Frontiers in Pharmacoepidemiology

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Potential conflicts of interest

- No paid consulting or speaker fees from pharmaceutical manufacturers
- Consulting/ board membership in past year:
  - HealthCore; The Lewin Group; RTI; ii4sm; WHISCON
- Investigator-initiated research grants from Pfizer, HealthCore, Novartis
- Grants from NIH, AHRQ, and FDA
- PI of the Brigham & Women's Hospital DEcIDE Research Center on Comparative Effectiveness Res.
- President of the Int'l Soc. for Pharmacoepidemiology
- **No conflict of any relevance to this symposium**

Frontiers in Pharmacoepidemiology

Generating valid evidence on the safety and effectiveness of medications in **routine care**

- Fundamental limitations of secondary data
- Making better use of our data
  - Complex longitudinal data > hd-PS
  - Multi-level structure of data > IV analyses
  - Distributed data networks > secure pooling with mv PS adj.
- Heterogeneity of treatment effects
- Other things

Information needed for informed drug treatment and coverage decisions

- Effectiveness compared with active drugs
- Generalizable to a population of actual users
- Large enough studies to rule out safety concerns
- Large enough to study many relevant subgroups

US:

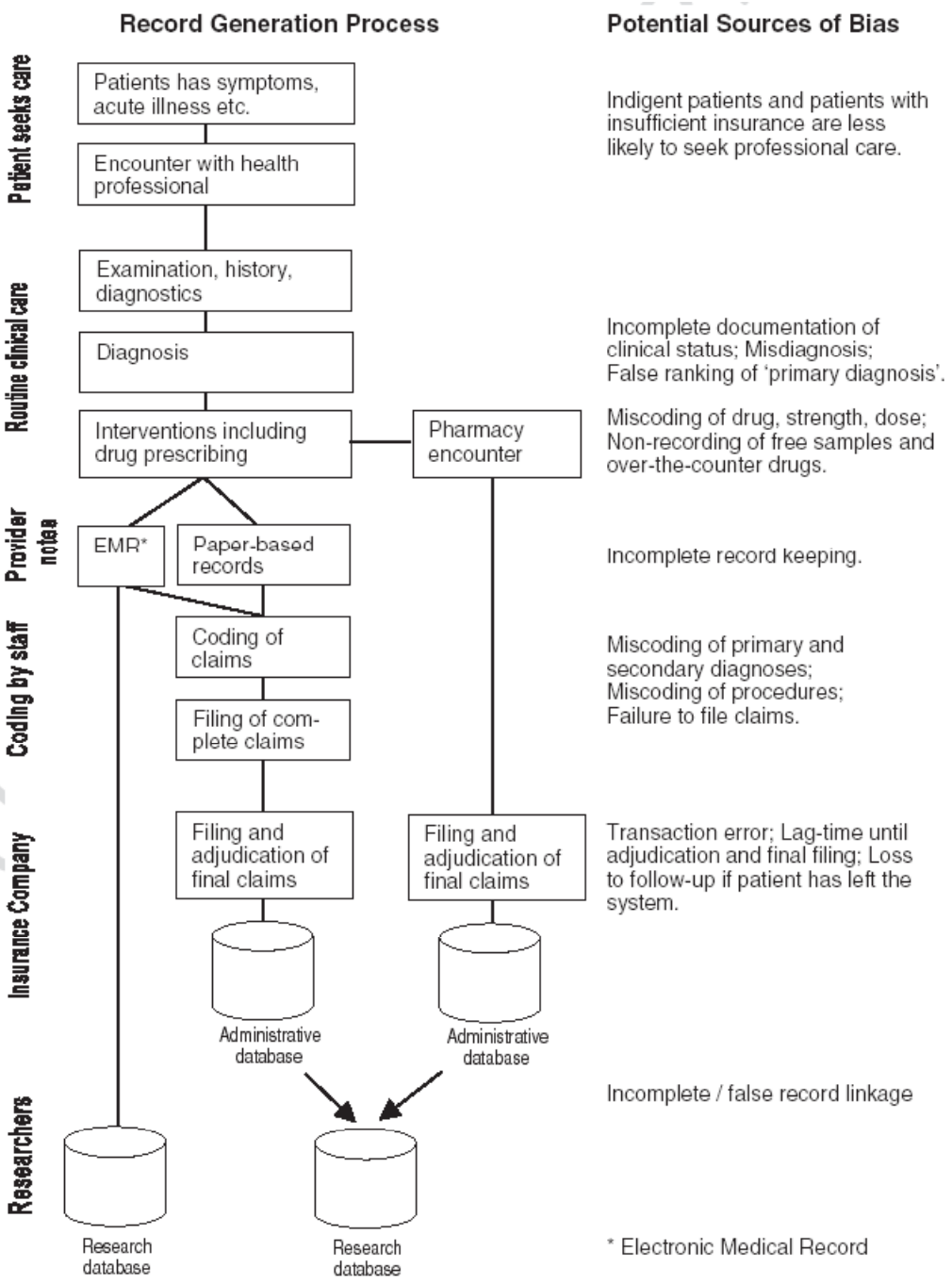
- Medicare Part D drug coverage (MMA) dramatically increased the stake of the federal government
- $1.1B for CER in ARRA, more in the new HC law
- A new CER agency? Within AHRQ vs. stand-alone?

Secondary Healthcare Data

Claims data describe the sociology of health care and its recording practice in light of economic interests

90% of PE studies

80% of CER



J Clin Epi 2005

Is there a fundamental difference between claims and EMR data?

- Claims
  - Completeness of service recording
  - Ease of linking with vital statistics
  - Lack of clinical detail
  - Lack of in-hospital drug use information
- EMR
  - Loss of out-of-network service information
  - More clinical detail, incl. test results
  - Often more in-hospital information
- But both are only reflecting what was delivered and recorded by the healthcare system

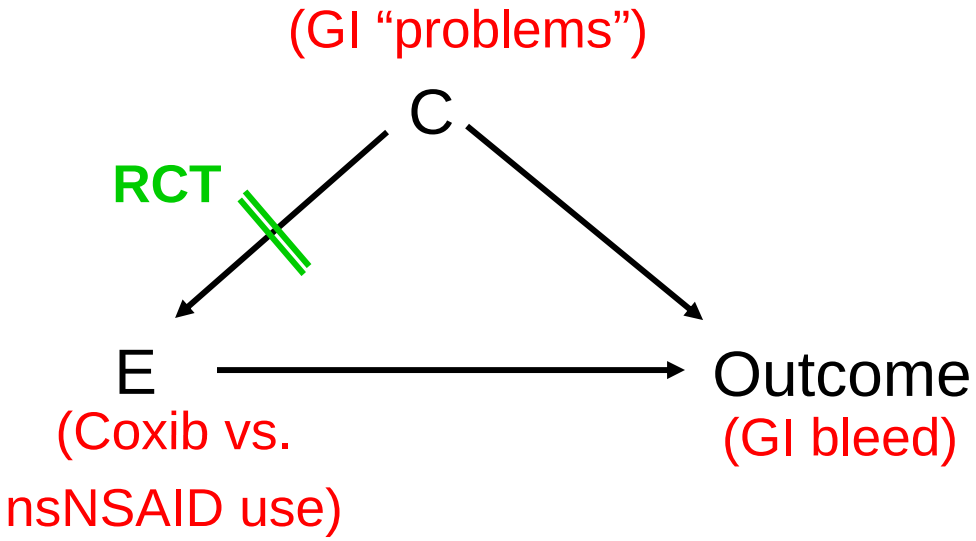
Combining data sources

- Many intended drug effects will not be assessed in claims data in the necessary detail
  - Depression scales
  - Functional improvement
  - [Intention is reduction of adverse disease outcomes]
- Combine claims data as the data backbone with
  - Electronic medical records
  - Prospective registry studies

Confounding

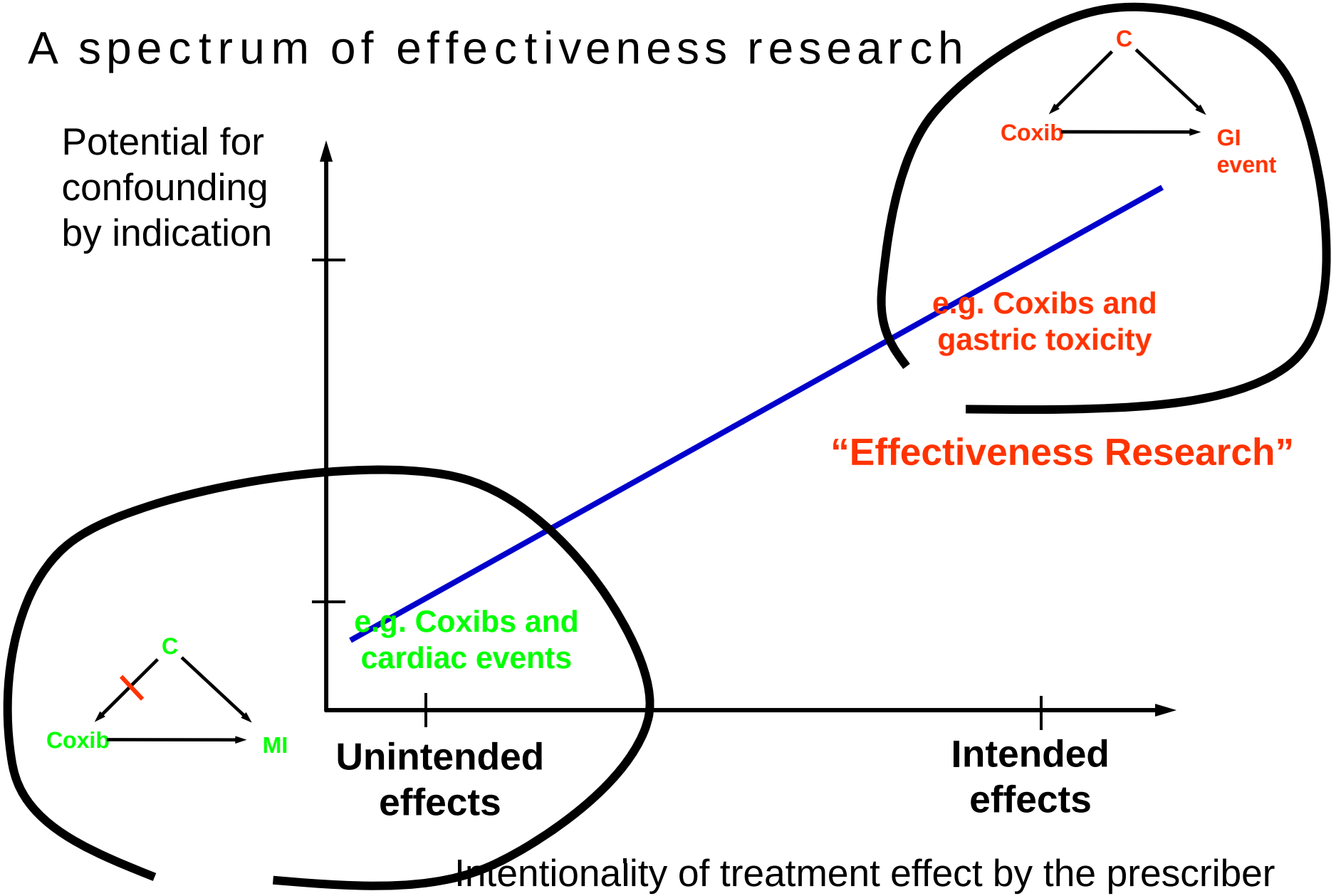
For confounding to occur:

1. C must be more frequent in E than in non-E (imbalance of confounder C between exposure groups) and
2. C must be a close correlate or cause of D, independent of exposure

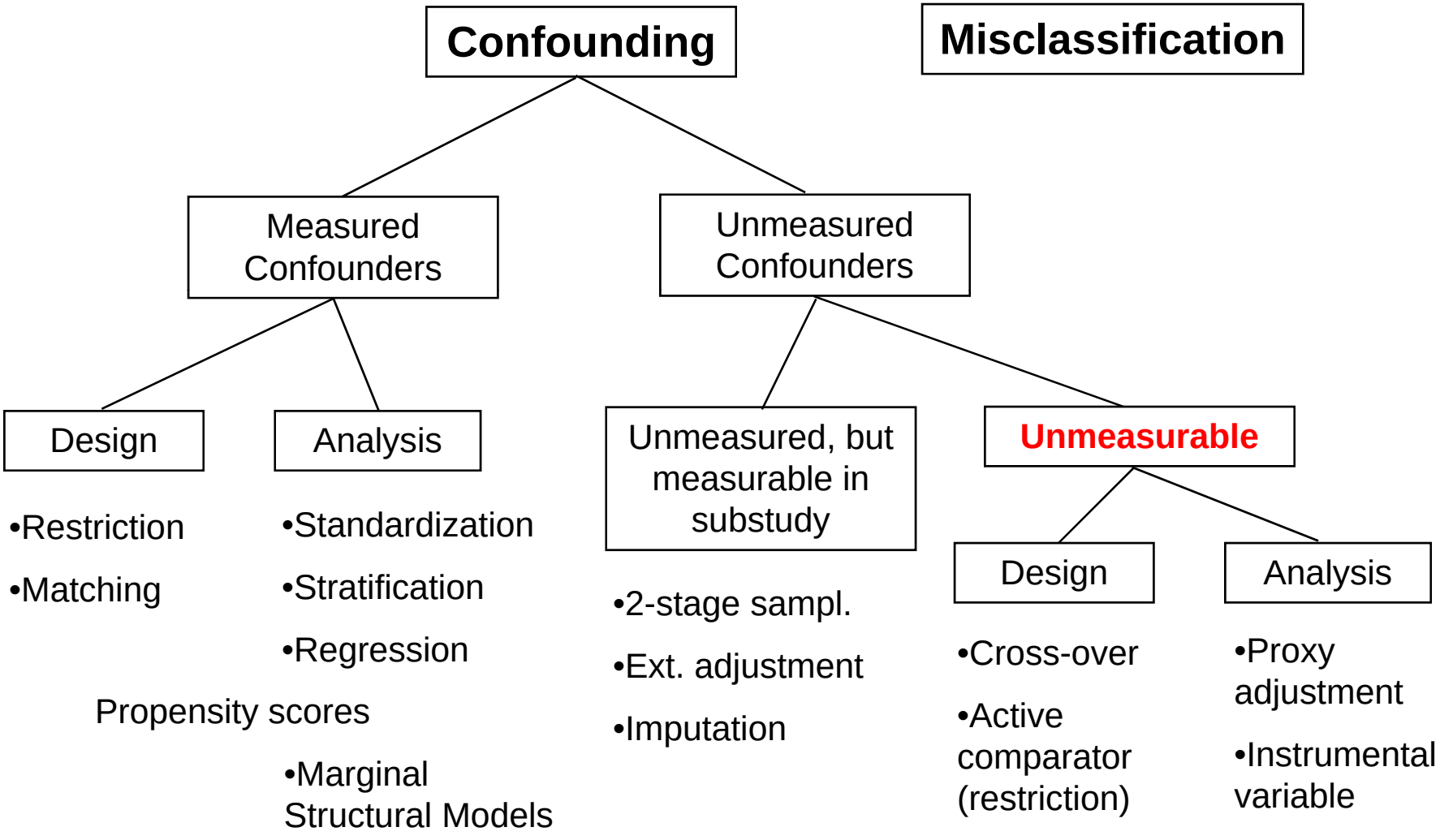


If EITHER association C->E or C->O is null then there is NO confounding!

A spectrum of effectiveness research



Frontier: Making better use of our data



Causal experiment (All the same but exposure)

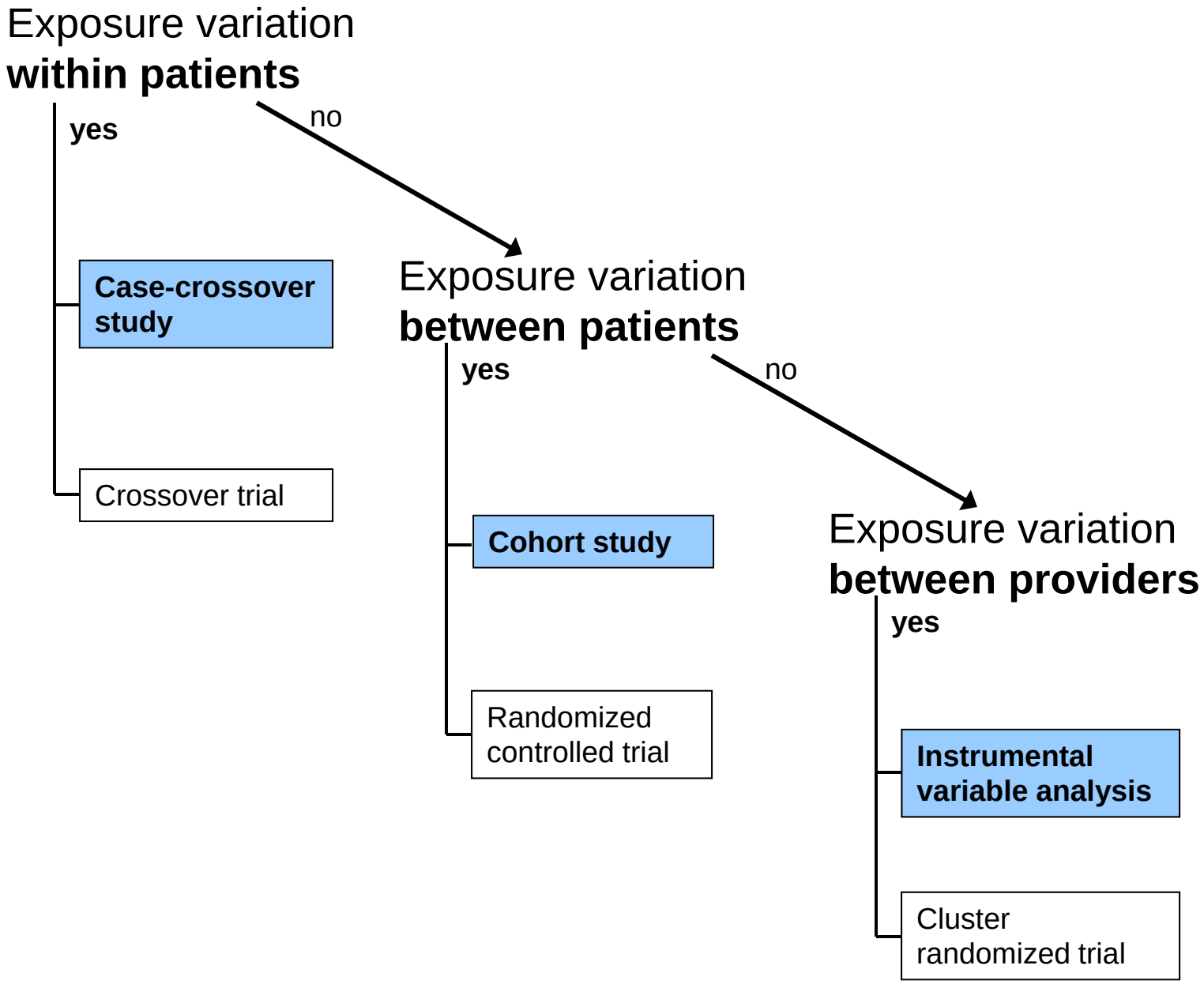
Patient A: Drug → Improvement

Rewind time

Patient A: No Drug → No improvement

Watterson B. The Authoritative Calvin and Hobbes, p67-2

Design choice by source of exposure variation

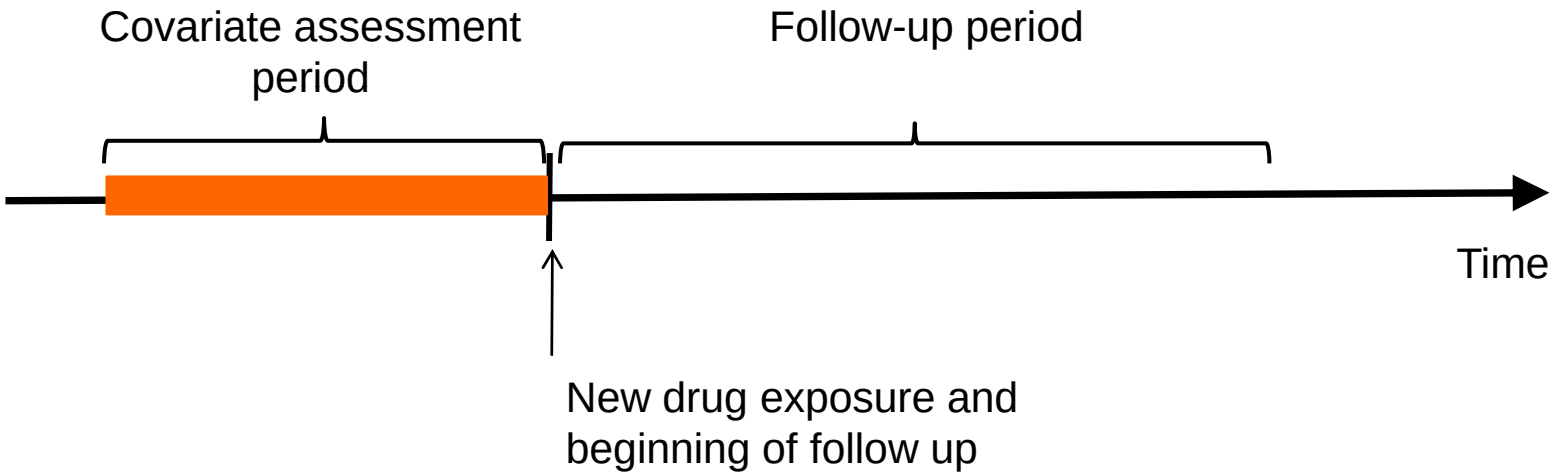


Case-crossover studies

- Why is the CCO design not more frequently used in PE?
  - Requires rapid onset outcomes
  - Requires time-varying exposure (treatment x-over)
  - Requires transient drug effects -> how well can we measure treatment discontinuation in our data?
  - Is subject to within-person (between-time) confounding:

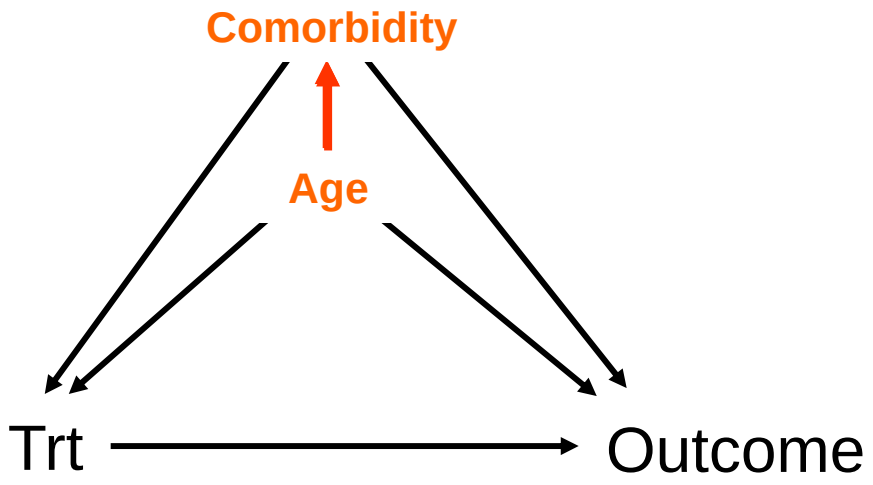
    Decreasing health status may correlate with increasing drug use
  - Can be expanded to the case-time-control design

Incident user cohort study design with active comparison



The power of proxies

Measured confounders (C) may serve as redundant proxies for unmeasured confounders (U):



The more proxies the better…

Propensity score analyses

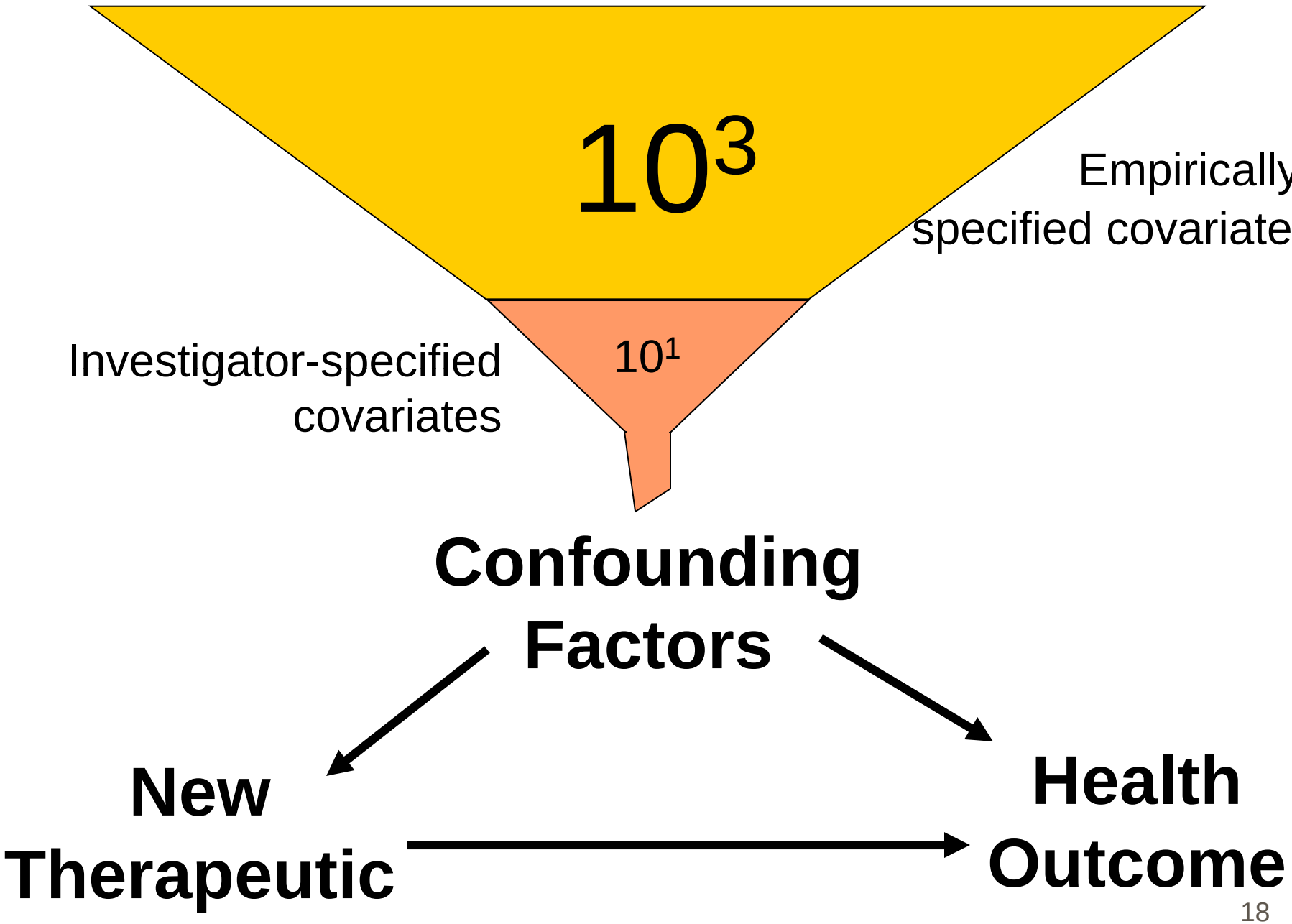
- Goal: To identify patients with the identical likelihood of receiving treatment but some will actually receive treatment others will not.
- Estimation:
  - Step 1: Estimate the propensity for treatment as a function of observed covariates:
    - mimic the prescribers decision process for treatment
    - if exposure is prevalent then little limitations to modeling
    - Predicted value is each patient's "propensity score"
  - Step 2: Use the estimated propensity score to adjust treatment model:
    - quintiles, deciles of propensity score, trimming, matching etc.
- Advantage: adjustment for MANY covariates even if outcomes are rare.

Limited clinical information in admin databases

---------- ID********** dob=**/**/1948 sex=M eligdt=1/2000 indexdt=6/2001 ----------

Service Date	Site of Service	Prov Type	Drug or Procedure Code	Drug or Procedure Description		Diagnosis * Code	Diagnosis Description
10/01/00	OFFICE	Family Practice	90658	INFLUENZA VIRUS VACC/SPLIT		V048	VACC FOR INFLUEN
10/01/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
11/05/00	OFFICE	Family Practice	17110	DESTRUCT OF FLAT WARTS, UP		0781	VIRAL WARTS
11/07/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
01/15/01	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
06/25/01	**OFFICE**	**Emerg Clinic**	**99070**	**SPECIAL SUPPLIES**	*	**84509**	**SPRAIN OF ANKLE**
						E927	**ACC OVEREXERTION**
06/30/01	**OFFICE**	**Orthopedist**	**99204**	**OV,NEW PT.,DETAILED H&P,LOW**	*	**72767**	**RUPT ACHILL TEND**
06/30/01	OFFICE	Internist/Gener	99202	OV,NEW PT.,EXPD.PROB-FOCSD	*	84509	SPRAIN OF ANKLE
	OUTPT HP	Anesthesiologis	01472	REPAIR OF RUPTURED ACHILLES	*	84509	SPRAIN OF ANKLE
		Hospital	27650	REPAIR ACHILLES TENDON	*	84509	SPRAIN OF ANKLE
			85018	BLOOD COUNT; HEMOGLOBIN	*	84509	SPRAIN OF ANKLE
		Orthopedist	27650	REPAIR ACHILLES TENDON	*	84509	SPRAIN OF ANKLE
06/30/01	OFFICE	Orthopedist	29405	APPLY SHORT LEG CAST	*	72767	RUPT ACHILL TEND
07/30/01	OFFICE	Orthopedist	29405	APPLY SHORT LEG CAST	*	72767	RUPT ACHILL TEND
08/13/01	OFFICE	Orthopedist	L2116	AFO TIBIAL FRACTURE RIGID	*	72767	RUPT ACHILL TEND

Can we make better use of this information ?


10^3
Empirically-specified covariates
10^1
Investigator-specified covariates
Confounding Factors
New Therapeutic
Health Outcome

High-dimensional proxy adjustment

el	Covariates Included in Propensity Score Model	No. Covariates Adjusted	Variables Tested per Data Source	Data Source Granularity	Covariate Prioritization Algorithm	c-Statistic of PS Model	Outcome Model RR (95% CI)
	Unadjusted					-	1.09 (0.91–1.30)
	Age, sex, race, year[a]	$d = 4$				0.61	1.01 (0.84–1.21)
	+ predefined covariates (Table 1)	$d = 4$; $l = 14$				0.66	0.94 (0.78–1.12)
	+ empirical covariates	$d = 4$; $l = 14$; $k = 200$	$n = 200$	3-digit ICD	$\text{Bias}_{\text{mult}}$	0.69	0.86 (0.72–1.04)
	+ empirical covariates	$d = 4$; $l = 14$; $k = 500$	$n = 200$	3-digit ICD	$\text{Bias}_{\text{mult}}$	0.71	0.88 (0.73–1.06)
	Only demographics + empirical covariates	$d = 4$; $k = 500$	$n = 200$	3-digit ICD	$\text{Bias}_{\text{mult}}$	0.71	0.87 (0.72–1.05)

Epidemiology 2009

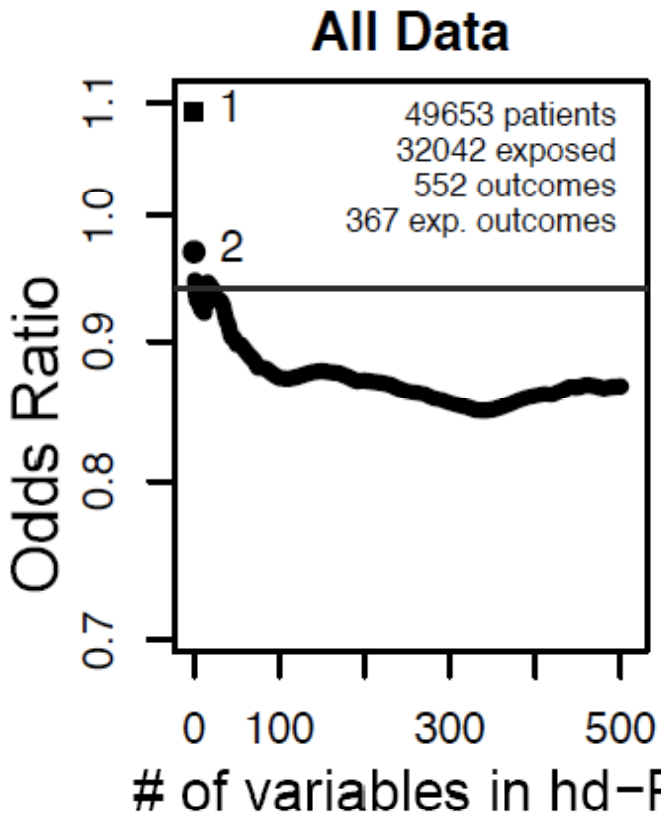
Small sample performance

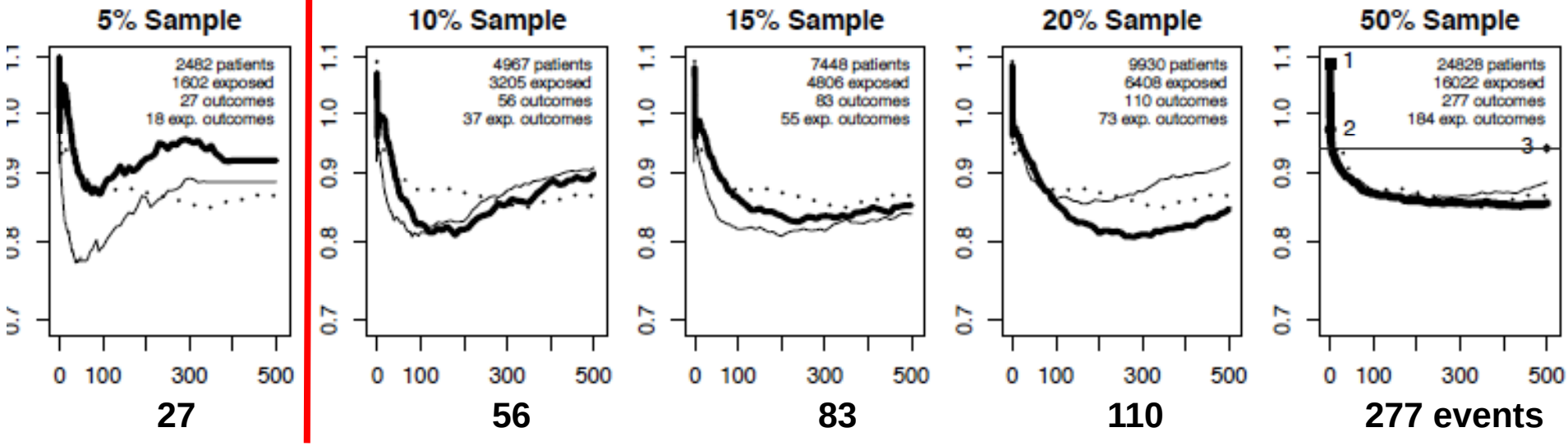
Example:

Coxibs vs. nsNSAIDs and GI complications in 180 days

Confounder prioritization now with 0-cell correction (+0.1)

hd-PS_2, SAS 9.2 or higher, substantially improved speed 20mins -> 2mins





Cardiovascular Outcomes and Mortality in Patients Using Clopidogrel With Proton Pump Inhibitors After Percutaneous Coronary Intervention or Acute Coronary Syndrome

Jeremy A. Rassen, ScD; Niteesh K. Choudhry, MD, PhD;
Jerry Avorn, MD; Sebastian Schneeweiss, MD, ScD

(*Circulation*. 2009;120:2322-2329.)

Outcome	Within-center analyses			
	British Columbia (*n* = 19 979)	Pennsylvania (*n* = 4176)	New Jersey (*n* = 3998)	Horizon (*n* = 3451)
Myocardial infarction hospitalization				
Cumulative risk analysis (odds ratios)				
Number of events (risk) among PPI users	135 (6.2%)	48 (3.6%)	41 (3.2%)	21 (2.6%)
Number of events (risk) among non-users	669 (3.8%)	85 (3.0%)	64 (2.4%)	46 (1.7%)
1 Crude	1.87 [1.49, 2.35]	2.03 [1.16, 3.56]	1.32 [0.74, 2.36]	1.21 [0.62, 2.33]
2 Adjusted by shareable variables	1.66 [1.32, 2.09]	2.12 [1.21, 3.71]	1.25 [0.70, 2.22]	1.18 [0.61, 2.27]
3 Adjusted by shareable and private variables	1.34 [1.06, 1.71]	1.99 [1.11, 3.56]	1.19 [0.65, 2.17]	0.75 [0.37, 1.54]
4 Adjusted by decile of universal PS	1.35 [1.07, 1.71]	2.11 [1.16, 3.81]	1.22 [0.67, 2.21]	0.88 [0.45, 1.72]
5 Adjusted by decile of hd-PS	1.28 [1.00, 1.63]	1.95 [1.03, 3.70]	1.05 [0.56, 1.98]	0.78 [0.38, 1.59]

AQ: A

Comparative Safety of Antidepressant Agents for Children and Adolescents Regarding ~~Suicide Attempts and Suicides~~ Suicidal Acts

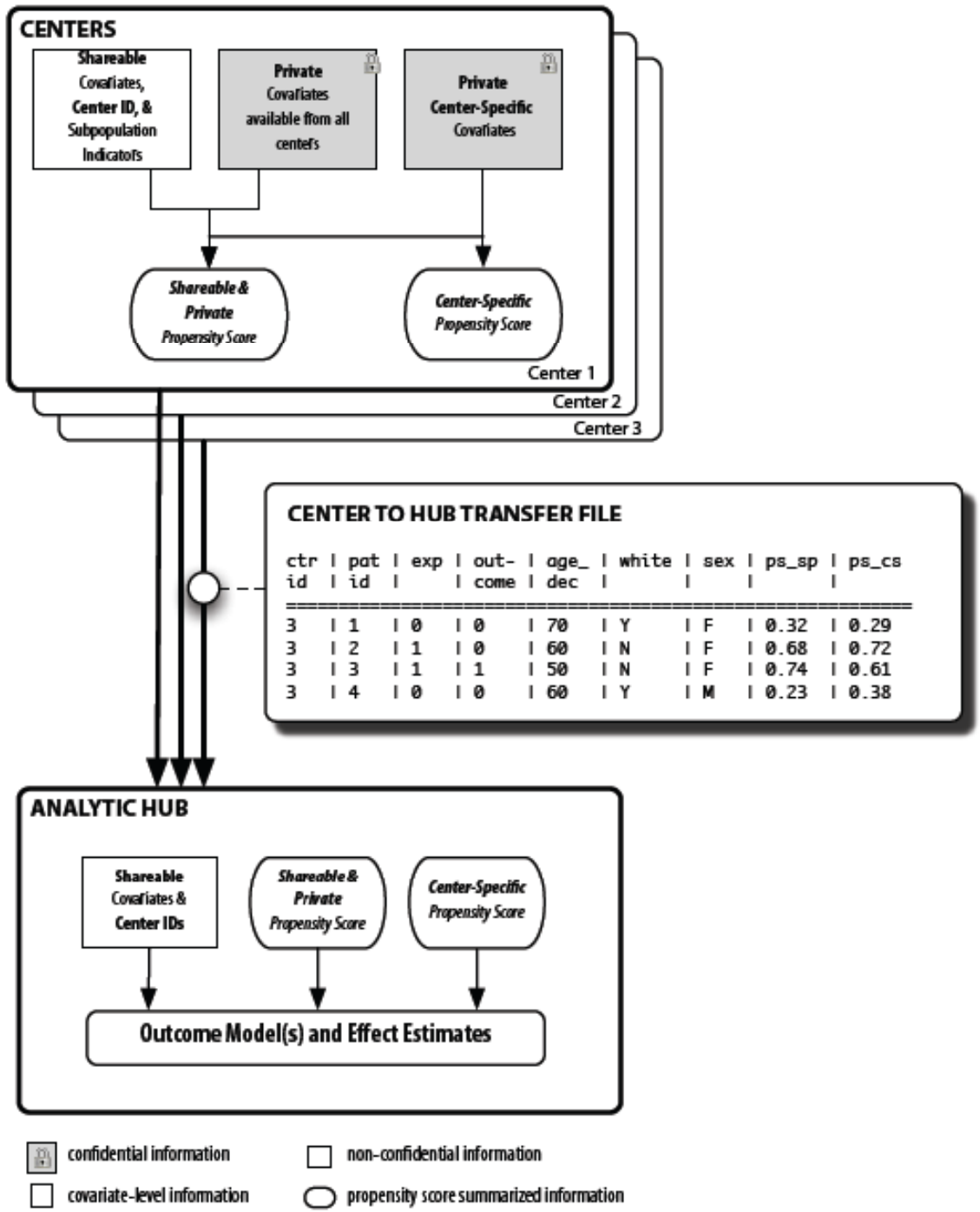
AUTHORS: Sebastian Schneeweiss, MD, ScD,[a] Amanda R. Patrick, MS,[a] Daniel H. Solomon, MD, MPH,[a] Colin R. Dormuth, MA, MS, ScD,[b] Matt Miller, MD, ScD,[c] Jyotsna Mehta, MS,[a] Jennifer C. Lee, BS,[a] and Philip S. Wang, MD, DrPH[a,d]

Pediatrics 2010;125:e000

TABLE 3 Event RRs for Suicidal Acts and Violent Suicidal Acts During 1-Year Follow-up Period

	RR (95% CI)			
	Suicidal Acts			
	Unadjusted	Adjusted for Age, Gender, and Calendar Year	Adjusted for Propensity Score Decile[a]	Adjusted for High-Dimensional Propensity Score Decile[b]
Children and adolescents with no antidepressant use in past 3 y				
Tricyclic drugs	0.59 (0.28–1.27)	0.66 (0.31–1.42)	0.71 (0.33–1.52)	0.92 (0.43–2.00)

Frontier: Secure pooling



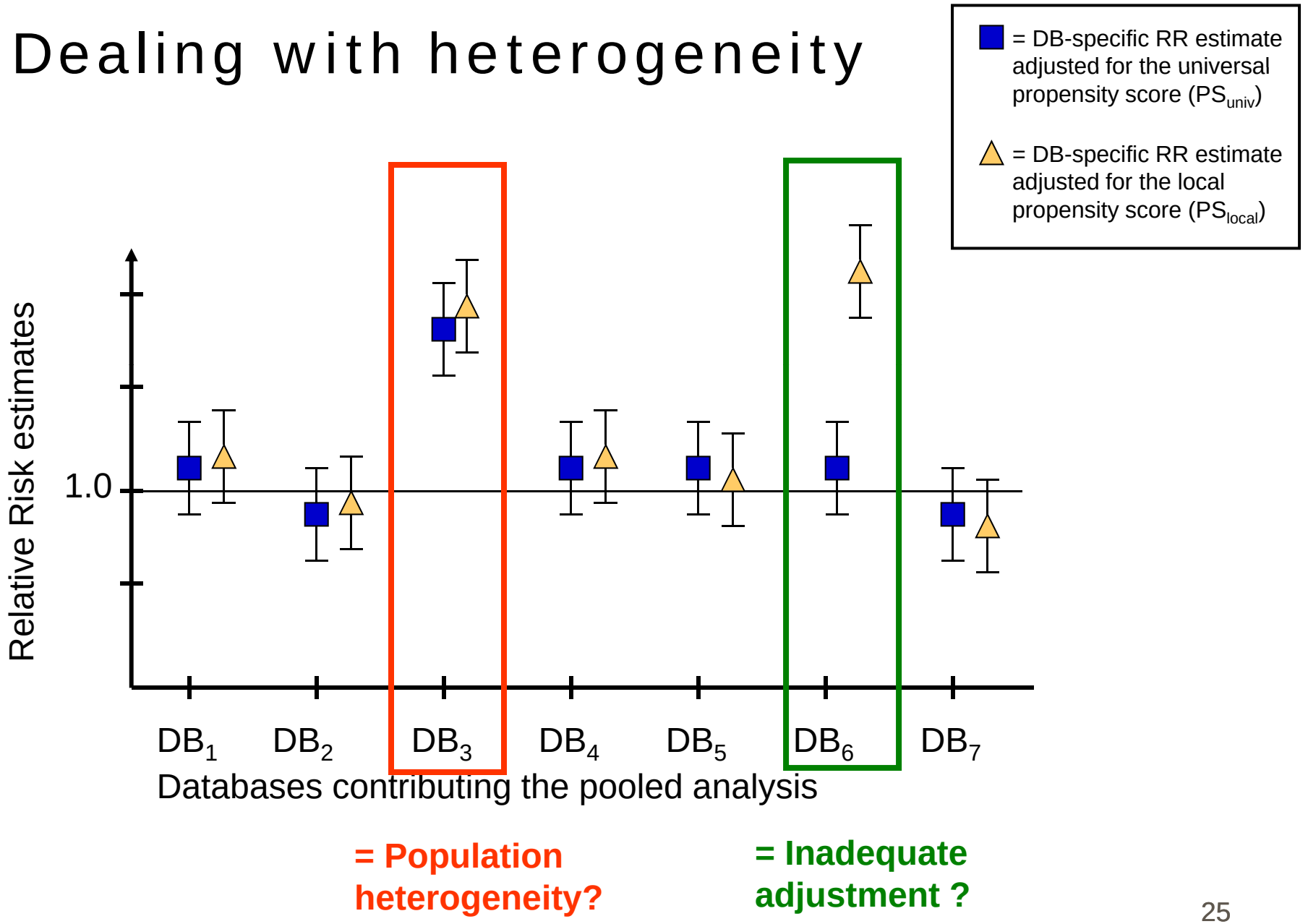
Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple health care utilization databases†

Jeremy A. Rassen ScD*, Jerry Avorn MD and Sebastian Schneeweiss MD, ScD

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2010)

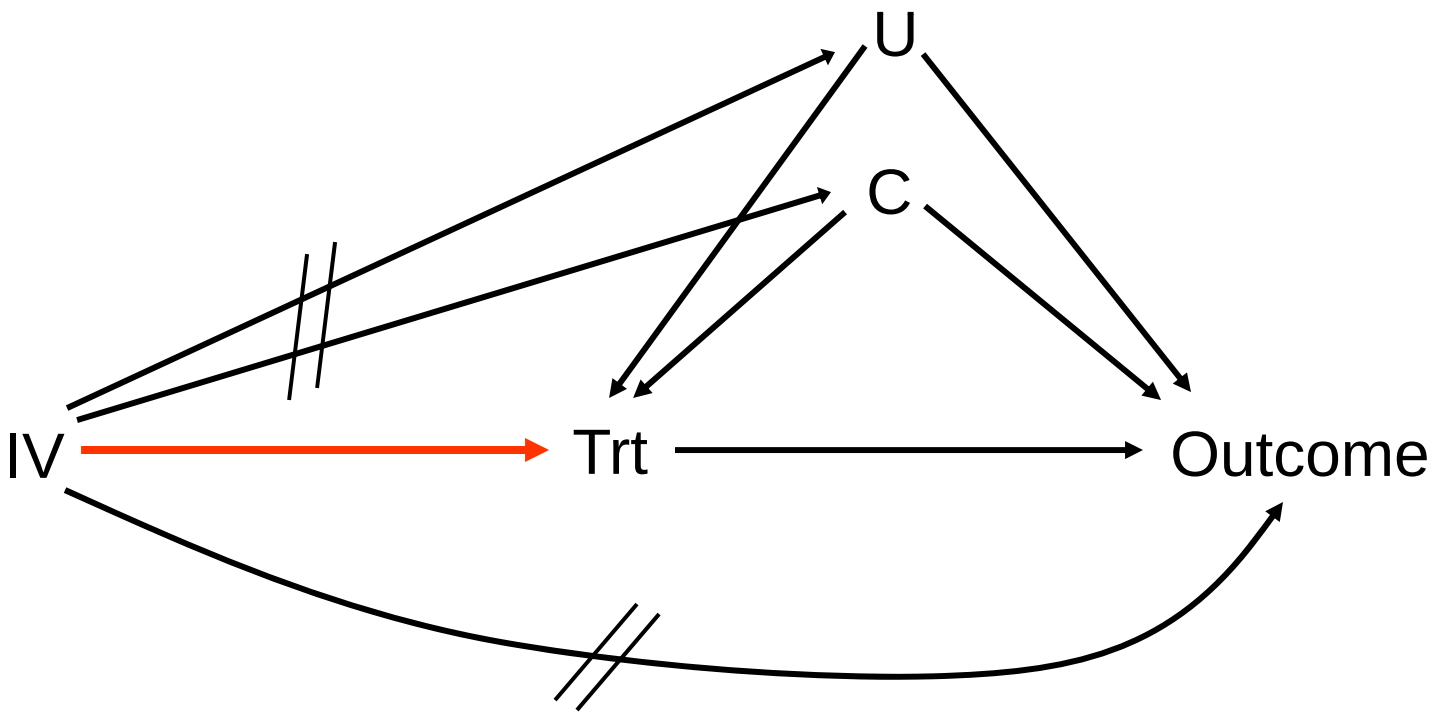
Outcome	Within-center analyses				
	British Columbia† (*n* = 19 979)	Pennsylvania (*n* = 4176)	New Jersey (*n* = 3998)	Horizon (*n* = 3451)	Pooled‡ (*n* = 31 604)
Myocardial infarction hospitalization					
Cumulative risk analysis (odds ratios)					
Number of events (risk) among PPI users	135 (6.2%)	48 (3.6%)	41 (3.2%)	21 (2.6%)	245 (4.3%)
Number of events (risk) among non-users	669 (3.8%)	85 (3.0%)	64 (2.4%)	46 (1.7%)	864 (3.3%)
1 Crude	1.87 [1.49, 2.35]	2.03 [1.16, 3.56]	1.32 [0.74, 2.36]	1.21 [0.62, 2.33]	1.74 [1.44, 2.11]
2 Adjusted by shareable variables	1.66 [1.32, 2.09]	2.12 [1.21, 3.71]	1.25 [0.70, 2.22]	1.18 [0.61, 2.27]	1.60 [1.32, 1.94]
3 Adjusted by shareable and private variables	1.34 [1.06, 1.71]	1.99 [1.11, 3.56]	1.19 [0.65, 2.17]	0.75 [0.37, 1.54]	1.34 [1.10, 1.63]
4 Adjusted by decile of universal PS	1.35 [1.07, 1.71]	2.11 [1.16, 3.81]	1.22 [0.67, 2.21]	0.88 [0.45, 1.72]	1.32 [1.09, 1.61]
5 Adjusted by decile of hd-PS	1.28 [1.00, 1.63]	1.95 [1.03, 3.70]	1.05 [0.56, 1.98]	0.78 [0.38, 1.59]	1.22 [0.99, 1.50]

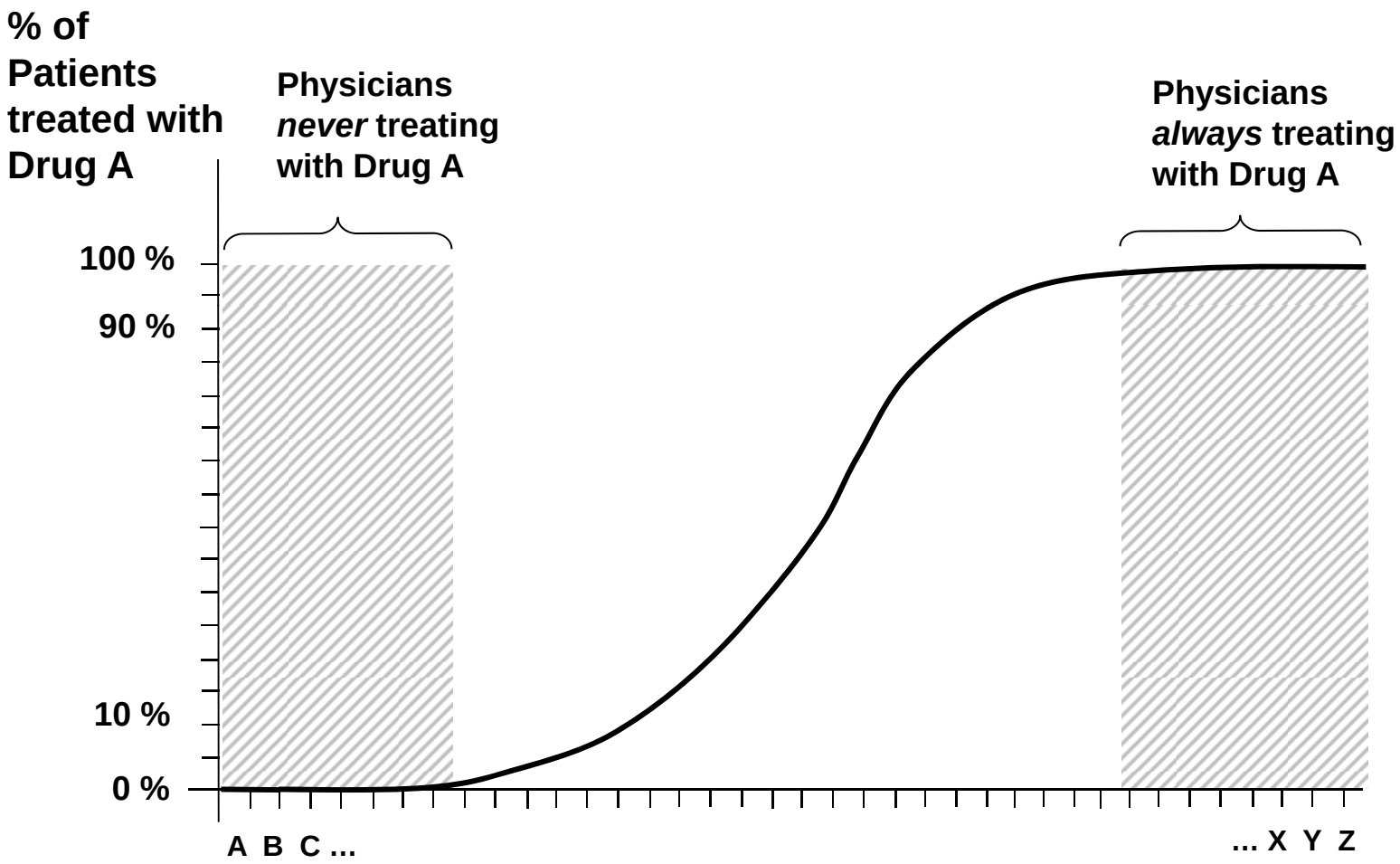
Dealing with heterogeneity



Instrumental variable analyses

An instrumental variable (IV) is an unconfounded substitute for the actual treatment (Trt):





Brookhart et al. Epidemiol 2006

Table 1: Selected examples of instrumental variable analyses in healthcare

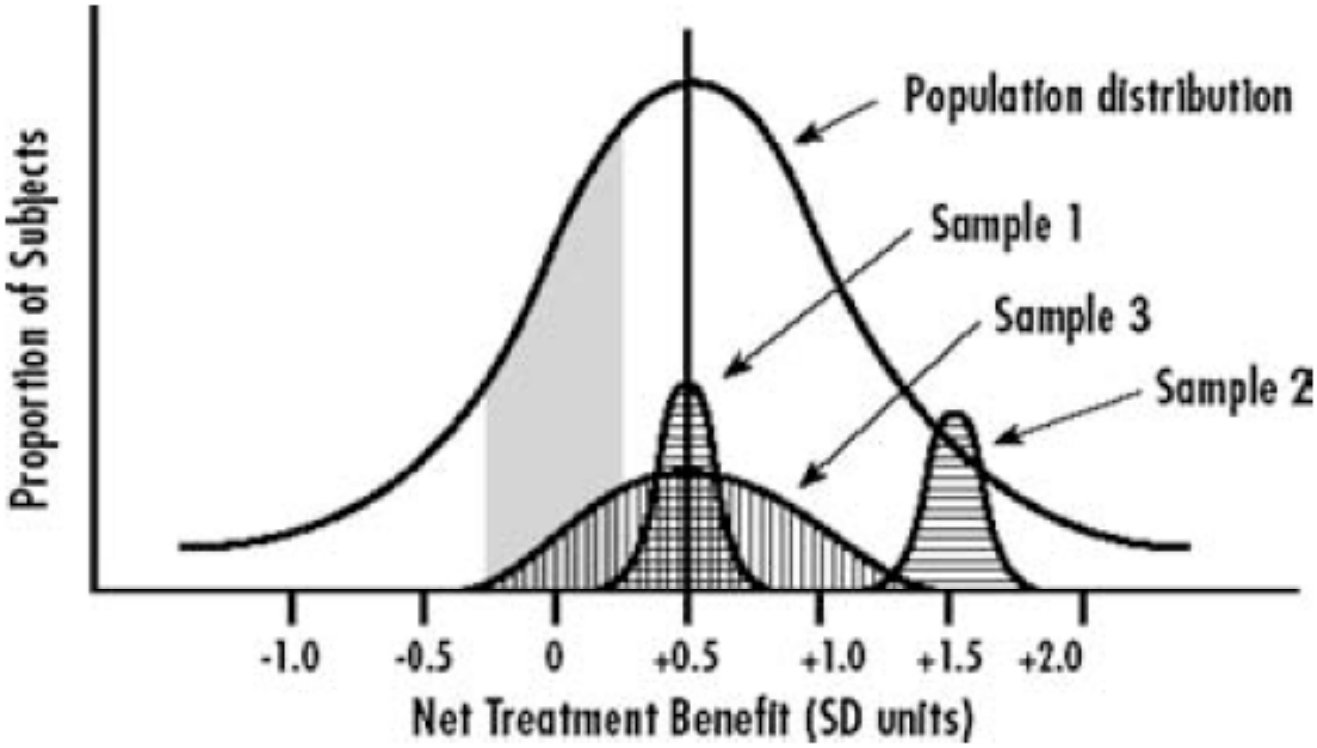
Instrument group	Instrument type	Examples
Sudden changes in treatment preference over time	Regulatory or coverage interventions	*Mamdani et al.:* Triampteren use in pats w/ HTN before and after the RALES trial
	Innovations and rapid adoption	*Johnston et al.:* BB use after HF hospitalization before and after 1998 Bare metal stent vs. drug eluting stent
Provider treatment preference	Distance to specialist provider	*McClellan et al.:* Distance to cardiac cath lab facility in pats w/ acute MI
	Physician prescribing preference (PPP)	*Brookhart et al.:* Physician's treatment initiation choice to the preceding patient
	Regional treatment preference	*Stukel et al.:* Variation if cardiac cath rates in 530 US regions in pats w/ MI
	Hospital formulary/ surgeon treatment preference	*Schneeweiss et al.:* Cardiac surgeons who always use aprotinin as antifibrinolytic agent
	Medication co-payment level	*Cole et al.:* Medication copayment level in pats with CHF and adherence
	Dialysis center preference	*Thamer et al.:* Epo dosing by non-profit vs. for-profit dialysis centers
Genetic variation	"Mendelian randomization"	*Davey-Smith et al.:* aldehyde dehydrogenase polymorphism

Instrumental Variable Analysis:
In search for unconfounded surrogates of treatment choice

Table 5: Risk differences for GI complications and acute MI during 60, 120, and 180 days after the start of selective COX2 inhibitor therapy compared with all non-selective NSAIDs.

	Conventional Multivariate Adjusted Analysis (OLS)†		Instrumental Variable Adjusted Analysis (IV)†	
	Risk Difference of GI complication (95% CI) ‡	Risk Difference of Acute MI (95% CI)	Risk Difference of GI complication (95% CI)	Risk Difference of Acute MI (95% CI)
Celecoxib				
60 days	-0.13 (-0.30;0.03)	0.15 (0.00; 0.29)	-1.07 (-2.07; -0.07)*	-0.10 (-0.94; 0.73)
120 days	-0.18 (-0.40; 0.04)	0.33 (0.14; 0.52)	-1.63 (-2.91; -0.35)*	-0.22 (-1.32; 0.88)
180 days	-0.18 (-0.43; 0.07)	0.34 (0.10; 0.57)	-1.42 (-2.89; 0.04)**	-0.68 (-2.01; 0.64)
Rofecoxib				
60 days	0.10 (-0.11; 0.30)	0.15 (-0.01; 0.31)	-1.12 (-2.15; -0.10)*	-0.27 (-1.17; 0.62)
120 days	0.07 (-0.20; 0.33)	0.32 (0.09; 0.54)	-1.12 (-2.52; 0.28)**	0.40 (-0.86; 1.66)
180 days	0.11 (-0.19; 0.41)	0.30 (0.03; 0.58)	-1.13 (-2.71; 0.45)	0.71 (-0.80; 2.23)

Frontier:
Treatment effect heterogeneity

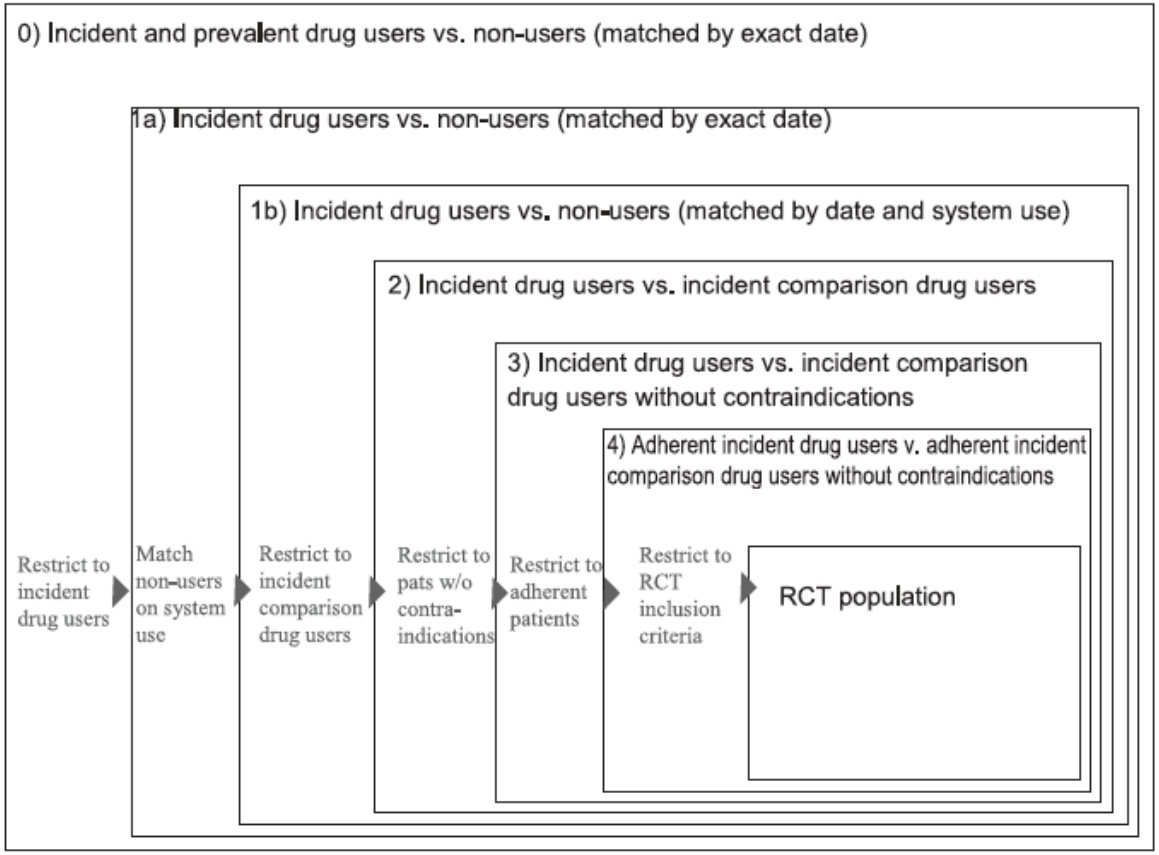


Kravitz Milbank 2004

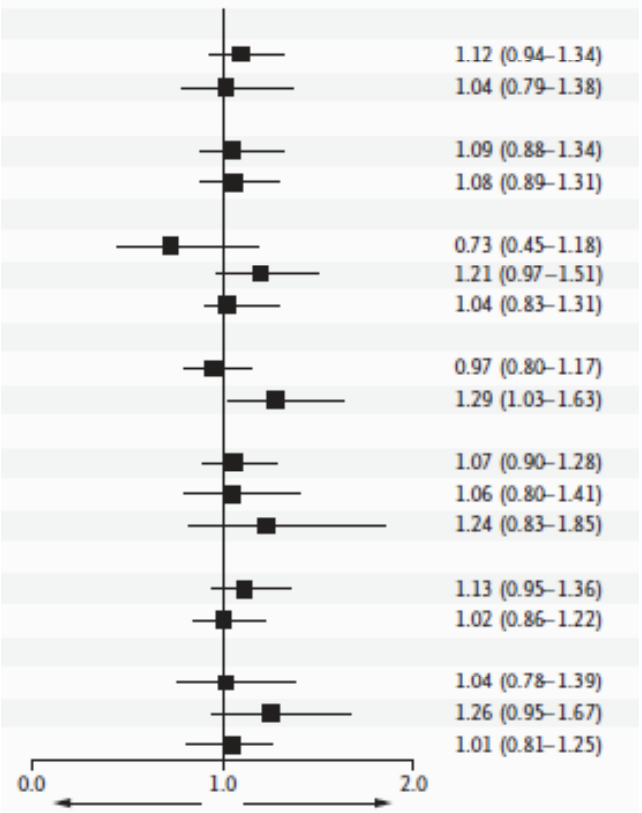
Treatment effect heterogeneity

- Let’s not limit ourselves to average treatment effects
- Large population-based DBs provide the opportunity to study / explore many subgroups

Calibration by mimicking RCT pops



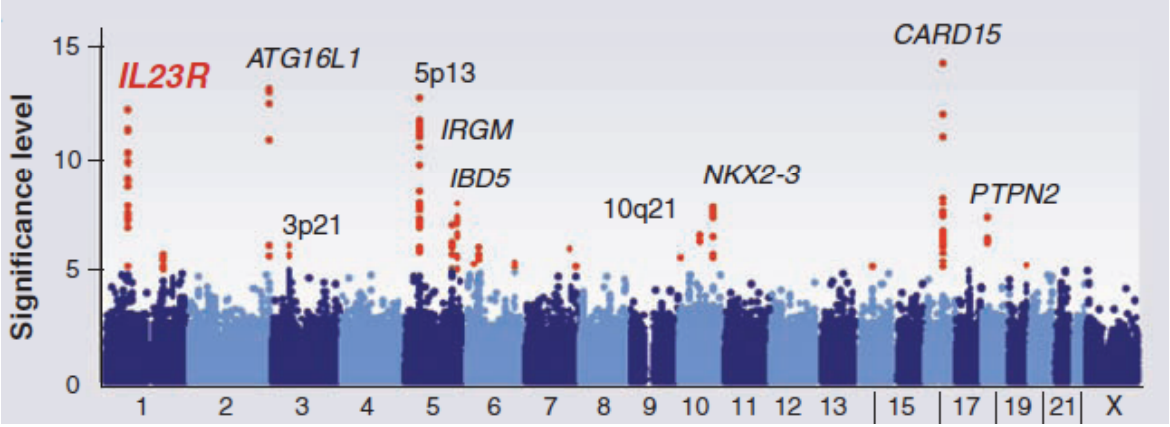
Exploration of heterogeneity



Med Care 2007

... and more Exploration

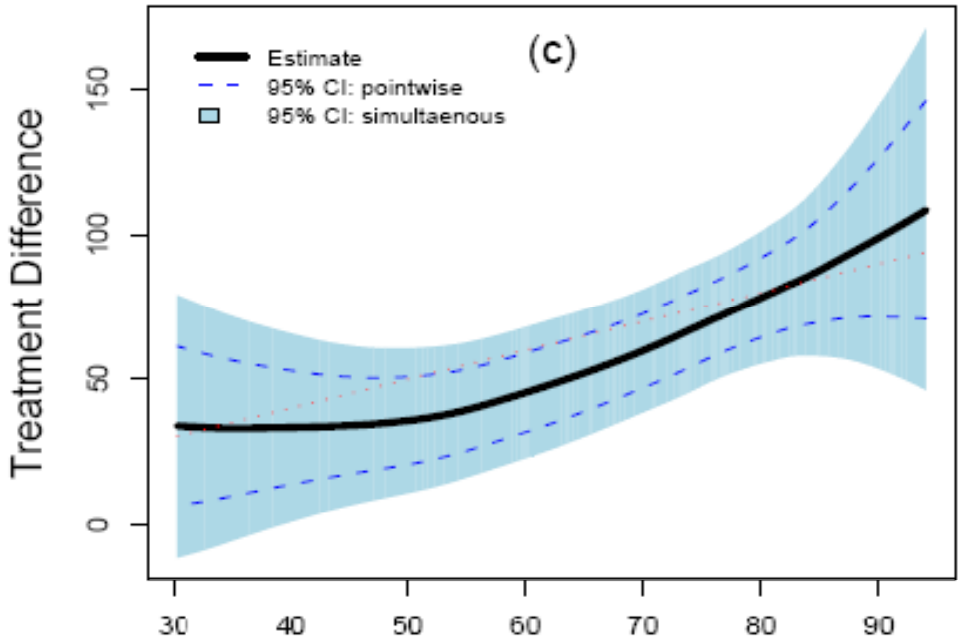
1st screening



Hundreds of patient factors

Clustering of factors

Outcome risk score



Cai 2009 pers. commun

Outcome risk **score** at baseline

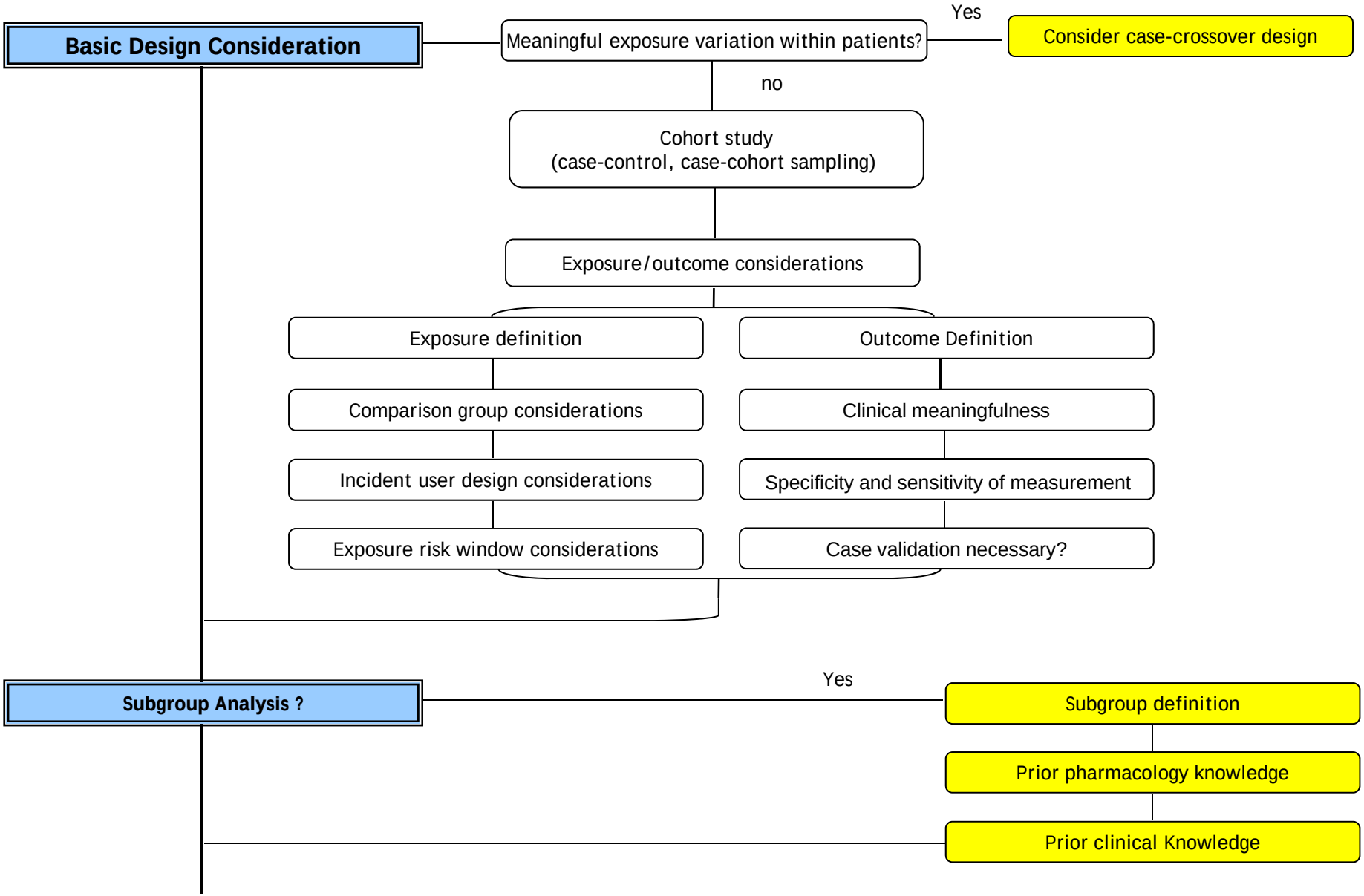
Frontier:
Communicating Benefits and Risks

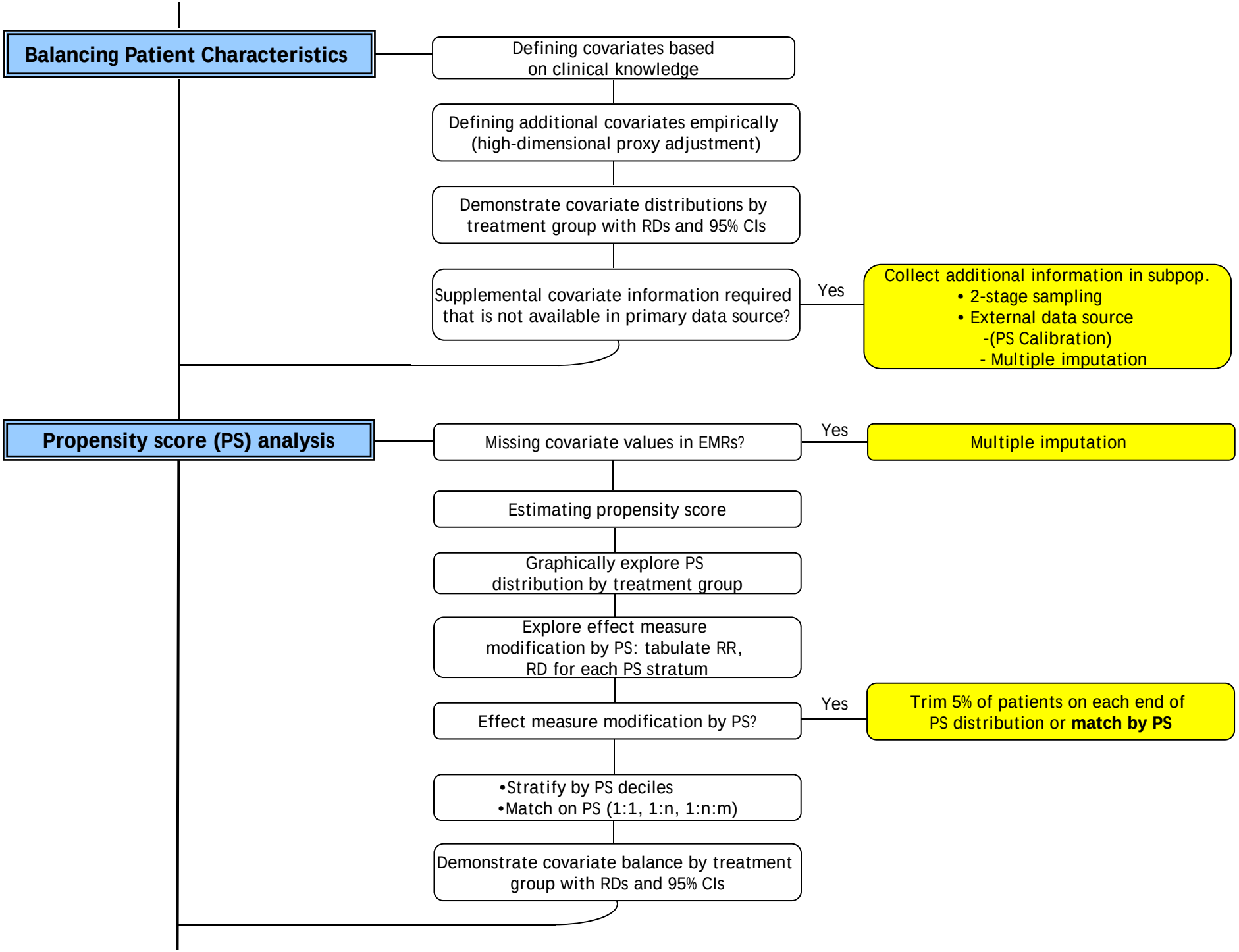
	Instrumental variable adjusted analysis†	
	GI complications, RD per 100 (95% CI)	Acute MI, RD per 100 (95% CI)
Celecoxib	0.00 (reference)	0.00 (reference)
Rofecoxib	0.30 (−1.28, 1.89)	1.40 (−0.20, 3.01)‡
Diclofenac	5.09 (−1.18, 11.36)‡	6.07 (−0.02, 12.15)§
Ibuprofen	0.88 (−1.93, 3.68)	−0.01 (−2.49, 2.46)
Naproxen	0.74 (−2.04, 3.52)	−0.30 (−2.74, 2.14)

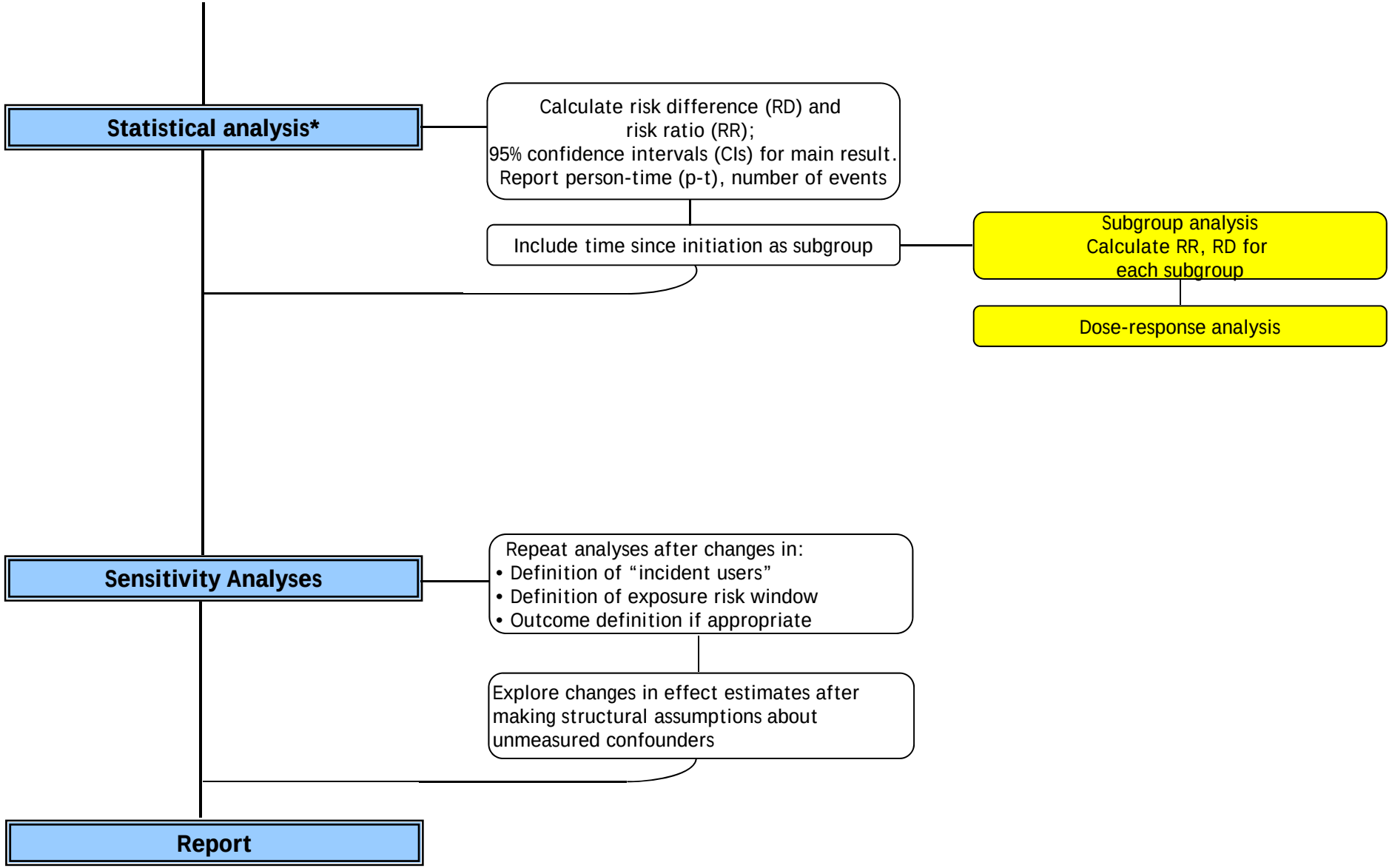
A&R 2006

Frontier: Investigator error

Reviewer oversight


Basic Design Consideration
Meaningful exposure variation within patients?
Yes
Consider case-crossover design
no
Cohort study
(case-control, case-cohort sampling)
Exposure/outcome considerations
Exposure definition
Comparison group considerations
Incident user design considerations
Exposure risk window considerations
Outcome Definition
Clinical meaningfulness
Specificity and sensitivity of measurement
Case validation necessary?
Subgroup Analysis ?
Yes
Subgroup definition
Prior pharmacology knowledge
Prior clinical Knowledge

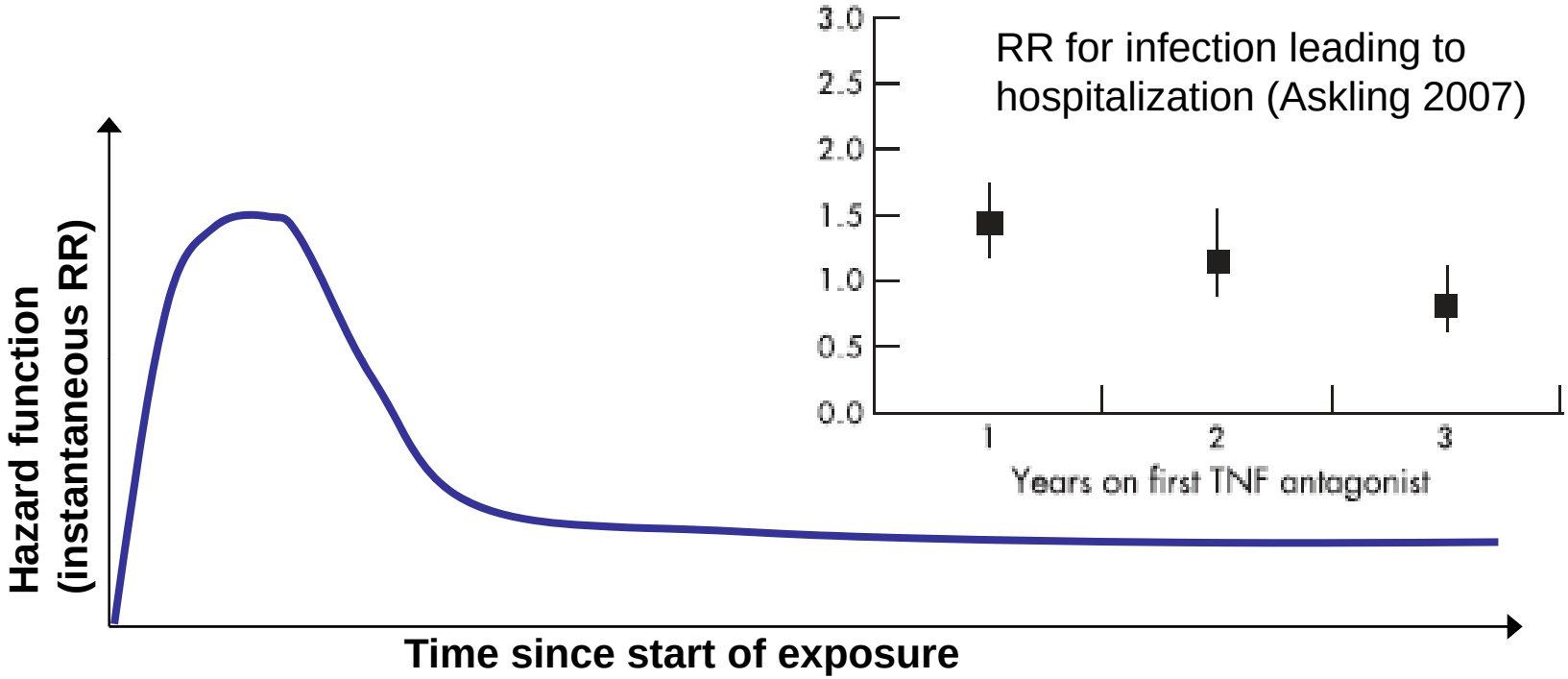

Balancing Patient Characteristics
Defining covariates based on clinical knowledge
Defining additional covariates empirically (high-dimensional proxy adjustment)
Demonstrate covariate distributions by treatment group with RDs and 95% CIs
Supplemental covariate information required that is not available in primary data source?
Yes
Collect additional information in subpop.
• 2-stage sampling
• External data source
-(PS Calibration)
- Multiple imputation
Propensity score (PS) analysis
Missing covariate values in EMRs?
Yes
Multiple imputation
Estimating propensity score
Graphically explore PS distribution by treatment group
Explore effect measure modification by PS: tabulate RR, RD for each PS stratum
Effect measure modification by PS?
Yes
Trim 5% of patients on each end of PS distribution or match by PS
•Stratify by PS deciles
•Match on PS (1:1, 1:n, 1:n:m)
Demonstrate covariate balance by treatment group with RDs and 95% CIs



*For illustration purposes only an analysis after PS matching is shown.

There are not only frontiers: Don’t forget the basics

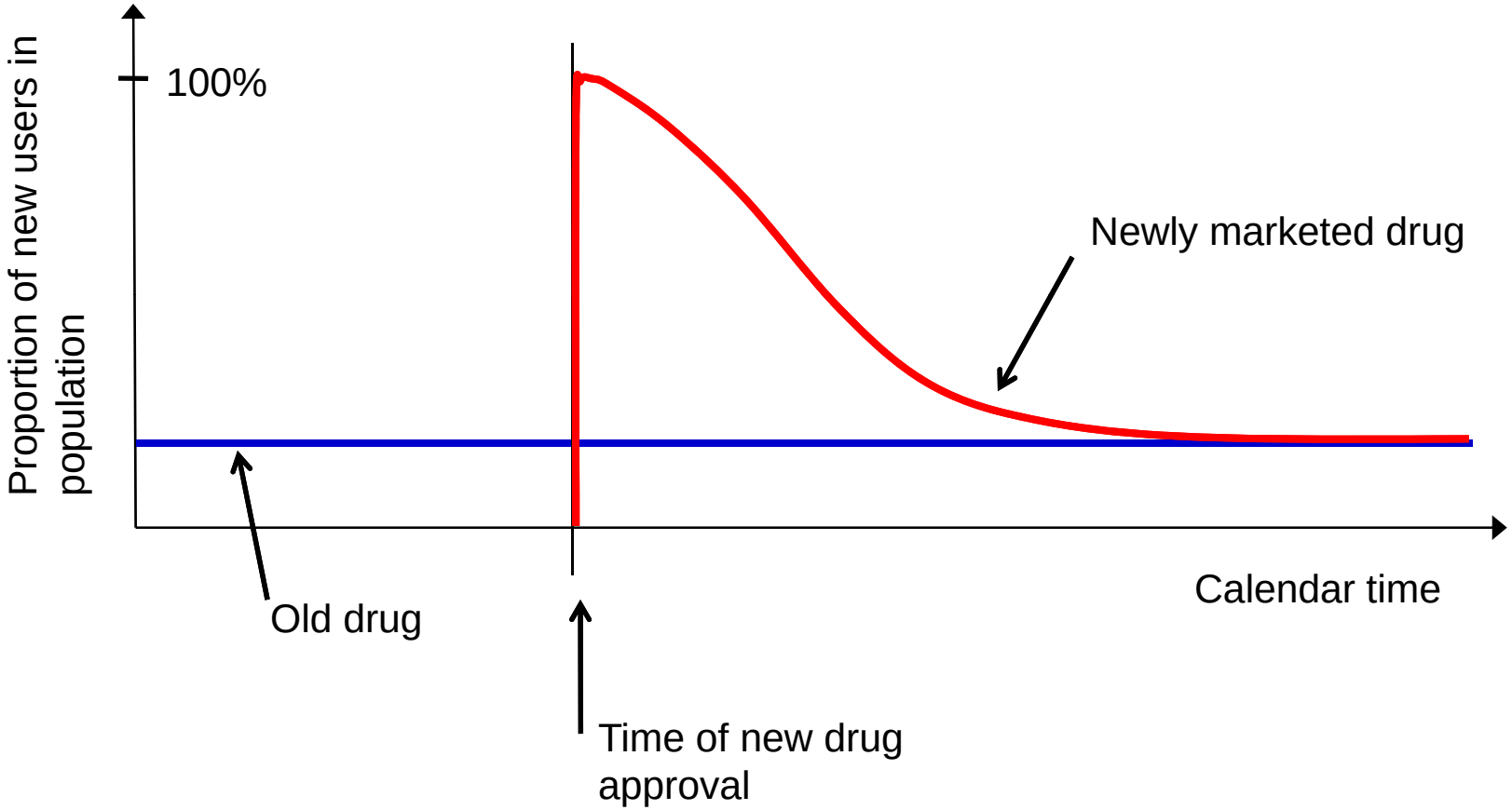
Incident User Design



- Can better assess time-varying hazard functions
- Can better study adverse effects shortly after treatment start

Ray AJE 2004

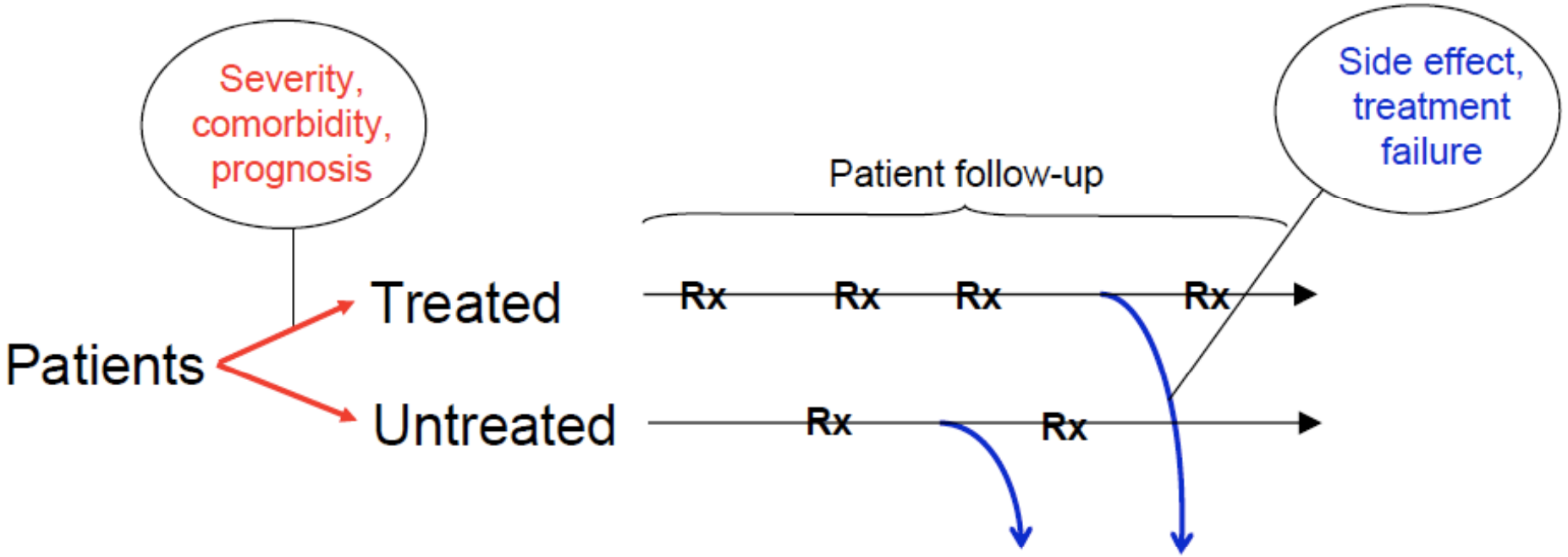
New drug on the block



PS matching and Incident user design

- Propensity score analysis and incident user design go hand in hand
- Exposure assessment before start of follow-up
  -> no immortal person time bias
- Covariate assessment before start of follow-up
  -> no adjustment for intermediates

The hic-ups of long-term follow-up



Observations

- Confounding control techniques are improving but doubts will remain
- Need to provide the relevant metrics for benefit-risk assessment
- Need better approaches for assessing and exploring treatment effect heterogeneity
- Produce diagnostics and sensitivity analyses to improve the ability to review findings

Concerns

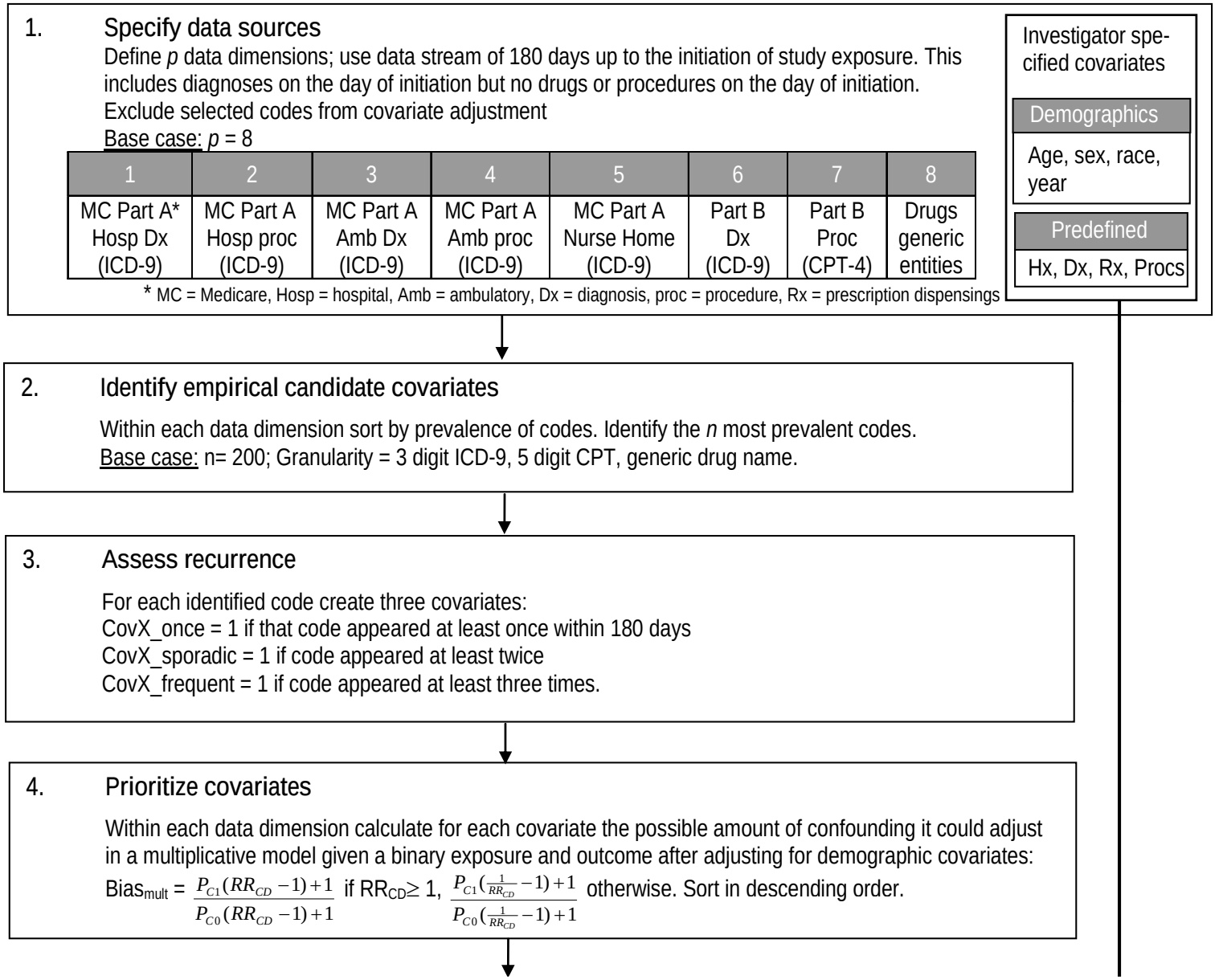
- More affordable data will result in more researchers with less training producing more findings
  - Get basics right
  - Make better use of the richness of healthcare data by using the right methods the right way
  - More transparency of analyses for fast and thorough review

Hopes

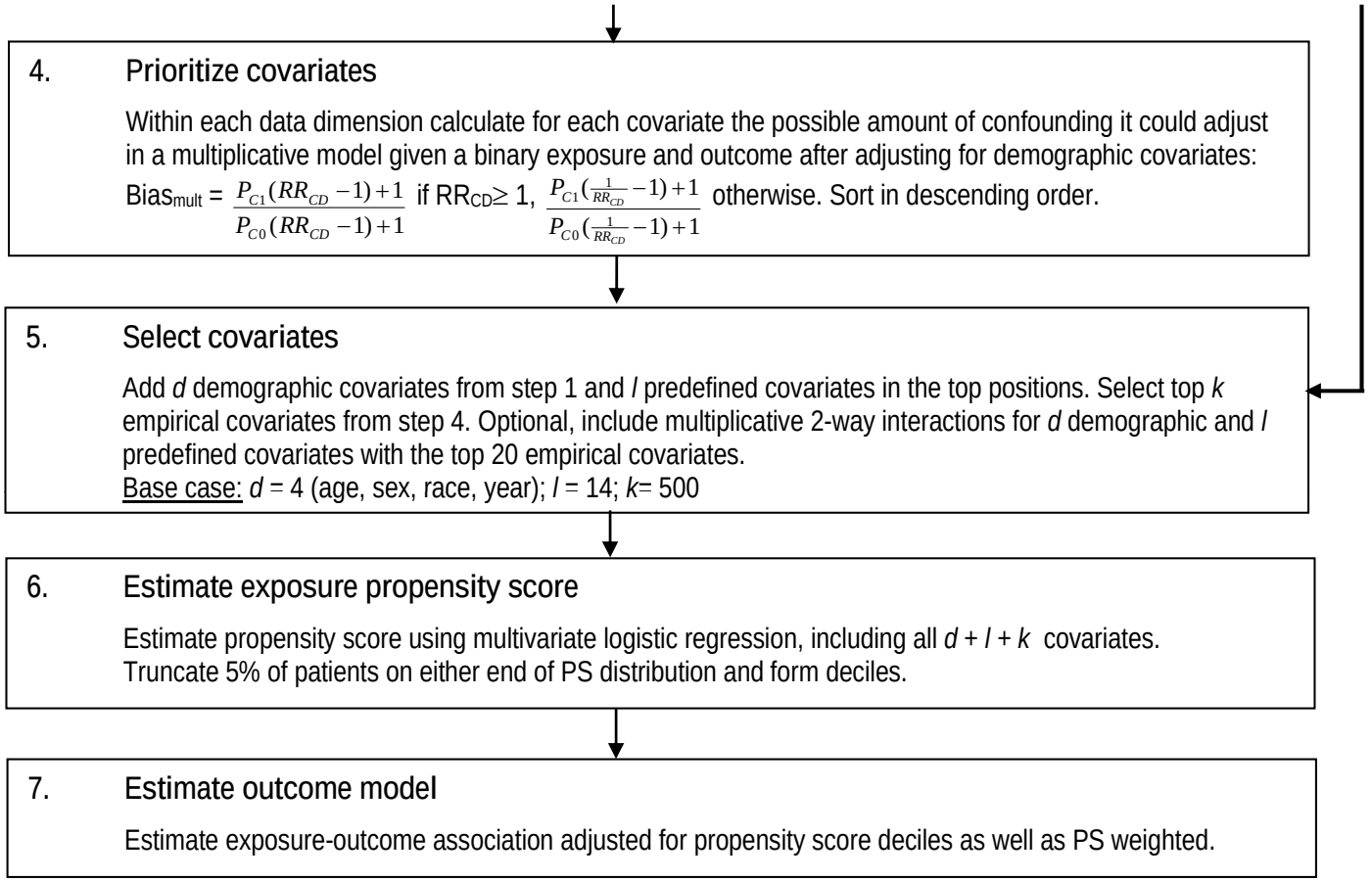
- Increased PE activities will result in better informed decision making
- More affordable data and increased public funding will result in a broader research agenda
- CAPT but also ISPE has the brain power to substantially contribute to the issues arising in CE
  - Teaching & training
  - Methods development
  - Exemplary studies
  - Translation of findings

Thank you very much

Flow chart for basic high-dimensional propensity score algorithm.



Schneeweiss, Epidemiol 2009



Schneeweiss, Epidemiol 2009

The hd-PS SAS macro.

The hd-PS SAS macro can be downloaded at www.drugepi.org … links … downloads.

EXAMPLE CODE

```
%include "/path/to/macro/directory/hdps.mcr";

Title1 'High-dimensional propensity score adjustment';
Title2 '(study description)';

%RunHighDimPropScore (
      var_patient_id          = id,
      var_exposure            = exposed,
      var_outcome             = outcome,
      vars_demographic        = age sex race,
      vars_force_categorical  = year,
      top_n                   = 200,
      k                       = 500,
      trim_mode               = BOTH,
      percent_trim            = 5,
      input_cohort            = master file,
      input_dim1              = drug_claims           generic_name,
      input_dim2              = outpatient_diagnoses  icd9_dx,
      input_dim3              = inpatient_diagnoses   icd9_dx,
      input_dim4              = inpatient_procedures  icd9_proc,
      input_dim5              = outpatient_procedures cpt,
      output_scored_cohort    = scored_cohort,
      output_detailed         = detailed cohort,
      results_estimates       = estimates,
      results_diagnostic      = variable_info
);
```

Example:

Cohort study on

Coxibs vs. nsNSAIDs and risk of GI complications in 180 days

Table 1: Characteristics of 49,653 initiators of selective COX-2 inhibitors or non-selective (ns) NSAIDs as defined during 6 months prior to first medication use.

	Initiators of Cox-2 selective NSAIDs		Initiators of nsNSAIDs			
	N	%	N	%	OR*	95% CI
N	32,042		17,611			
Age75 years or older	24,079	75%	11,496	65%	1.61	1.545-1.674
Sex, % female	27,528	86%	14,293	81%	1.42	1.348-1.487
Race: white	30,583	95%	15,808	90%	2.39	2.23-2.57
black	1,133	4%	1,580	9%	0.37	0.34-0.403
other	326	1%	223	1%	0.80	0.68-0.95
Charlson comorbidity score >= 1	24,343	76%	12,521	71%	1.29	1.233-1.340
Use of >4 distinct drugs in prior year	24,120	75%	11,852	67%	1.48	1.421-1.541
>4 physician visits in prior year	22,919	72%	11,363	65%	1.38	1.328-1.437
Hospitalized in prior year	9,804	31%	4,591	26%	1.25	1.200-1.303
Nursing home resident	2,671	8%	996	6%	1.52	1.407-1.635
Prior use of gastroprotective drugs	8,785	27%	3,600	20%	1.47	1.407-1.536
Prior use of warfarin	4,252	13%	1,153	7%	2.18	2.041-2.337
Prior use of oral steroids	2,800	9%	1,373	8%	1.13	1.059-1.211
History of OA	15,549	49%	5,898	33%	1.87	1.802-1.945
History of RA	1,602	5%	476	3%	1.90	1.707-2.102
History of peptic ulcer disease	1,189	4%	426	2%	1.55	1.389-1.739
History of gastrointestinal hemorrhage	551	2%	196	1%	1.55	1.319-1.831
History of hypertension	23,332	76%	12,363	70%	1.14	1.092-1.184
History of congestive heart failure	9,727	30%	4,328	25%	1.34	1.283-1.395
History of coronary artery disease	5,266	16%	2,603	15%	1.13	1.078-1.193

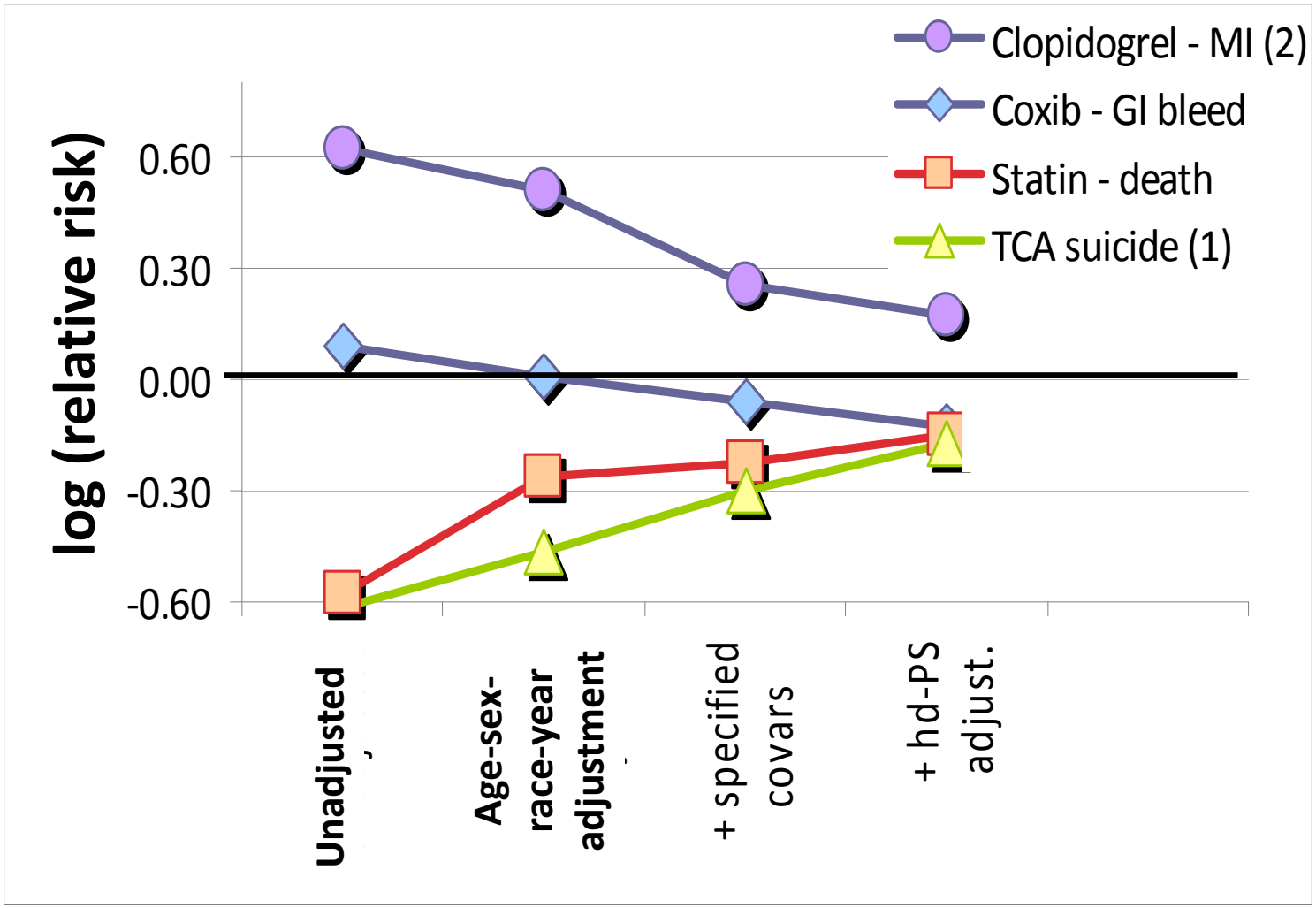
* OR = odds ratio; CI = confidence interval

Table 3: Variations in covariate adjustment and relative risk estimates for the association of selective cox-2 inhibitors and GI complications within 180 days of first medication use.

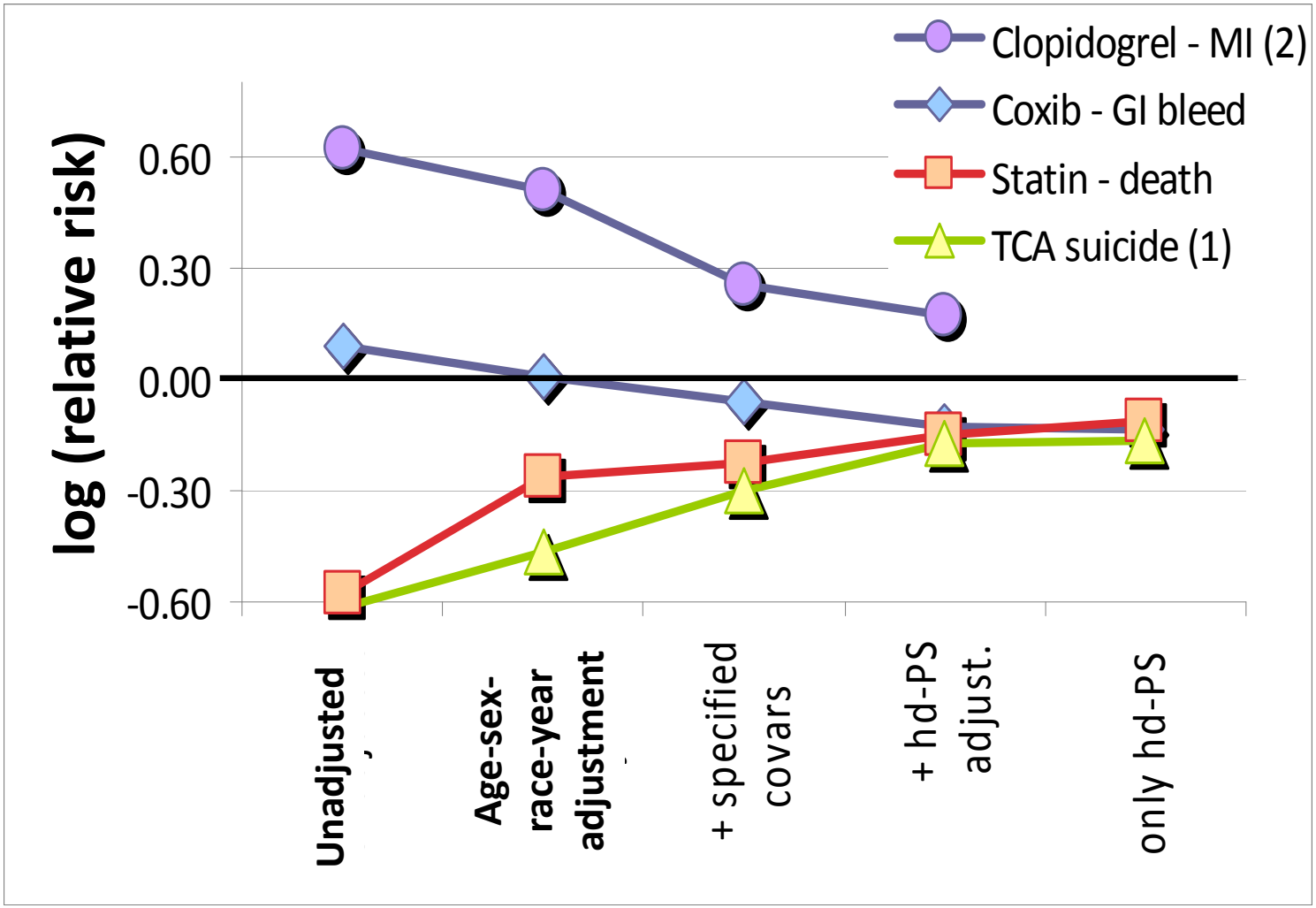
Model #	Covariates included in propensity score model	Number of covariates adjusted	Variables tested per data source	Data source granularity	Covariate prioriti-zation algorithm	c-statistic of PS model	Outcome model Relative risk	95% CI
							N = 49,653	
1	Unadjusted					-	1.09	0.91-1.30
2	Age, sex, race, year**	*d*=4				0.61	1.01	0.84-1.21
3	+ predefined covars (Tab1)	*d*=4; *l*=14				0.66	0.94	0.78-1.12
4	+ empirical covariates	*d*=4;*l*=14;*k*=200	*n*=200	3-digit ICD	$Bias_{mult}$	0.69	0.86	0.72-1.04
5*	**+ empirical covariates**	***d*=4;*l*=14;*k*=500**	***n*=200**	**3-digit ICD**	**$Bias_{mult}$**	**0.71**	**0.88**	**0.73-1.06**
							Bootstrapped 95% CIs:	0.73-1.06
5b	Only demographics + empirical covariates	*d*=4; *k*=500	*n*=200	3-digit ICD	$Bias_{mult}$	0.71	0.87	0.72-1.05

No further improvement by adding quadratic terms
No further improvement by adding 2-way, 3-way, and 4-way interactions

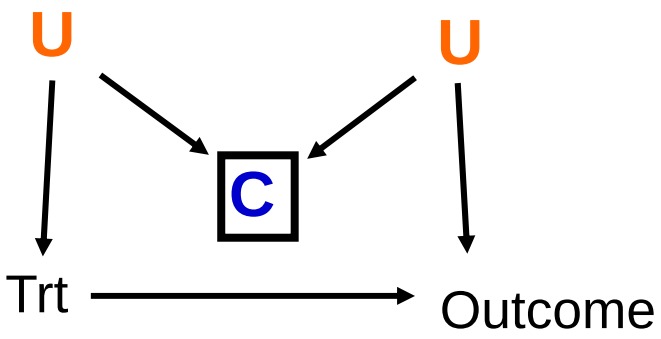
Performance of different adjustment procedures, including hd-PS adjustment

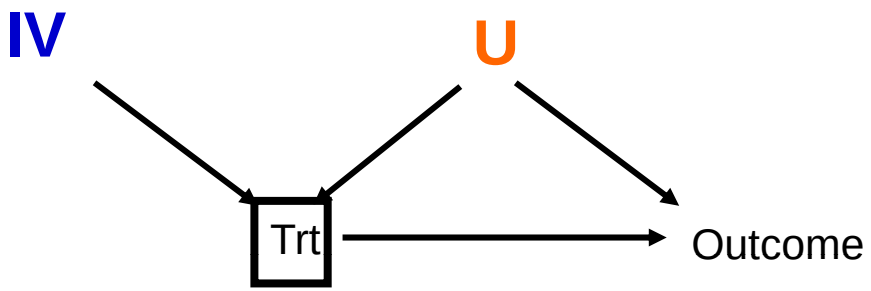


… and hd-PS adjustment alone



Kitchen sink models and the risk of collider-stratification bias





- M-bias confounding is usually considered weak
- Z-bias is a bit more likely: conditioning on treatment will open a back-door path and an IV-like variable will become a confounder
- Do we need variable un-selection?

Greenland, Epidemiol 2003

Brookhart, Schneeweiss et al. AJE 2006

Output of a screening tool for close correlates of treatment choice that are not related to the study outcome (coxib example).

Nsaid - Cox. Outcome = GI complication
K500 N200 Dx3 Generic 12:31 Wednesday, June 25, 2008

Dimension	code	frequency_ type	rr_ce	rr_cd	rr_ce_ rankStars	
x3_ambdx	274	once	0.57413	1.33750	1.0	***
dx3_mddx	274	once	0.59632	1.55786	2.0	*
dx3_hospdx	618	once	0.68079	1.29027	3.0	***
dx3_ambdx	618	once	0.68825	1.20109	4.0	****
dx3_ambdx	162	sporadic	0.75304	1.23305	6.0	****
generic_drugs	warfarin sodium	frequent	1.29333	1.33805	12.0	***
dx3_nhdx	715	frequent	1.28900	1.34443	14.0	***
prcdr_mdproc	85610	sporadic	1.28382	1.56258	16.0	*
prcdr_ambproc	863	once	0.77982	1.27691	17.0	****
generic_drugs	warfarin sodium	sporadic	1.28004	1.34342	20.0	***
dx3_mddx	714	frequent	1.27896	1.05056	21.0	*****
dx3_ambdx	714	frequent	1.27299	1.46914	23.0	**
generic_drugs	warfarin sodium	once	1.26605	1.39066	25.0	**
dx3_mddx	714	sporadic	1.26183	1.14412	27.0	*****
dx3_ambdx	162	once	0.79712	1.14912	31.0	****
dx3_mddx	725	once	1.24455	1.15490	35.0	****
generic_drugs	olanzapine	frequent	0.80962	1.46871	38.0	**
generic_drugs	folic acid	frequent	1.23513	1.52650	39.0	*
prcdr_mdproc	85610	once	1.22844	1.38142	44.0	***
dx3_hospdx	332	frequent	1.22719	1.24977	45.0	****
generic_drugs	tramadol hcl	sporadic	1.22716	1.46824	46.0	**
dx3_nhdx	427	frequent	1.22433	1.50125	50.0	*
dx3_mddx	714	once	1.22422	1.22965	51.0	****
generic_drugs	calcitonin,salmon,synthetic	sporadic	1.22363	1.22610	52.0	****
dx3_nhdx	V43	once	1.22324	1.21224	53.5	****
generic_drugs	calcitonin,salmon,synthetic	frequent	1.22253	1.50926	55.0	*
dx3_mddx	715	once	1.22232	1.06860	56.0	*****
dx3_nhdx	414	frequent	1.22148	1.07309	58.0	*****

Arthritis

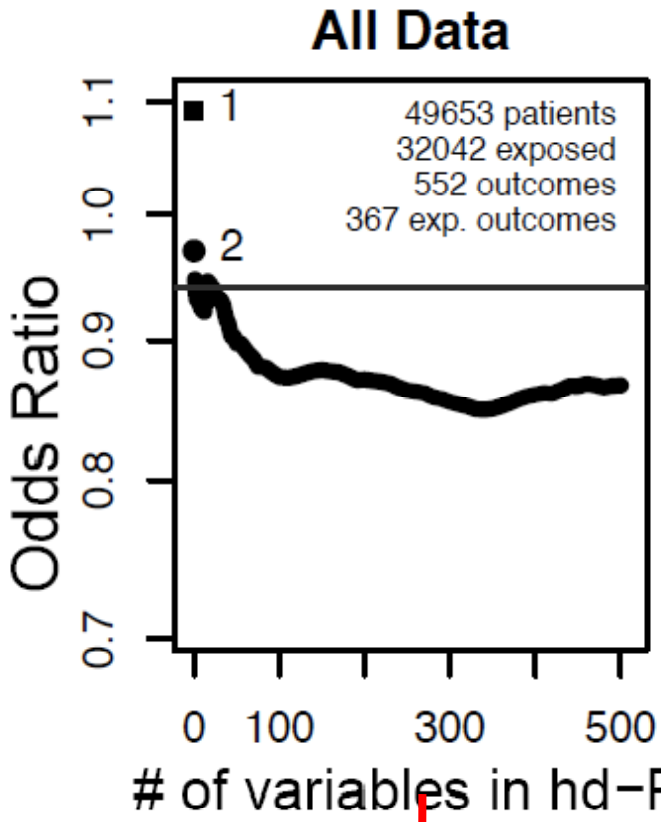
Concerns I heard

- "Over-adjustment"
  - Not to confuse with over-adjustment in case-control studies
  - Consider RR estimates: 0.5 -> 0.8 -> 1.0 -> 1.2
  - Theoretically conceivable. Anybody knows an example?
- M-bias, Z-bias -> sensitivity analysis
- Adjusting for intermediates
- "overfitting of PS model", can't find any matches anymore
- "not transparent"
- "a job-loss program for pharmacoepidemiologists"

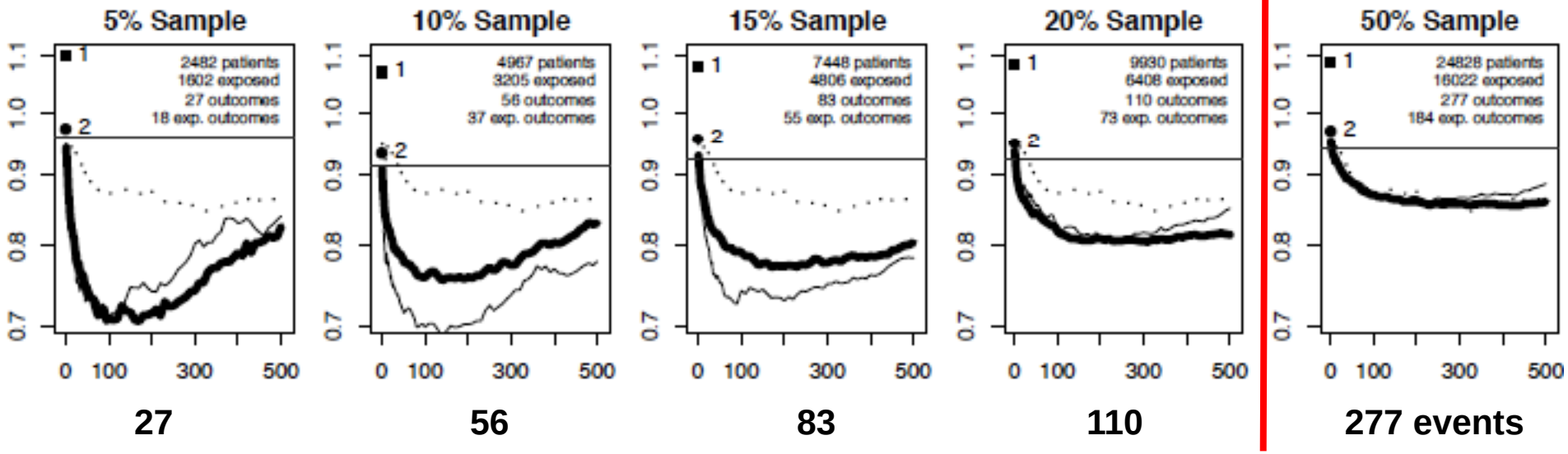
Small sample performance

Example:

Coxibs vs. nsNSAIDs and GI complications in 180 days



50 random samples, but margins stable:



Small sample performance

Example:

Coxibs vs. nsNSAIDs and GI complications in 180 days

Confounder prioritization now with 0-cell correction (+0.1)

hd-PS_2, SAS 9.2 or higher, substantially improved speed 20mins -> 2mins