CAUSAL EFFECT HETEROGENEITY IN OBSERVATIONAL DATA

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Background

- Generating evidence on effect heterogeneity in important to inform efficient decision making.
  - Translate to clinical decisions with sufficient reliability of evidence
  - Hypothesis generation for targeting future research
  - Creating algorithms for clinical decision support systems, and evaluation of CDSS
  - Making sub-group specific coverage decisions, where plausible
  - Appropriate value calculation (Today's F4 session on curative therapies)

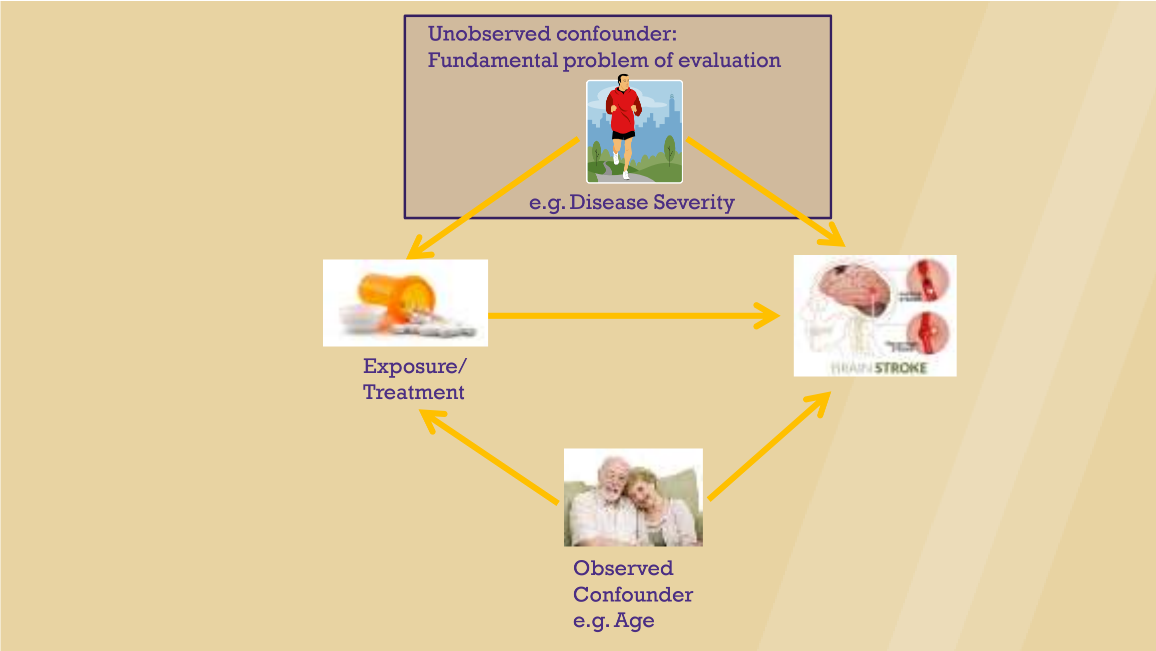
Background

> Reliable evidence -> accurate and unbiased

> Seek large samples for accuracy
> Seek some form of randomization for unbiasedness
> Seek cost-effective ways to produce such information

> Typical RCTs often fail on all aspects and are not the best mechanism to produce information on heterogeneity.
  – Usually do not have large sample sizes
  – Generalizability issues
  – Costly

OBSERVATION STUDIES TO RESCUE?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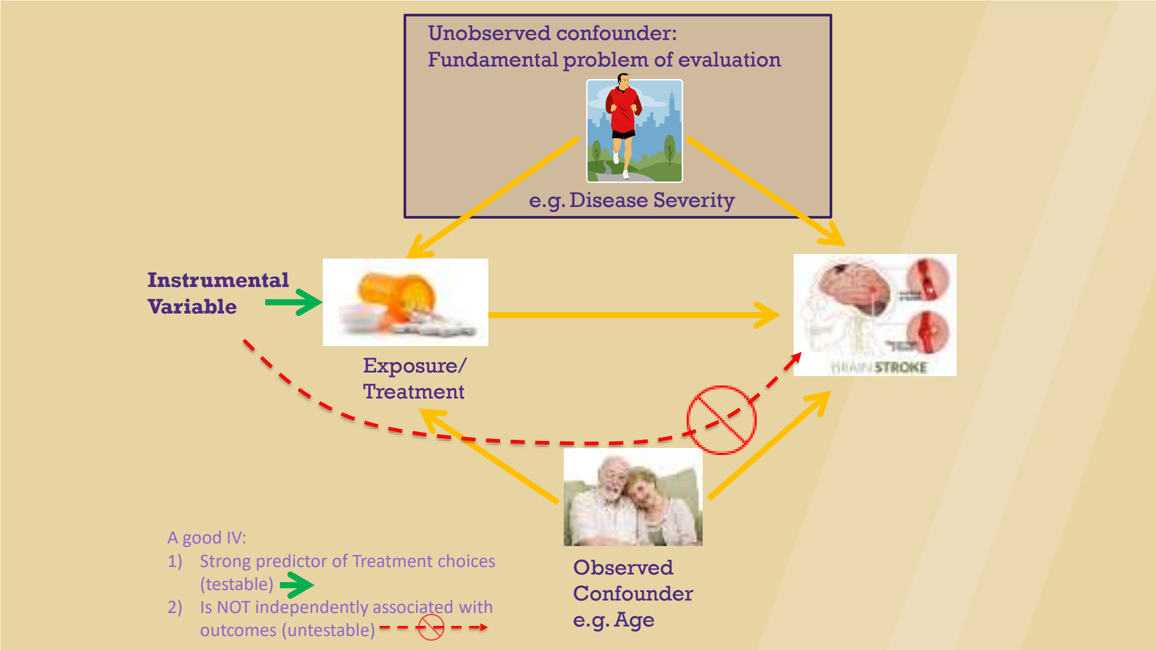
Fundamental problem of evaluation
e.g. Disease Severity
Exposure/
Treatment
BRAIN STROKE
Observed
Confounder
e.g. Age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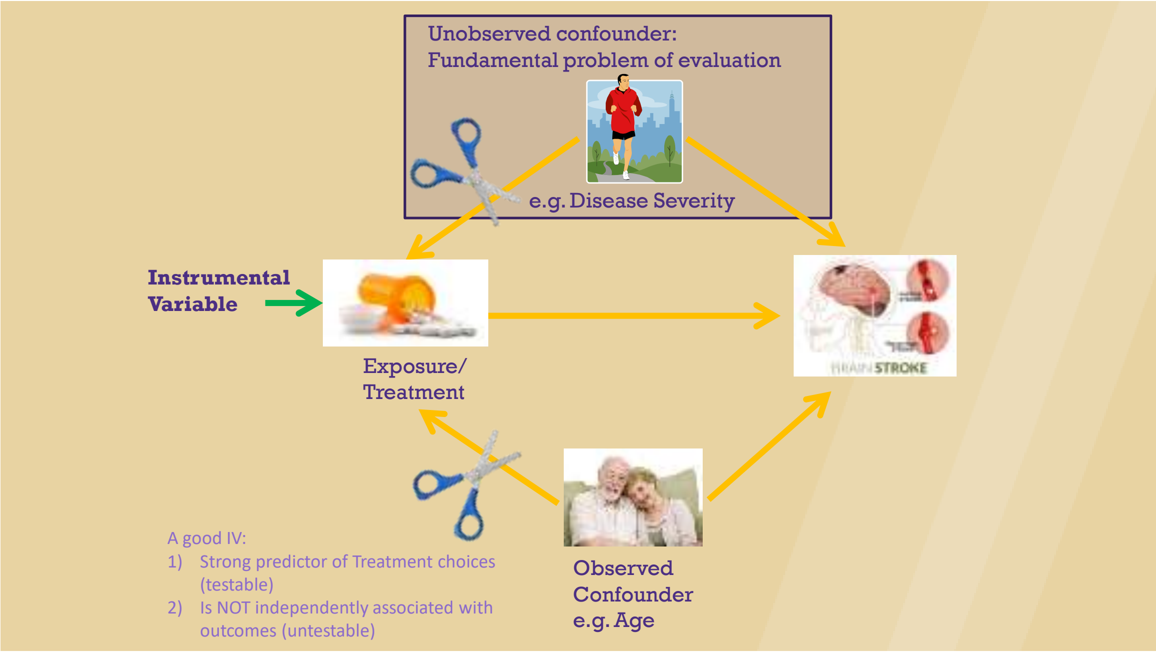
1) Strong predictor of Treatment choices (testable)
2) Is NOT independently associated with outcomes (untestable)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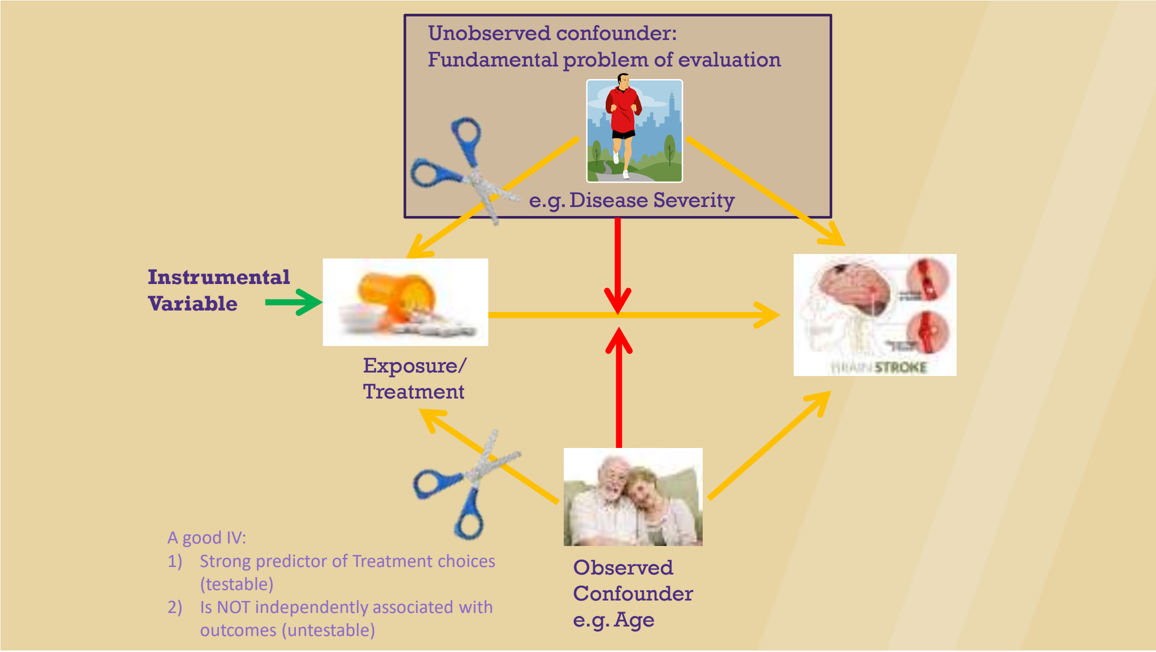
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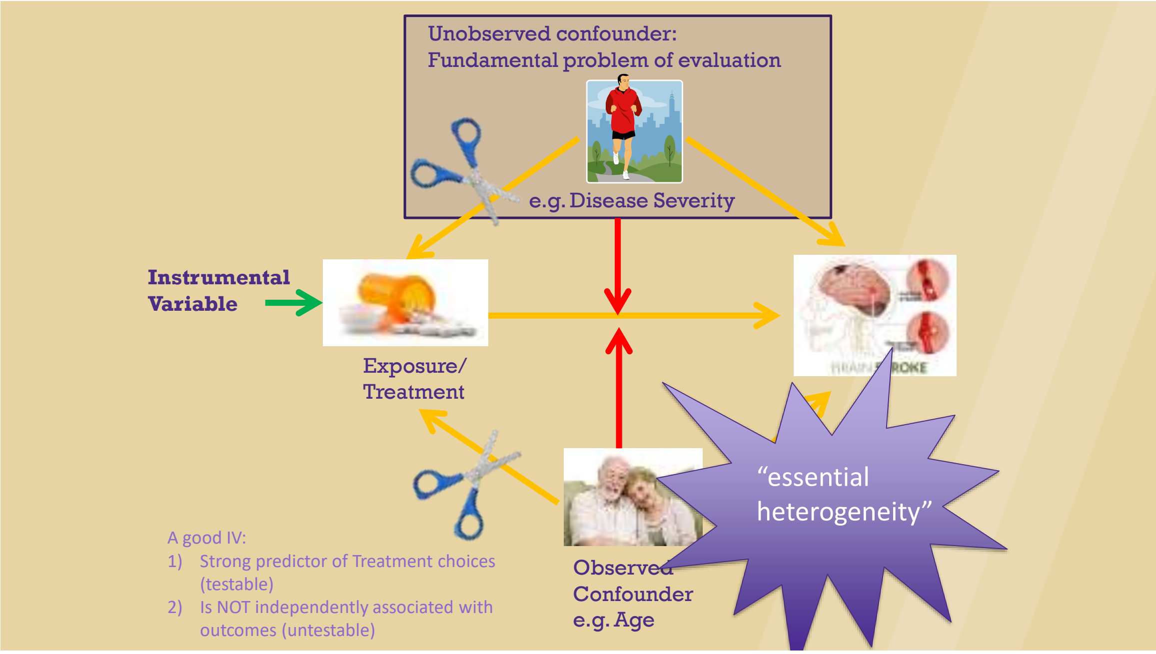


What is an IV estimating?

> With a binary IV (e.g. two levels of formulary)
  – Local Average Treatment effect (Angrist and Rubin 1996)

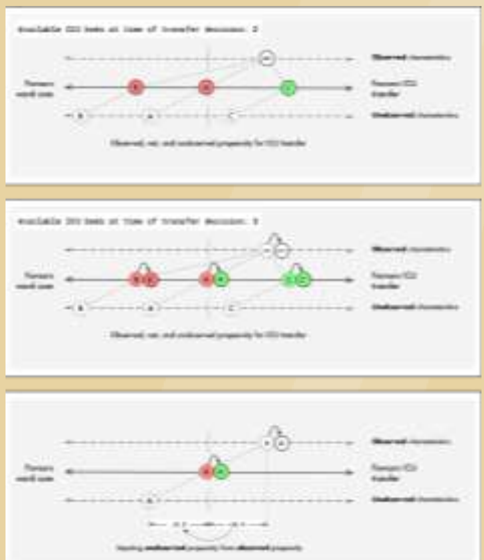
  – Challenges:
    > Who are these people (remember we don't observe some confounders in the data)?
    > How generalizable are there effects to other?

  – Partial salvation:
    > When the binary IV is a policy variable – LATE is at least interpretable
    > e.g. Oregon Medicaid Lottery
    > Better methods available with strong continuous instruments

Advanced Econometric Methods

Employ an Economic Choice Model

- Choice model tells us who is at the "margin" of choice
- Manipulation of IV levels help identify "marginal treatment effects" (MTEs)
- MTEs are building blocks for any interpretable mean treatment effect parameters
  - ATE
  - CATE
  - TT/TUT
  - PeT



Person-centered Treatment (PeT) Effects

> In a perfect RCT, one can estimate a
  - Population average treatment effect (pATE)
  - Conditional average treatment effect (CATE), e.g. the average effect of treatment for, say, 60-year old. → averages over all unobserved confounders

> With observational data, even with the same confounders measured, you can additionally learn about the unobserved confounder levels for a person by observing one's choice and the circumstance (IV-level) in which the choice was made

> PeT effects are individualized effects conditioned on their observed confounder levels and averaged over their choice-specific unobserved confounder distribution.
  - Effect for each person in your sample, easily averaged over any factor

Empirical Example

Does transfer to intensive care units reduce mortality for deteriorating ward patients?

Richard Grieve, Stephen O'Neill, Anirban Basu, Luke Keele, and Steve Harris

Background

> ICU Transfer versus stay in General Ward for hospitalized patients

> Prospective cohort study of the deteriorating ward patients referred for assessment for ICU transfer in the UK

> Primary Outcome: Death 7 days post assessment

> Secondary Outcomes: Death within 28 and 90 days

> Baseline covariates: demographics, some comorbidities, risk score

> IV: # of ICU beds available at the time of risk assessment. Vary across hospital and over time

Average Effects

	2 SLS	Bivariate probit	PeT Approach
7-day mortality	-27.9%	-10.5%	-11.7%
	(-73.8%, 18.0%)	(-47.1%, 26.2%)	(-25%, 1.5%)
28-day mortality	-34.0%	-7.9%	-4.9%
	(-89.9%, 21.9%)	(-44.2%, 28.4%)	(-26.4%, 16.7%)
90-day mortality	-25.6%	-9.5%	-4.7%
	(-83.8%, 32.5%)	(-48.1%, 29.1%)	(-28.5%, 19.2%)

LATE

ATE under Normality assumption

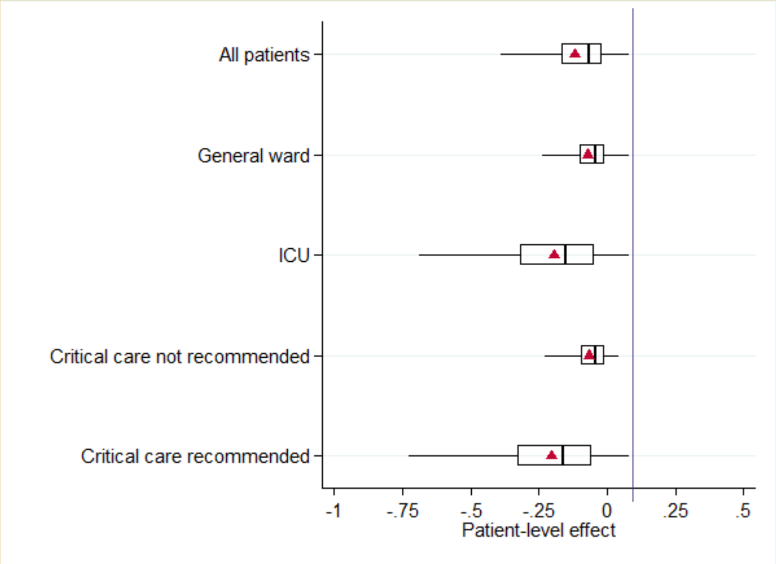
ATE with semi-parametric estimation

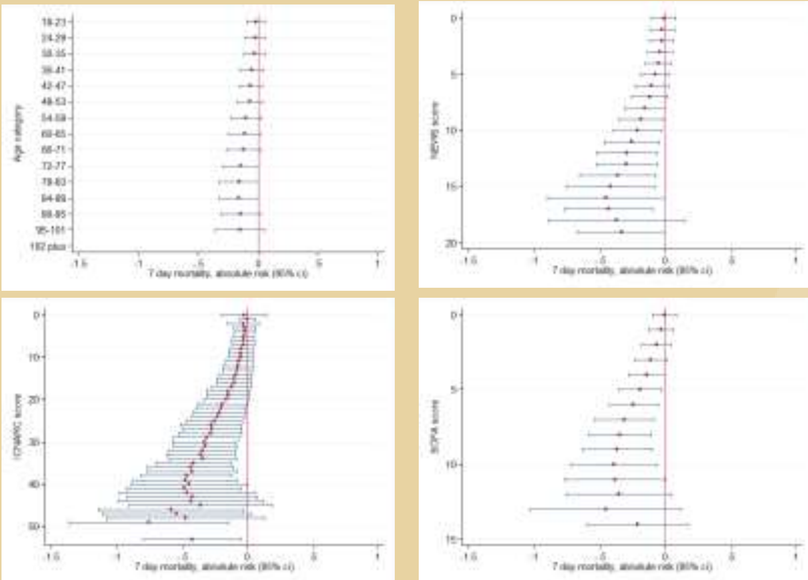
- Notice the PeT estimates have narrower confidence intervals

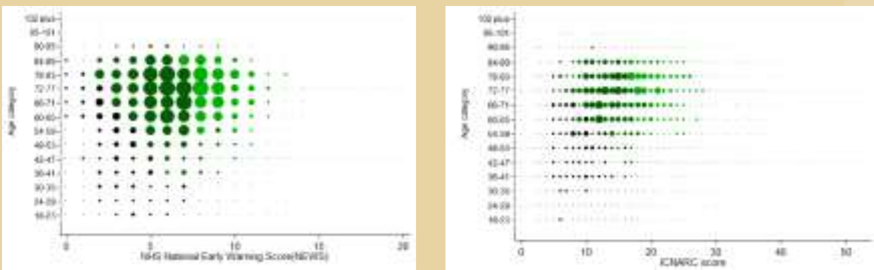
Focus of 7-day mortality

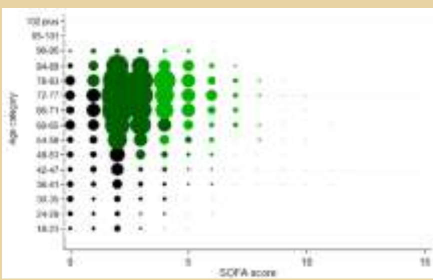
Distribution of PeT Effects

Distribution of PeT effects





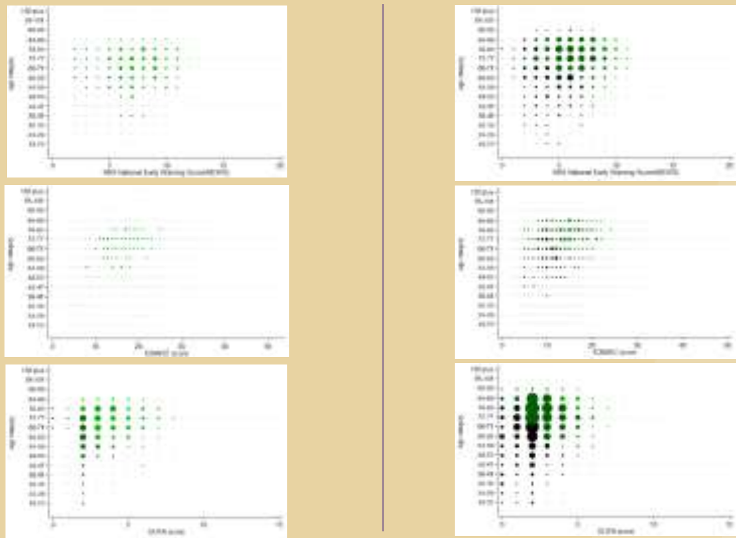




Individual Effect sizes
PeT > -0.05 (N = 3952)
-0.15 < PeT < -0.05 (N=2553)
PeT < -0.15 (N = 2508)

Size of circle represents number of patients

Among those who transfer to ICU | Among those who stay in wards



Exploratory Multivariate Het. Prediction

logit_dead7	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.099409	.0284813	-3.49	0.000	-.1552314	-.0435867
age2	-.0003175	.0002478	-1.28	0.200	-.0008033	.0001682
male	-.4829999	.1071483	-4.51	0.000	-.6930068	-.2729931
sepsis_dx	.1307296	.1519559	0.86	0.390	-.1670985	.4285578
periarrest	-.439148	.4189958	-1.05	0.295	-1.260365	.3820686
ccmds1	1.74724	.6659889	2.62	0.009	.4419257	3.052554
ccmds2	-1.908907	.6518933	-2.93	0.003	-3.186594	-.6312193
ccmds3	-4.687485	1.344332	-3.49	0.000	-7.322327	-2.052642
ccmds_missing	-.73532	1.009079	-0.73	0.466	-2.713079	1.242439
news_score	-.7093541	.0508766	-13.94	0.000	-.8090705	-.6096378
icnarc_score	-.1796798	.0155197	-11.58	0.000	-.2100979	-.1492618
sofa_score	-1.267285	.0788085	-16.08	0.000	-1.421747	-1.112823
out_of_hours	.8853215	.1646926	5.38	0.000	.5625298	1.208113
weekend	1.317777	.1152948	11.43	0.000	1.091803	1.54375
winter	.7233735	.2653278	2.73	0.006	.2033406	1.243406
_cons	20.16815	1.383138	14.58	0.000	17.45725	22.87905

Conclusions

- Application of novel econometrics methods to real-world data can be extremely productive
- Not all methods are created equal!
- Analysts need to weigh methods across domains of
  - causality,
  - interpretability,
  - precision,
  - ease of use
- Validation is a requirement for hypothesis generation exercises

References

Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. Medical Decision Making 2007; 27(2):112-127.

Basu A, Heckman J, Navarro-Lozano S, et al. Use of instrumental variables in the presence of heterogeneity and self-selection: An application to treatments of breast cancer patients. Health Econ 2007; 16(11): 1133 -1157.

Basu A. 2009. Individualization at the heart of comparative effectiveness research: The time for i-CER has come. Medical Decision Making, 29(6): N9-N11.

Basu A, Jena AB, Philipson TJ. The impact of comparative effectiveness research on health and health care spending. J Health Econ. 2011;30(4):695-706.

Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. J Health Econ. 2011; 30(3):549-559.

Basu A. Person-Centered Treatment (PeT) effects using instrumental variables: An application to evaluating prostate cancer treatments. Journal of Applied Econometrics (In Press).

Heckman JJ, Vytlacil EJ. Local instrumental variables and latent variable models for identifying and bounding treatment effects. Proc Nat Acad Sci 1999; 96(8): 4730-34

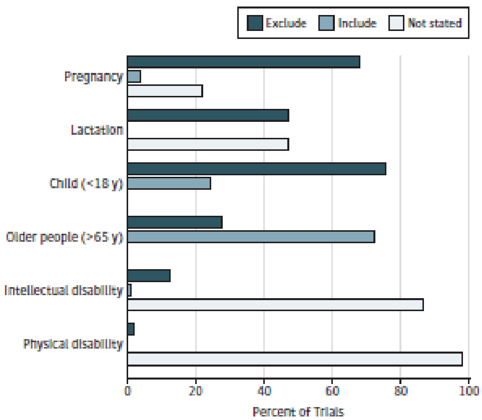
Heckman JJ, Urzua S, Vytlacil E. Understanding instrumental variables in models with essential heterogeneity. Rev Econ Stat 2006; 88(3): 389-432.

Kaplan S, Billimek J, Sorkin D, Ngo-Metzger Q, Greenfield S. Who Can Respond to Treatment?: Identifying Patient Characteristics Related to Heterogeneity of Treatment Effects. Medical Care 2010; 48(6): S9-S16

VIEWPOINT

Improving Public Health Requires Inclusion of Underrepresented Populations in Research

Figure. Open NIH-Funded Phase 3 and 4 Studies as of October 19, 2017



JAMA, 2018 Volume 319, Number 4

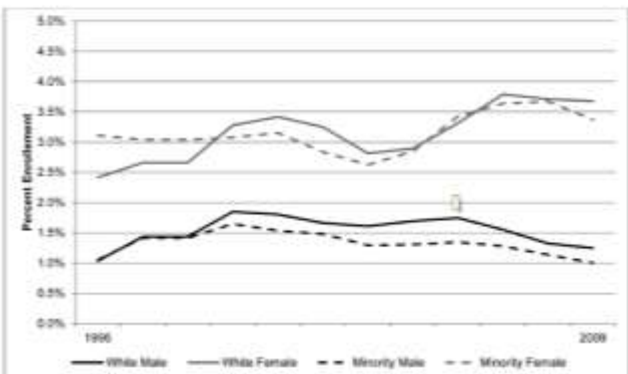


Figure 2.
Trends in NCI treatment trial enrollment rates in North Carolina, by gender and race, 3-year averages, 1996–2009.

Zullig et al. N C Med J. 2016
Jan-Feb; 77(1): 52–58

Background

- Adult Intensive Care Units (ICU) costly and scarce resource
  - Supply usually lags demand
- No RCT evidence
- Observational study evidence
  - Do not deal with the endogeneity of transfer
  - Do not recognizing heterogeneity in returns from transfer
- Transfers to ICU typically relies on clinical judgement
  - Not perfect proxy for reliable and causal evidence

Our Study

- Exploit natural variation in ICU transfer according to ICU bed availability for deteriorating ward patients in the UK
- The (SPOT)light Study (N = 15,158)
  - Prospective cohort study of the deteriorating ward patients referred for assessment for ICU transfer
  - Hospitals were eligible for inclusion if they participated in the ICNARC Case Mix Programme
  - Patients recruited between Nov 1, 2010 - Dec 31, 2011 from 49 UK NHS hospitals
  - A variety of exclusion conditions were applied to identify deteriorating ward patients who are equipoised to be transferred to ICU

Data

> Primary Outcome: Death 7 days post assessment

> Secondary Outcomes: Death within 28 and 90 days

> Exposure: ICU transfer vs care on general wards

> Baseline covariates: Age, diagnosis of sepsis, peri-arrest, dependency at ward assessment and recommended level of care post assessment (4 levels) and three physiology measures

- National Early Warning Score (NEWS) : whether respiratory rate, oxygen saturations, temperature, systolic blood pressure, pulse rate, a level of consciousness vary from the norm,
- the Sequential Organ Failure Assessment (SOFA), and
- the ICNARC physiology score

IV

> IV = NBA: Vary across hospital and over time

> Key Assumptions:

- NBA at ward patient's assessment directly affects one's probability of transfer to ICU
- NBA unconditionally independent of mortality of patients