Transportability, External Validity, and Implementation Science

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18 May 2017

Outline

Overview

Introduction

Transportability

30 second review of DAGs

Implementation Science Example: Community Adherence Groups

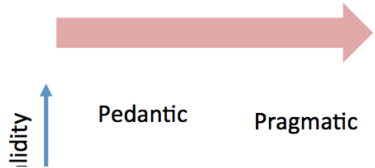
Conclusions

- Synthetic definition?
  - Implementation science is a multidisciplinary specialty that seeks **generalizable** knowledge about the behavior of stakeholders, organizations, communities, and individuals in order to understand the scale of, reasons for, and strategies to close the gap between evidence and routine practice for health in real world contexts.

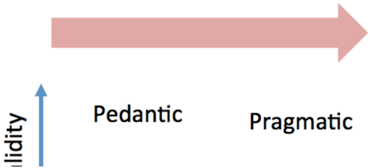
Focus of PRECIS-2

The PRECIS-2 tool focuses on trial design choices which determine the applicability of a trial. Applicability (the ability for a trial result to be applied or used in a particular situation) is the outcome of these choices, which

Making research more relevant in diverse settings



Making research more relevant in diverse settings



...and Context

- Adaptation to specific locations, populations or contexts was mentioned in 81% of definitions
  - "Implementation Research ...[is] concerned with t

Relevance

Generalizable

Pragmatic

Context

Applicability

External Validity

Implementation science **demands** external validity

External Validity:

Using results of a study conducted in one population to make inferences about **another population**.

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Transportability provides a formal framework for assessing external validity and extending the results of a study to a target population.

Overview

Definitions

Study Population:

The population in which the study was conducted.

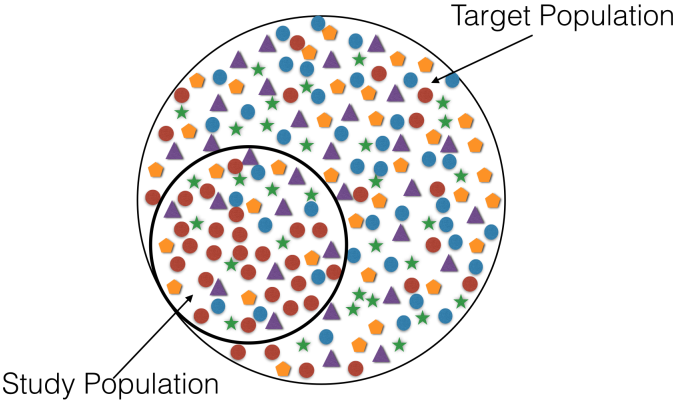
Target Population:

The population of interest.

Your city/community/country etc.

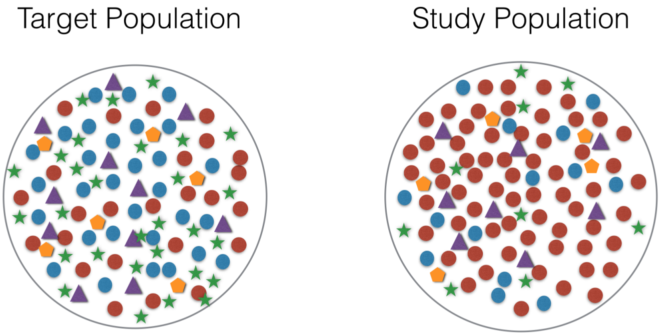
Definitions

Generalizability:



Definitions

Transportability:

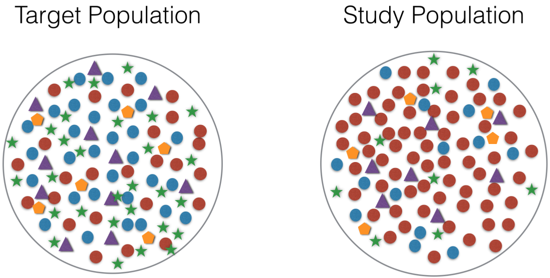


What makes a study externally valid?

Among other things,

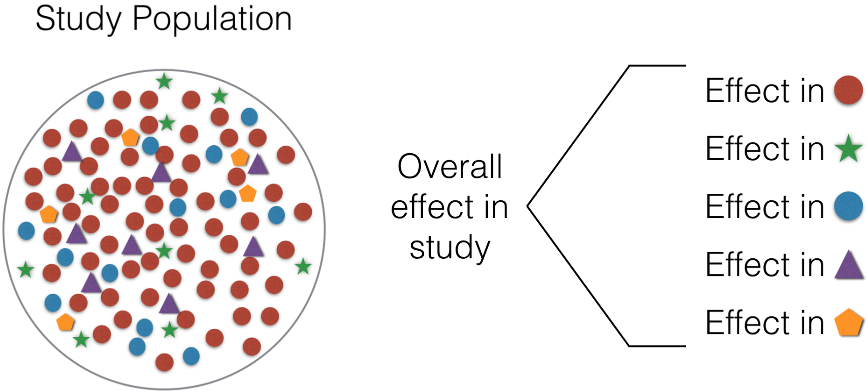
Population Composition.

Does the study population *resemble* the target population?



Intuition

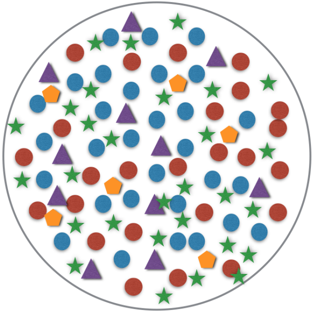
An intervention may be more or less effective given certain characteristics



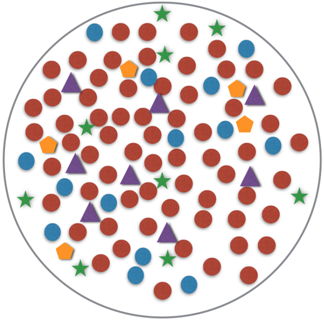
Intuition

The distribution of these characteristics may vary across populations

Target Population

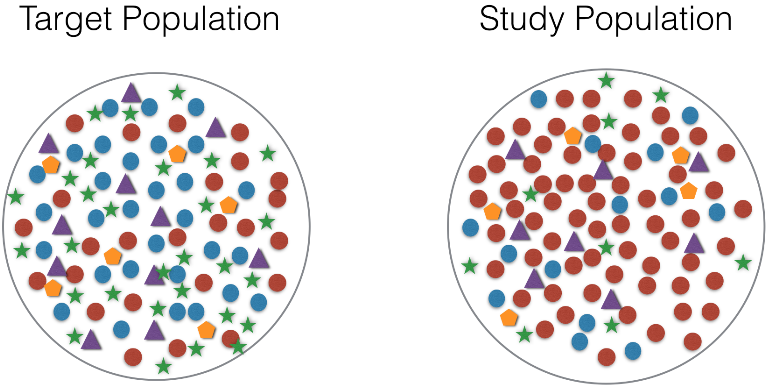


Study Population

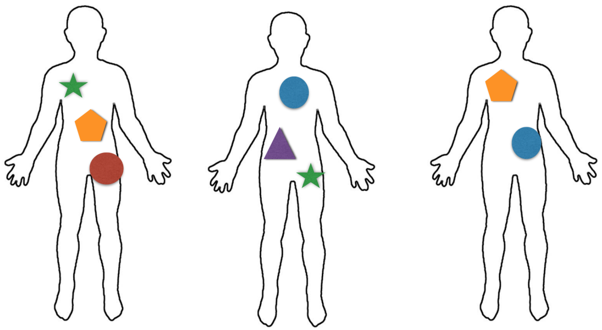


Intuition

To transport an effect from a study population to a target population, we need to adjust for the differences in the distribution of effect modifiers between the two populations. *Population Exchangeability*



Intuition



- However, there is overlap of characteristics in individuals in a population!

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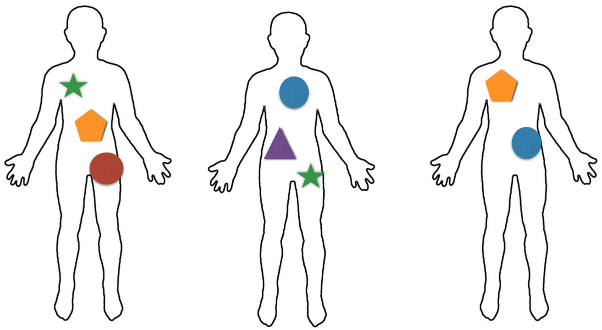

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- And interaction between characteristics often affects the outcome

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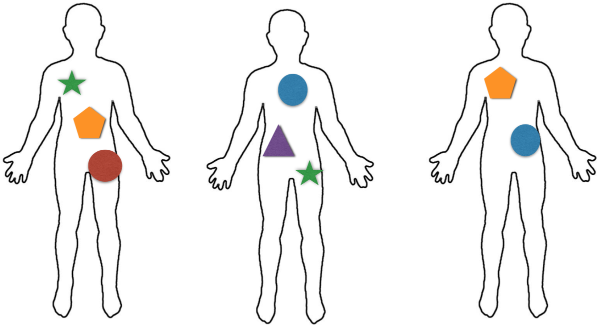

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- So we need to know about the *joint distribution* in **both** populations

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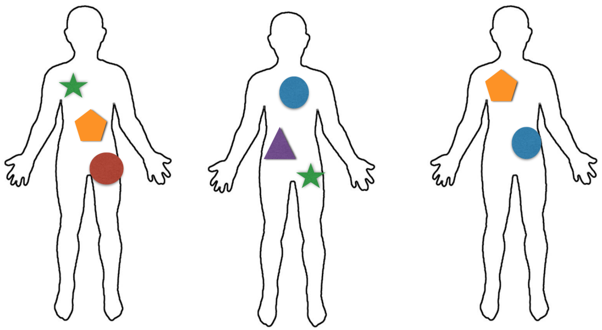

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- And interaction between characteristics often affects the outcome
- So we need to know about the *joint distribution* in **both** populations
- Which characteristics matter?!

Overview

Directed Acyclic Graphs:

Components:

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Components:

- Nodes: variables of interest

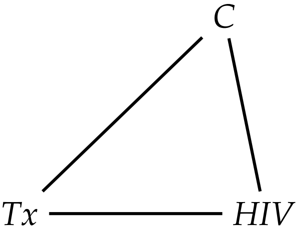
C

Tx HIV

Directed Acyclic Graphs:

Components:

- Nodes: variables of interest
- Edges: Causal associations



Directed Acyclic Graphs:

Components:

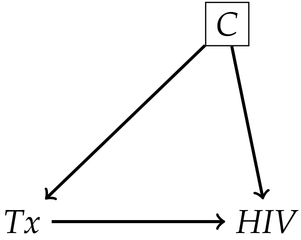
- Nodes: variables of interest
- Edges: Causal associations
- Directed: Direction of causes

$$\begin{tikzcd} & & C \arrow[dll] \arrow[d] \\ Tx \arrow[rr] & & HIV \end{tikzcd}$$

Directed Acyclic Graphs:

Components:

- Nodes: variables of interest
- Edges: Causal associations
- Directed: Direction of causes
- Conditioning on a variable



DAGs and Causality

There are 3 structural sources of statistical correlation between two given variables:

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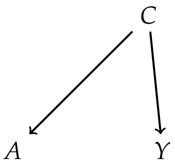
A causes Y

$$A \longrightarrow Y$$

DAGs and Causality

There are 3 structural sources of statistical correlation between two given variables:

A and Y share a common cause (C), and it is **not** conditioned on.



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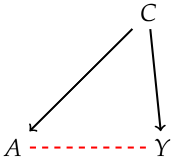
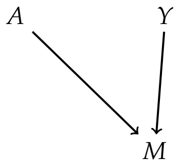


DAGs and Causality

There are 3 structural sources of statistical correlation between two given variables:

A and Y share a common effect, and that effect is conditioned on (M).



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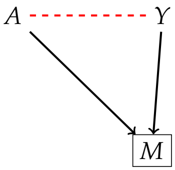


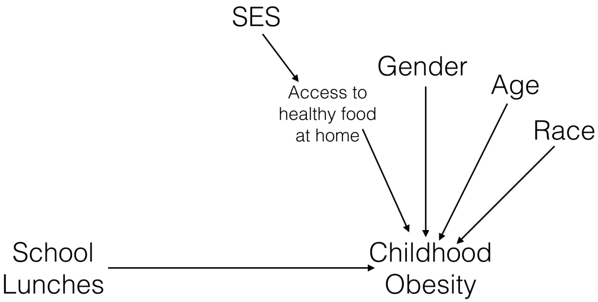
Effect Heterogeneity in DAGs

$$\begin{tikzcd} & & Z \arrow[dl] \\ A \arrow[r] & Y & \end{tikzcd}$$

If 2 variables are associated with an outcome, we are guaranteed to observe effect heterogeneity on at least one scale.
(Rothman et al, 2008)

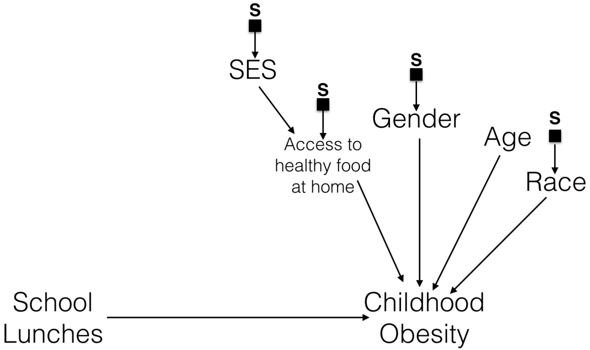
Selection Diagrams

1. Draw DAG representing study population. Include all possible effect modifiers.



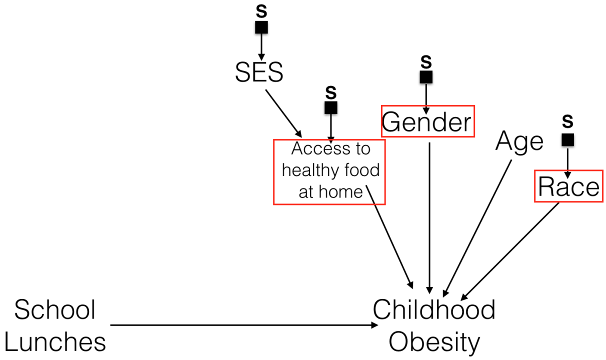
Selection Diagrams

2. Add **selection nodes** directed at any characteristics that differ between the study population and target population



Selection Diagrams

3. Adjust for effect modifiers such that all selection nodes are independent of the outcome (d-separated)



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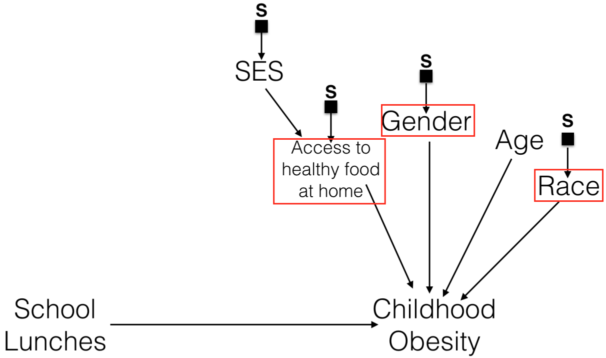
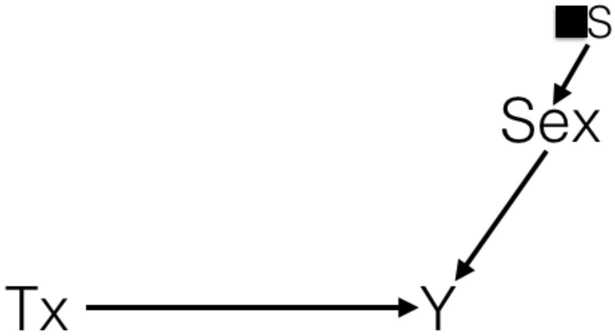


To adjust for the selected effect modifiers, we must have **individual-level** measurements of them in both the study and target populations!

Examples



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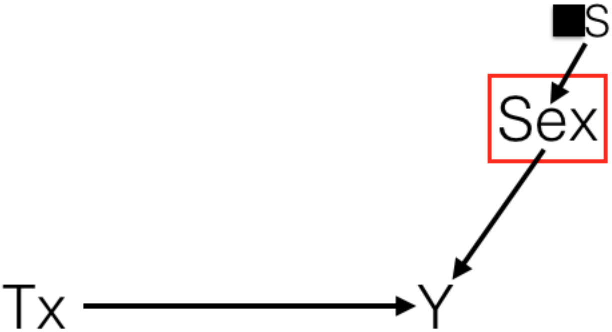

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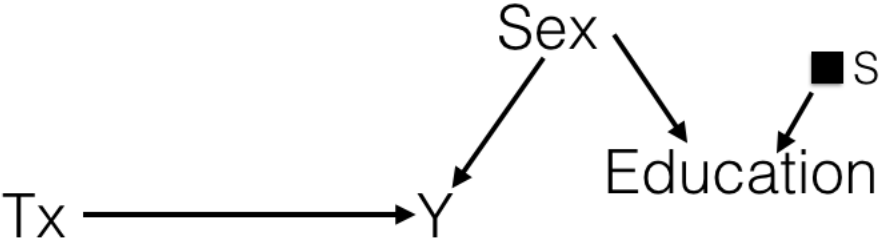

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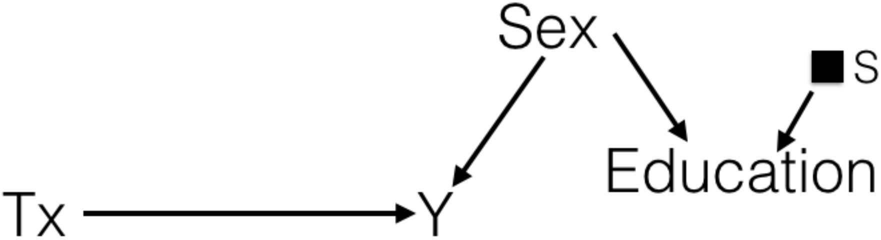
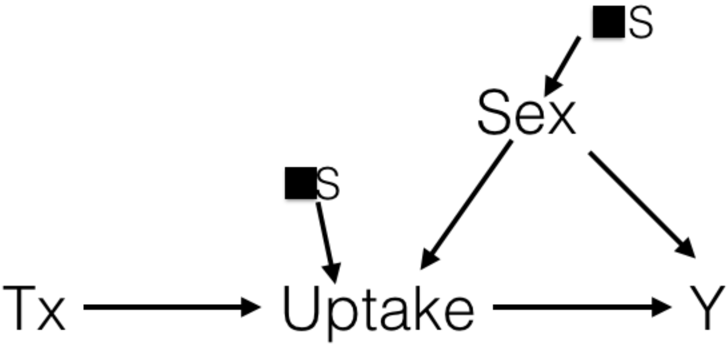


No need to adjust!

Examples



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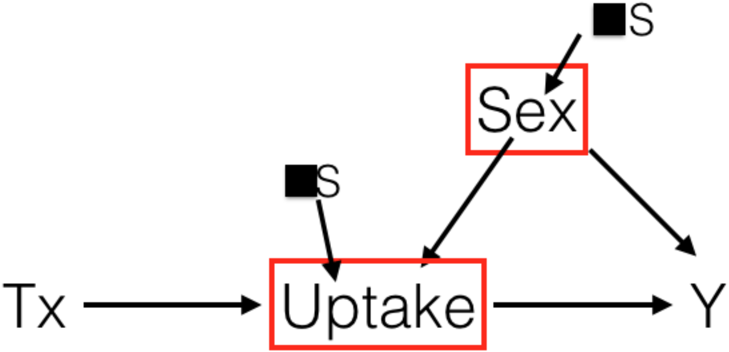

Estimation

There are several approaches to estimation:

- Model-based standardization (G-estimation)

  (Lesko et. al., 2017)

- Inverse weighting

  (Cole et al., 2010 and Westreich et. al., 2017)

- Targeted Maximum Likelihood Estimation

  (Rudolph et. al., 2014)

Big Picture

- Transportability provides a formal framework and graphical approach for extending results of studies to populations of interest
- MUST DEFINE TARGET POPULATION
- Individual-level data from the target population is **critical.**
- The approach is flexible and can be applied to a wide range of scenarios

Overview

Background

Motivating problem and setting: Challenges attending regular clinic visits can lead to less viral suppression of HIV, particularly in rural settings.

Intervention: Community Adherence Groups- home or village-based adherence groups to facilitate HIV medication adherence.

Outcome: HIV RNA Viral Load

When rolled out into other communities, CAGs are not always successful

Populations

Study population: Study conducted in clinics in a small community that is part of a an HIV research network; 30% of HIV patients live far from a clinic.

Target Population: Larger but more rural region that has been less involved in prior HIV research studies.

Populations

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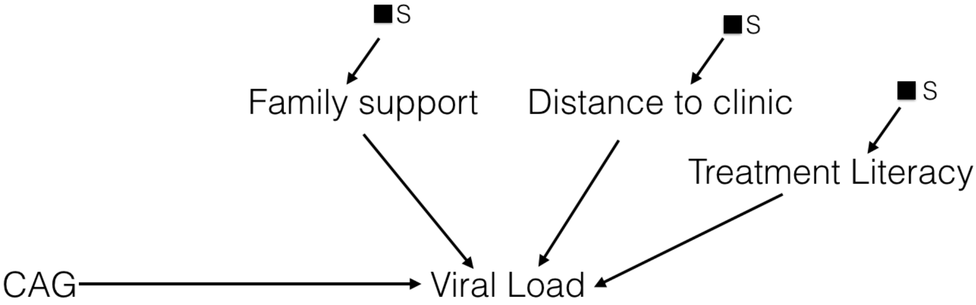
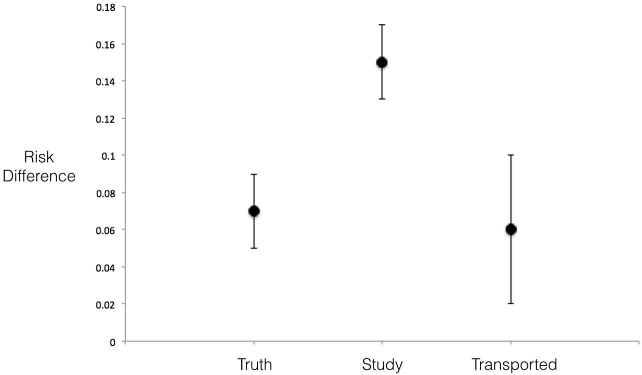
CONTEXT!

Target Population: Larger but more rural region that has been less involved in prior HIV research studies.

Selection Diagram



Results



	Risk Difference	95% Confidence Interval
Truth	0.07	[.06, .09]
Study	0.15	[.12, .17]
Transported	0.06	[.02, .10]

Conclusions

Overview

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- Causal graphs are a useful and powerful tool for external validity
- Many of the major issues facing implementation science can be characterized in terms of transportability–allowing for rigorous and quantitative assessment of context and adaptability. *But we need good data in our target populations!*

Acknowledgements

THANK YOU!

- Committee Members:
  - David Glidden (chair)
  - Elvin Geng
  - Maria Glymour
  - Daniel Westreich
- Bob Grant
- Maya Petersen

Funding: Ruth L. Kirschstein National Research Service Award (NRSA) Fellowship: F31MH111346

UCSF

References

[1] S. R. Cole and E. A. Stuart. Generalizing Evidence From Randomized Clinical Trials to Target Populations The ACTG 320 Trial. *Am. J. Epidemiol.*, 172(1):107–115, July 2010.

[2] M. B. Deutsch, D. V. Glidden, J. Sevelius, J. Keatley, V. McMahan, J. Guanira, E. G. Kallas, S. Chariyalertsak, and R. M. Grant. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. *The Lancet HIV*, Nov. 2015.

[3] R. M. Grant, J. R. Lama, P. L. Anderson, V. McMahan, A. Y. Liu, L. Vargas, P. Goicochea, M. Casapía, J. V. Guanira-Carranza, M. E. Ramirez-Cardich, O. Montoya-Herrera, T. Fernández, V. G. Veloso, S. P. Buchbinder, S. Chariyalertsak, M. Schechter, L.-G. Bekker, K. H. Mayer, E. G. Kallás, K. R. Amico, K. Mulligan, L. R. Bushman, R. J. Hance, C. Ganoza, P. Defechereux, B. Postle, F. Wang, J. J. McConnell, J.-H. Zheng, J. Lee, J. F. Rooney, H. S. Jaffe, A. I. Martinez, D. N. Burns, D. V. Glidden, and iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.*, 363(27):2587–2599, Dec. 2010.

[4] M. A. Hernán and J. M. Robins. *Causal Inference*. 2016.

[5] J. Pearl. *Causality: Models, Reasoning, and Inference*. Cambridge University Press, New York, NY, USA, 2000. pgs.98-115.

[6] J. Pearl and E. Bareinboim. External Validity: From Do-Calculus to Transportability Across Populations. *Statistical Science*, 29(4):579–595, Nov. 2014.

References

[7] K. J. Rothman, S. Greenland, and T. L. Lash. *Modern epidemiology*. Lippincott Williams & Wilkins, 2008.

[8] K. E. Rudolph, I. Díaz, M. Rosenblum, and E. A. Stuart. Estimating Population Treatment Effects From a Survey Subsample. *Am. J. Epidemiol.*, page kwu197, Sept. 2014.

[9] S. Rueda, L. Y. Park-Wyllie, A. M. Bayoumi, A. M. Tynan, T. A. Antoniou, S. B. Rourke, and R. H. Glazier. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. *Cochrane Database Syst Rev*, (3):CD001442, July 2006.

[10] D. Westreich and J. K. Edwards. Invited Commentary: Every Good Randomization Deserves Observation. *Am. J. Epidemiol.*, page kwv200, Oct. 2015.

[11] D. Westreich, J. K. Edwards, C. R. Lesko, E. A. Stuart, and S. R. Cole. Transportability of trial results using inverse odds of sampling weights. *American Journal of Epidemiology*.