Accuracy of an Automated Knowledgebase for Identifying Adverse Drug Reactions

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(Martijn Schuemie presenting)

Background

For method **evaluation** and **calibration** we need controls:

- **Positive controls** – drugs-outcome pairs where the drug is known to cause the outcome
- **Negative controls** – drug-outcome pairs where we're pretty sure there's no causal relationship

Background

In the past, creating positive and negative controls was hard work

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ORIGINAL RESEARCH ARTICLE

Defining a Reference Set to Support Methodological Research in Drug Safety

Patrick B. Ryan · Martijn J. Schuemie · Emily Welebob · Jon Duke · Sarah Valentine · Abraham G. Hartzema

Abstract
Background Methodological research to evalu
performance of methods requires a benchmark to s
referent comparison. In drug safety, the perform
analyses of spontaneous adverse event reporting d
and observational healthcare data, such as admin
claims and electronic health records, has been lir

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SHORT COMMUNICATION

A Reference Standard for Evaluation of Methods for Drug Safety Signal Detection Using Electronic Healthcare Record Databases

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Published online: 23 November 2012

Objective

To build a machine learning classifier using LAERTES to automatically identify positive and negative controls

Predictors

Data Source Type	Data Source & Description
Literature	Medline MeSH Clinical Trials
	Medline MeSH Case Reports
	Medline MeSH Other
	Medline SemMedDB Clinical Trials
	Medline SemMedDB Case Reports
	Medline SemMedDB Other
Product Labels	European Product Label Adverse Drug Reactions
	Structured Product Label Adverse Drug Reactions from SPLICER
Spontaneous Reports	FAERS Report Count
	FDA Adverse Event Reporting System (FAERS) Proportional Reporting Ratio (PRR)

Model

Regularized logistic regression

Result: single score reflecting probability that drug causes outcome (given the available information)

Negative control: $p < x$

Positive control: $p > y$

The LAERTES Universe

Need to have enough evidence on the drug and the outcome to have some confidence that

Lack of evidence of an effect

=

Evidence of lack of an effect

The LAERTES Universe

Drugs (ingredients) and outcomes must have at least

- 1 FAERS record, and
- 1 Medline ADR record, and
- 1 product label

Outcomes use hierarchy: evidence of child counts as evidence for parent (e.g. acute MI is counted as MI)

The LAERTES Universe

- 992 distinct drugs (ingredients)
- 3,488 outcomes
- 992 x 3,488 = 3.5 mln drug-outcome pairs where we can predict

Evaluation

Use previously created reference sets for training + evaluation (using cross-validation):

- OMOP reference set
- EU-ADR reference set

External set for evaluation only (train on OMOP and EU-ADR sets):

- AZCERT

Results – OMOP & EU-ADR sets

Column(s) in Model	OMOP AUC	EU-ADR AUC
Medline Clinical Trial	0.74 (0.69-0.79)	0.73 (0.63-0.83)
Medline Case Reports	0.85 (0.81-0.89)	0.88 (0.81-0.96)
Medline Other	0.85 (0.80-0.89)	0.87 (0.79-0.95)
Medline SemMedDB Clinical Trial	0.58 (0.55-0.61)	0.57 (0.51-0.63)
Medline SemMedDB Case Reports	0.58 (0.55-0.61)	0.59 (0.52-0.65)
EU Product Labels	0.57 (0.54-0.60)	0.53 (0.49-0.57)
US Product Labels	0.87 (0.84-0.91)	0.80 (0.71-0.89)
FAERS	0.73 (0.67-0.78)	0.70 (0.57-0.82)
FAERS PRR	0.64 (0.58-0.70)	0.75 (0.63-0.86)
All Predictors	0.94 (0.91-0.97)	0.92 (0.86-0.98)

Using leave-one-out crossvalidation

Results – AZCERT set

55 drugs in universe and AZCERT ‘certain’ category are considered *positive*

Assuming all 865 drugs in universe and not in AZCERT are *negative*:

AUC = 0.92 (0.89-0.95)

Assuming worst case: 1% lowest predicted are *positive*:

AUC = 0.79

Assuming best case: 5% highest predicted are *positive*:

AUC = 0.94

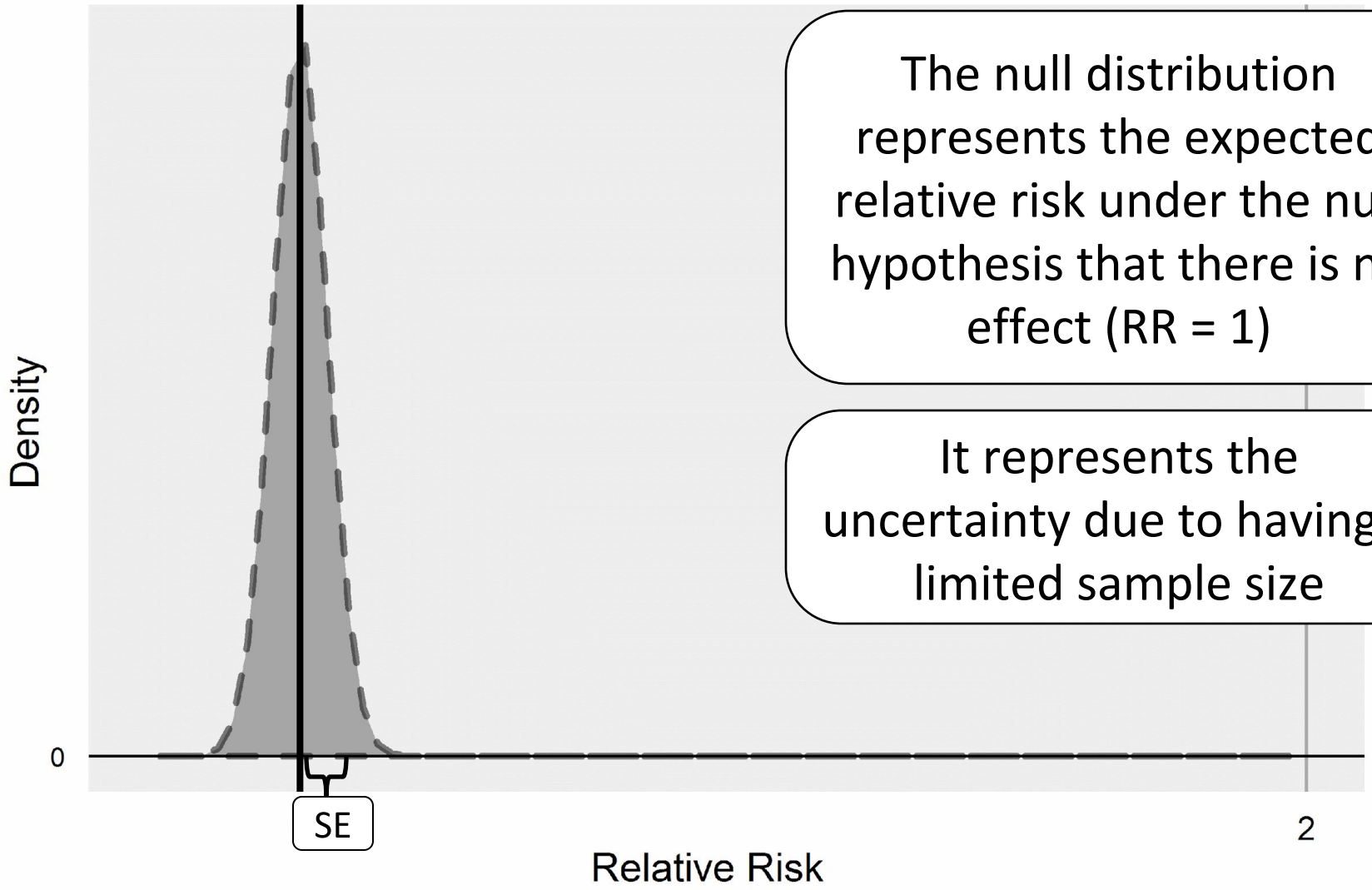
Conclusions

- Able to automatically ‘predict’ positive and negative controls with high accuracy
- Challenge: outcomes can be at all levels in the hierarchy (e.g. lots of evidence for ‘Condition’, and all drugs seem to cause conditions)

Next steps

- Apply the model to find controls
- Continue fitting the model as data in LAERTES is refreshed
- Include additional predictors?
- Try other types of classifiers?

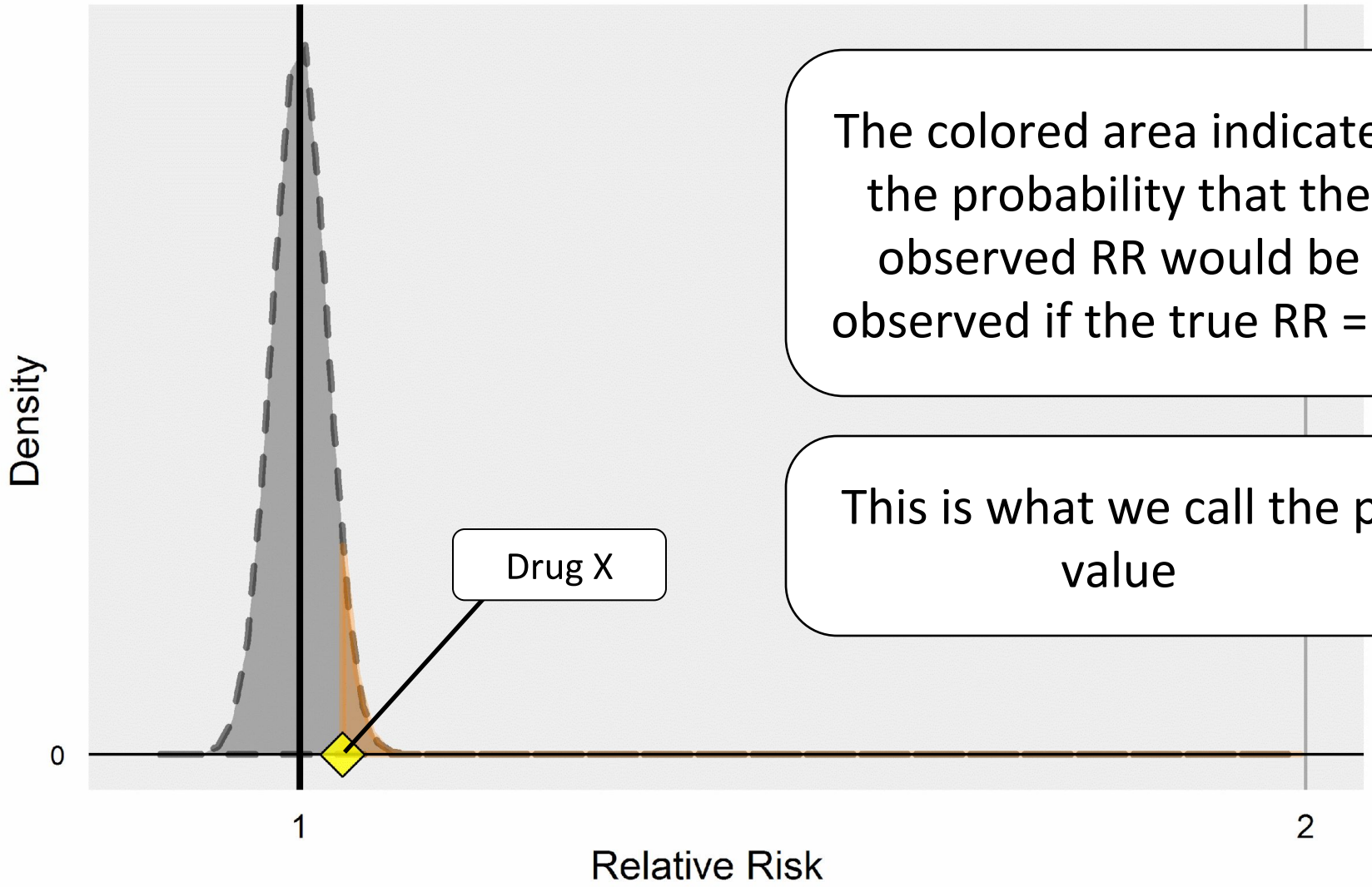
Null distribution



The null distribution represents the expected relative risk under the null hypothesis that there is no effect (RR = 1)

It represents the uncertainty due to having a limited sample size

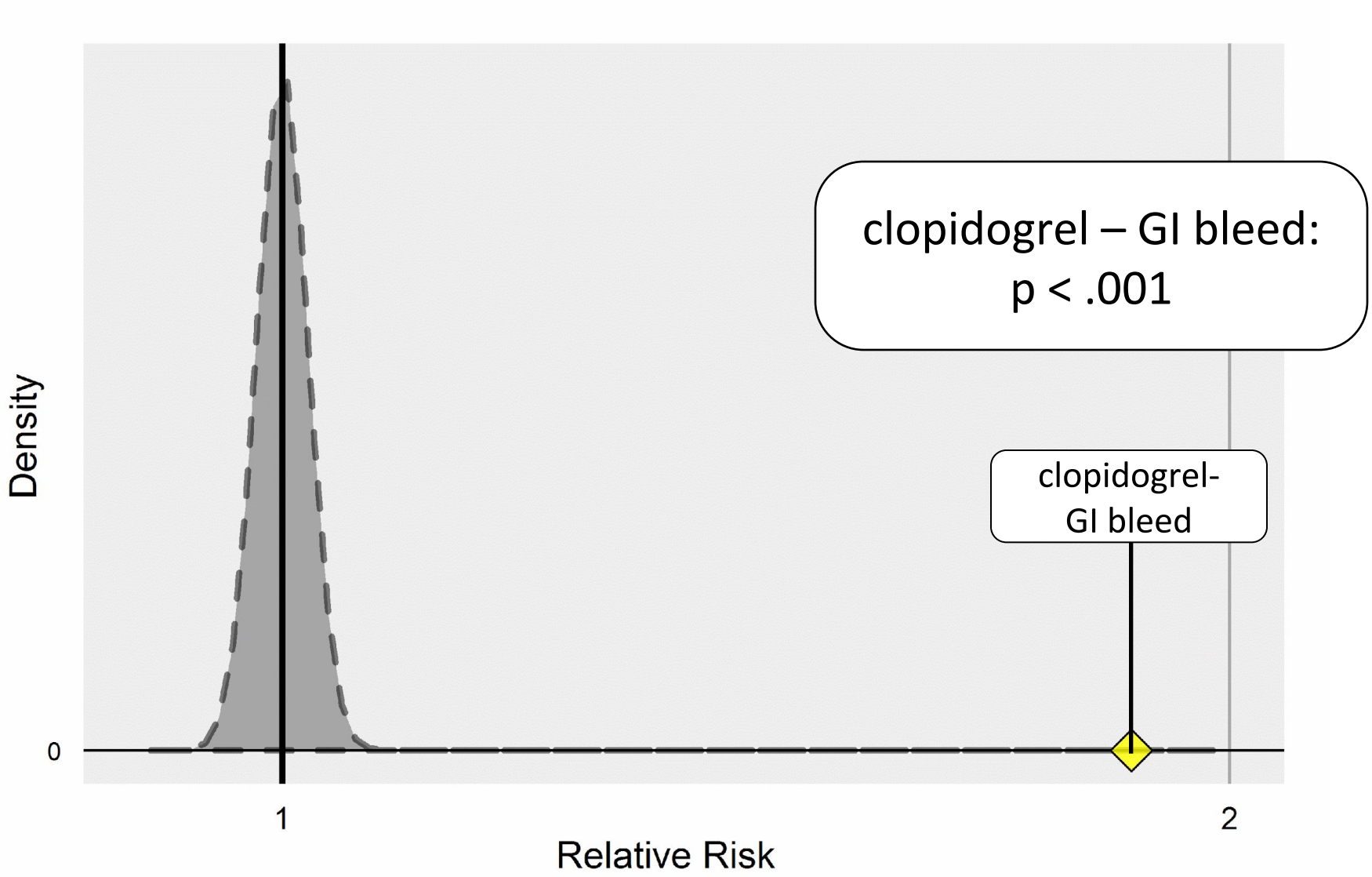
Null distribution



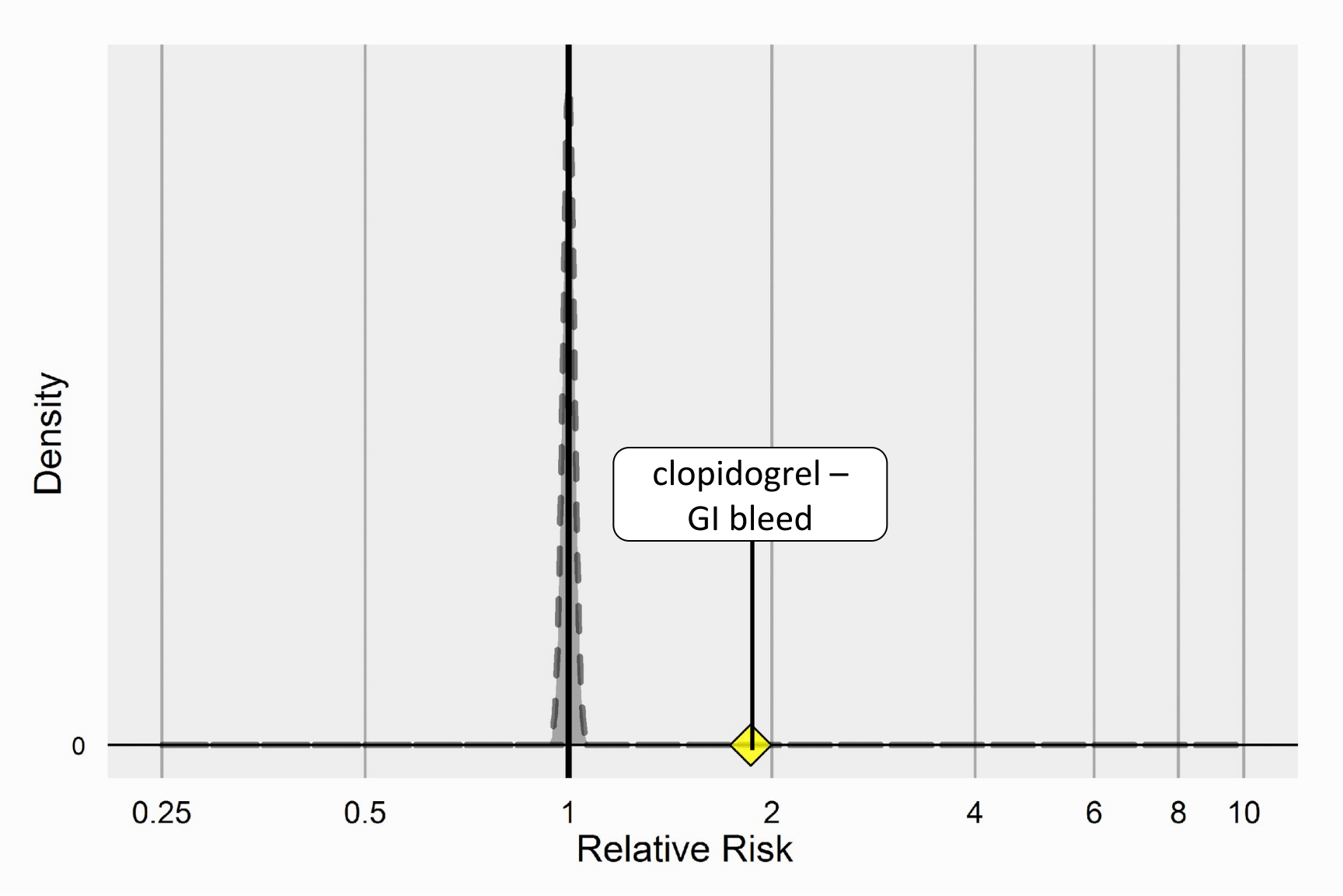
The colored area indicates the probability that the observed RR would be observed if the true RR = 1

This is what we call the p-value

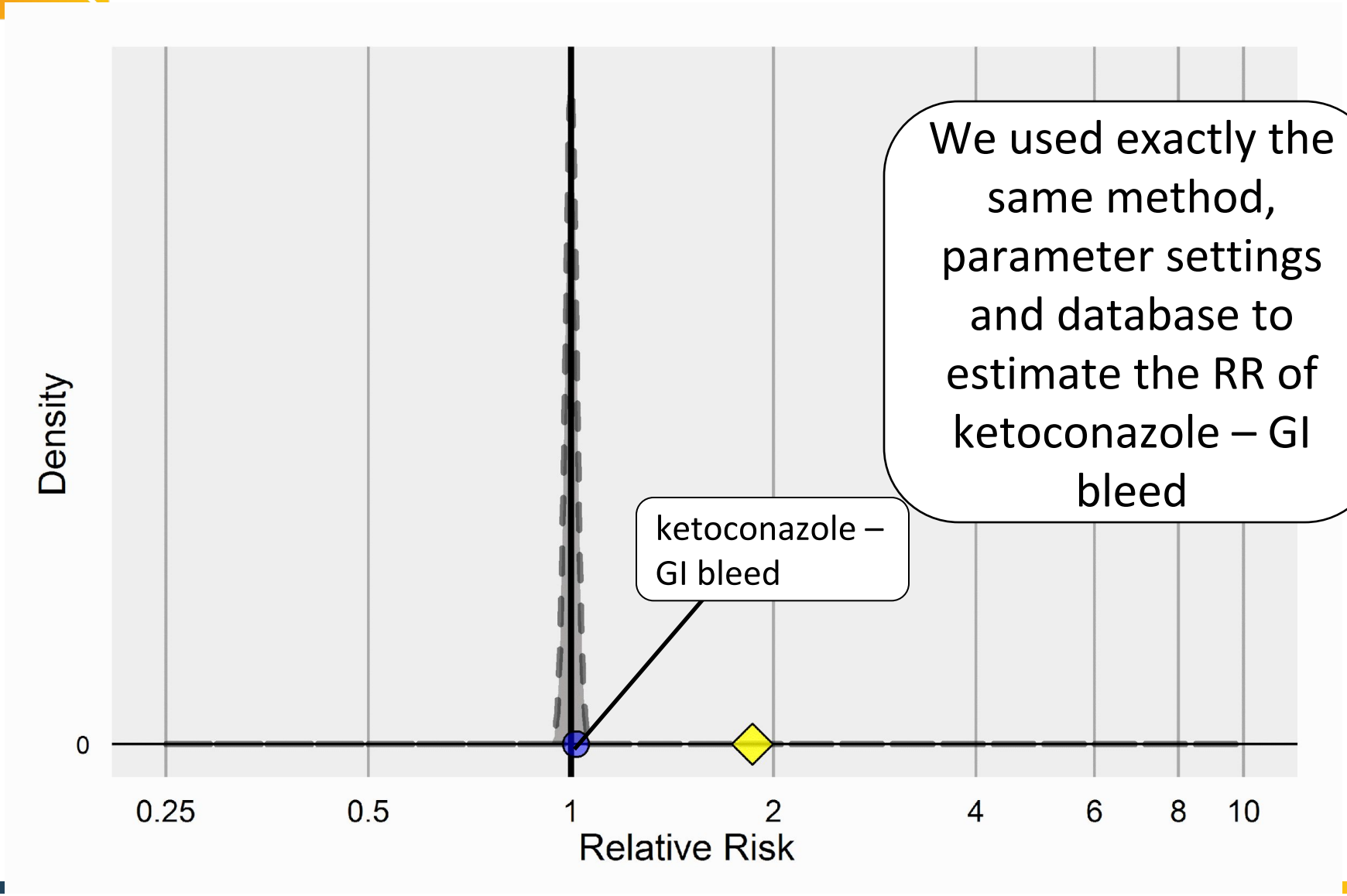
Null distribution



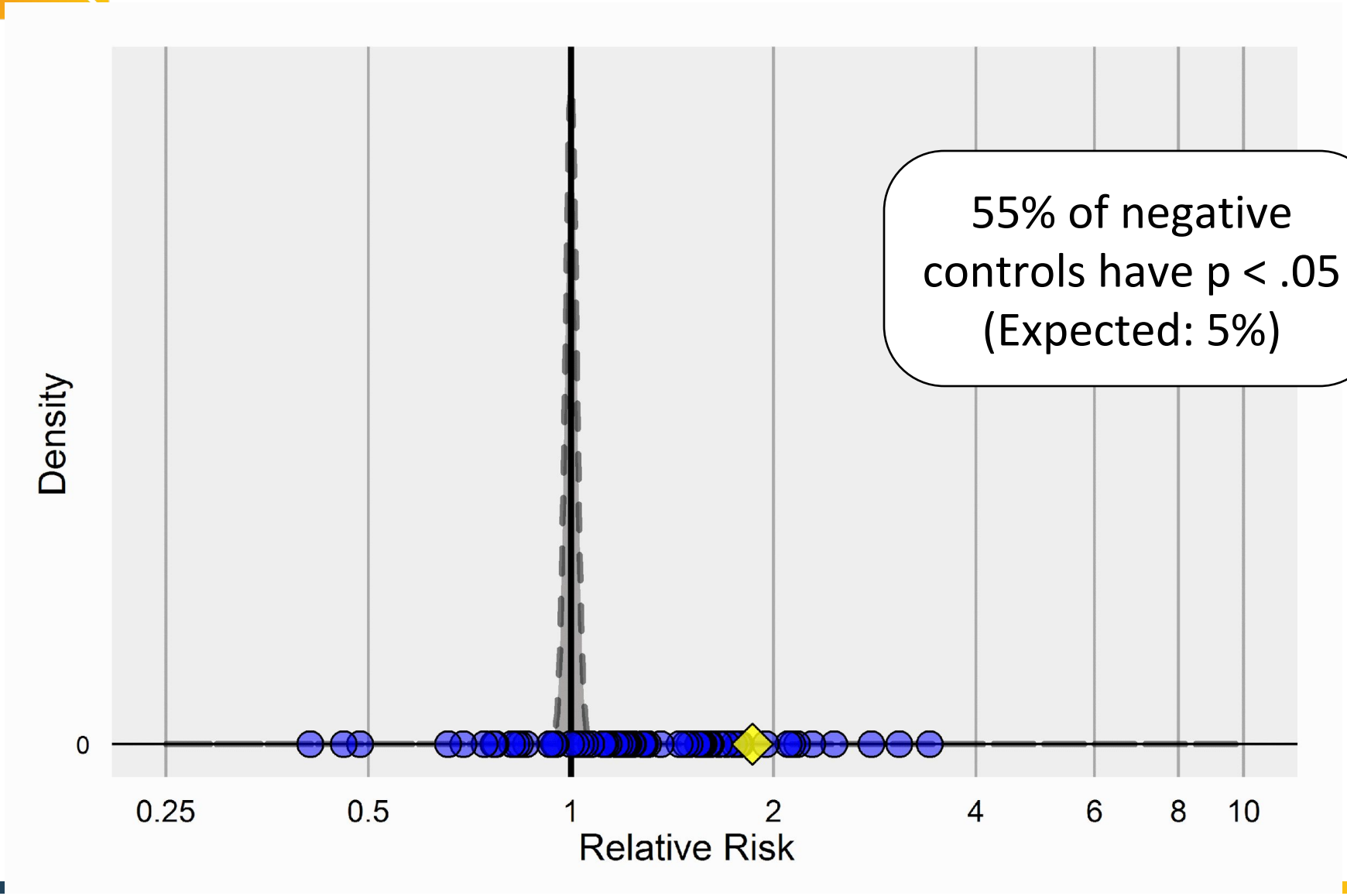
Null distribution



Negative controls

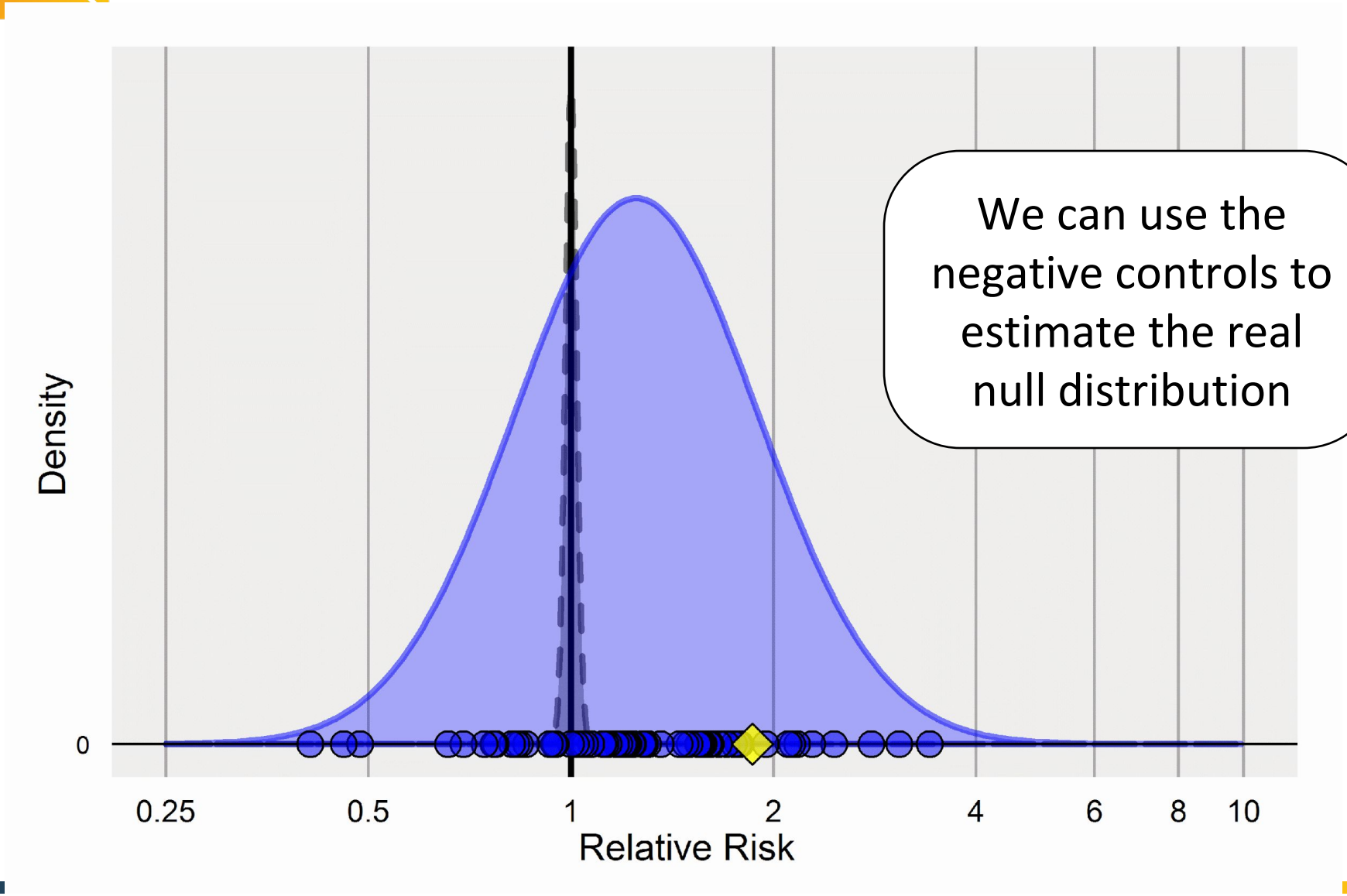


Negative controls

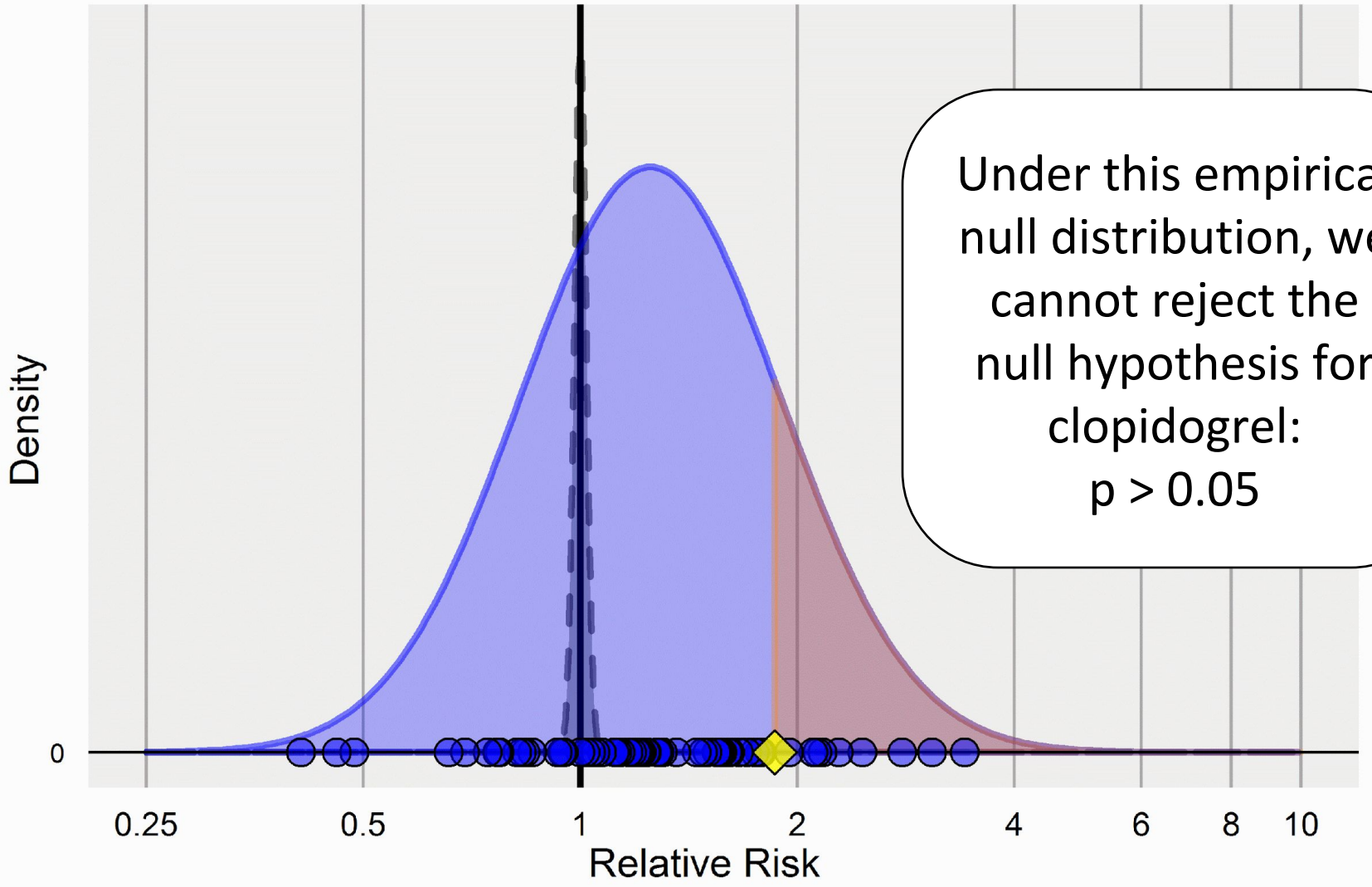


55% of negative controls have p < .05 (Expected: 5%)

Negative controls



Negative



Under this empirical null distribution, we cannot reject the null hypothesis for clopidogrel:
$p > 0.05$