Large-scale Evidence Generation and Evaluation across a Network of Databases (LEGEND)

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www.ohdsi.org
Large-scale Data Analytics
Goal: To generate real world evidence on the effects of medical interventions using observational healthcare data to support clinical decision making

How: Developing a comprehensive framework for doing observational health-care science at scale
The trouble with observational research....

Maybe the data is a bit dirty!

Maybe just tweak the analysis a little bit!

An Answer!

Another Answer!

Another Answer!

P-hacking!

Publication bias

If at first you don’t succeed, try 3 more times so that your failure is statistically significant.
P-hacking and publication bias!

Schuemie M. et al. Improving reproducibility by using high-throughput observational studies with empirical calibration. Phil Trans Royal Society 2018
Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Marc A Suchard, Martijn J Schuemie, Harlan M Krumholz, Seng Chan You, Ruijun Chen, Nicole Pratt, Christian G Reich, Jon Duke, David Madigan, George Hripcsak, Patrick B Ryan

www.thelancet.com Published online October 24, 2019 https://doi.org/10.1016/S0140-6736(19)32317-7
LEGEND in action...

Head-to-head HTN drug comparisons

- Trials: 40
- $N = 102 - [1148] - 33K$
LEGEND in action...

LEGEND knowledge base for hypertension

Head-to-head HTN drug comparisons

- Trials: 40
- N = 102 – [1148] – 33K
- Comparisons: 10,278
- N = 3502 – [212K] – 1.9M

55 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 preinfection syndrome
- Hyperkalemia
- Hypokalemia
- Hypomagnesemia
- Hypotenension
- 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

22,000 calibrated, propensity score adjusted hazard ratios
A picture is worth a 1000 ANALYSES.....
Published observational study results

59,196 estimates
19.0% of CIs include 1

Suspicious cutoff at p=0.05
- Publication bias (leads to false positives)
- P-hacking (leads to false positives)

LEGEND results

1,321,696 estimates
83.4% of CIs includes 1
Enhancing the dissemination of results (the results have their own data model!)
### Study specification

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### Generated results

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### Metadata

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

- Attrition
  - database_id
  - exposure_id
  - target_id
  - comparator_id
  - min_date
  - max_date

- Covariate
  - database_id
  - exposure_id
  - target_id
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  - outcome_id
  - analysis_id

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### Diagnostics

- Kaplan_meyer_dist
  - database_id
  - target_id
  - comparator_id
  - preference_score
  - target_density
  - comparator_density

- Propensity_model
  - database_id
  - target_id
  - comparator_id
  - coefficients

* indicates fields with a minimum value to avoid identifiability

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[] indicates nullable

underscore indicates primary key
https://data.ohdsi.org/LegendBasicViewer/
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</table>

**Table:** The table displays the effect sizes of different treatments compared to placebo, with 95% confidence intervals (CI) and p-values. The outcomes are presented for patients treated with ACE inhibitors, comparing the effect of different treatments on the primary outcome.
Figure 2. Preference score distribution. The preference score is a transformation of the propensity score that adjusts for differences in the scores of the two treatment groups. A higher overlap indicates subjects in the two groups were more similar in terms of their predicted probability of receiving one treatment over the other.