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Factor analysis of impact of outcome misclassification on dose-response conclusions in radiation epidemiology

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About the USTUR

Who we are

The United States Transuranium & Uranium Registries

What we do

Biokinetics and dosimetry of actinides in human body

Plutonium | Americium | Uranium

Organ samples voluntarily donated by our Registrants

Former actinide workers | Documented intakes

Autopsy is required for each Registrant

How our data are used

De-identified radiochemistry, health physics, and pathology data

- Validate bioassay-based dose estimates
- Improve biokinetic models of actinide distribution in the body
- Calculate radiation doses to body organs
- Study actinide deposition
- Recommend occupational exposure limits

Radiation dose

Biokinetic models evaluate the quality of dose data

Classic USTUR research

Health outcome

Misclassification studies evaluate the quality of cause-of-death data

This study

Radiation epidemiology

What level of radiation exposure significantly affects health outcomes?

Occupational radiation protection standards

What exposure limits should be set to protect workers from adverse health outcomes

Cause of Death Misclassification

Cause of Death on Death Certificate	Cause of Death on Autopsy Report	Match Status	Effect on Study
Lung cancer	**Lung cancer**	Match	No misclassification True outcome
Pneumonia	**Lung cancer**	**Not match**	**Under misclassification** False negative
Lung cancer	Respiratory distress syndrome	**Not match**	**Over misclassification** False positive

Three Phases of Misclassification Study

1. Validation

How often is the cause of death misclassified?
Does it change study results?

268 Registrants

2. Simulation

How likely is the change?
Under what conditions is it most likely?

20,000 iterations

3. Correction

Can misclassification be corrected?
What are the limitations?

Rogan-Gladen method

Misclassification Rates

ICD-10 Chapter Level

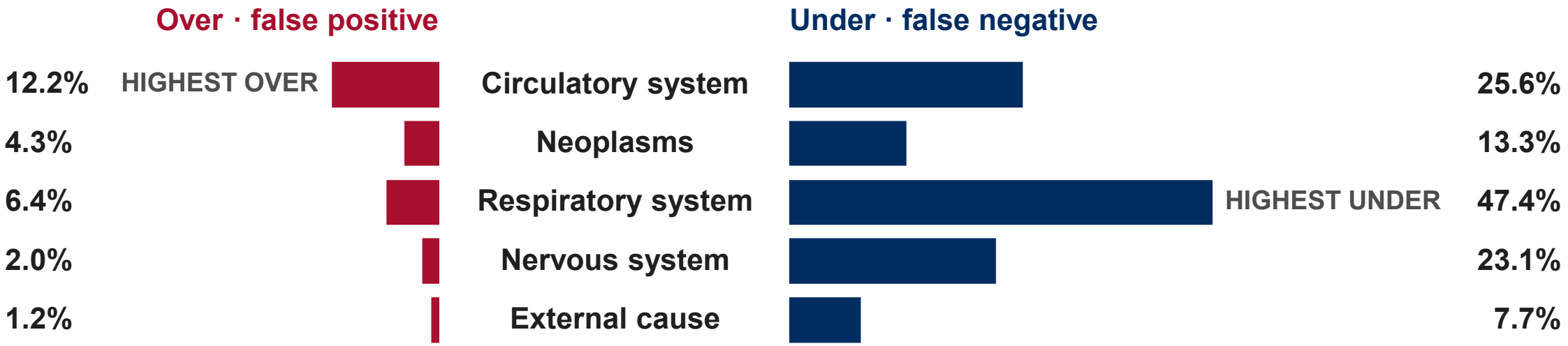
25.4%

of death certificates misclassified the underlying cause of death [1]

What increases the match rate?

3.4× Odds ratio of 3.4 for autopsy report used

2.8× Odds ratio of 2.8 for clinical history in autopsy report



[1] McComish et al. "Misclassification of causes of death among a small all-autopsied group of former nuclear workers: Death certificates vs. autopsy reports." *PloS one* vol. 19,5 e0302069. 2024

Impact on Risk Estimate

	USTUR Data		Results		
	Radiation dose, Sv (exposure)	Diagnosed cancer death (outcome)	Odds ratio	95% CI	*p*-value
Non-misclassified	Cumulative external	**Autopsy report**	0.36†	(0.05, 2.77)	0.326
Misclassified	Cumulative external	**Death certificate**	0.53†	(0.07, 4.04)	0.540

YES,

Consistent with general belief

- Misclassification always weakens the association between risk factors and health outcomes
- Correcting such misclassification will make the association stronger

BUT

Only examine one scenario

- Do other possible scenarios exist?
- Does the impact always follow the general belief?
- Can we quantify the impact when the results contradict the general belief?

Misclassified outcome yields odds ratio toward the null

† Odds ratio less than 1 likely due to bias in recruitment process

Neither shows a significant association

Borderline Scenario Simulation Design

1

Borderline reference dataset

- Radiation dose vs. cancer death
- *p*-value just above 0.05

2

Reassign outcomes at random

- Both over and under misclassification
- Rates range from 0% to 30%

3

Recalculate and repeat

- Misclassified odds ratio and corresponding *p*-value
- 20,000 iterations

4

Percentage of flipped conclusions

- *p*-value turned significant from non-significant

BEFORE · outcomes without misclassification

Borderline non-significant

$p = 0.05001$, just above threshold

→ Simulate misclassification

AFTER · misclassified outcomes

Change to significant

$p < 0.05$

A borderline non-significant starting point represents the maximum impact of misclassification on study conclusions

Borderline Scenario Results

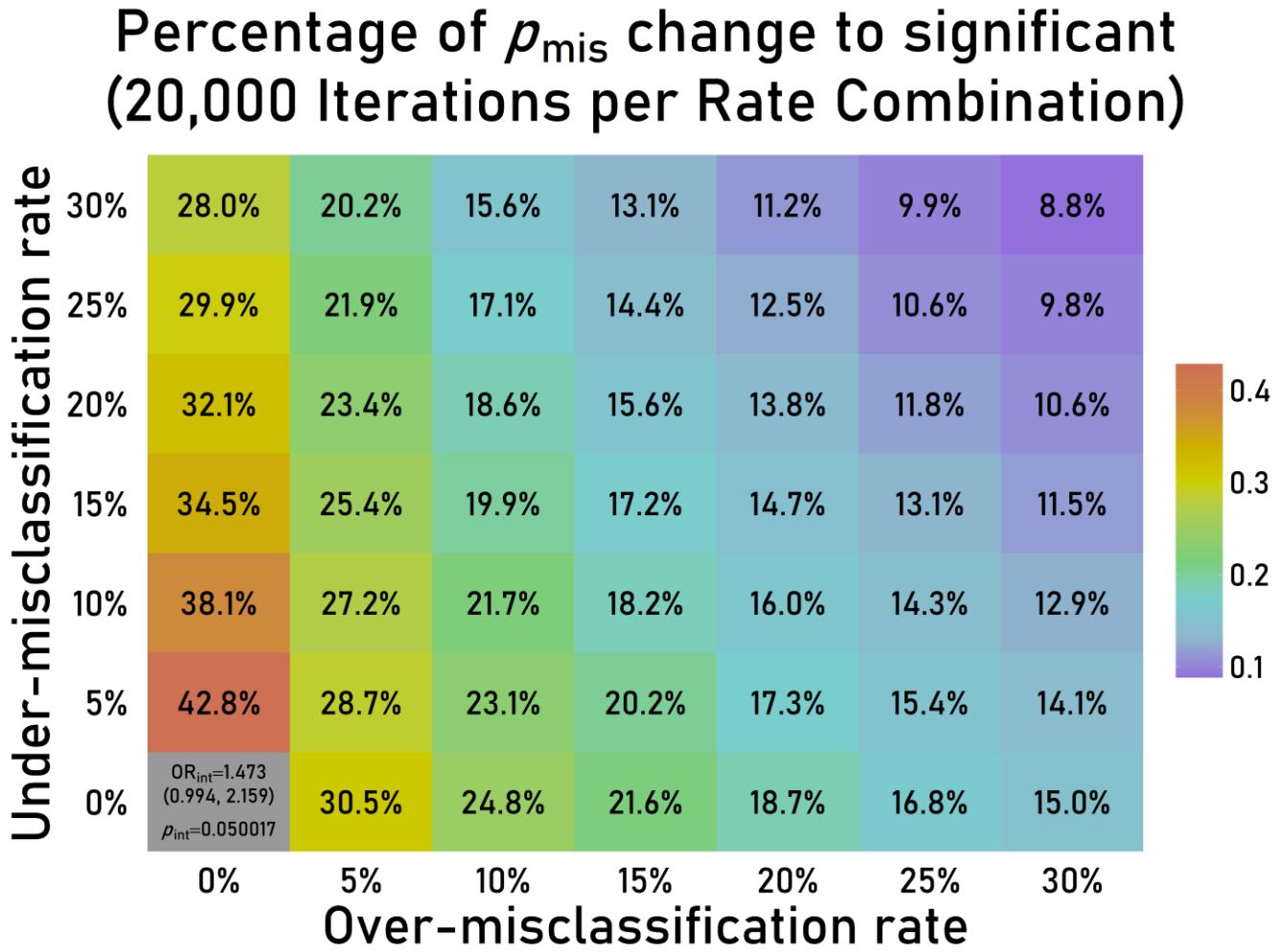
In **borderline** scenarios, conclusions flipped from non-significant to significant

8.8% to 42.8%

of the time, from outcome misclassification impact alone [2]

Main Pattern

lower misclassification rates led to a higher percentage of altered conclusions



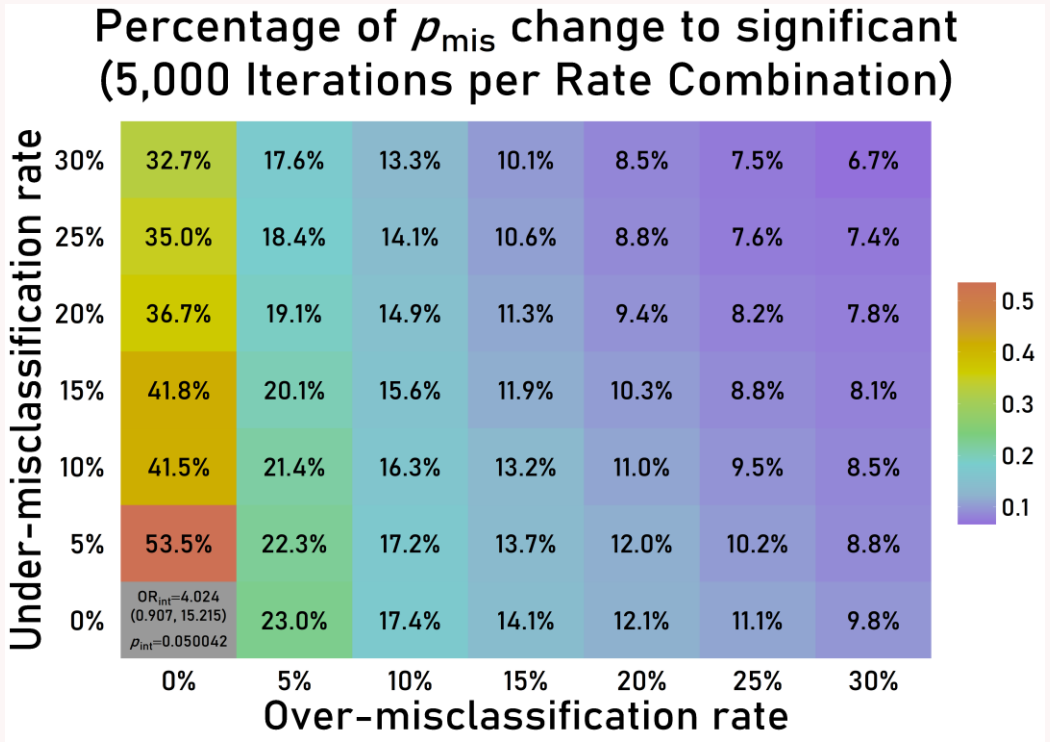
[2] Liu et al. "Inference under outcome misclassification in health risk models using a simulation study with a validation dataset." *Sci Rep* vol. 16, 1 11981. 2026

Factor Analysis

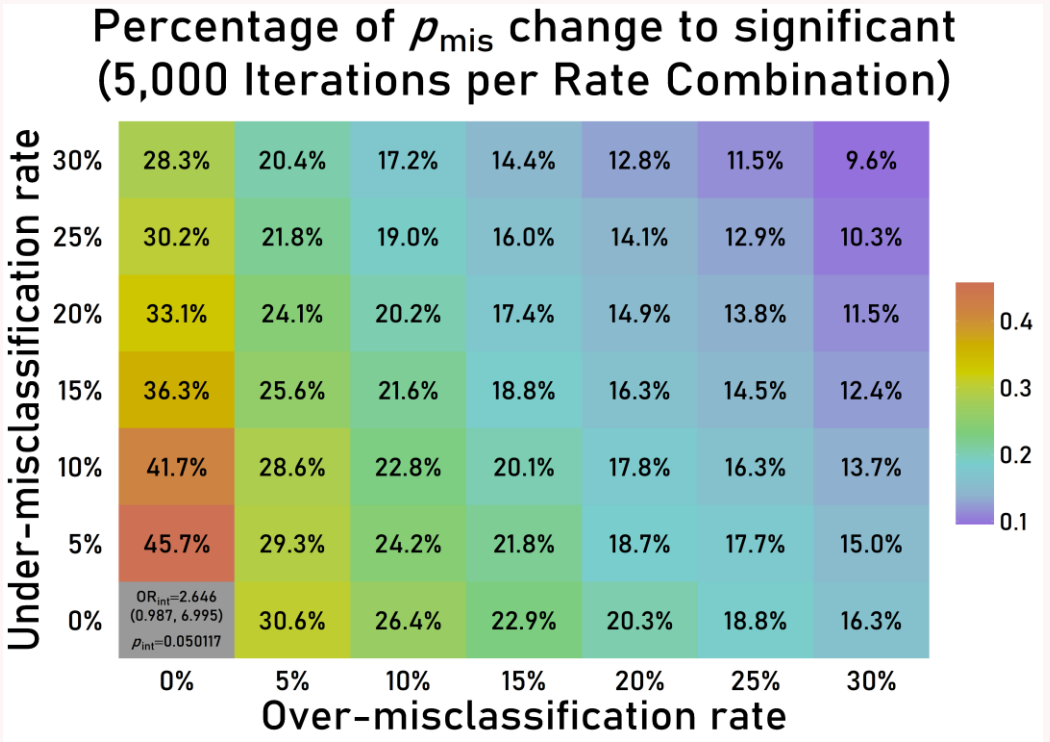
FACTOR 1	FACTOR 2
Disease baseline probability	**Significance level**
10% → 20% → 30%	0.01 → 0.05 → 0.10

Factor 1 Disease Baseline Probability

Disease baseline probability = 10%
more sensitive to rate changes



Disease baseline probability = 30%
less sensitive to rate changes

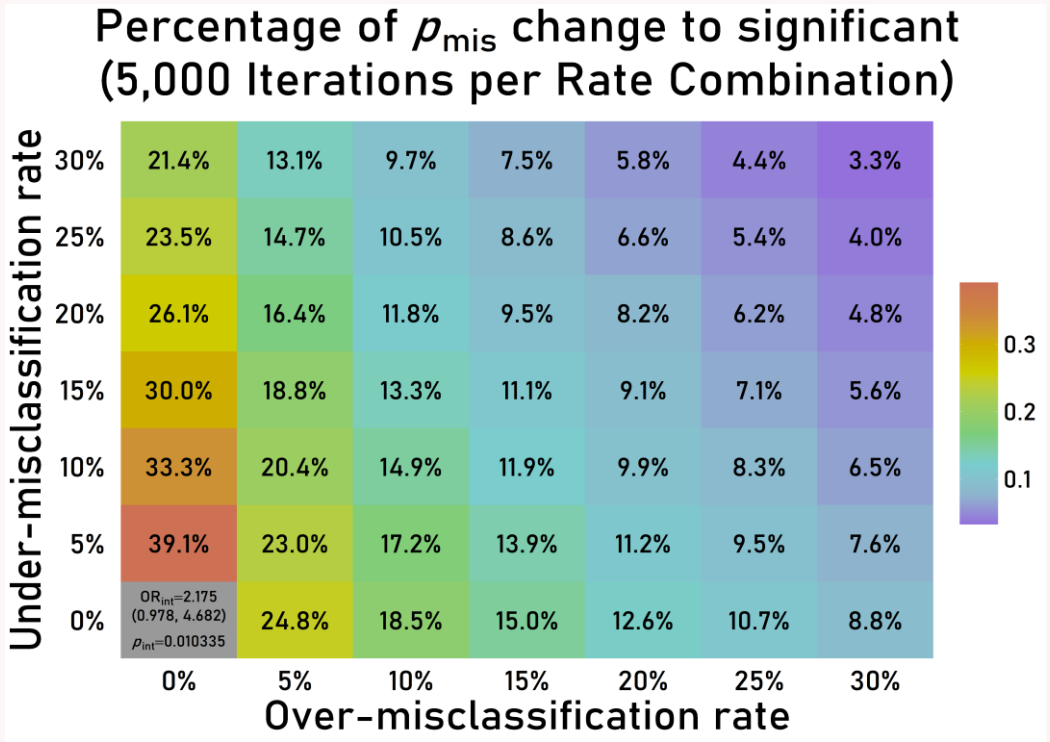


Less common diseases are more sensitive to changes in misclassification rates

Factor 2 Disease Significance Level

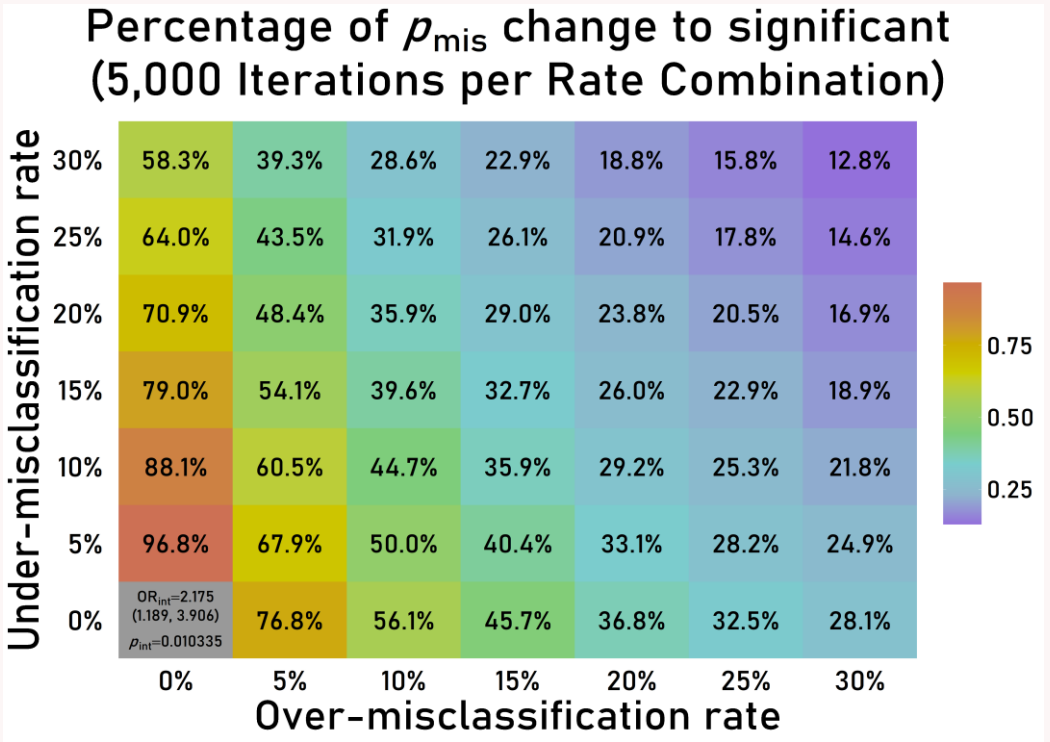
***p*-value < 0.01**

fewer conclusions impacted



***p*-value < 0.10**

more conclusions impacted

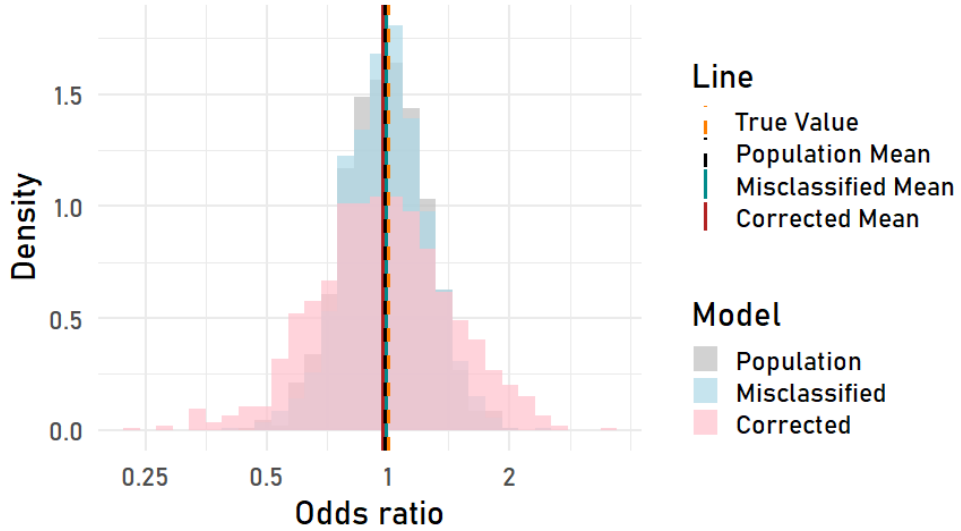


Raising the significance level increases the likelihood that a conclusion will change from non-significant to significant.

Ongoing Work: Correction

- **Population** — Preset true odds ratios
- **Misclassification** — Misclassified outcomes
- **Correction** — $p_{true} = (p_{observe} + Sp - 1) / (Se + Sp - 1)$ [3]
- **Distribution Comparison** — 10,000 datasets each

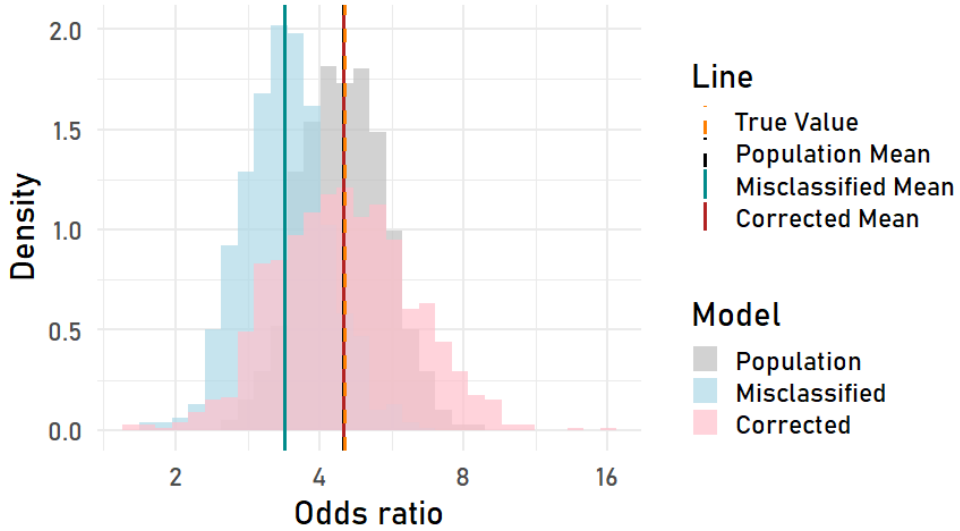
No effect association — Underlying OR = 1



False positive rate significant results when no effect association

5.0%	5.0%	21.0%
Population	Misclassified	Corrected
Target rate	Good	Four times the target

Underlying association — Underlying OR = 4.5



False negative rate Non-significant results when a true association exists

0.0%	1.7%	0.4%
Population	Misclassified	Corrected
Target rate	Little high	Close to target

The correction recenters the odds ratio on the true value but inflates the standard deviation

[3] Rogan and Gladen. "Estimating prevalence from the results of a screening test." *Am J Epidemiol* vol. 107,1 71–76. 1978.

Summary

1. **Misclassification can change a study conclusion from non-significant to significant**

2. **The vulnerability of dose-response conclusions depends on study conditions**
   - Less common diseases are more sensitive to changes in misclassification rates
   - Increasing the significance level from p=0.05 to 0.10 raises the likelihood that a conclusion will change from non-significant to significant.

3. **Ongoing work is exploring methods to correct misclassification**



Thank you! :)

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