A permutation procedure to detect heterogeneous treatments effects in RCTs while controlling the Type-I error rate

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Disclosures

Jack Wolf: I have no commercial relationships or other special interests to disclose.

Tobacco Regulatory Science

Nicotine is the primary addictive agent that promotes cigarette smoking.

The FDA intends to reduce the amount of nicotine in all cigarettes sold to minimally addictive levels.

Several trials have studied the effects of very low nicotine content (VLNC) cigarettes on the US smoking population *on average*.

Tobacco Regulatory Science

Question

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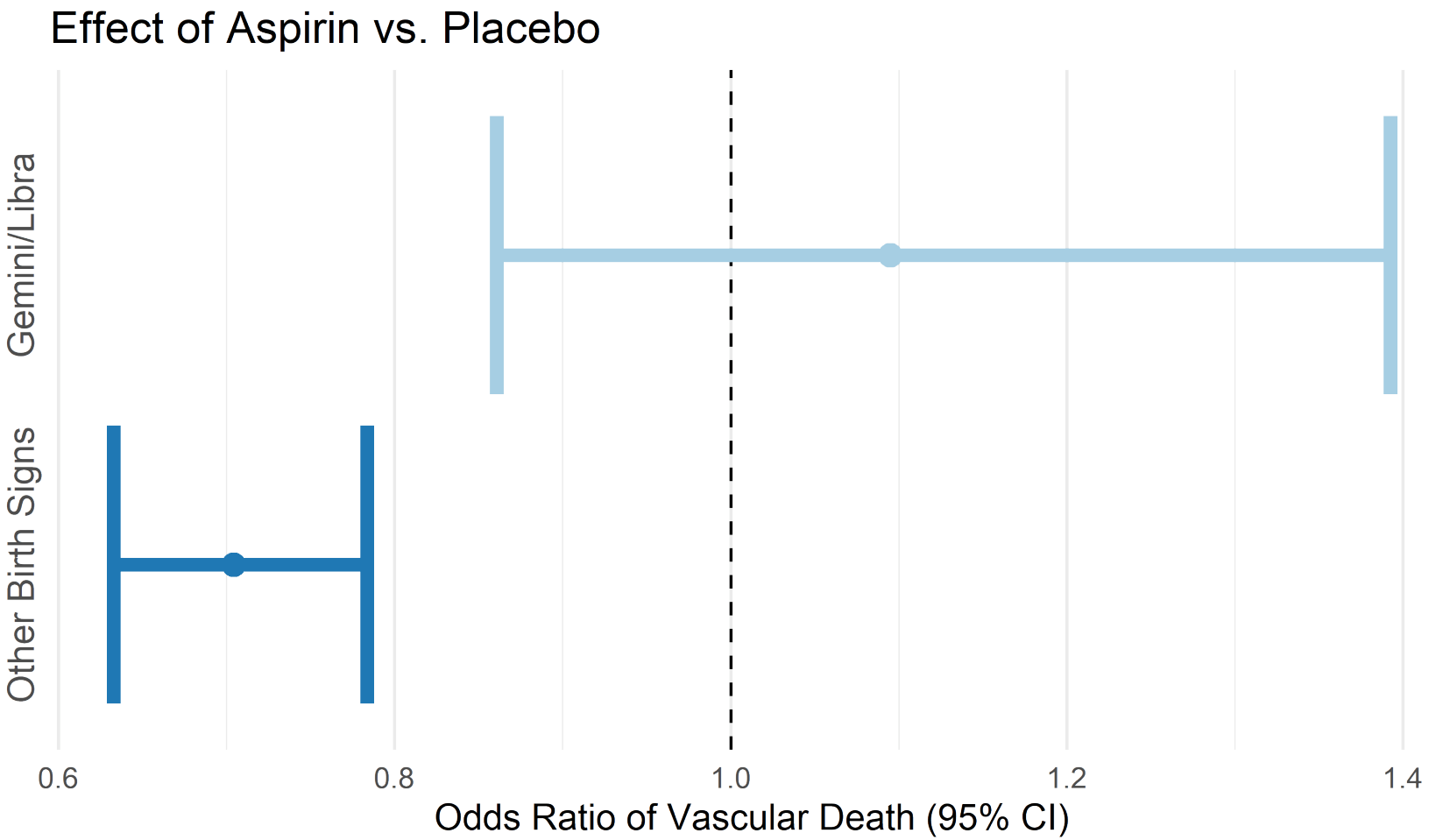
Significance

If the effect varies across the population and some smokers can be expected to respond negatively to VLNC cigarettes, we might want to develop additional targeted interventions.

Type-I Error Concerns



Data: Collaborative Group (1988)

Type-I Error Concerns

Our Question

How can we control the probability of falsely detecting subgroup effects?

Virtual Twins

Step 1

Estimate each subject's treatment effect through a *flexible and dense* model (random forest, super learner, ...)

$$\mathrm{E}(Y_i|\boldsymbol{X}_i, T_i = 1) - \mathrm{E}(Y_i|\boldsymbol{X}_i, T_i = 0) \approx \hat{f}_1(\boldsymbol{X}_i) - \hat{f}_0(\boldsymbol{X}_i)$$

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Step 2

Explain variability in the estimated treatment effects through an *interpretable* model (linear regression, tree-based models, ...)

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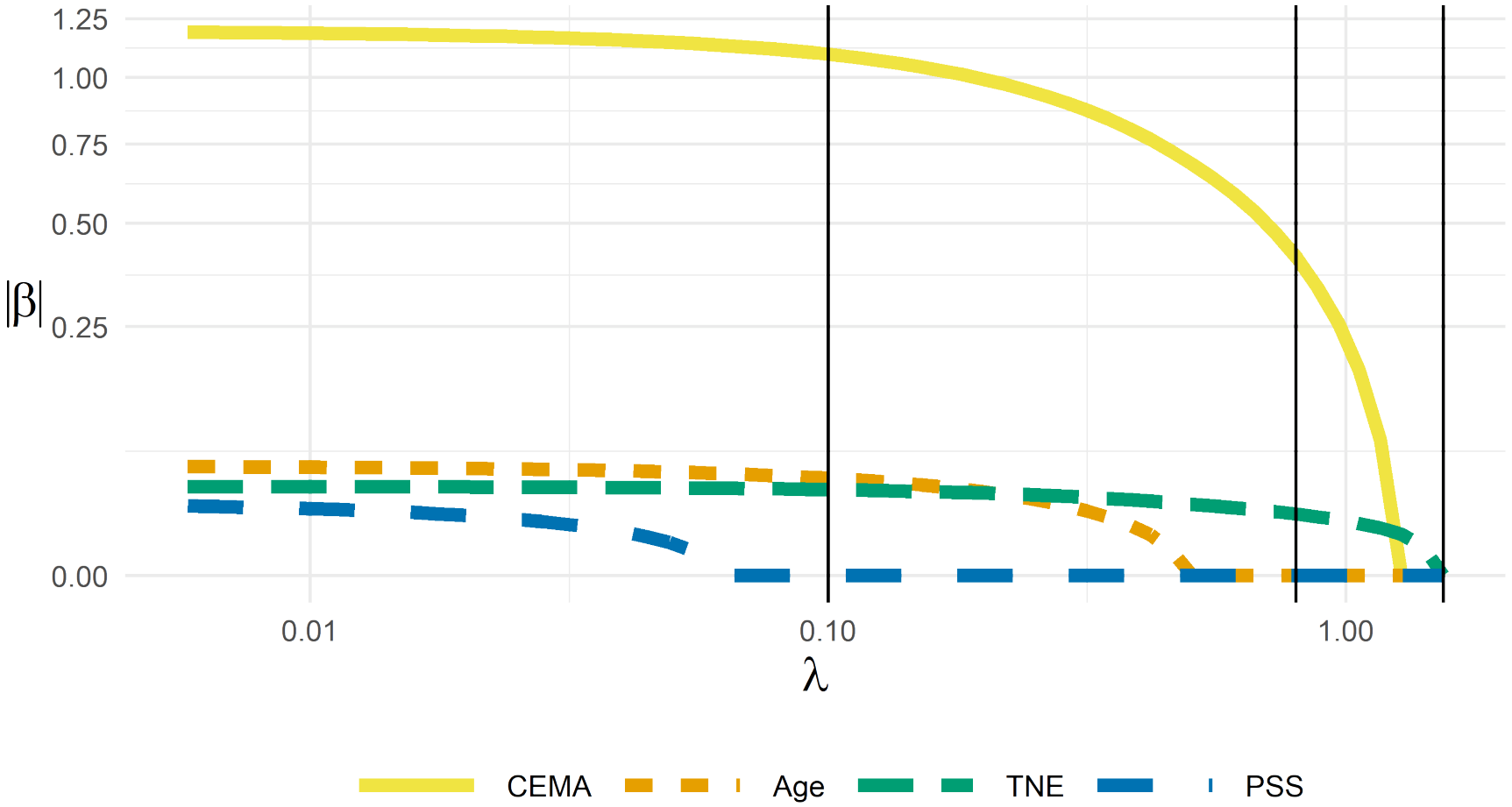
Limitations of Virtual Twins

Limitation

The conclusion depends on the choice of a penalty parameter



Limitations of Virtual Twins

Goal

Choose the penalty parameter to control the model's behavior when there is no treatment effect heterogeneity.

$$\lambda^* : \Pr\{\hat{g}(\boldsymbol{X}_i; \lambda^*) = \Delta | \text{No Heterogeneity}\} \geq 1 - \alpha$$

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The Solution

A Permutation Procedure:

For $i = 1, \ldots, M$

1. Permute the data to obscure treatment by covariate interactions
2. Identify the *smallest penalty parameter* ($\hat{\lambda}^{(i)}$) that yields a model that includes no covariates

Use the $1 - \alpha$ percentile of $\hat{\lambda}^{(1)}, \ldots, \hat{\lambda}^{(M)}$ in the Step 2 model

Application

Hatsukami et al. (2018) investigated the marginal average treatment effect of immediate vs. gradual reduction in nicotine content in VLNC cigarettes on US smokers.

We assessed the conditional average treatment effect of immediate nicotine reduction on the *decrease in cigarettes smoked per day* (CPD) from baseline to 20-weeks post randomization across 40 measured covariates.

Application

Both total nicotine equivalents (TNE) and cyanoethyl mercapturic acid (CEMA) were included in the tuned Step 2 model:

$$\begin{aligned} &\mathrm{E}[-\Delta\mathrm{CPD}_i|\mathrm{Immediate}] - \mathrm{E}[-\Delta\mathrm{CPD}_i|\mathrm{Gradual}] \\ &\qquad \approx 5.78 + 0.187(\mathrm{TNE}_i^*) + 0.009(\mathrm{CEMA}_i^*) \end{aligned}$$

TNE: Nicotine exposure
CEMA: Metabolite of toxicants in cigarette smoke

*centered and IQR-standardized

Diversity Equity and Inclusion

Standard primary analyses in tobacco regulatory science have focused on marginal treatment effects.

We need to consider potential subgroups of patients who may respond differently (negatively) to the intervention. In particular, this is of importance for subgroups of patients that are underrepresented in the trial population.

It is important to be able to detect such effect heterogeneity and identify groups that may need additional targeted interventions to benefit in a principled, data-driven manner

Discussion

Results

Our permutation procedure can accurately control probability of making a Type-I error when there is no treatment effect heterogeneity, and is able to detect heterogeneous effects when they are present.

Future Work

Currently cannot control the *a priori* probability of including a specific covariate when it has no treatment interaction

Discussion

Implication

Researchers can engage in secondary analyses of data from RCTs to assess treatment effect heterogeneity while controlling the rate at which heterogeneity is falsely concluded without pre-specifying subgroups.

Thank you!

Slides:	`bit.ly/SCT_Type-I`
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References

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