Design considerations for subgroup analyses in cluster-randomized trials

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https://bdwilliamson.github.io/#talks

Acknowledgments

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Heterogeneity of treatment effects: what and why

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If HTE is present:

- resources can be prioritized to maximize benefit and reduce risks [Knol and VanderWeele (2012)]
- can determine whether intervention remediates or exacerbates health disparities [Petkovic et al. (2020)]

Case study: ENSPIRE trial

ENSPIRE: Engaging Staff to Improve COVID-19 Vaccination Response at Long-term Care Facilities

Background:

- Rates of COVID-19 disease and death higher in long-term care than general population [Chidambaram (2022)]
- Lag in COVID-19 vaccinations among long-term care workers
- Long-term care (LTC) workers often low-wage, represent diverse social, cultural, racial, and ethnic backgrounds

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Design:

- Enrolled 40 LTC centers, encompassing approximately 4000 staff members
- Recruited from 2 US states (Georgia and Washington)
- Recruited from urban (Atlanta or Seattle) and suburban/rural locations

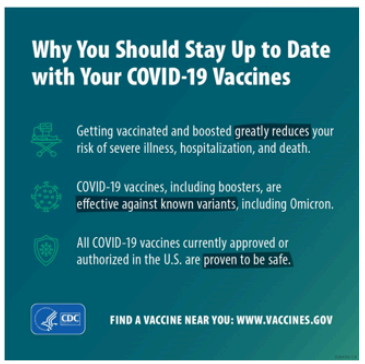
Case study: ENSPIRE trial

Primary outcomes:

1. LTC center COVID-19 booster rate (cluster-level)
    - chosen due to concerns about data capture
2. LTC care staff net promoter score (individual-level)

Intervention: booster promotion materials co-designed with LTC staff

"Usual care"
(Standard materials)



VS.

"Co-design"
(Materials designed by teams of staff)

THE ENSPIRE STUDY

Case study: ENSPIRE trial

Co-design: tailoring messages to specific audiences

- In ENSPIRE, focused on language, cultural, and ethnic affinity groups
- Measured race and ethnicity allowing 57 total options

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HTE analysis natural for interventions, particularly co-designed:

- Planned analyses based on state, urban vs suburban/rural, baseline booster uptake
- Self-reported race/ethnicity both interesting and important, however:
  - neither sites nor other entity had comprehensive and accurate race and ethnicity data for staff
  - staff survey would only capture a portion of staff members
  - also, didn't know what this would look like with a cluster-level outcome!

Individual-level data structure

Data on n_c staff members in each cluster $c = 1, \ldots, K$:

- A_{ci}: indicator of intervention assignment (cluster-level)
- $Z_{ci} \in \mathbb{R}^q$: cluster-level subgroup variables
- $W_{ci} \in \mathbb{R}^p$: baseline covariates
- Y_{ci}: binary outcome

HTE with individual-level outcomes

Suppose we are interested in HTE by a single binary variable W_{ci}.

Target estimand: the difference in the risk difference based on levels of W_{ci}.

Estimate using linear regression:

$$E(Y_{ci} \mid A_{ci} = a, Z_{ci} = z, W_{ci} = w) = \beta_0 + \beta_1 a + \beta_2 z + \beta_3 w + \beta_4 aw.$$

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Under standard assumptions, β_4 quantifies HTE.

Cluster-level data structure

In many settings, we observe cluster-level data:

- $\overline{Y}_c := \frac{1}{n_c} \sum_{i=1}^{n_c} Y_{ci}$: cluster-level outcome proportion
- A_c: indicator of intervention assignment
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Possible options for aggregating an individual-level covariate W_{cj}:

- $X_{cj} = V_{cj} - \frac{1}{K} \sum_{c=1}^{K} V_{cj}$, where $V_{cj} = \frac{1}{n_c} \sum_{i=1}^{n_c} W_{cji}$
- $X_{cj} = I\left(V_{cj} > t\right)$ for threshold t

Aggregated data: complications

Individual-level effects may not be identifiable based on aggregate data

- Often referred to as ecological bias [Wakefield (2008)]
- Exposure-outcome association can be biased: [Greenland & Morgenstern (1989)]
  - by aggregated confounders
  - by aggregated HTE variables

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Compositional data cause challenges in interpretation:

- Arise when aggregating mutually-exclusive binary variables
- Changing the value of one proportion necessarily changes at least one other

HTE with cluster-level outcomes

Now, outcome $\overline{Y}_c$ is a proportion; interest in HTE by single variable X_c.

Target estimand: difference in difference of proportions based on values of X_c.

Estimate using linear regression:

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If W represents a single binary variable, then aggregation determines interpretation:

- Using mean-centered proportion: difference in difference for 1-unit increase from the across-cluster mean proportion
- Using threshold: difference in difference comparing "high" to "low"

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If W is compositional, this is further complicated:

- how are the categories transformed to enable model fitting?
- what does a one-unit change imply?

Simulation setup

Data mimic ENSPIRE trial:

- Sample $K \in \{30, 40, 80\}$ clusters within two regions
- Clusters are urban or suburban/rural
- Randomization constrained to balance on region, urban vs suburban/rural
- Each center has 100 staff members, who each:
  - have record of receiving COVID-19 booster vaccine
  - have self-reported race (recorded as single binary variable)
- Define cluster-level booster rate $\overline{Y}_c$
- Define two aggregations of self-reported race:
  - center-level proportion
  - indicator of whether proportion > 0.5

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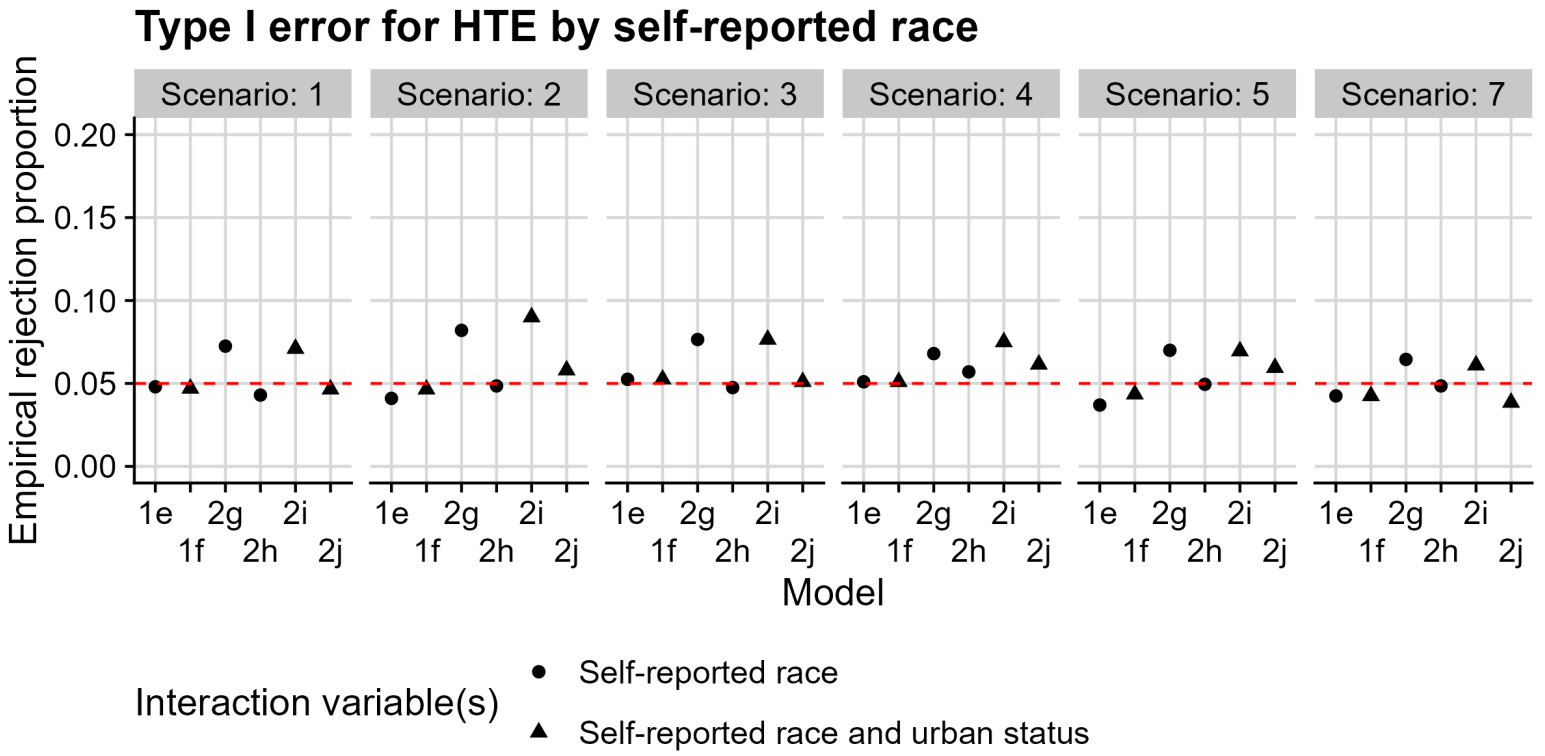
Fit both individual-level and cluster-level regression models

Tested for HTE by self-reported race, investigated type I error and power

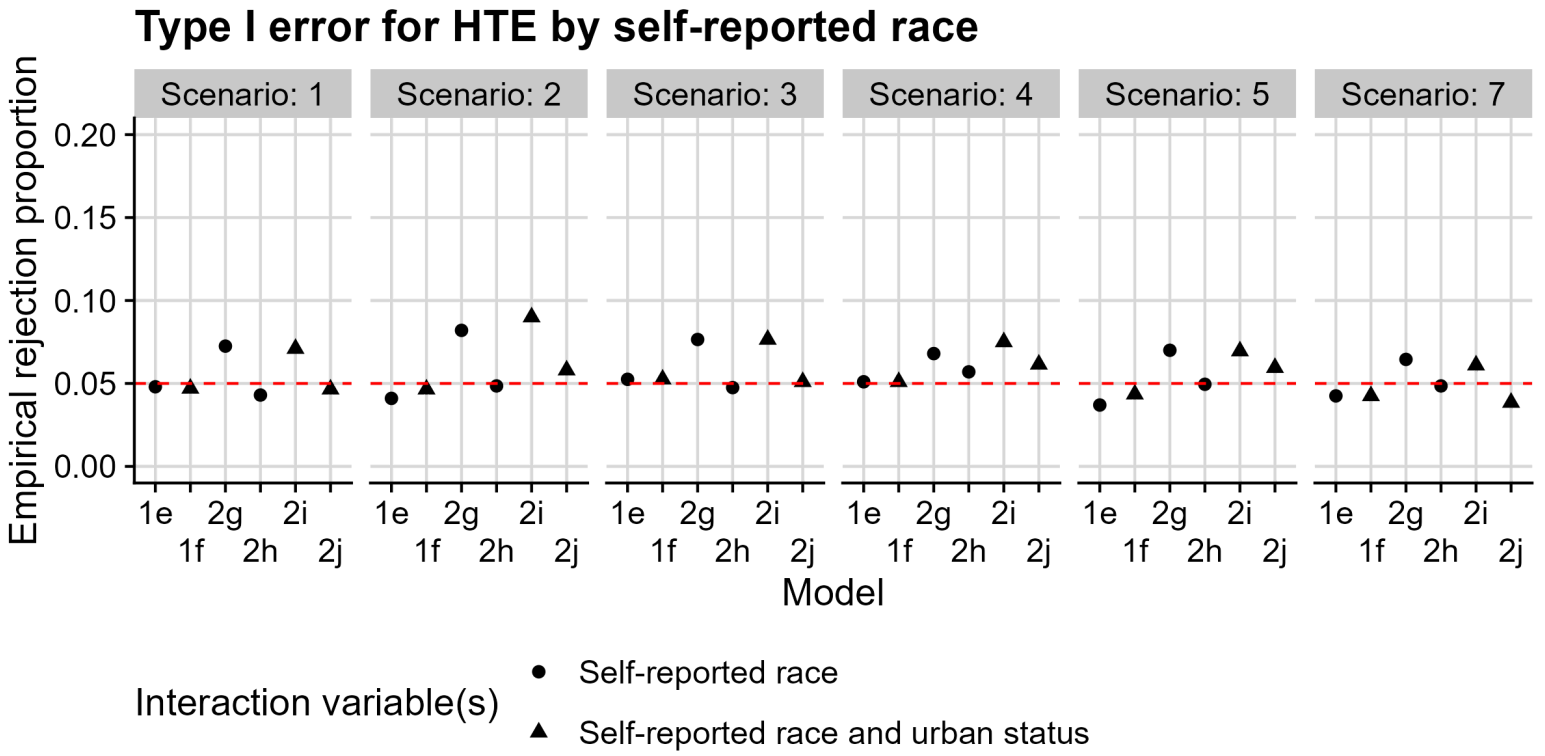
Results: type I error



Scenarios encode presence of true differences in booster rate or HTE:

- 1, 2, 5: no difference in booster rate by self-reported race, no HTE
- 3, 4, 7: difference in booster rate by self-reported race, no HTE

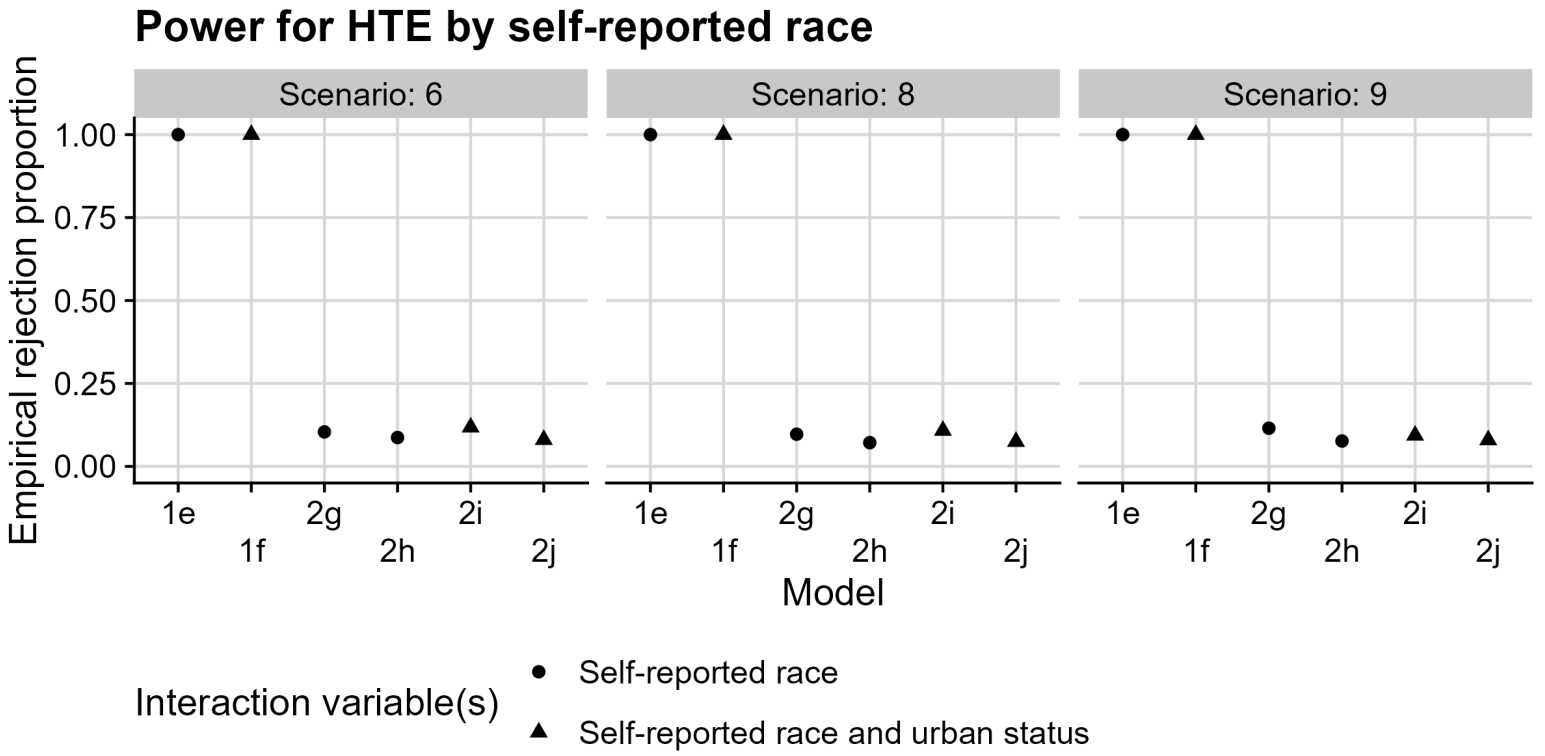
Results: type I error



Models encode individual- (1) vs cluster-level (2), adjustment and interaction variables:

- 1e, 1f: adjust for self-reported race, allow HTE by self-reported race (1f also by urban)
- 2g, 2i: adjust for center-level race proportion, allow HTE by self-reported race (2i also by urban)
- 2h, 2j: adjust for proportion > 0.5, allow HTE by self-reported race (2j also by urban)

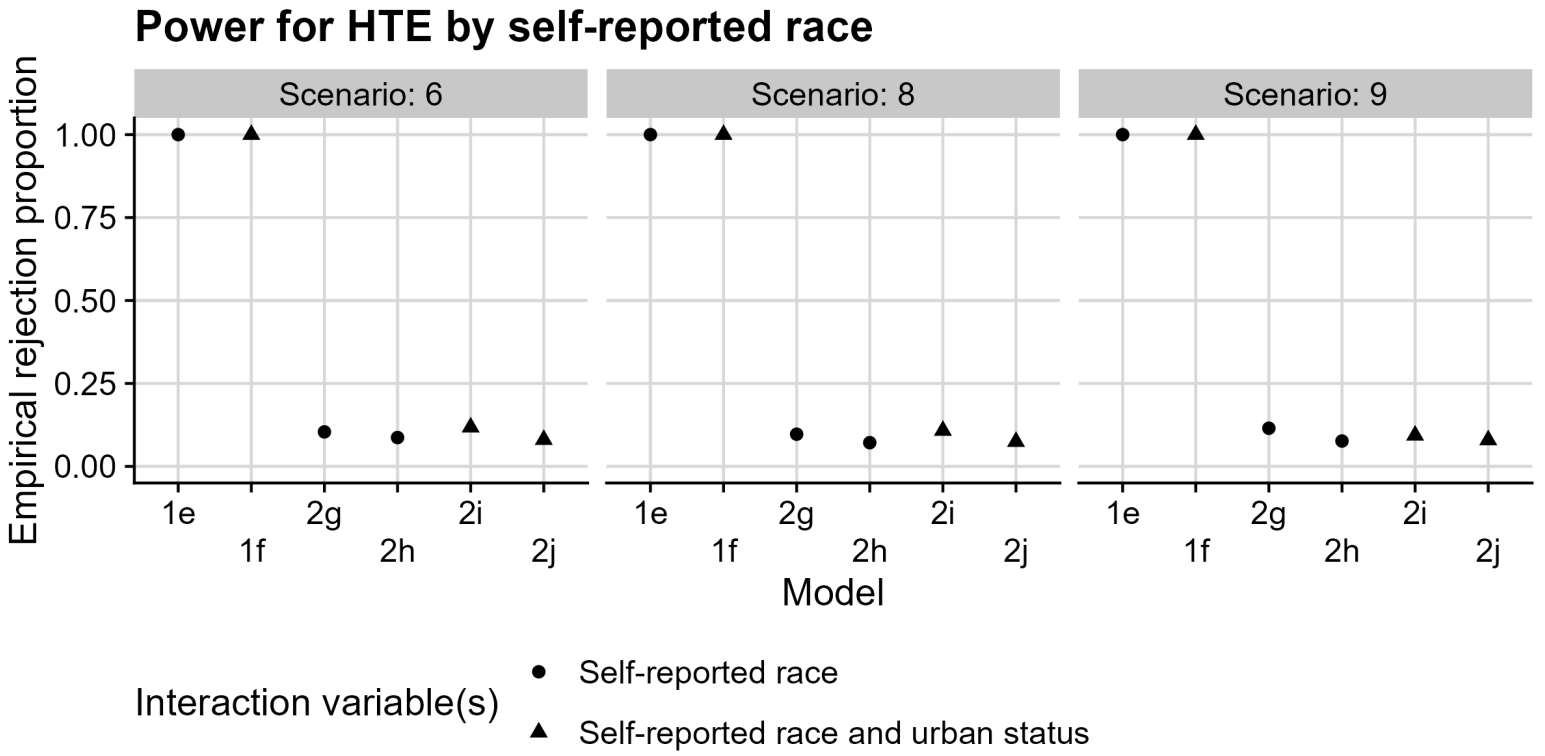
Results: power



Scenarios encode presence of true differences in booster rate or HTE:

- 6: difference in booster rate by self-reported race, HTE by self-reported race
- 8: difference in booster rate by urban and self-reported race, HTE by self-reported race
- 9: difference in booster rate by urban and self-reported race, HTE by urban and self-reported race

Results: power



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Closing thoughts

High power, controlled type I error to detect HTE in the individual-level analysis

- where possible, this approach is key for identifying an remedying disparities

Low power to detect HTE by an aggregated individual-level predictor

- even in simple setting with only two possible categories!
- likely exacerbated in more realistic settings
- elevated type I error when using proportion in some settings

However, meaningful estimated differences across groups can still be acted upon

Power calculations should aggregate simulated individual-level data, rather than simulating cluster-level data directly.

For more details, including more realistic simulation settings:

Williamson BD, Coley RY, Hsu C, McCracken CE, Cook AJ (2023). Considerations for subgroup analyses in cluster-randomized trials based on individual-level predictors. *Prevention Science*.

References

- Knol MJ and VanderWeele TJ (2012). Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology*.
- Petkovic et al. (2020). Reporting of health equity considerations in cluster and individually randomized trials. *Trials*.
- Chidambaram P (2022). Over 200,000 residents and staff in long-term care facilities have died from COVID-19. *Kaiser Family Foundation*.
- Wakefield J (2008). Ecologic studies revisited. *Annual Review of Public Health*.
- Greenland S & Morgenstern H (1989). Ecological bias, confounding, and effect modification. *International Journal of Epidemiology*.