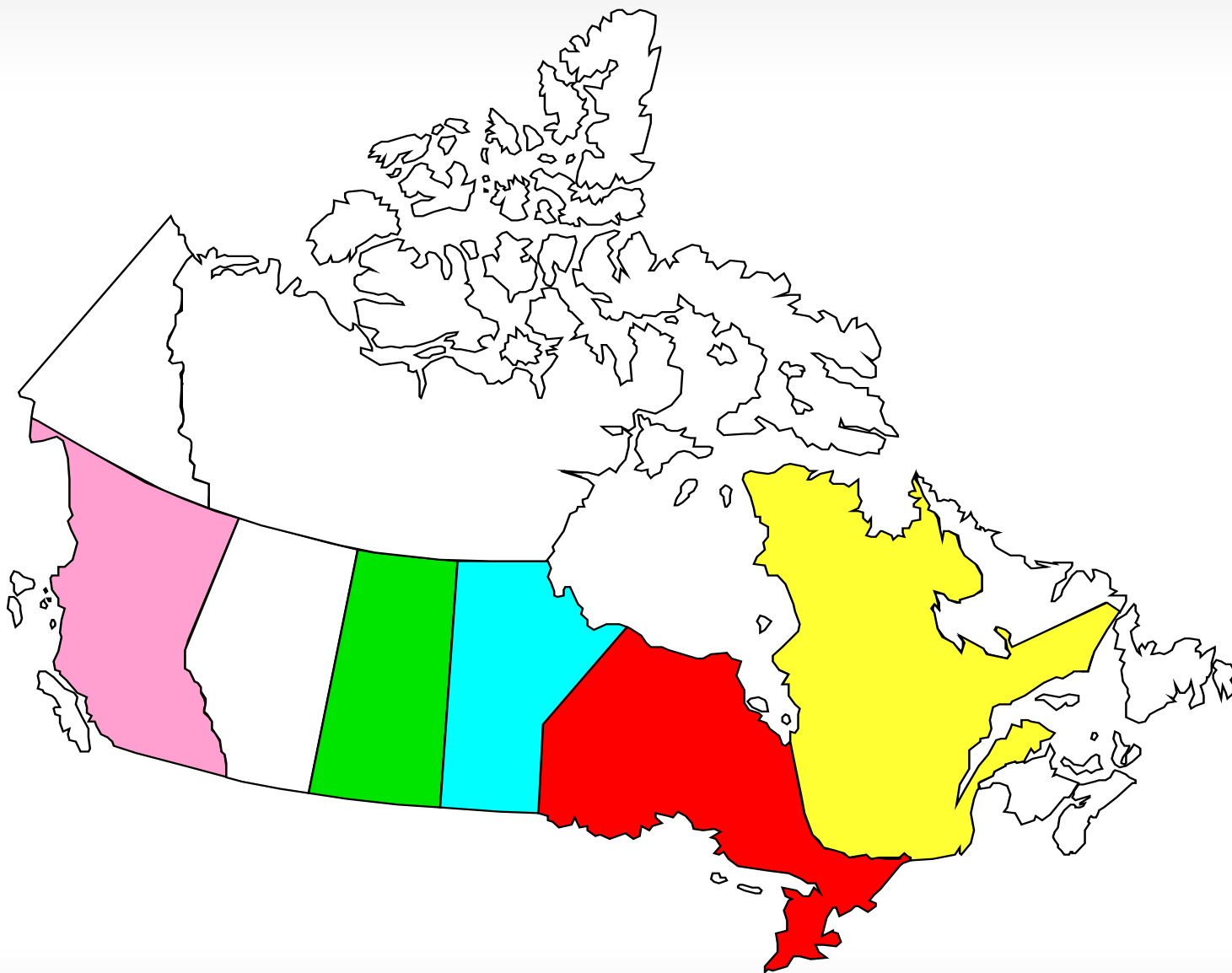


# CNODES: A Canadian Initiative

Samy Suissa  
Lady Davis Institute, Jewish General Hospital  
McGill University  
Montreal, Canada

---

PROTECT Conference, EMA, London,  
19 February, 2015



# PROVINCE OF QUEBEC, CANADA

- 7.3 million inhabitants
- Universal health insurance
  - Data on all in and outpatient services
  - Data on prescription drugs dispensed
- Universal motor vehicle insurance
  - Motor vehicle



## LOW-DOSE INHALED CORTICOSTEROIDS AND THE PREVENTION OF DEATH FROM ASTHMA

SAMY SUISSA, MD

ONLINE FIRST

### Nocturnal That Prece

*A Sequence Sym*

Scott R. Garrison, MD; C

OPEN ACCESS Freely a

### Cholineste Bradycardi

Laura Y. Park-Wylli  
Laupacis<sup>2,3,5,7</sup>, David H. Solomon

uture Risk:

am D. Leslie

ican Medical Association

# Why CNODES ?

## Original Contributions

### Benzodiazepine Use and the Risk of Motor Vehicle Crash in the Elderly

Brenda Hemmelgarn, MN; Samy Suissa, PhD; Allen Huang, MD; Jean-Francois Boivin, MD; Gilbert Pinard, MD

The New England Journal of Medicine

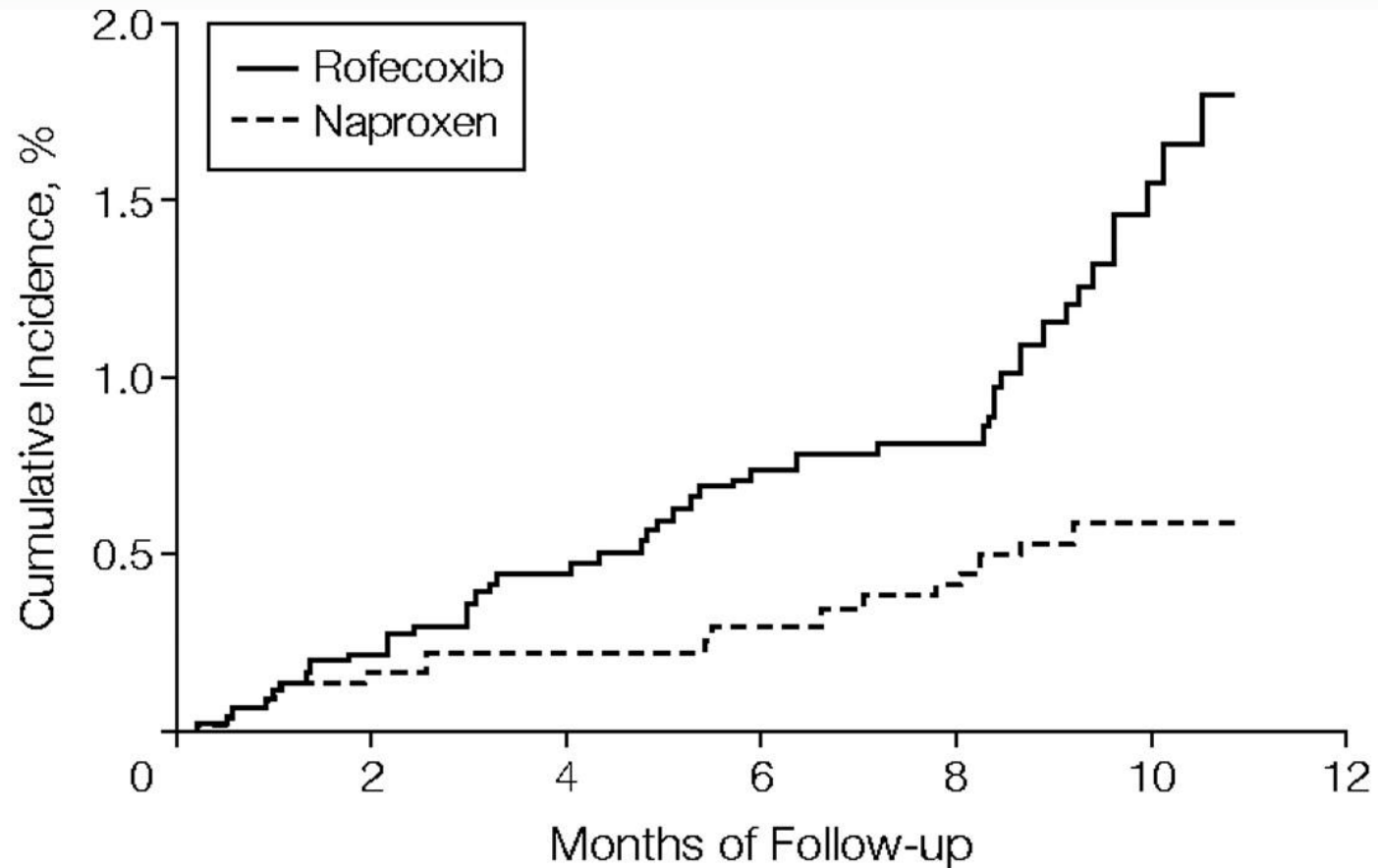
---

## COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H.,  
RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D.,  
CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D.,  
AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

November 23, 2000

# CV risk in VIGOR trial



No. at Risk

Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514



# HEALTH

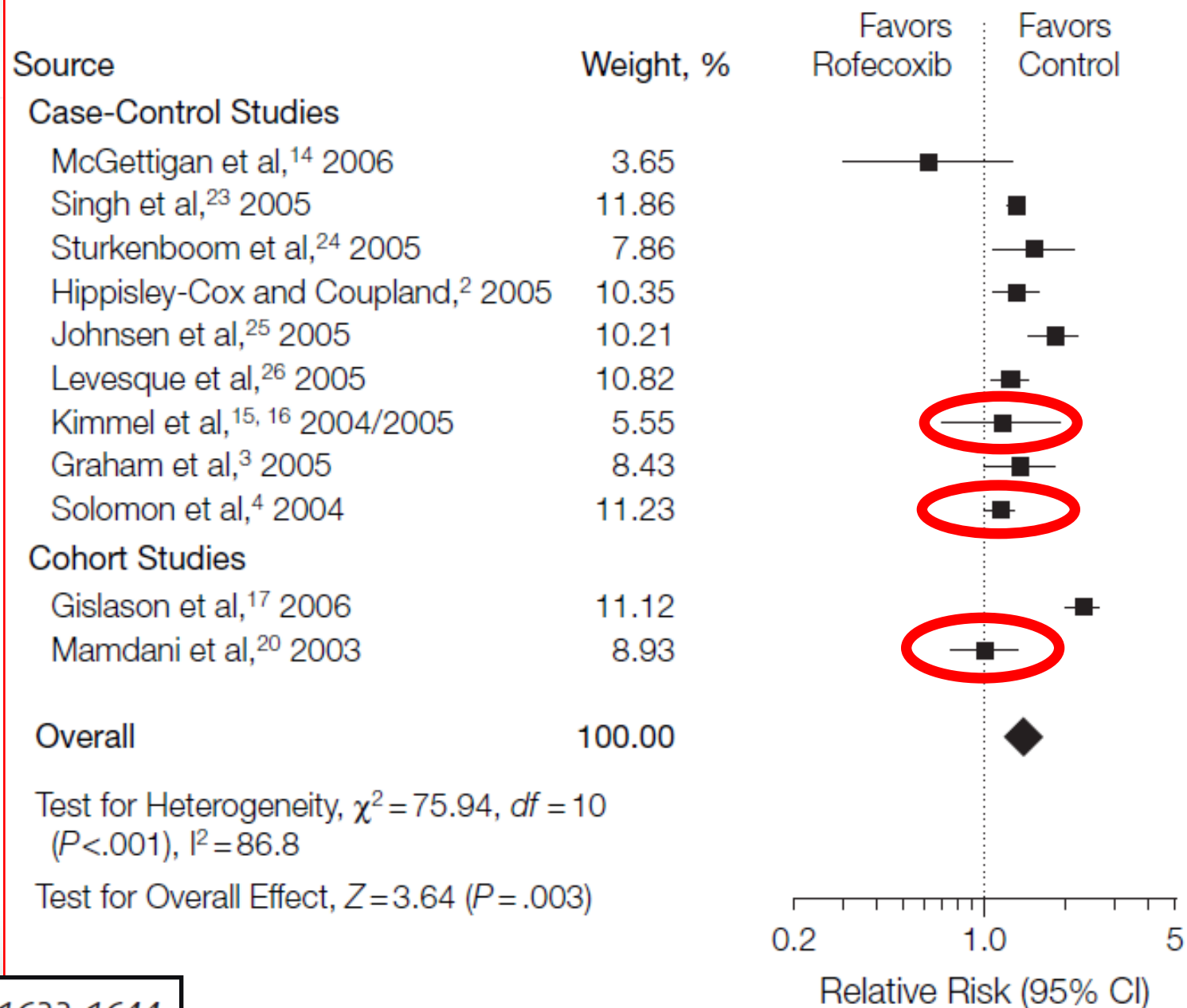
WASHINGTON (Reuters) -- Pharmaceutical giant Merck & Co Inc. had evidence by 2000 that its painkiller Vioxx, which was pulled off the market on **Sept. 30 (2004)**, was not safe, a heart specialist told CBS News program "60 Minutes" on Sunday.



(AP PHOTO)

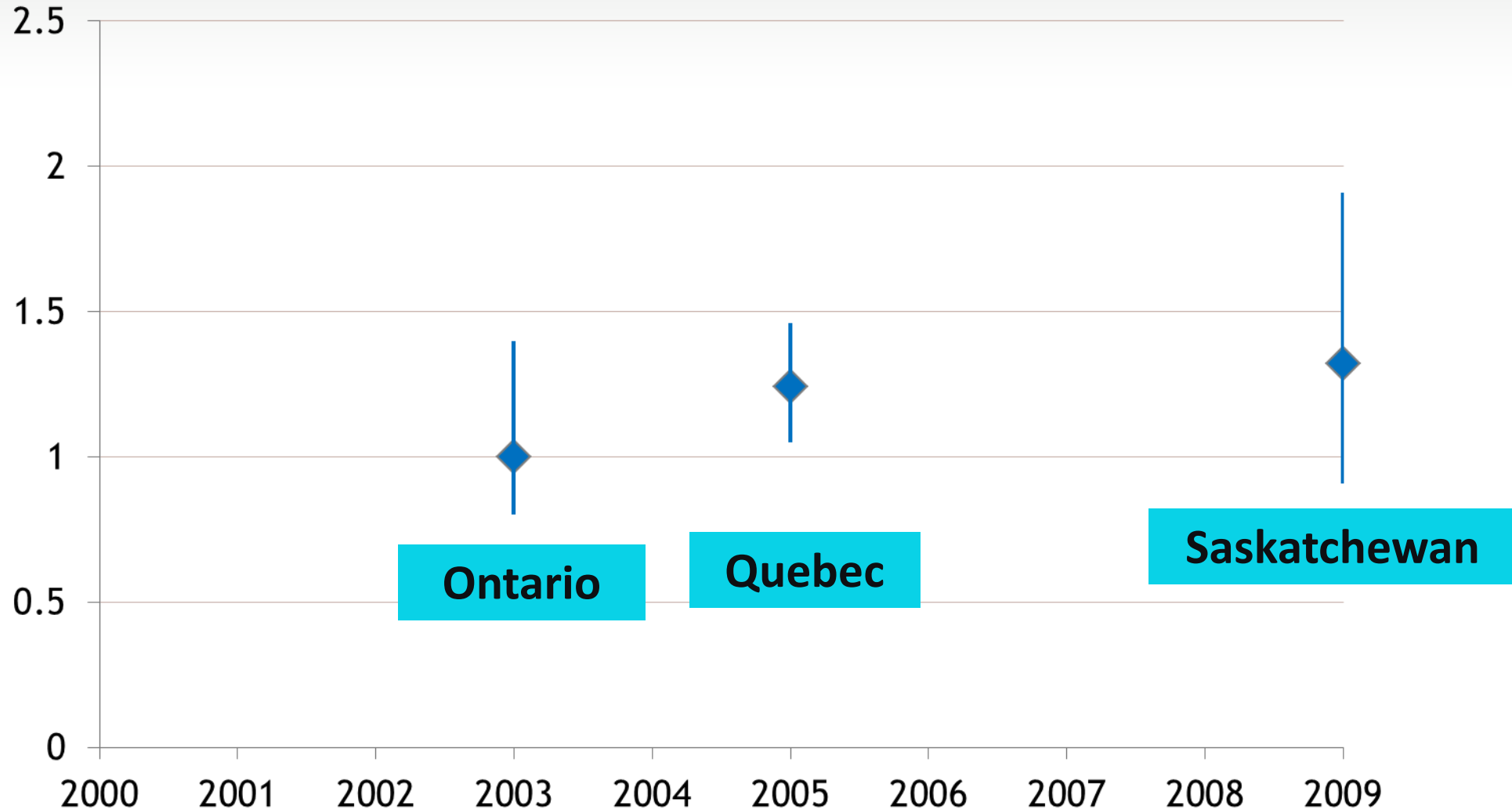


## Rofecoxib



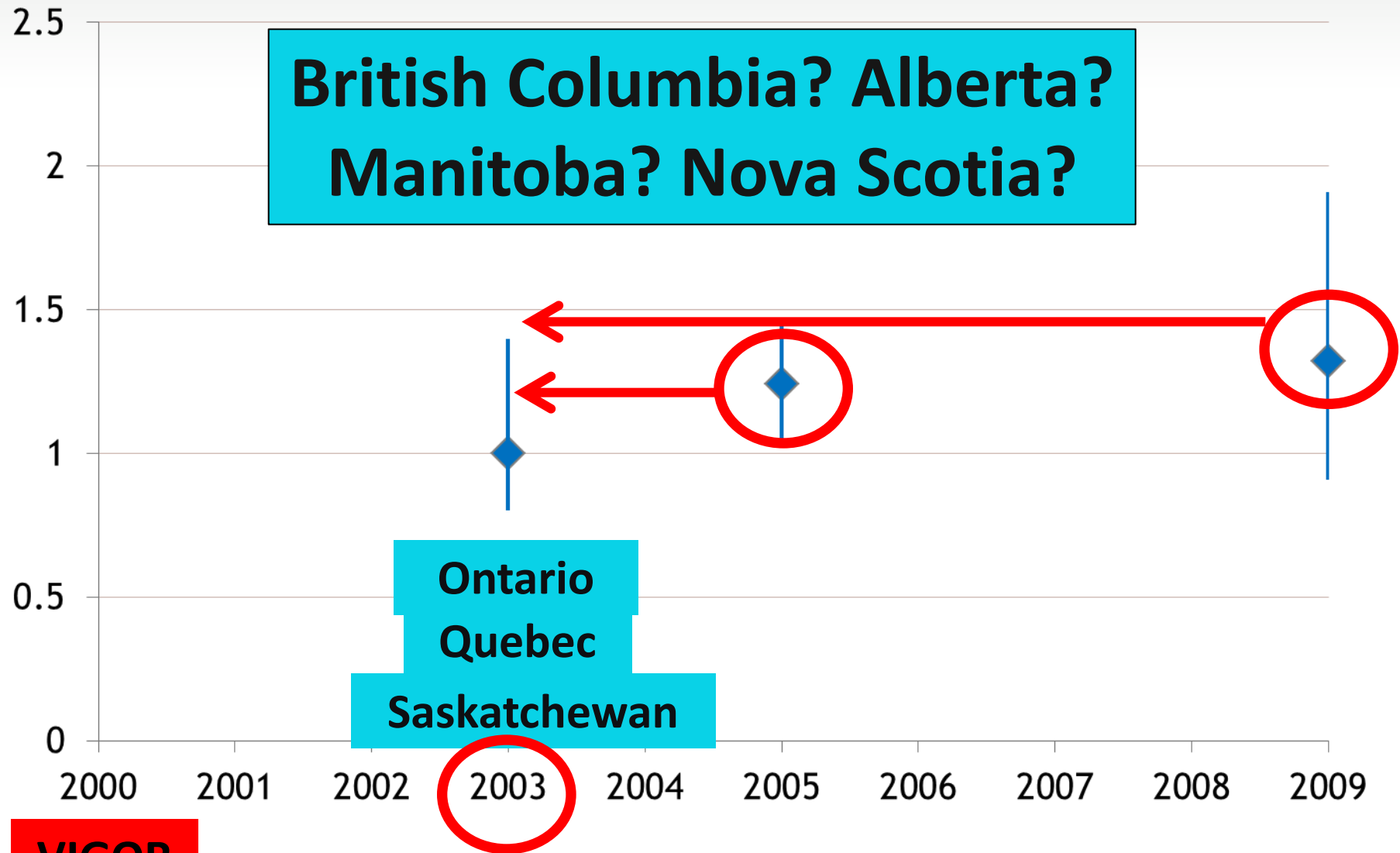


# Canadian VIOXX observational studies



**VIGOR  
RCT**

# Canadian VIOXX observational studies



**VIGOR  
RCT**

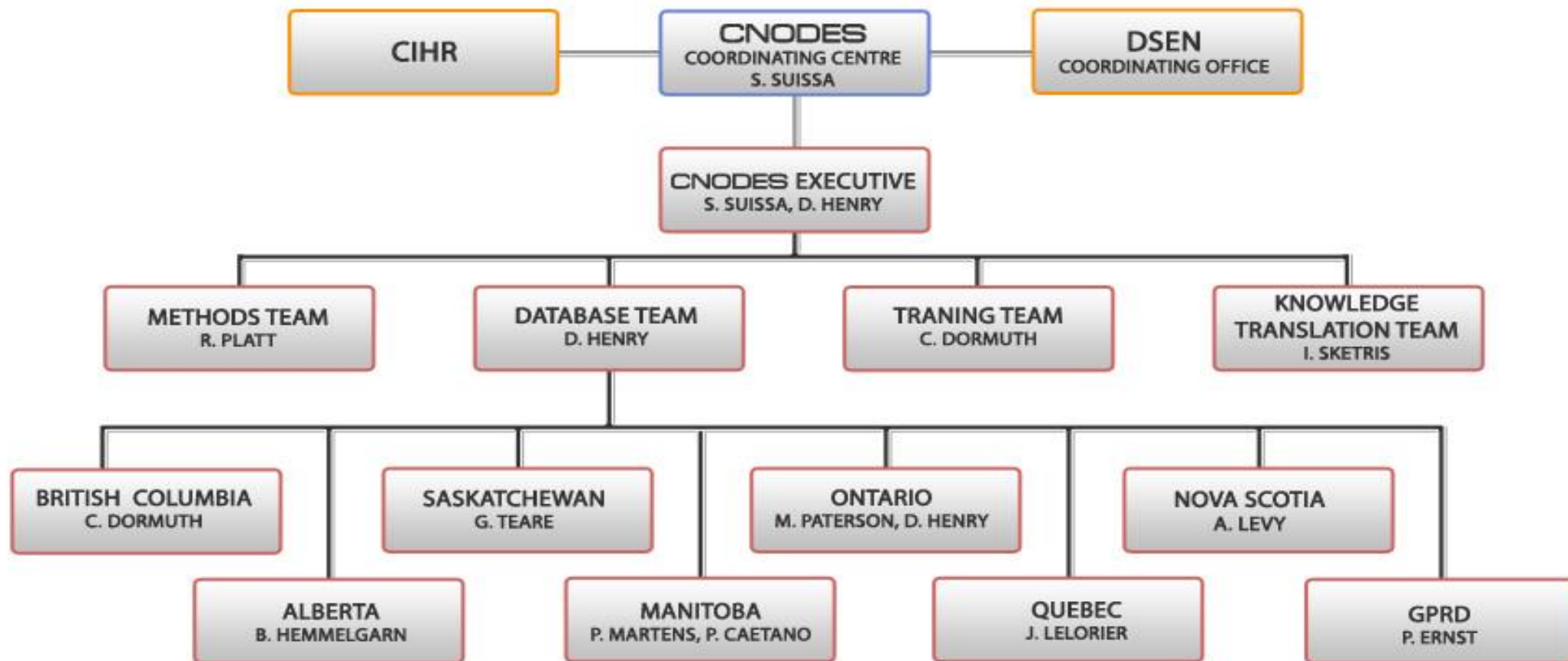
# CNODES ?

- A network of Canadian scientists ready to respond to queries from Canadian stakeholders through access to linked administrative health records:
  - Respond in a timely manner to queries relating to the drug safety and effectiveness evidence needs of decision makers and end-users
  - Investigators representing 8 provincial research centers
  - Funded in March 2011 for five years
  - Initiative of Health Canada



# CNODES

CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES

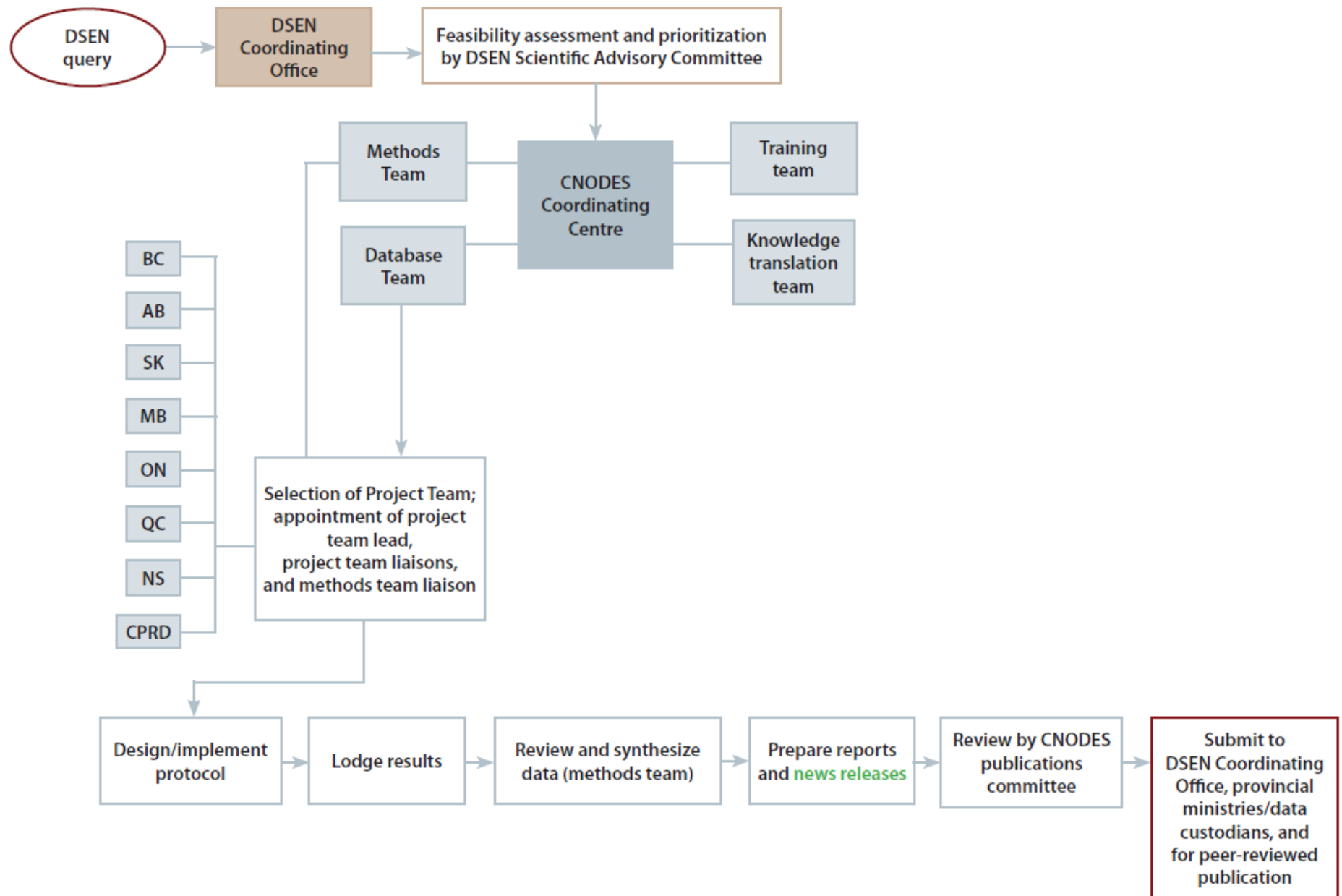


# CNODES: the Canadian Network for Observational Drug Effect Studies

**Samy Suissa, David Henry, Patricia Caetano, Colin R. Dormuth, Pierre Ernst, Brenda Hemmelgarn, Jacques LeLorier, Adrian Levy, Patricia J. Martens, J. Michael Paterson, Robert W. Platt, Ingrid Sketris, Gary Teare; for the Canadian Network for Observational Drug Effect Studies (CNODES)**

Open Medicine 2012;6(3)e134

# How CNODES WORKS



# CNODES: Challenges

- To detect small but important drug effects
- Feasible using computerized databases
- Requiring large sample sizes
- Reproducibility of results: variation should not be due to different study methods
- Results should be rapidly available



# CNODES: Quality measures

- Strong methods and clinical input
- Standardized analytical protocols with predefined endpoints
- Replication and reproducibility – multicenter estimates of the association and effect size
- Blinded site-specific results for Methods Team review, error checking
- Independent meta-analysis

# CNODES: Studies

- High-dose statins and the risk of acute kidney injury
- Proton-pump inhibitors and the risk of community-acquired pneumonia
- Atypical antipsychotics and the risk of diabetic ketoacidosis

# BACKGROUND:

Ridker PM et al, JUPITER Study Group. *N Engl J Med* 2008;359

Event	Rosuvastatin 20mg n=8901		Placebo n=8901		Rate Ratio	P-value
	n	%	n	%		
Primary Endpoint	142	1.6	251	2.8	0.57	<0.0001

# BACKGROUND:

Ridker PM et al, JUPITER Study Group. *N Engl J Med* 2008;359

Event	Rosuvastatin 20mg n=8901		Placebo n=8901		Rate Ratio	P-value
	n	%	n	%		
Primary Endpoint	142	1.6	251	2.8	0.57	<0.0001
Renal disorder	535	6.0	480	5.4	1.19	0.08

**Does treatment with high potency statins  
increase the risk of serious  
acute kidney injury ?**

# METHODS

- 9 new-user cohorts of statin initiators 1997-08
- Statin doses: high versus low potency
- Follow-up for 2 years or until hospitalization for acute kidney injury
- ITT and as-treated analyses separately in CKD and non-CKD patients
- Adjusting for high-dimensional propensity scores
- Results combined using meta-analytic methods

# RESULTS

---

- 2,067,639 patients initiating statin therapy
- 1/3 starting on high-dose statins
- 24,418 patients hospitalized for AKI during the first 2 years of follow-up

## RESEARCH

# Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases



OPEN ACCESS

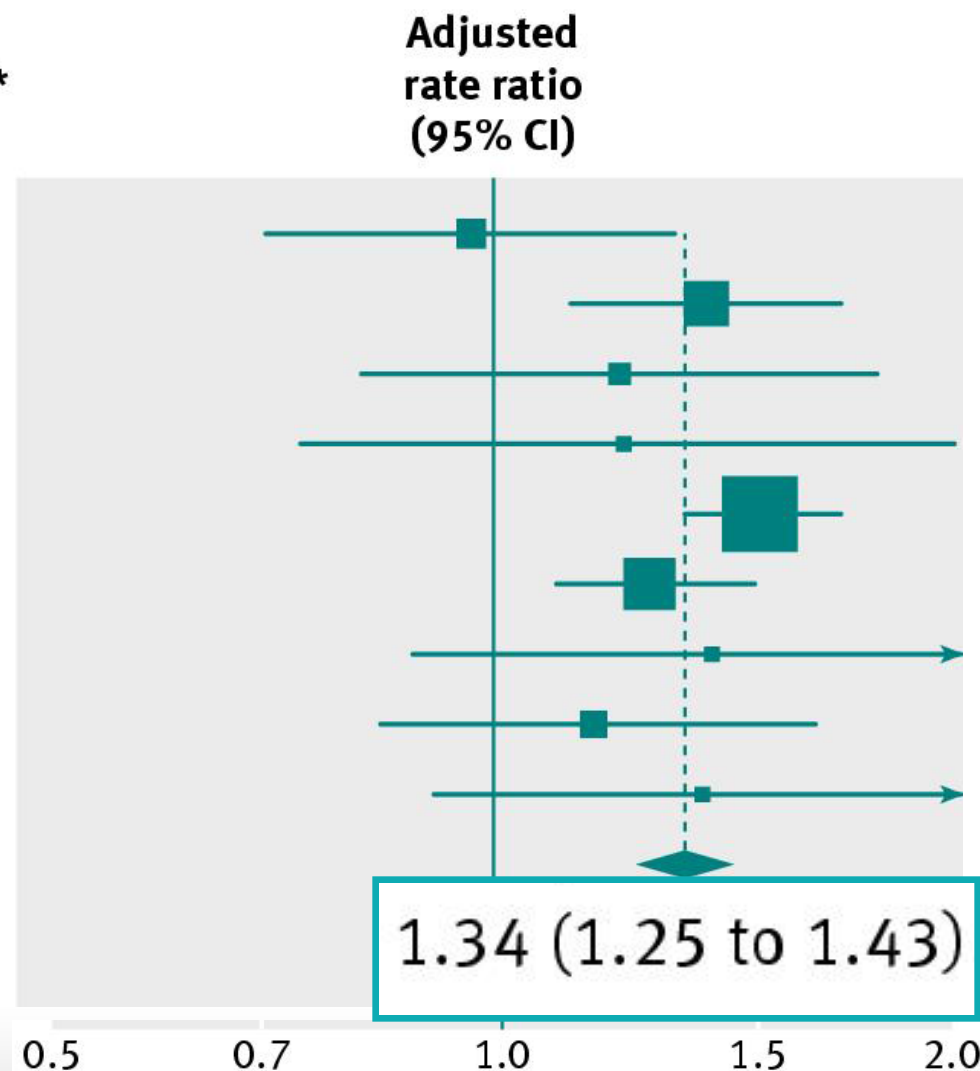
Colin R Dormuth *assistant professor*<sup>1</sup>, Brenda R Hemmelgarn *associate professor*<sup>2</sup>, J Michael Paterson *scientist*<sup>3</sup>, Matthew T James *assistant professor*<sup>2</sup>, Gary F Teare *director of quality management and analysis*<sup>4</sup>, Colette B Raymond *research scientist*<sup>5</sup>, Jean-Philippe Lafrance *assistant professor*<sup>6</sup>, Adrian Levy *head*<sup>7</sup>, Amit X Garg *professor of medicine*<sup>8</sup>, Pierre Ernst *professor of medicine*<sup>9</sup>, Canadian Network for Observational Drug Effect Studies (CNODES)



# HIGH-POTENCY STATINS AND AKI

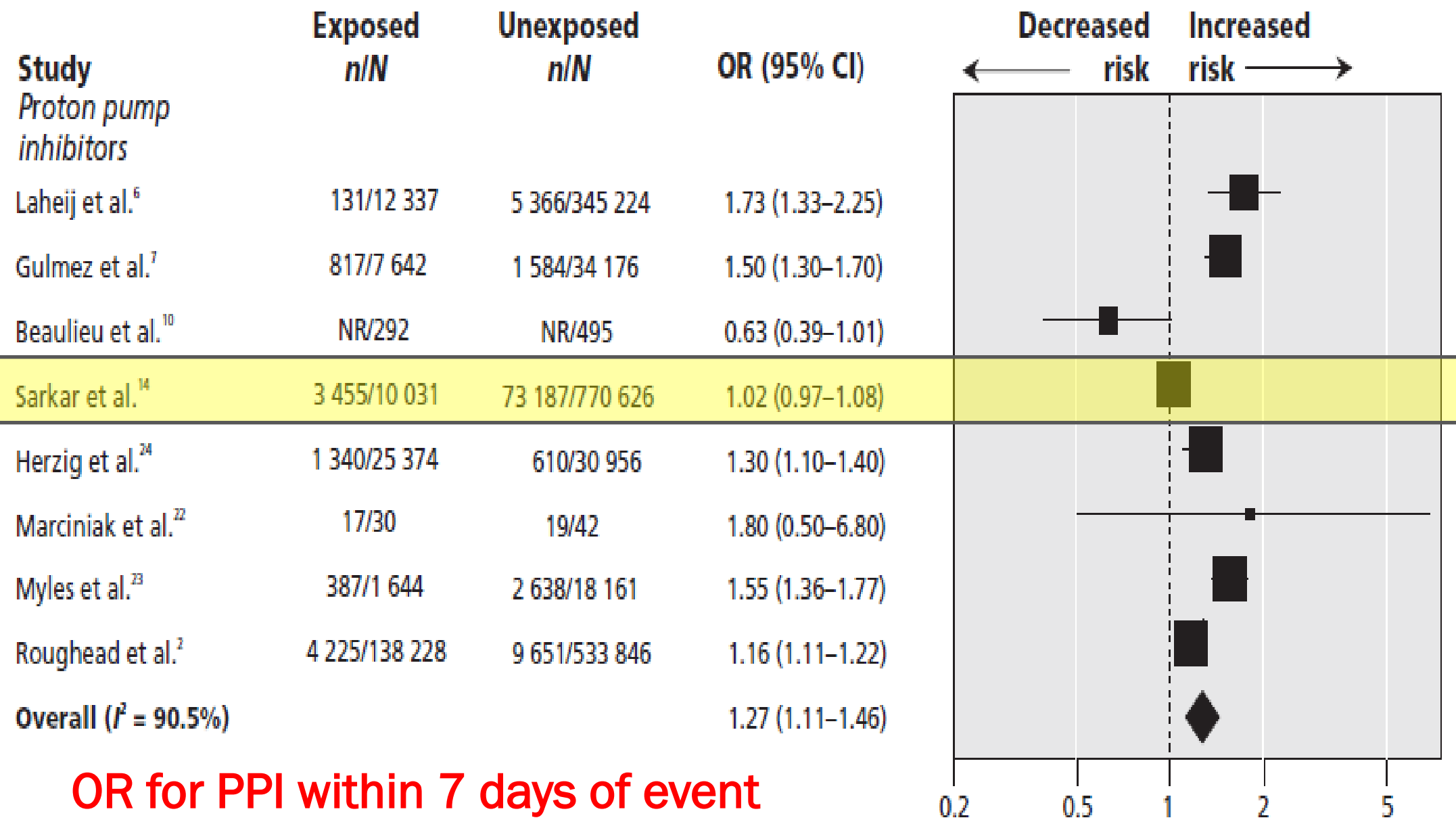
Study	Cases/control		Crude rate ratio*
	Low dose statins	High dose statins	
≤120 days of current therapy			
Alberta	158/1520	99/873	1.11
British Columbia	325/3164	285/2097	1.34
Manitoba	77/827	85/680	1.38
Nova Scotia	51/527	46/371	1.33
Ontario	793/9723	988/7340	1.73
Quebec	716/7037	602/4106	1.42
Saskatchewan	52/465	81/526	1.47
GPRD	114/1192	89/755	1.24
Medicare	68/767	62/509	1.39
Total	2354/26 168	2337/18 599	

Test for heterogeneity:  $\chi^2=9.99$ , df=7, P=0.27



# CNODES: Studies

- High-dose statins and the risk of acute kidney injury
- Proton-pump inhibitors and the risk of community-acquired pneumonia
- Atypical antipsychotics and the risk of diabetic ketoacidosis



**OR for PPI within 7 days of event  
4.0 (95% CI: 2.9 - 5.5)**

# Non-Causal Interpretation

- **Confounding by Indication:** PPIs prescribed for GERD which is a risk factor for CAP
- **Protopathic Bias:** Early symptoms of pneumonia misinterpreted, leading to PPI prescription.
- **Proposed Solution:** Extreme cohort restriction; use a cohort of new NSAID users



**OPEN ACCESS**

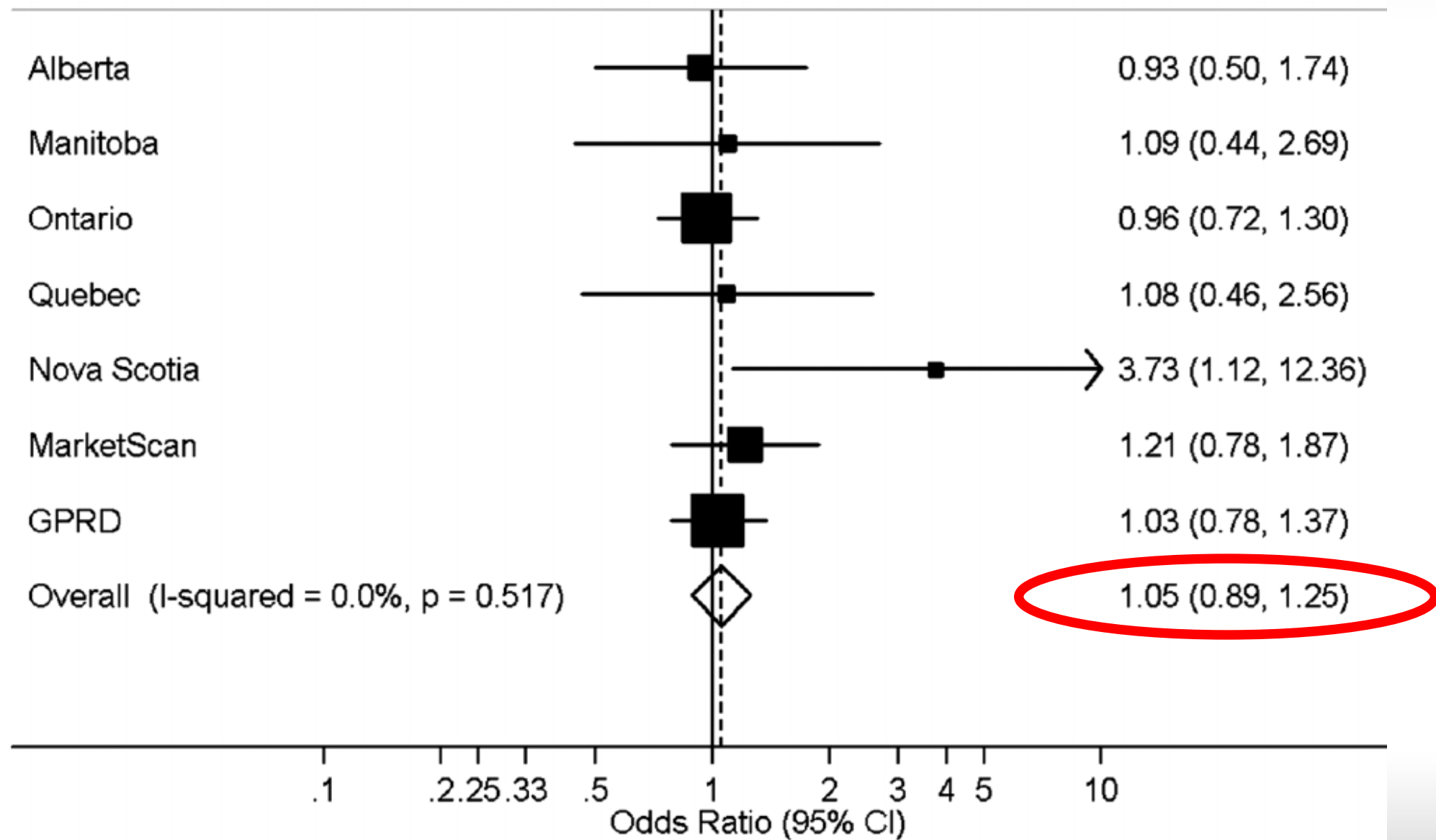
ORIGINAL ARTICLE

## Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis

Kristian B Fillion,<sup>1</sup> Dan Chateau,<sup>2</sup> Laura E Targownik,<sup>3</sup> Andrea Gershon,<sup>4</sup> Madeleine Durand,<sup>5</sup> Hala Tamim,<sup>6</sup> Gary F Teare,<sup>7</sup> Pietro Ravani,<sup>8</sup> Pierre Ernst,<sup>1</sup> Colin R Dormuth,<sup>9</sup> the CNODES Investigators

Fillion KB, *et al. Gut* 2013;**0**:1–7. doi:10.1136/gutjnl-2013-304738

# PPIs AND PNEUMONIA



# Query Process

## DSEN QUERY SUMMARY

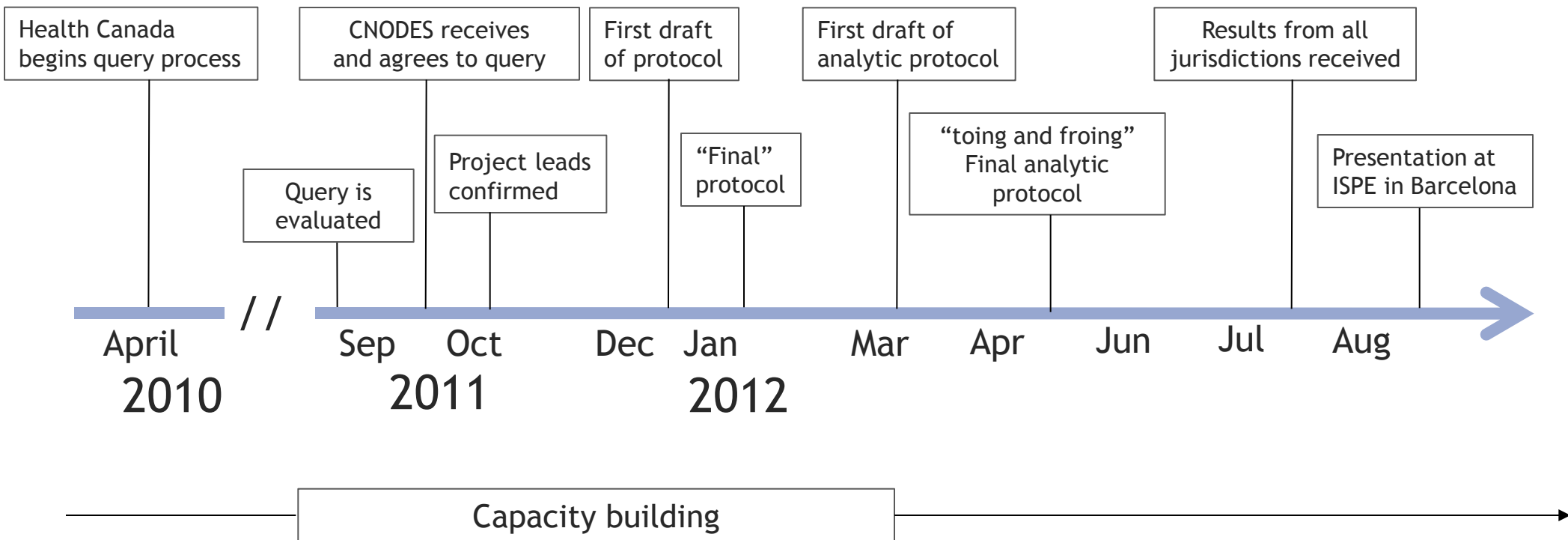
<b>DSEN Query Title</b>	<b>Atypical Antipsychotics and Diabetic KetoAcidosis (DKA)</b>
<b>DSEN Reference Number</b>	10-12
<b>Date (version) prepared</b>	April 22, 2010
<b>Source</b>	Health Canada

## DSEN Query Proposal

1.	<b>What is the specific DSEN Query (in the form of a research question)?</b>  <u>Primary question:</u> What risk factors can predict who is at greater risk of developing diabetic keto-acidosis (DKA) when exposed to atypical anti-psychotics?  <u>Secondary research question:</u> What is the incidence of DKA within the 6 drug groups?	
2.	<b>What is the relevant information regarding the drug product(s) for which the DSEN query is being proposed?</b>	
	2.1 <i>Active ingredient(s) ("generic" name(s)):</i>	Clozapine, olanzapine, quetiapine, risperidone, ziprasidone and paliperidone
	2.2 <i>Brand (proprietary) name(s):</i>	Clozaril <sup>®</sup> (clozapine), Zyprexa <sup>®</sup> (olanzapine), Seroquel <sup>®</sup> (quetiapine), Risperdal <sup>®</sup> (risperidone), Zeldox <sup>®</sup> (ziprasidone) and Invega <sup>®</sup> (paliperidone).
	2.3 <i>Product class:</i>	Anti-psychotics, sub-class atypical



# Antipsychotics-DKA Project Timeline





Contents lists available at [ScienceDirect](#)

## Schizophrenia Research

journal homepage: [www.elsevier.com/locate/schres](http://www.elsevier.com/locate/schres)

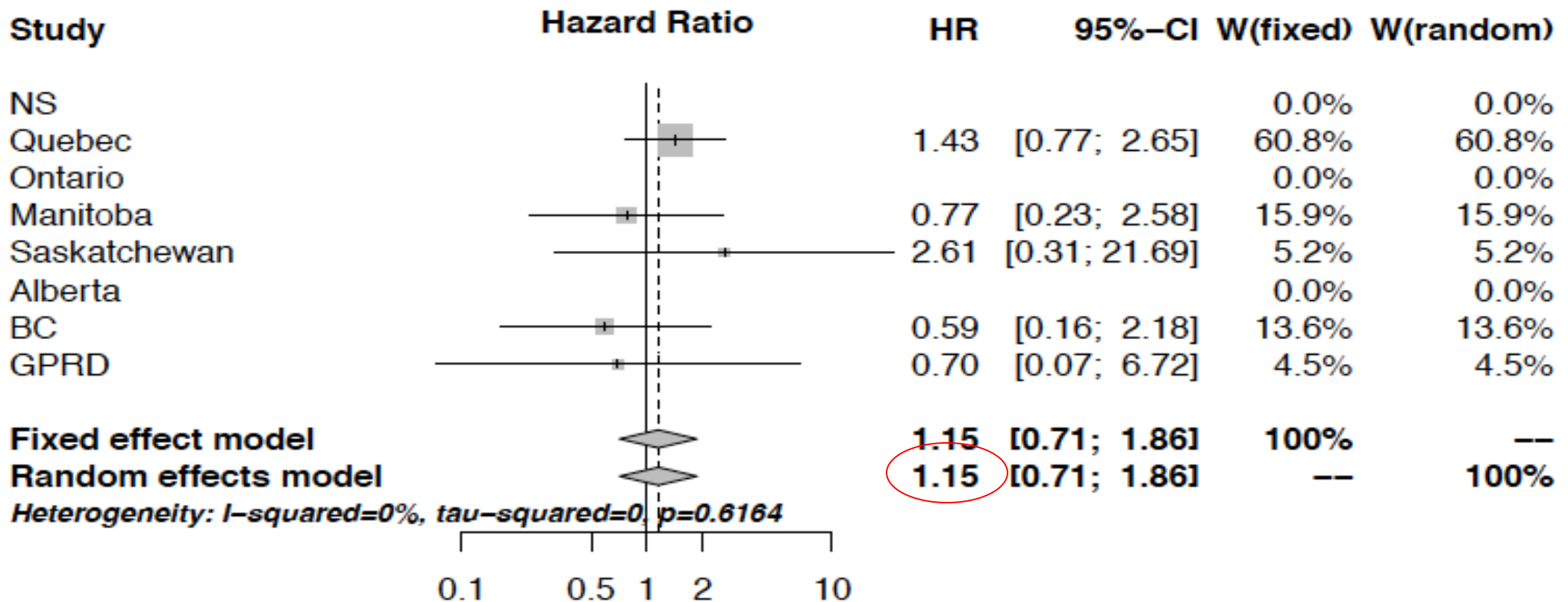


### Atypical antipsychotics and hyperglycemic emergencies: Multicentre, retrospective cohort study of administrative data<sup>☆</sup>

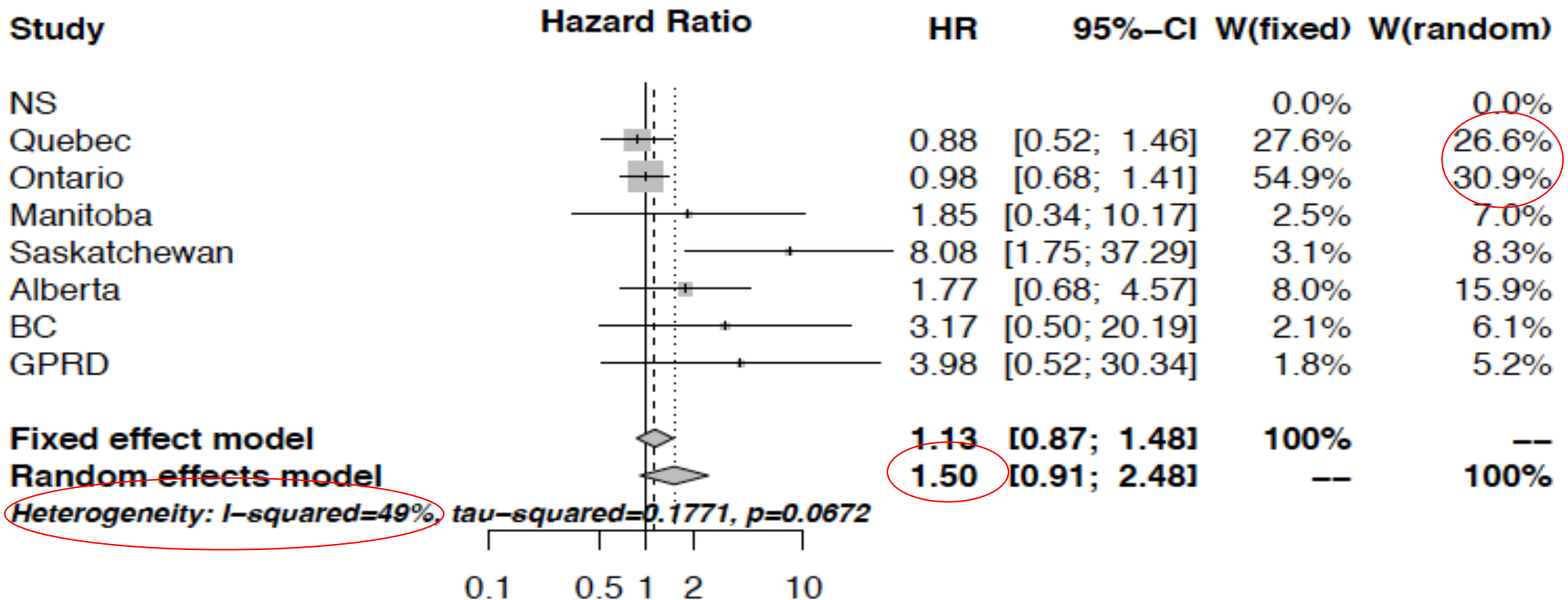


Lorraine L. Lipscombe<sup>a,m,\*</sup>, Peter C. Austin<sup>a</sup>, Silvia Alessi-Severini<sup>b,c</sup>, David F. Blackburn<sup>d</sup>, Lucie Blais<sup>e</sup>, Lauren Bresee<sup>f</sup>, Kristian B. Filion<sup>g,h</sup>, Yuko Kawasumi<sup>i</sup>, Paul Kurdyak<sup>a,n</sup>, Robert W. Platt<sup>j</sup>, Hala Tamim<sup>k,l</sup>, J. Michael Paterson<sup>a</sup>,  
The Canadian Network for Observational Drug Effect Studies (CNODES) Investigators<sup>1</sup>

# Primary ITT: Olanzapine vs. Risperidone Age 18-65 years



# Primary ITT: Olanzapine vs. Risperidone Age 66+ years

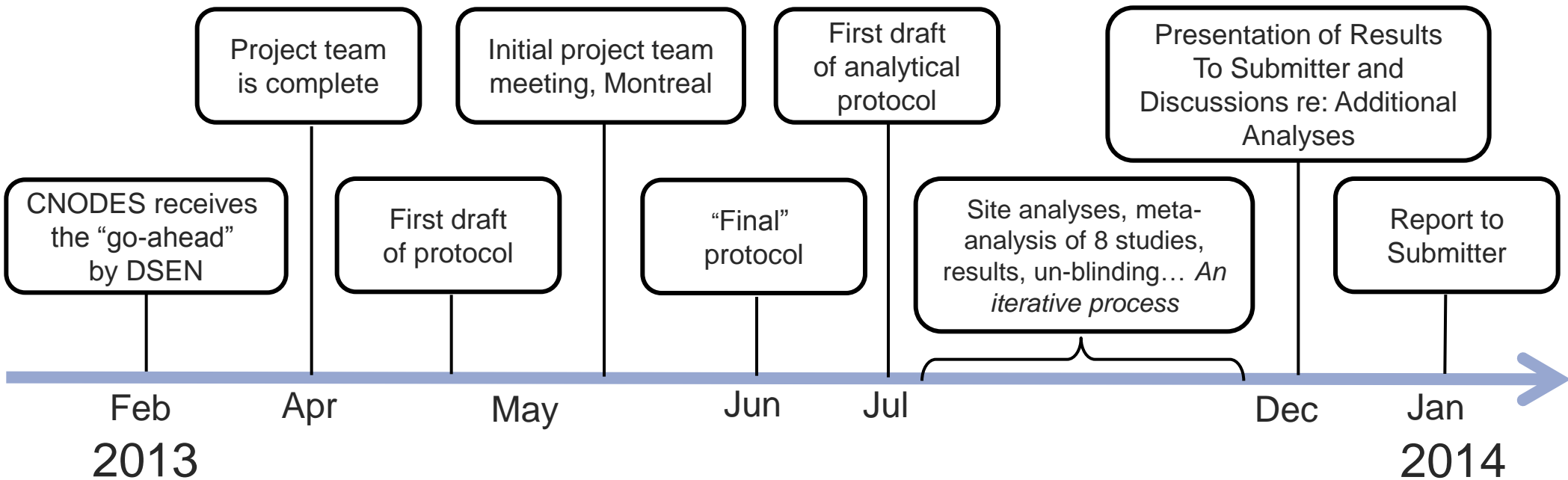


# CNODES Studies - Completed

- **High-potency statins and risk of acute kidney injury**
  - *Dormuth CR, et al., BMJ 2013; 346: f880*
- **PPIs and risk of community-acquired pneumonia**
  - *Filion KB, et al., Gut. 2014 Apr;63(4):552-8.*
- **Antipsychotics and risk of hyperglycemic emergencies**
  - *Lipscombe LL, et al., Schizophr Res. 2014 Apr;154(1-3):54-60*
- **High-potency statins and risk of diabetes**
  - *Dormuth CR, et al., BMJ. 2014 May 29;348:g3244.*
- **SNRIs and risk of acute kidney injury**
  - Submitted for publication

# SNRIs and Renal Failure

## Project Timeline



# CNODES Studies - Ongoing

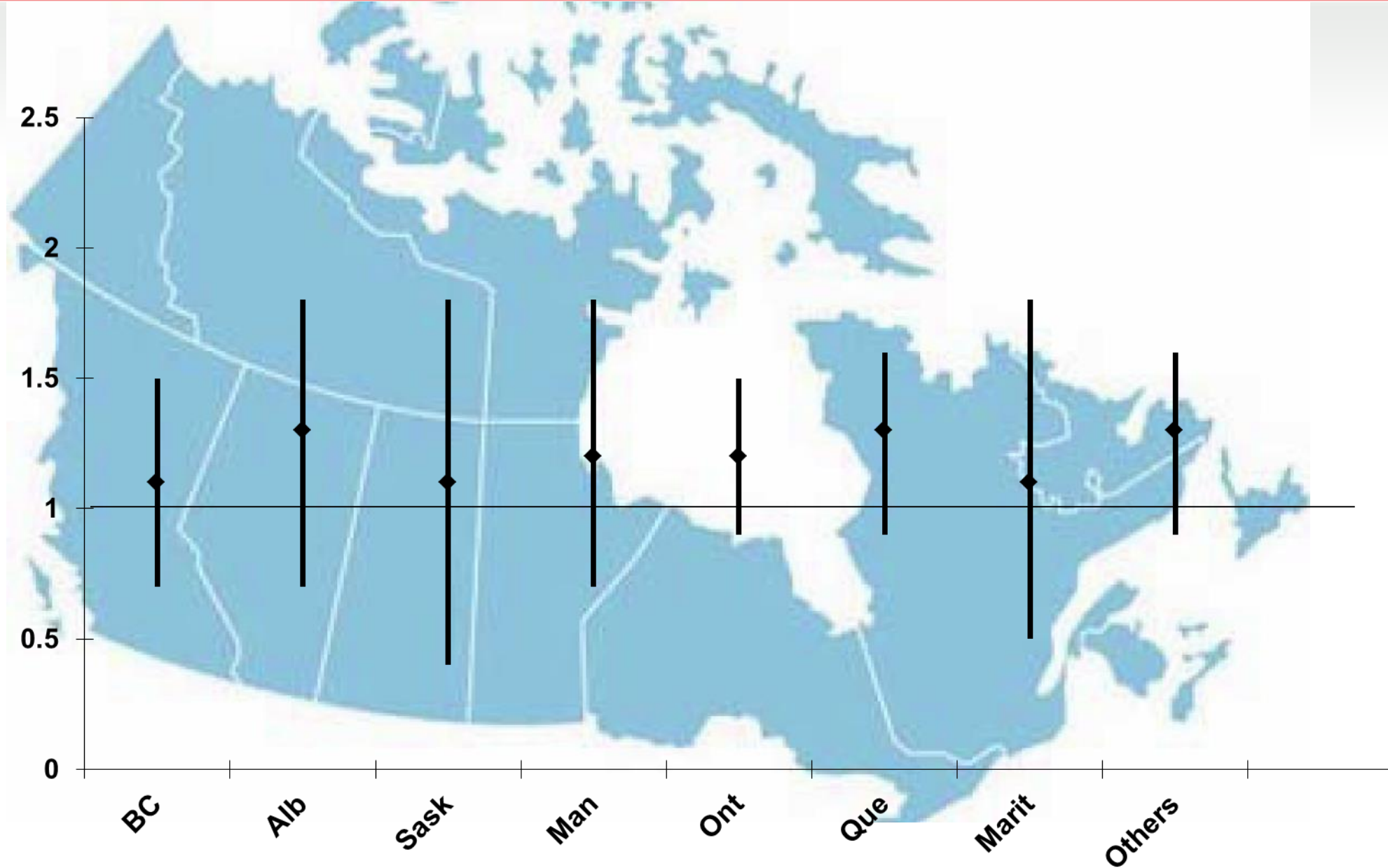
- Isotretinoin use in pregnancy
- Domperidone use in Parkinson's disease: risk of serious cardiac events
- Quetiapine and risk of cardiomyopathy and acute liver injury
- Newer antidepressants and PPHN
- Safety of opioids since introduction of OxyNEO
- Incretin-based therapies and risk of pancreatitis, pancreatic cancer and heart failure

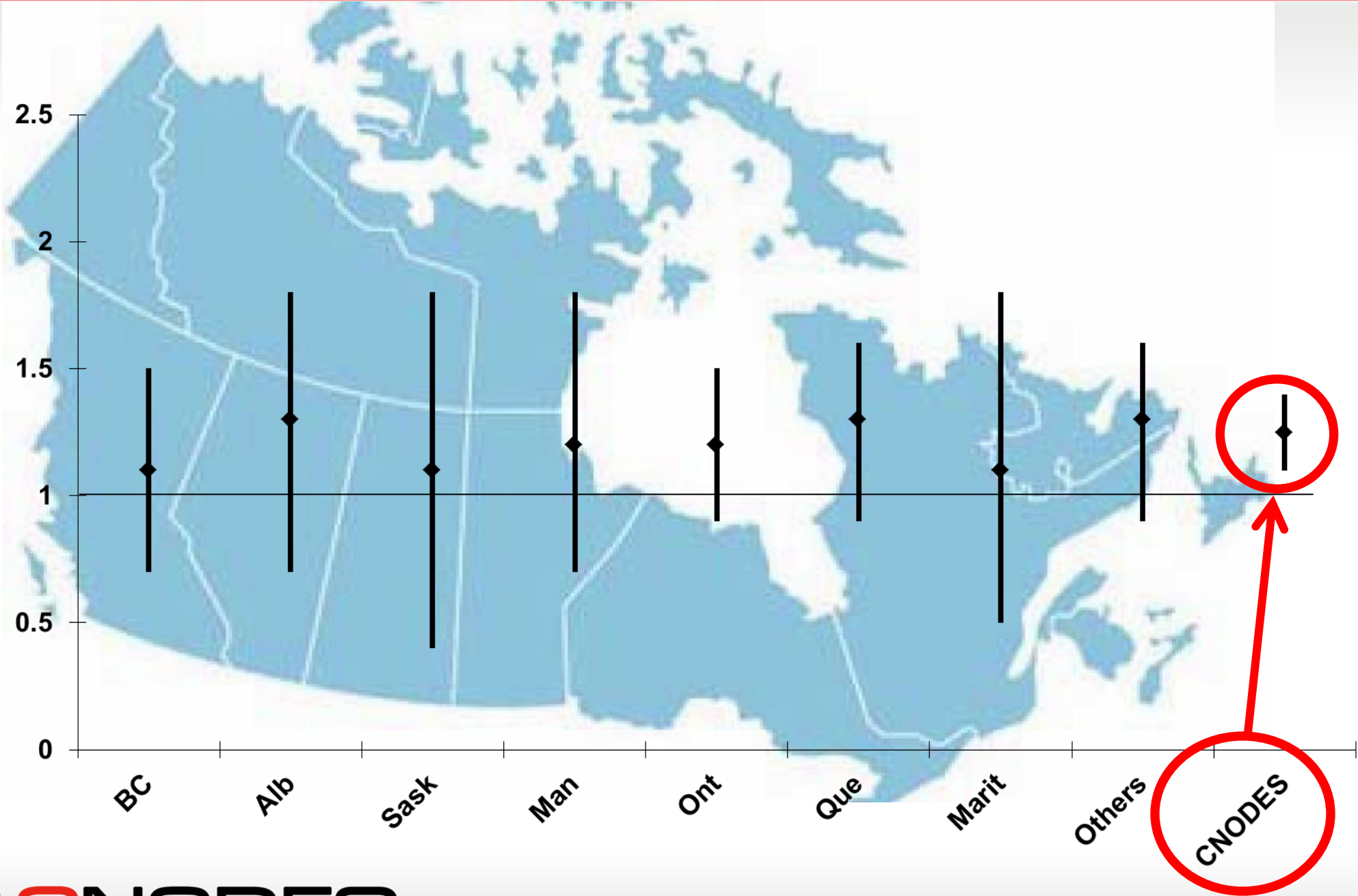


# CNODES Methods Publications

- The performance of different propensity score methods for estimating absolute effects of treatments on survival outcomes: A simulation study. (*Austin PC, et al., Stat Methods Med Res. 2014 Feb 3.*)
- The robustness of meta-analyses - an illustration using statins treatment and acute kidney injury data (*Chevance A, et al., J Clin Epidemiol*)
- The role of confounder prevalence: implications for the high-dimensional propensity score algorithm (*Schuster T, et al., Am J Epidemiol. Submitted*)
- Application of Targeted Maximum Likelihood Estimation in Pharmacoepidemiological Studies (*Pang M, et al., Epidemiology, submitted*)
- Propensity score matching and the auxiliary role of the prediction standard error (*Schuster T, et al., Statistics in Medicine, submitted*)







# ACKNOWLEDGEMENTS

- Canadian Network for Observational Drug Effect Studies (CNODES), a collaborating center of the Drug Safety and Effectiveness Network (DSEN), funded by Health Canada and the Canadian Institutes of Health Research (CIHR).

## CNODES Investigators

- Coordinating Centre: Samy Suissa (Principal Investigator)
- British Columbia: Colin Dormuth
- Alberta: Brenda Hemmelgarn
- Saskatchewan: Gary Teare
- Manitoba: Patricia Martens, Patricia Caetano
- Ontario: David Henry, Michael Paterson
- Québec: Jacques LeLorier
- Nova Scotia: Adrian Levy
- GPRD: Pierre Ernst
- KT: Ingrid Sketris
- Methods: Robert Platt

---

# THANK YOU!

Visit us at: [WWW.CNODES.CA](http://WWW.CNODES.CA)

---