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Impact of Observational Analysis Design: Lessons from the Observational Medical Outcomes Partnership

Patrick Ryan, Johnson & Johnson
on behalf of OMOP research team
17 June 2011

Full results and audio presentations from OMOP Symposium available at:
http://omop.fnih.org/OMOP2011Symposium

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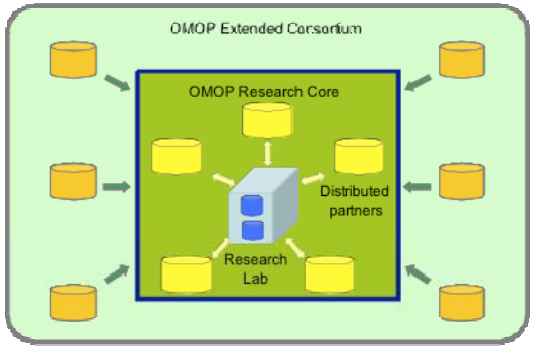
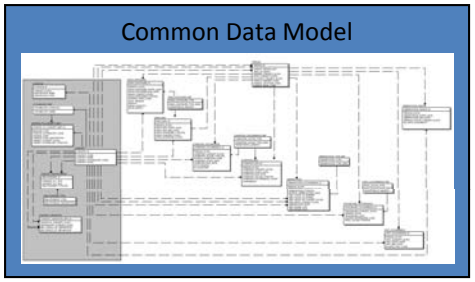
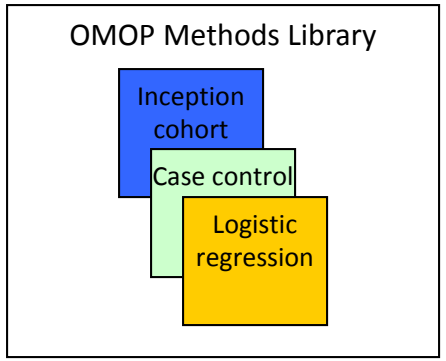
OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 200M+ lives

- Open-source
- Standards-based





- 14 methods
- Epidemiology designs
- Statistical approaches adapted for longitudinal data

Drug

Outcome	**ACE Inhibitors**	**Amphotericin B**	**Antibiotics:** erythromycins, sulfonamides, tetracyclines	**Antiepileptics:** carbamazepine, phenytoin	**Benzodiazepines**	**Beta blockers**	**Bisphosphonates:** alendronate	**Tricyclic antidepressants**	**Typical antipsychotics**	**Warfarin**
Angioedema										
Aplastic Anemia										
Acute Liver Injury										
Bleeding										
Hip Fracture										
Hospitalization										
Myocardial Infarction										
Mortality after MI										
Renal Failure										
GI Ulcer Hospitalization										

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Risk identification methods under evaluation in OMOP experiment

Method name	Contributor	Release date	Parameter combinations
Disproportionality analysis			
Disproportionality analysis (DP)	Columbia / Merck	15-Mar-10	112
IC Temporal Pattern Discovery (ICTPD)	Uppsala Monitoring Centre	23-May-10	84
HSIU cohort method (HSIU)	Regenstrief / Indiana University	8-Jun-10	6
Case-based methods			
Univariate self-controlled case series (USCCS)	Columbia	2-Apr-10	64
Multi-set case control estimation (MSCCE)	Columbia / GlaxoSmithKline	16-Apr-10	32
Bayesian logistic regression (BLR)	Rutgers / Columbia	21-Apr-10	24
Case-control surveillance (CCS)	Lilly	2-May-10	48
Case-crossover (CCO)	University of Utah	1-Jun-10	48
Exposure-based methods			
Observational screening (OS)	ProSanos / GlaxoSmithKline	8-Apr-10	162
High-dimensional propensity score (HDPS)	Columbia	6-Aug-10	144
Incident user design (IUD-HOI)	University of North Carolina	26-Oct-10	160
Sequential testing methods			
Maximized Sequential Probability Ratio Test (MSPRT)	Harvard Pilgrim / Group Health	25-Jul-10	144
Conditional sequential sampling procedure (CSSP)	Harvard Pilgrim / Group Health	30-Aug-10	144

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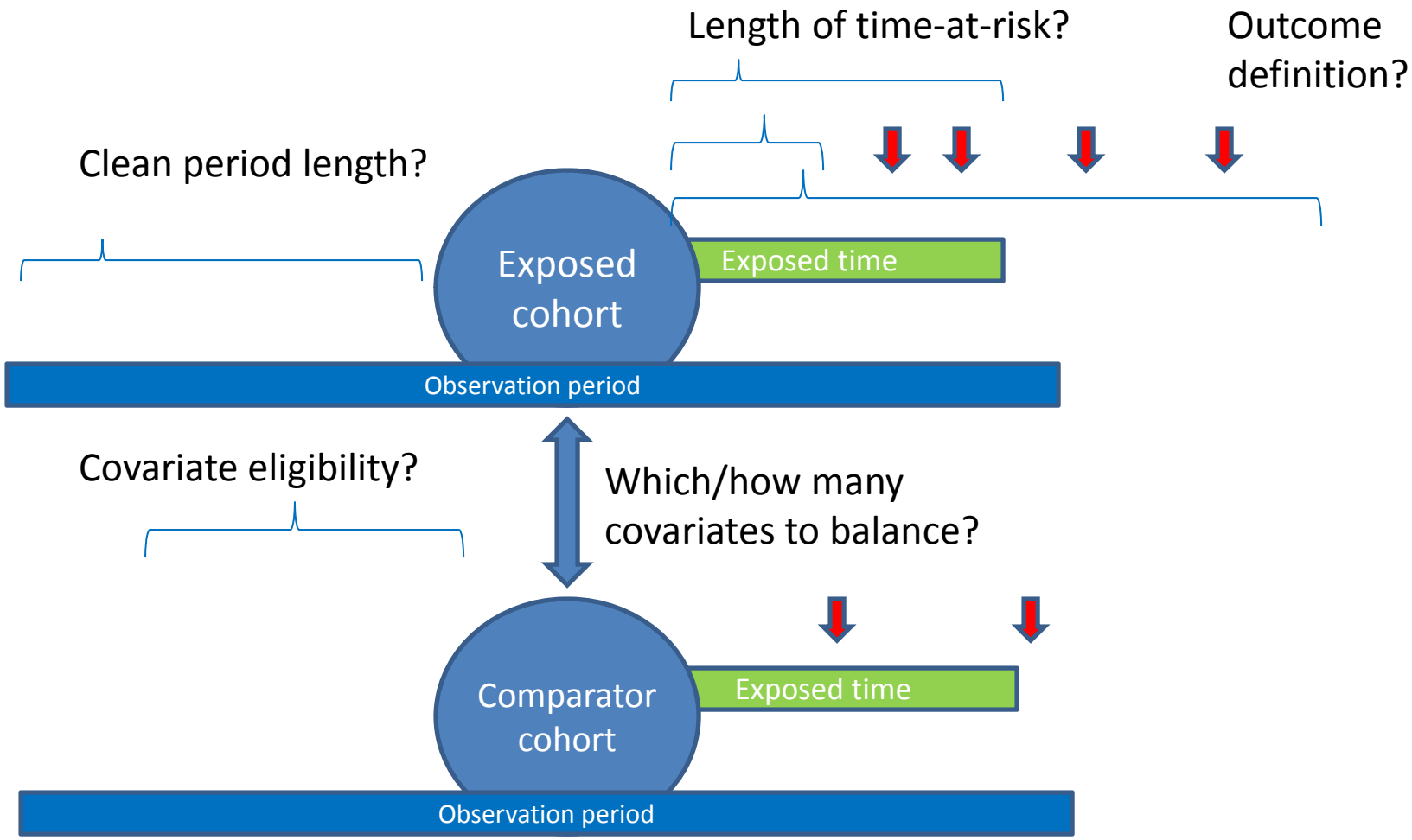
Exploration of test cases within inception cohort design



Exclusion criteria:
Indications
Contraindications

Which active comparator?

Propensity score adjustment strategy?
Stratification
Multivariate adjustment

BMJ

RESEARCH

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

BMJ 2010; 341:c4444

Conclusions The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period.

BMJ study design choices

- Data source: General Practice Research Database
- Study design: Nested case-control
- Inclusion criteria: Age > 40
- Case: cancer diagnosis between 1995-2005 with 12-months of follow-up pre-diagnosis
- 5 controls per case
- Matched on age at index date, sex, practice, observation period prior to index
- Exposure definition: >=1 prescription during observation period
- "RR" estimated with conditional logistic regression
- Covariates: smoking, alcohol, BMI before *outcome* index date
- Sensitivity analyses:
  - exposure = 2+ prescriptions
  - covariates not missing
  - time-at-risk = >1 yr post-exposure
- Subgroup analyses:
  - Short vs. long exposure duration
  - Age, Sex, smoking, alcohol, BMI
  - Osteoporosis or osteopenia
  - Fracture pre-exposure
  - Prior diagnosis of Upper GI dx pre-exposure
  - NSAID, corticosteroid, H2blocker, PPI utilization pre-exposure

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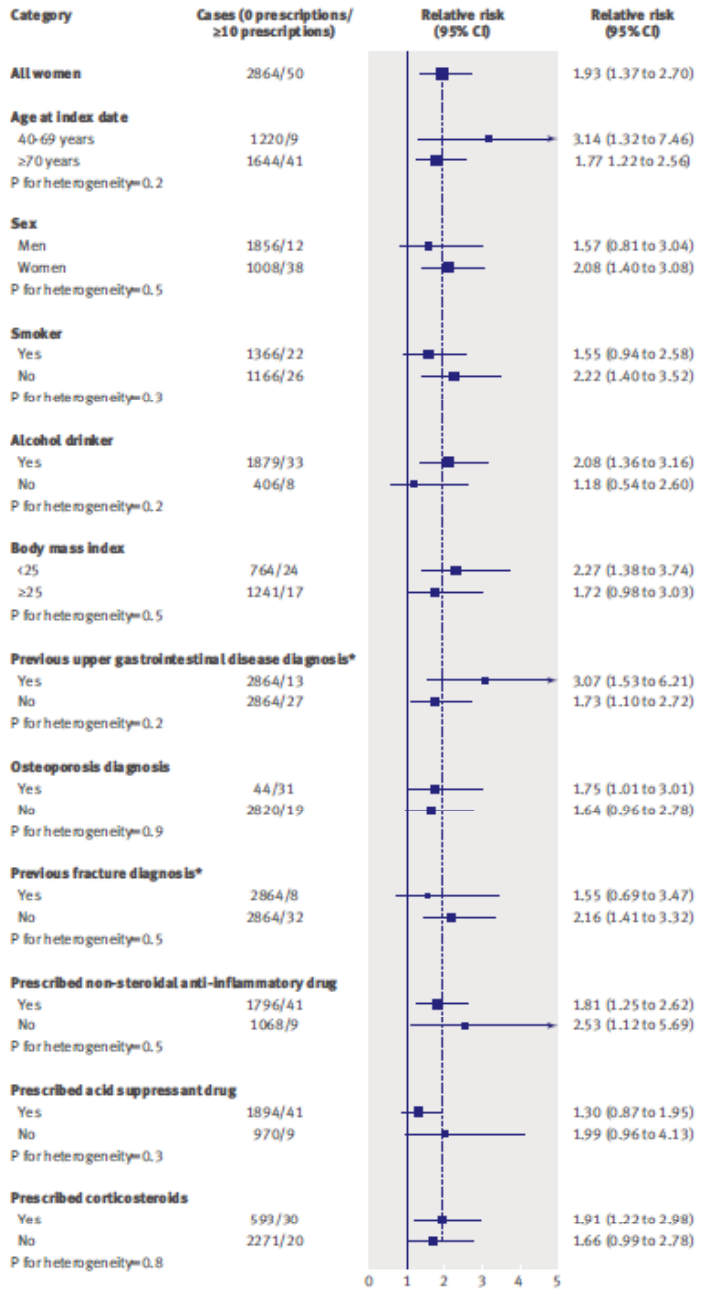
BMJ Results

Table 2 | Relative risks (RRs) and 95% confidence intervals (CIs) fo bisphosphonates

	Oesophagus		
Oral bisphosphonates	Prescriptions*	Cases/ controls	RR† (95% CI)
Not prescribed	NA	2864/14 376	1.00
Prescribed	13.6/2.4	90/345	1.30 (1.02 to 1.66)
No of prescriptions:			
1-9	3.6/1.0	40/214	0.93 (0.66 to 1.31)
≥10	21.6/3.5	50/131	1.93 (1.37 to 2.70)
Estimated duration of use‡:			
≤1 year	4.9/0.3	31/155	0.98 (0.66 to 1.46)
1-3 years	13.0/2.0	26/114	1.12 (0.73 to 1.73)
≥3 years	22.2/4.6	33/76	2.24 (1.47 to 3.43)

NA=not applicable.
*Prescriptions of bisphosphonates in cases; reported as mean number/mean ye
†All relative risks adjusted for smoking status, alcohol intake, and body mass i
‡Time between first and last prescription.



Relative risks of incident oesophageal cancer in people with ≥10 prescriptions for oral bisphosphonates, compared with those with no prescriptions, by various factors. Relative risks adjusted for smoking status, alcohol intake, and body mass index, as appropriate. *Diagnosis before prescription of bisphosphonates: analyses restricted to those with ≥12 months' observation before first bisphosphonate prescription

BMJ 2010; 341:c4444

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ORIGINAL CONTRIBUTION

JAMA®

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Chris R. Cardwell, PhD
Christian C. Abnet, PhD
Marie M. Cantwell, PhD
Liam J. Murray, MD

Context Use of oral bisphosphonates has increased dramatically in the United States and elsewhere. Esophagitis is a known adverse effect of bisphosphonate use, and recent reports suggest a link between bisphosphonate use and esophageal cancer, but this has not been robustly investigated.

Objective To investigate the association between bisphosphonate use and esoph-

JAMA 2010; 304(6): 657-663

Conclusion the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer.

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JAMA study design choices

- Data source: General Practice Research Database
- Study design: Cohort
- Inclusion criteria: Age > 40
- Exclusion criteria: Cancer diagnosis in 3 years before index date
- Exposed cohort: Patients with >=1 prescription between 1996-2006 — 1995-2005 in BMJ
- "Unexposed" cohort: 1-to-1 match with exposed cohort — Match exposure vs. outcome status; not 5-to-1
- Matched on year of birth, sex, practice — Not observation length
- "HR" estimated with Cox proportional hazards model
- Time-at-risk: >6mo from index date — Time-at-risk is 'between' two definitions used in BMJ: All time post-exposure and >1yr after index
- Covariates:
  - Smoking, alcohol, BMI before *exposure* index date — Different index date
  - Hormone therapy, NSAIDs, H2blockers, PPIs — BMJ didn't stratify by hormone therapy
- Sensitivity analyses:
  - Excluding people that were in both exposed and unexposed cohorts
  - Exclude patients with missing confounders (not reported)
- Subgroup analyses:
  - Low vs. medium vs. high use, based on defined daily dose
  - Alendronate vs. nitrogen-containing bisphosphonates vs. non-nitrogen-contraining bisphosphonates

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JAMA Results

Table 3. Esophageal (Only) Cancer Incidence in the Bisphosphonate and Matched Control Cohorts

	Bisphosphonate		Control		Risk			
					Unadjusted		Adjusted[a]	
Bisphosphonate Category	Cases	Person-Years	Cases	Person-Years	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Any bisphosphonate								
Prescribed	79	165 400	72	163 480	1.08 (0.79-1.49)	.63	1.07 (0.77-1.49)	.67
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
183	51	104 676	49	104 104	1.04 (0.70-1.53)	.86	1.05 (0.70-1.57)	.82
365	31	73 364	35	73 170	0.88 (0.55-1.43)	.62	0.92 (0.56-1.51)	.74
730	22	40 326	22	40 492	1.00 (0.56-1.81)	.99	0.98 (0.53-1.81)	.95
1095	15	22 813	14	22 891	1.08 (0.52-2.23)	.84	1.01 (0.48-2.12)	.99
Total bisphosphonate intake during follow-up (in DDDs/d)[c]								
Low (0-<0.24)	35	62 922	27	63 648	1.31 (0.80-2.17)	.29	1.24 (0.74-2.09)	.41
Medium (≥0.24-<0.89)	24	58 162	23	55 334	0.98 (0.55-1.74)	.94	1.03 (0.57-1.86)	.92
High (≥0.89)	20	44 316	22	44 497	0.91 (0.50-1.67)	.78	0.90 (0.48-1.68)	.74
Nitrogen-containing bisphosphonates								
First prescribed	44	106 480	47	106 412	0.94 (0.62-1.41)	.75	0.96 (0.63-1.47)	.86
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
365	30	70 251	34	69 935	0.88 (0.54-1.44)	.61	0.93 (0.56-1.54)	.78
730	22	39 022	22	39 187	1.01 (0.56-1.82)	.99	0.98 (0.53-1.80)	.95
Alendronate								
First prescribed	33	81 369	42	80 837	0.78 (0.50-1.23)	.29	0.77 (0.48-1.23)	.27
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
365	22	52 308	31	51 741	0.70 (0.41-1.21)	.20	0.68 (0.39-1.19)	.18
730	19	28 898	21	28 904	0.91 (0.49-1.68)	.75	0.85 (0.45-1.61)	.62
Non–nitrogen-containing bisphosphonates								
First prescribed	35	58 920	25	57 068	1.35 (0.81-2.25)	.25	1.25 (0.73-2.12)	.37

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio.

[a] Adjusted for body mass index, alcohol, smoking, hormone therapy prescription (before index date), nonsteroidal anti-inflammatory drug prescription (before index date), Barrett esophagus diagnosis (before index date), gastroesophageal reflux disease diagnosis (before index date), H_2 receptor antagonist prescription (before index date), and proton pump inhibitor prescription (before index date).

[b] Person-years and cancer cases occurring after the date of specified prescriptions received for each bisphosphonate cohort member and their matched control. Daily divided dose equivalents: 183 DDDs are equivalent to a 6-month supply; 365 DDDs to a 1-year supply; 730 DDDs to a 2-year supply; and 1095 DDDs to a 3-year supply.

[c] In bisphosphonate cohort (see "Methods" for details of selection of cohorts).

JAMA 2010; 304(6): 657-663

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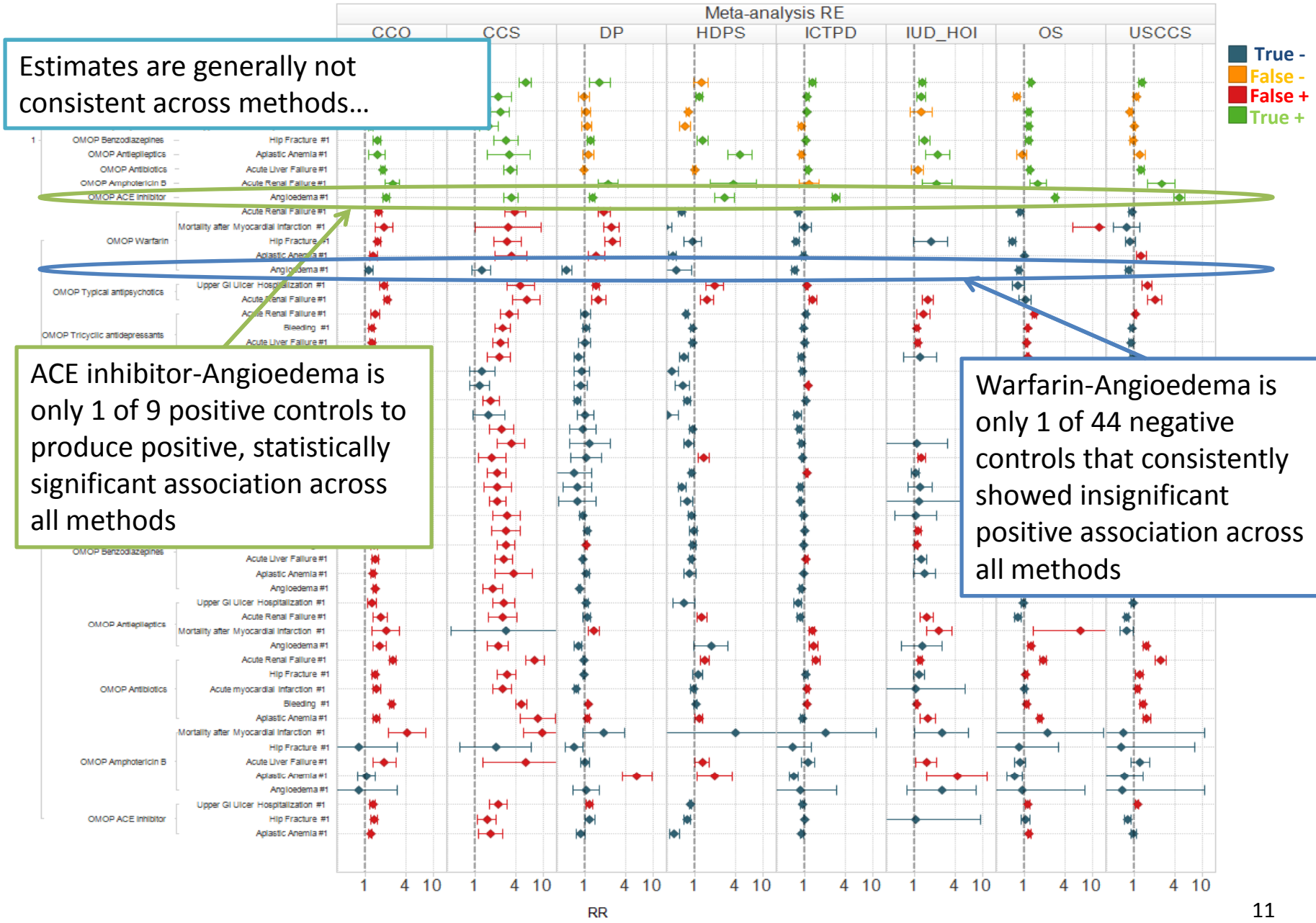
Distribution of estimates across all drug-outcome pairs

Estimates are generally not consistent across methods…



ACE inhibitor-Angioedema is only 1 of 9 positive controls to produce positive, statistically significant association across all methods

Warfarin-Angioedema is only 1 of 44 negative controls that consistently showed insignificant positive association across all methods

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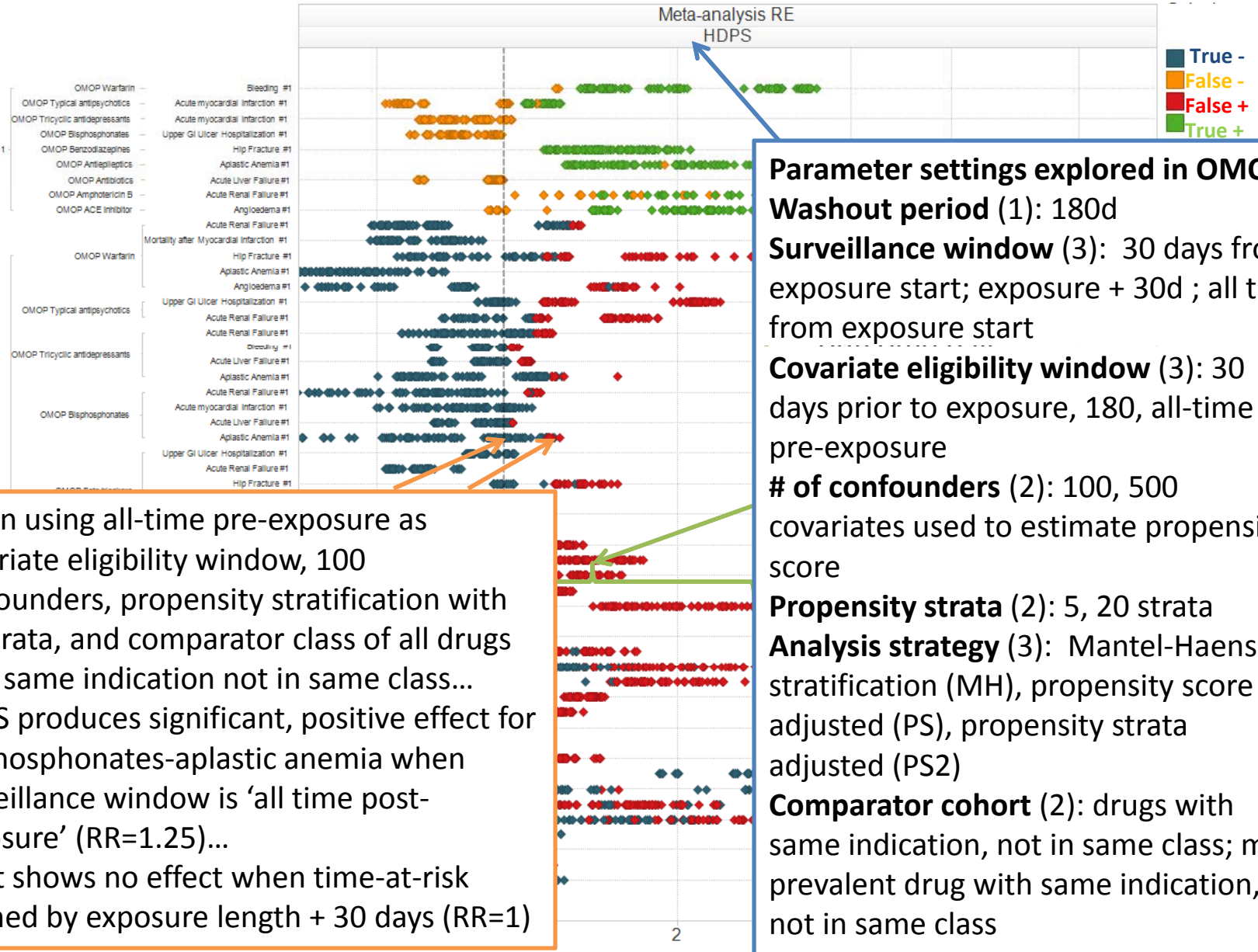
Range of estimates across high-dimensional propensity score inception cohort (HDPS) parameter settings



- When using all-time pre-exposure as covariate eligibility window, 100 confounders, propensity stratification with 20 strata, and comparator class of all drugs with same indication not in same class…
- HDPS produces significant, positive effect for bisphosphonates-aplastic anemia when surveillance window is 'all time post-exposure' (RR=1.25)…
- …but shows no effect when time-at-risk defined by exposure length + 30 days (RR=1)

Parameter settings explored in OMOP:

Washout period (1): 180d

Surveillance window (3): 30 days from exposure start; exposure + 30d ; all time from exposure start

Covariate eligibility window (3): 30 days prior to exposure, 180, all-time pre-exposure

# of confounders (2): 100, 500 covariates used to estimate propensity score

Propensity strata (2): 5, 20 strata

Analysis strategy (3): Mantel-Haenszel stratification (MH), propensity score adjusted (PS), propensity strata adjusted (PS2)

Comparator cohort (2): drugs with same indication, not in same class; most prevalent drug with same indication, not in same class

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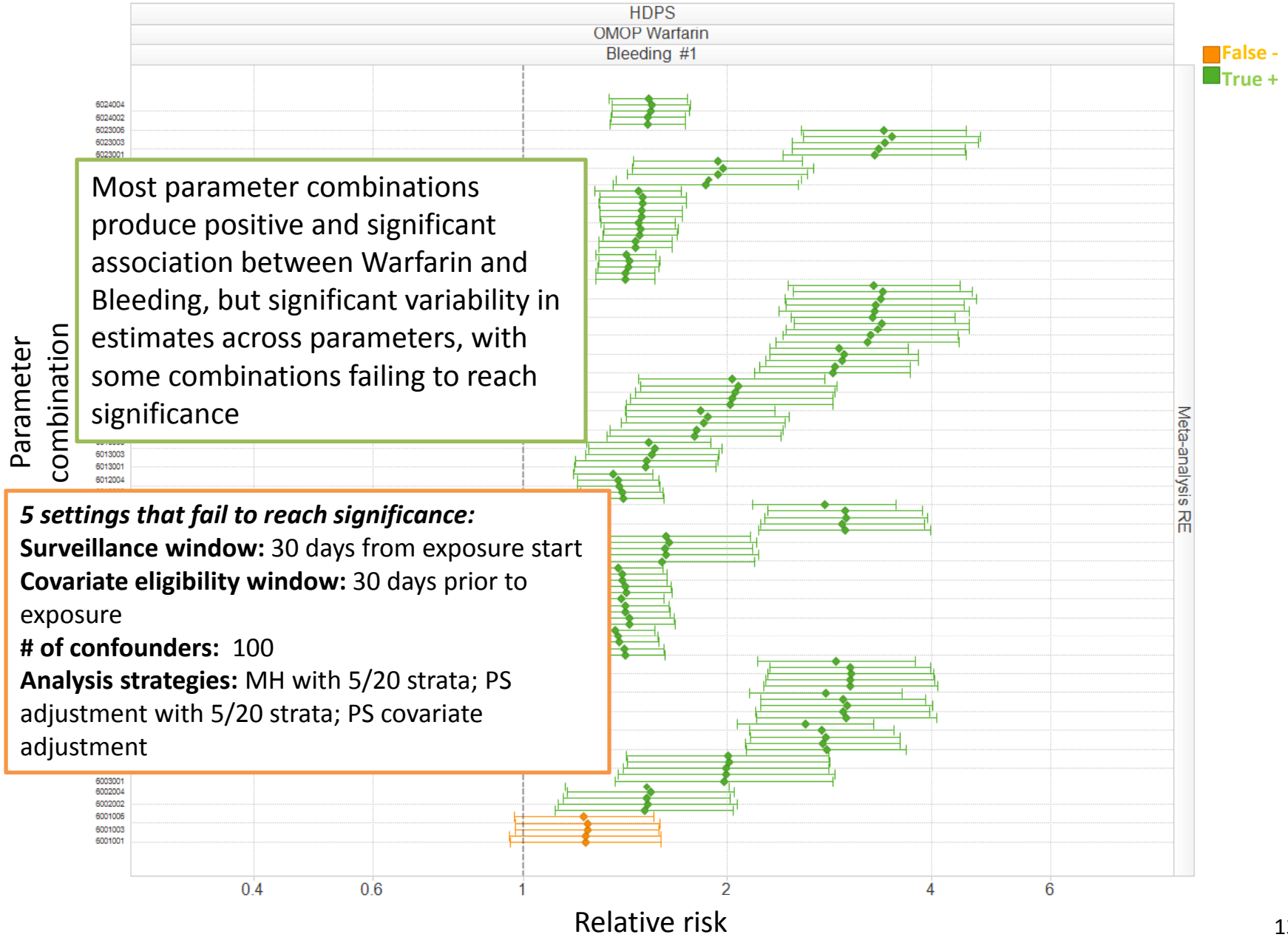
Evaluating the sensitivity of the estimated association between Warfarin and Bleeding when using HDPS



Most parameter combinations produce positive and significant association between Warfarin and Bleeding, but significant variability in estimates across parameters, with some combinations failing to reach significance

5 settings that fail to reach significance:
Surveillance window: 30 days from exposure start
Covariate eligibility window: 30 days prior to exposure
# of confounders: 100
Analysis strategies: MH with 5/20 strata; PS adjustment with 5/20 strata; PS covariate adjustment

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HDPS parameter sensitivity

- No single parameter completely separates 'true' vs. 'false' findings for drug-outcome pairs
- Effect estimates are more sensitive to:
  - Time-at-risk surveillance window (30d from exposure start, exposure length + 30d, all time post-exposure start)
  - Choice of comparator (all drugs with same indication but in different class, one drug with same indication but different class)
- Effect estimates are less sensitive for:
  - Covariate eligibility window (30d, 180d, all time pre-exposure)
  - Number of covariates (100, 500)
  - Propensity score adjustment strategy (stratification with 5 or 20 strata, multivariate regression with strata categories, regression with PS as covariate)

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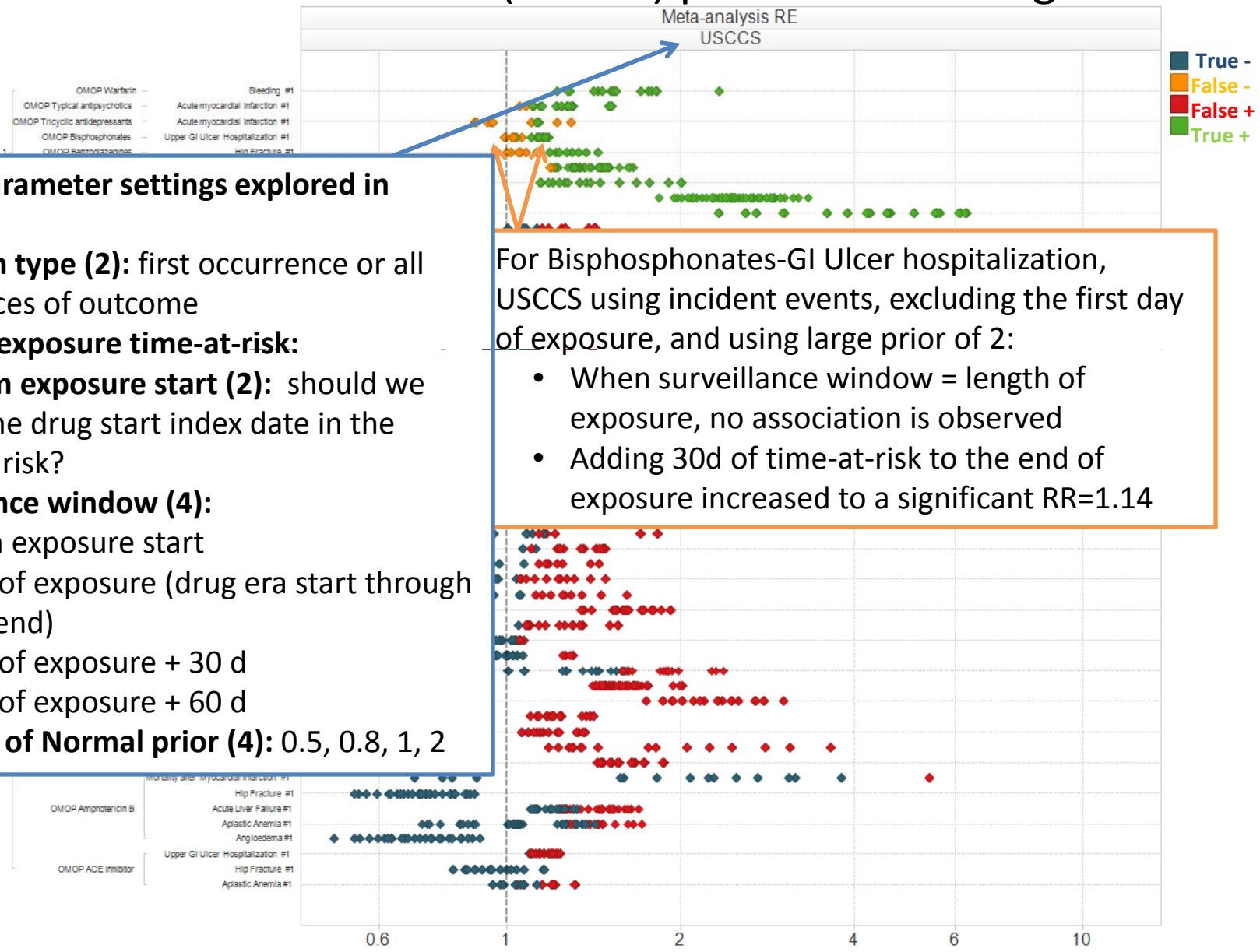
Range of estimates across univariate self-controlled case series (USCCS) parameter settings



USCCS Parameter settings explored in OMOP:

Condition type (2): first occurrence or all occurrences of outcome

Defining exposure time-at-risk:

Days from exposure start (2): should we include the drug start index date in the period at risk?

Surveillance window (4):

30 d from exposure start

Duration of exposure (drug era start through drug era end)

Duration of exposure + 30 d

Duration of exposure + 60 d

Precision of Normal prior (4): 0.5, 0.8, 1, 2

For Bisphosphonates-GI Ulcer hospitalization, USCCS using incident events, excluding the first day of exposure, and using large prior of 2:

- When surveillance window = length of exposure, no association is observed
- Adding 30d of time-at-risk to the end of exposure increased to a significant RR=1.14

USCCS parameter sensitivity

- No single parameter completely separates 'true' vs. 'false' findings for drug-outcome pairs
- Effect estimates are more sensitive to:
  - Whether to include the exposure start date as exposed time-at-risk: including day 0 produced higher estimates than excluding day 0 for many pairs
  - Exposed time-at-risk surveillance window
    - Length of exposure
    - Length of exposure + 30d
    - Length of exposure + 60d
    - 30d from exposure start
    - NOTE: Time 'unexposed' = Total observation period – time exposed
- Effect estimates are less sensitive for:
  - Use of first occurrence vs. all occurrences of events
  - Precision of the prior (0.5, 0.8, 1, 2)

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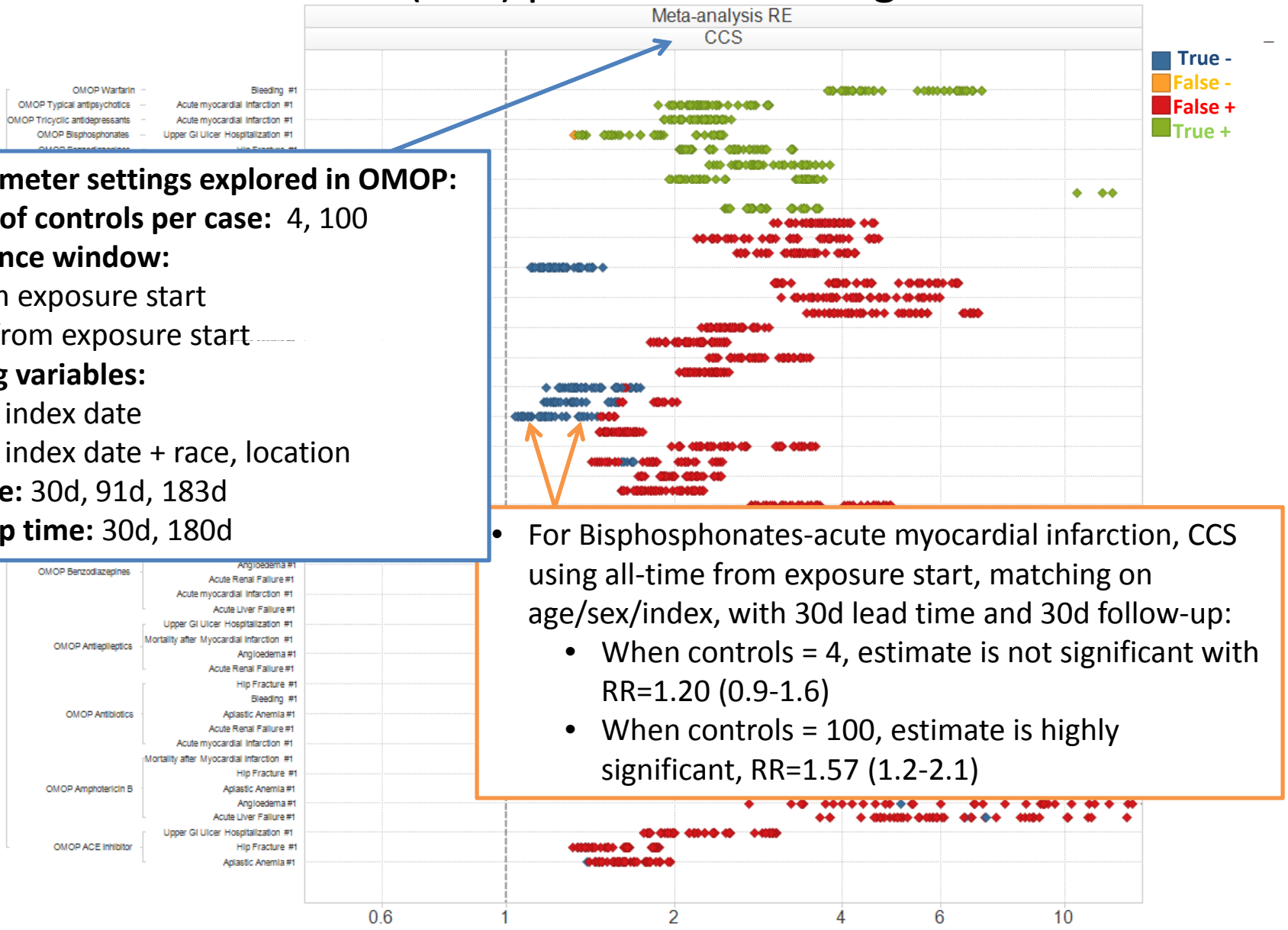
Range of estimates across case-control surveillance (CCS) parameter settings



CCS Parameter settings explored in OMOP:

Number of controls per case: 4, 100

Surveillance window:

30 d from exposure start

All time from exposure start

Matching variables:

Age, sex, index date

Age, sex, index date + race, location

Lead time: 30d, 91d, 183d

Follow-up time: 30d, 180d

- For Bisphosphonates-acute myocardial infarction, CCS using all-time from exposure start, matching on age/sex/index, with 30d lead time and 30d follow-up:
  - When controls = 4, estimate is not significant with RR=1.20 (0.9-1.6)
  - When controls = 100, estimate is highly significant, RR=1.57 (1.2-2.1)

CCS parameter sensitivity

- No single parameter completely separates 'true' vs. 'false' findings for drug-outcome pairs
- Effect estimates are more sensitive to:
  - Number of controls per case (4, 100)
    - 100 controls generated higher estimates than 4 controls for many drug-outcome pairs
  - Whether to match on race and location
    - Matching on race and location generated lower estimates than not matching for many drug-outcome pairs
  - Time-at-risk surveillance window (30d post-exposure, all-time post-exposure start)
    - 30d post-exposure generated higher estimates than all-time post-exposure for many drug-outcome pairs
- Effect estimates are less sensitive:
  - Lead time (30d, 91d, 183d)
  - Follow-up time (30d, 180d)

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Mini-Sentinel Taxonomy report

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

Monitoring scenario characteristics with implication for design choice[a]							Monitoring scenario characteristics with implication for analytic choice[a]		
	Characteristics of the (potential) exposure-HOI link								
			Strength of confounding						
Exposure persistence *(transient, sustained)*	**Onset of exposure risk window** *(Immediate, delayed)*	**Duration of exposure risk window** *(short, long)*	**Within-person** *(negligible, needs to be addressed)*	**Between-person** *(negligible, needs to be addressed)*	**HOI onset** *(abrupt, insidious)*	**Design choice**[b] *(self-controlled, cohort)*	**Background frequency of exposure** *(infrequent, rare)*	**Background frequency of HOI** *(infrequent, rare)*	**Analytic choice**
Transient (e.g. vaccine, *initiation* of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature)	Immediate	Short	Negligible	Negligible	Abrupt	1 self-controlled (or cohort)	Infrequent	Infrequent	1
								Rare	2
							Rare	Infrequent	3
								Rare	4
					Insidious	2 cohort (or self-controlled)	Infrequent	Infrequent	5
								Rare	6
							Rare	Infrequent	7
								Rare	8
				Needs to be addressed	Abrupt	3 self-controlled (or cohort)	Infrequent	Infrequent	9
								Rare	10
							Rare	Infrequent	11
								Rare	12
					Insidious	4 self-controlled or cohort	Infrequent	Infrequent	13
								Rare	14
							Rare	Infrequent	15
								Rare	16
			Needs to be	Negligible	Abrupt	5	Infrequent	Infrequent	17

http://www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_FinalTaxonomyReport.pdf

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Mapping clinical problems to analytical solutions

Attributes of the problem	When in the scenario of…	…the best practice would be:	Parameters of the analysis

ILLUSTRATIVE EXAMPLE

Drug

- Highly prevalent exposure
- Long persistent duration of exposure
- Indication of chronic disease in metabolic therapeutic area

Outcome

- Condit…

Drug-outc… relations…

- …et with a …stant hazard
- Expected acute time-to-onset

Databases

…ign

…r

Outcome definition

Inclusion/exclusion criteria

Covariate adjustment strategy

EMPIRICAL EVIDENCE IS NEEDED FROM A LARGE SAMPLE OF REAL-WORLD SCENARIOS APPLIED TO REAL-WORLD OBSERVATIONAL DATA TO ESTABLISH THIS MAPPING

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Establishing robust practice through empirical research

- For 'risk identification', many of the attributes of drug-outcome relationship may not be known a priori, so systematic analysis requires comprehensive exploratory framework
- Current data suggest need for systematic sensitivity analysis across all variables that have not been empirically demonstrated to be stable in the scenario
- A viable best practice may be:
  "Don't use observational data for this scenario, due to lack of evidence that a reliable estimate can be obtained"
- Further empirical research needed to have more complete understanding of operating characteristics and sensitivities before widespread adoption