When are health inequalities unfair?

Yukiko Asada, PhD

Department of Bioethics

NIH Clinical Center

Disclaimer

- The views expressed in this talk are my own and do not represent the position or policy of the NIH, DHHS, or US government

- I have no conflicts of interest to declare

This talk

- Focus: equity considerations in the design and conduct of clinical research

- Key points
  - Equity considerations are not a check box – they are woven into principles for ethical clinical research

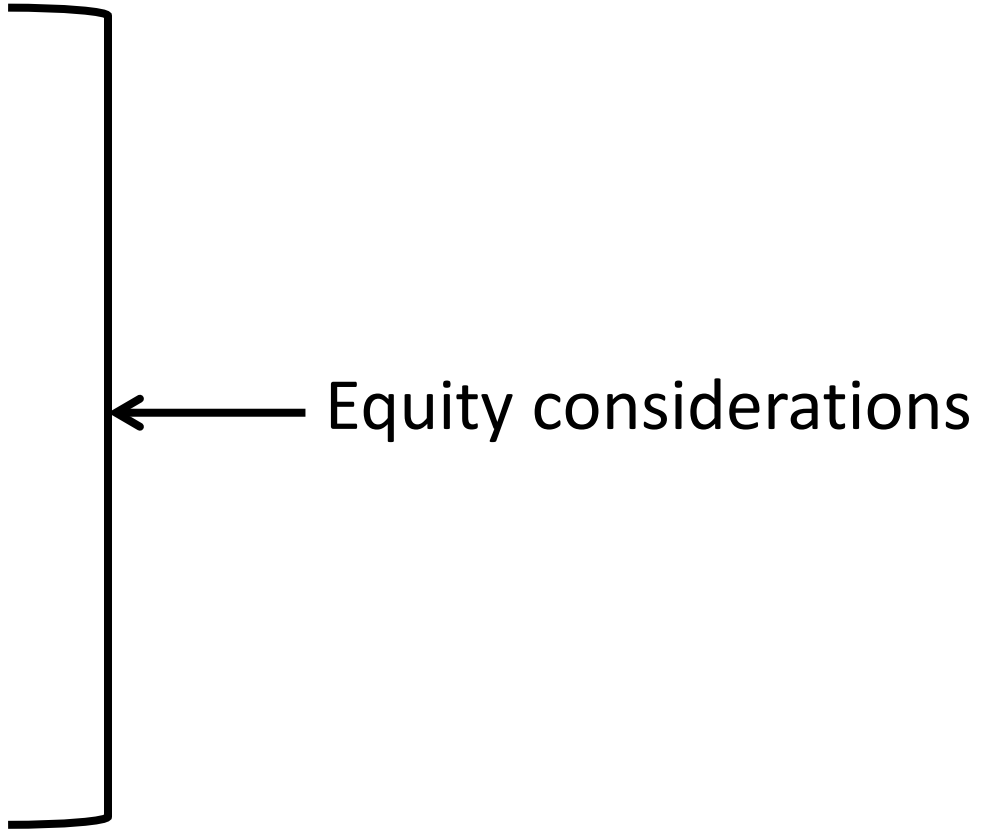
Eight principles for ethical clinical research

- Collaborative partnership
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel, Wendler, Grady (2000), Emanuel et al (2004)

Eight principles for ethical clinical research

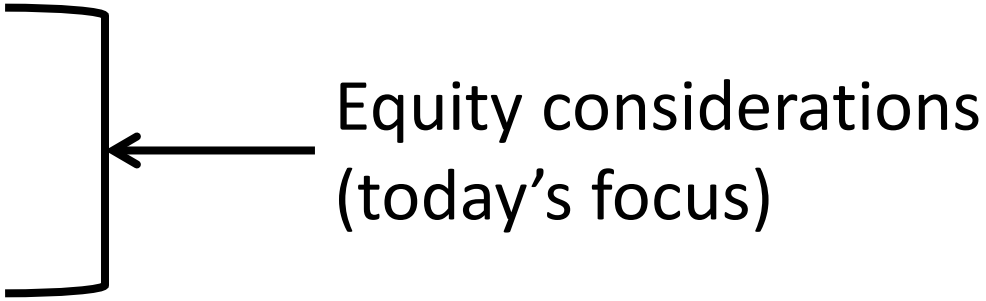
- Collaborative partnership
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
- Respect for enrolled subjects



Emanuel, Wendler, Grady (2000), Emanuel et al (2004)

Eight principles for ethical clinical research

- Collaborative partnership
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
- Respect for enrolled subjects



Emanuel, Wendler, Grady (2000), Emanuel et al (2004)

This talk

- Focus: equity considerations in the design and conduct of clinical research

- Key points
  - Equity considerations are not a check box – they are woven into principles for ethical clinical research
  - To make equity considerations explicit and meaningful, it is important to think carefully about when health inequalities are unfair

Today’s plan: three guiding questions

- Who should be in the study and why?
- Which health inequalities are unfair and why?
- How do equity considerations influence the study design, analysis plan, and reporting?

Who should be in the study and why?

Who should be in the study and why?

- Participation
- Biology
- Societal concern

Participation

- Consideration here is the fair distribution of benefits and burden
- What it means to participate in studies has changed from bearing the burden to accessing to innovations

Who should be in the study and why?

- Participation
- Biology
- Societal concern

Potentially differential impact of interventions - biology

- The causality in question (X → Y) may work differently in different groups of human beings because of biological differences
- An example: cardiovascular disease by sex

HEART ATTACK SYMPTOMS: MEN VS. WOMEN

By American Heart Association News

The most common symptom of a heart attack for both men and women is chest pain. But women may experience less obvious warning signs.

MEN

- Nausea or vomiting
- Jaw, neck or back pain
- Squeezing chest pressure or pain
- Shortness of breath

WOMEN

- Nausea or vomiting
- Jaw, neck or **upper** back pain
- Chest pain, **but not always**
- Pain or pressure in the **lower chest** or **upper abdomen**
- Shortness of breath
- **Fainting**
- **Indigestion**
- **Extreme fatigue**

Source: American Heart Association's journal, Circulation

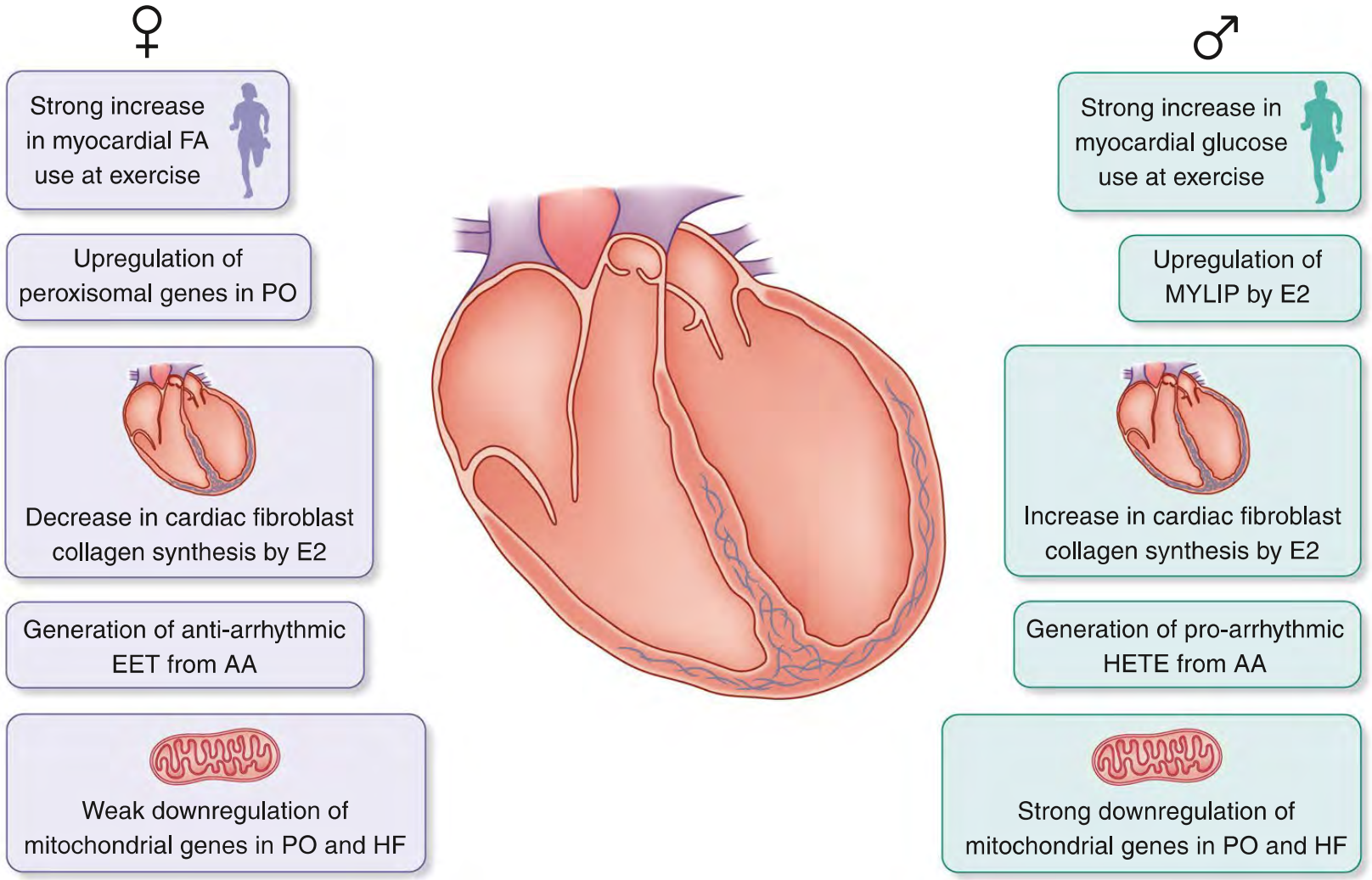


Fig. 2 | Sex-specific features in cardiometabolic disorders. Several mechanisms can be shown to occur predominantly in women or men and to contribute to these disorders predominantly in one sex. AA, arachidonic acid; E2, estradiol; EET, epoxyeicosanoids; FA, fatty acids; HETE, hydroxyeicosatetraenoids; HF, heart failure; MYLIP, myosin regulatory light chain interacting protein; PO, pressure overload. Credit: Debbie Maizels/Springer Nature.

Gerdts and Regitz-Zagrosek (2019)

Potentially differential impact of interventions - biology

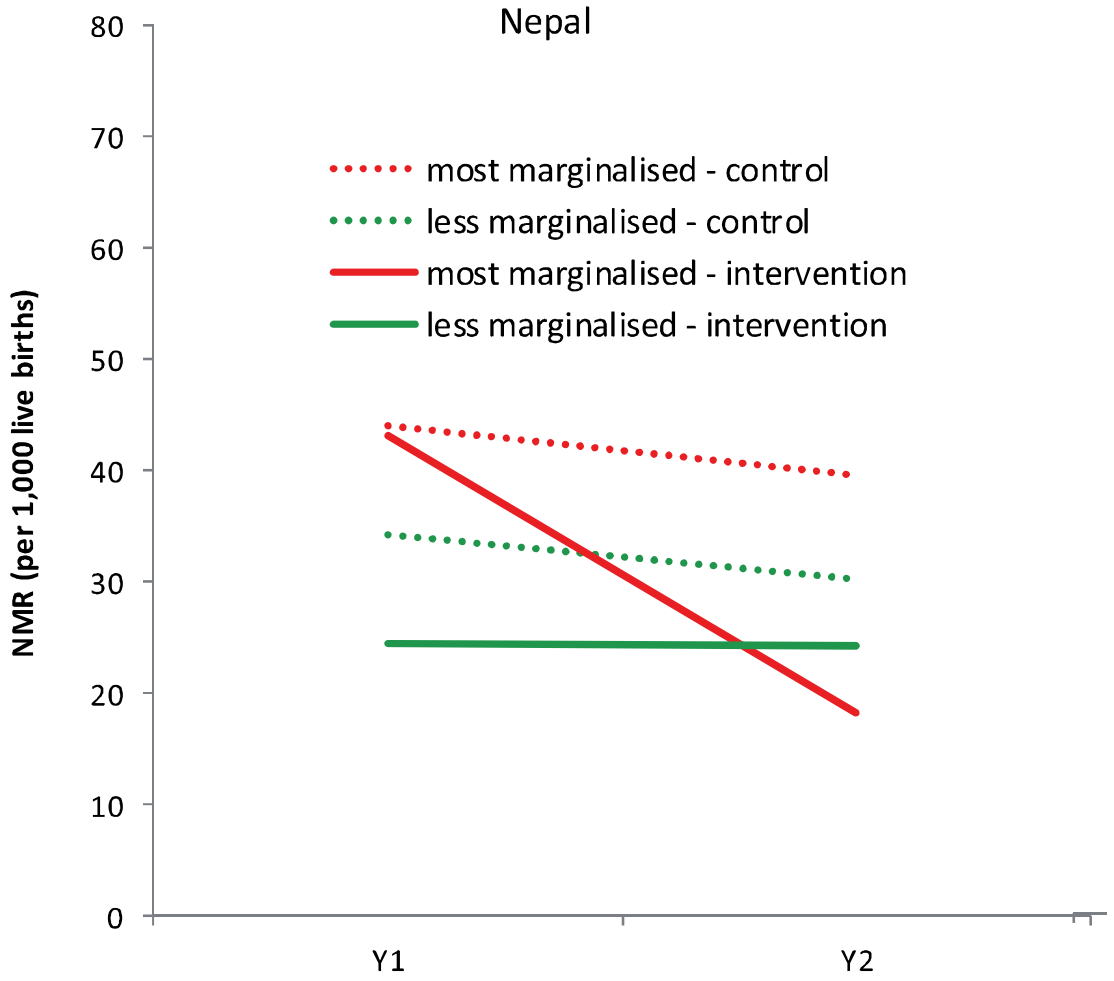
- The causality in question (X → Y) may work differently in different groups of human beings because of biological differences
- An example: cardiovascular disease by sex
- The primary focus here is potentially differential causal pathways in different groups

Potentially differential impact of interventions – Societal concern

- The causality in question (X → Y) may work differently in different groups of human beings because of how we organize our society
- Differential intervention effects by social group characteristic
  - An example: Effects of women's group participation on neonatal mortality rate by marginalization

Effects of women's group participation on neonatal mortality rate by marginalization

- Population: Nepal
- Intervention: A participatory and action intervention with women's groups
- Comparisons: With vs. without the intervention
- Outcome: Neonatal mortality
- Most marginalized: Women who were illiterate and poor
- Less marginalized: The rest of women



Houweling et al. (2019)

Potentially differential impact of interventions – Societal concern

- The causality in question (X → Y) may work differently in different groups of human beings because of how we organize our society
- Differential intervention effects by social group characteristic
  - An example: Effects of women's group participation on neonatal mortality rate by marginalization
- Differential intervention effects within a traditionally excluded group
  - An example: Effects of a high intensity, lifestyle-based program for obesity treatment in primary care clinics in low-income neighborhoods

Effects of a lifestyle-based program for obesity treatment in low-income neighborhoods

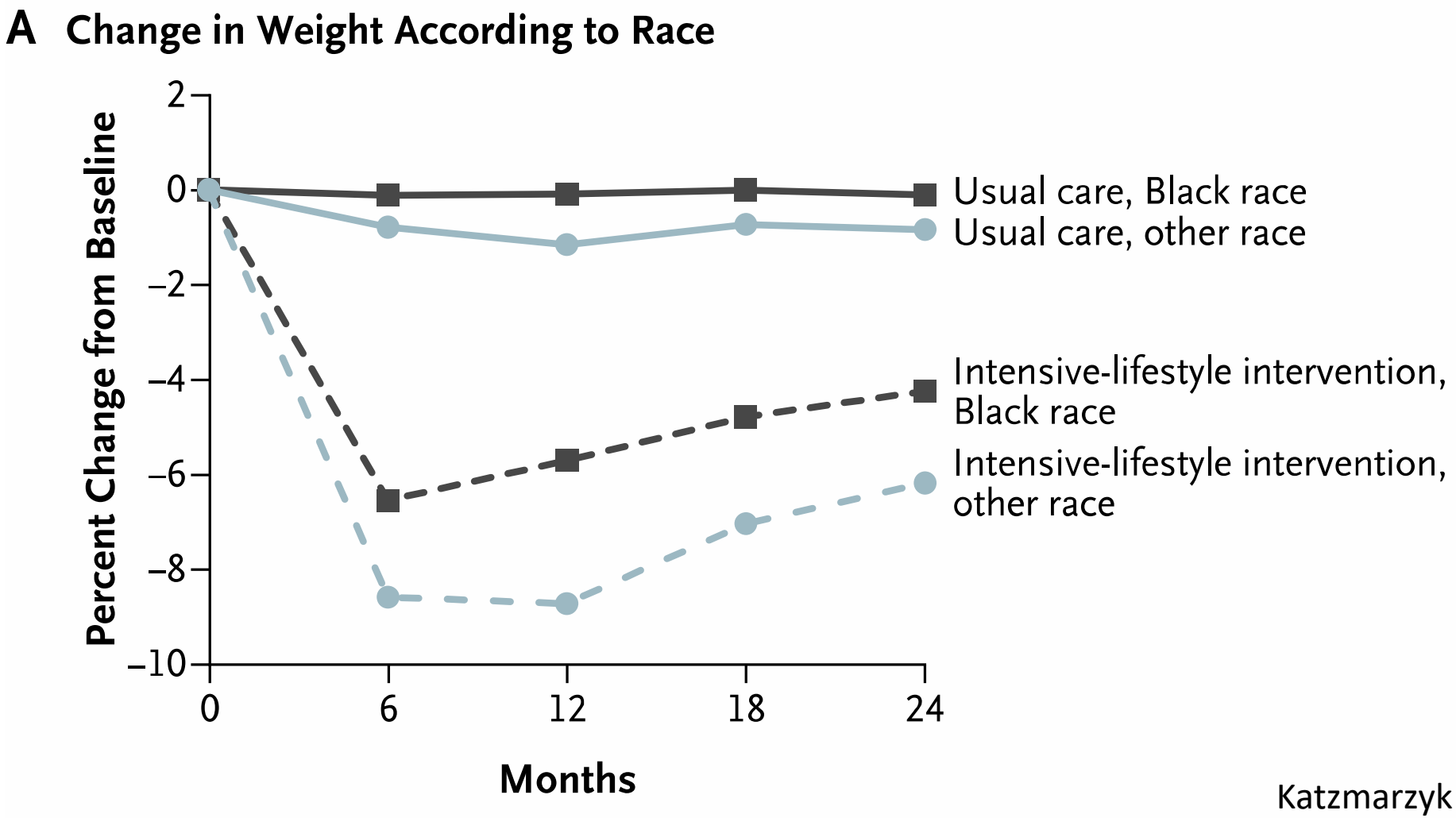
- Population: Primary care patients living in low-income neighborhoods
- Intervention: High intensity, lifestyle-based program for obesity treatment
- Comparisons: Intensive-lifestyle program vs. usual care
- Outcome: Percent change in body weight

- Major finding: Percent change in body weight at 24 months (95% confidence interval)

Intensive-lifestyle group	Usual care group	Difference
-4.99 (-6.02 to -3.96)	-0.48 (-1.57 to 0.61)	-4.51 (-5.93 to -3.10)

Katzmarzyk et al. (2020)

Effects of a lifestyle-based program for obesity treatment in low-income neighborhoods by race

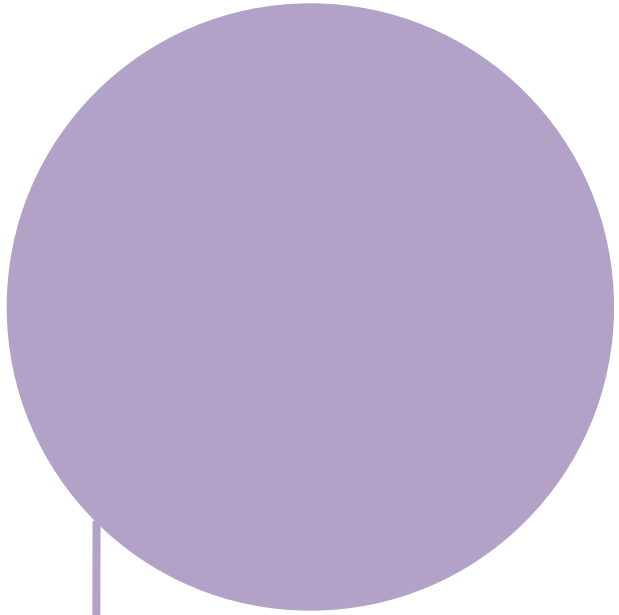


Katzmarzyk et al. (2020)

Potentially differential impact of interventions – Societal concern

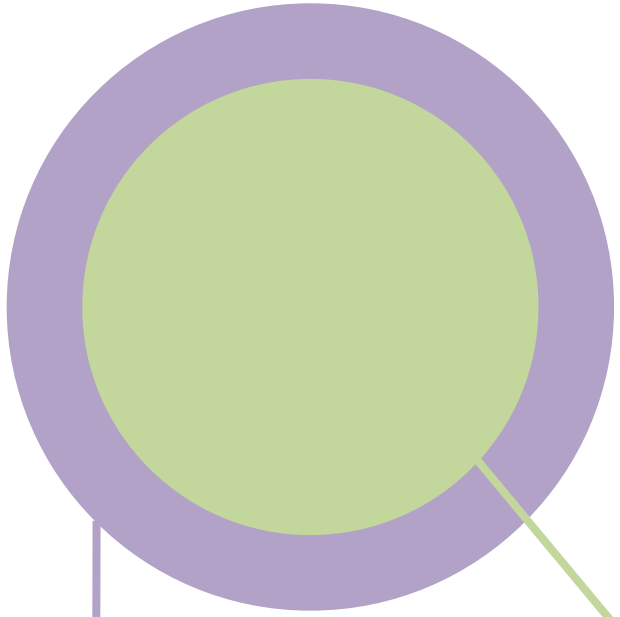
- The causality in question (X → Y) may work differently in different groups of human beings because of
- Differential intervention effects by social group characteristic
  - An example: Effects of women's group participation on neonatal mortality rate by marginalization
- Differential intervention effects within a traditionally excluded group
  - An example: Effects of a high intensity, lifestyle-based program for obesity treatment in primary care clinics in low-income neighborhoods
- The primary interest here is differences across groups or how a traditionally excluded group fares, and this interest derives from concerns for unfairness or inequity

Terminology



Health inequalities

Health differences between groups or individuals

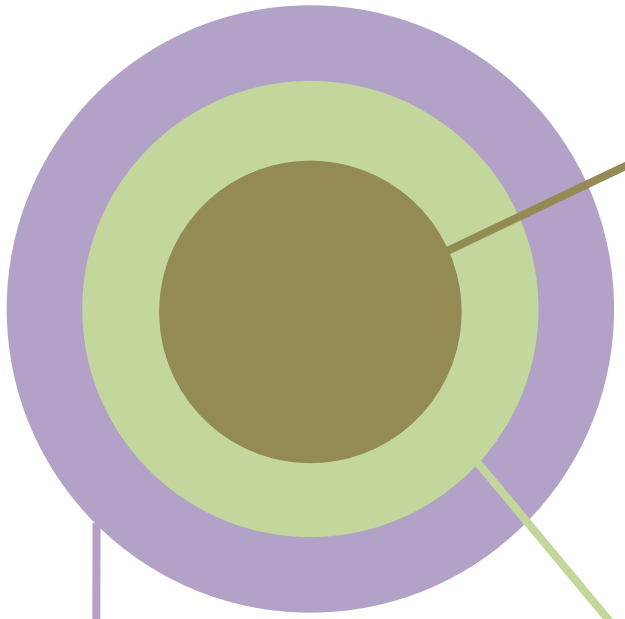


Health inequities

Unfair health differences between groups or across individuals

Health inequalities

Health differences between groups or individuals



Health disparities

Health differences associated with socially meaningful characteristics often indicative of social disadvantage

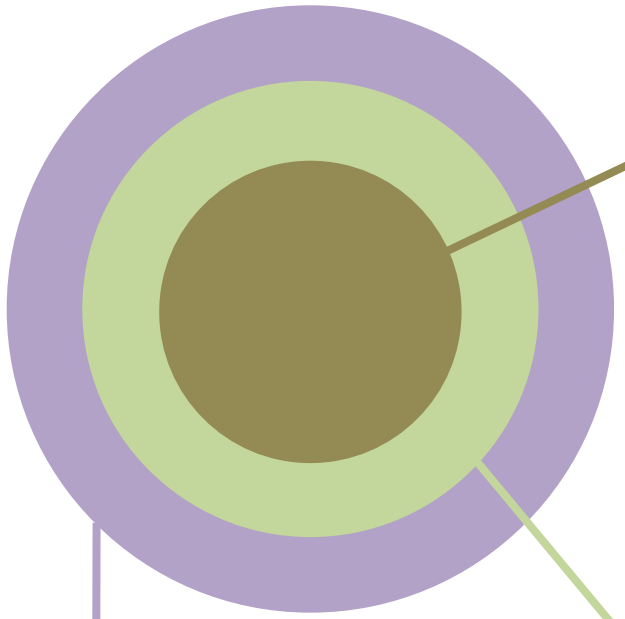
One way to define what is unfair

Health inequities

Unfair health differences between groups or across individuals

Health inequalities

Health differences between groups or individuals



Health disparities

Health differences associated with socially meaningful characteristics often indicative of social disadvantage

One way to define what is unfair

Health inequities

Unfair health differences between groups or across individuals

Health equity

The absence of health inequities

Health inequalities

Health differences between groups or individuals

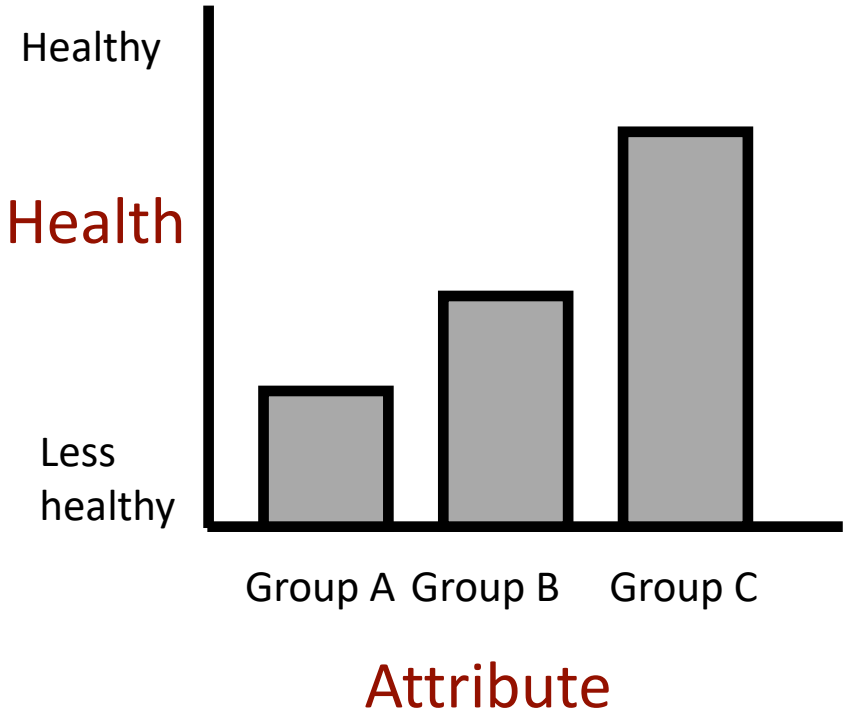
Who should be in the study and why?

- Participation
- Biology
- Societal concern

Which health inequalities are unfair and why?

Including diverse study subjects for societal concern

- Often operationalized to include or focus on historically overlooked social groups
- Groups selected signify social disadvantage and power imbalance
- Examples of groups
  - NIH guidelines on the inclusion of women and minorities as subjects in clinical research (1994)
    - "A minority group is a readily identifiable subset of the US population which is distinguished by either racial, ethnic, and/or cultural heritage"
  - PROGRESS-Plus: **P**lace of residence, **R**ace/ethnicity/culture/language, **O**ccupation, **G**ender/Sex, **R**eligion, **E**ducation, **S**ocioeconomic status, **S**ocial capital, and additional context-specific personal or setting characteristics (Jull et al. 2017)
- The common thread: bivariate approach


Healthy
Health
Less
healthy
Group A
Group B
Group C
Attribute

Asada (2013)

Challenges of the bivariate approach

- Increasing number of groups is identified as important
- Within-group variation and intersectionality are often overlooked
- Concerns for intersectionality will increase the number of groups
- The group definition can change (e.g., from binary variable to continuous variable)
- Reasons why the selected group characteristic signify concerns for unfairness and inequity are often intuitive and implicit
- Many bits of information lack a coherent picture

Deeper philosophical discussion is needed to include diverse study subjects for societal concern

- Examples of social groups of concern:
  - Racial/ethnic minorities, sexual/gender minorities
  - People with low income, low education, and/or disability

- Which groups to choose? – The answer depends on why one is concerned about social groups
  - Concerns for recognition (status)? – Racial/ethnic or sexual/gender minorities
  - Concerns for resources (class)? – People with low income or education
  - Concerns for representation (political)? – People with disability
  - Concerns for the current or historical situations?

Blacksher (2023)

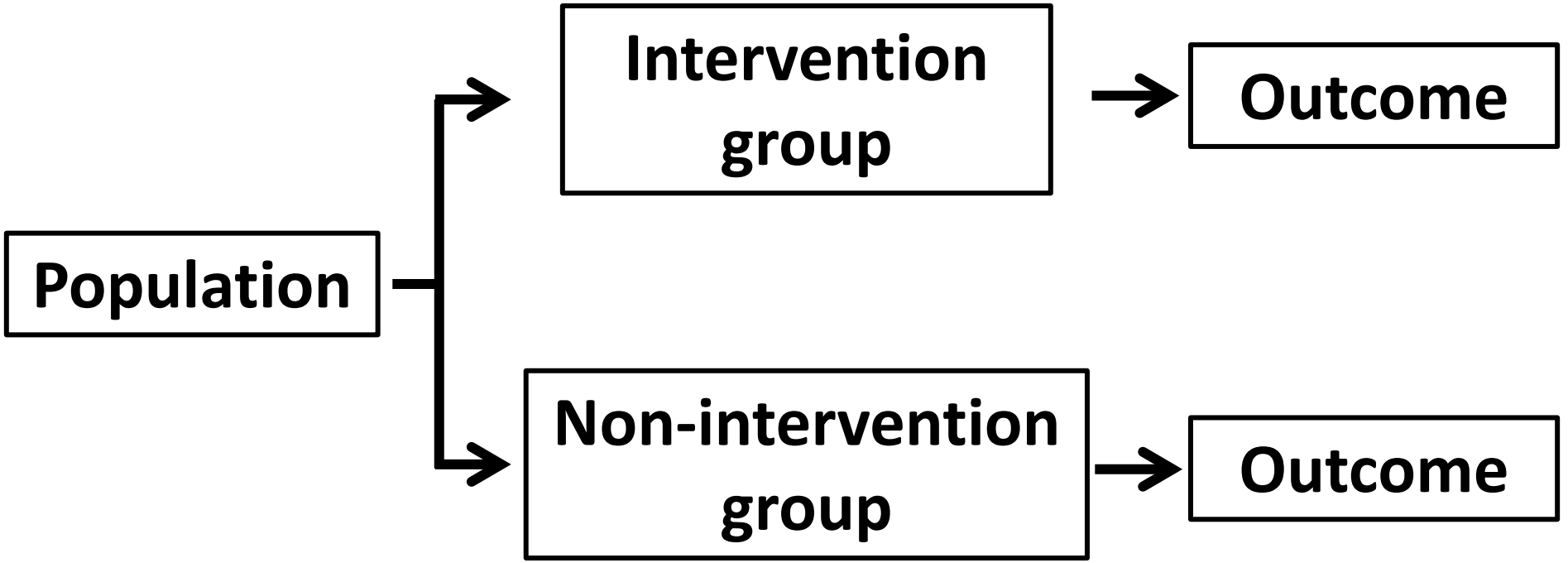
How do equity considerations influence the study design, analysis plan, and reporting?

Reasons why study subjects should be diverse inform study design, analysis plan, and reporting

Reasons why study subjects should be diverse inform study design, analysis plan, and reporting

- Participation
- Biology
- Societal concerns

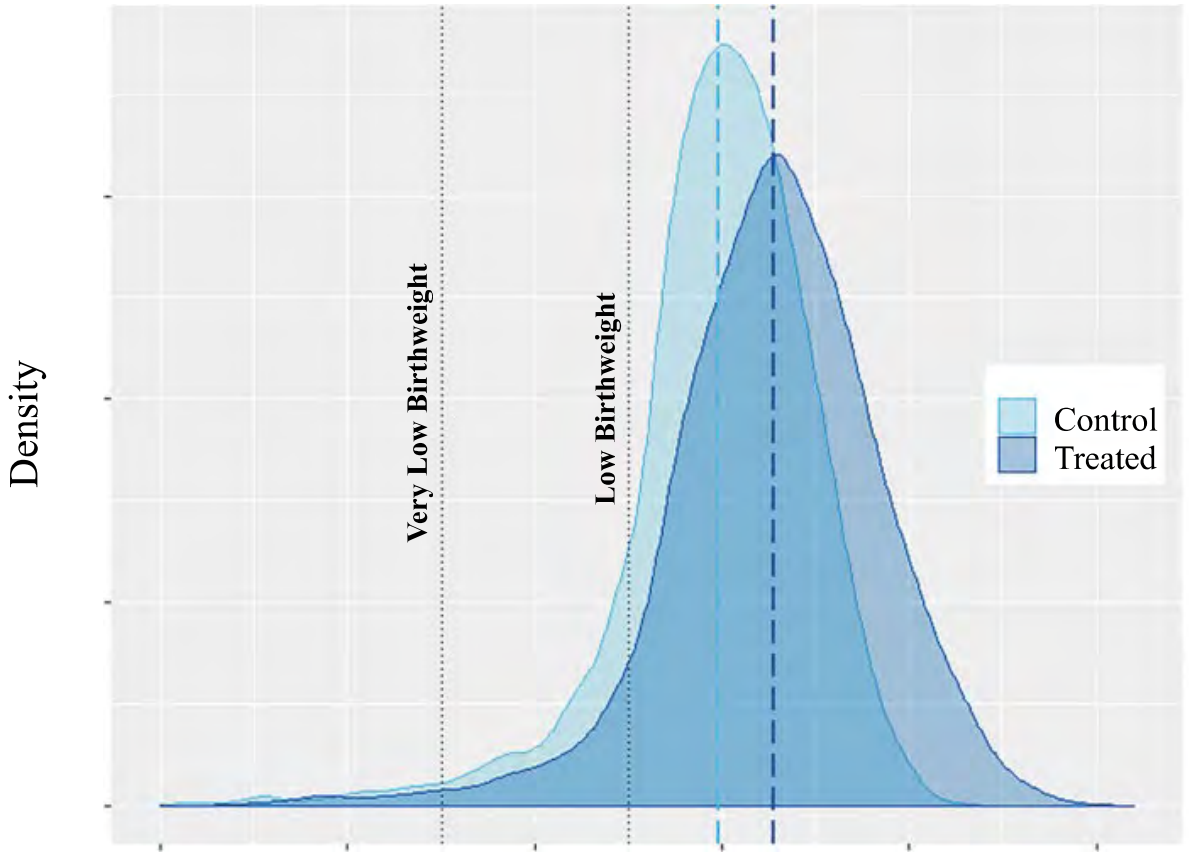
A traditional study



A hypothetical example: Cookson et al (2021)

- Population: A low-income country
- Intervention: Antenatal dietary education and supplementation program
- Comparison: Babies whose mothers received the intervention vs. babies whose mothers did not receive the intervention
- Outcome: Birthweight

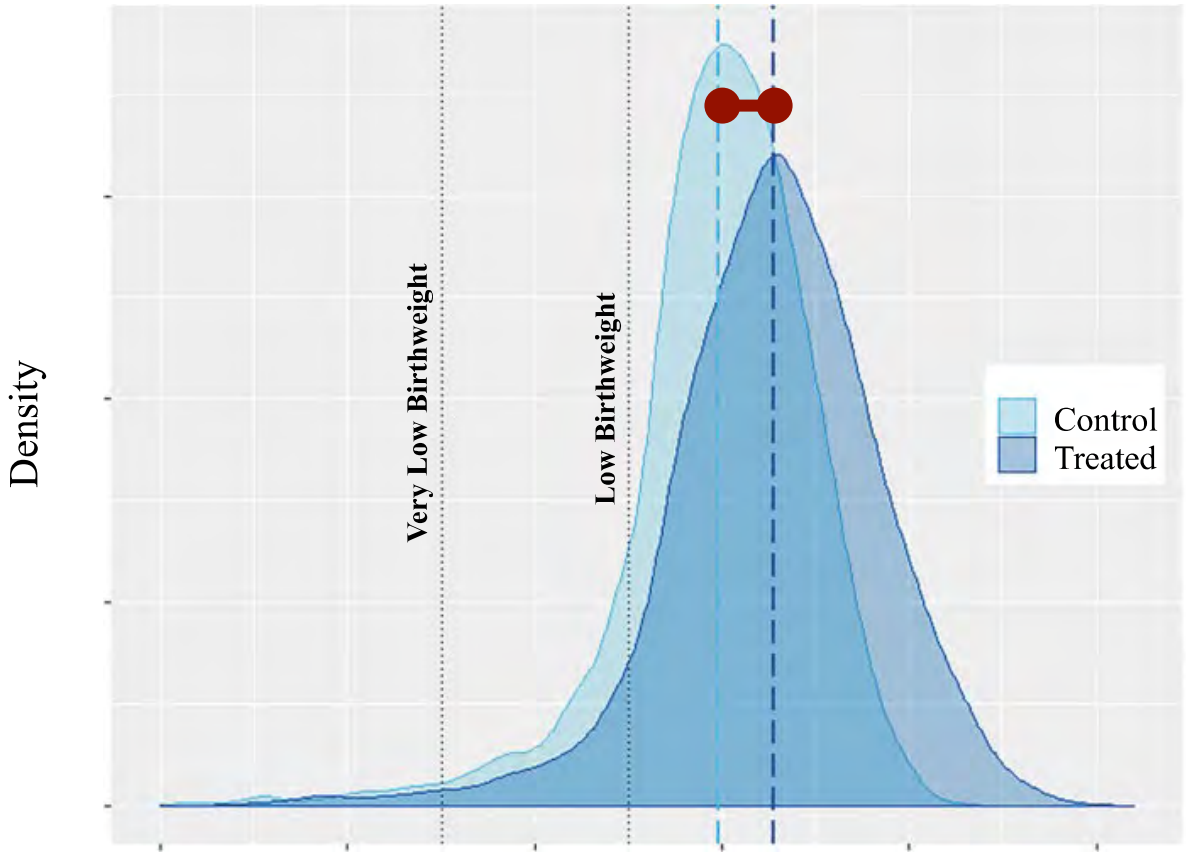
Traditional study – average treatment effect



Coockson et al. 2021

Traditional study – average treatment effect

Analyze

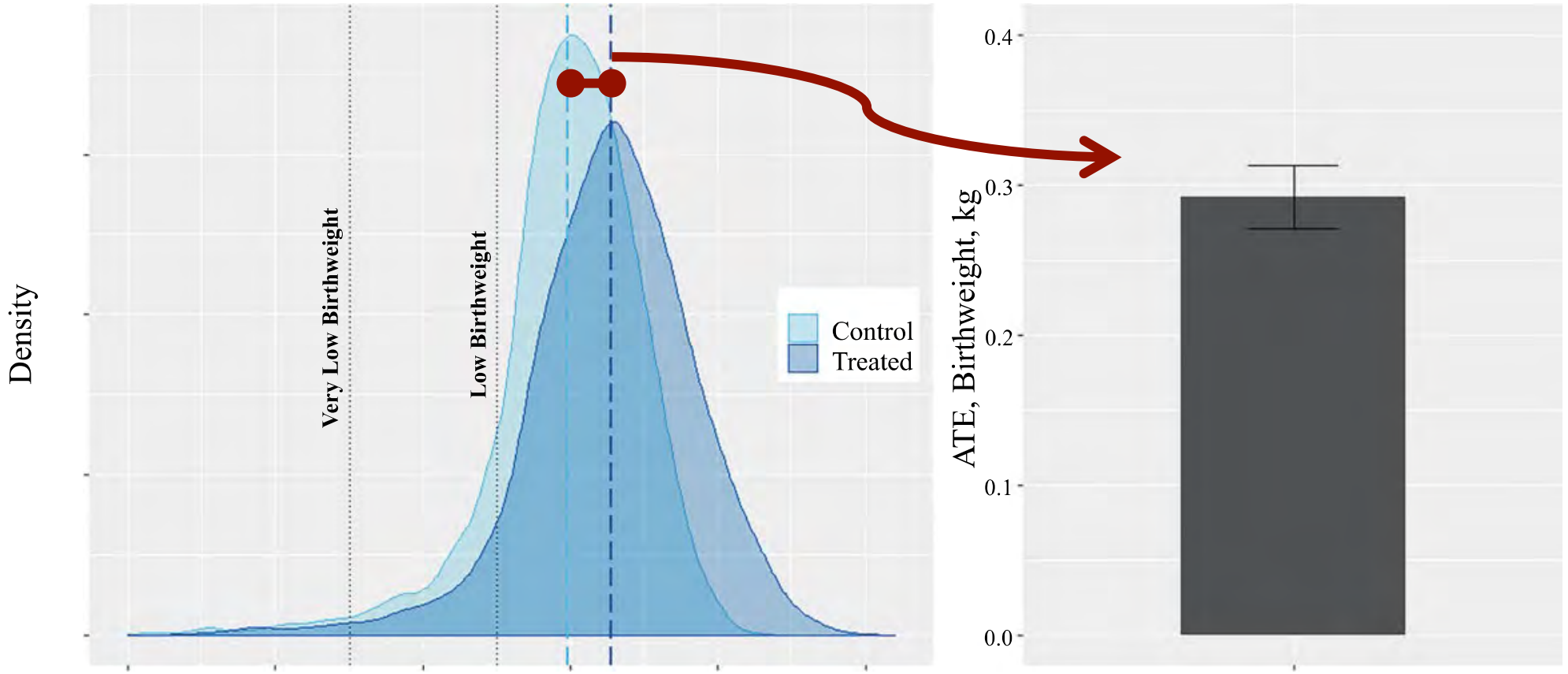


Coockson et al. 2021

Traditional study – average treatment effect

Analyze

Report

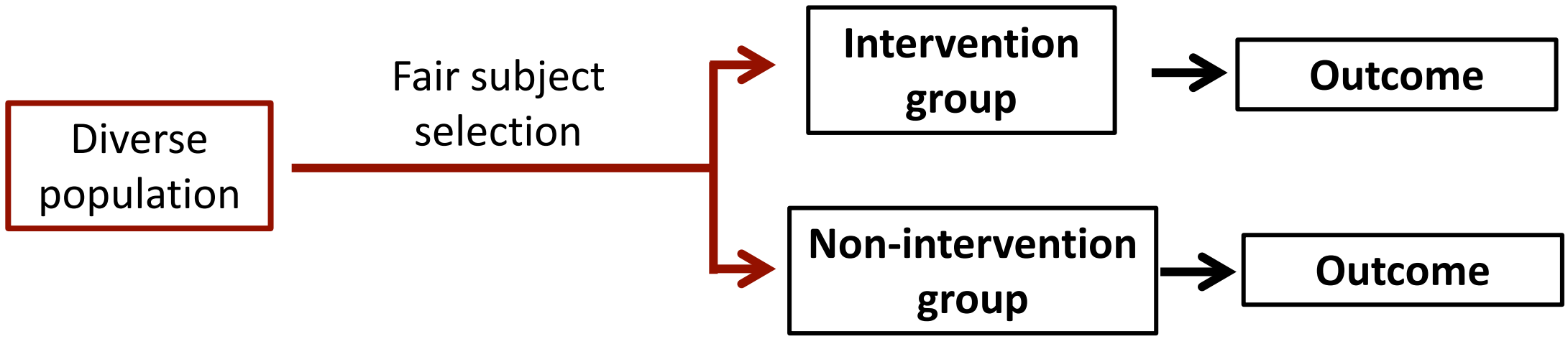


Coockson et al. 2021

Why should study subjects be diverse?

Participation

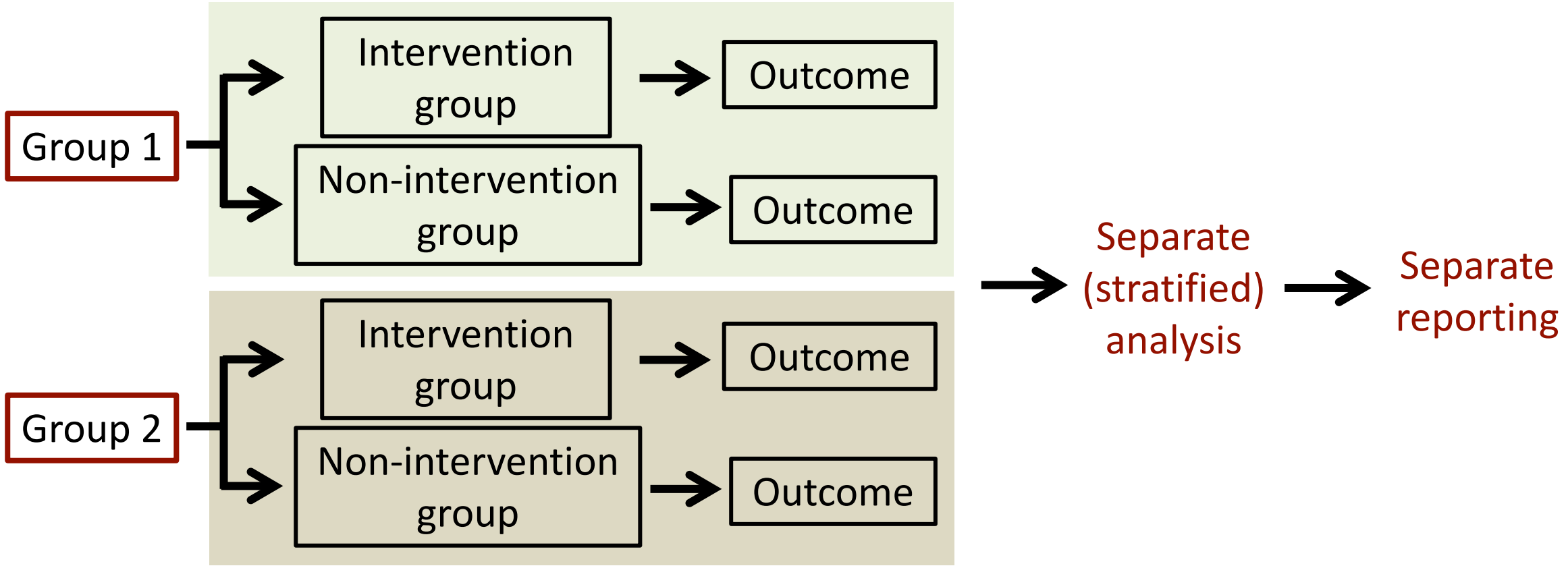
- Fair subject selection is the primary concern
- If there is no reason to suspect or be interested in potentially differential intervention effects due to biology or societal concern, no additional considerations for the study design, analysis plan, and reporting may be necessary



Why should study subjects be diverse?

Biology

- The study design, analysis plan, and reporting should meet the objective of examining potentially differential causal pathways in different groups



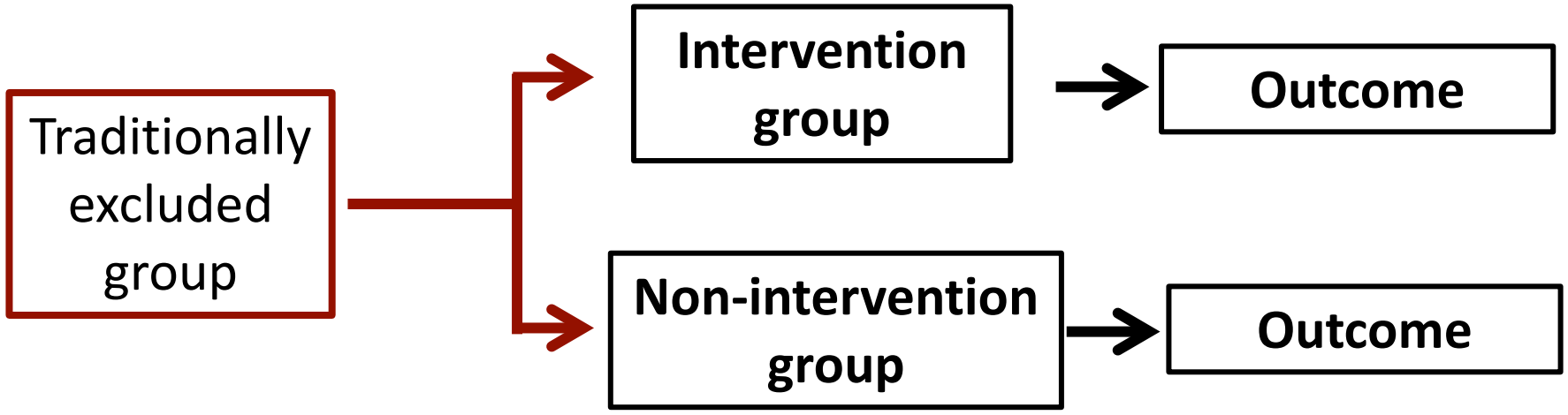
Why should study subjects be diverse?
Societal concern (equity)

- The study design, analysis plan, and reporting should meet the objective of identifying differences across groups that indicate unfairness or inequity
- “Health equity-relevant randomized trials” (Jull et al. 2017)
- “Equity-informative methods” (Cookson et al. 2021)

- Two approaches
  - Focusing on a traditionally excluded group
  - Assessing differences across social groups

Focusing on a traditionally excluded group

- The study design, analysis plan, and reporting remain the same as the traditional study
- The difference is from which population study participants is recruited

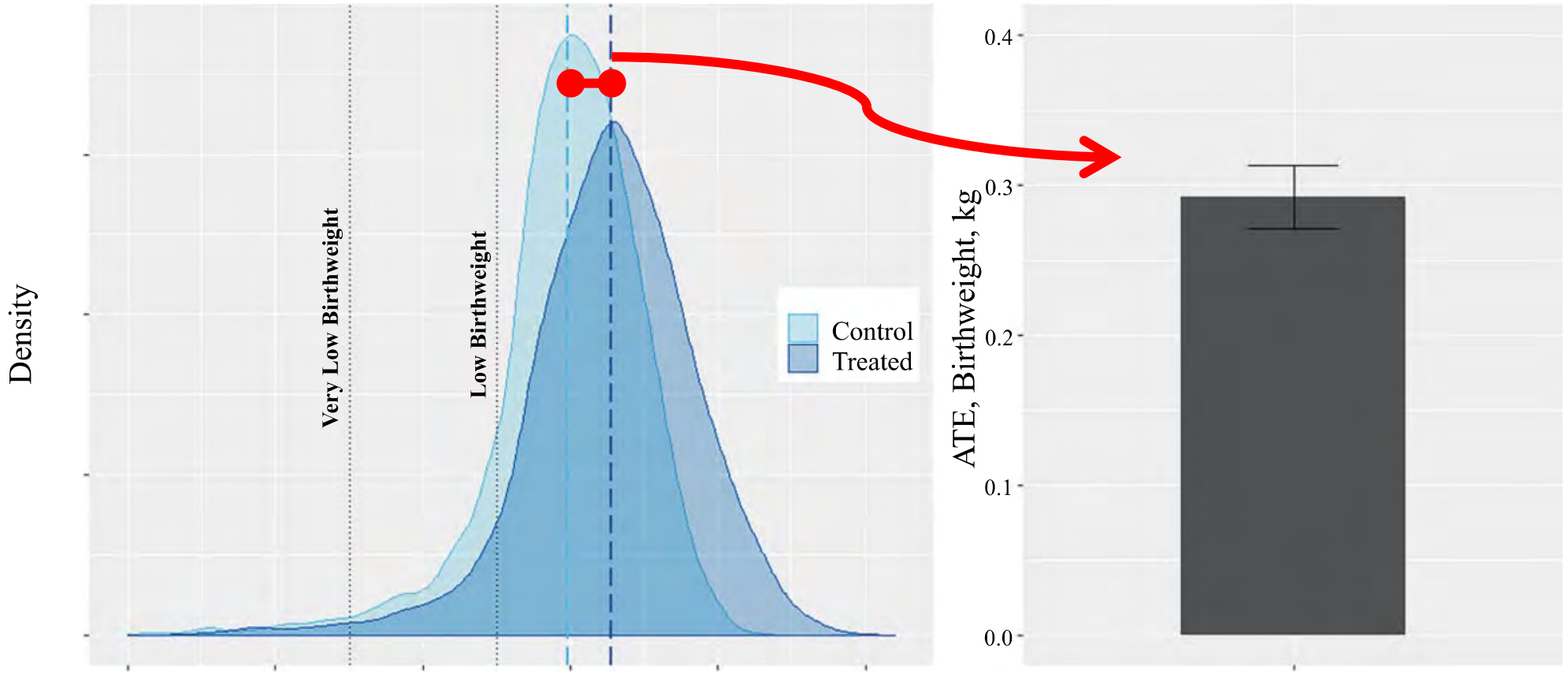


Focusing on a traditionally excluded group

Average treatment effect

Analyze

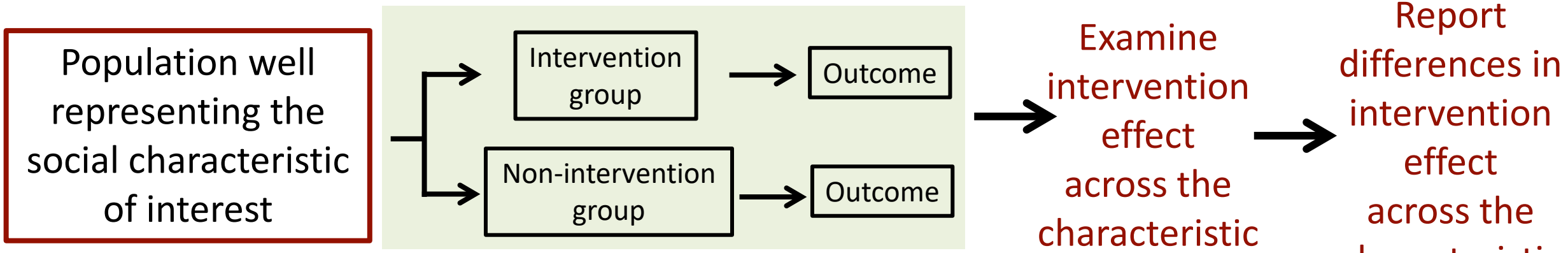
Report



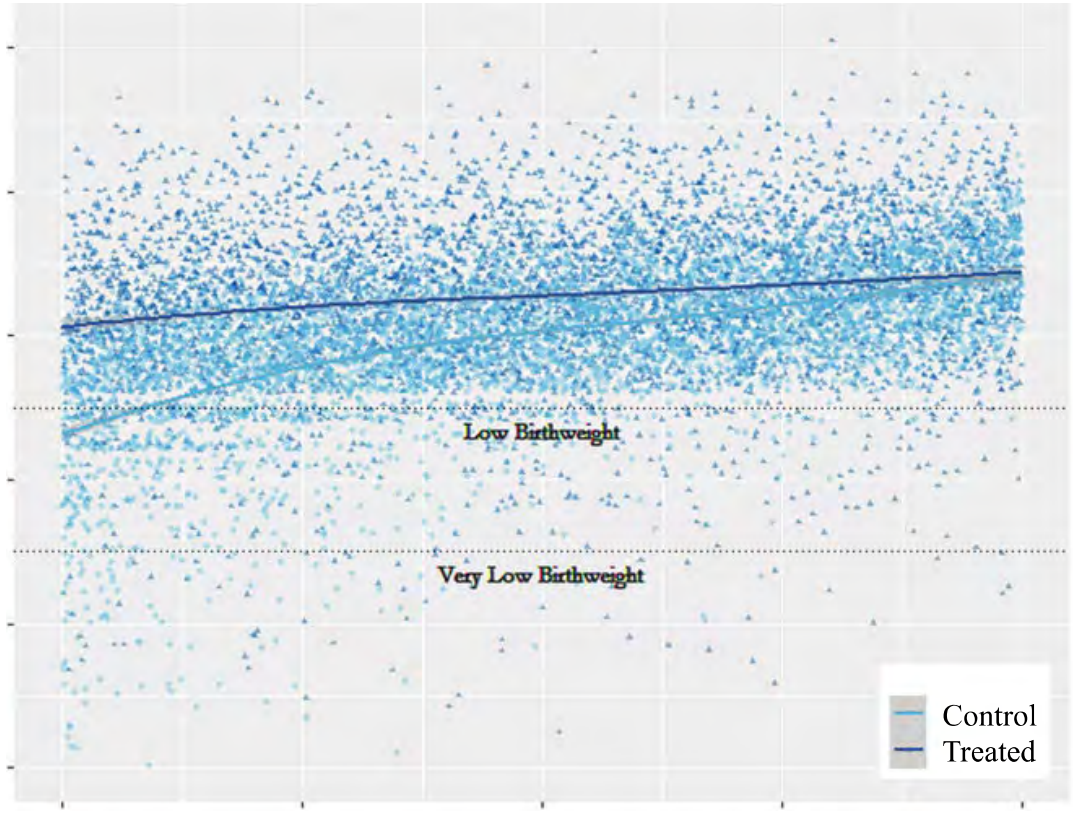
Coockson et al. 2021

Assessing differences across social groups

- The study design, analysis plan, and reporting becomes more complex than the traditional study

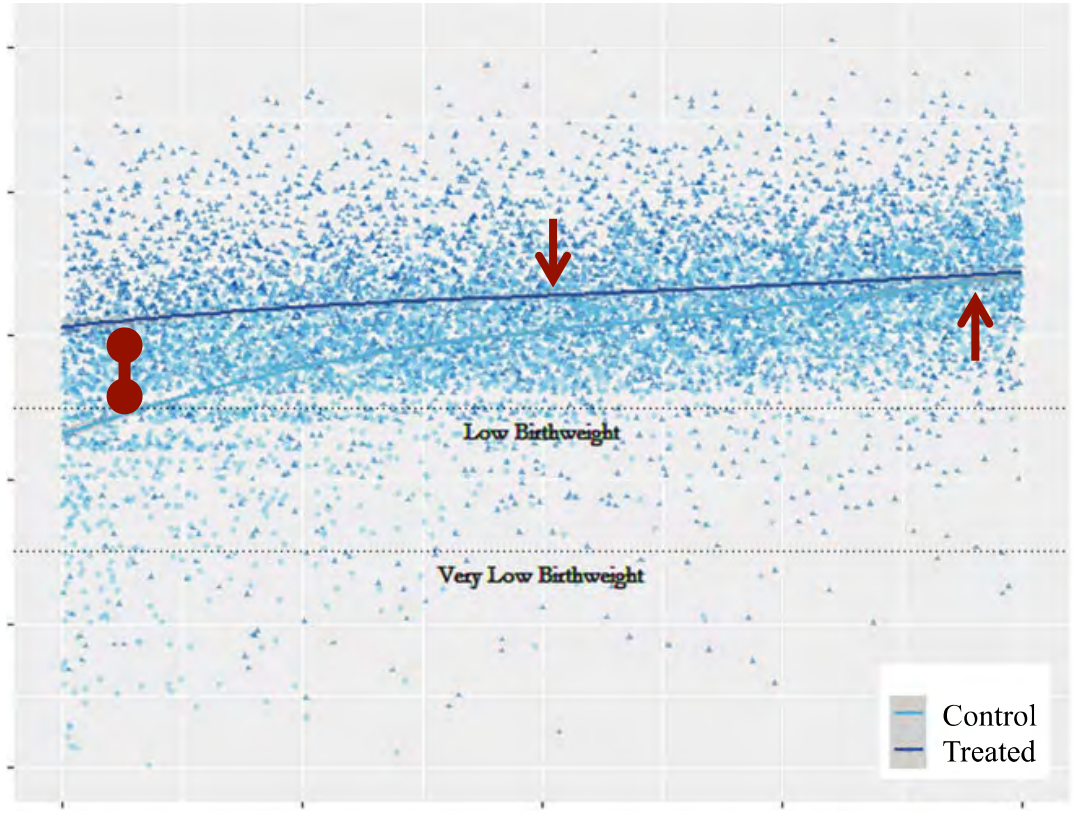


Equity-relevant/informative study – conditional average treatment effects



Equity-relevant/informative study – conditional average treatment effects

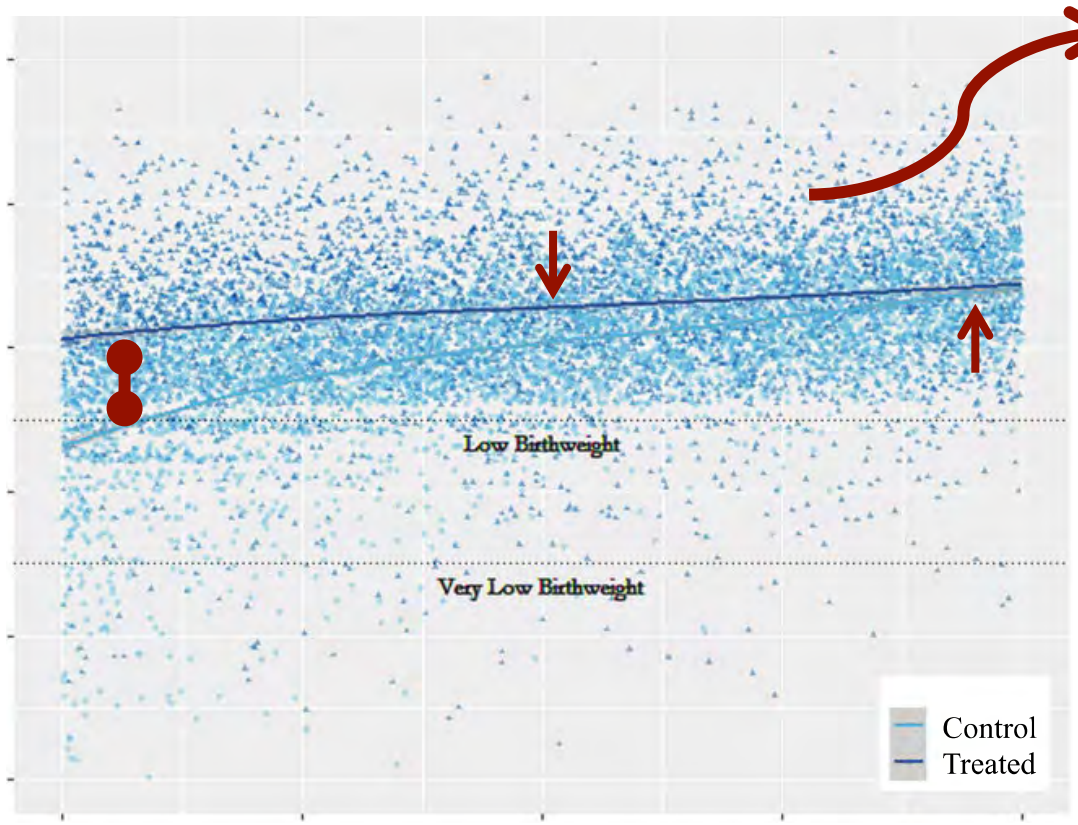
Analyze

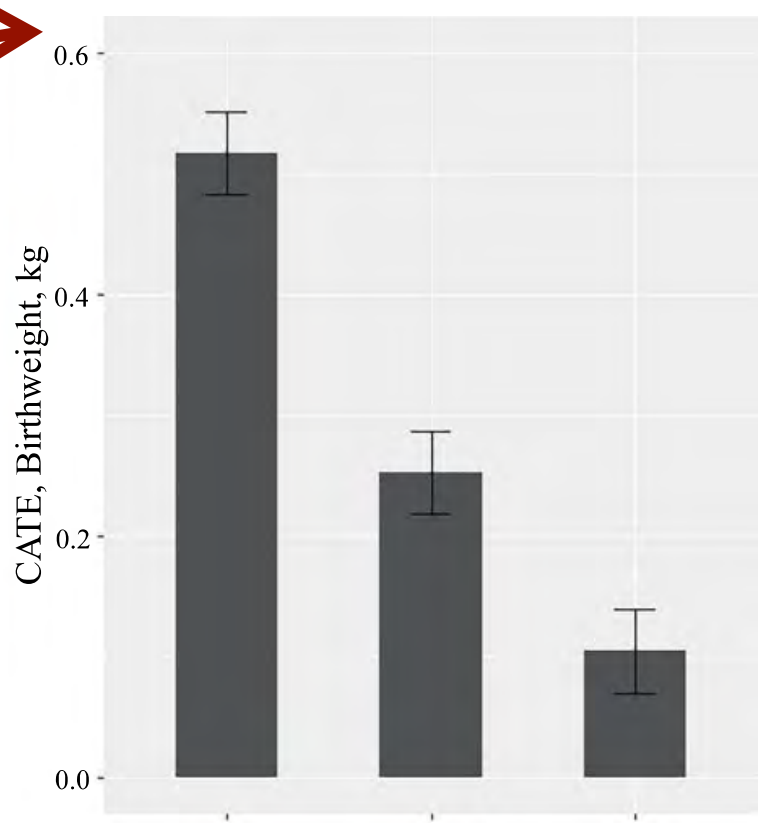


Equity-relevant/informative study – conditional average treatment effects

Analyze

Report





Challenges of equity-relevant/informative studies

- Sample size
  - Larger sample size is needed from typically smaller groups
  - As long as diverse sociodemographic characteristics are reported, studies can be equity-relevant/informative post-hoc
  - Combining data from many studies (meta-analysis)
  - Using Bayesian methods that use established evidence to overcome small samples
- Cost
  - NIH guidelines on the inclusion of women and minorities as subjects in clinical research (1994) state costs cannot be the reason for exclusion
- Complexity

Summary

- Three guiding questions
  - Who should be in the study and why?
  - Which health inequalities are unfair and why?
  - How do equity considerations influence the study design, analysis plan, and reporting?

- Key points
  - Equity considerations are not a check box – they are woven into principles for ethical clinical research
  - To make equity considerations explicit and meaningful, it is important to think carefully about when health inequalities are unfair

Work cited

- Alegria M et al. JAMA Network Open. 2021; 4(5): e2111516
- Asada Y. A summary measure of health inequalities: incorporating group and individual inequalities. In: Eyal N, ed. *Inequalities in health: concepts, measures and ethics*. Oxford: Oxford University Press, 2013
- Blacksher E. Redistribution and recognition in the pursuit of health justice: An application of Nancy Fraser's framework. In Bhakuni H & Miotto L, ed. *Justice in global health: New perspectives and current issues*. Routledge, 2023.
- Cookson R et al. J Health Organization and Management 2021; 35(6):665-681
- Daniels N. *Just health: meeting health needs fairly*. Cambridge: Cambridge University Press, 2008
- Emanuel Z, Wendler D, Grady C. JAMA. 2000; 283(20):2701-11
- Emanuel Z et al. J Infect Diseases 2004; 189:930-7
- Gerdts E & Regitz-Zagrosek V. Nature Medicine. 2018; 25:1657-1666
- Houweling TA et al. Intl J Epidemiology. 2019;168-182
- Jull J et al. BMJ Open. 2017;7:e015815
- Katzmarzyk PT et al. NEJM. 2020; 383:909-918
- Kawachi I, Subramanian SV, Almeida-Filho N. JECH. 2002;56:647-652