, while reducing healthcare costs.[1,2] Since the majority of healthcare utilization and expenditure is attributable to a small group of individuals in the population commonly referred to as "super utilizers" or "high-cost healthcare users" (HCUs), there is growing attention and accrued efforts directed to improving the management of this small patient cohort. HCUs use a disproportionate amount of healthcare resources compared to their counterparts. In 2015, for example, the top 1% and top 5% of persons in the United States ranked by their healthcare expenditures accounted for 22.5% and 50.8% of total healthcare expenditures (annual mean $112,395 and $50,572) respectively.[3]

Older adults are disproportionately represented in the higher healthcare spending tiers and account for the majority of HCUs.[3,4] Although acute hospitalization costs typically represent the largest healthcare expenditure in older adult HCUs, medications are important financial contributors to their HCU expenditures and attainment of incident HCU status.[5] We have previously shown that medications account for 41.3% of total healthcare expenditures in the year prior to becoming a HCU and expenditures rise nearly 1.7-fold in following HCU transitional year.[5] More than half of HCUs take more than 10 medications and nearly one quarter take more than 15 medications. However, our knowledge about the characteristics of this population (including their medication use) before they become HCUs and how these attributes compare to their counterpart non-HCUs is limited. Specifically, little is known about the quality of this prescribing and medication use and

whether these could be significant contributors to their adverse health outcomes and development of HCU status.

Given that medication optimization interventions have been proposed as potential HCU prevention or management strategies, we conducted this study to explore whether potentially inappropriate prescribing is associated with increased yearly individual healthcare expenditures and incident HCU development in older adults.

METHODS

Design and Setting

We conducted a retrospective population-based matched case-control study of incident older adult HCUs in the province of Ontario (Canada's largest province by population, 38.8%, n= 14,734,014).[6] The protocol for this study has been previously published in more detail, but we have briefly summarized below.[7]

The accrual period to ascertain HCU status extended from the index date of April 1, 2013 to March 31, 2014 (fiscal year 2013 [FY2013]). We defined this period to be the "incident year" and the previous fiscal year to be the baseline or "pre-incident year". The observational study period ran from April 1, 2010 to March 31, 2014 to allow for a 1-year look-back period to determine baseline demographics, health services utilization and medication use prior to HCU status as well as a 3-year look-back period to determine co-morbidities.

Population

We defined cases as incident older adult HCUs aged ≥66 years with annual total healthcare expenditures within the top 5% threshold of all residents in the province of Ontario, Canada in FY2013, but not in the FY2012. This financial threshold was determined by calculating total annual expenditures associated with healthcare utilization for each eligible resident using person-level health utilization costing algorithms developed by ICES.[8]

Incident HCUs were matched without replacement to non-HCU controls using a 3:1 matching ratio (non-HCU to HCU) based on age at cohort entry (+/- 1 month), sex and geographic location. Non-HCUs were individuals who had annual healthcare expenditures that were less than the top 5% financial threshold in both FY2012 and FY2013. Geographic location was based on Local Health Integration Networks (LHINs), which were the health authorities responsible for regional administration of public healthcare services in Ontario at the time.

Data Sources

Individual patient-level data for all health service encounters and prescription medications were obtained from linked health administrative databases housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). ICES is an independent, non-profit research institute that holds health services records for all patients covered by the publicly-funded health insurance program in Ontario. This includes socio-demographic data, physician fee claims, prescription drug claims and records for inpatient and

ambulatory health services. In total, 19 health administrative databases were used (Supplementary Table 1). These databases and their contents have been previously described in our study protocol.[7]

Baseline co-morbidities were determined using a combination of the John Hopkins Expanded Diagnosis Clusters (EDCs) derived from the John Hopkin's ACG® System (version 10) and chart-validated chronic disease cohorts (e.g., for chronic obstructive pulmonary disease, congestive heart failure, etc.) developed by ICES. The ICES chronic disease cohorts were used preferentially for any diagnoses that had complementary EDCs. We used the Ontario Drug Benefit (ODB) database to identify all prescription medications dispensed to the matched cases and controls over the study period. We defined medication use of a specific medication as the occurrence of at least one prescription claim based on generic drug name.

Definition of Exposure

Using the pharmacologic-therapeutic classification system employed in the Ontario Drug Benefit formulary (which is based on the American Hospital Formulary Service (AHFS) system of the American Society of Health-System Pharmacists), we selected several medication classes a priori as prescribing quality indicators for a series of individual analyses (Supplementary Table 2). First, we selected several potentially inappropriate "high-risk" medications because they have a strong evidence base for harms outweighing potential benefits and that are commonly targeted for deprescribing in older adults (i.e. benzodiazepines, opioids, antipsychotics, non-steroidal anti-inflammatory drugs, digoxin,

proton pump inhibitors). Second, we selected several medications known to be "high-cost" drugs per unit. We chose medication classes as high-priority for evaluation within each of these categories based on review of expert consensus guidelines on potentially inappropriate prescribing in older adults (i.e. START/STOPP, Beers Criteria), Canadian deprescribing guidelines, and previous studies of potentially inappropriate prescribing and high-cost medication use.[9–14] In all analyses, we defined medication exposure as the receipt of at least 1 prescription of the specified medication class during the specified year.

STATISTICAL ANALYSIS

We summarized patient and medication use characteristics using descriptive statistics. Given the large sample size, we used standardized differences instead of p-values to compare cases and controls. We interpreted a standardized difference (SD) greater than 0.1 as a meaningful difference.[15] Missing data for any covariates in the analysis were reported as separate categories. In accordance with ICES privacy policies, cell counts ≤ 5 were censored to avoid potential re-identification of personal health information.

We conducted logistic regression to explore the relationship between incident HCU status and the use of the pre-selected potentially inappropriate high-risk medications and high-cost drugs. Each medication class was analyzed independently in a series of analyses to estimate individual odds ratios (ORs) and 95% CIs. In order to minimize potential bias from confounding by indication and severity of illness, estimates were adjusted for several important covariates determined a priori, including age, sex, number of co-morbidities,

number of major John Hopkins ADGs (which is an indicator of high illness severity and probable need for specialty care), and the most common conditions for which each the specific drug(s) are indicated.

To further explore the data for evidence for potential associations, we incorporated duration of medication use into analyses of potentially inappropriate high-risk medication use to examine associations with HCU development based on increasing exposure to each medication.[16] Duration was defined by the cumulative days of medication supplied within the specified year.

In a secondary case-control analysis, we used logistic regression to explore whether potentially inappropriate high-risk medication use by incident HCUs was associated with all-cause mortality in addition to their hypothesized effects on healthcare utilization and costs.

RESULTS

The study population consisted of 706,216 older adults. There were 175,847 incident HCUs matched to 527,541 non-HCUs. HCUs accounted for $433 million in medication costs and $5.2 billion in total healthcare expenditures.

The baseline characteristics of the HCUs and non-HCUs are shown in Table 1. The study population was 53% female with a median age of 77 years (IQR 71-83). The majority of individuals lived in a non-institutionalized urban setting. Comparing the HCUs (cases)

and non-HCUs (controls), there was balanced representation across all income quintiles. There were no meaningful differences in income status or receipt of social assistance (i.e., as defined by those qualifying for deductible and co-payment reductions for prescription drugs due to low income). HCUs had a higher burden of co-morbidities (John Hopkins EDCs 14 vs 10, SD 0.55) with a greater proportion affected by several common chronic conditions (i.e., ischemic heart disease, heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease, diabetes, degenerative joint disease, and cognitive impairment).

HCUs had a larger circle of physician care and they were more likely to have seen a geriatrician, but the overall prevalence was low (2.8% vs 1.1%, SD 0.12). Compared to non-HCUs, HCUs had a higher median number of medications (8 vs. 5, SD 0.62) with severe polypharmacy (>15 medications) being significantly more prevalent (30.8% vs. 13.9%, $p < 0.001$).

Potentially Inappropriate High-Risk Medication Use

Use of potentially inappropriate high-risk medications was more than twice as prevalent per capita amongst HCUs compared to non-HCUs in the pre-incident year (Table 2). With exception to non-steroidal inflammatory agents, their use based on prescription claim frequency amongst HCUs increased in the incident HCU year, but remained relatively stable in non-HCUs. Opioid use, for example, occurred at a rate 112.5 claims per 100 persons amongst HCUs in the pre-incident year and increased to 203.4 claims per 100

persons in the incident year. In contrast, use amongst non-HCUs only increased from 46.4 to 49.6 claims per 100 persons over the same period.

Potentially inappropriate high-risk medication use during the 2-year observational period was associated with an increased likelihood of becoming a HCU. These associations persisted after adjustment for age, sex, illness severity, co-morbidities, and the most common indicated conditions for their use (Figure 1). The medication classes associated with the highest odds of HCU development were opioids (adjusted odds ratio [aOR] 3.56, 95% CI 3.52-3.60) and antipsychotics (aOR 4.45, 95% CI 4.34-4.58). The observed associations with HCU status persisted when drug use exposure was restricted only to the baseline (pre-HCU) year and demonstrated that the association is not solely the result of exposure during or after a critical event or acute hospitalization in the incident HCU year.

The incorporation of duration of use into the analyses demonstrated a cumulative duration-outcome relationship based on increasing drug exposure (Figure 2). For all of the specified medication classes, each additional day of potentially inappropriate high-risk medication supplied increased the likelihood of HCU development. The medication classes associated with the highest odds based on duration of use were opioids and antipsychotics, with estimates that each additional year of use increases the odds of HCU status by 1.61 (95% CI 1.58-1.63) and 1.57 (95% CI 1.54-1.60) respectively.

In HCUs, the use of opioids, antipsychotics, benzodiazepines and digoxin during the study period increased their odds of mortality in the incident HCU year (Figure 3).

Antipsychotic use during the HCU year was associated with the highest odds of mortality (aOR 2.93, 95% CI 2.80-3.06).

High-Cost Drug Use

Annual medication expenditures alone were responsible for incident HCU status in 6258 HCUs (3.6%). In 5216 HCUs (3.0%), these high medication costs were based solely on the use of one of the four specific medication classes that were selected for analysis as higher-cost drugs: ophthalmologicals, immunomodulators, antineoplastics and biologic response modifying agents.

Use of higher-cost drugs was more prevalent amongst HCUs and prescription claims for these drug classes increased significantly in their incident HCU year (Table 2). Compared to the previous year, the relative increase in prescription claims was 1.4-fold for immunomodulators (e.g., mycophenolic acid, sirolimus), 8.3-fold for opthalmologicals (e.g. ranibizumab), 10.5-fold for biologic response modifying agents (e.g. adalimumab, interferons) and 286.6-fold for antineoplastics (e.g. imatinib). In contrast, the relative increase in prescription claims for the same medication classes for non-HCUs was 1.1, 1.5, 1.8 and 78.0-fold respectively and much lower on an absolute per capita basis.

Use of any of these higher-cost medications in the HCU year significantly increased the likelihood of HCU status (Figure 1) in both unadjusted and adjusted analyses for age, sex, illness severity, co-morbidities, and the most common indicated conditions for their use. The use of biologics and antineoplastics were the most likely to be associated with

HCU status with an increased adjusted odds of HCU status by 30.85 (95% CI 20.97 to 45.39) and 53.46 (95% CI 36.75 to 77.77) respectively.

DISCUSSION

Older adults are disproportionately represented at higher healthcare expenditure levels and account for the majority of high-cost healthcare users. In this study, we show that prescription medications are important contributors to their healthcare expenditures and risk of becoming high-cost healthcare users. Utilizing a population-based case-control study design, we determined that there appears to be at least two distinct medication-related factors contributing to HCU development: (1) older adults receiving potentially inappropriate high-risk medications where harms may be outweighing potential benefits of their use, and (2) patients receiving expensive higher-cost (per unit) medications such as biologics.

Previous studies have shown that significant healthcare dollars are used on the direct drug costs of potentially inappropriate medications.[12,17] Our study demonstrates that there are also significant indirect health and healthcare utilization costs attributable to the use of these medications. Potentially inappropriate medication use is highly prevalent amongst older adult HCUs and our data suggest that may be a temporal relationship between their prescribing and the future development of HCU status and possibly even death. The possibility of causal association is supported by the observation of a cumulative "duration outcome" relationship even after adjustment for variables associated with the

prescribing of each medication. For all potentially inappropriate high-risk medication classes evaluated, increasing duration of exposure increased the likelihood of becoming a HCU.

These results are consistent with previous studies in other patient populations and international healthcare systems which have shown an association between potentially inappropriate medication use and adverse events, health service utilization (particularly hospitalization), and costs.[18,19] However, we are not aware of any other study that has shown that such exposures can be associated with HCU development nor examined the association with specific medication classes (rather than potentially inappropriate medications [PIMs] as a collective category) to determine which medications may be more problematic.

Our findings suggest that the development of policies and strategies to reduce (or shorten exposure) to potentially inappropriate prescribing may generate significant health system savings. This could be achieved not only by decreasing medication expenditures, but by concurrently providing major benefits to the health of older adults and avoiding large downstream costs of unnecessary adverse drug events, hospitalizations and ED visits. As a result, clinicians, researchers and policymakers interested in managing the HCU phenomenon should consider developing targeted deprescribing and medication optimization interventions and then test them for effectiveness using rigorous health research methodology. Advances in knowledge in this area is much needed as complex HCU management models are being implemented internationally (and often without a

strong evidence base to support their effectiveness) and none to our knowledge have focused on evidence-based drug optimization interventions.[2]

The judicious use of high-cost drugs is another issue amongst older adult HCUs that needs to be monitored. Our study shows that healthcare expenditures for individual higher-cost (per unit) medications are responsible for a growing population of new high-cost healthcare users independent of their overall health status and other healthcare utilization. In some cases, these treatments are temporary (e.g., Hepatitis C). However, in others, they are chronic (e.g., macular degeneration) and thereby contribute to a growing population of persistent HCUs directly through their drug costs. This phenomenon of high drug cost HCUs will likely grow due to the increasing development and availability of expensive medications.[20]

The potential implications are a changing concentration of healthcare expenditures from a small proportion of the population to one that is distributed, but rising exponentially, over a large segment of the population.[21] This raises potential concerns regarding the future sustainability of prescription drug reimbursement programs. Prescription drug spending is the fastest growing category of healthcare expenditures in Canada and the United States with projections that its growth will consistently outpace other healthcare spending over the next decade.[22,23] In Canada, it is outpacing both hospital and physician expenditures at an annual growth rate of 4.2%.[22] This highlights the need to develop strategies to manage drug costs and safeguard equitable access to innovative medicines. This could include formulary modernization and innovative drug policies (e.g. indication-based, reference-based or biosimilar substitution) to ensure that the use of higher-cost drugs is evidence-

based and avoided when there is minimal or unproven benefit over less-expensive therapies.

This study has several strengths, including the large sample size and the focus on incident rather than prevalent HCUs. The latter allowed for identification of potential contributors to HCU development that may be amenable to preventative intervention. The large population-based cohort permitted evaluation of the associations between medications and high-cost healthcare use in a way that is statistically efficient and that transcends differences in local prescribing patterns.

However, this study is subject to the limitations and residual confounding inherent in observational data from health administrative databases. Although we demonstrate a significant duration-outcome relationship that would support a hypothesis of possible causal association, we cannot be certain that medications cause HCU status outside of the situation when cumulative direct costs exceed the HCU financial threshold. Other unknown, unmeasured or unmeasurable factors may have influenced healthcare utilization and prescribing. Second, it is also not possible to guarantee patients were adherent to dispensed medications nor that they were used as prescribed. Third, our ability to account for the duration of medication exposure is limited to two years of available prescription data. This limits the inferences we can conclude related to the timing of medication initiation, exposure duration, and HCU transition. Fourth, HCUs and non-HCUs were identified based on healthcare utilization costs accrued during a fiscal year. The HCU status of some individuals (including those in their last year of life) may have been classified

differently if an alternative method (e.g. calendar year) was used depending on when they accrued costs and/or died.

CONCLUSION

Use of potentially inappropriate high-risk medications and high-cost drugs are both associated with an increased likelihood of becoming a HCU. Medications can be significant contributors to high-cost healthcare, both directly through up-front drug costs and indirectly through their effects on health and downstream events such as adverse drug events, hospitalizations and ED visits. Future research should focus on developing and testing medication optimization strategies and policies for intervention at both the health system and individual level.

ACKNOWLEDGEMENTS

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information and IQVIA Solutions Canada Inc. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding and data sources; no endorsement is intended or should be inferred.

Author Contributions:

JL and AH conceptualized the study. All authors contributed to its design. WK and JL conducted the statistical analysis. All authors contributed to the interpretation of the data. JL drafted the initial manuscript and all authors contributed to revision and final approval.

Conflicts of Interest:

The authors have no conflicts of interest for this article.

Role of the Funder:

The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data. They were not involved in the preparation of the manuscript or the decision to submit the manuscript for publication.

REFERENCES

1. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. *Health Aff (Millwood)*. 2008;27(3):759-769. doi:10.1377/hlthaff.27.3.759

2. Lee J, Muratov S, Tarride J-E, Holbrook A. Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies. *J Am Geriatr Soc*. 2018;66(5):1002-1008.

3. Mitchell EM, Machlin SR. *Concentration of Health Expenditures and Selected Characteristics of High Spenders, U.S. Civilian Noninstitutionalized Population, 2015*.; 2017.

4. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ*. 2016;188(3):182–188. doi:10.1503/cmaj.150064

5. Lee J, Muratov S, Tarride J, et al. Contribution of Prescribed Medications to High Cost Healthcare User Status in Ontario. *Can Geriatr J*. 2017;20(3):207.

6. Statistics Canada. Table 17-10-0009-01 Population estimates, quarterly. 2020. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901. Accessed November 25, 2020.

7. Lee J, Muratov S, Tarride J-E, et al. Medication use and its impact on high-cost health care users among older adults: protocol for the population-based matched cohort HiCOSTT study. *C Open*. 2021;9(1):E44-E52. doi:10.9778/cmajo.20190196

8. Wodchis WP, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on person-level costing using administrative databases in Ontario. 2013;1(May):1-71.

9. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):213-218.

10. Deprescribing.org. Deprescribing Guidelines and Algorithms. https://deprescribing.org/resources/deprescribing-guidelines-algorithms. Accessed March 3, 2019.

11. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-694. doi:10.1111/jgs.15767

12. Morgan SG, Hunt J, Rioux J, Proulx J, Weymann D, Tannenbaum C. Frequency and cost of potentially inappropriate prescribing for older adults: a cross-sectional study. *C open*. 2016;4(2):E346-51. doi:10.9778/cmajo.20150131

13. Black CD, Thavorn K, Coyle D, Bjerre LM. The Health System Costs of Potentially Inappropriate Prescribing: A Population-Based, Retrospective Cohort Study Using Linked Health Administrative Databases in Ontario, Canada. *PharmacoEconomics - Open*. 2020;4(1):27-36. doi:10.1007/s41669-019-0143-2

14. Tadrous M, Martins D, Mamdani MM, Gomes T. Characteristics of high–drug-cost beneficiaries of public drug plans in 9 Canadian provinces: a cross-sectional

analysis. *C Open*. 2020;8(2):E297-E303. doi:10.9778/cmajo.20190231

15. Austin P. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Comm Stat Simul Comput*. 2009;38(6):1228-1234.

16. Hill AB. The Environment and Disease: Association or Causation? *J R Soc Med*. 1965;58(5):295-300. doi:10.1177/003591576505800503

17. Bradley MC, Fahey T, Cahir C, et al. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. *Eur J Clin Pharmacol*. 2012;68(10):1425-1433. doi:10.1007/s00228-012-1249-y

18. Heider D, Matschinger H, Meid AD, et al. Health Service Use, Costs, and Adverse Events Associated with Potentially Inappropriate Medication in Old Age in Germany: Retrospective Matched Cohort Study. *Drugs and Aging*. 2017;34(4):289-301. doi:10.1007/s40266-017-0441-2

19. Clark CM, Shaver AL, Aurelio LA, et al. Potentially Inappropriate Medications Are Associated with Increased Healthcare Utilization and Costs. *J Am Geriatr Soc*. 2020;68(11):2542-2550. doi:10.1111/jgs.16743

20. Vincent Rajkumar S. The high cost of prescription drugs: causes and solutions. *Blood Cancer J*. 2020;10(6). doi:10.1038/s41408-020-0338-x

21. Zuvekas SH, Cohen JW. Prescription drugs and the changing concentration of

health care expenditures. *Health Aff*. 2007;26(1):249-257. doi:10.1377/hlthaff.26.1.249

22. Canadian Institute for Health Information. *National Health Expenditure Trends, 1975 to 2018*. Ottawa, ON; 2018.

23. Cuckler GA, Sisko AM, Poisal JA, et al. National health expenditure projections, 2017-26: Despite uncertainty, fundamentals primarily drive spending growth. *Health Aff*. 2018;37(3):482-492. doi:10.1377/hlthaff.2017.1655

24. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.

25. Iron K, Lu H, Manuel D, Henry D, Gershon A. Using linked health administrative data to assess the clinical and healthcare system impact of chronic diseases in Ontario. *Healthc Q*. 2011;14(3):23-27. doi:10.12927/hcq.2011.22486

26. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516. doi:10.2337/diacare.25.3.512

27. Tu K, Campbell NR, Chen Z-L, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Med*. 2007;1(1):e18-26.

Table 1: Baseline Characteristics of Matched HCUs (Cases) and Non-HCUs (Controls)

Baseline Characteristics	Incident HCUs N=175,847	Non-HCUs N=527,541	Standardized Difference[a]
SOCIODEMOGRAPHICS			
Age (years), n (%)			
66-74	68,644 (39.0%)	205,932 (39.0%)	N/A
75-84	70,156 (39.9%)	210,465 (39.9%)	N/A
85-94	34,665 (19.7%)	104,011 (19.7%)	N/A
95+	2,382 (1.4%)	7,133 (1.4%)	N/A
Median (IQR)	77 (71-83)	77 (71-83)	N/A
Female, n (%)	93,167 (53.0%)	279,501 (53.0%)	N/A
Residence in Long-Term Care, n (%)	632 (0.4%)	199 (0.0%)	0.07
Geographic Location Based on Rurality Index for Ontario (RIO)[b,c], n (%)			
Urban (RIO < 10)	115,305 (65.6%)	354,536 (67.2%)	0.03
Suburban (RIO 10-39)	41,551 (23.6%)	117,353 (22.2%)	0.03
Rural (RIO ≥ 40)	17,645 (10.0%)	51,403 (9.7%)	0.01
Income Quintile[c]			
Q1	34,417 (19.6%)	98,036 (18.6%)	0.03
Q5	35,094 (20.0%)	110,427 (20.9%)	0.02
Social Assistance Recipient, n (%)	30,686 (17.5%)	74,527 (14.1%)	0.09
PHYSICIAN CARE			
Circle of Medical Care			
Number of unique physicians, Median (IQR)	7 (5-11)	5 (3-8)	0.56
CO-MORBIDITY BURDEN			
John Hopkins ADGs[d]			
Total Number, Mean (SD)	10.22 (4.00)	7.93 (4.47)	0.54
Specific Comorbidities			
Heart Failure	25,203 (14.3%)	36,877 (7.0%)	0.24
Cardiac Arrhythmia	34,960 (19.9%)	62,215 (11.8%)	0.22
Ischemic Heart Disease	46,678 (26.5%)	90,135 (17.1%)	0.23
Chronic Obstructive Pulmonary Disease	48,761 (27.7%)	96,513 (18.3%)	0.23
Diabetes	62,031 (35.3%)	138,794 (26.3%)	0.2
Degenerative Joint Disease	67,487 (38.4%)	136,031 (25.8%)	0.27
Cognitive Impairment	21,462 (12.2%)	28,264 (5.4%)	0.24

Abbreviations: ADG, adjusted diagnostic group; HCU, high cost user; IQR, interquartile range; N/A, not applicable; RIO, rurality index for Ontario; SD, standardized difference

[a] SD greater than 0.1 represents a meaningful difference

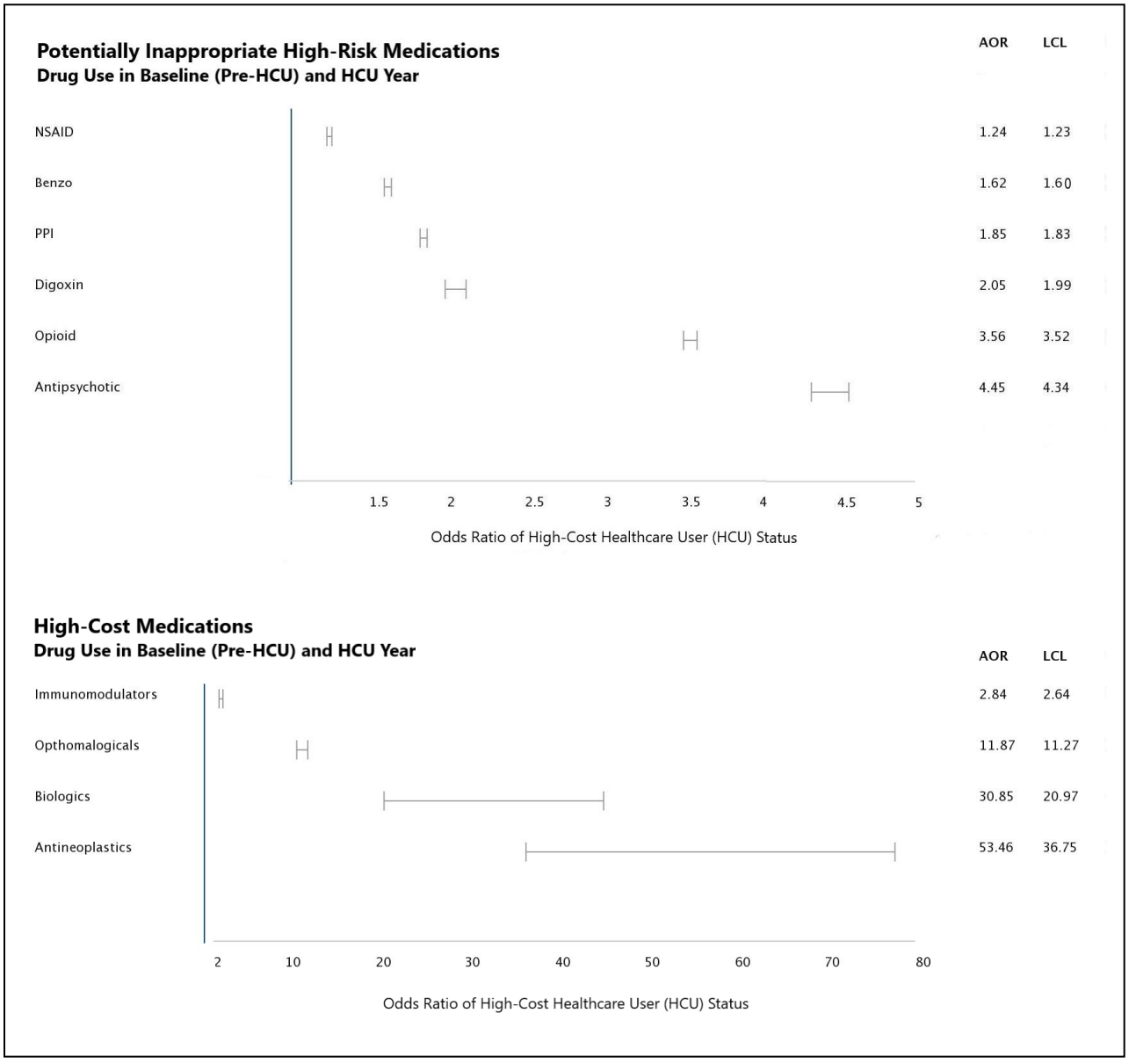
[b] Cumulative total may not equal to N (100%) due to missing values (<1%)
[c] RIO is determines rurality based on community population size, population density, and travel times to the nearest basic and advanced referral centres
[d] Higher number of ADGs per patient indicates a greater burden of illness.

Table 2: Prescription Claims for High-Cost and Potentially Inappropriate High-Risk Medications

	HCUs			Non-HCUs		
	Prescription Claims (Per 10000 Persons)			Prescription Claims (Per 10000 Persons)		
	Baseline Year	HCU Year	Relative Change	Baseline Year	HCU Year	Relative Change
High-Cost (Per Unit) Drugs						
Biologics	13.36	139.95	10.47	0.61	1.08	1.78
Ophthalmological	296.00	2,445.76	8.26	52.07	80.09	1.54
Antineoplastic	0.45	130.40	286.63	0.02	1.48	78.00
Immunomodulator	467.51	661.09	1.41	137.26	147.29	1.07
Potentially Inappropriate High-Risk Medications						
NSAID	9,199.47	9,112.07	0.99	5,088.65	5,166.75	1.02
Proton Pump Inhibitor	29,365.53	41,843.02	1.42	14,153.90	15,852.34	1.12
Opioids	11,250.92	20,341.43	1.81	4,644.47	4,963.44	1.07
Benzodiazepines	13,532.96	15,892.45	1.17	6,663.94	6,911.75	1.04
Digoxin	3,815.99	5,455.94	1.43	1,416.27	1,535.29	1.08
Antipsychotics	7,268.88	14,521.43	2.00	2,319.29	2,715.26	1.17

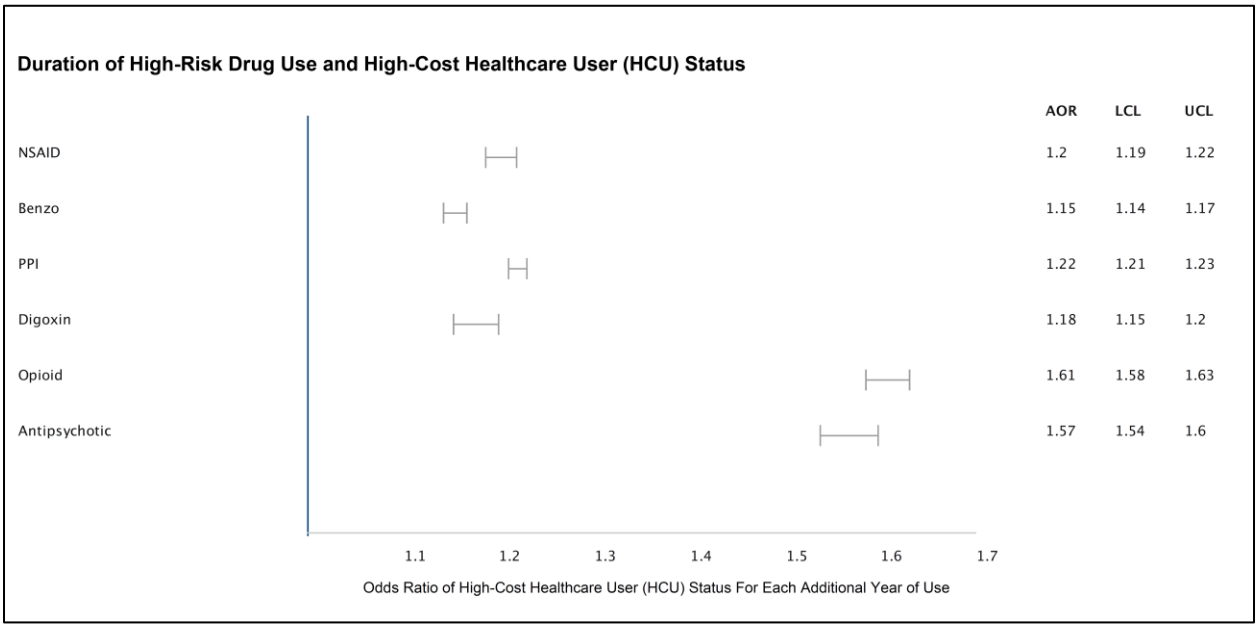
Figure 1: Association Between Potentially Inappropriate High-Risk and High-Cost Medication Use and High-Cost Healthcare User Status

Abbreviations: AOR = adjusted odds ratio; LCL = 95% lower confidence interval limit;



UCL = 95% upper confidence interval limit; Benzo = Benzodiazepine; NSAID = Non-steroidal anti-inflammatory drug; PPI = Proton pump inhibitor

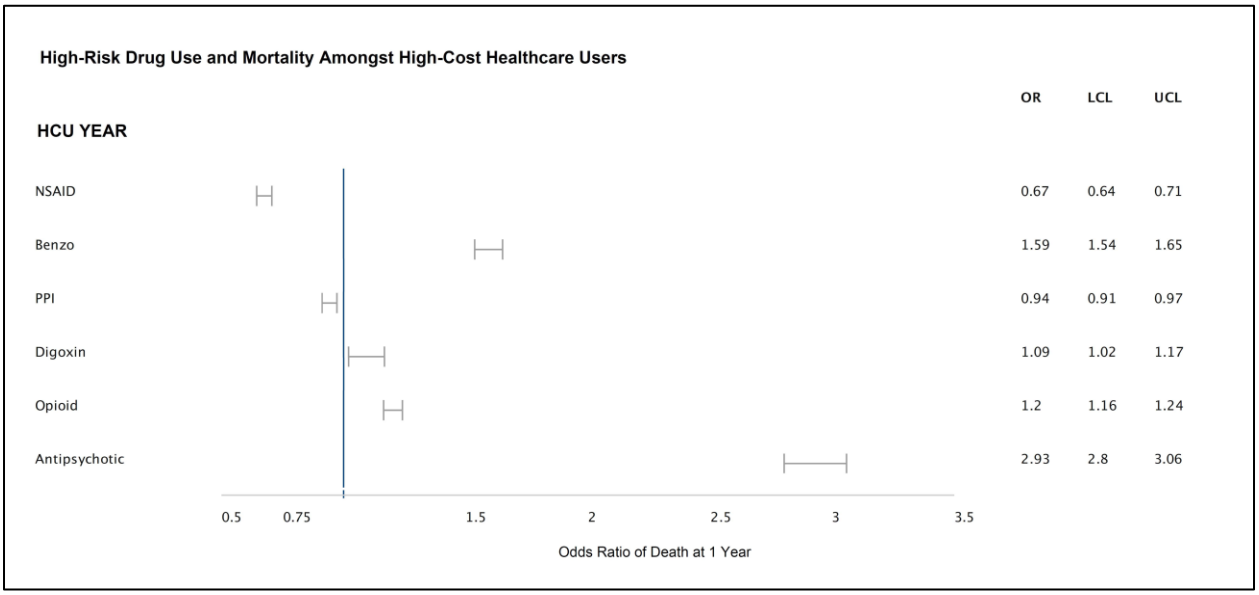
Figure 2: Association Between Duration of Potentially Inappropriate High-Risk Medication Use and High-Cost Healthcare User (HCU) Status



*Duration of use determined by cumulative days supply of prescription claims per patient

Abbreviations: AOR = adjusted odds ratio; LCL = 95% lower confidence interval limit; UCL = 95% upper confidence interval limit; Benzo = Benzodiazepine; NSAID = Non-steroidal anti-inflammatory drug; PPI = Proton pump inhibitor

Figure 3: Association Between Potentially Inppropriate High-Risk Medication Use and Mortality Among High-Cost Healthcare Users



*Duration of use determined by cumulative days supply of prescription claims per patient

Abbreviations: AOR = adjusted odds ratio; LCL = 95% lower confidence interval limit; UCL = 95% upper confidence interval limit; Benzo = Benzodiazepine; NSAID = Non-steroidal anti-inflammatory drug; PPI = Proton pump inhibitor

APPENDICES

Supplementary Table 1: Health Administrative Databases

Health Administrative Database	Description	Database Variables/Data Used
Ontario Health Insurance Plan (OHIP) Registered Persons Database (RPDB)	The OHIP Registered Persons Database (RPDB) records health insurance status and vital status, including date of death.	• Date of death • Rurality Index Ontario Score • Age • Sex
Immigration, Refugees and Citizenship Canada Permanent Resident (IRCC-PR) database	Immigration, Refugees and Citizenship Canada Permanent Resident (IRCC-PR) database contains landing records for every permanent legal immigrant to Canada who arrived from 1985 onward.	• Date of landing/immigration
Local Health Integration Network (LHIN) database	The Local Health Integration Network (LHIN) database contains records the health authorities responsible for the regional administration of public healthcare services in the province of Ontario, Canada.	• Geographic location of residence of included patients
Ontario Drug Benefit (ODB) database	The Ontario Drug Benefit (ODB) database contains highly accurate records for outpatient prescriptions dispensed to patients aged 65 years or older (with error rates reported to be less than 1%).[24]	• Prescription drug fill dates and costing • Long-term care indicator
Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD) contains validated patient-level demographic, diagnostic, procedural and treatment information on all acute- and chronic-care hospitalizations.	• ICD-10 Codes for Hospital Discharge Diagnoses for John Hopkins ACGs and EDCs • Hospitalizations (elective and urgent) and costing

CIHI—National Ambulatory Care Reporting System (CIHI-NACRS) database	The CIHI—National Ambulatory Care Reporting System (CIHI-NACRS) database contains patient-level demographic, diagnostic, procedural and treatment information for all hospital-based and community-based ambulatory care including day surgery, outpatient and community-based clinics, and emergency departments.	• ICD-10 Codes for Hospital Discharge Diagnoses for John Hopkins ACGs and EDCs • Visits and costing
CIHI-Same Day Surgery (SDS)	The CIHI-Same Day Surgery (SDS) contains patient-level demographic, diagnostic, procedural and treatment information on all day surgeries.	• ICD-10 Codes for Hospital Discharge Diagnoses for John Hopkins ACGs and EDCs • Visits and costing
CIHI-National Rehabilitation Reporting System (NRS)	The CIHI-National Rehabilitation Reporting System (NRS) contains patient-level demographic, diagnostic, procedural and treatment information from participating adult inpatient rehabilitation facilities and programs.	• Visits and costing
Ontario Home Care Database (HCD)	The Ontario Home Care Database (HCD) contains patient-level demographic, diagnostic, procedural and treatment information on all home care visits.	• Home care visits • Type of home care service provided • Visits and costing
Ontario Continuing Care Reporting System (CCRS)	The Ontario Continuing Care Reporting System (CCRS) contains demographic, clinical, functional and resource utilization information on individuals receiving continuing care services in hospitals or long-term care homes in Canada.	• Visits and costing
Ontario Mental Health Reporting System (OMHRS) database	The Ontario Mental Health Reporting System database contains patient-level demographic, diagnostic, procedural and treatment information on all adult psychiatric facility visits.	• Visits and costing

ICES Physician Database (IPDB)	The ICES Physician Database (IPDB) captures physician characteristics and is validated against the Ontario Physician Human Resource Data Centre (OPHRDC) database.	• Characteristics of primary care and specialist physicians
Ontario Health Insurance Plan database (OHIP)	The Ontario Health Insurance Plan database (OHIP) which includes health claims for physician services.	• ICD-9 Diagnosis Codes for physician encounters for John Hopkins ACGs and EDCs • Physician visits and costs
Client Agency Program Enrolment (CAPE) database	The Client Agency Program Enrolment (CAPE) database contains enrolment information of an individual in a programme with a specific practitioner and group.	• Primary care practitioner reimbursement model of included patients
ICES-derived cohorts: • Congestive Heart Failure (CHF) database • Chronic Obstructive Pulmonary Disease (COPD) database • Ontario Crohn's and Colitis Cohort Database (OCCD) • Ontario Diabetes Database (ODD) • Ontario Myocardial Infarction Database (OMID) • Ontario Rheumatoid Arthritis Database (ORAD)	The ICES-derived cohorts are chart-validated cohorts of individuals with specific diseases and conditions. These cohorts are created using health administrative case definitions that link hospital in-patient and outpatient care, physician claims and drug benefits data over time using an anonymous, unique identifier.[25] The case definitions were validated by clinical scientists at ICES using data collected directly from reviews of medical charts in the community. For example, the diabetes and hypertension definitions have a positive predictive value of 80% and 87% respectively.[26,27]	• Co-morbidities of included patients

Supplementary Table 2 – Potentially Inappropriate High-Risk Medications and High Cost Drugs Selected for Analysis

Potentially Inappropriate High-Risk Medication Use	High Cost (Per Unit) Medication Use
• Proton pump inhibitors • Benzodiazepines • Narcotics (Opiate Agonists) • Antipsychotics • NSAIDs (non-ASA) • Digitalis Preparations (Digoxin)	• Immunosuppressive agents (e.g. mycophenolic acid, natalizumab, sirolimus, tacrolimus, thalidomide) • Antineoplastic agents (e.g. tocilizumab, imatinib, dasatinib) • Opthalmologicals (e.g. Ranibizumb) • Biologic Response Modifying Agents (e.g. adalimumab, aldesleukin, certolizumab, etanercept, glatiramer, golimumab, infliximab, interferons, levamisole)

Abbreviations: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, ASA = acetylsalicylic acid, DOAC = direct oral anticoagulant, NSAID = nonsteroidal anti-inflammatory drug.

CHAPTER 6: Thesis Discussion and Conclusion

High-cost healthcare users (HCUs) are a small, but important group of individuals in the population that can have a significant effect on the sustainability and delivery of healthcare. Although they are commonly the focus of initiatives designed to achieve the "Triple Aim" (i.e. better quality of care, improved population health, and reduced healthcare costs), their epidemiology is not well understood because they are a heterogenous group with multiple contributing factors and complex healthcare needs. In this thesis, we advance the knowledge of high-cost healthcare users (HCUs) by: (1) synthesizing and critically appraising knowledge about their characteristics and interventions designed to prevent or manage their high-cost healthcare use, and (2) systematically characterizing the older adult HCU and the impact that prescribing quality and medication use has on their health outcomes and costs. This concluding chapter reviews the main findings of this thesis, discusses the implications of these results, and explores opportunities for future research.

Key Findings

Characteristics of High-Cost Healthcare Users and Evidence for Effective Interventions

In Chapter 2, we reviewed what is known about HCUs and the available evidence for the effectiveness of interventions designed to prevent or manage their high healthcare use and costs. Although the phenomena of HCUs and concentrated healthcare spending has been known for decades HCU and observed internationally, we found that there is no

agreement on a common definition or description. In general, they are characterized by heavy use of one or more healthcare services as defined by various thresholds of frequency and/or cumulative costs. Common characteristics of HCUs observed internationally include older age, multi-morbidity, polypharmacy, and increased morbidity and mortality.[10,14,17,28,29] However, the body of literature suggests there are many HCU subgroups beyond this common patient archetype that should be considered including those across the entire age spectrum with low socioeconomic status, high burden of mental illness or terminal illness at the end of life.[17,20,21,30]

Our comprehensive and systematic literature search did not identify any randomized controlled trials that defined their study population using a high-cost healthcare user definition (e.g. those within the top 1% or 5% of healthcare expenditures), but rather studies of various designs that focused on a variety of high-risk or high-need individuals that likely included many HCUs. Most interventions evaluated have been "reactive" and have directed additional resources to those already experiencing adverse outcomes or high healthcare costs to try to contain costs through the minimization of future ED visits and hospitalizations. They have focused on care management strategies with varying degrees of case management, care coordination, or disease management. However, these care management strategies have had mixed or unsuccessful effects on health service use and costs, particularly those with more rigorous study designs (i.e. randomized controlled trials).

The majority of available studies are small observational studies using before-and-after analyses with short follow-up periods and without matched comparison groups. They

are at high risk of bias due to potential regression to the mean, selection bias, and other unmeasured confounders. As a result, we found the overall quality of the body of evidence supporting existing HCU care management interventions is low using the GRADE framework based on methodological quality of study design, indirectness of study populations, and the inconsistency and imprecision of results.[31]

Characteristics and Prognosis of Incident Older Adult High-Cost Healthcare Users

Through a population-based matched cohort study involving 704,793 older adults described in Chapters 3 and 4, we conducted a more in-depth evaluation of incident older adult HCUs by comparing them to matched older adult non-HCUs. We demonstrated that older adult HCUs have a higher co-morbidity burden compared to their matched non-HCU peers (John Hopkins Expanded Diagnosis Clusters [EDCs], 15.2 vs. 11.1, SD 0.55) with a greater proportion affected by several common chronic conditions (e.g. ischemic heart disease, chronic obstructive pulmonary disease, diabetes, degenerative joint disease, and cognitive impairment). There were no meaningful differences attributable to primary care reimbursement models (e.g. fee-for-service, capitation), income status, or social assistance.

During their incident HCU year, we demonstrated that older adult HCUs have significant differences in healthcare utilization compared to their matched non-HCU peers including an increased likelihood for more acute hospitalization, physician visits, and home care visits. We found that acute hospitalization expenditures is the primary, but not sole driver for differences in healthcare costs compared to non-HCUs.

The short-term prognosis of HCUs compared to non-HCUs is poor with higher one-year all-cause mortality (RR 14.4, 1039% vs. 0.72%, p<0.001) and rates of hospitalization (RR 53.3, 3.2 vs. 0.06 hospitalizations per 1000 person-years, p<0.001). These results emphasize the vulnerability and frailty of this patient group.

Medication Use Patterns and Their Contributions to High-Cost Healthcare User Status

In the matched cohort study described in Chapter 4, we expanded on previous HCU studies that have only reported their cumulative cost as a cost category and provided more in-depth information about older adult prescription medication use.[1] Although acute hospitalization costs typically represent the largest healthcare expenditure in older adult HCUs, we demonstrated that medications are very important direct financial contributors to HCU expenditures and incident HCU status. Older adult HCUs have higher mean annual medications costs both in the pre-HCU and HCU year. Prior to becoming an HCU, prescription medication use is the highest healthcare cost category (amongst a comprehensive list of 12 healthcare sectors) and accounts for approximately 41% of total healthcare expenditures. Moreover, these medication costs increase nearly two-fold for HCUs during the HCU transitional period and many incident HCUs achieve high-cost status based on annual drug expenditures alone. In our study, 6,358 individuals (3.6% of all incident HCUs) achieved incident HCU status in this fashion.

We also demonstrated that the large cost contribution of prescription medications to HCU healthcare expenditures is explained in part by a high volume medication use and

in part by a rising use of very expensive drugs. In our study, older adult HCUs had significantly higher severe polypharmacy rates compared to non-HCUs (>10 medications: 55.1% vs. 14.5%, p<0.0001; >15 medications: 24.1% vs. 3.0%, p <0.0001). There was also a significant increase in the use of high (per unit) cost medications (e.g. immunosuppressive agents, anti-neoplastics, ophthalmologicals, and biologic response modifying agents) during non-HCU to HCU transition period. In fact, 5216 individuals (3.0% of all incident HCUs) achieved their incident HCU status solely based on the use of one of these high-cost drug classes.

Quality of Prescribing and Medication Use and Their Contributions to High-Cost Healthcare User Status

In the matched case-control study described in Chapter 5, we explored whether the quality of medications prescribed and used contribute to differences in healthcare costs and HCU development. Through a series of multivariable logistic regression analyses planned a priori, we demonstrated that all 6 potentially inappropriate high-risk medication classes in older adults (i.e. non-steroidal anti-inflammatory drugs, benzodiazepines, proton pump inhibitors, digoxin, opioids and antipsychotics) and all 4 high-cost (per unit) drug classes (i.e. immunomodulators, ophthalmologicals, biologic response modifying agents and anti-neoplastics) that we selected a priori for analysis were associated with an increased risk of becoming a high-cost healthcare user. These associations persisted after adjustment for age, sex, illness severity, number of co-morbidities, and the most common indicated

conditions for their use. Duration of use analyses also demonstrated cumulative duration-outcome relationships based on increasing medication exposure and further strengthened the credibility of the observed associations.

The use (or lack thereof) of "high quality" medication classes (i.e. those with a strong evidence base for primary or secondary prevention of common high-priority disease states in older adults) may represent another contributor to differences in healthcare costs and HCU development. In the matched cohort study described in Chapter 4, for example, the most common reasons for hospitalization observed in HCUs contrasted with those observed in non-HCUs. They were characterized to a greater extent by sudden, acute health events for which several medications with a strong evidence base for prevention are available (e.g. bisphosphonates for osteoporosis and fracture prevention, cholesterol and blood pressure control agents for cardiovascular and cerebrovascular disease prevention). It is unclear whether there is a significant gap in medication best practices in this population and whether there is a need to optimize the use of "high quality" medications to improve the health of individuals on the trajectory of becoming potential HCUs.[32,33] Evaluation of the impact of these medications is currently ongoing as per our protocol described in Chapter 2.

Overall, the results of this thesis study demonstrate that there are at least two medication-related factors contributing to the risk of older adults becoming high-cost healthcare users. First, the rising use of high-cost (per unit) drugs are causing more older adults to reach the financial thresholds of high-cost healthcare use directly through drug costs alone independent of their health status. Second, the use of potentially inappropriate

high-risk medications appear to be contributing to high-cost healthcare through adverse effects on health and subsequent health utilization (i.e. the harms of the use of these medications may be outweighing their potential benefits).

Health Policy Implications

The findings of the thesis suggest that a strategic approach to HCU research, policy, and management is needed. Since our evidence review identified that there are many HCU subgroups, there is no "one size fits all" approach and interventions needed to be tailored to specific subgroups and health contexts. We propose that older adult HCUs are one of the most important subgroups to target because of the magnitude of their population size and cumulative health costs. However, there are many others that also require attention (e.g. patients in the last year of their life, those with mental illness, those with unmet social needs such as housing).

At the same time, given that many health systems are implementing complex interventions based on observational studies that are often small or short in duration, it is equally important that any interventions developed are evaluated using rigorous research methodology to validate their efficacy and cost-effectiveness. This may require significant time and financial investments from health systems, administrators, and researchers, but safeguards against long-term implementation of programs that are not achieving their intended effects and may be even more costly than the status quo.

The recent randomized controlled trial of the Camden Coalition "hotspotting" model for superutilizers (published after our review in Chapter 2) is a landmark example of the risk of bias of observational studies and the necessity of these evaluations.[12] In this RCT involving 800 patients with very high use of healthcare services, the intensive care management program had no significant effect on participants' 180-day readmission rates compared to those receiving usual care. This contrasted to an apparent, but misleading 38% decrease in the probability of readmission for those in the intervention arm when analyzed over the same time period with a before and after analysis. Potential regression to the mean, episodic versus persistent HCUs, and avoidable versus unavoidable healthcare use are important health policy and intervention considerations.

It is also important to consider how medication optimization interventions and policies at a health system and individual level may be underutilized strategies to achieve the desired "Triple Aim" goal of population health. This thesis suggests that reducing inappropriate medication use and ensuring cost-effective use of expensive medications could complement existing interventions and help minimize high-cost healthcare and prevent high-cost user development. For example, although potentially inappropriate prescribing has been previously shown to be associated with an increased of adverse events, hospitalization and healthcare costs, our findings demonstrate that this association is not trivial and the exposure, especially if prolonged, may contribute to individuals requiring increased healthcare utilization and costs that reach the highest tiers within the population (e.g. Top 5%).[34] The prevalence of polypharmacy (especially at levels that

many have characterized as “hyper” or “severe”) in this population is also very high and concerning.

For these reasons, as discussed in detailed in Chapters 4 and 5, the development of deprescribing and medication optimization interventions targeting potentially inappropriate prescribing should be one of the priority areas for HCU research and interventions. Given the extent of polypharmacy observed in this population, regular periodic medication reviews with a focus on deprescribing and cost-effective medication use should also be considered as a standard of practice. These initiatives, if designed well and successful, could potentially help health systems “bend” the cost curve for this vulnerable group by decreasing upfront medication costs and downstream costs of adverse events and related healthcare utilization. Although there are some academic and non-governmental organizations, including the Choosing Wisely campaign, the Canadian Deprescribing Network, and the Bruyère Research Institute Deprescribing Guidelines initiative, that provide educational resources for the individual prescriber or patient to combat this problem, system level policy interventions that could influence change for millions of individuals at a time warrant further exploration as a means promoting health system sustainability (e.g. financial incentives, behavioural economics, or institutional best practice prescribing indicators/targets).[35,36]

Similarly, the development and implementation of drug policies (e.g. indication-based, reference-based, or biosimilar substitution) could also help ensure that health systems maximum value with expensive high-cost drugs and ensure that their use is evidence-based, necessary and unavoidable on both a case-by-case basis and population

level simultaneously. This will require more research and health economic evaluations to understand which high-cost drugs (and in which contexts) have minimal or unproven benefit over less-expensive alternatives. As demonstrated in this thesis, there is an important subgroup of patients that are becoming new HCUs (and potentially persistent HCUs) every year based on the costs of one medication alone. These findings may be useful to healthcare decision-makers in breaking down financial "silos" and aligning priorities of those managing institutional or public drug programs with those focused on community and population health initiatives.[37]

Directions for Future Research

In this thesis, we bridged some HCU knowledge gaps by focusing on older adult HCUs during their transition period from non-HCU to HCU and examining the quality of prescribing and medication use in more detail than previous studies. The following describe areas that warrant further investigation as well as the next stages of our research program.

Confirmatory Studies

First, future research should confirm the importance of prescriptions medications to HCU expenditures and status in other jurisdictions (both in Canada and internationally). This thesis leveraged linked health administrative data from the province of Ontario and it

is possible that results could be different in other Canadian provinces or jurisdictions that do not have publicly funded universal healthcare or prescription drug coverage.

Second, the association between the use of potentially inappropriate high-risk medications and high-cost drugs would benefit from confirmation using alternate study designs. In this thesis, we employed a 2-year observational window of prescription drug claims and we used traditional regression methods to examine a broad range of medication classes of interest. Future studies could consider dedicated evaluations of specific medication classes in order to facilitate the use of propensity score methods (e.g. matching based on propensity for new prescription initiation of the medication of interest), longitudinal evaluations over a much longer observational window (e.g. 10 years), and exploration of the impact of medication adherence. These would help evaluate the robustness of our results, understand the degree of potential residual confounding, and provide more information on the nature of the associations between medication use and HCU status (e.g. short-term vs. long-term risk).

Further Characterization of Older Adult HCUs

This thesis use a population segmentation approach and focused on newly incident HCUs to understand factors that may contributing to the non-HCU to HCU transition. However, this population could benefit from further segmentation to better understand the context and individualized needs of older adult HCU subgroups.

Future research characterizing persistent HCUs and contrasting them to transient HCUs, for example, might advance our understanding of the health experience of HCUs and help refine priority areas for targeted intervention (e.g. identification of potentially avoidable versus unavoidable high-cost healthcare use, factors contributing to short-term versus long-term high-cost healthcare use, and high-cost healthcare services that are appropriate, cost-effective or value-based.

Further population segmentation and in-depth evaluation based on baseline characteristics rather than differences in trajectories of high-cost healthcare use may also further our understanding of the older adult HCU health needs and/or the impact of medication use on HCU status. For example, our incident older adult HCU cohort showed a slightly higher proportion of females. Future studies should explore whether there are sex and gender differences in HCU needs and their use of specific high-cost healthcare services including medication use. Previous studies in the general population have shown that there are physiologic differences based on sex that may make women more sensitive to medications and at higher risk of adverse drug events. There is also data to suggest that, compared to men, women are more likely to be prescribed more medications (i.e. higher prevalence of polypharmacy), more likely to be prescribed potentially inappropriate medications, and tend to have higher healthcare utilization rates.[38] As a result, disaggregated sex and gender data might identify some novel insights and provide more specific information to inform possible interventions.

Similarly, an exploration whether frailty influences the risk of becoming a HCU and/or modifies the net clinical benefit (or harm) of medications used by older adults may

also help inform HCU interventions. Given its prevalence in the older adult population and its association with healthcare utilization, frailty assessment may represent a potential means to identify older adults at increased risk of requiring high-cost healthcare and/or prioritize those that might benefit from a modified approach to prescribing to prevent adverse drug events.[39,40]

There are also likely important differences in health status and use of healthcare resources between those living within different age brackets (e.g. youngest-old vs. oldest-old), those living in the community versus those living in institutionalized or other congregate care settings (e.g. long-term care), those living with cognitive impairment or mental illness, and those in the last year of their life. Modified approaches to population segmentation could reveal distinct insights about each of these special populations.

Medication Optimization Interventions for Older Adult HCUs

The results of this thesis have informed the next phase of our research program. As previously mentioned, we found that interventions for older adult HCUs have largely focused on case management and care coordination activities (with low to moderate quality studies so far showing modest, if any, benefit). However, we did not identify any that have focused on medication optimization. This is an important gap in knowledge, especially since we also demonstrated that potentially inappropriate prescribing may be an important contributor to high-cost healthcare and the odds of becoming a HCU. We have therefore developed a proposed medication optimization intervention for older adults on potentially

inappropriate medications who are at risk of becoming HCUs to be rigorously tested in a randomized controlled trial. We are starting with a pilot RCT that assesses feasibility to provide preliminary info regarding its potential clinical impact, and to improve the design and success of future large scale definitive trial. The underlying hypothesis is that, since many ADEs and their associated hospitalizations are preventable, deprescribing and medication optimization may be an underutilized intervention with potential to save significant resources, while maintaining (or improving) the quality of healthcare delivery.

Strengths and Limitations

The studies presented in this thesis have several strengths. First, as mentioned in Chapter 1, the focus on incident (i.e. new) HCUs rather than prevalent HCUs allowed for examination of the factors influencing the period of transition from non-HCU to HCU. This facilitated the identification of contributing factors that may be amenable to potential "upstream" preventative interventions prevent or delay HCU transition. In this thesis, this led to many hypotheses regarding optimization of the quality and cost-effectiveness of prescribing and medication use.

Second, the use of linked provincial health administrative data facilitated the creation of large population-based cohorts with near complete inclusion of all older adult HCUs in Ontario. Without the need for informed consent, these studies were not prone to selection bias due to recruitment sampling or participation response. The longitudinal matched cohort design also created relevant non-HCU comparators that improves on the

predominantly cross-sectional studies of HCUs (without comparators) that have been conducted to date.[10,18] These features allowed us to evaluate differences between HCUs and non-HCUs and explore associations between medications and HCU status in a way that was very statistically efficient and that transcended differences in local prescribing and medical practice patterns. To our knowledge, this is one of the first population-based matched cohort analyses of HCUs and their medication use.

Third, our analyses used medication records from the provincial Ontario Drug Benefit (ODB) program. Since the ODB program covers the majority of prescription costs for older adults in Ontario, the data are generally more accurate than self-recorded information on drug use (with error rates reported to be less than 1%) and reduces some of the confounding due to variable access to medications.[41]

There are also some limitations to the studies in this thesis that are important to understand in order to place their results into context. First, the studies described in Chapters 3, 4 and 5 used retrospective observational study designs that leveraged the use of linked health administrative databases. Despite our attempts to minimize confounding (especially confounding by indication), residual confounding is inherent in observational data and we only provide evidence of association (not causality) between potentially inappropriate medications and HCU status. We cannot be certain that medications cause HCU status outside of the situation when cumulative direct costs exceed the HCU financial threshold. It is possible that other unknown, unmeasured or unmeasurable factors may have influenced healthcare utilization and prescribing. However, the strength of associations observed as well as the consistency of our results with previous studies suggesting

associations between potentially inappropriate prescribing and healthcare utilization are supportive and reassuring that our findings of association are not spurious.[34,42,43]

Second, our data regarding medication use is based on prescription drug reimbursement claims data and our ability to account for the duration of medication exposure is limited to two years of available prescription data. This limits the conclusions we can be infer regarding the timing of medication initiation and duration of exposure relative to HCU transition. It also means that it is not possible to guarantee patients were adherent to dispensed medications nor that they used them as prescribed. Future confirmatory studies, as described earlier in this chapter, could re-evaluate our results using an alternative study design that has a longer observation window and restricts observations to new users of specific medication classes.

Third, HCUs and non-HCUs were identified based on healthcare utilization costs accrued during a fiscal year for pragmatic reasons related to the use of the ICES costing algorithms. If an alternative method (e.g. costing based on calendar year or period fixed to adjacent index event) was used, the HCU status of some individuals within the study cohorts may have been classified differently depending on when they accrued costs or died.

Conclusion

Older adult HCUs are a small, but complex and heterogenous group of individuals that use disproportionate healthcare resources compared to their peers. Although their management is a priority area for health systems trying to achieve the "Triple Aim," better

systematic characterization of HCU subgroups and more rigorous approach to intervention development and evaluation are needed. Although acute and prolonged hospitalization costs are the predominant drivers of their healthcare expenditures, medications are a significant and underappreciated contributor to HCU costs and development. They can contribute to high-cost healthcare directly through drug costs, but also indirectly through the adverse health consequences of severe polypharmacy and potentially inappropriate prescribing, which may be even more costly. In order to manage high-cost healthcare and prevent high-cost user development in older adults, medication optimization interventions and policies to reduce inappropriate medication use and ensure cost-effective use of expensive medications are needed at the health system and individual level.

REFERENCES

1. Anderson M, Revie CW, Stryhn H, et al. Defining “actionable” high- cost health care use: Results using the Canadian Institute for Health Information population grouping methodology. *Int J Equity Health*. 2019;18(1). doi:10.1186/s12939-019-1074-3

2. Ke Xu, Agnès Soucat, Joseph Kutzin, Andrew Siroka, Maria Aranguren Garcia, Julien Dupuy, Natalja Eigo, Dongxue Li, Chandika Indikadahena, Hapsatou Touré HB and GF. Global spending on health: a world in transition. World Health Organisation. https://www.who.int/health_financing/documents/health-expenditure-report-2019.pdf?ua=1. Published 2019. Accessed March 16, 2021.

3. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. *Health Aff (Millwood)*. 2008;27(3):759-769. doi:10.1377/hlthaff.27.3.759

4. Lee J, Muratov S, Tarride J-E, Holbrook A. Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies. *J Am Geriatr Soc*. 2018;66(5):1002-1008.

5. Myers GW, Roemer MI. Multiple admissions to hospital. *Can J Public Heal*. 1956;47(11):469-481.

6. Blumenthal D, Chernof B, Fulmer T, Lumpkin J, Selberg J. Caring for High-Need, High-Cost Patients - An Urgent Priority. *N Engl J Med*. 2016;375(10):909-911.

7. Bodenheimer T, Fernandez A. High and rising health care costs. Part 4: Can costs

be controlled while preserving quality? *Ann Intern Med*. 2005;143(1):26-31. doi:10.7326/0003-4819-143-1-200507050-00007

8. Colla CH, Lewis VA, Kao LS, O'Malley AJ, Chang CH, Fisher ES. Association between medicare accountable care organization implementation and spending among clinically vulnerable beneficiaries. *JAMA Intern Med*. 2016;176(8):1167-1175. doi:10.1001/jamainternmed.2016.2827

9. Wennberg JE, Bronner K, Skinner JS, Fisher ES, Goodman DC. Inpatient care intensity and patients' ratings of their hospital experiences. *Health Aff*. 2009;28(1):103-112. doi:10.1377/hlthaff.28.1.103

10. Wammes JJG, Van Der Wees PJ, Tanke MAC, Westert GP, Jeurissen PPT. Systematic review of high-cost patients' characteristics and healthcare utilisation. *BMJ Open*. 2018;8(9):23113. doi:10.1136/bmjopen-2018-023113

11. Blumenthal D, Anderson G, Burke S, Fulmer T, Jha AK, Long P. Tailoring Complex-Care Management, Coordination, and Integration for High-Need, High-Cost Patients: A Vital Direction for Health and Health Care. *NAM Perspect*. 2016;6(9). doi:10.31478/201609q

12. Finkelstein A, Zhou A, Taubman S, Doyle J. Health Care Hotspotting — A Randomized, Controlled Trial. *N Engl J Med*. 2020;382(2):152-162. doi:10.1056/nejmsa1906848

13. Wodchis WP. The Concentration of Health Care Spending: Little Ado (yet) About

Much (money). 2012 Canadian Association for Health Services and Policy Research Conference. https://www.cahspr.ca/web/uploads/presentations/C6.1_Walter_P._Wodchis.pdf. Published 2012. Accessed October 1, 2015.

14. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ*. 2016;188(3):182–188. doi:10.1503/cmaj.150064

15. Rais S, Nazerian A, Ardal S, et al. High-cost users of Ontario's healthcare services. *Healthc policy*. 2013;9(1):44-51.

16. Guilcher SJT, Bronskill SE, Guan J, Wodchis WP. Who are the high-cost users? A method for person-centred attribution of health care spending. *PLoS One*. 2016;11(3). doi:10.1371/journal.pone.0149179

17. Rosella LC, Fitzpatrick T, Wodchis WP, Calzavara A, Manson H, Goel V. High-cost health care users in Ontario, Canada: demographic, socio-economic, and health status characteristics. *BMC Health Serv Res*. 2014;14:532. doi:10.1186/s12913-014-0532-2

18. Fitzpatrick T, Rosella LC, Calzavara A, et al. Looking beyond Income and Education: Socioeconomic Status Gradients among Future High-Cost Users of Health Care. *Am J Prev Med*. 2015;49(2):161-171. doi:10.1016/j.amepre.2015.02.018

19. Hensel JM, Taylor VH, Fung K, Vigod SN. Rates of mental illness and addiction

among high-cost users of medical services in Ontario. *Can J Psychiatry*. 2016;61(6):358-366. doi:10.1177/0706743716644764

20. De Oliveira C, Cheng J, Vigod S, Rehm J, Kurdyak P. Patients With high mental health costs incur over 30 percent more costs than other high-cost patients. *Health Aff*. 2016;35(1):36-43. doi:10.1377/hlthaff.2015.0278

21. Qureshi D, Isenberg S, Tanuseputro P, et al. Describing the characteristics and healthcare use of high-cost acute care users at the end of life: a pan-Canadian population-based study. *BMC Health Serv Res*. 2020;20(1). doi:10.1186/s12913-020-05837-8

22. Roos NP, Shapiro E, Tate R. Does a Small Minority of Elderly Account for a Majority of Health Care Expenditures?: A Sixteen-Year Perspective. *Milbank Q*. 1989;67(3/4):347. doi:10.2307/3350220

23. Breslow N, Day N. The Analysis of Case-Control Studies. In: *Statistical Methods in Cancer Research*. Vol 1. Lyon, France: International Agency for Research on Cancer; 1980:169.

24. Pearce N. Analysis of matched case-control studies. *BMJ*. 2016;352. doi:10.1136/bmj.i969

25. Brookmeyer R, Liang KY, Linet M. Matched case-control designs and overmatched analyses. *Am J Epidemiol*. 1986;124(4):693-701. doi:10.1093/oxfordjournals.aje.a114443

26. Shah BR, Laupacis A, Hux JE, Austin PC. Propensity score methods gave similar results to traditional regression modeling in observational studies: A systematic review. *J Clin Epidemiol*. 2005;58(6):550-559. doi:10.1016/j.jclinepi.2004.10.016

27. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003;158(3):280-287. doi:10.1093/aje/kwg115

28. Calver J, Brameld KJ, Preen DB, et al. High-cost users of hospital beds in Western Australia: A population-based record linkage study. *Med J Aust*. 2006;184(8):393-397.

29. Ng SHX, Rahman N, Ang IYH, et al. Characterization of high healthcare utilizer groups using administrative data from an electronic medical record database. *BMC Health Serv Res*. 2019;19(1). doi:10.1186/s12913-019-4239-2

30. Vaillancourt S, Shahin I, Aggarwal P, et al. Using archetypes to design services for high users of healthcare. *Healthc Pap*. 2014;14(2):37-41.

31. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD

32. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348(26):2635-2645. doi:10.1056/NEJMsa022615

33. Levine DM, Linder JA, Landon BE. The quality of outpatient care delivered to adults in the United States, 2002 to 2013. *JAMA Intern Med*. 2016;176(12):1778-1790. doi:10.1001/jamainternmed.2016.6217

34. Clark CM, Shaver AL, Aurelio LA, et al. Potentially Inappropriate Medications Are Associated with Increased Healthcare Utilization and Costs. *J Am Geriatr Soc*. 2020;68(11):2542-2550. doi:10.1111/jgs.16743

35. Rashidian A, Omidvari AH, Vali Y, Sturm H, Oxman AD. Pharmaceutical policies: Effects of financial incentives for prescribers. *Cochrane Database Syst Rev*. 2015;2015(8). doi:10.1002/14651858.CD006731.pub2

36. Suleman F, Movik E. Pharmaceutical policies: effects of educational or regulatory policies targeting prescribers. *Cochrane Database Syst Rev*. 2019;2019(11). doi:10.1002/14651858.CD013478

37. Sutherland JM. Integrated Funding: Connecting the Silos for the Healthcare We Need. C.D. Howe Institute Commentary. https://www.cdhowe.org/sites/default/files/attachments/research_papers/mixed/Commentary_463.pdf. Published 2017. Accessed March 28, 2021.

38. Rochon PA, Petrovic M, Cherubini A, et al. Polypharmacy, inappropriate prescribing, and deprescribing in older people: through a sex and gender lens. *Lancet Heal Longev*. 2021;2(5):e290-e300. doi:10.1016/S2666-7568(21)00054-4

39. Roe L, Normand C, Wren MA, Browne J, O'Halloran AM. The impact of frailty

on healthcare utilisation in Ireland: Evidence from the Irish longitudinal study on ageing. *BMC Geriatr*. 2017;17(1). doi:10.1186/s12877-017-0579-0

40. Ensrud KE, Kats AM, Schousboe JT, et al. Frailty Phenotype and Healthcare Costs and Utilization in Older Women. *J Am Geriatr Soc*. 2018;66(7):1276-1283. doi:10.1111/jgs.15381

41. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.

42. Bradley MC, Fahey T, Cahir C, et al. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. *Eur J Clin Pharmacol*. 2012;68(10):1425-1433. doi:10.1007/s00228-012-1249-y

43. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: A national population study. *Br J Clin Pharmacol*. 2010;69(5):543-552. doi:10.1111/j.1365-2125.2010.03628.x