The use of negative control in Pharmacoepidemiological study

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Dr Kenneth Man

CW Maplethorpe Fellow

UCL School of Pharmacy

Email: kenneth.man@ucl.ac.uk

Outline

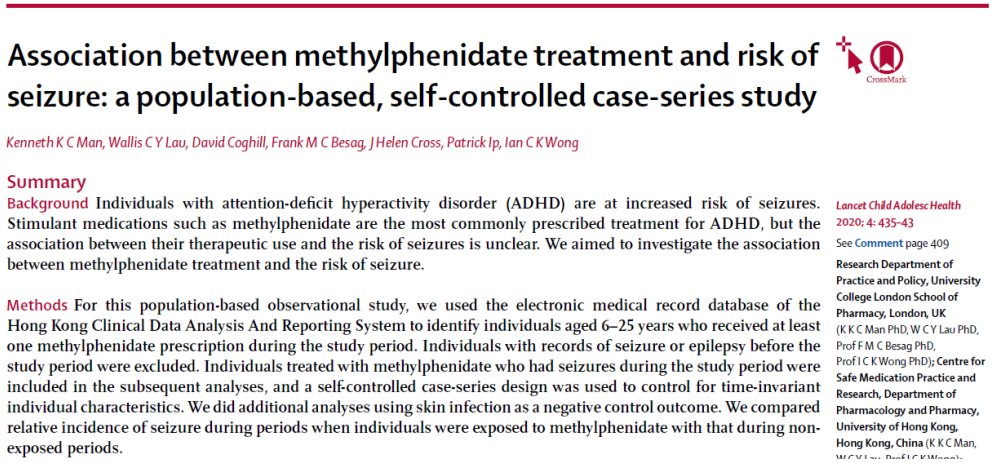
- Background
- Alternative outcome as negative control
  - Methylphenidate and seizure
- Alternative exposure as negative control
  - Prenatal antidepressant and risk of ADHD
- P-value and Confidence interval calibration with negative controls

Background: Negative controls

- Non-causal associations between exposures and outcomes are a threat to validity of causal inference in observational studies
- In laboratory studies, the use of “negative controls” is designed to detect both suspected and unexpected sources of bias
- A negative control analysis isn't expected to have positive results
  - can be used as sensitivity analysis
- In pharmacoepidemiology, negative controls can help to:
  - Identify (or maybe resolve) confounding
  - Identify other sources of bias or analytic flaws

Alternative outcome as negative control

- Exposure: Methylphenidate (MPH)
- Outcome: Seizure
- Data source: Hong Kong CDARS
- Participants: Age 6 to 25
- Study design: Self-controlled case series
- Negative control outcome: Skin infection



Association between methylphenidate treatment and risk of seizure: a population-based, self-controlled case-series study

Kenneth K C Man, Wallis C Y Lau, David Coghill, Frank M C Besag, J Helen Cross, Patrick Ip, Ian C K Wong

Summary

Background Individuals with attention-deficit hyperactivity disorder (ADHD) are at increased risk of seizures. Stimulant medications such as methylphenidate are the most commonly prescribed treatment for ADHD, but the association between their therapeutic use and the risk of seizures is unclear. We aimed to investigate the association between methylphenidate treatment and the risk of seizure.

Methods For this population-based observational study, we used the electronic medical record database of the Hong Kong Clinical Data Analysis And Reporting System to identify individuals aged 6–25 years who received at least one methylphenidate prescription during the study period. Individuals with records of seizure or epilepsy before the study period were excluded. Individuals treated with methylphenidate who had seizures during the study period were included in the subsequent analyses, and a self-controlled case-series design was used to control for time-invariant individual characteristics. We did additional analyses using skin infection as a negative control outcome. We compared relative incidence of seizure during periods when individuals were exposed to methylphenidate with that during non-exposed periods.

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Research Department of Practice and Policy, University College London School of Pharmacy, London, UK (K K C Man PhD, W C Y Lau PhD, Prof F M C Besag PhD, Prof I C K Wong PhD); **Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, China** (K K C Man,

Man KKC et al. Lancet Child & Adolescent Health. 2020

Alternative exposure as negative control

- Exposure: Antidepressant in pregnancy
- Outcome: ADHD in offspring
- Data source: Hong Kong CDARS
- Participants: mother-child pairs
- Study design: cohort
- Negative control exposure:
  - Antidepressant before pregnancy

RESEARCH

Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study

Kenneth K C Man,[1,2,3,4] Esther W Chan,[1] Patrick Ip,[2] David Coghill,[5,6] Emily Simonoff,[7] Phyllis K L Chan,[8] Wallis C Y Lau,[1] Martijn J Schuemie,[9] Miriam C J M Sturkenboom,[4] Ian C K Wong[1,2,3]

For numbered affiliations see end of article.

Correspondence to: I C K Wong, Research Department of Practice and Policy, UCL School of Pharmacy, London WC1N 1AX, UK i.wong@ucl.ac.uk

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ABSTRACT

OBJECTIVE

To assess the potential association between prenatal use of antidepressants and the risk of attention-deficit/hyperactivity disorder (ADHD) in offspring.

DESIGN

Population based cohort study.

SETTING

Data from the Hong Kong population based electronic medical records on the Clinical Data Analysis and Reporting System.

PARTICIPANTS

190 618 children born in Hong Kong public hospitals between January 2001 and December 2009 and followed-up to December 2015.

MAIN OUTCOME MEASURE

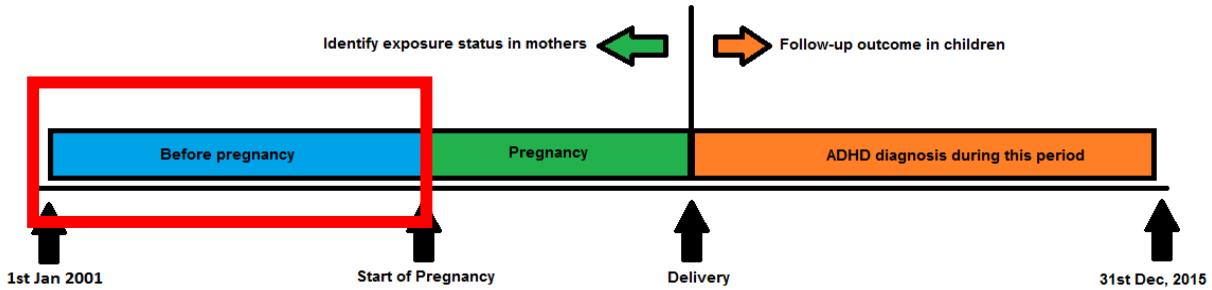
Hazard ratio of maternal antidepressant use during

to 2.30, P<0.01). The risk of ADHD in the children of mothers with psychiatric disorders was higher compared with the children of mothers without psychiatric disorders even if the mothers had never used antidepressants (1.84, 1.54 to 2.18, P<0.01). All sensitivity analyses yielded similar results. Sibling matched analysis identified no significant difference in risk of ADHD in siblings exposed to antidepressants during gestation and those not exposed during gestation (0.54, 0.17 to 1.74, P=0.30).

CONCLUSIONS

The findings suggest that the association between prenatal use of antidepressants and risk of ADHD in offspring can be partially explained by confounding by indication of antidepressants. If there is a causal association, the size of the effect is probably smaller than that reported previously.

Man KKC et al. BMJ. 2017

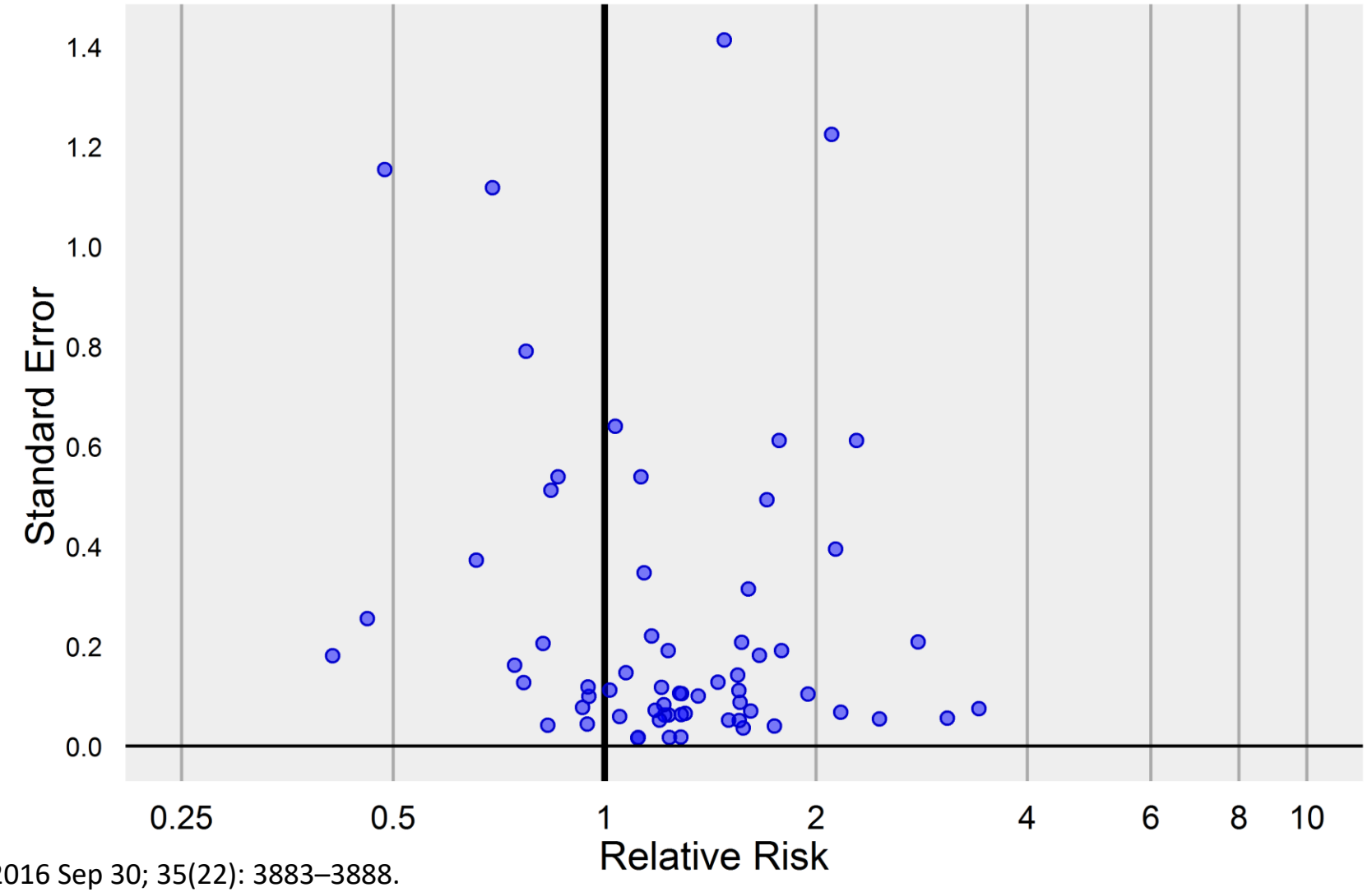


Problem with negative controls?

- Selection of negative control: no causal relationship
- However, sometimes the estimates for negative controls can be significantly deviated from null.
- That will affect the interpretation of the results
- Difficulties to draw conclusions

- What if we use a larger sample of negative controls?

Using negative controls to estimate the “real null” distribution



Schuemie et al. Stat Med. 2016 Sep 30; 35(22): 3883–3888.

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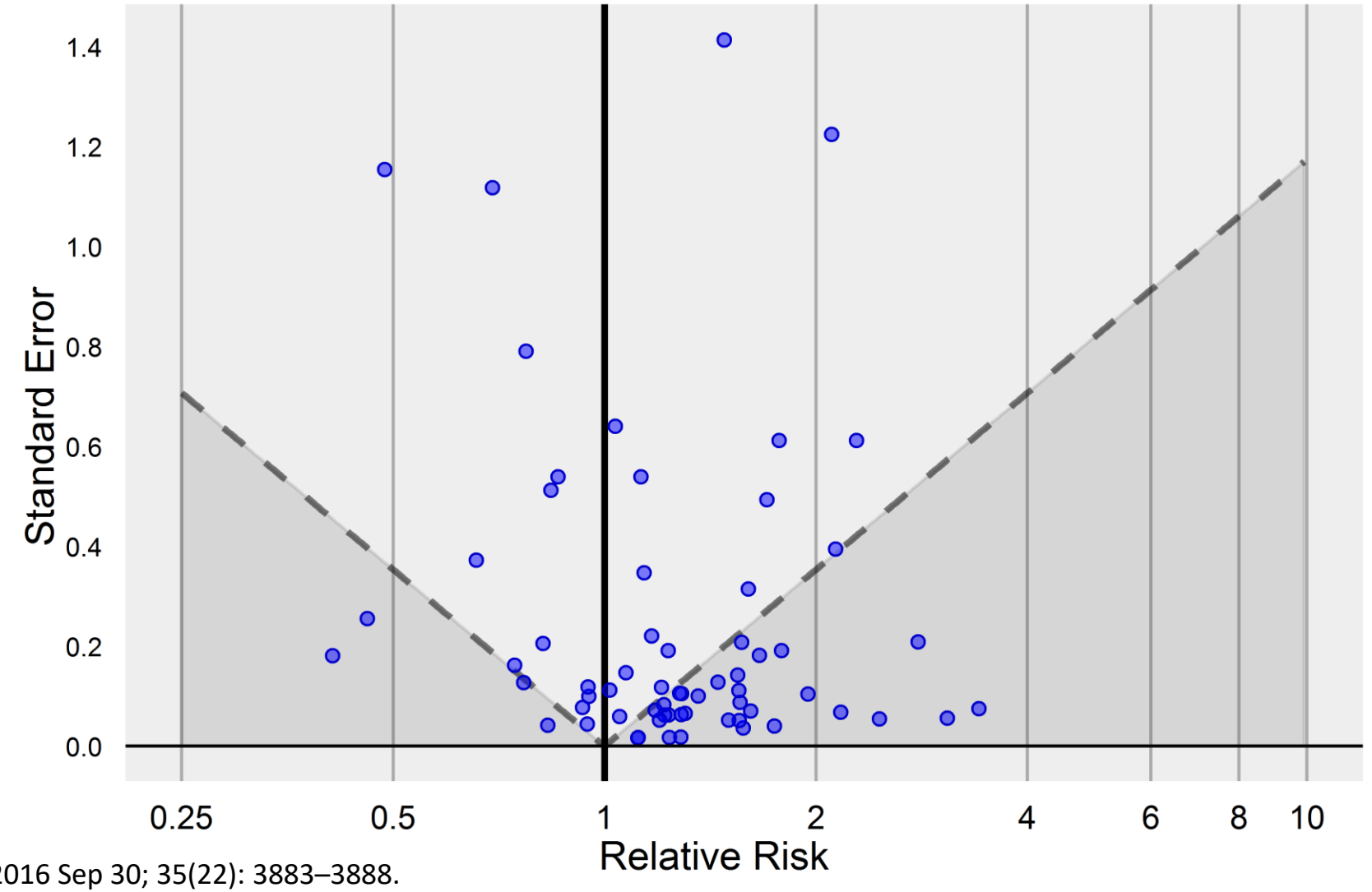

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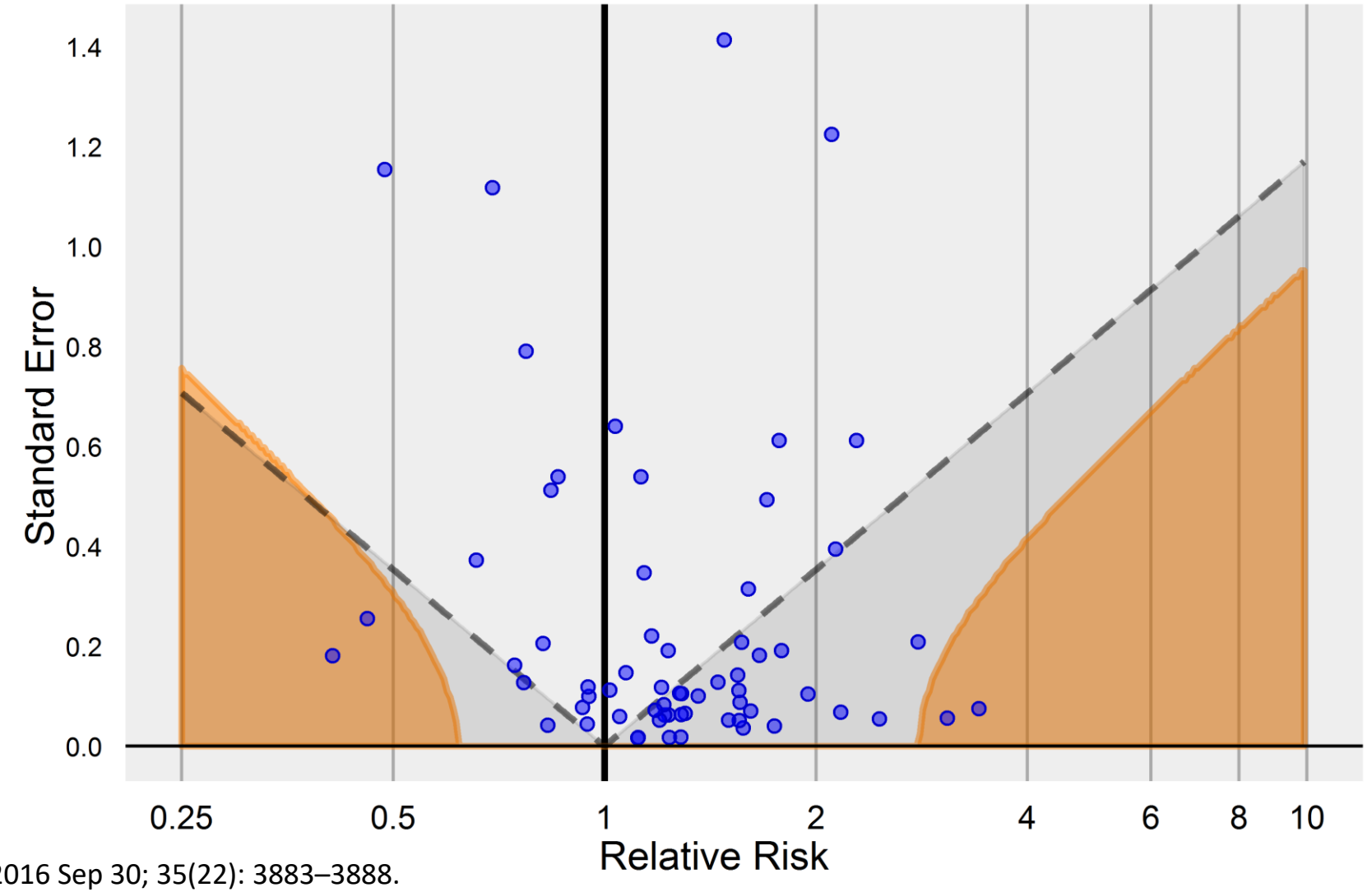

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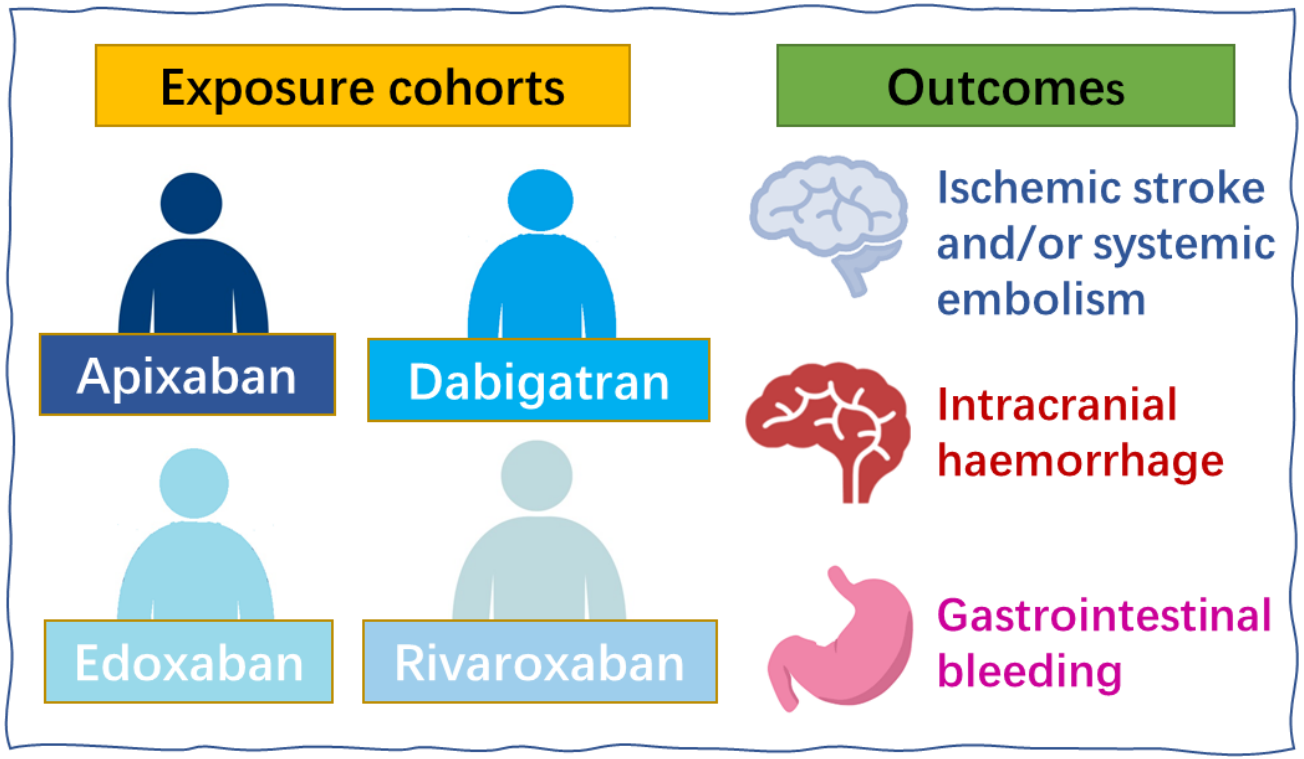
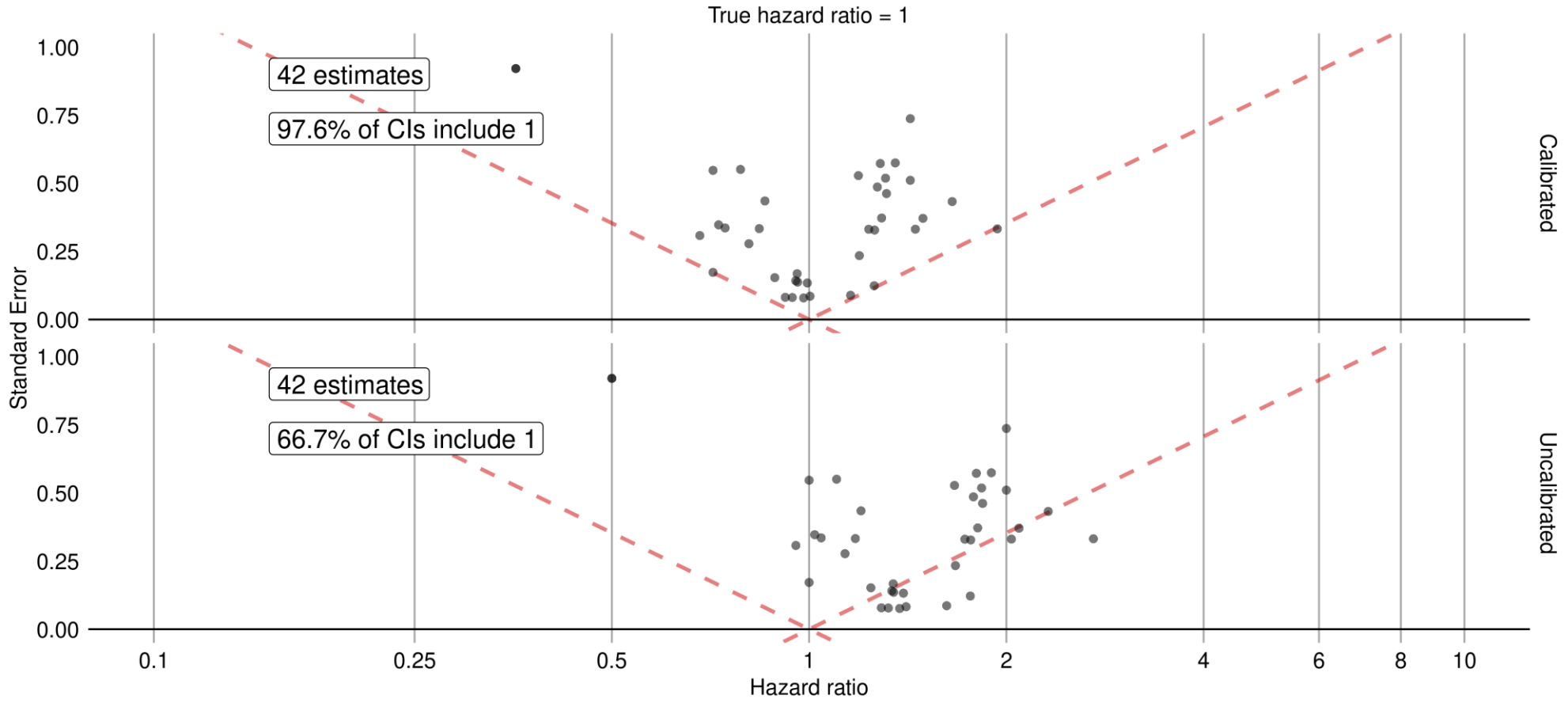
Example study: Calibration with negative controls

- Cohort study with 5 different databases (https://github.com/ohdsi-studies/Corazon)
- Propensity score model was built for each pairwise comparison
  - regularised logistic regression
  - 10,000+ predefined baseline characteristics
- PS stratification with five strata and matching at a variable-matching ratio
- 40+ negative controls were selected



Calibration with negative controls

Analysis	Data source	HR	LB	UB	P	Cal.HR	Cal.LB	Cal.UB	Cal.P
Cox regression with propensity score matching: on-treatment	HOSPITAL	1.29	1.01	1.67	0.05	0.92	0.71	1.19	0.56



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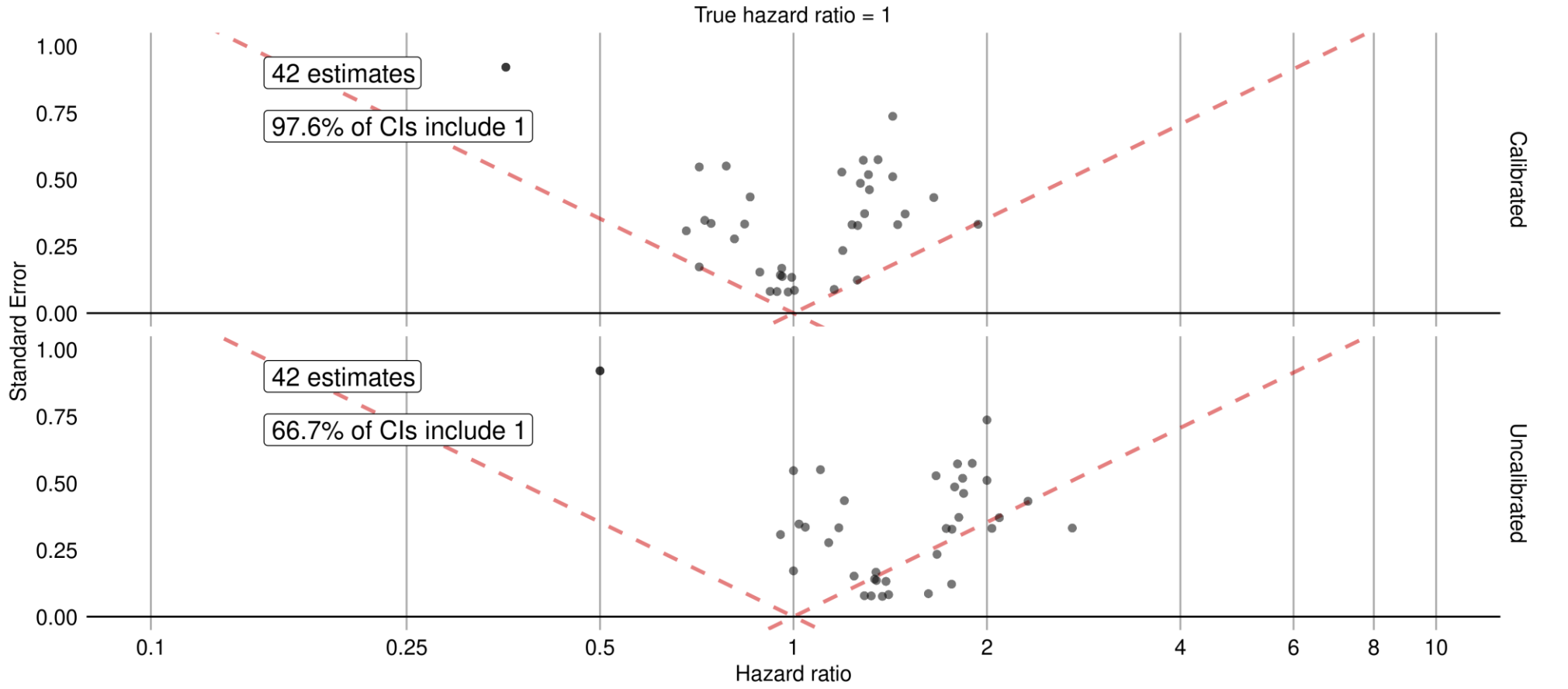

Conclusion

- Negative controls can provide an additional diagnostic for our study design
- Using large numbers of negative controls for calibration
- Allows interpretation of results from negative controls analysis

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References

- Lipsitch M et al. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology. 2010 May;21(3):383-8.
- Man KKC et al. Association between methylphenidate treatment and risk of seizure: a population-based, self-controlled case-series study. Lancet Child Adolesc Health. 2020 Jun;4(6):435-443.
- Man KKC et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population-based cohort study. BMJ. 2017 May 31;357:j2350.
- Schuemie MJ et al. Interpreting observational studies: why empirical calibration is needed to correct p-values. Stat Med. 2014 Jan 30;33(2):209-18.
- Schuemie MJ et al. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. Proc Natl Acad Sci U S A. 2018 Mar 13;115(11):2571-2577.