Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND)

Patrick Ryan, Martijn Schuemie, Marc Suchard
on behalf of the LEGEND team

OHDSI Symposium

12 October 2018

Trouble with observational research

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 3417–3438
doi:10.1093/eurheartj/ehy407

CLINICAL REVIEW
Controversies in cardiovascular medicine

Association is not causation: treatment effects cannot be estimated from observational data in heart failure

Christopher J. Rush, Ross T. Campbell, Pardeep S. Jhund, Mark C. Petrie, and John J.V. McMurray*

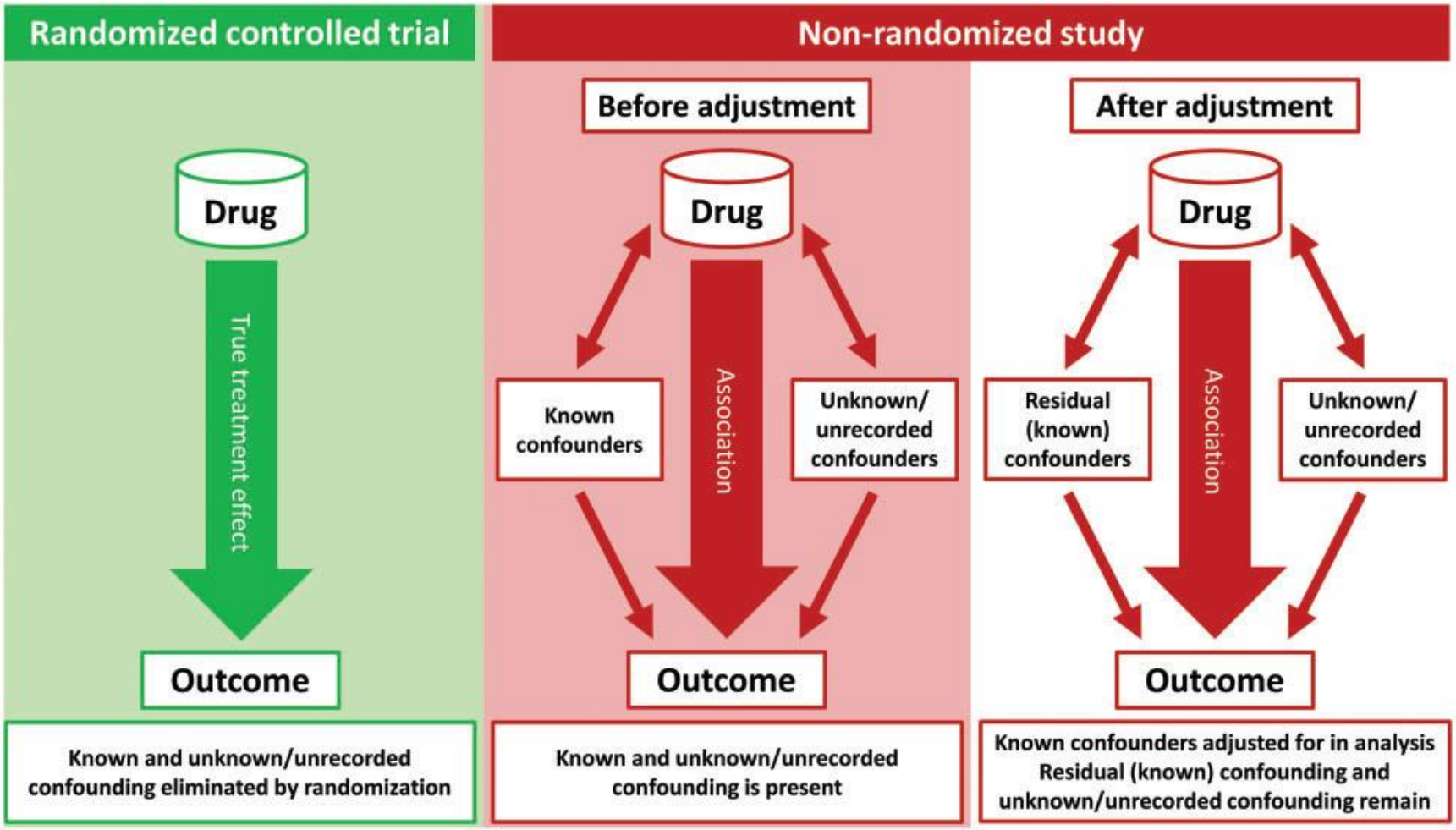
British Heart Foundation Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK

Received 16 January 2018; revised 1 April 2018; editorial decision 22 June 2018; accepted 27 June 2018; online publish-ahead-of-print 1 August 2018

Aims Treatment 'effects' are often inferred from non-randomized and observational studies. These studies have inherent biases and limitations, which may make therapeutic inferences based on their results unreliable. We compared the conflicting findings of these studies to those of prospective randomized controlled trials (RCTs) in relation to pharmacological treatments for heart failure (HF).

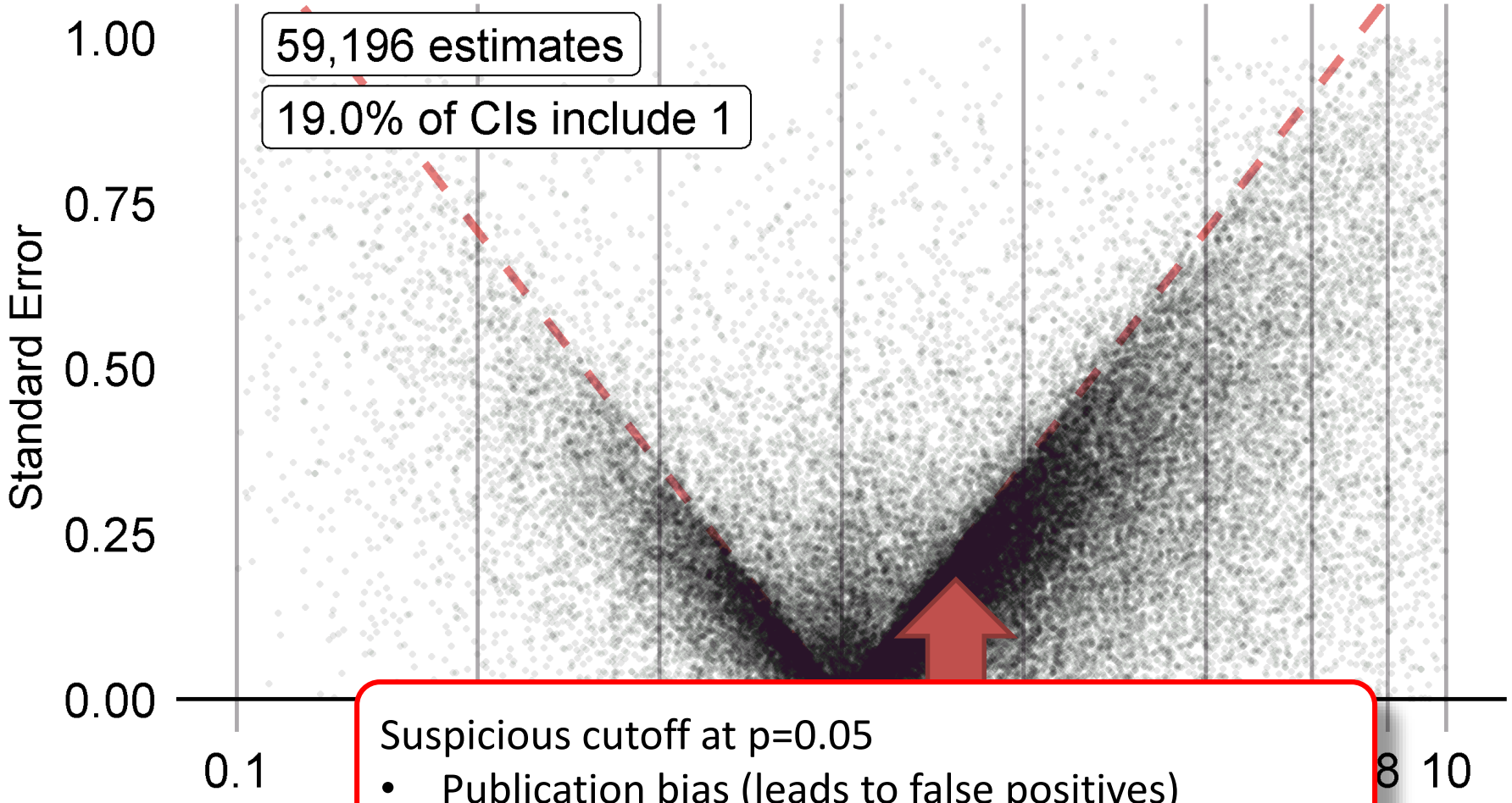
Methods and results We searched Medline and Embase to identify studies of the association between non-randomized drug therapy and all-cause mortality in patients with HF until 31 December 2017. The treatments of interest were: angiotensin-

Residual study bias



Rush et al., 2018

Published observational study results



Suspicious cutoff at p=0.05

- Publication bias (leads to false positives)
- P-hacking (leads to false positives)

Trouble with observational research

- Individual studies are often biased due to **confounding**, **selection bias**, and **measurement error**

- Across studies, observational research as a whole is even more biased due to **publication bias** and **p-hacking**

Improving methods to address confounding

- Construct large generic set of covariates
  - 10,000 < n < 100,000
- Use regularized regression to fit propensity model
- Match or stratify on propensity score

International Journal of Epidemiology, 2018, 1–10
doi: 10.1093/ije/dyy120
Original article

Original article

Evaluating large-scale propensity score performance through real-world and synthetic data experiments

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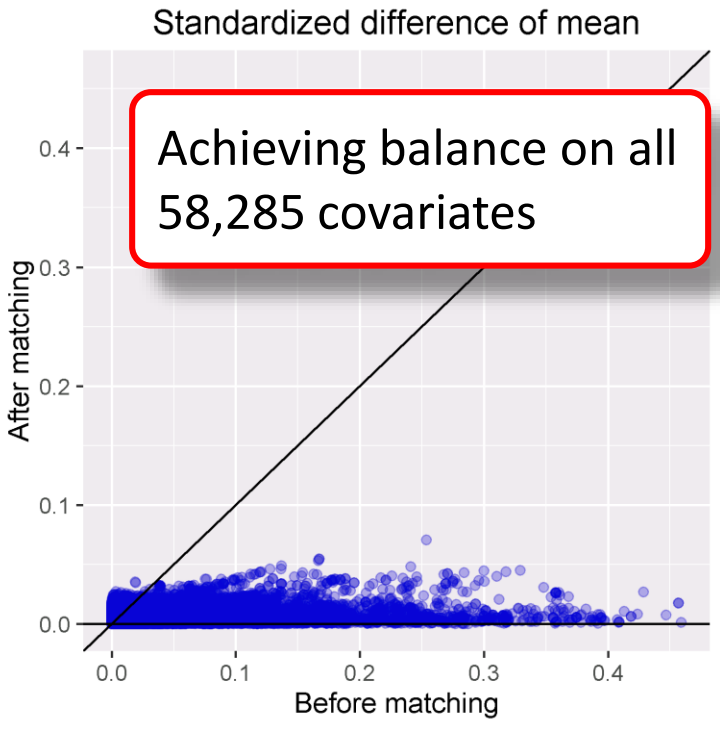
[1]Department of Biomathematics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA, USA, [2]Epidemiology Department, Janssen Research and Development LLC, Titusville, NJ, USA, [3]Department of Biostatistics, UCLA Fielding School of Public Health, University of California, Los Angeles, CA, USA and [4]Department of Human Genetics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA, USA



Measuring residual bias

Control questions:

- exposure-outcome pairs with known effect size
- negative and positive controls

Empirical calibration:

- Adjust p-value and confidence interval using estimates for controls

PNAS

COLLOQUIUM PAPER

Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data

Martijn J. Schuemie[a,b,1], George Hripcsak[a,c,d], Patrick B. Ryan[a,b,c], David Madigan[a,e], and Marc A. Suchard[a,f,g,h]

[a]Observational Health Data Sciences and Informatics, New York, NY 10032; [b]Epidemiology Analytics, Janssen Research & Development, Titusville, NJ 08560; [c]Department of Biomedical Informatics, Columbia University, New York, NY 10032; [d]Medical Informatics Services, New York–Presbyterian Hospital, New York, NY 10032; [e]Department of Statistics, Columbia University, New York, NY 10027; [f]Department of Biomathematics, University of California, Los Angeles, CA 90095; [g]Department of Biostatistics, University of California, Los Angeles, CA 90095; and [h]Department of Human Genetics, University of California, Los Angeles, CA 90095

Edited by Victoria Stodden, University of Illinois at Urbana–Champaign, Champaign, IL, and accepted by Editorial Board Member Susan T. Fiske October 26, 2017 (received for review June 15, 2017)

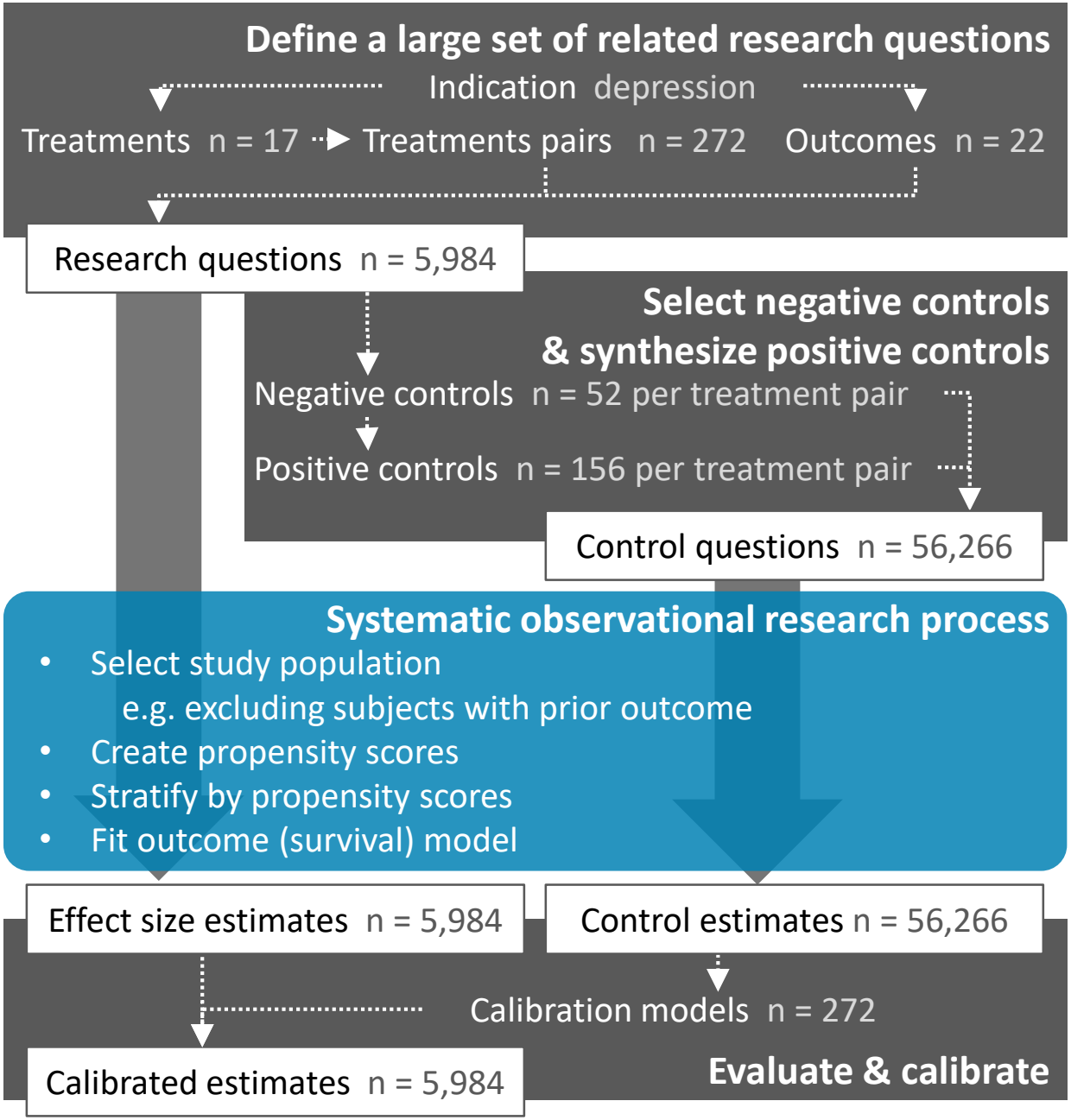
Observational healthcare data, such as electronic health records and administrative claims, offer potential to estimate effects of medical products at scale. Observational studies have often been found to be nonreproducible, however, generating conflicting results even when using the same database to answer the

age treatment effect. Systematic error can manifest from multiple sources, including confounding, selection bias, and measurement error. While there is widespread awareness of the potential for systematic error in observational studies and a large body of research that examines how to diagnose and statistically adjust

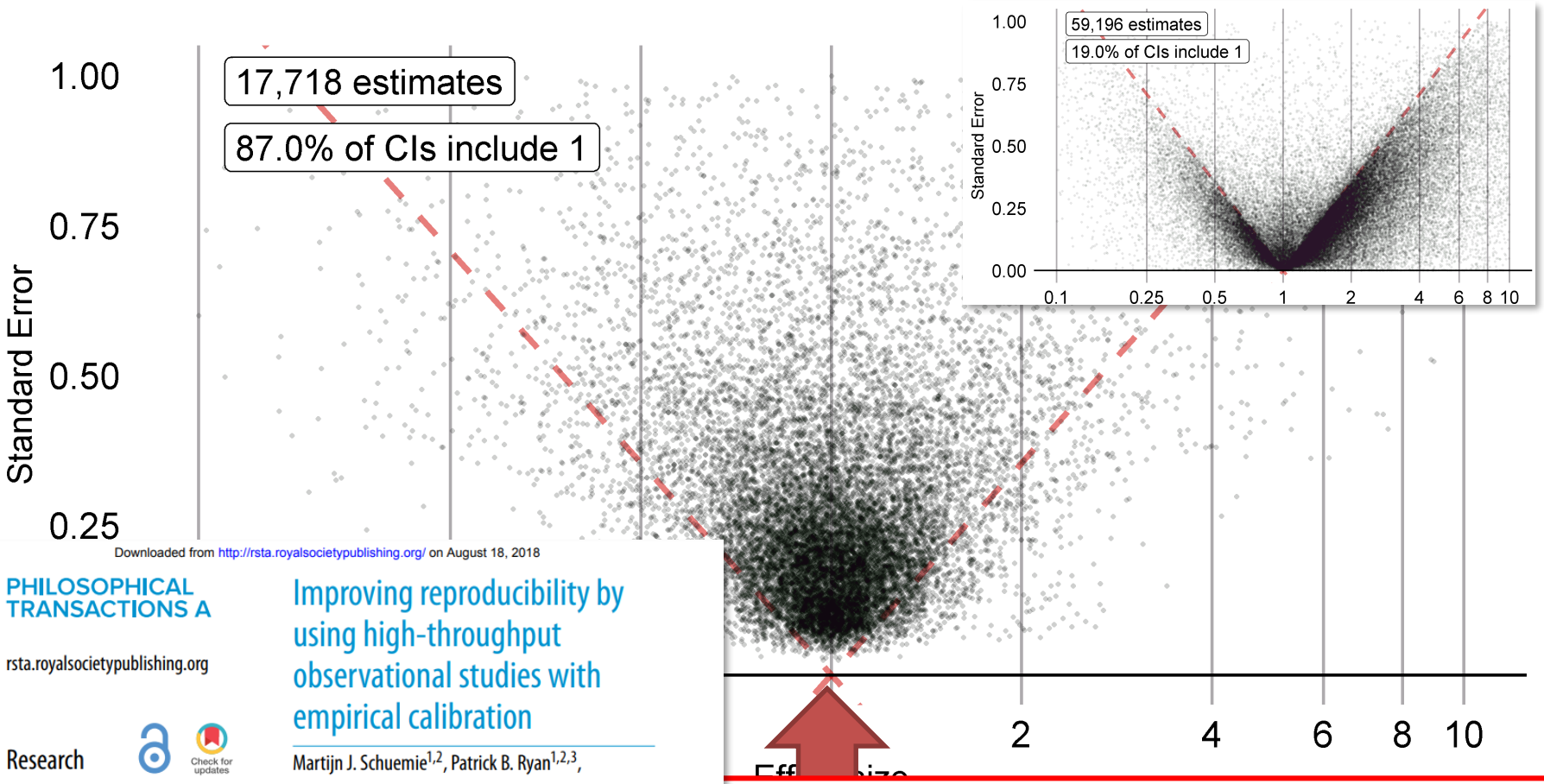
Solving publication bias and p-hacking

- Fully specified protocols
- Pre-registering studies
- Open science
- Large-scale studies…

Depression proof of concept



Results of proposed solution



PHILOSOPHICAL TRANSACTIONS A

rsta.royalsocietypublishing.org

Research

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http://dx.doi.org/10.1098/rsta.2017.0356

Accepted: 8 May 2018

Improving reproducibility by using high-throughput observational studies with empirical calibration

Martijn J. Schuemie[1,2], Patrick B. Ryan[1,2,3], George Hripcsak[1,3,4], David Madigan[1,5] and Marc A. Suchard[1,6,7,8]

[1]Observational Health Data Sciences and Informatics (OHDSI), New York, NY 10032, USA
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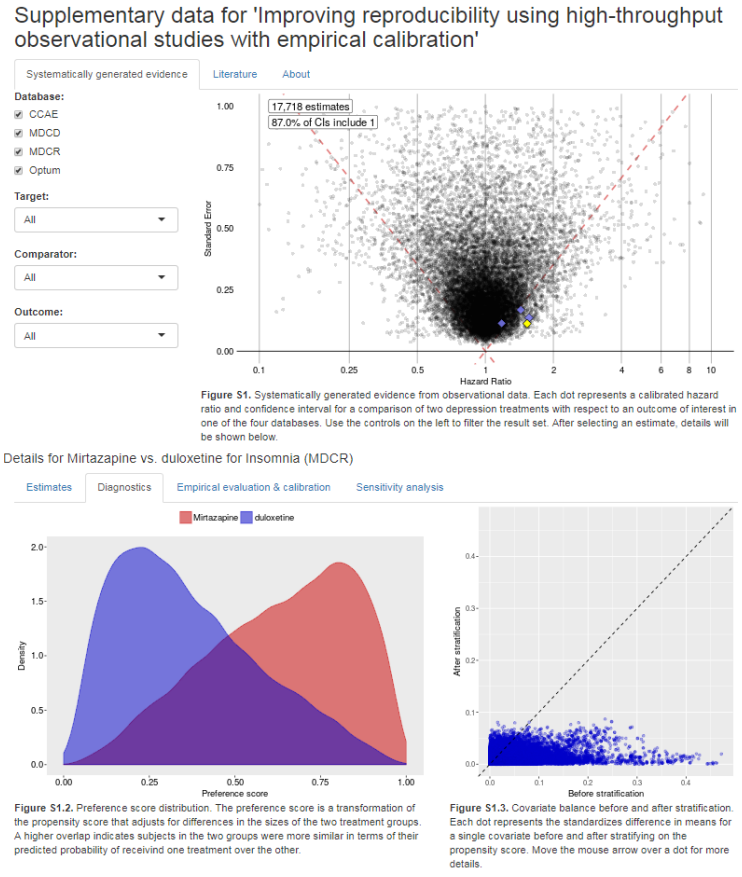
[3]Department of Biomedical Informatics, Columbia University Medical Center, New York, NY 10032, USA

- …nation on small effect sizes
- …essed using negative and positive controls
- …no publication bias

Depression results publicly available

http://data.ohdsi.org/SystematicEvidence/



LEGEND

LARGE-SCALE EVIDENCE GENERATION AND EVALUATION IN A NETWORK OF DATABASES

Building the process to generate the evidence

LEGEND Guiding Principles

1. Evidence will be generated at **large-scale**.
2. **Dissemination** of the evidence will not depend on the estimated effects.
3. Evidence will be generated by consistently applying a **systematic approach** across all research questions.
4. The evidence will be generated using a **pre-specified** analysis design.
5. The evidence will be generated using **open source** software that is freely available to all.
6. The evidence generation process will be **empirically evaluated** by including control research questions where the true effect size is known.
7. The evidence will be generated using **best-practices**.
8. LEGEND will **not** be used to **evaluate methods**.
9. The evidence will be **updated** on a regular basis.
10. **No patient-level data** will be shared between sites in the network, only aggregated data.

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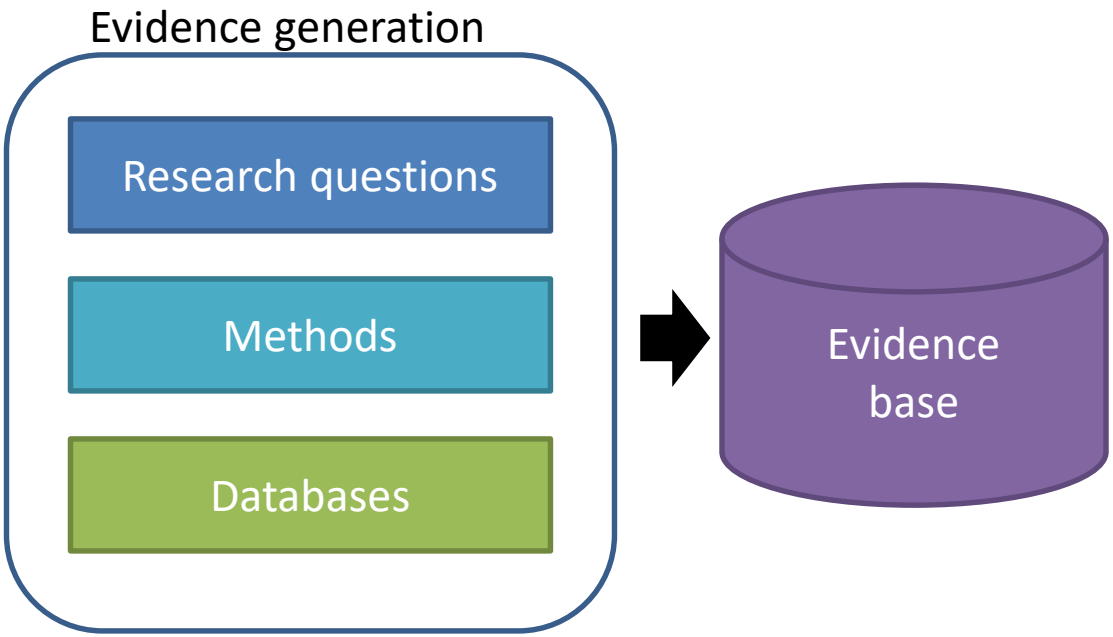
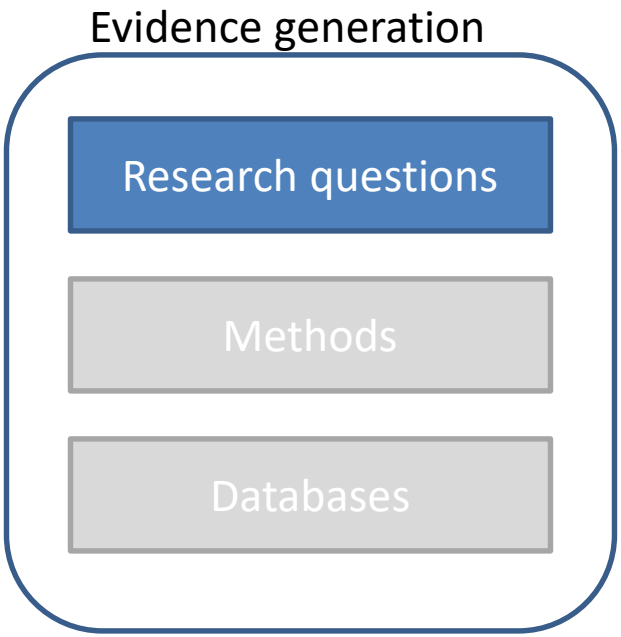
LEGEND


Evidence generation
Research questions
Methods
Databases
Evidence base

Research questions



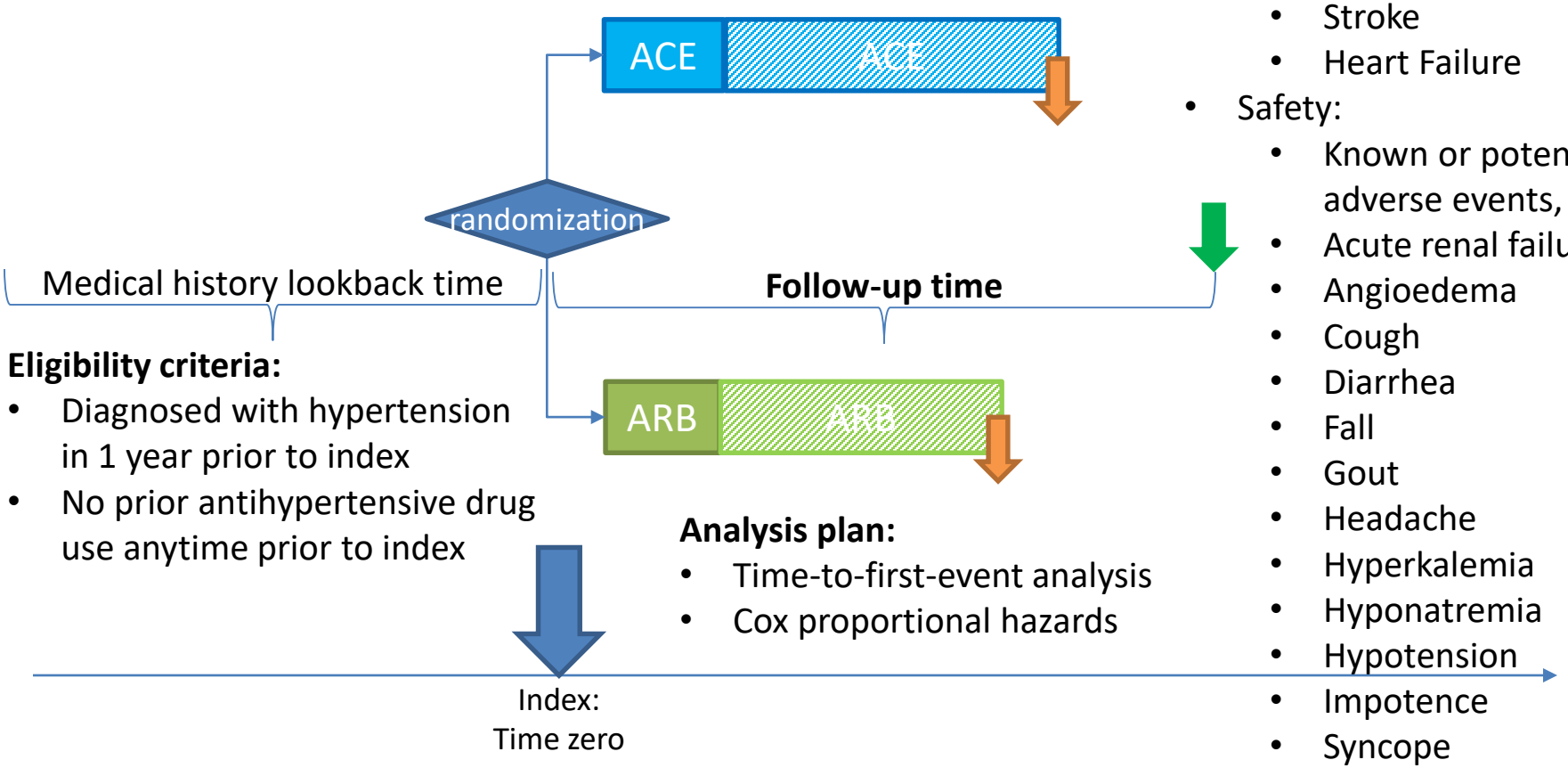
Previously: Depression treatments

This run: Hypertension treatments

‘Target trial’ to compare two initial therapies

Treatment strategies:
- Monotherapy with ACE
- Monotherapy with ARB

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect



Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure
- Safety:
  - Known or potential adverse events, e.g.
  - Acute renal failure
  - Angioedema
  - Cough
  - Diarrhea
  - Fall
  - Gout
  - Headache
  - Hyperkalemia
  - Hyponatremia
  - Hypotension
  - Impotence
  - Syncope
  - Vertigo

Observational study to compare two initial therapies

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- Monotherapy with ARB

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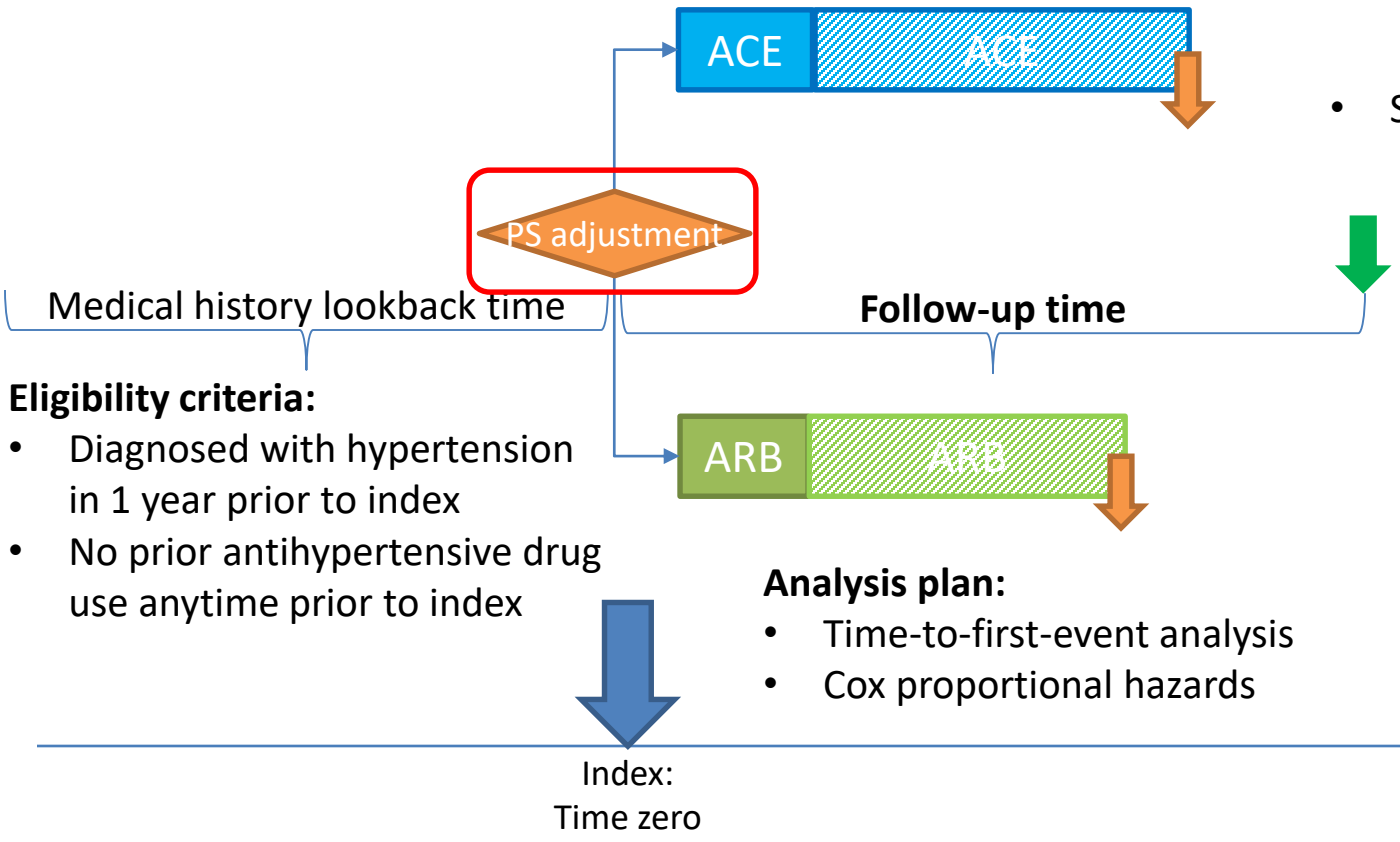

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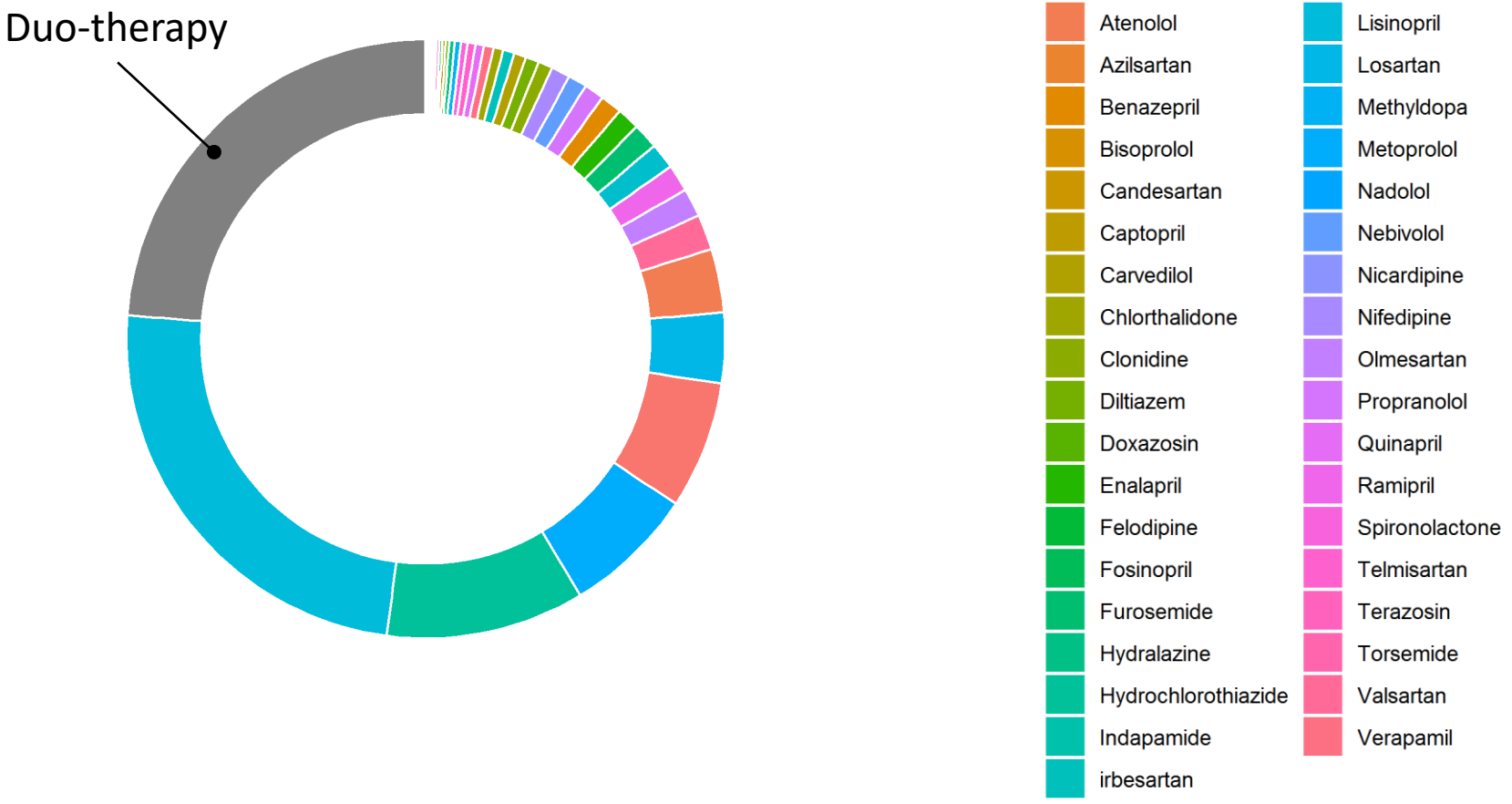
Hypertension mono-therapy



Truven Health MarketScan CCAE. Therapies > 2 ingredients not shown

Comparisons of hypertension treatments

	Theoretical	Observed (n > 2,500)
Single ingredients	58	39
Single ingredient comparisons	58 * 57 = 3,306	1,296
Single drug classes	15	13
Single class comparisons	15 * 14 = 210	156

‘Target trial’ to compare mono vs combination therapy

Treatment strategies:

- Monotherapy with ACE
- Monotherapy with THZ
- Combination therapy with ACE+THZ

Causal contrasts of interest:

- Intent-to-treat effect
- On-treatment effect

Outcomes:

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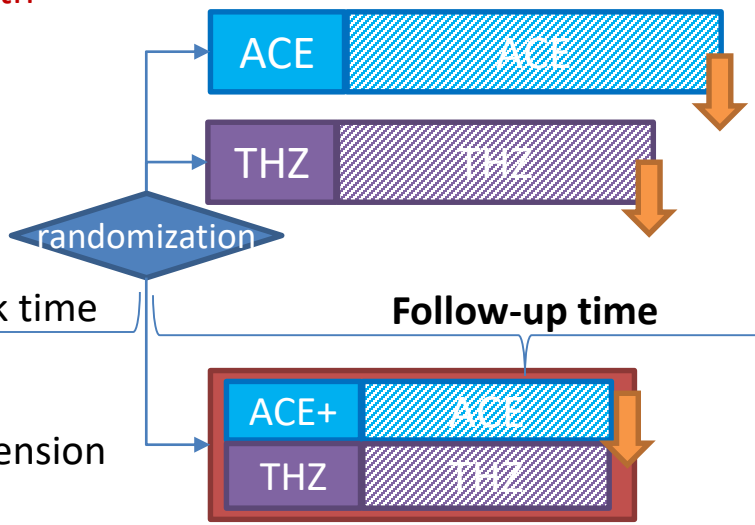

Medical history lookback time

Follow-up time

Eligibility criteria:

- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Index:
Time zero

Analysis plan:

- Time-to-first-event analysis
- Cox proportional hazards
- Two pairwise comparisons:
  - ACE vs. ACE+THZ
  - THZ vs. ACE+THZ

Observational study to compare mono vs combination therapy

Treatment strategies:
- Monotherapy with ACE
- Monotherapy with THZ
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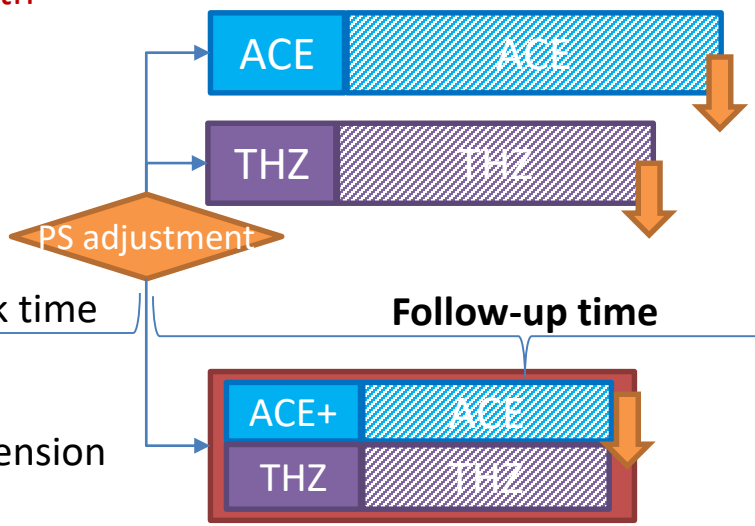

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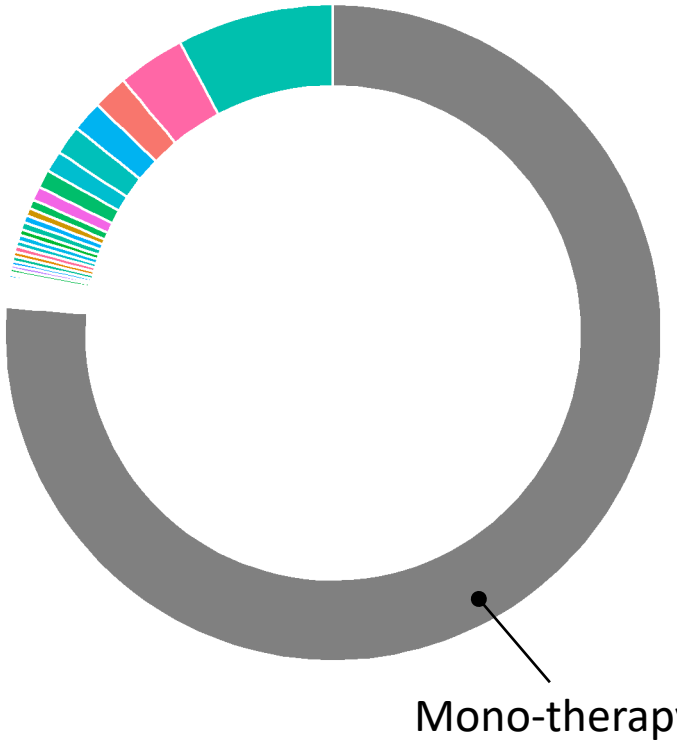
Hypertension duo-therapy



- Amlodipine & Benazepril
- Amlodipine & Carvedilol
- Amlodipine & Clonidine
- Amlodipine & Losartan
- Amlodipine & Olmesartan
- Amlodipine & Ramipril
- Atenolol & Amlodipine
- Atenolol & Chlorthalidone
- Atenolol & Losartan
- Carvedilol & Losartan
- Furosemide & Amlodipine
- Furosemide & Atenolol
- Furosemide & Carvedilol
- Furosemide & Diltiazem
- Furosemide & Lisinopril
- Furosemide & Losartan
- Furosemide & Metoprolol
- Furosemide & Spironolactone
- Hydralazine & Labetalol
- Hydrochlorothiazide & Amlodipine
- Hydrochlorothiazide & Atenolol
- Hydrochlorothiazide & Benazepril
- Hydrochlorothiazide & Bisoprolol
- Hydrochlorothiazide & Candesartan
- Hydrochlorothiazide & Diltiazem
- Hydrochlorothiazide & Enalapril
- Hydrochlorothiazide & irbesartan
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- Hydrochlorothiazide & Quinapril
- Hydrochlorothiazide & Ramipril
- Hydrochlorothiazide & Telmisartan
- Hydrochlorothiazide & Valsartan
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- Lisinopril & Atenolol
- Lisinopril & Carvedilol
- Lisinopril & Clonidine
- Lisinopril & Diltiazem
- Lisinopril & Labetalol
- Lisinopril & Losartan
- Lisinopril & Propranolol
- Metoprolol & Amlodipine
- Metoprolol & Diltiazem
- Metoprolol & Enalapril
- Metoprolol & Hydralazine
- Metoprolol & Labetalol
- Metoprolol & Lisinopril
- Metoprolol & Losartan
- Metoprolol & Ramipril
- Metoprolol & Valsartan
- Nifedipine & Labetalol
- Ramipril & Bisoprolol
- Triamterene & Hydrochlorothiazide
- Valsartan & Amlodipine
- Verapamil & Lisinopril
- Verapamil & Trandolapril

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Single class comparisons	15 * 14 = 210	156
Dual ingredients	58 * 57 / 2 = 1,653	58
Single vs duo drug comparisons	58 * 1,653 = 95,874	3,810
Dual classes	15 * 14 / 2 = 105	32
Single vs duo class comparisons	15 * 105 = 1,575	832

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Duo vs duo drug comparisons	1,653 * 1,652 = 2,730,756	2,784
Duo vs duo class comparisons	105 * 104 = 10,920	992

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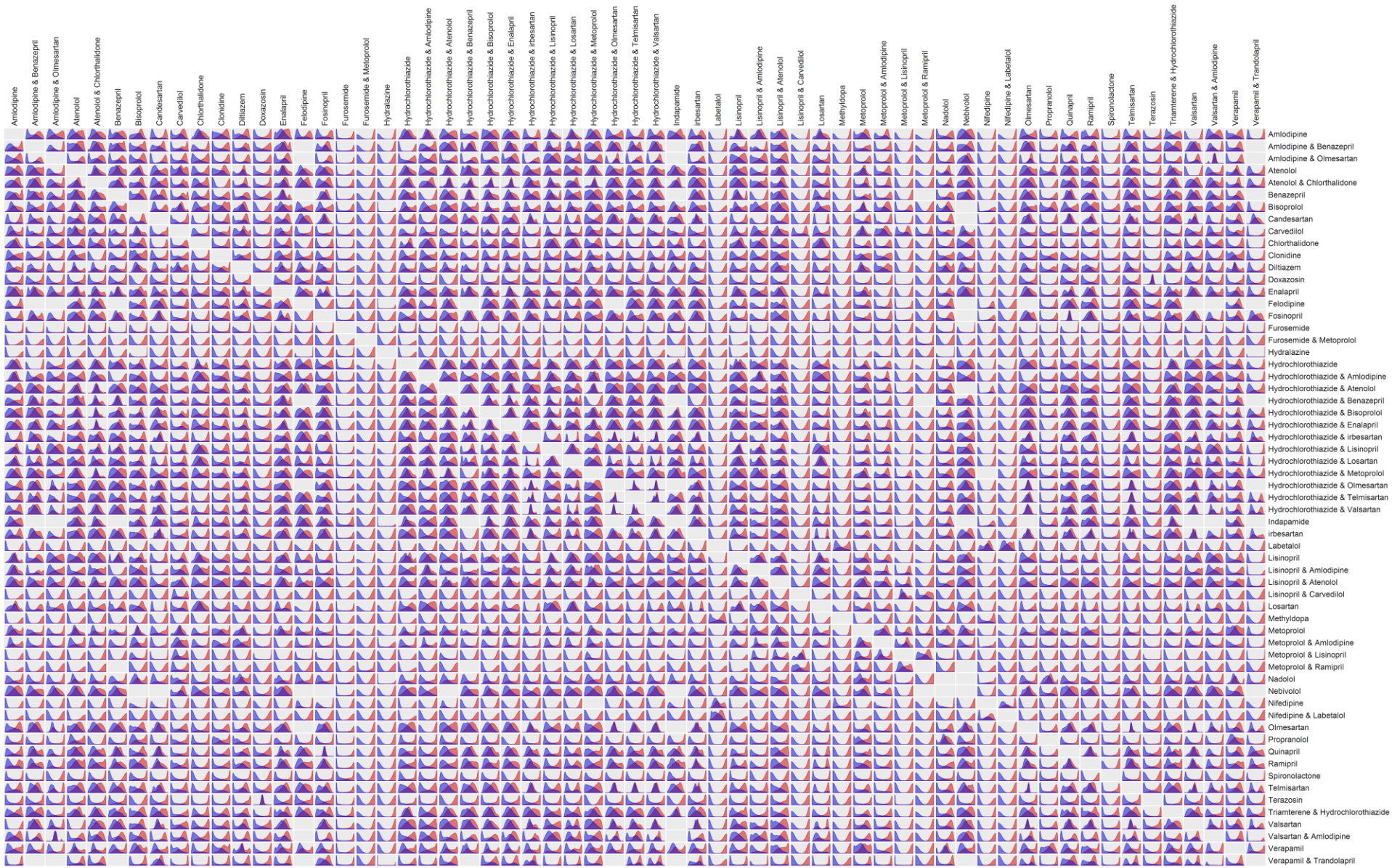
Duo vs duo drug comparisons	1,653 * 1,652 = 2,730,756	2,784
Duo vs duo class comparisons	105 * 104 = 10,920	992
…	…	…
Total comparisons	2,843,250	10,278

Not all comparisons are valid



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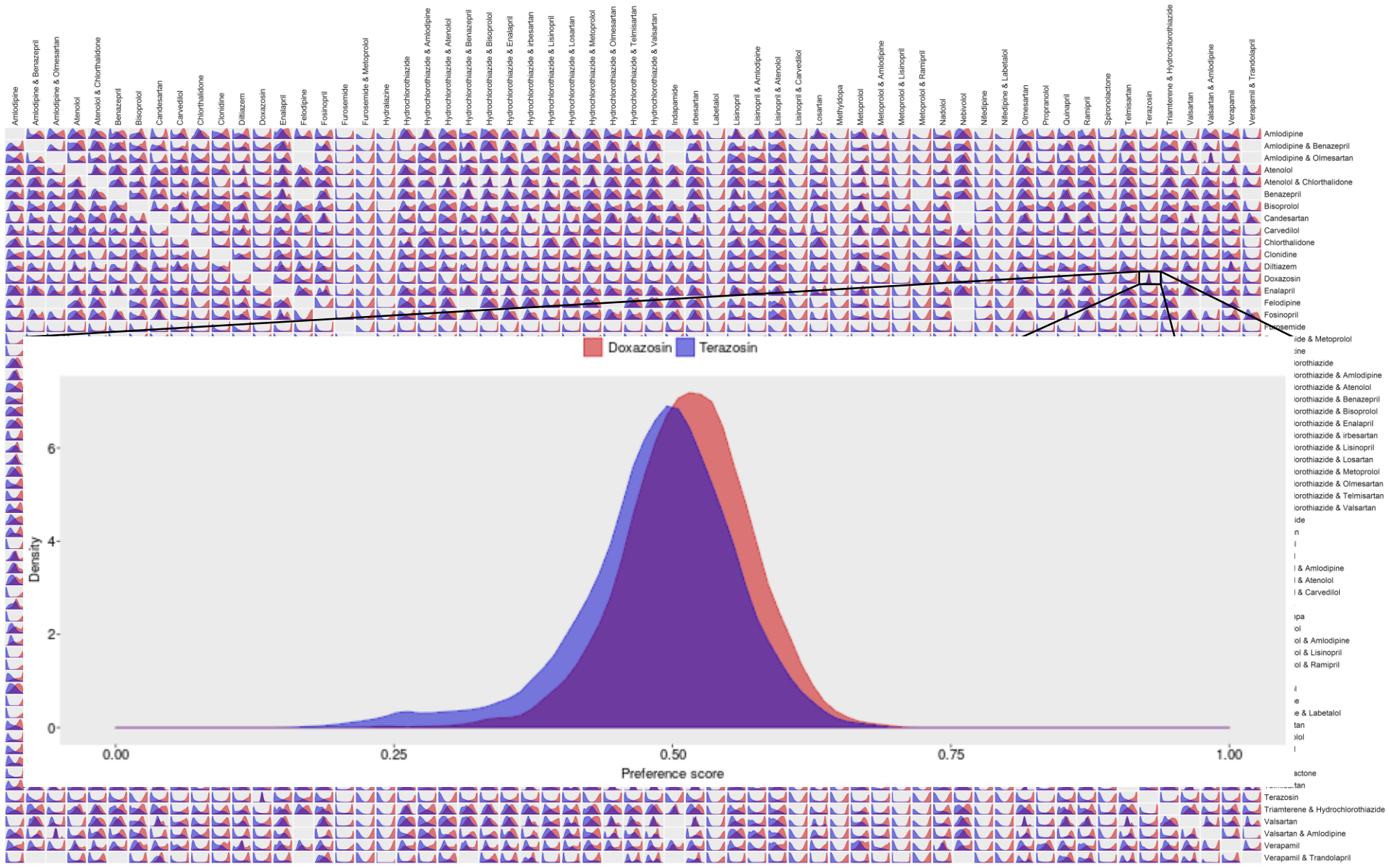

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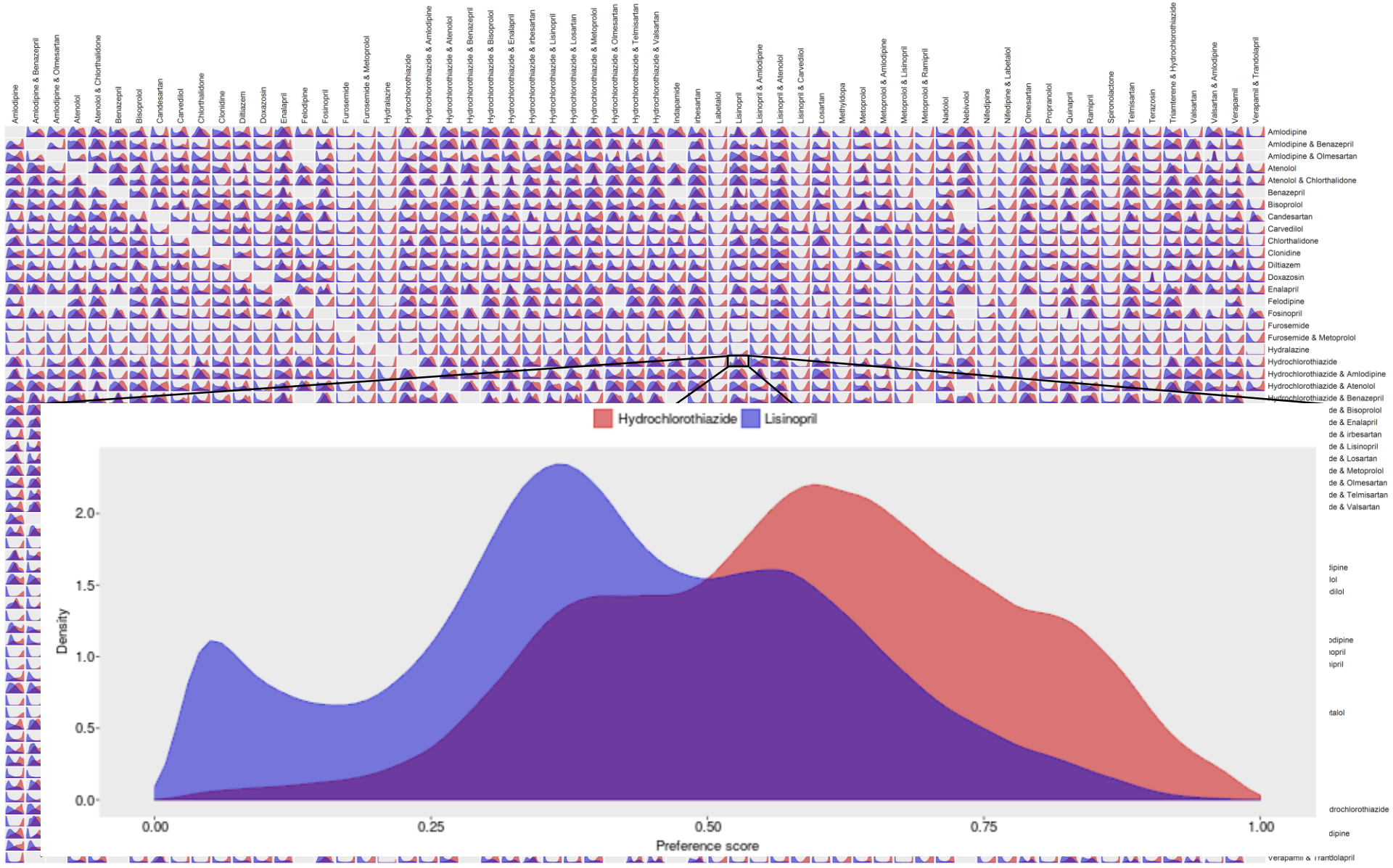

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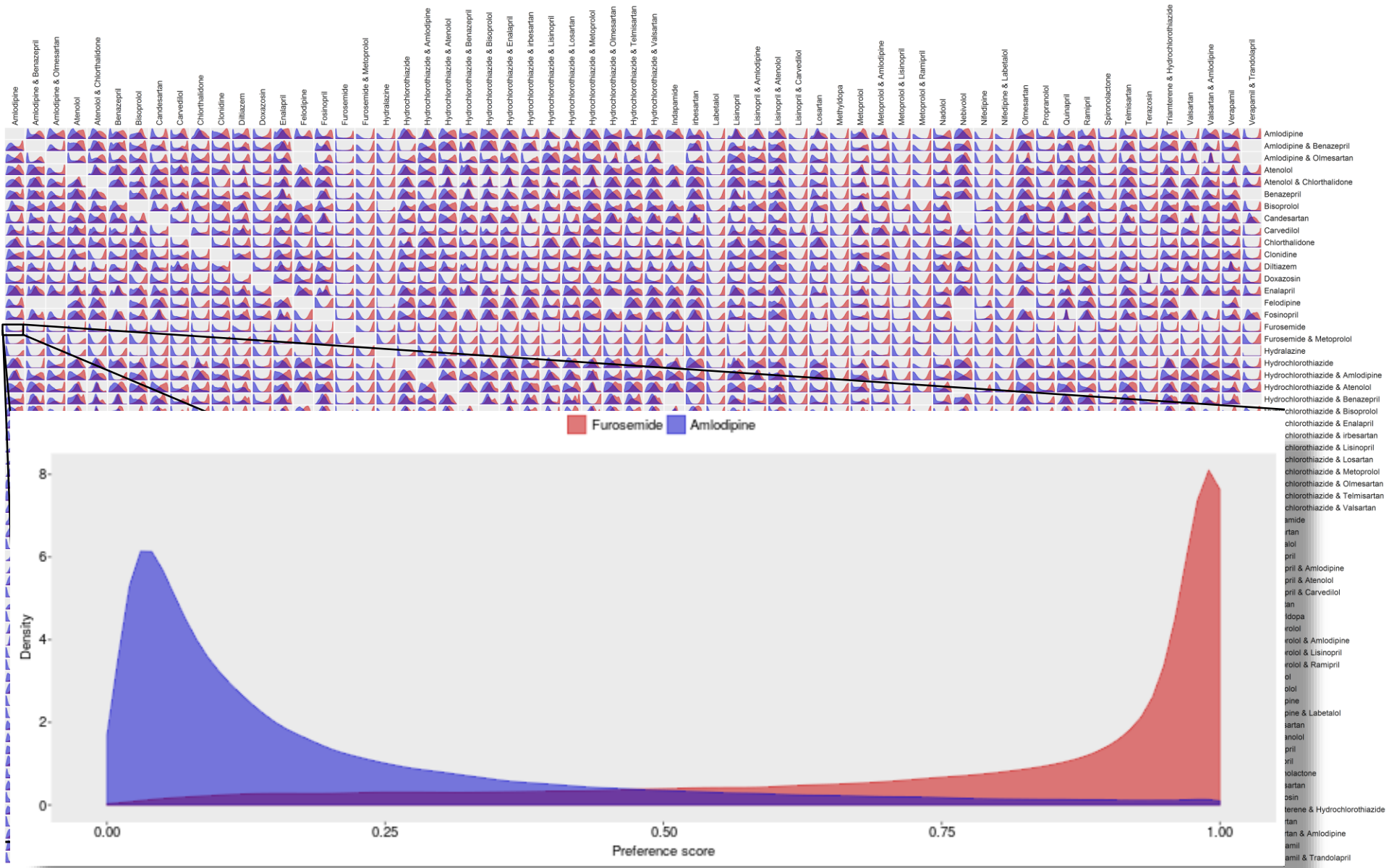


58 outcomes of interest

Abdominal pain
Abnormal weight gain
Abnormal weight loss
Acute myocardial infarction
Acute pancreatitis
Acute renal failure
All-cause mortality
Anaphylactoid reaction
Anemia
Angioedema
Anxiety
Bradycardia
Cardiac arrhythmia
Cardiovascular disease
Cardiovascular-related mortality
Chest pain or angina
Chronic kidney disease
Coronary heart disease
Cough
Decreased libido
Dementia
Depression
Diarrhea
Edema
End stage renal disease
Fall
Gastrointestinal bleeding
Gout
Headache
Heart failure
Hemorrhagic stroke
Hepatic failure
Hospitalization with heart failure
Hospitalization with preinfarction syndrome
Hyperkalemia
Hypokalemia
Hypomagnesemia
Hyponatremia
Hypotension
Impotence
Ischemic stroke
Kidney disease
Malignant neoplasm
Measured renal dysfunction
Nausea
Neutropenia or agranulocytosis
Rash
Rhabdomyolysis
Stroke
Sudden cardiac death
Syncope
Thrombocytopenia
Transient ischemic attack
Type 2 diabetes mellitus
Vasculitis
Venous thromboembolic events
Vertigo
Vomiting

58 outcomes of interest

Abdominal pain
Abnormal weight gain
Abnormal weight loss
Acute myocardial infarction
Acute pancreatitis
Acute renal failure
All-cause mortality
Bradycardia
Cardiac arrhythmia
Cardiovascular disease
Cardiovascular-related mortality
Chest pain or angina
Chronic kidney disease
Coronary heart disease
Cough
Decreased libido
Dementia
Depression
Diarrhea
Edema
End stage renal disease
Fall
Gastrointestinal bleeding
Hepatic failure
Hospitalization with heart failure
Hospitalization with preinfarction syndrome
Hyperkalemia
Hypokalemia
Hypomagnesemia
Hyponatremia
Hypotension
Impotence
Ischemic stroke
Kidney disease
Malignant neoplasm
Measured renal dysfunction
Nausea
Neutropenia or agranulocytosis
Rash
Thrombocytopenia
Transient ischemic attack
Type 2 diabetes mellitus
Vasculitis
Venous thromboembolic events
Vertigo
Vomiting

	Theoretical	Observed (n > 2,500)
Outcomes of interest	58	58
Target-comparator-outcomes	2,843,250 * 58 = 164,908,500	587,020

Each research question requires

- Evaluation of the propensity score distribution
- Evaluation of covariate balance
- Inclusion of negative and positive controls
- Empirical calibration

76 negative controls

Abnormal cervical smear
Abnormal pupil
Abrasion and/or friction burn of trunk without infection
Absence of breast
Absent kidney
Acid reflux
Acquired hallux valgus
Acquired keratoderma
Acquired trigger finger
Acute conjunctivitis
Amputated foot
Anal and rectal polyp
Burn of forearm
Calcaneal spur
Cannabis abuse
Cervical somatic dysfunction
Changes in skin texture
Chondromalacia of patella
Cocaine abuse
Colostomy present
Complication due to Crohn's disease
Contact dermatitis
Contusion of knee
Crohn's disease
Derangement of knee
Difficulty sleeping
Disproportion of reconstructed breast
Effects of hunger
Endometriosis
Epidermoid cyst
Feces contents abnormal
Foreign body in orifice
Ganglion cyst
Genetic predisposition
Hammer toe
Hereditary thrombophilia
Herpes zoster without complication
High risk sexual behavior
Homocystinuria
Human papilloma virus infection
Ileostomy present
Impacted cerumen
Impingement syndrome of shoulder region
Ingrowing nail
Injury of knee
Irregular periods
Kwashiorkor
Late effect of contusion
Late effect of motor vehicle accident
Leukorrhea
Macular drusen
Melena
Nicotine dependence
Noise effects on inner ear
Nonspecific tuberculin test reaction
Non-toxic multinodular goiter
Onychomycosis due to dermatophyte
Opioid abuse
Passing flatus
Postviral fatigue syndrome
Presbyopia
Problem related to lifestyle
Psychalgia
Ptotic breast
Regular astigmatism
Senile hyperkeratosis
Somatic dysfunction of lumbar region
Splinter of face, without major open wound
Sprain of ankle
Strain of rotator cuff capsule
Tear film insufficiency
Tobacco dependence syndrome
Vaginitis and vulvovaginitis
Verruca vulgaris
Wrist joint pain
Wristdrop

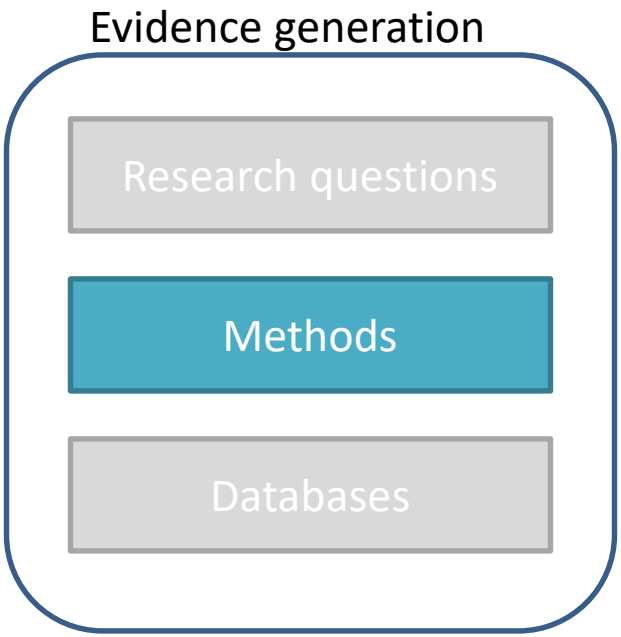
76 negative controls

Abnormal cervical smear
Abnormal pupil
Abrasion and/or friction burn of trunk without infection
Absence of breast
Absent kidney
Acid reflux
Acquired hallux valgus
Acquired keratoderma
Acquired trigger finger
Disproportion of reconstructed breast
Effects of hunger
Endometriosis
Epidermoid cyst
Feces contents abnormal
Foreign body in orifice
Ganglion cyst
Genetic predisposition
Hammer toe
Nicotine dependence
Noise effects on inner ear
Nonspecific tuberculin test reaction
Non-toxic multinodular goiter
Onychomycosis due to dermatophyte
Opioid abuse
Passing flatus
Postviral fatigue syndrome
Presbyopia

	Theoretical	Observed (n > 2,500)
Negative control outcomes	76	76
Target-comparator-neg controls	2,843,250 * 76 = 216,087,000	769,476
Positive control outcomes	76 * 3 = 228	228
Target-comparator-pos controls	2,843,250 * 228 = 648,261,000	662,484
Total control target-comparator- outcomes	864,348,000	1,431,960

Contusion of knee
Crohn's disease
Derangement of knee
Difficulty sleeping
Late effect of motor vehicle accident
Leukorrhea
Macular drusen
Melena
Wrist joint pain
Wristdrop

Methods



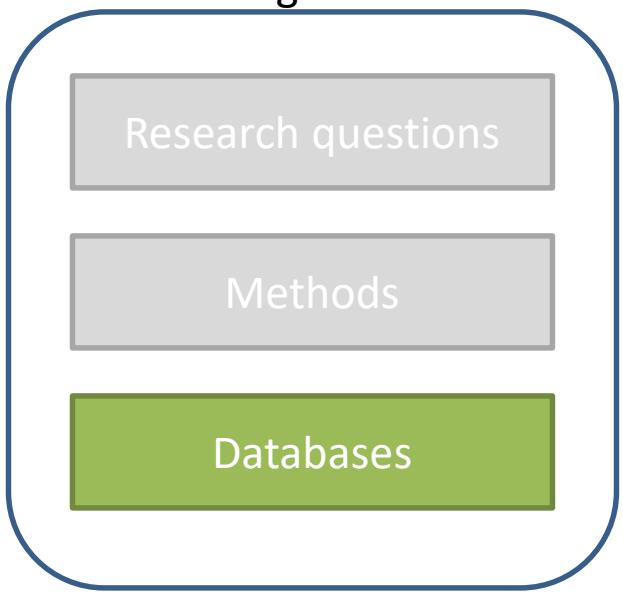
This run:

- Emulate target trial: new-user cohort design
- Expert-crafted outcome definitions
- Large scale propensity models
- Stratification + variable ratio matching
- Empirical calibration

Not static. Driven by **defined best practices**, driven by **empirical evaluation**

Databases

Evidence generation



Ajou University

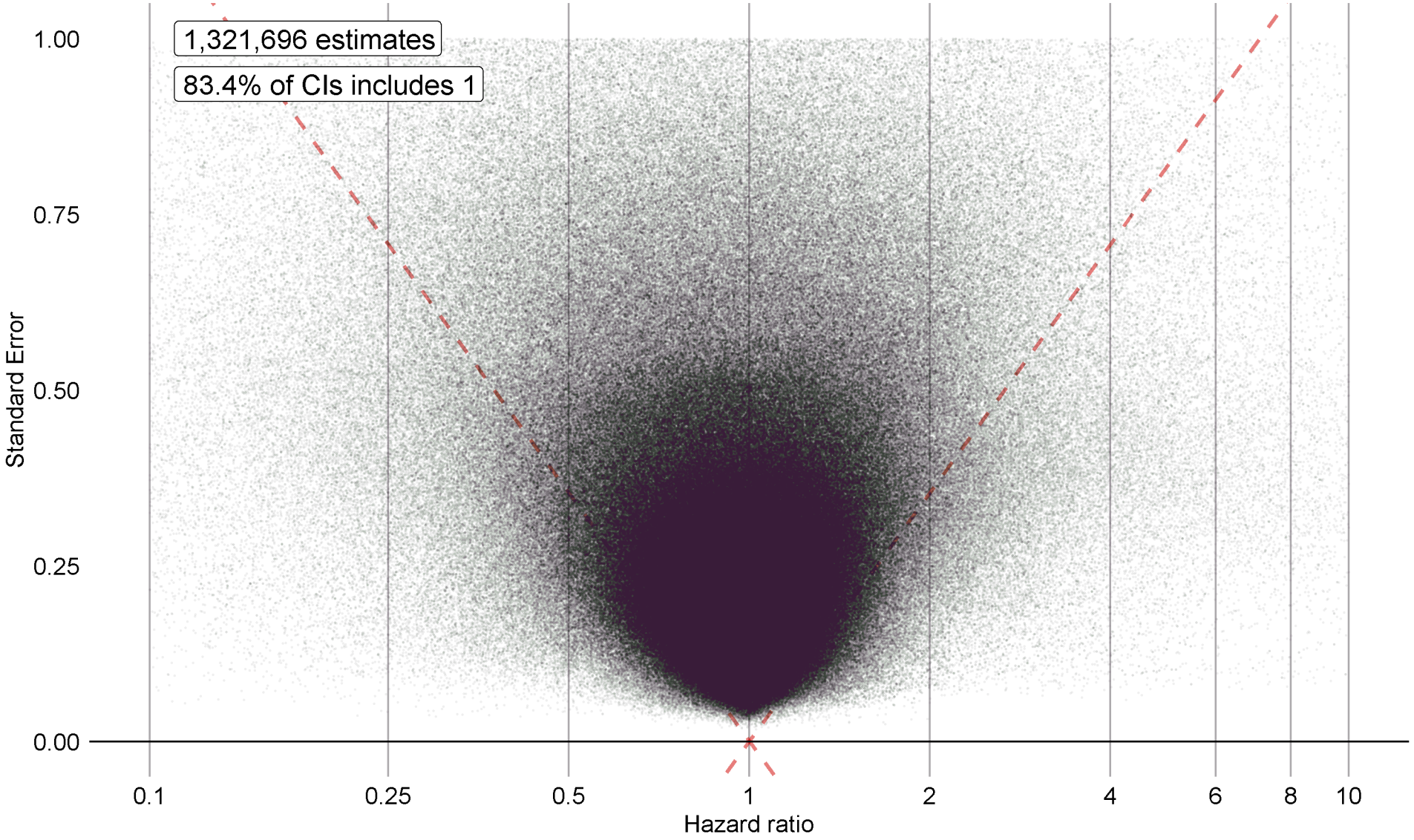
Columbia University

Previously: 4 US insurance databases

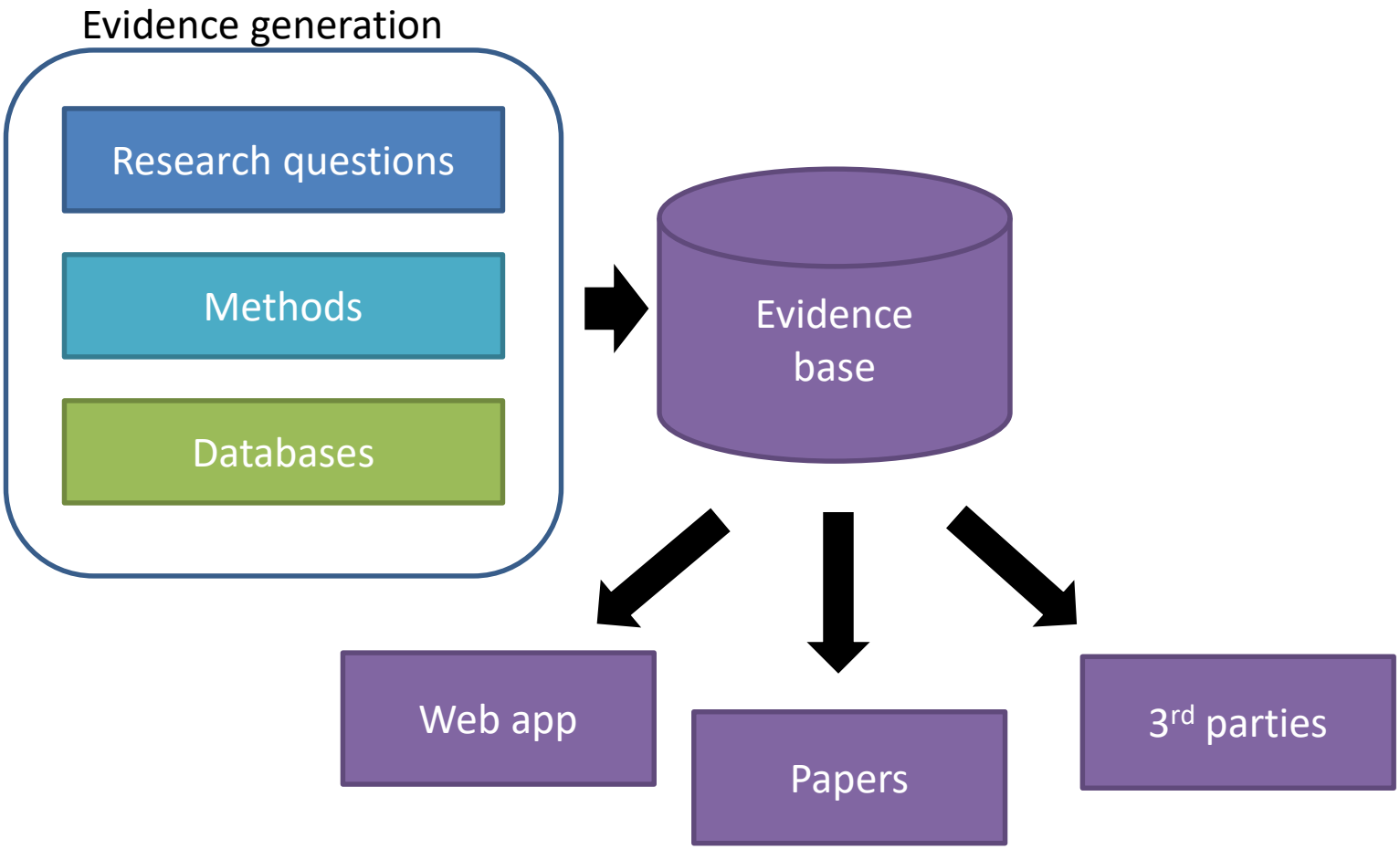
This run:

- US insurance databases
  - IBM® MarketScan® CCAE
  - IBM® MarketScan® MDCD
  - IBM® MarketScan® MDCR
  - Optum© Clinformatics®
- Japanese insurance database
  - Japan Medical Data Center
- Korean national insurance database
  - NHIS-NSC
- US EHR databases
  - Columbia University Medical Center
  - Optum© PANTHER®
- German EHR database
  - QuintilesIMS Disease Analyzer (DA) Germany

LEGEND results



Dissemination



LEGEND results model

Study specification

indications

indication
- indication_id
- Indication_name
- definition

analyses

cohort_method_analysis
- analysis_id
- description
- definition

covariate_analysis
- covariate_analysis_id
- covariate_analysis_name

incidence_analysis
- incidence_analysis_id
- incidence_analysis_name

exposures

single_exposure_of_interest
- exposure_id
- exposure_name
- description
- indication_id
- definition
- filter_concept_ids

combi_exposure_of_interest
- exposure_id
- exposure_name
- description
- single_exposure_id_1
- single_exposure_id_2
- indication_id

exposure_group
- exposure_id
- exposure_group

outcomes

outcome_of_interest
- outcome_id
- outcome_name
- description
- definition
- indication_id

positive_control_outcome
- outcome_id
- outcome_name
- exposure_id
- negative_control_id
- effect_size
- indication_id

negative_control_outcome
- outcome_id
- outcome_name
- concept_id
- indication_id

Generated results

metadata

database
- database_id
- database_name
- description
- is_meta_analysis

exposure_summary
- database_id
- exposure_id
- min_date
- max_date

comparison_summary
- database_id
- target_id
- comparator_id
- min_date
- max_date

attrition
- database_id
- exposure_id
- [target_id]
- [comparator_id]
- [outcome_id]
- [analysis_id]
- sequence_number
- description
- subjects*

cm_follow_up_dist
- database_id
- target_id
- comparator_id
- outcome_id
- analysis_id
- target_min_days
- target_p10_days
- target_p25_days
- target_median_days
- target_p75_days
- target_p90_days
- target_max_days
- comparator_min_days
- comparator_p10_days
- comparator_p25_days
- comparator_median_days
- comparator_p75_days
- comparator_p90_days
- comparator_max_days

covariate
- database_id
- covariate_id
- covariate_name
- covariate_analysis_id

main results

cohort_method_result
- database_id
- target_id
- comparator_id
- outcome_id
- analysis_id
- rr
- ci_95_lb
- ci_95_ub
- p
- [i_2]
- log_rr
- se_log_rr
- target_subjects*
- comparator_subjects*
- target_days
- comparator_days
- target_outcomes*
- comparator_outcomes*
- calibrated_p
- calibrated_rr
- calibrated_ci_95_lb
- calibrated_ci_95_ub
- calibrated_log_rr
- calibrated_se_log_rr

cm_interaction_result
- database_id
- target_id
- comparator_id
- outcome_id
- analysis_id
- interaction_covariate_id
- rrr
- ci_95_lb
- ci_95_ub
- p
- [i_2]
- log_rrr
- se_log_rrr
- target_subjects*
- comparator_subjects*
- target_days
- comparator_days
- target_outcomes*
- comparator_outcomes*
- calibrated_p

chronograph
- database_id
- exposure_id
- outcome_id
- time
- outcomes*
- expected_outcomes
- ic*
- ic_lb*
- ic_ub*

incidence
- database_id
- exposure_id
- [interaction_covariate_id]
- outcome_id
- incidence_analysis_id
- subjects*
- days
- outcomes*

diagnostics

covariate_balance
- database_id
- target_id
- comparator_id
- [outcome_id]
- [analysis_id]
- [interaction_covariate_id]
- covariate_id
- target_mean_before*
- comparator_mean_before*
- std_diff_before
- target_mean_after*
- comparator_mean_after*
- std_diff_after

preference_score_dist
- database_id
- target_id
- comparator_id
- preference_score
- target_density
- comparator_density

kaplan_meier_dist
- database_id
- target_id
- comparator_id
- outcome_id
- analysis_id
- time
- [target_at_risk*]
- [comparator_at_risk*]
- target_survival
- target_survival_lb
- target_survival_ub
- comparator_survival
- comparator_survival_lb
- comparator_survival_ub

propensity_model
- database_id
- target_id
- comparator_id
- covariate_id
- coefficient

underscore indicates primary key

[ ] indicates nullable

* indicates fields with a minimum value to avoid identifiability

LEGEND basic viewer

http://data.ohdsi.org/LegendBasicViewer/

LEGENDMed Central

http://data.ohdsi.org/LegendMedCentral/

Concluding remarks

- Grave concerns exist over published observational research results, due to study bias, publication bias, and p-hacking
- Large-scale observational studies allow for
  - Empirical evaluation and calibration
  - Unbiased dissemination
  - Providing a more complete evidence base
- LEGEND applies this to real world problems
  - Depression
  - Hypertension