Models and Methods in Health Economics and the Decision-Making Process

Monday, October 17, 2016

MaRS Discovery District, Toronto

CAPT ACTP

Meet the Panel

Moderator:

- Murray Krahn (University of Toronto)

Speakers:

- Jaime Caro (McGill University)
- Claire deOliveira (CAMH)
- Kristian Fillion (McGill University)

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Session Overview

Agencies such as CADTH and INESSS have the mandate to assess health technologies in order to make them available for Canadians. Economic evaluations are a valuable tool that is used, yet many of them are carried out in situations of competing needs, uncertainty and limited knowledge. New approaches are intended to decrease the uncertainty of these evaluations and to optimize the access of new technologies, but their utilization by decision-makers might be suboptimal.

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Opportunities to improve the access to new technologies, Development of new methods in health economics and their adoption in the decision-making process: DICE Simulation

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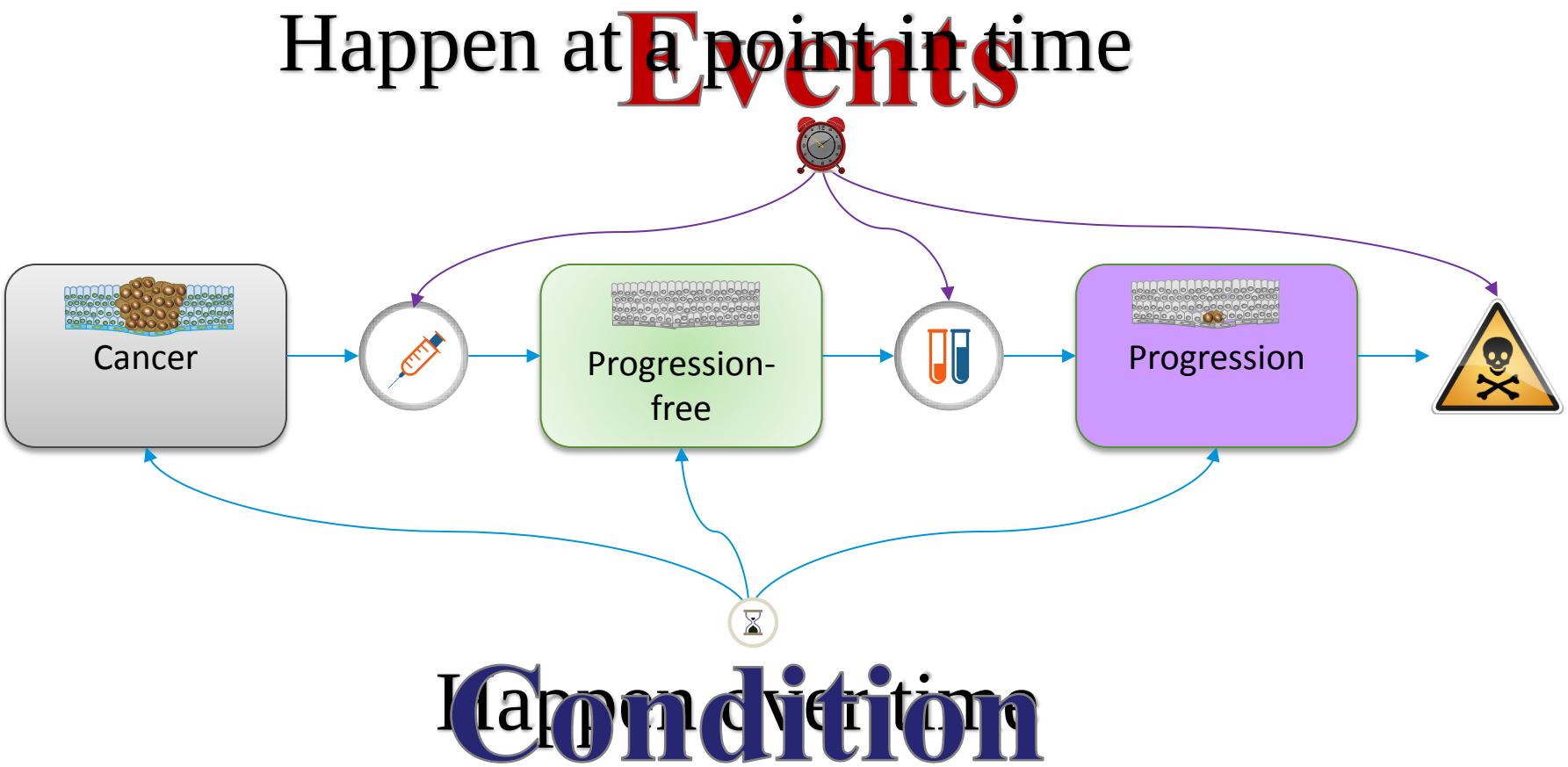
(Discretely-Integrated Condition Event)

Evidera

McGill

Cancer example



What is DICE?

A modeling technique that conceptualizes the decision-analytic problem in terms of two fundamental aspects:

Conditions

- Aspects that persist over time
- Have levels, which can change & affect events
- Many conditions can be present at once
- Interested in time spent at a given level (value)

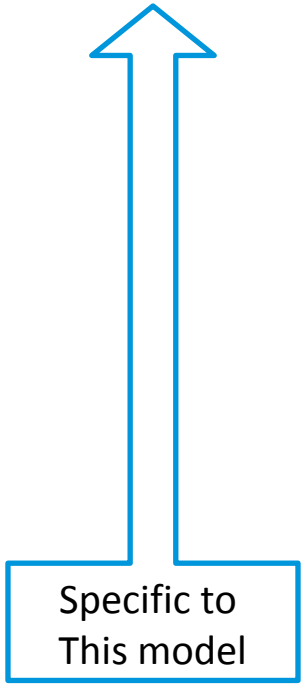
discrete integration

Events

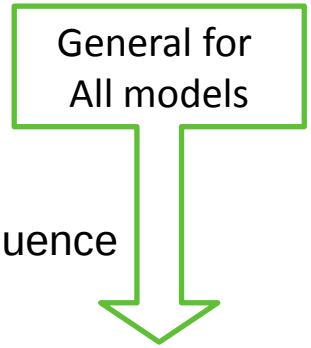
- Aspects that happen at a point in time
- Can affect the level of a condition or other events
- Many can happen, at any time
- Interested in number that happen (and when)

The essentials of DICE

- **List of conditions**
  - Name (unique)
  - Level (at a given point in time)
- **List of events**
  - Name (unique)
  - Time of occurrence
- **Consequences of each event**
  - For itself (recurrence?)
  - For other events
  - For conditions



- **Discrete-integrator**
  - Read conditions list
  - Read event list
  - Process event consequences in sequence
  - End simulation & report results.



DICE Structure

- **List of conditions**
  - Name (unique)
  - Level (at a given point in time)
- **List of events**
  - Name (unique)
  - Time of occurrence
- **Consequences of each event**
  - For itself (recurrence?)
  - For other events
  - For conditions

- **Discrete-integrator**
  - Read conditions list
  - Read event list
  - Process event consequences in sequence
  - End simulation & report results.

1. List of conditions

Vital status

Treatment

Conditions

	Level
Vital status	Alive
Treatment	SoC

2. List of events

Death

Sta

Events

Name	Time To Event
Start	Never
Death	$Formula_{SoC}$

3. Consequences of each event

Start

- don't happen again
- select treatment = SoC
- estimate time of death
- set vital status = alive

Death

- Accrue QALYs
- Add up costs

DICE Implementation - software

- **List of conditions**
  - Name (unique)
  - Level (at a given point in time)
- **List of events**
  - Name (unique)
  - Time of occurrence
- **Consequences of each event**
  - For itself (recurrence?)
  - For other events
  - For conditions

Specific to This model

- **Discrete-integrator**
  - Read conditions list
  - Read event list
  - Process event consequences in sequence
  - End simulation & report results.

General for All models

Software

FORTRAN

C++

Excel

python™

R

Microsoft VB .net

DICE Excel® Implementation

1. **List of conditions**
   - Vital status
   - Treatment
2. **List of events**
   - Death
   - Start

Conditions

Name	Level
Vital Status	Alive
Treatment	SoC
QALYs	
Cost	

Events

Name	Time To Event
Start	Never
Death	$Formula_{SoC}$

DICE Excel® Implementation

1. **List of conditions**
   - Vital status
   - Treatment
2. **List of events**
   - Death
   - Start
3. **Consequences of each event**
   - Start
     - don't happen again
     - select treatment = SoC
     - estimate time of death
     - set vital status = alive
   - Death
     - Accrue QALYs
     - Add up costs

Conditions

Name	Level
Vital Status	Alive
Treatment	SoC
QALYs	
Cost	

Events

Name	Time To Event
Start	Now
Death	Never

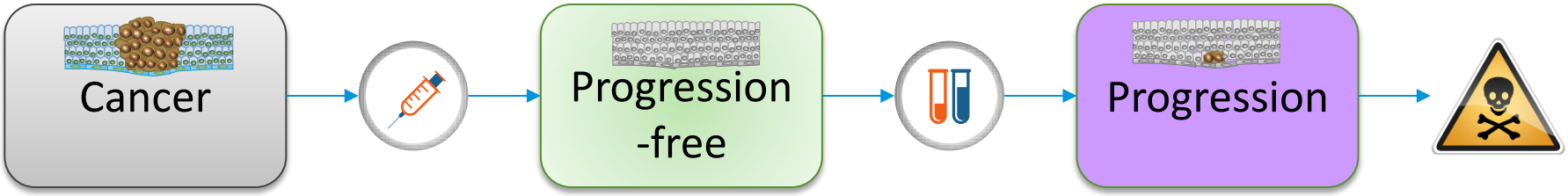
Type	Name	Expression
Event	Start	Never
Condition	Treatment	SoC
Event	Death	Ln(1-rand())/-hazard
Condition	Vital status	Alive

Getting the expressions to do something

Type	Name		Expression
Event	Start	=	Never
Condition	Treatment	=	SoC
Event	Death	=	Ln(1-rand())/-hazard
Condition	Vital status	=	Alive
Output	QALYs	=	0
Output	Costs	=	0

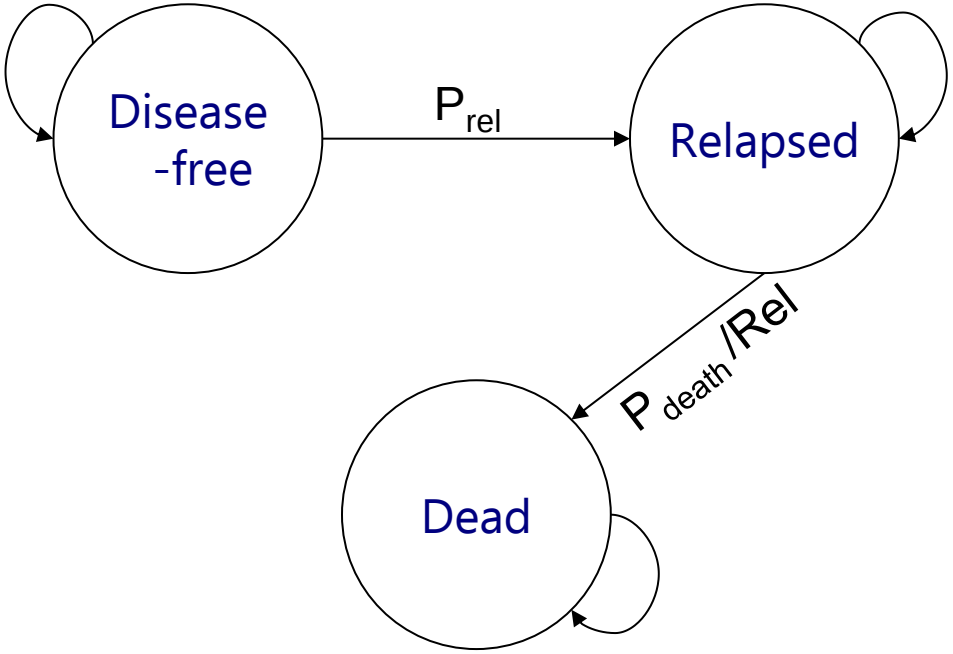

```
Do
    ThisEventName = UCase(EventTypes(Range("NextEvent"), 3))
    ThisEvent = Range(EventTypes(Range("NextEvent"), 3) & "Rge")
    For i = 1 To UBound(ThisEvent, 1)
        If ThisEvent(i, 3) <> "" Then
            Range("CalcCell") = "=" & ThisEvent(i, 3)
            Range(ThisEvent(i, 2)) = Range("CalcCell").Value
        End If
    Next i
    Range("CalcCell") = ""      'Housekeeping
Loop Until ThisEventName = "END"
```

Simple example



- **Fatal cancer if untreated**
  - Both risk of progression and of death depend on age, sex and the level of a biomarker
  - SoC achieves remission but eventually progresses
    - Main side-effect: neutropenia
  - New treatment, *MetaMin*, increases PFS and OS
    - Main side-effect: anaphylaxis
  - At progression, SoC switches to second line, *MetaMin* continues
- **Interest is in LYG, QALYs, Costs, ICER.**

Cohort Markov approach



Time (m)	Disease-free	Relapsed	Dead
0	1,000	0	
1	1000-P	1000 x P_{rel}	0xP_{death}/Rel
2			
…	…	…	…
300	…	…	…

DICE Cohort Markov version

Conditions Table

Name	Value
Disease-free	
Relapsed	
Death	%D

Transition event Table

Type	Assigned Item	Expression
Condition	Death	Death+ P_{death}*Relapsed
Condition	Relapsed	Relapsed*(1-P_{death}) +Disease-free*(P_{rel})
Condition	Disease-free	Disease-free*(1-P_{rel})
Event	Transition	Now + cycle
Event	End	If ((Time>=TimeHorizon), Now, Never)

Constants Table

Name	Value
TimeHorizon	10
Never	99,999
Now	0
P_{rel}	.015
P_{death}	.001
Cycle	1

- **Compact specification**
  - Doesn't change if longer time horizon
  - Or shorter cycles
    - Can make these variable!
- **Expressions written only once reducing error**
- **No programming!**
- **Transparent, easy to grasp**

DICE Microsimulation version

Conditions Table

Name	Initial Value
Disease	Disease-free

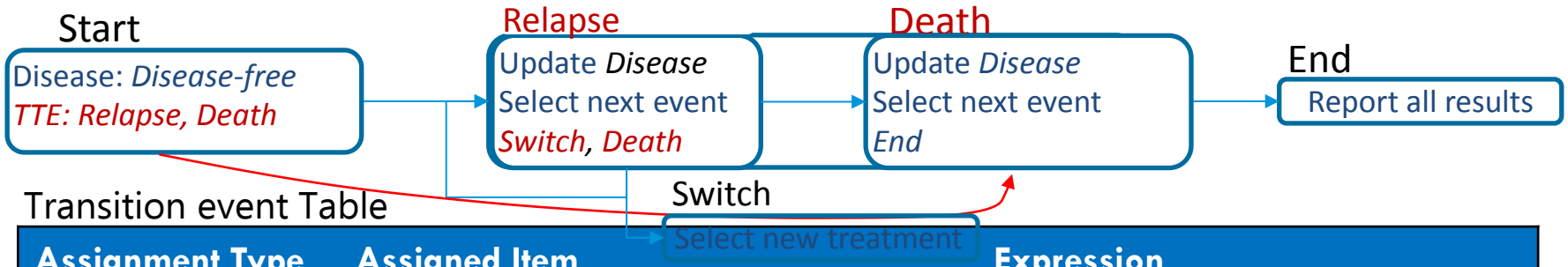
Profiles Table

Age	Sex	BioM
45	Male	124
45	Female	216
…	…	

Transition event Table

Assignment Type	Assigned Item	Expression
Condition	Disease	If (Disease="Disease-free",if(rand()<P_{rel},"Relapsed", "Disease-free"),If(rand()<P_{death},"Dead", "Relapsed")
Event	Transition	Now + cycle
Event	End	If ((Time>=TimeHorizon), Now, Never)

DICE Time-to-Event Model



Transition event Table

Assignment Type	Assigned Item	Expression
Start event Table		

Assignment Type	Assigned Item	Expression
Event	Relapse	$-\ln(1-\text{rand}())/\text{hazard}_{rel}$
Event	Death	$-\ln(1-\text{rand}())/\text{hazard}_{otherDeath}$

Relapse event Table

Assignment Type	Assigned Item	Expression
Condition	Disease	Relapsed
Event	Death	$\text{Min}(-\ln(1-\text{rand}())/\text{hazard}_{death/rel}, \text{Death})$
Event	Treatment switch	Now

Treatment switch event Table

DICE outputs

Conditions Table

Name	Initial Value
Disease	Disease-free

Relapse event Table

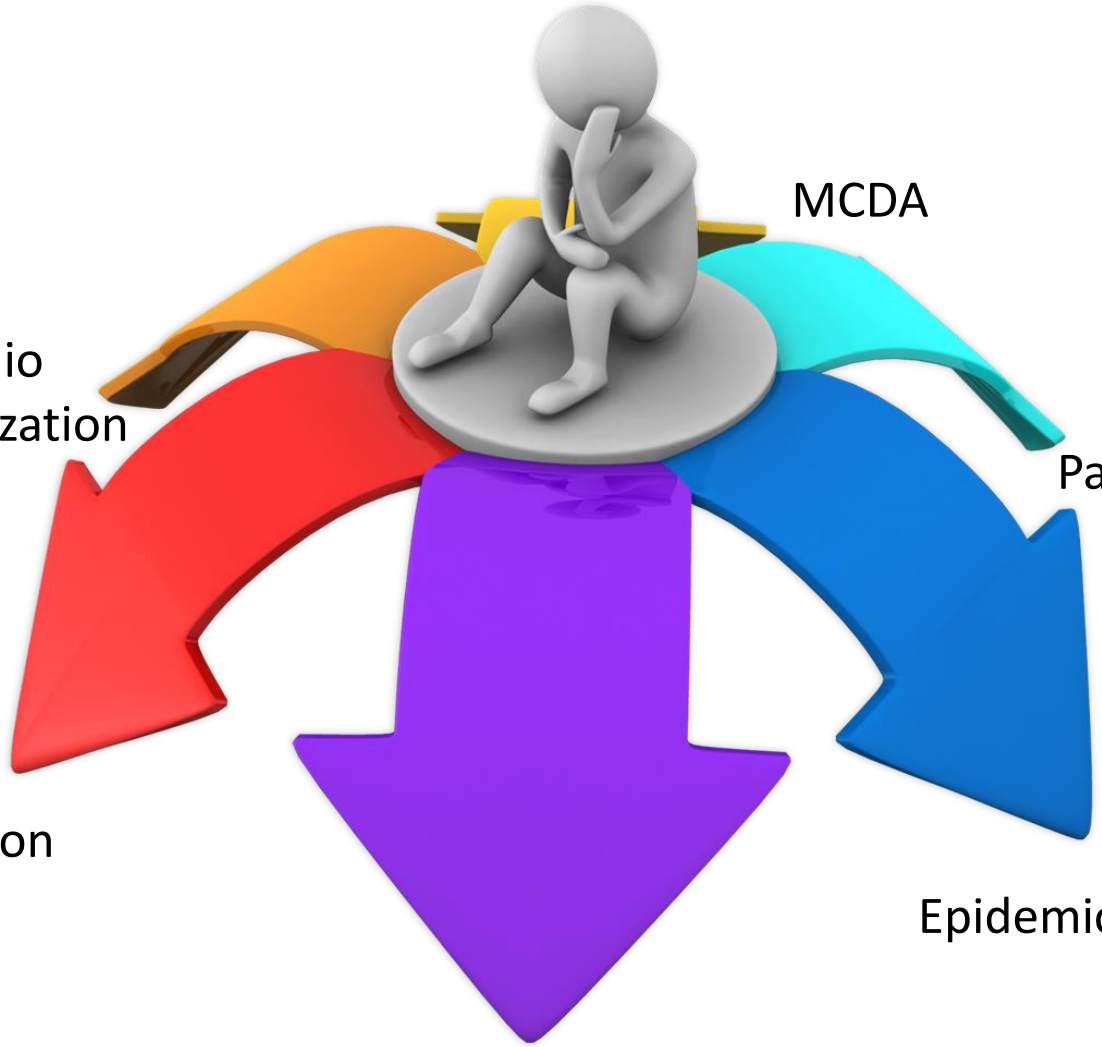
Assignment Type	Assigned Item	Expression
Condition	Disease	Relapse
Event	Death	-ln(1-rand())/$hazard_{death/relapse}$
Event	Treatment switch	If (Treatment="SoC", Now, Never)

Advantages & limitations

- Very flexible & natural
- Can combine cohort, individual & time-to-event approaches
- Transparent, simple to communicate
- Standard framework (easy to learn)
- Less error-prone
- Enables structural sensitivity analysis
- Straightforward to review
- Fast to create, easy to modify

- Excel is slow
- No individuals, interactions
- No resources, queues
- (lacking experience, validation, publications)

What can DICE be used for?



DICE transforms the way we develop models

Old way

Pick a technique (e.g., Markov)

↓

Adapt decision problem To selected technique

↓

Spend wks/m programming

↓

Final Model

- Complex
- Huge
- Tricky to verify
- Hard to explain
- Forget changing structure!

New way

Focus on decision problem

↓

Design model to suit decision problem

↓

Implement DICE in days

↓

Final Model

- Straightforward
- Compact
- Easy to verify
- Simple to explain
- Change structure any time

camh Centre for Addiction and Mental Health

Models and Methods in Health Economics and the Decision-Making Process

Claire de Oliveira, M.A. PhD

Introduction

- there are scarce health care dollars
- policy makers who fund and organize health care struggle to provide patients with latest therapies, given limited financial resources
- accurate cost estimates are required to estimate burden of care
- also, important input for health technology assessment (e.g. economic evaluations)
- thus, **need** to measure costs appropriately

objective of talk

- discuss new costing methods using administrative health care databases and provide examples

Road map of talk

- cost estimation using administrative data
  - required data elements
- cumulative cost functions
- methods to estimate cumulative costs
  - inverse probability weighting (IPW)
  - phases of care approach
    - net cost method
- modelling costs through regression analysis

Cost estimation using administrative data

- provinces can link population-based registries, clinical, and administrative data to measure costs
- existing costing methods follow CADTH guidelines

- measuring costs generally requires **2** types of data elements:
  - utilization (how many resources are used)
  - unit cost (how much each resource costs)
- data elements not always available in databases

- once we have cost data, we can estimate cumulative cost functions

Cost estimation using administrative data

- both utilization and unit costs in data:
  - physician services (billings data)
  - outpatient prescription drugs (claims data)
- utilization + estimates of unit costs:
  - inpatient hospitalizations → CIHI DAD
  - ED visits → CIHI NACRS
- only utilization (+ unit costs from other sources):
  - home care (in many provinces)
  - other care

Cumulative cost functions

- variable of interest in health care costing studies is typically mean health cost (i.e. incidence-based costs)
  - cumulative cost from index event over some interval
- rate of cost accumulation tends to increase around index events, such as hospitalizations and death
- theoretically could follow all participants until death, but death rarely observed for every patient due to short study horizons
- portion of health care cost that is unobserved may be especially important → costs tend to rise dramatically in pre-death period

Cumulative cost functions

- typically focus on mean total costs for restricted time period → 2 major issues

- 1) among patients who die, death drives up costs in period before death, BUT costs may also be driven down because no costs are accrued after death
- to deal with this, consider death as a terminal event
- subjects will accrue costs until they die, or until they reach time horizon of analysis → complete case
- in each case, patients no longer accumulate relevant costs

Cumulative cost functions

- 2) however, some patients are not complete cases

a) portion of relevant health costs for these participants will be unobserved → data are right censored before outcome of interest has occurred (i.e. observation that ends prematurely)

b) study may enroll patients over a period of time but discontinue follow-up on a fixed calendar date

- in both cases, censoring is random, and observed health care costs represent the lower limit of relevant costs
- to adjust cumulative cost estimates for censoring → develop function that describes way in which data are censored, use reweighting

Inverse Probability Weighting (IPW)

- IPW reweights each complete case so that it represents not only itself but also some number of incomplete or censored cases
- cumulative cost of each patient who died or reached full period of observation must represent cost of that patient and of censored cases that would have been observed had there been no censoring
- number of censored cases represented by complete case at observation time *t* is proportional to probability of that case being censored
- costs for complete cases with short follow-up should be weighted less than cases with longer observation period, accounting for higher probability of censoring with longer observation periods

Inverse Probability Weighting (IPW)

advantages

- deals with censoring
- can be expanded within regression framework to control for covariates

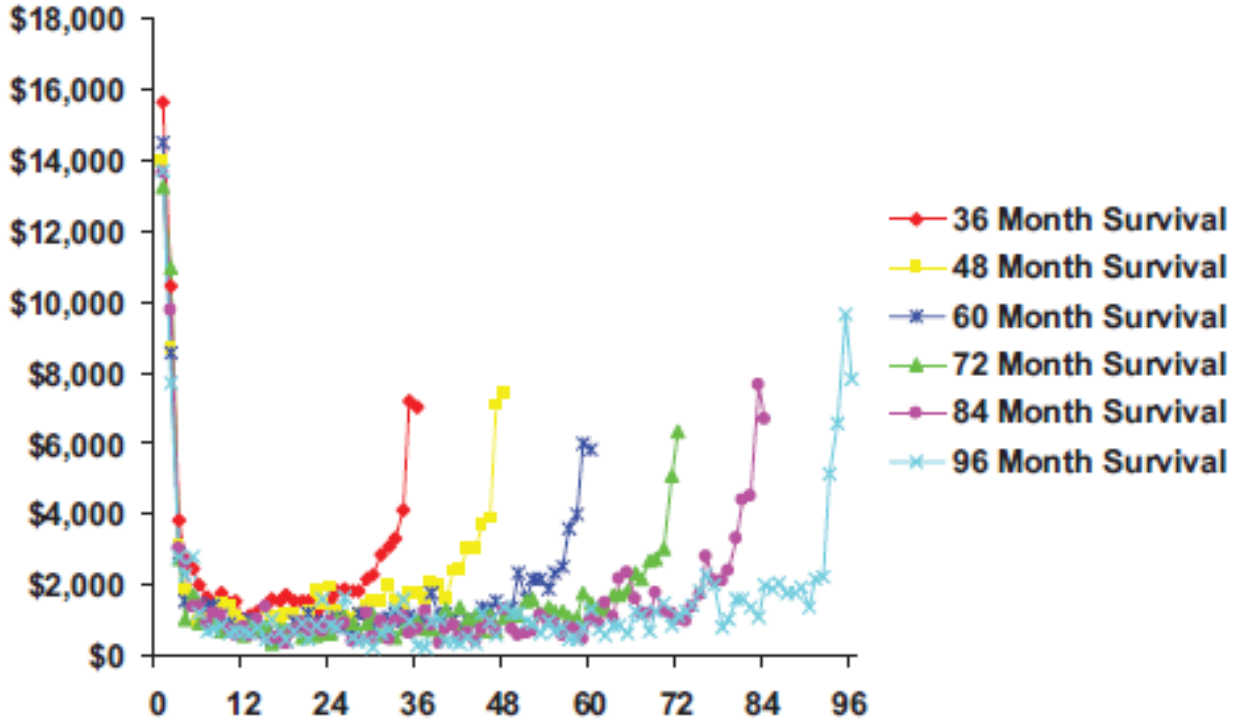
disadvantages

- when evaluating covariate effects, cannot distinguish effects on cost accumulation from effects on survival
- does not account for differential rates of heath care cost accumulation near death

Phases of care approach to estimate costs

- alternative method to estimate cumulative costs (variant of incidence cost approach)
- useful to estimate lifetime costs or costs in presence of heavy censoring
- defines time periods of interest following diagnosis where costs may differ across periods; typically 3 phases:
  - initial care phase;
  - continuing care phase;
  - terminal care phase
- used many times with **net cost method**, where net costs = cost difference between patients and controls
  - typically done with matching (hard and/or propensity score matching)

Phases of care - examples



SOURCE: Adapted from Brown et al. Medical Care 2002;40 (supp):III-63 – III-72.

FIGURE 1. Monthly costs of care for colorectal cancer patients by length of survival.

Phases of care - examples

Tumour Site	Phase, estimated cost (95 % CI)			
	Pre-diagnosis (3 months)	Initial (6 months)	Continuing (annual)	Terminal (12 months)
Males				
Head and neck	$595 ($326–$865)	$19,702 ($19,691–$19,714)	$5151 ($5143–$5159)	$37,346 ($37,332–$37,360)
Esophagus	$818 ($455–$1180)	$41,567 ($41,539–$41,596)	$5491 ($5474–$5509)	$54,354 ($54,336–$54,371)
Gastric	$848 ($481–$1215)	$32,240 ($32,203–$32,278)	$3329 ($3315–$3342)	$53,708 ($53,695–$53,722)
Colorectal	$275 (−$101-$651)	$25,138 ($25,131–$25,146)	$5446 ($5442–$5451)	$32,408 ($32,401–$32,415)
Liver	$3381 ($2906–$3855)	$21,355 ($21,325–$21,384)	$11,954 ($11,937–$11,971)	$30,265 ($30,242–$30,289)
Pancreas	$1892 ($1468–$2315)	$29,979 ($29,950–$30,008)	$6296 ($6272–$6319)	$54,152 ($54,138–$54,167)
Lung	$1833 ($1458–$2209)	$22,409 ($22,402–$22,417)	$5533 ($5526–$5539)	$39,241 ($39,236–$39,247)
Melanoma	$553 ($331–$774)	$4649 ($4635–$4664)	$4005 ($3998–$4012)	$18,494 ($18,479–$18,509)
Prostate	$637 ($375–$899)	$8394 ($8391–$8397)	$5017 ($5015–$5020)	$17,391 ($17,385–$17,397)
Bladder	$236 (−$189–$661)	$10,429 ($10,412–$10,447)	$3394 ($3386–$3403)	$35,749 ($35,737–$35,760)
Renal	$1503 ($1111–$1895)	$14,950 ($14,936–$14,964)	$3991 ($3981–$4002)	$38,292 ($38,274–$38,309)
Brain	$1548 ($1192–$1904)	$33,241 ($33,227–$33,225)	$6563 ($6546–$6581)	$72,463 ($72,444–$72,483)
Lymphoma	$1484 ($1125–$1843)	$17,831 ($17,820–$17,842)	$6276 ($6268–$6285)	$59,202 ($59,182–$59,222)
Myeloma	$3142 ($2675–$3609)	$24,447 ($24,418–$24,476)	$15,153 ($15,138–$15,169)	$43,989 ($43,969–$44,010)
Leukemia	$1325 ($1006–$1645)	$18,214 ($18,194–$18,233)	$8035 ($8024–$8045)	$74,857 ($74,837–$74,877)

Phases of care approach to estimate costs

advantages

- phase-specific costs can be combined with survival data to estimate average lifetime costs from diagnosis to death
- actual costs do not have to be observed over entire period between diagnosis and death (no need to deal with censoring)
- average phase-specific costs can be estimated from only a few years of cost data → can use only recent years of cost data, which reflect current patterns of care
- makes use of data more efficiently than a cohort approach

Phases of care approach to estimate costs

disadvantages

- makes assumptions about cost patterns, particularly during continuing care phase
- lifetime cost estimates difficult to compare among different groups due to difficulties in adjusting for differences in covariates
- need to be careful when discounting costs
- patients can contribute data to multiple phases → non-ignorable correlations between phase-specific cost estimates

- nonetheless, easily understood and straight forward estimation

Modelling costs through regression analysis

- once complete cost data available → can model costs; this can be challenging
- typically, individual-level cost data:
  - large proportion of zeroes (non-users)
  - strongly skewed distribution
  - long right-hand tail
- non-normality of data typically due to small proportion of individuals who account for large share of costs
- error term typically exhibits high degree of heteroskedasticity
- relationship between costs and regressors and/or the correct model specification generally not linear

Modelling costs through regression analysis

- generalised linear model (GLM) has become preferred strategy for modelling health care costs when there are unknown forms of heteroskedasticity

- **advantages**
  - predictions made on raw cost scale, thus no retransformation is required
  - allow for heteroskedasticity through choice of distributional family
- **disadvantage**
  - can suffer substantial loss in precision in face of heavy-tailed, log scale residuals or when variance function is misspecified

- nonetheless, GLM is generally recommended

Modelling costs through regression analysis

- which distribution to use?
- use **modified Park test** (Manning and Mullahy, 2001)
  - chooses family distribution based on most likely appropriate variance function
  - idea underlying: GLM distribution should reflect relationship between variance and mean
- researcher chooses link function
  - link function specifies shape of conditional mean function and characterises how mean is related to set of covariates

- usually family distribution is either Gamma or Poisson
- given skewness of cost data, typically chose log link

Modelling costs through regression analysis

- how to handle **zeroes**?
- no zero mass problem → GLM
- zero mass problem → two-part model
  - 1. pr(any expenditures) using full sample (estimate with logit or probit model)
  - 2. level of expenditures (conditional on y>0) using subsample with y>0 (estimate with appropriate continuous model → usually GLM)

Thank you.

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Confounding by Drug Formulary Restriction in Pharmacoepidemiologic Research

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Disclosures

- This study was funded by an operating grant from the Canadian Institutes of Health Research (CIHR).

- No relationships to disclose.

Introduction

- Pharmacoeconomic studies
  - Often rely on model inputs obtained from pharmacoepidemiologic research, especially when considering drug effectiveness and safety in a real-world setting.
  - Are affected by the limitations of the studies used to estimate model inputs.

- Although much attention has focused on traditional epidemiologic biases (i.e., selection bias, information bias, confounding), the impact of biases particular to pharmacoepidemiology should also be considered.

Formulary Restrictions

- The prescription of newly-marketed medications is often limited by formulary restrictions.

- Recent analyses have revealed that formulary restrictions can introduce important exposure misclassification in administrative databases due to incomplete data capture.

- However, the potential consequences of confounding due to drug formulary restrictions in pharmacoepidemiologic research remain incompletely understood.

Objective

To illustrate this potential bias using the example of fluticasone/salmeterol combination therapy (Advair©), an oral inhaler used for the treatment of asthma and chronic obstructive pulmonary disease (COPD), whose use is restricted in the province of Quebec, Canada.

Study Population

- Quebec's administrative databases
  - Hospitalizations, physician visits, and vital statistics for Quebec residents
  - Drugs dispensed for those who participate in the provincial drug plan (restricted to those with coverage)

- Retrospective cohort study of new users of respiratory medications
  - Any bronchodilator, inhaled corticosteroid, cromone, or anti-leukotriene (January 1, 1990 - December 31, 2005)

- Identified new users of fluticasone/salmeterol combination and excluded:
  - Aged < 18 years
  - < 1 year of continuous drug coverage
  - Dispensed fluticasone and salmeterol as 2 separate drugs on the same day in the year before cohort entry

Formulary Restrictions

- Fluticasone/salmeterol (inhaled corticosteroid/long-acting β2 adrenergic receptor agonist) combination therapy became restricted in October 2003
  - Over-use as 1st line therapy by general practitioners
  - Restricted to patients with 1) asthma or other reversible obstructive diseases who remained poorly controlled despite their use of an inhaled corticosteroid; or 2) patients with moderate or severe COPD with an exacerbation in the last year despite regular use of a long-acting bronchodilator

- Classified according to initial dispensation:
  - Liberal period: September 1999 to September 2003
  - Restricted period: January 2004 to October 2006
  - Excluded: October 2003 to December 2003

Endpoints and Follow-up

- Primary outcome:
  - First hospitalization for respiratory causes

- Secondary outcomes:
  - Hospitalization for any cause
  - All-cause mortality

- Censoring:
  - Death (hospitalization endpoints)
  - End of continuous drug coverage (7-day grace period)
  - Departure from the database
  - End of the 12-month follow-up
  - End of the study period (March 31st, 2007)

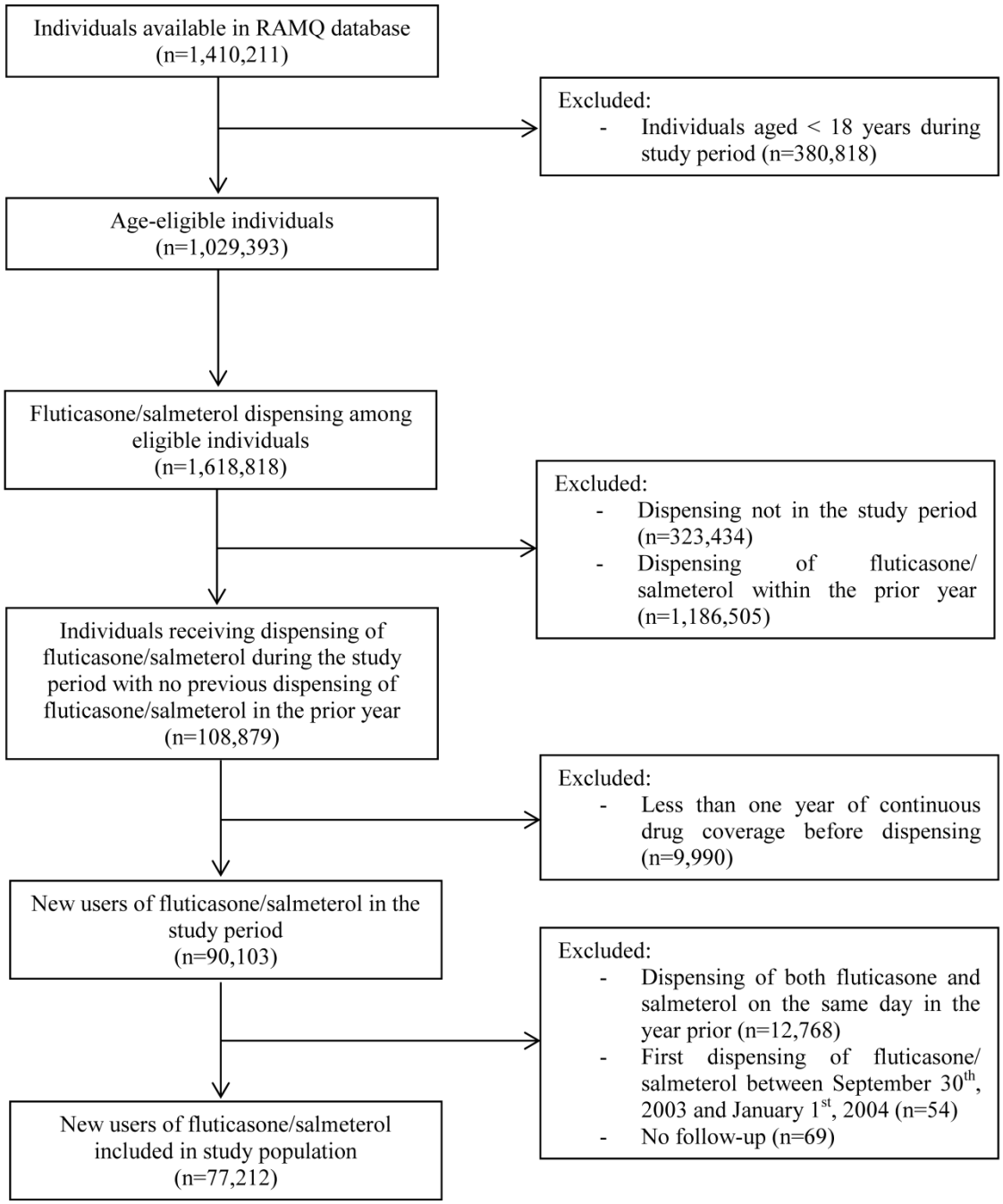
Statistical Analyses

- Prescription rate and rate of new use:
  - Interrupted time-series analyses with autocorrelation parameters included in segmented regression models
  - Predicted rate in the absence of formulary change

- 12-month event rates:
  - Estimated using Poisson regression
  - Periods compared using six Cox proportional hazards models with increasing level of statistical adjustment

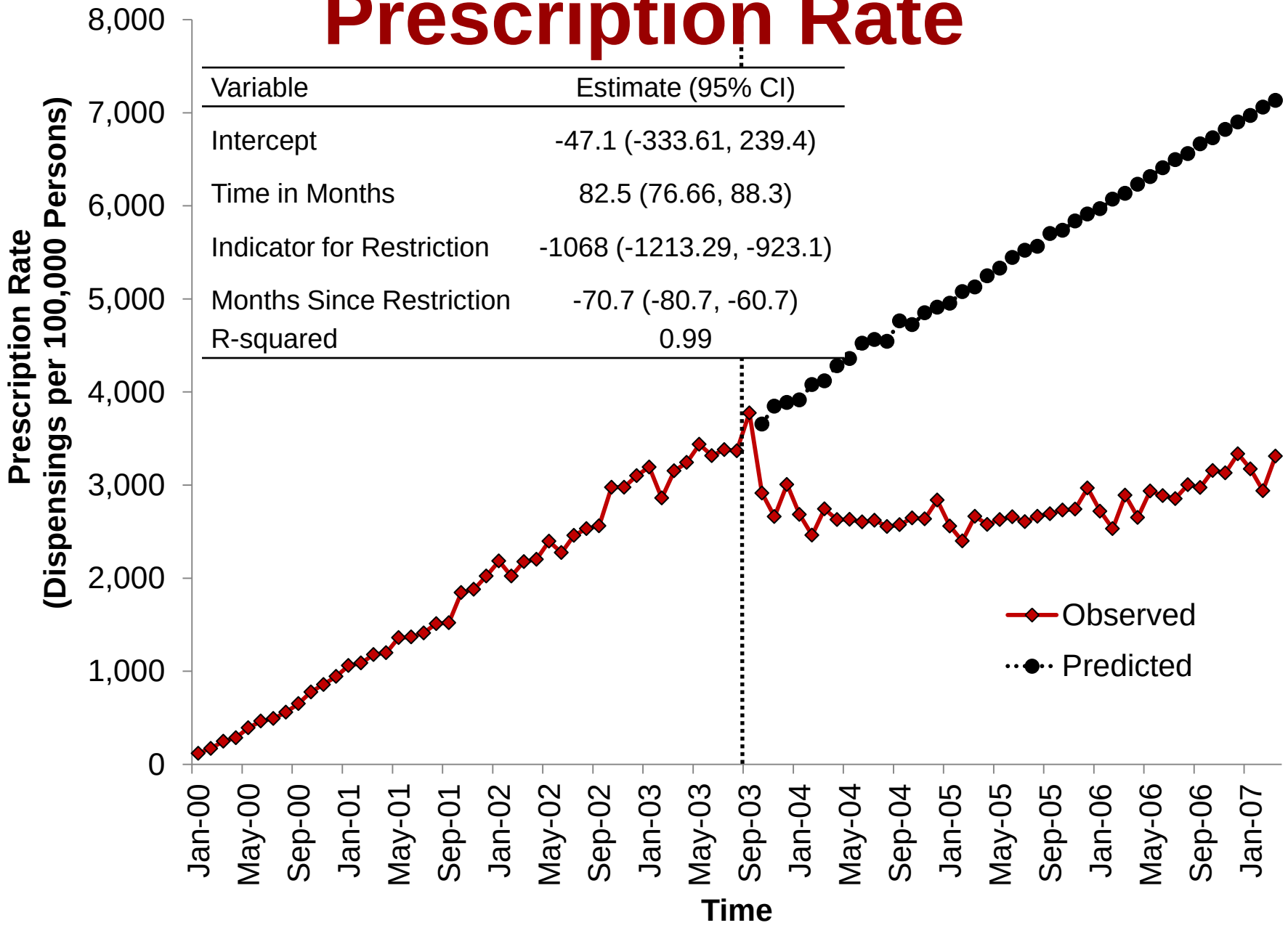
Statistical Analyses (Con't)

Model	Covariates
Crude	None
Age- and sex adjusted	Age, sex
Partially-adjusted model 1	+ hospitalization for asthma, COPD, or pneumonia in the year before cohort entry
Partially-adjusted model 2	+ **measures of overall** (number of hospitalizations for any cause in the year before cohort entry, number of physician visits in the year before cohort entry, number of prescription drugs dispensed in the prior year, Charlson comorbidity index) **and respiratory health** (a history of asthma, COPD, or pneumonia) in the prior year, as well as **non-respiratory drugs** (narcotics, NSAIDs, non-topical antibiotics, oral corticosteroids, and statins)
Partially-adjusted model 3	+ **respiratory drugs** (bronchodilators, short-acting beta-agonists, long-acting beta-agonists, long-acting beta-agonists with inhaled corticosteroid, short-acting beta-agonists with anticholinergic combination, cromoglycates, inhaled corticosteroids, inhaled corticosteroid/bronchodilator, leukotrienes, and xanthines)
Fully-adjusted	+ **prescribing physician specialty** (respirologist, general practitioner, and other), dispensing during the **summer** months (April – September)


Individuals available in RAMQ database (n=1,410,211)
Excluded:
- Individuals aged < 18 years during study period (n=380,818)
Age-eligible individuals (n=1,029,393)
Fluticasone/salmeterol dispensing among eligible individuals (n=1,618,818)
Excluded:
- Dispensing not in the study period (n=323,434)
- Dispensing of fluticasone/ salmeterol within the prior year (n=1,186,505)
Individuals receiving dispensing of fluticasone/salmeterol during the study period with no previous dispensing of fluticasone/salmeterol in the prior year (n=108,879)
Excluded:
- Less than one year of continuous drug coverage before dispensing (n=9,990)
New users of fluticasone/salmeterol in the study period (n=90,103)
Excluded:
- Dispensing of both fluticasone and salmeterol on the same day in the year prior (n=12,768)
- First dispensing of fluticasone/ salmeterol between September 30th, 2003 and January 1st, 2004 (n=54)
- No follow-up (n=69)
New users of fluticasone/salmeterol included in study population (n=77,212)

Prescription Rate

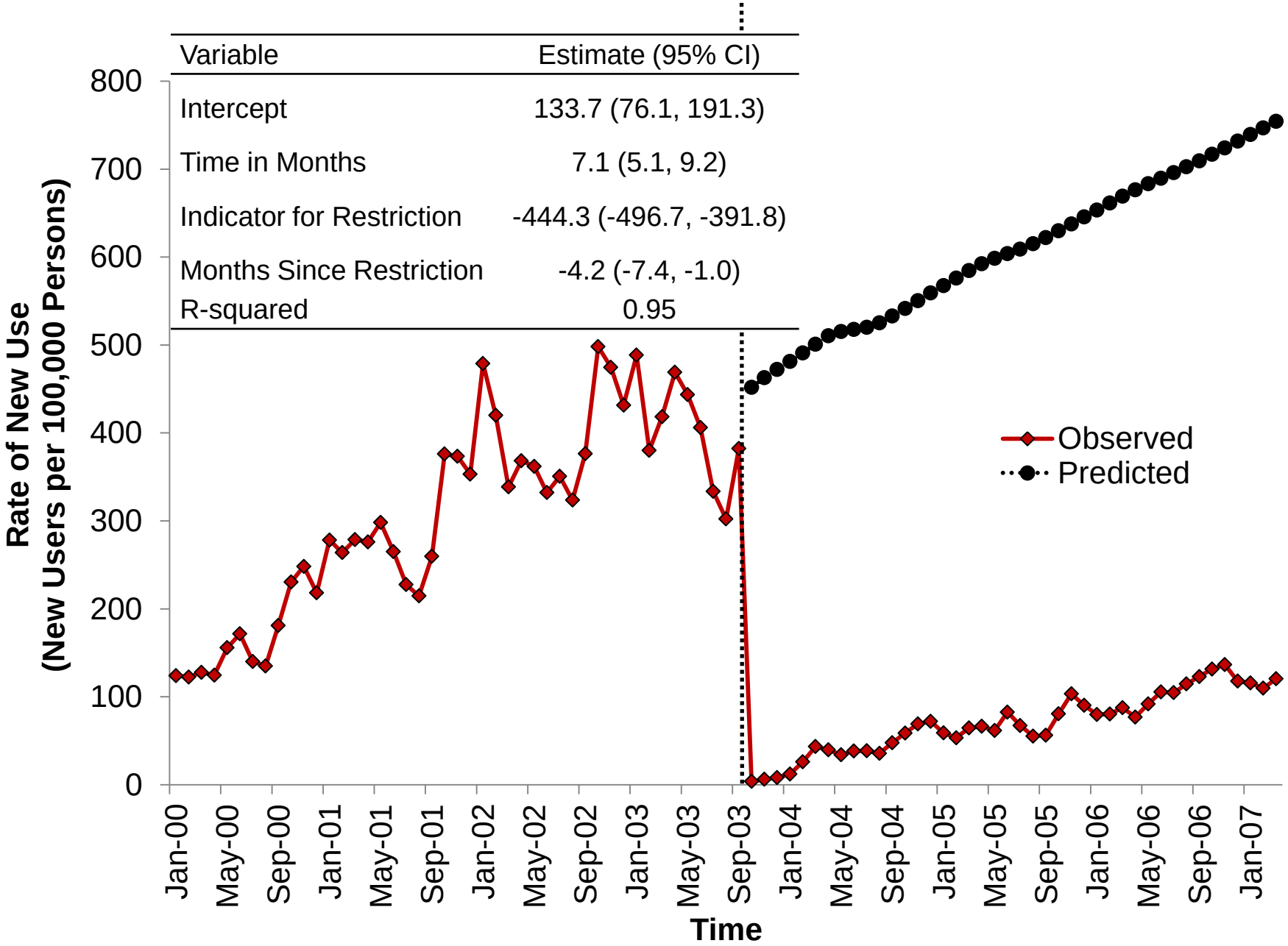
Variable	Estimate (95% CI)
Intercept	-47.1 (-333.61, 239.4)
Time in Months	82.5 (76.66, 88.3)
Indicator for Restriction	-1068 (-1213.29, -923.1)
Months Since Restriction	-70.7 (-80.7, -60.7)
R-squared	0.99



Note: Denominator = all patients prescribed a respiratory drug.

Rate of New Use

Variable	Estimate (95% CI)
Intercept	133.7 (76.1, 191.3)
Time in Months	7.1 (5.1, 9.2)
Indicator for Restriction	-444.3 (-496.7, -391.8)
Months Since Restriction	-4.2 (-7.4, -1.0)
R-squared	0.95



Patient Characteristics

Characteristics	Liberal (n = 72,154)	Restricted (n = 5,058)	Difference (95% CI)
Demographic			
Age, years	62.1 (17)	64.0 (17)	1.9 (1.4, 2.3)
Male	29,647 (41)	2,139 (42)	1 (0, 3)
Respiratory History			
Medical History in the Prior Year			
Asthma	23,666 (33)	2,475 (49)	16 (15, 18)
COPD	31,747 (44)	2,476 (49)	5 (4, 6)
Pneumonia	9,863 (14)	717 (14)	1 (-1, 2)
Hospitalization in the Prior Year for Respiratory Cause			
Asthma	2,961 (4)	397 (8)	4 (3, 5)
COPD	8,078 (11)	1,103 (22)	11 (9, 12)
Pneumonia	2,273 (3)	316 (6)	3 (2, 4)

Abbreviations: COPD = chronic obstructive pulmonary disease. Data are presented as mean (standard deviation) or count (%).

Patient Characteristics (Con't)

Characteristics	Liberal (n = 72,154)	Restricted (n = 5,058)	Difference (95% CI)
Measures of Disease Burden			
Hospitalization for Any Cause in the Prior Year	14,937 (21)	1,523 (30)	9 (8, 11)
Physician Visits in the Prior Year			
0-5	16,125 (22)	877 (17)	-5 (-6, -4)
6-10	18,617 (26)	1,241 (25)	-1 (-3, 0)
11-15	13,520 (19)	935 (18)	0 (-1, 1)
16+	23,892 (33)	2,005 (40)	7 (5, 8)
Charlson Comorbidity Index			
0	17,985 (25)	739 (15)	-10 (-11,-9)
1	34,662 (48)	2,575 (51)	3 (1, 4)
2	8,616 (12)	650 (13)	1 (0, 2)
≥ 3	10,891 (15)	1,094 (22)	7 (5, 8)
Prescribing Physician Specialty			
General Practitioner	59,101 (82)	3,488 (69)	-13 (-14, -12)
Respirologist	10,173 (14)	1,361 (27)	13 (12, 14)
Other	2,880 (4)	209 (4)	0 (0, 1)

Patient Characteristics (Con't)

Characteristics	Liberal (n = 72,154)	Restricted (n = 5,058)	Difference (95% CI)
Prior Medication Use			
Number of Unique Prescription Drugs	9.3 (5)	11.6 (5)	2.3 (2.1, 2.4)
Respiratory Medications			
Bronchodilators	8,256 (11)	1,513 (30)	19 (17, 20)
Cromoglycates	117 (0)	5 (0)	0 (0, 0)
Inhaled corticosteroids	31,339 (43)	3,581 (71)	27 (26, 29)
Leukotrienes	3,522 (5)	432 (9)	4 (3, 4)
Beta-agonists			
LABA	5,827 (8)	1,198 (24)	16 (14, 17)
LABA with Inhaled Corticosteroid	168 (0)	237 (5)	5 (4, 5)
SABA	35,198 (49)	3,716 (73)	25 (23, 26)
SABA/Anticholinergic Combined	13,451 (19)	1,828 (36)	18 (16, 19)
Xanthines	4,915 (7)	325 (6)	0 (-1, 0)

Abbreviations: LABA = long-acting beta-agonist; NSAIDs = non-steroidal anti-inflammatory drugs; SABA = short-acting beta-agonist. Data are presented as mean (standard deviation) or count (%).

Hospitalization Rates

Period	Number of Events	Number of Person-Years	Rate (95% CI) † Crude	Rate (95% CI) † Age- and Sex Adjusted‡
Hospitalizations for Respiratory Causes:				
Restricted	1,020	3,889	26.2 (24.7, 27.9)	25.1 (23.5, 26.8)
Liberal	10,001	53,537	18.7 (18.3, 19.1)	18.9 (18.4, 19.5)
Hospitalizations for Any Cause:				
Restricted	1,248	3,783	33.0 (31.2, 34.9)	32.1 (30.3, 34.1)
Liberal	14,378	51,490	27.9 (27.5, 28.4)	28.5 (27.8, 29.2)
All-Cause Mortality:				
Restricted	274	4,359	6.3 (5.6, 7.1)	5.1 (4.5, 5.8)
Liberal	2,610	58,126	4.5 (4.3, 4.7)	4.0 (3.7, 4.2)

†Rates are expressed as events per 100 person-years.
‡Estimated for a male at the mean age of 62 years.

Restricted vs Liberal

Crude	Age- and Sex-Adjusted	Partially-Adjusted Model 1	Partially-Adjusted Model 2	Partially-Adjusted Model 3	Fully-Adjusted
Hospitalizations for Respiratory Causes:					
1.41 (1.32, 1.51)	1.33 (1.25, 1.42)	1.05 (0.98, 1.12)	0.87 (0.81, 0.93)	0.79 (0.74, 0.84)	0.78 (0.73, 0.83)
Hospitalizations for Any Cause:					
1.19 (1.12, 1.26)	1.13 (1.07, 1.20)	0.96 (0.90, 1.02)	0.85 (0.80, 0.90)	0.83 (0.78, 0.88)	0.82 (0.77, 0.87)
All-Cause Mortality:					
1.40 (1.24, 1.59)	1.28 (1.13, 1.45)	1.10 (0.97, 1.25)	1.03 (0.91, 1.17)	0.98 (0.86, 1.13)	0.97 (0.84, 1.11)

Data are presented as HR (95% CI). The liberal period serves as the reference period for all analyses.

Strengths and Limitations

- Strengths:
  - True measure of association is known
  - Impact on prescribing practices assessed
  - Restricted to new users

- Limitations:
  - COPD added as approved indications during study period
    - Sensitivity analyses excluded patients hospitalized for COPD
  - Residual confounding due to missing smoking status
  - Restricted period: a modest number of new users
  - Generalizability to other formulary restrictions or other jurisdictions?
  - Did not assess the impact of the policy on clinical outcomes

Conclusions

- Drug formulary restrictions can result in substantial and unexpected confounding.

- In the case of fluticasone/salmeterol, crude estimates indicate that there was an increased risk of hospitalizations for respiratory causes during the liberal period relative to the restricted period but a statistically significant decreased risk during the restricted period following statistical adjustment.

- To ensure that study results are valid, formulary restrictions should be considered during the design and analysis of pharmacoepidemiologic studies.

For Additional Information

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; 25: 278–286
Published online 9 December 2015 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3923

ORIGINAL REPORT

Confounding by drug formulary restriction in pharmacoepidemiologic research†

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ABSTRACT

Purpose The potential consequences of confounding due to drug formulary restrictions in pharmacoepidemiologic research remain incompletely understood. Our objective was to illustrate this potential bias using the example of fluticasone/salmeterol combination therapy, an oral inhaler used to treat asthma and chronic obstructive pulmonary disease, whose use is restricted in the province of Quebec, Canada.

Methods We identified all new users of fluticasone/salmeterol in Quebec's administrative databases and classified those who received their initial dispensing of fluticasone/salmeterol between 1 September 1999 and 30 September 2003 as users from the liberal period and those who received it between 1 January 2004 and 31 October 2006 as users from the restricted period. The primary outcome was time to first hospitalization for respiratory causes within 12 months of cohort entry.

Results Our cohort included 72 154 new users from the liberal period and 5058 from the restricted period. Compared with use during the liberal period, use during the restricted period was associated with an increased rate of hospitalization for respiratory causes (crude hazard ratio [HR] = 1.41, 95% confidence interval [CI] = 1.32, 1.51). Subsequent adjustment for age, sex, and hospitalization for respiratory causes in the previous year attenuated the association (HR = 1.05, 95%CI = 0.98, 1.12). Further adjustment for other potential confounders resulted in a lower rate during the restricted period (HR = 0.78, 95%CI = 0.73, 0.83).

Conclusions Formulary restrictions can result in substantial and unexpected confounding and should be considered during the design and analysis of pharmacoepidemiologic studies.

Acknowledgements

- Collaborators
  - Pierre Ernst
  - Maria Eberg

- Personal Support
  - CIHR New Investigator Award

- CIHR Operating Grant

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Thank You!

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