Introduction to causal inference

Community health workers in a school, Rabai county, Kenya, September 2021

WASHA, Takwimu, UKZN, 25 August 2023

Till Bärnighausen, Heidelberg Institute of Global Health, University Hospital and Medical Faculty, Heidelberg University

Quantitative analysis serve many important functions in health systems research

4 FUNCTIONS

1. Description
2. Discovery
3. Prediction
4. Causation

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ANNUAL REVIEWS

Annual Review of Economics

Machine Learning Methods That Economists Should Know About

Susan Athey[1,2,3] and Guido W. Imbens[1,2,3,4]

[1]Graduate School of Business, Stanford University, Stanford, California 94305, USA; email: athey@stanford.edu, imbens@stanford.edu

[2]Stanford Institute for Economic Policy Research, Stanford University, Stanford, California 94305, USA

[3]National Bureau of Economic Research, Cambridge, Massachusetts 02138, USA

[4]Department of Economics, Stanford University, Stanford, California 94305, USA

Machine learning and causal inference are independent movements, which are currently integrating

INTEGRATIONS

1. ‘Big data’
2. Causal inference may provide the most stable prediction
3. Causal inference may be the best ‘explainable AI’
4. Mining for effect heterogeneities (‘Causal forests’)
5. Machine tasks in causal inference (e.g., optimal bandwidth in regression discontinuity)

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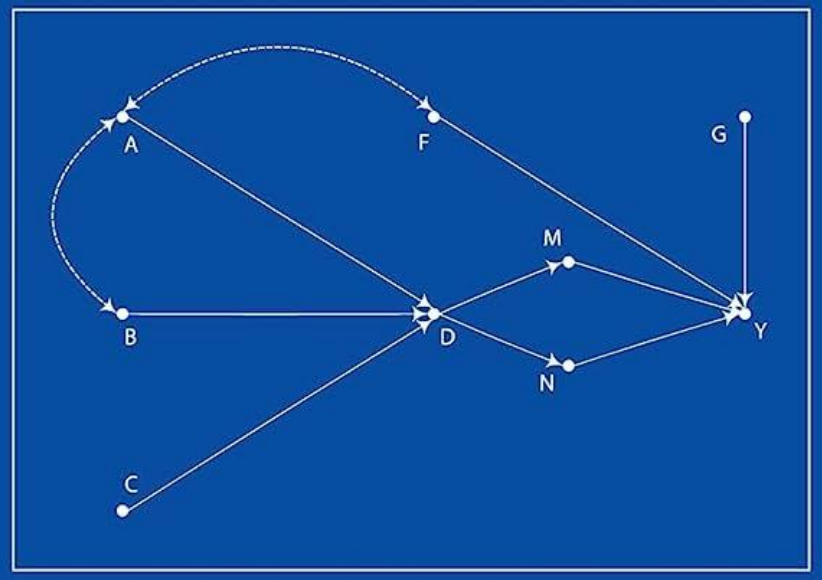
ANALYTICAL METHODS FOR SOCIAL RESEARCH



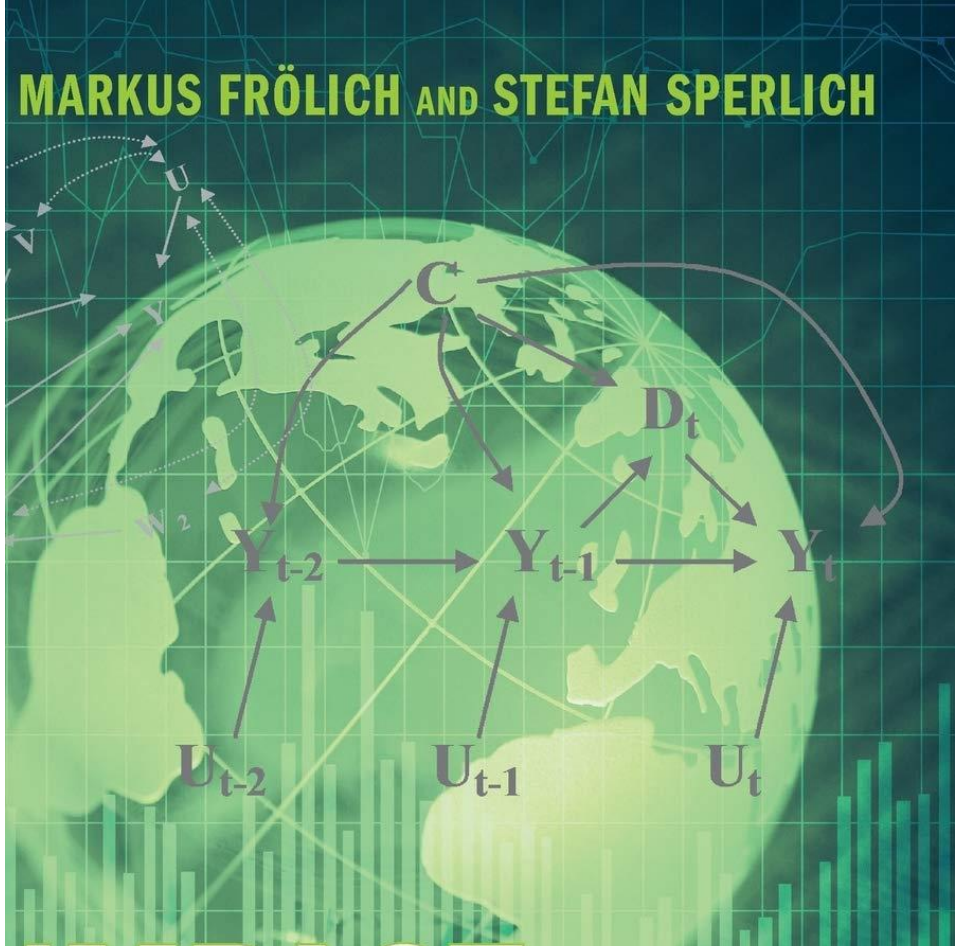
Counterfactuals and Causal Inference

Methods and Principles for Social Research

SECOND EDITION

STEPHEN L. MORGAN
CHRISTOPHER WINSHIP

MARKUS FRÖLICH AND STEFAN SPERLICH



IMPACT EVALUATION

TREATMENT EFFECTS AND CAUSAL ANALYSIS

For applied research, intuition is king

5 LEVELS OF UNDERSTANDING QUASI-EXPERIMENTAL DESIGNS

1. Conceptual intuition
2. Mathematical intuition
3. Programming execution
4. Mathematical replication
5. Mathematical development

till.baernighausen@uni-heidelberg.de

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Why do we randomize?

POTENTIAL OUTCOMES FRAMEWORK = RUBIN CAUSAL MODEL = COUNTERFACTUAL FRAMEWORK

Group	Y^1	Y^0
Treatment group (D=1)	Observable as Y	Counterfactual
Control group (D=0)	Counterfactual	Observable as Y

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Regression Discontinuity Designs in Epidemiology

Causal Inference Without Randomized Trials

Jacob Bor,[a,b,c] *Ellen Moscoe,*[c] *Portia Mutevedzi,*[b] *Marie-Louise Newell,*[b,d] *and Till Bärnighausen*[b,c]

Abstract: When patients receive an intervention based on whether they score below or above some threshold value on a continuously measured random variable, the intervention will be randomly assigned for patients close to the threshold. The regression discontinuity design exploits this fact to estimate causal treatment effects. In spite of its recent proliferation in economics, the regression discontinuity design has not been widely adopted in epidemiology. We describe regression discontinuity, its implementation, and the assumptions required for causal inference. We show that regression discontinuity is generalizable to the survival and nonlinear models that are mainstays of epidemiologic analysis. We then present an application of regression discontinuity to the much-debated epidemiologic question of when to start HIV patients on antiretroviral therapy. Using data from a large South African cohort (2007–2011), we estimate the causal effect of early versus deferred treatment eligibility on mortality. Patients whose first CD4 count was just below the 200 cells/μL CD4 count threshold had a 35% lower hazard of death (hazard ratio = 0.65 [95% confidence interval = 0.45–0.94]) than patients presenting with CD4 counts just above the threshold. We close by discussing the strengths and limitations of regression discontinuity designs for epidemiology.

(*Epidemiology* 2014;25: 729–737)

Causal inference in nonexperimental studies typically requires a strong, untestable assumption: that no unobserved factors confound the relationship between the exposure and the outcome.[1] Violations of this assumption will lead to biased estimation of causal effects. The regression discontinuity design is one important quasi-experimental study design in which this assumption is not required for causal inference. Regression discontinuity designs can be implemented when the exposure of interest is assigned—at least in part—by the value of a continuously measured random variable and whether that variable lies above (or below) some threshold value. Provided that subjects cannot precisely manipulate the value of this variable, assignment of the exposure is as good as random for observations close to the threshold, and valid causal effects can be identified.[2]

The regression discontinuity design first appeared in the educational psychology literature in 1960,[3–5] was further developed in the 1970s and 1980s,[6,7] and has become well established in economics over the last 2 decades.[2,8,9] In recent years, a number of clinical and population health studies have been published in economics journals using regression discontinuity designs.[10–17] These studies have used regression discontinuity to estimate the health effects of clinical care,[10,11]

Quasi-experiments can control unobserved confounding

METHODS FRAMEWORK

	Control of unobserved confounding	Assumptions regarding unobserved confounding
• **Experiments**	Complete	Weak
• **Quasi-experiments**		
– Instrumental variable approaches – Regressions discontinuity	Complete	Less weak
– Difference-in-differences approaches – Fixed effects approaches	Partial	Less weak
• **Non-experiments**		
– Regression – Matching – Stratification	None	Strong

Bärnighausen et al. *Journal of Clinical Epidemiology* 2017

The causal methods revolution has not yet entered many health domains

EXAMPLE PRODUCTIVITY

Ogbuoji, Vollmer, Jamison, Bärnighausen
BMJ 2022

Table 1 | Studies estimating the economic consequences of diseases and treatments

Type of study	Contribution	Rationale	Challenges	Example
Adding economic outcomes to trials data				
Intent-to-treat estimation[54]	Estimation of causal effects of treatments on economic outcomes	Assignment to treatment *v* control conditions in randomised controlled trials can be used for intent-to-treat estimation of causal treatment effects on economic outcomes Economic outcomes such as income, employment, or education could be routinely added to future trials and measured during re-visits of cohorts that participated in past trials	Changes to economic outcomes may manifest themselves only in the long term, requiring follow-up many years after the assessment of clinical endpoints has been completed Long term follow-up of trial cohorts may have substantial attrition owing to mortality, migration, or name changes	Hoddinott et al. Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults[10]
Instrumental variable estimation[55]	Estimation of causal effects of diseases on economic outcomes	If randomly assigned treatments induce significant changes in a disease, the treatments can be used as an instrumental variable to estimate the effects of the disease on economic outcomes Economic outcomes, such as income, employment, or education, could be routinely added to future trials and measured during re-visits of cohorts that participated in past trials	The exclusion restriction needs to be met—the treatments can affect the economic outcomes only through their effect on the disease and not through any other pathway Changes to economic outcomes may manifest themselves only in the long term, requiring follow-up many years after assessment of clinical endpoints has been completed	Daepp and Arcaya. The effect of health on socioeconomic status: using instrumental variables to revisit a successful randomised controlled trial[58]
Adding economic outcomes to cohort data				
Regression discontinuity estimation[56 51]	Estimation of causal effects of treatments on economic outcomes	Eligibility for many treatments is determined by applying a threshold to a continuously measured indicator (such as blood pressure or CD4 count). In these cases, we can estimate treatment effects by comparing outcomes among people whose indicator value fell just below the threshold with outcomes in those whose indicator value fell just above the threshold	Clinical cohorts may provide an opportunity to measure economic outcomes only among those who were deemed treatment eligible—and not among those on the other side of the treatment threshold—because only the former return regularly to health facilities for clinical follow-up Needs large numbers of people whose indicator value falls in a small window around the treatment eligibility threshold to ensure sufficient statistical power in the effect estimation. Regression discontinuity analyses may thus not be a useful study design to estimate economic outcomes of rare diseases and treatments	Patenaude et al. The impact of ART initiation on household food security over time[49]
Instrumental variable estimation[57]	Estimation of causal effects of treatments on economic outcomes	We can estimate the economic effects of a treatment using a variable that significantly affects treatment but is as good as randomly assigned to patients in a clinical cohort (that is, an instrumental variable), such as physician's prescribing preference or treatment guideline changes	The exclusion restriction needs to be met—the instrumental variable can affect the economic outcomes only through its effect on treatment and not through any other pathway The exchangeability condition needs to be met—the instrumental variable does not share common causes with the economic outcomes	Finkelstein et al. The Oregon health insurance experiment[59]

The causal methods revolution has not yet entered many health domains

SYSTEMATIC REVIEW

ELSEVIER

Check for updates

Journal of Clinical Epidemiology 145 (2022) 29–38

Journal of Clinical Epidemiology

REVIEW

Systematic Review Reveals Lack of Causal Methodology Applied to Pooled Longitudinal Observational Infectious Disease Studies

Heather Hufstedler[a,*], Sabahat Rahman[b], Alexander M. Danzer[c,d,e], Hannah Goymann[a], Valentijn M.T. de Jong[f,g], Harlan Campbell[h], Paul Gustafson[h], Thomas P.A. Debray[f,g], Thomas Jaenisch[a,i,j], Lauren Maxwell[a], Ellicott C. Matthay[k], Till Bärnighausen[a,l]

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[b] *University of Massachusetts Medical School, University of Massachusetts, Worcester, Massachusetts, USA*
[c] *KU Eichstätt-Ingolstadt, Ingolstadt School of Management and Economics (WFI), Germany*
[d] *IZA Bonn, Germany*
[e] *CESifo Munich, Germany*
[f] *Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[g] *Cochrane Netherlands, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[h] *Department of Statistics, University of British Columbia, Vancouver, British Columbia, Canada*
[i] *Center for Global Health, Colorado School of Public Health, Aurora, Colorado, USA*
[j] *Department of Epidemiology, Colorado School of Public Health, Aurora, USA*
[k] *Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA*
[l] *Harvard T H Chan School of Public Health, Harvard University, Boston, Massachusetts, USA*

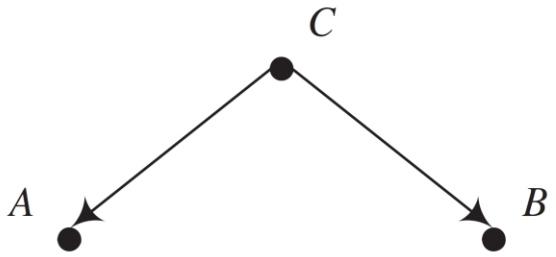
Accepted 13 January 2022; Available online 16 January 2022

Horizon Europe
THE NEXT EU RESEARCH & INNOVATION PROGRAMME (2021–2027)

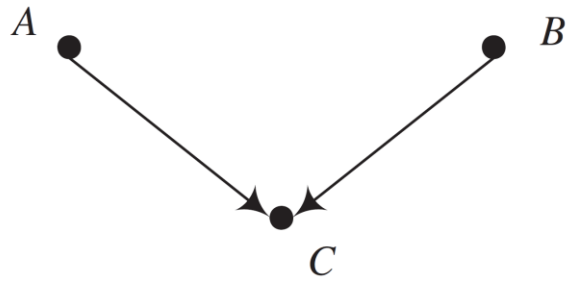
Directed acyclical graphs (DAGs) can boost intuition

3 CONCEPTS EXPRESSED IN DAGS

(a) Mediation

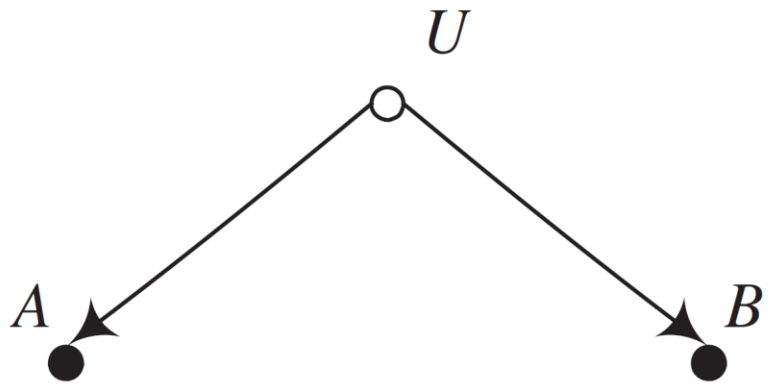


(b) Mutual dependence

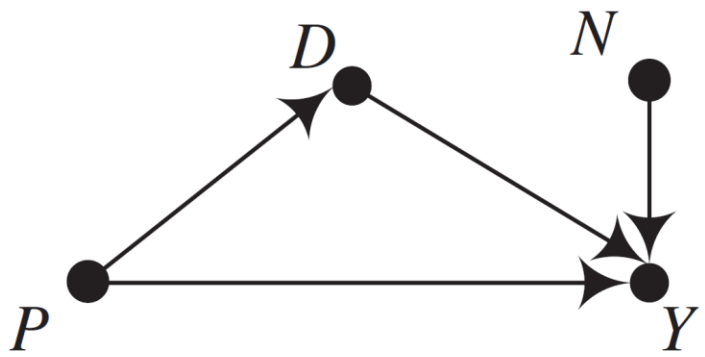


(c) Mutual causation

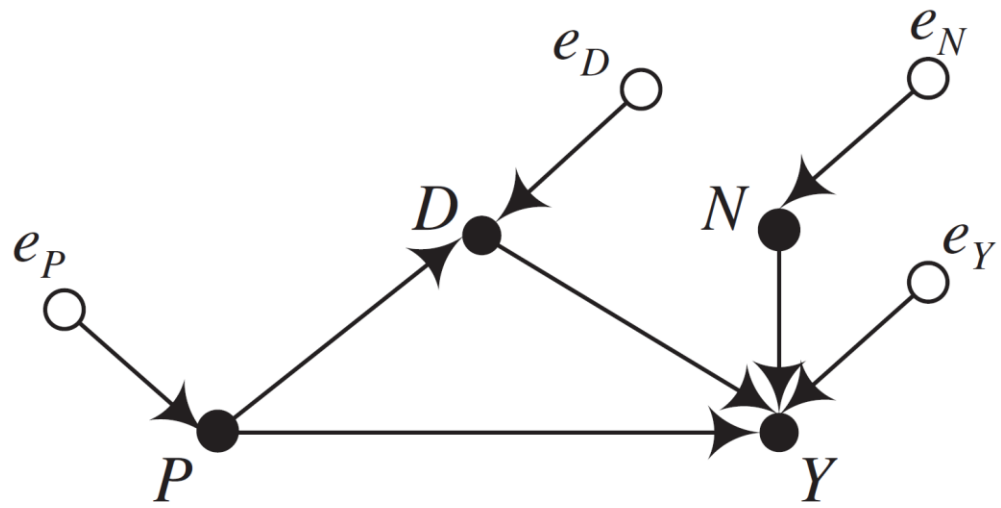
Morgan & Winship *Counterfactuals and Causal Inference* 2015



Morgan & Winship *Counterfactuals and Causal Inference* 2015



(a) Standard representation



(b) Under magnification

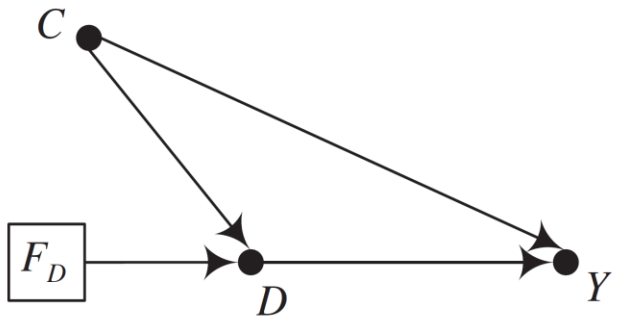
Morgan & Winship *Counterfactuals and Causal Inference* 2015

Agenda

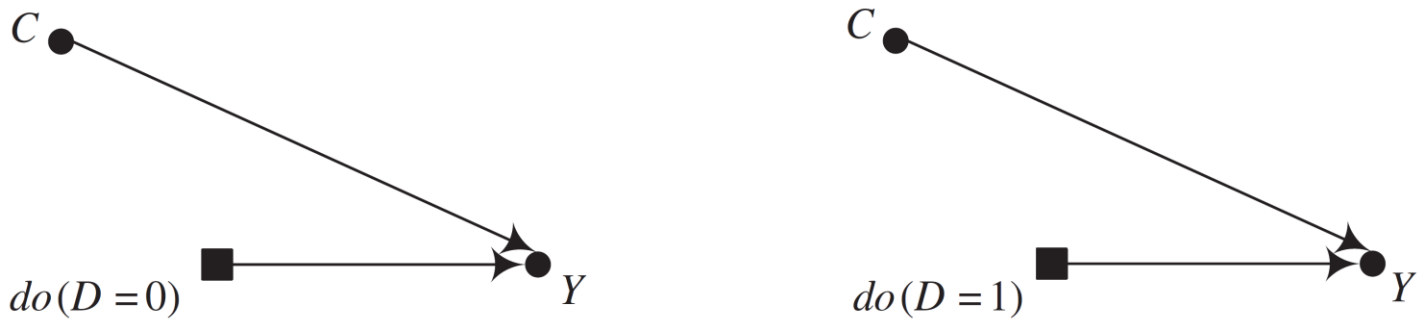
- IV
- RD
- FE

Agenda

- **IV**
- RD
- FE

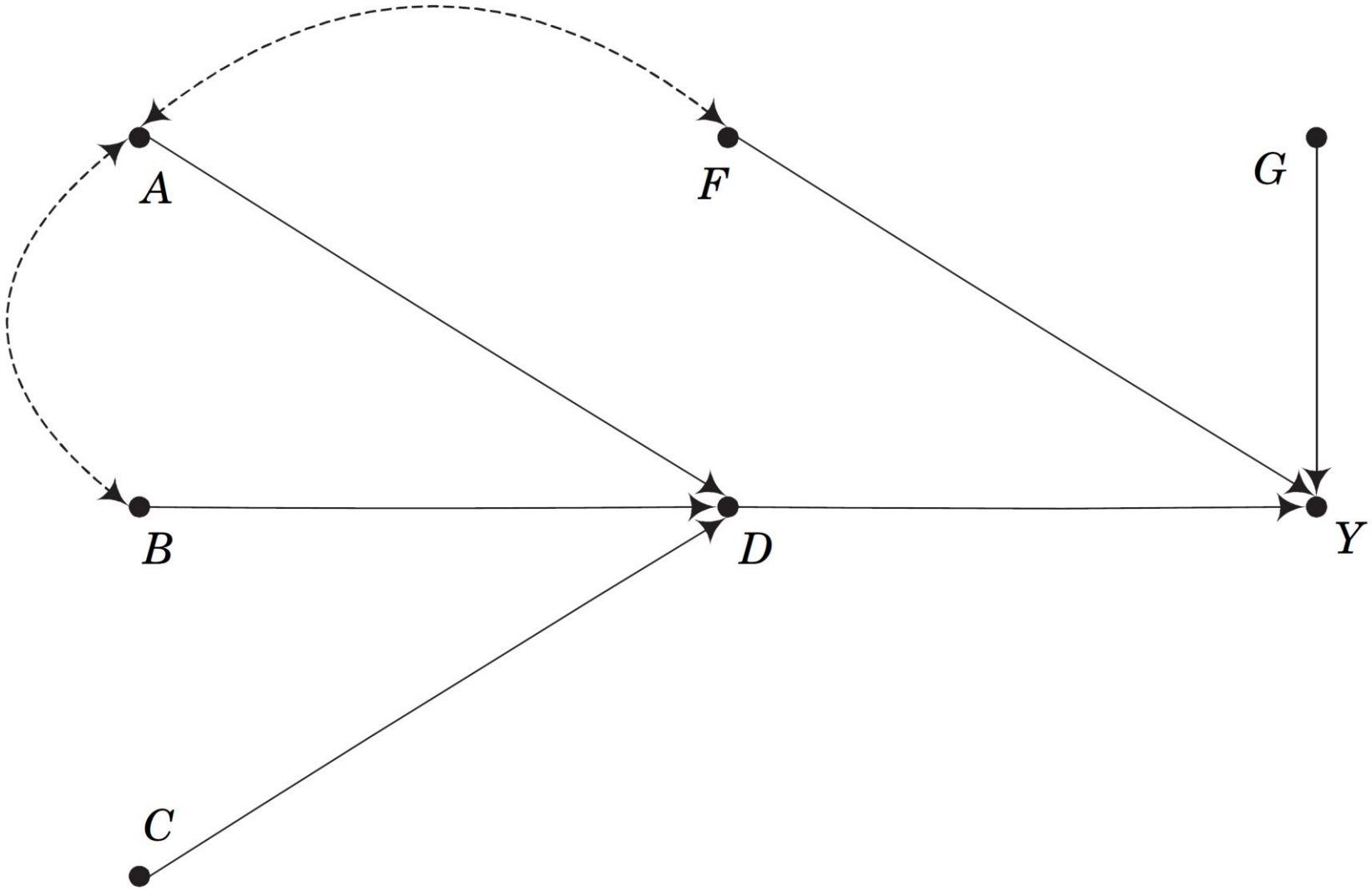


(a) Augmented casual graph with a "forcing" variable that represents an intervention

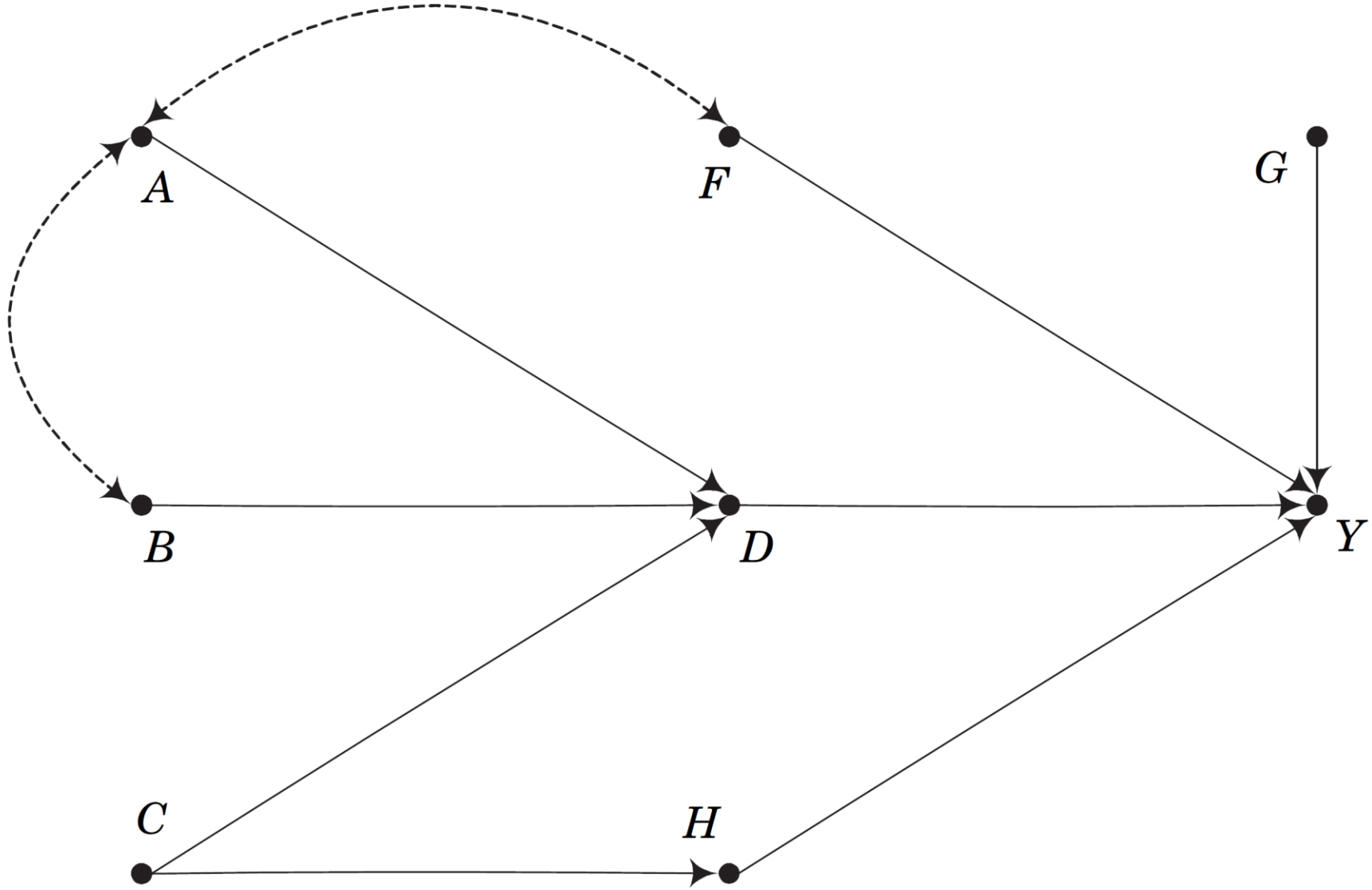


(b) "Mutilated" graphs that demonstrate the *do*(.) operator for the two values of *D*

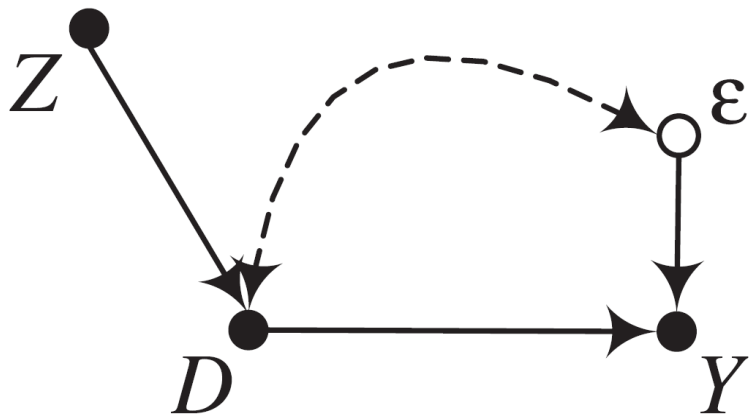
Morgan & Winship *Counterfactuals and Causal Inference* 2015

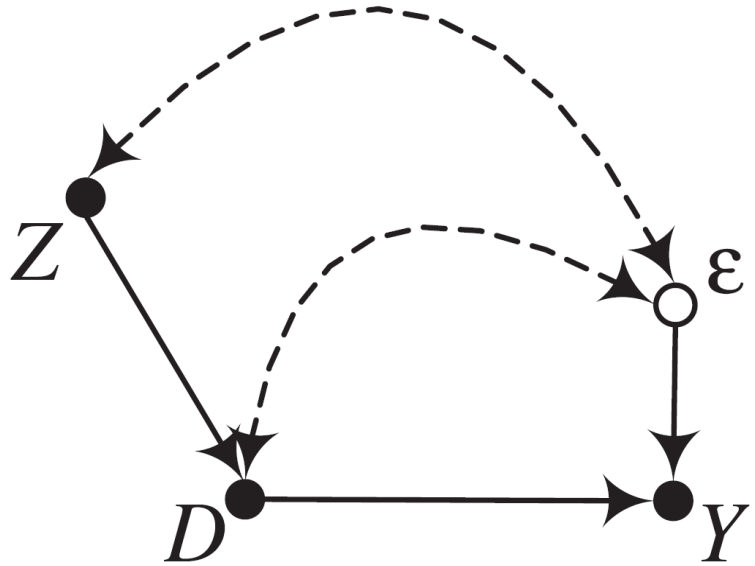


Morgan & Winship *Counterfactuals and Causal Inference* 2015



Morgan & Winship *Counterfactuals and Causal Inference* 2015

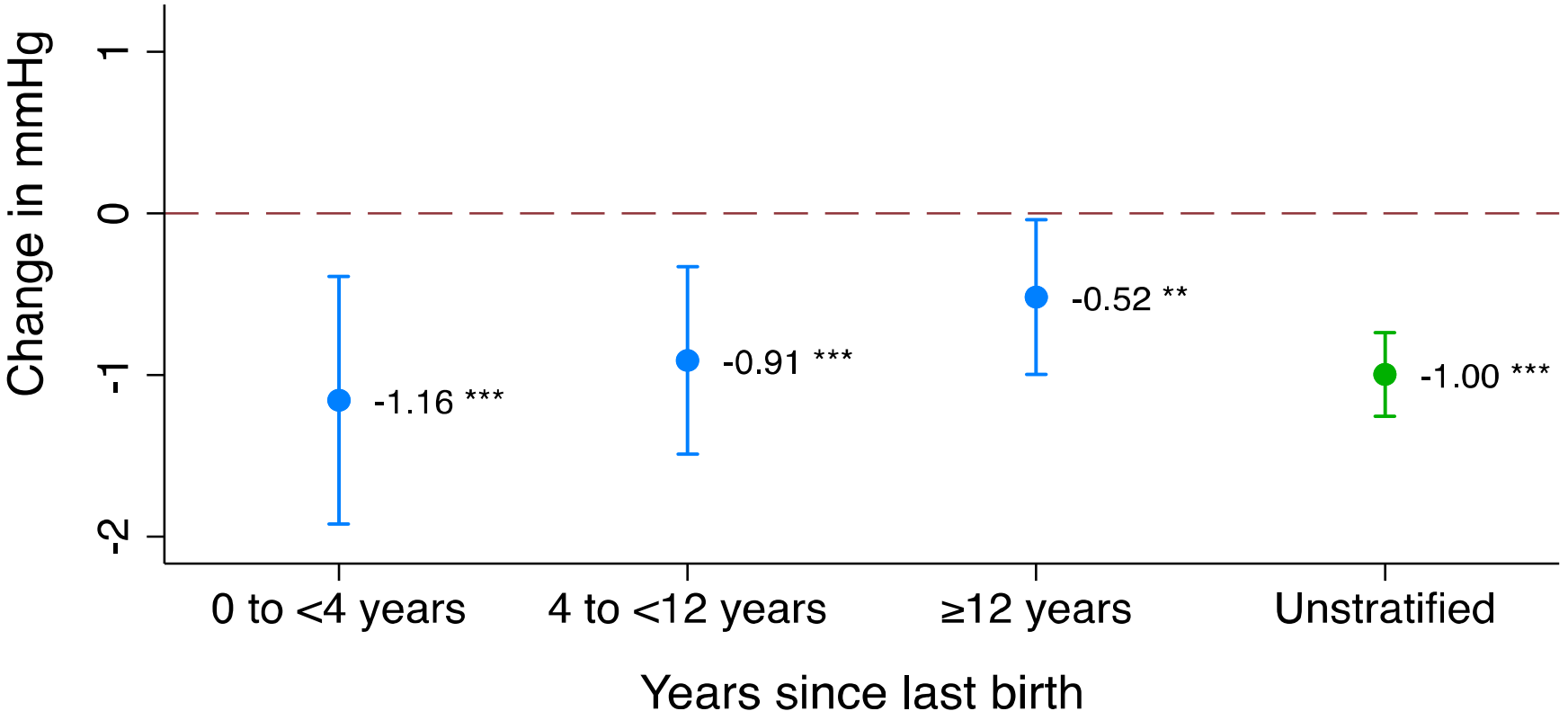




Morgan & Winship *Counterfactuals and Causal Inference* 2015

What is the impact of child bearing and rearing on maternal blood pressure?

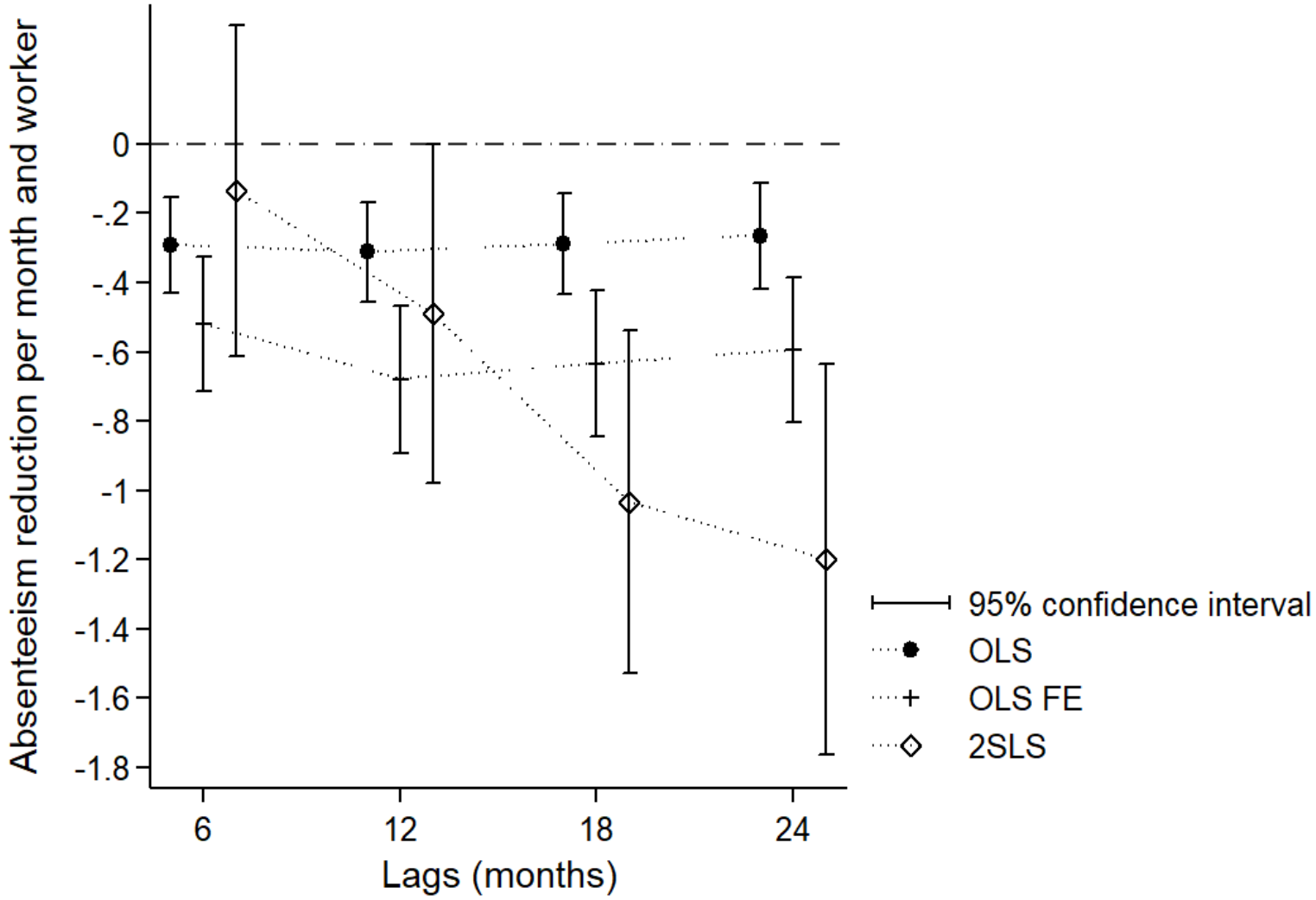
NATIONALLY REPRESENTATIVE INSTRUMENTAL VARIABLE ANALYSIS AMONG 444,611 MOTHERS IN INDIA



Teufel, Geldsetzer, Sudharsanan, Subrarmanyam, Yapa, De Neve, Vollmer, Bärnighausen *International Journal of Epidemiology* 2021

HIV treatment reduces absenteeism

INSTRUMENTAL VARIABLE ANALYSIS, SOUTH AFRICA MINING COMPANY



N = 128,052 observations among 1,924 adult mining workers, from 2009 to 2017

Jockers, Langlotz, French, Bärnighausen
Journal of Health Economics 2021

Agenda

- IV
- **RD**
- FE

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 68 (2015) 132–143

Journal of Clinical Epidemiology

Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: a review of current and best practice

Ellen Moscoe[a,*], Jacob Bor[b,c], Till Bärnighausen[a,c]

[a]*Department of Global Health and Population, Harvard School of Public Health, 665 Huntington Avenue Building 1, room 1104, Boston, MA, USA*
[b]*Department of Global Health, Boston University School of Public Health, 801 Massachusetts Ave, 3rd Floor, Boston, MA, USA*
[c]*Africa Centre for Health and Population Studies, University of KwaZulu-Natal, P.O. Box 198, Mtubatuba, 3935, South Africa*

Accepted 1 June 2014

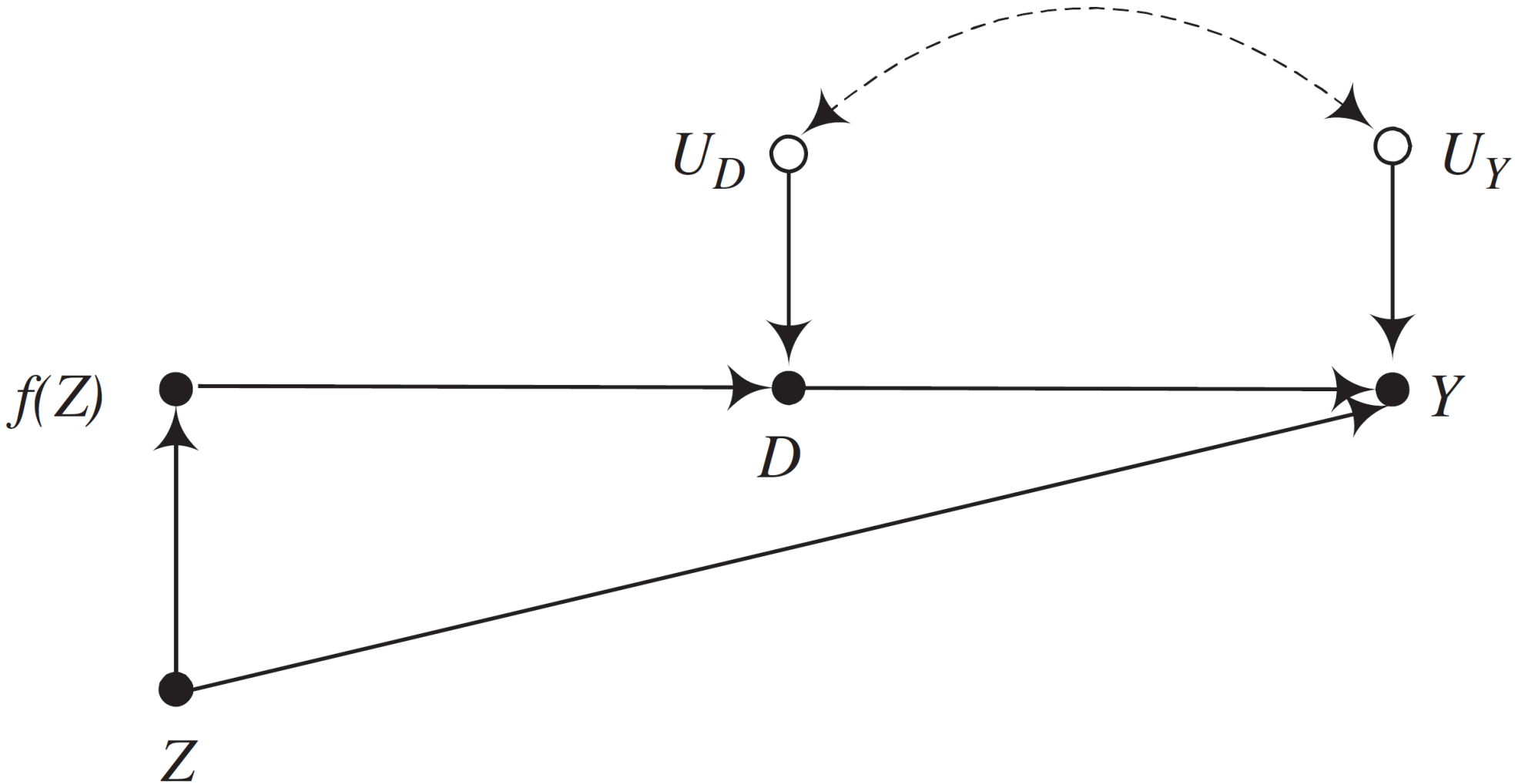
Abstract

Objectives: Regression discontinuity (RD) designs allow for rigorous causal inference when patients receive a treatment based on scoring above or below a cutoff point on a continuously measured variable. We provide an introduction to the theory of RD and a systematic review and assessment of the RD literature in medicine, epidemiology, and public health.

Study Design and Setting: We review the necessary conditions for valid RD results, provide a practical guide to RD implementation, compare RD to other methodologies, and conduct a systematic review of the RD literature in PubMed.

Results: We describe five key elements of analysis all RD studies should report, including tests of validity conditions and robustness checks. Thirty two empirical RD studies in PubMed met our selection criteria. Most of the 32 RD articles analyzed the effectiveness of social policies or mental health interventions, with only two evaluating clinical interventions to improve physical health. Seven out of the 32 studies reported on all the five key elements.

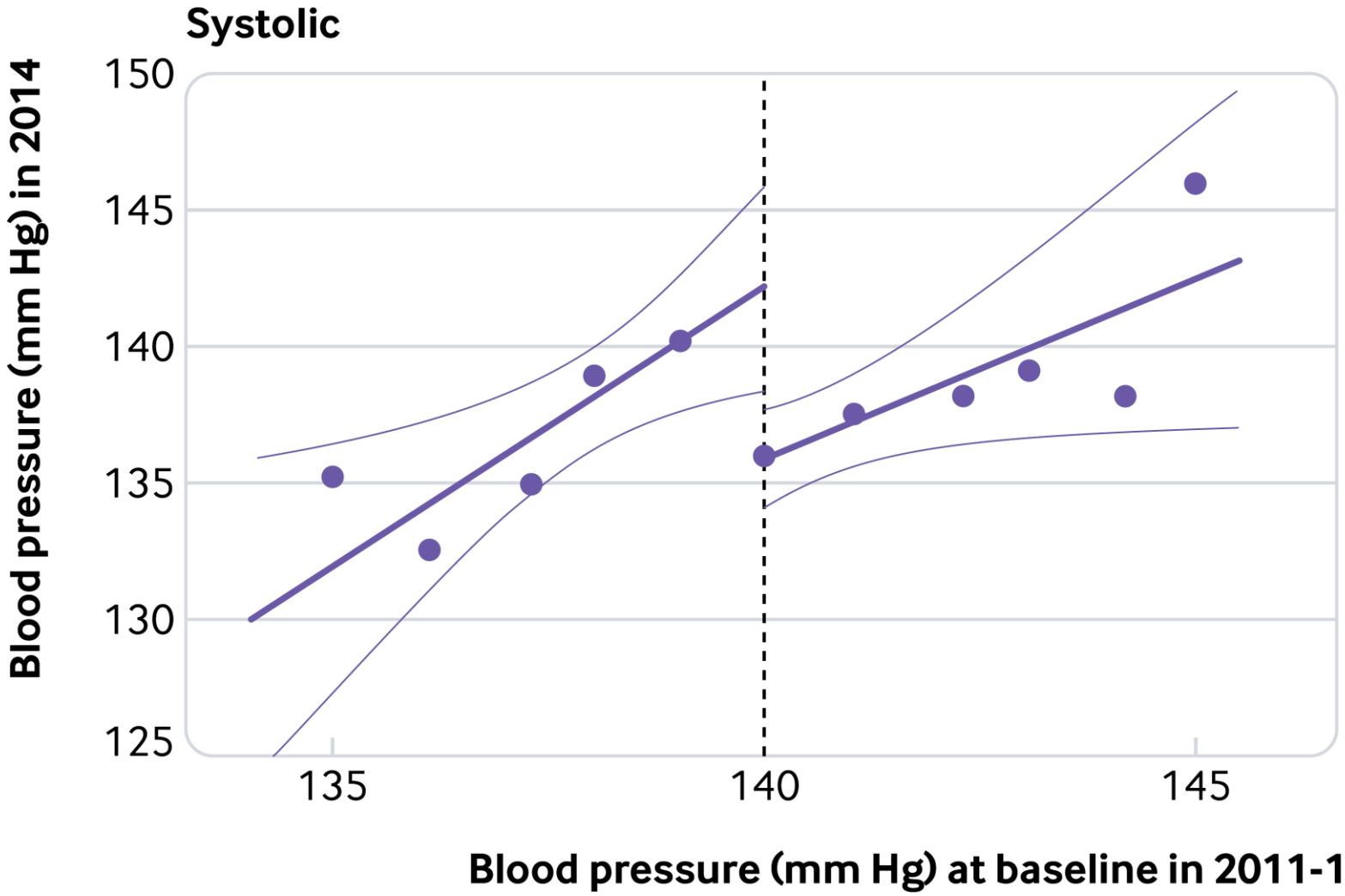
Conclusion: Increased use of RD provides an exciting opportunity for obtaining unbiased causal effect estimates when experiments are not feasible or when we want to evaluate programs under ''real-life'' conditions. Although treatment eligibility in medicine, epidemiology, and public health is commonly determined by threshold rules, use of RD in these fields has been very limited until now.



Morgan & Winship *Counterfactuals and Causal Inference* 2015

Do lay health workers who screen blood pressure in homes reduce blood pressure?

PROSPECTIVE RDD, 2012-2014, CHINA



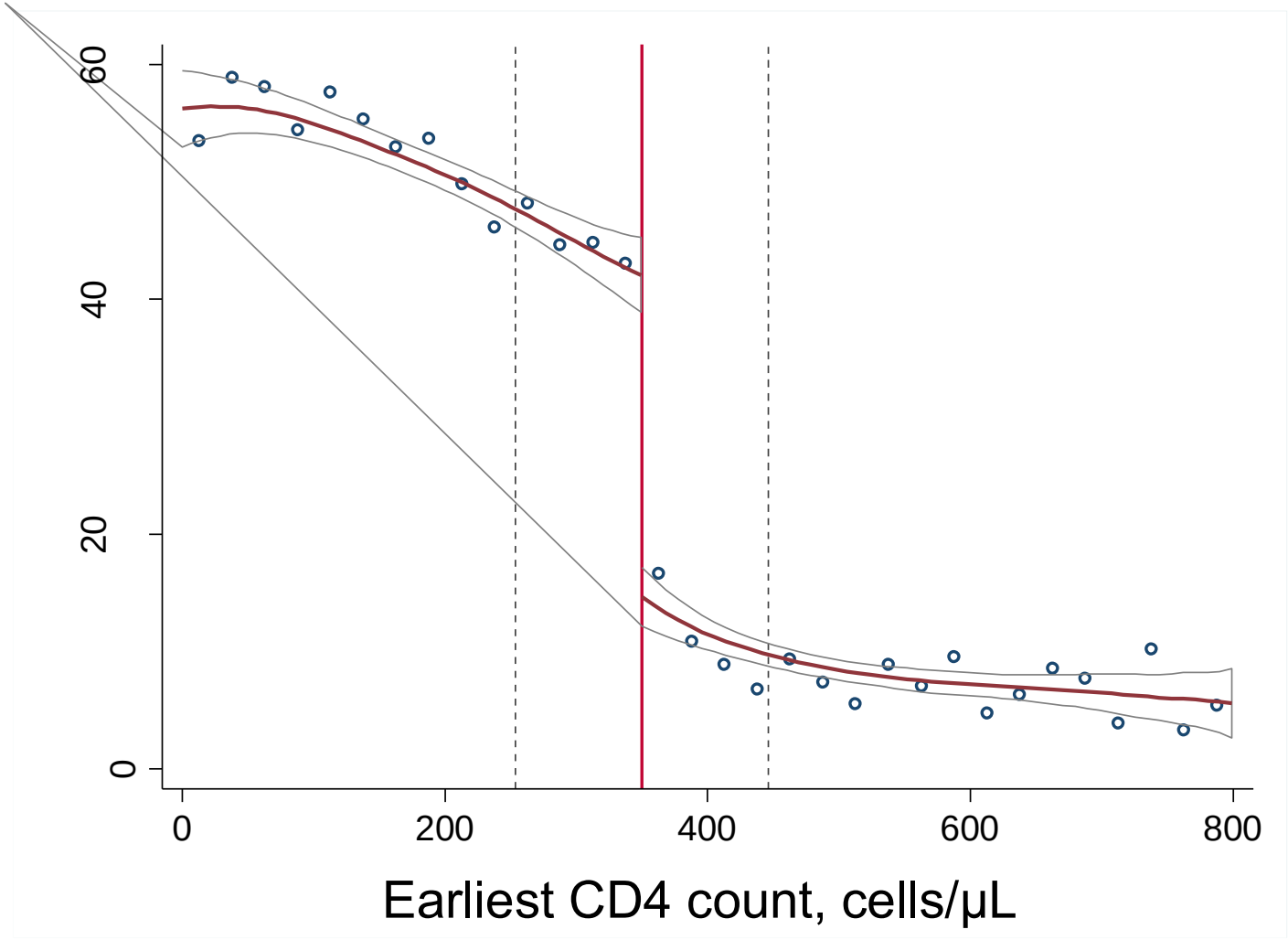
Nationally representative sample of 3,899 very elderly adults (≥60 y/a) who had previously undiagnosed hypertension

Chen, Sudharasan, Liu, Feng, Geldsetzer, Bärnighausen
BMJ 2019

BMJ

Do ART thresholds affect retention in care?

REGRESSION DISCONTINUITY DESIGN

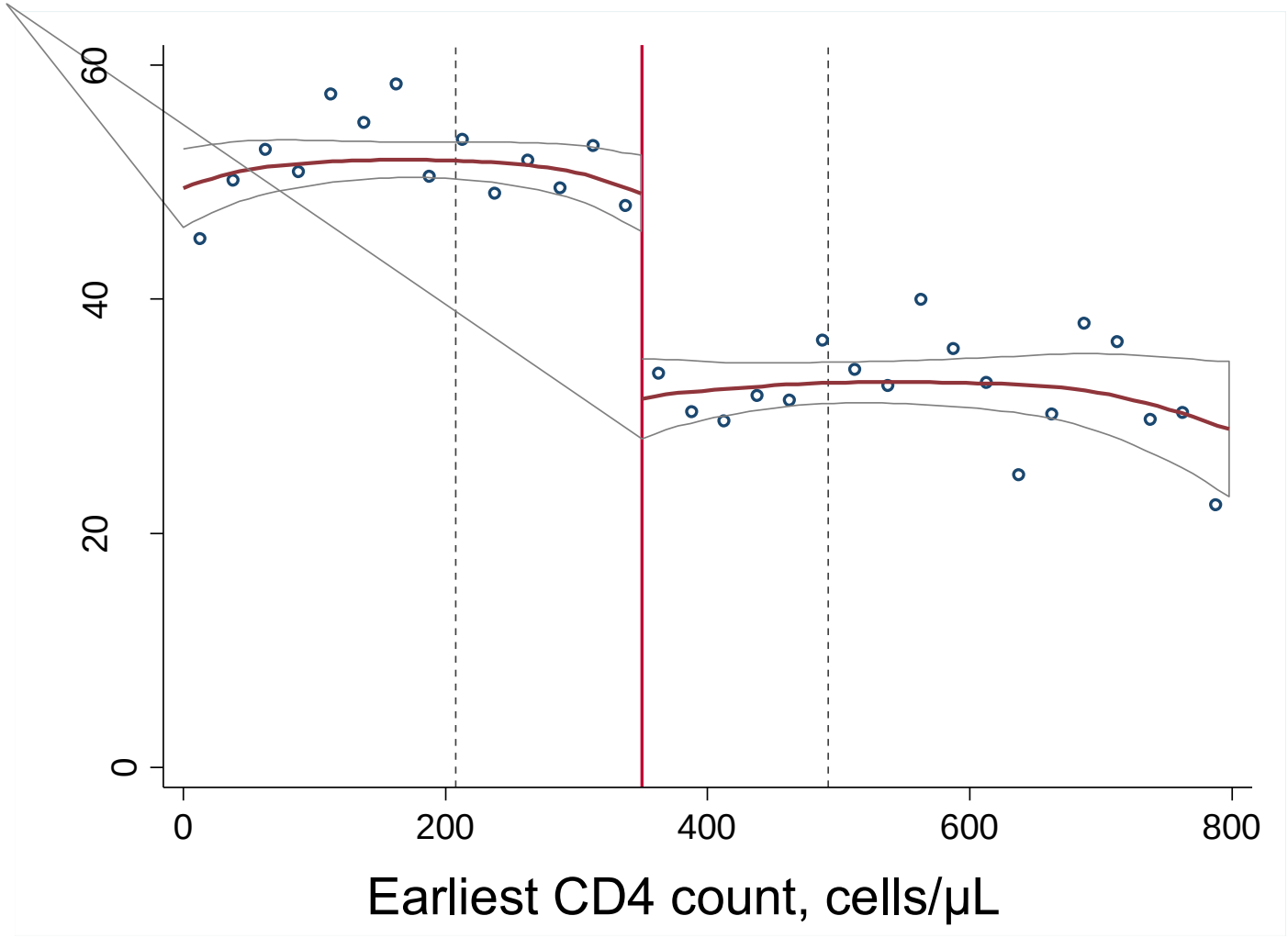


Epidemiology 2014
Epidemiology 2015
Journal of Clinical Epidemiology 2015
Current Epidemiology Reports 2016
Journal of Clinical Epidemiology 2017
PLOS ONE 2017
PLOS Medicine 2017
Tropical Medicine & International Health 2018
Social Science and Medicine 2018
American Journal of Epidemiology 2018
BMJ 2019
Nature 2023

David Sackett Price 2017 for Ellen Moscoe

Delayed ART has behavioral effects

RDD, 7,387 PATIENTS IN PUBLIC-SECTOR ART PROGRAM



Bor, Fox, Rosen, Atheenar, Tanser, Pillay, Bärnighausen

PLOS Medicine 2017

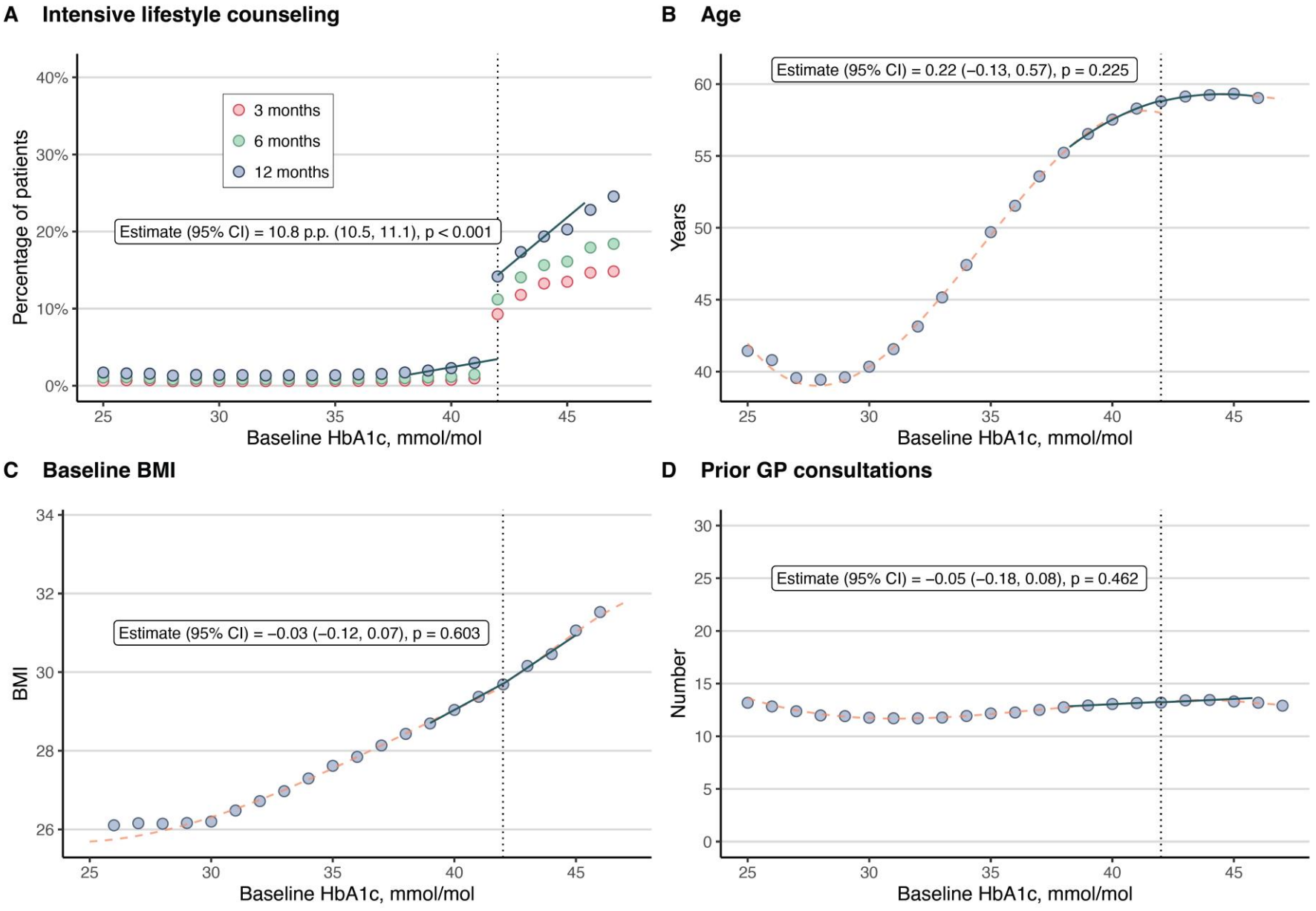
PLOS | MEDICINE

Does referral to lifestyle counselling help pre-diabetics?

RDD, 2 052 480 PATIENTS IN UK NHS PRIMARY CARE

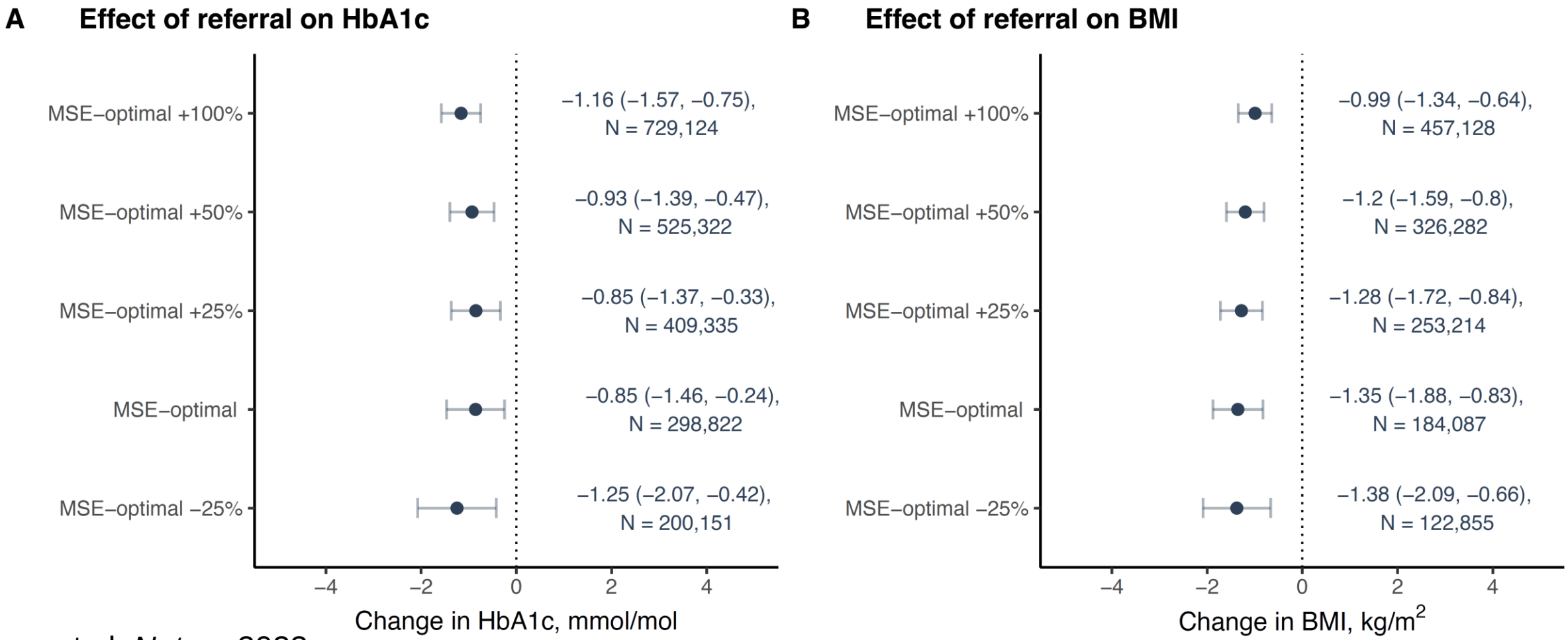
Lemp et al.
Nature 2023

nature



Does referral to lifestyle counselling help pre-diabetics?

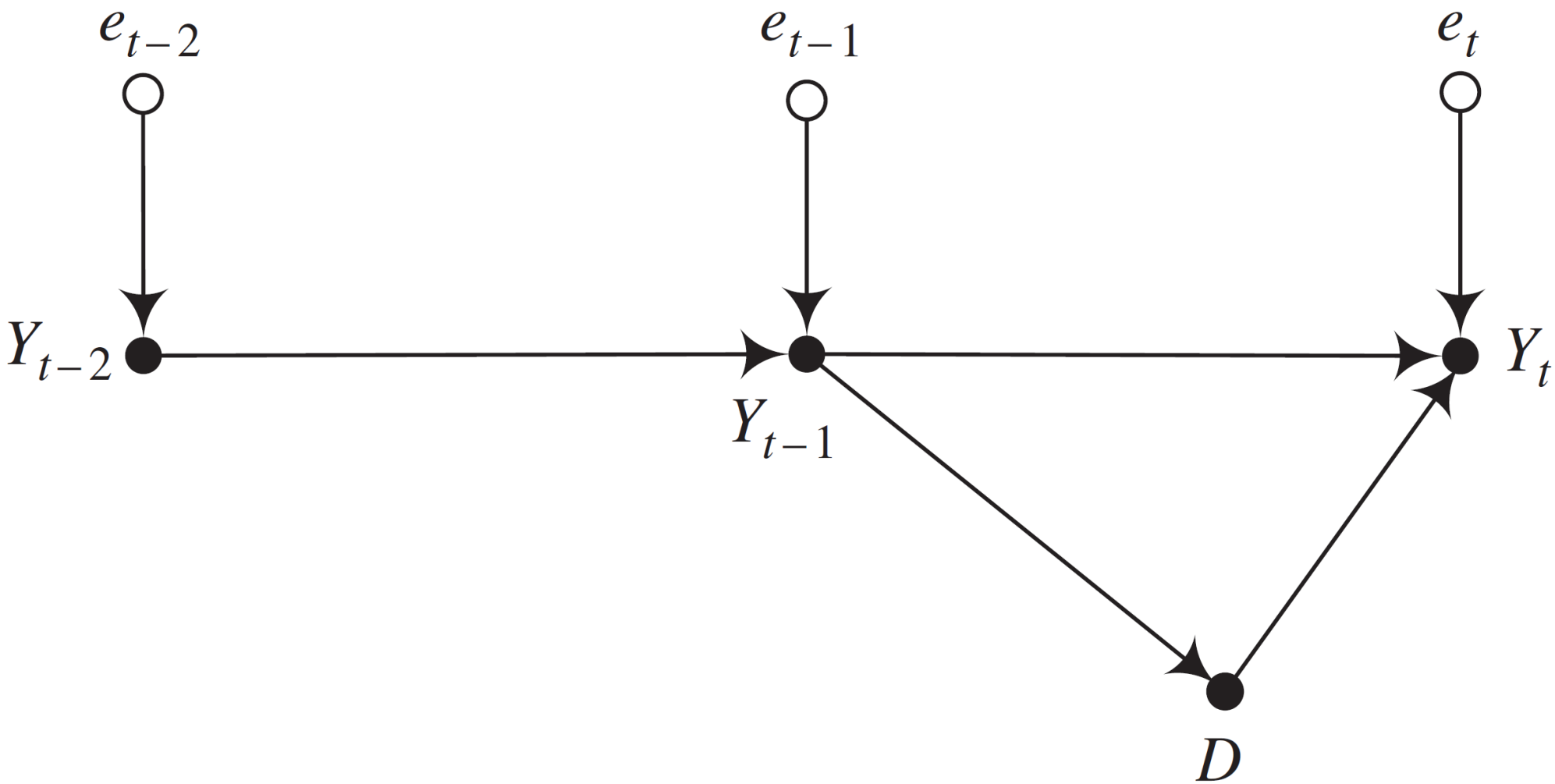
EFFECT ESTIMATES



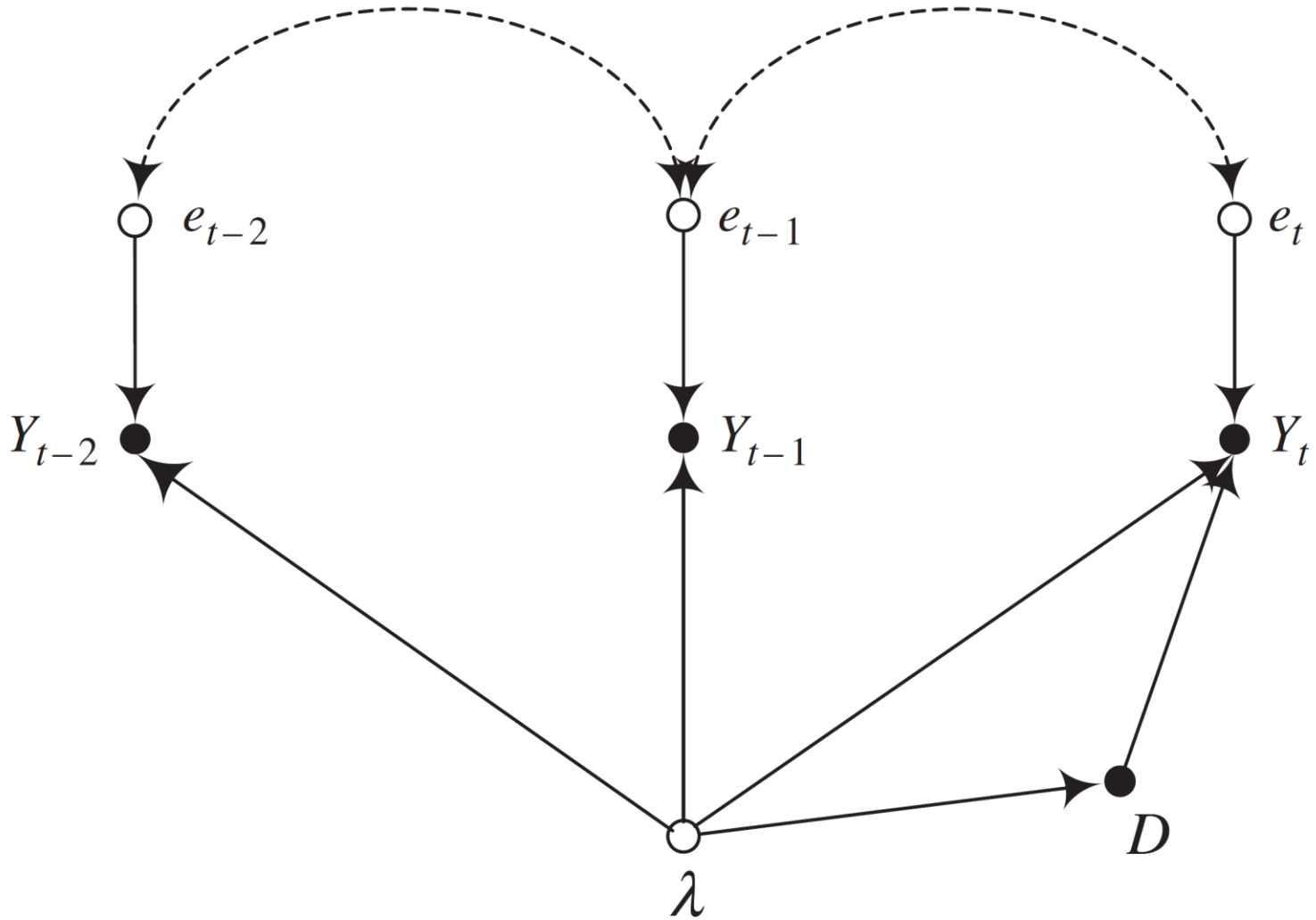
Lemp et al. *Nature* 2023

Agenda

- IV
- RD
- **FE**



Morgan & Winship *Counterfactuals and Causal Inference* 2015



Morgan & Winship *Counterfactuals and Causal Inference* 2015

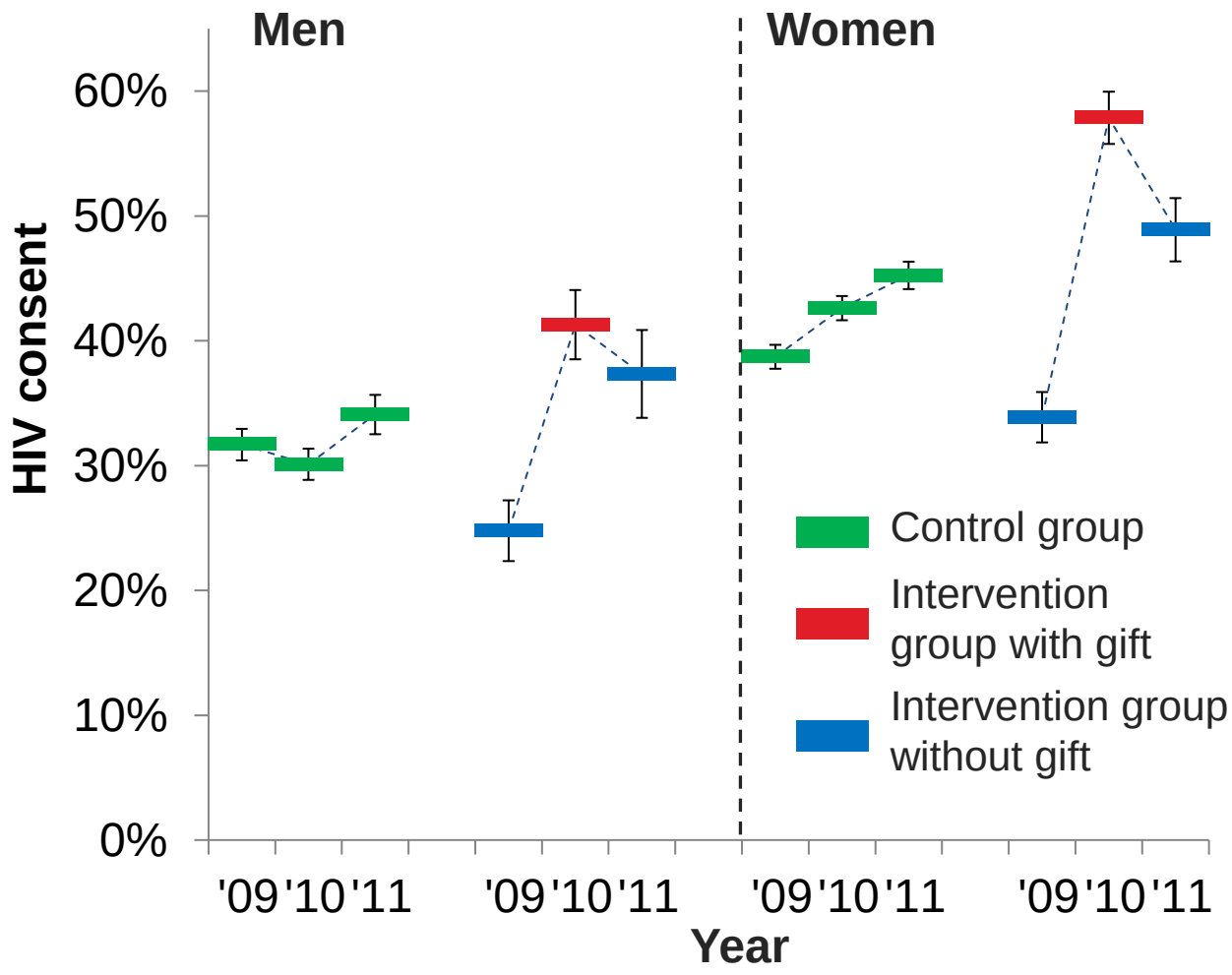
Can gifts increase HIV testing?

DIFFERENCE-IN-DIFFERENCES RESULTS

Intervention

- Food gift voucher to families given to household head before testing offer
- Gift = unconditional cash transfer
- Size (~3 EUR) = micro-gift

Data



Results

- *N* = 18,478
- HIV testing consent:
- **+25 % points** (95% CI 21-30)

McGovern, Herbst, Tanser, Mutevedzi, Canning, Gareta, Pillay, Bärnighausen

International Journal of Epidemiology 2016

International Journal of Epidemiology

The causal effect of childhood measles vaccination on educational attainment: A mother fixed-effects study in rural South Africa

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[c] *University of Southampton, Southampton SO17 1BJ, UK*
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[e] *Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA*

ARTICLE INFO

Article history:
Received 3 November 2014
Received in revised form 13 April 2015
Accepted 20 April 2015
Available online 30 April 2015

Keywords:
Childhood measles vaccination
Educational attainment
Mother fixed-effects study

ABSTRACT

Background: Because measles vaccination prevents acute measles disease and morbidities secondary to measles, such as undernutrition, blindness, and brain damage, the vaccination may also lead to higher educational attainment. However, there has been little evidence to support this hypothesis at the population level. In this study, we estimate the causal effect of childhood measles vaccination on educational attainment among children born between 1995 and 2000 in South Africa.

Methods and findings: We use longitudinal data on measles vaccination status and school grade attainment among 4783 children. The data were collected by the Wellcome Trust Africa Centre Demographic Information System (ACDIS), which is one of Africa's largest health and demographic surveillance systems. ACDIS is located in a poor, predominantly rural, Zulu-speaking community in KwaZulu-Natal, South Africa. Using mother fixed-effects regression, we compare the school grade attainment of siblings who are discordant in their measles vaccination status but share the same mother and household. This fixed-effects approach controls for confounding due to both observed and unobserved factors that do not vary between siblings, including sibling-invariant mother and household characteristics such as attitudes toward risk, conscientiousness, and aspirations for children. We further control for a range of potential

Measles vaccination reduces undernutrition

DEMOGRAPHIC AND HEALTH SURVEY (DHS) DATA

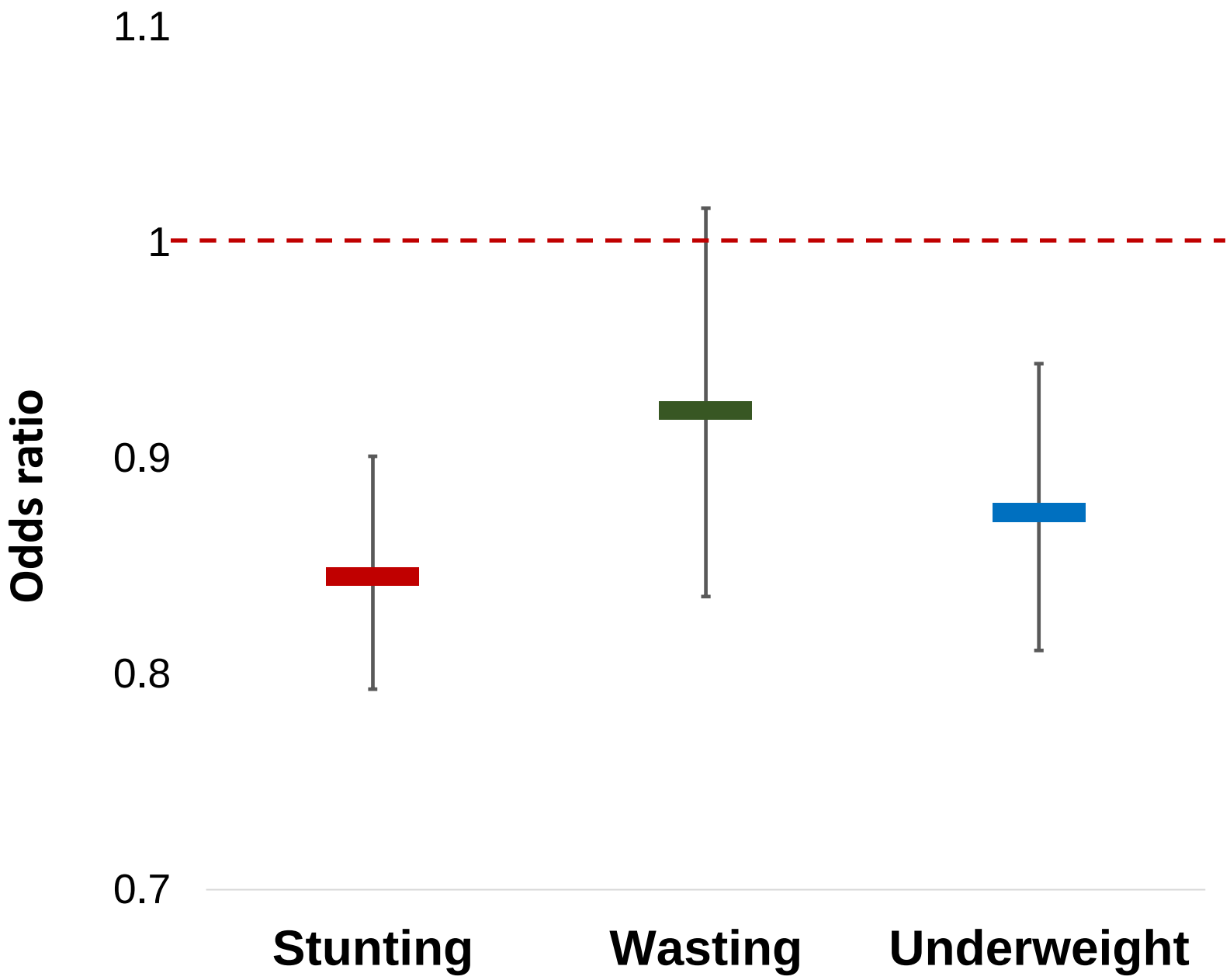
191 DHS from 65 countries, household fixed effects plus wide range of control variables

N (stunting) = 347,808

N (wasting) = 430,963

N (underweight) = 353,520

Bogler, Jantos, Bärnighausen, Vollmer *Vaccine* 2019

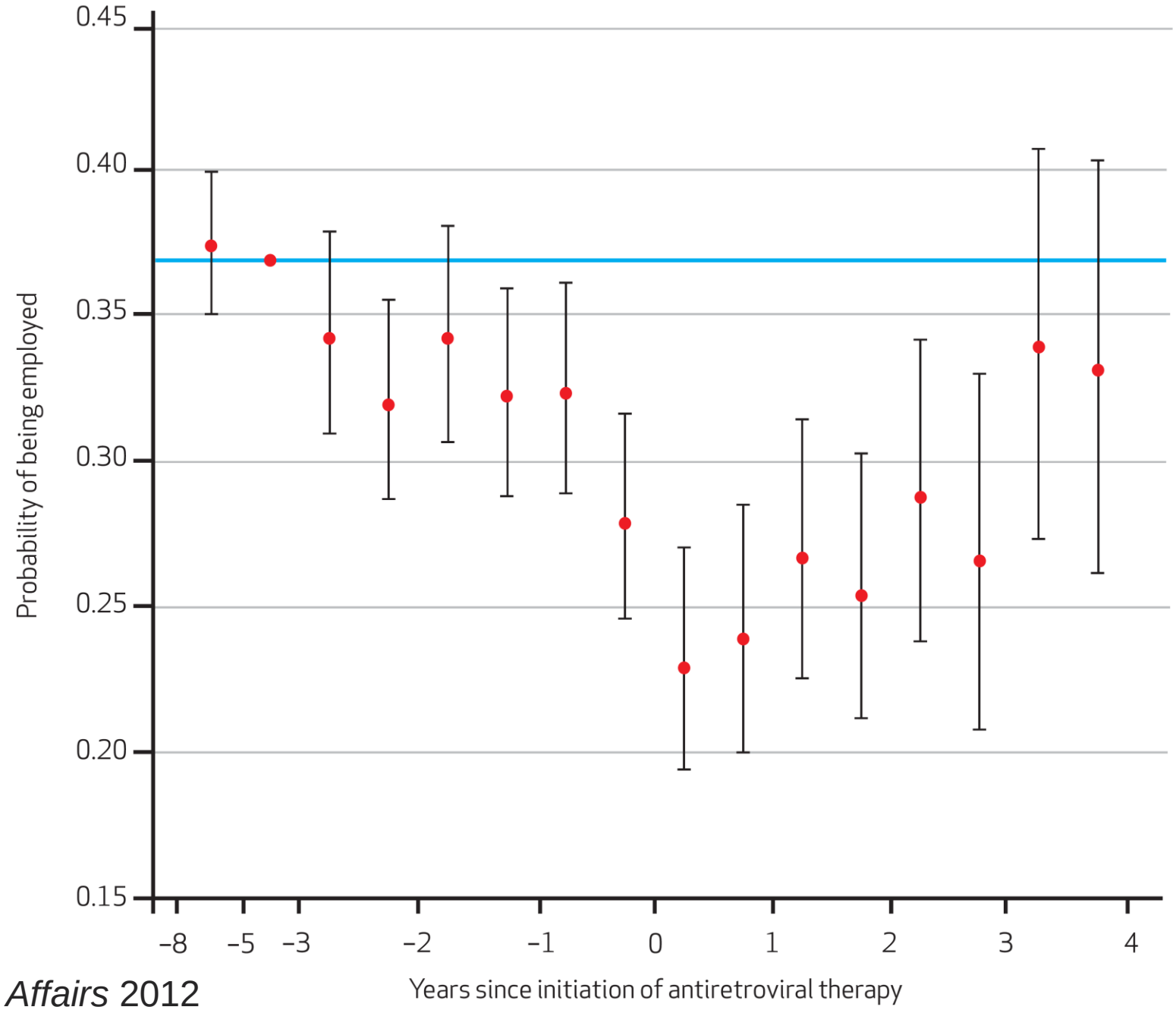


ART recovers employment — individual (SDG 8)

FIXED EFFECTS RESULTS

Individual fixed effects regressions, linear probability model controlling for sex, age, education, calendar year, month and day of survey.

N = 32,316 persons with 138,020 observations



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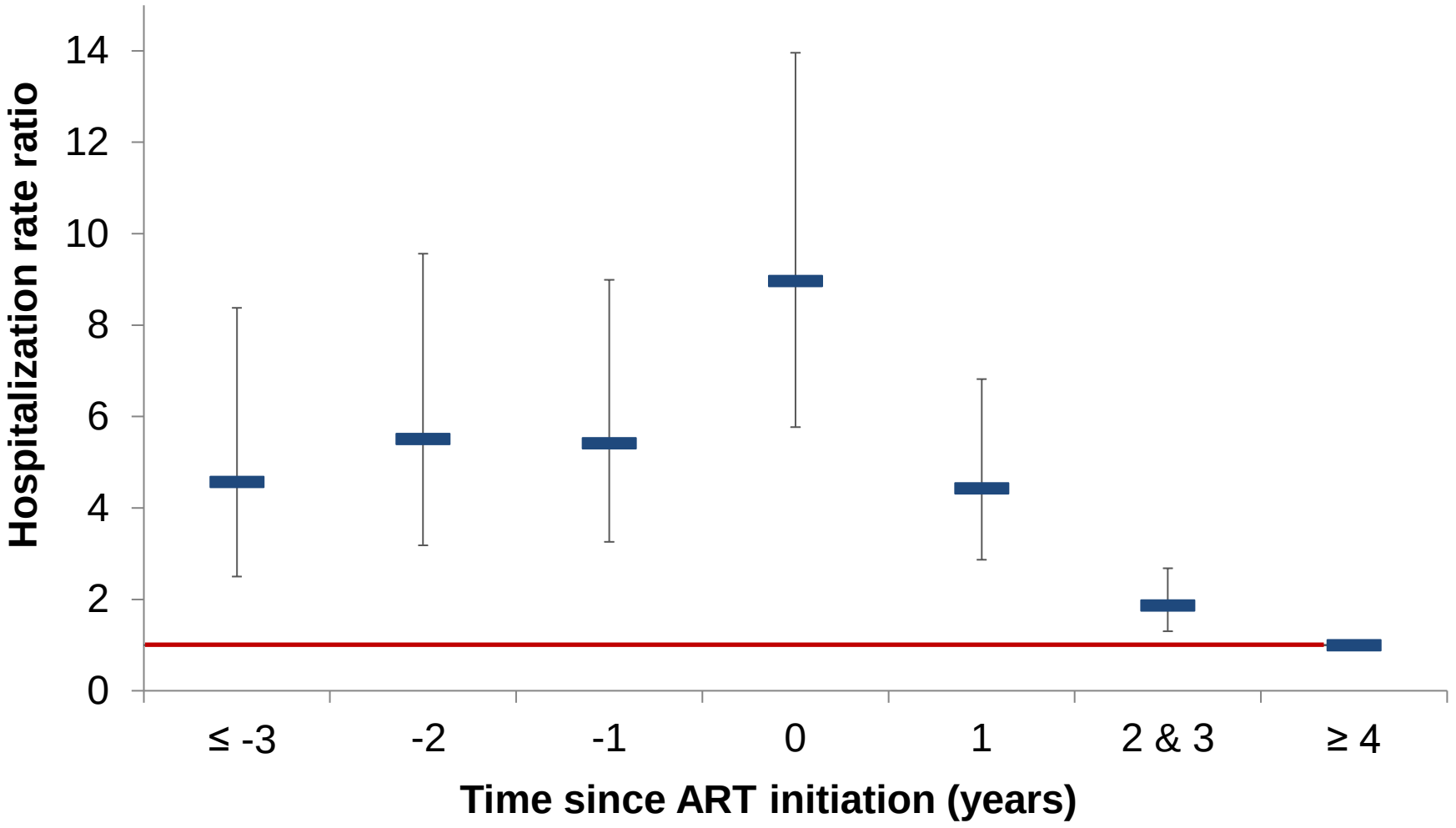
Bor, Tanser, Newell, Bärnighausen *Health Affairs* 2012

HIV treatment reduces hospitalization

FIXED EFFECTS RESULTS



Individual fixed effects regression, controlling for calendar year and age; 6,505 observations in 2,252 individuals (2009-2013).

103 hospitalizations per 1,000 person-years.

ART = antiretroviral treatment

Hontelez, Bor, Tanser, Pillay, Moshabela & Bärnighausen *Health Affairs* 2018

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Quasi-experiments can control unobserved confounding

METHODS FRAMEWORK

	Control of unobserved confounding	Assumptions regarding unobserved confounding
• **Experiments**	Complete	Weak
• **Quasi-experiments**		
– Instrumental variable approaches – Regressions discontinuity	Complete	Less weak
– Difference-in-differences approaches – Fixed effects approaches	Partial	Less weak
• **Non-experiments**		
– Regression – Matching – Stratification	None	Strong

Bärnighausen et al. *Journal of Clinical Epidemiology* 2017