Non-Randomized Trials

ADA Research Toolkit

ADA Research Committee

Learning Objectives

At the end of this presentation the participant will be able to:

- Define a non-randomized trial and its components
- Describe the study design
- Describe the strengths and limitations of non-randomized trials
- Identify the main statistical tools used to analyze non-randomized trials

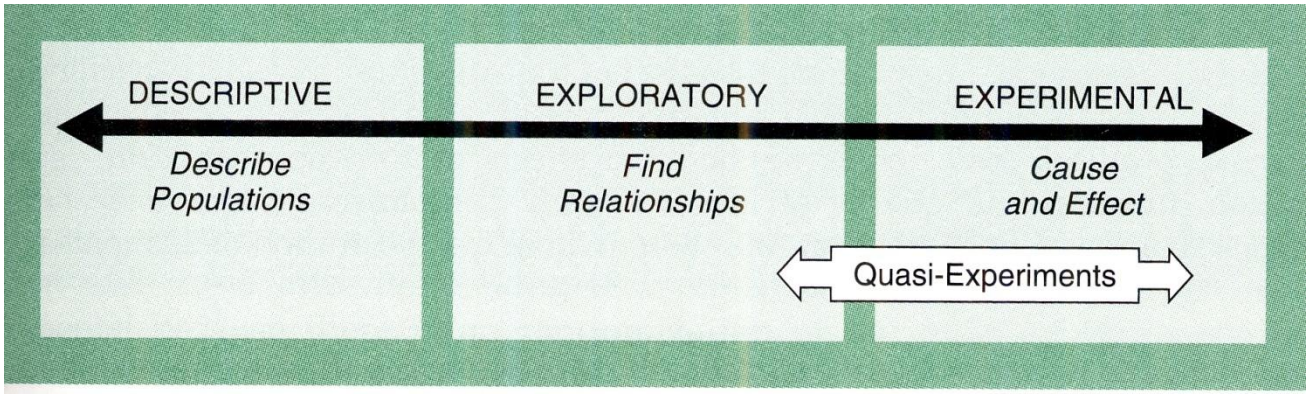
Introduction

Definition of a Non-Randomized Trial

- A study where participants have been assigned to the treatment, procedure, or intervention alternatives by a method that is not random. The investigator defines and manages the alternatives. (ADA terms on EAL)

Introduction

Non-randomized trials are a type of quasi-experimental design



Quasi-experimental designs are those that do not meet the criteria for a true experimental design such as random assignment of participants to groups or having a control group.

Portney L.G., Watkins MP. *Foundations of Clinical Research. 3rd ed*. Upper Saddle River, NJ: Pearson/Prentice Hall; 2009:223.

Distinguishing Features

- Uses natural groups or assigns participants to groups using
  a non-random procedure
- The investigator controls the exposure of groups to the intervention
- Prospective
- Confounders exist due to non-randomization

When to Use a Non-Randomized Trial

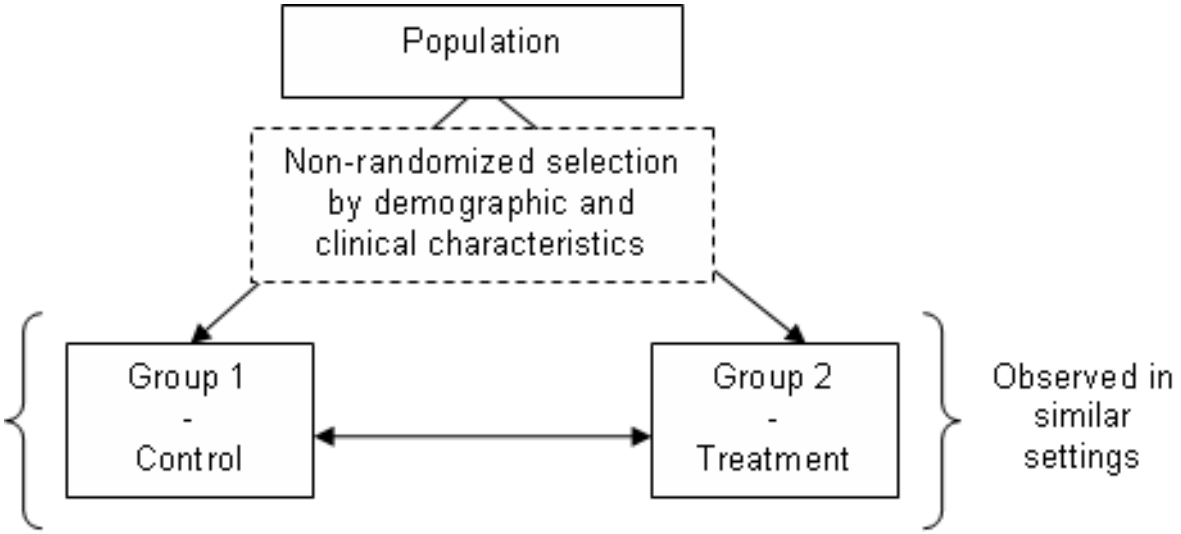
When is it appropriate to use a non-randomized trial design?

- When the act of random allocation may reduce the effectiveness of the intervention
  - Occurs when the effectiveness of the intervention depends on the participant's active participation which is influenced by their beliefs and preferences)
- When it would be unethical to do random allocation
- When it is impractical to do random allocation (e.g. cost or convenience factors)
- When there are legal or political obstacles to random allocation

Use of Controls

There are different types of controls that can be used in non-randomized trials

Concurrent controls: Treatment and control group participants are matched at the group level based on demographic and other characteristics, and receive different treatment conditions at the same time.



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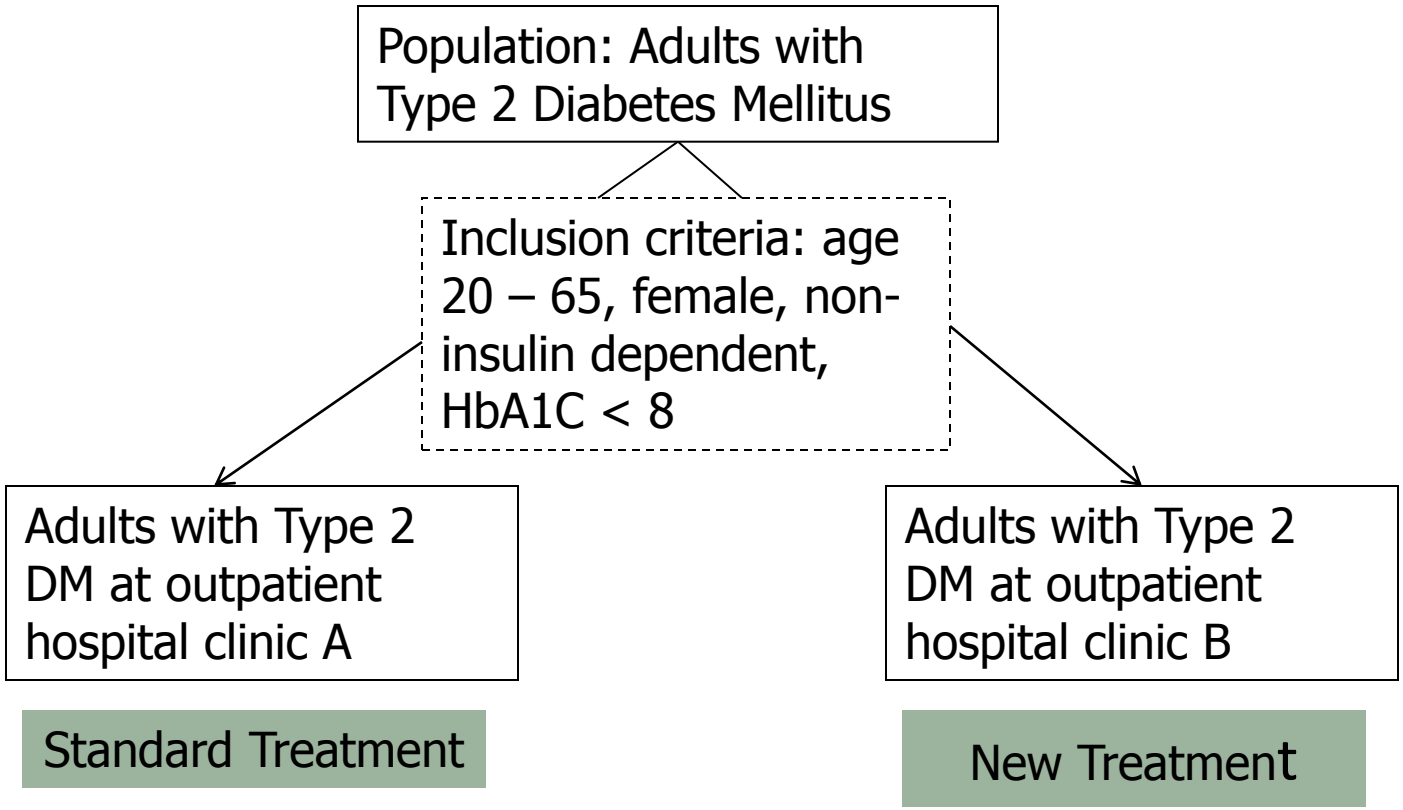
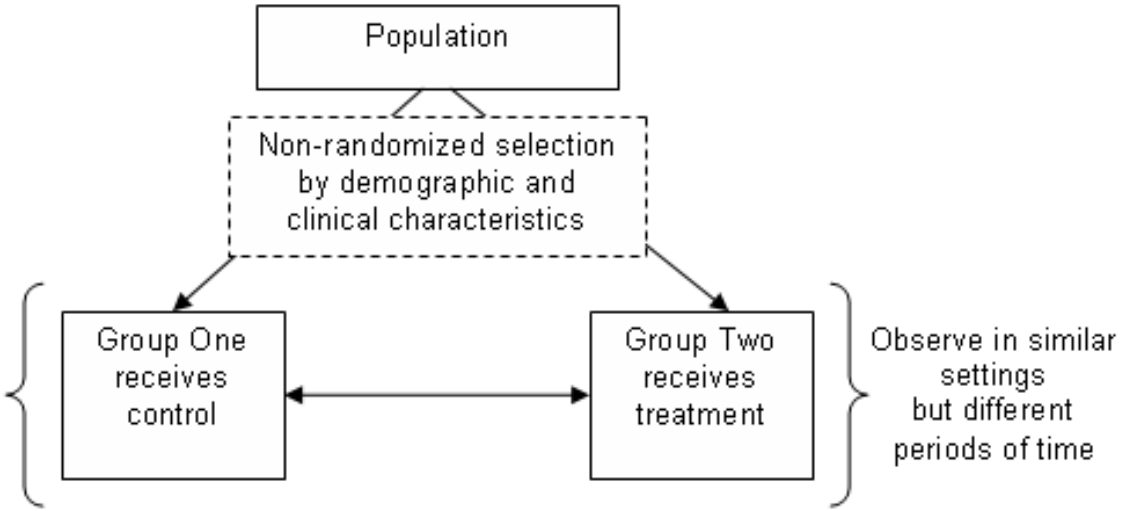
Use of Controls

Example 1: Concurrent Control



Use of Controls

Historical controls: Investigators compare outcomes among a group of participants who are receiving a new treatment (experimental group) with outcomes among participants who received standard treatment in a previous period (control group).



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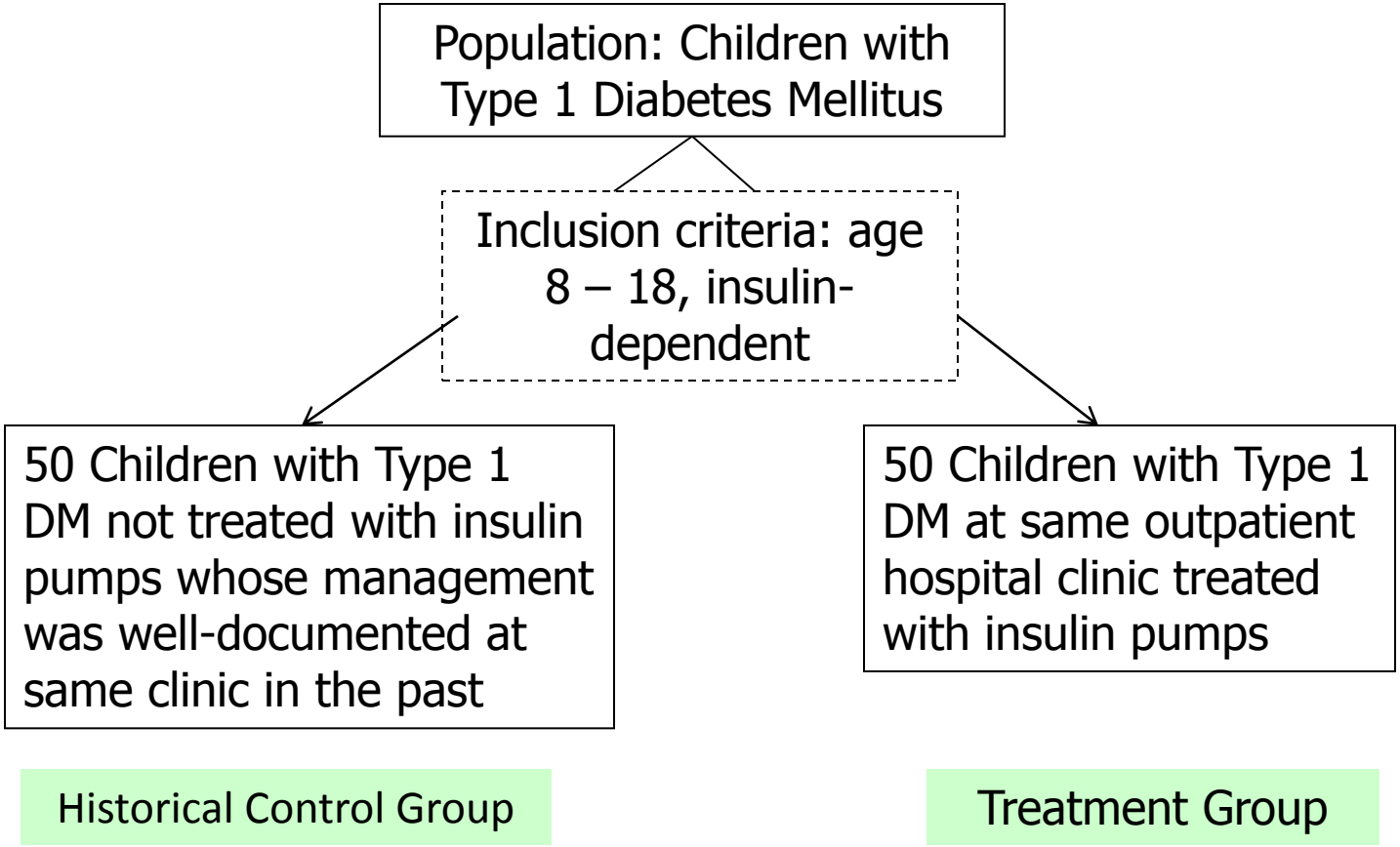
Use of Controls

Example 2: Historical Control

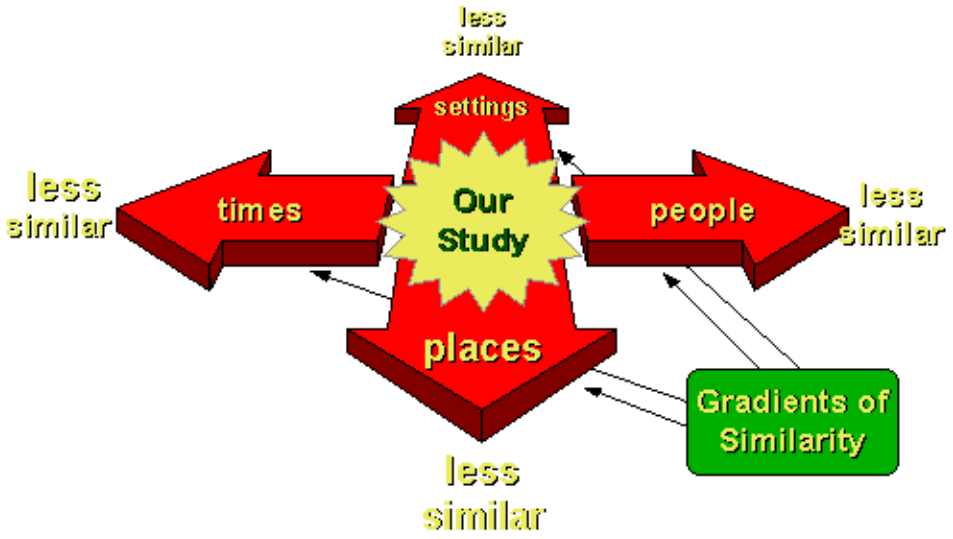


Questions Answered

- What is the effectiveness of the intervention/exposure?
  - Does it work?
- What is the magnitude of the effect?
  - How large is the difference in the measured outcome (dependent) variable between the treatment group and the control group?
- What proportion of the sample/population will benefit?
  - What percentage of the treatment group benefited?
- Which approach is better?
  - Did the intervention group have a better outcome than the control group?

Generalizability (external validity)

- Generalizability is dependent on how representative the sample is of the reference population (the population to which results would apply
- External validity is the extent to which study findings can be generalized beyond the sample used in the study (Burns and Grove)

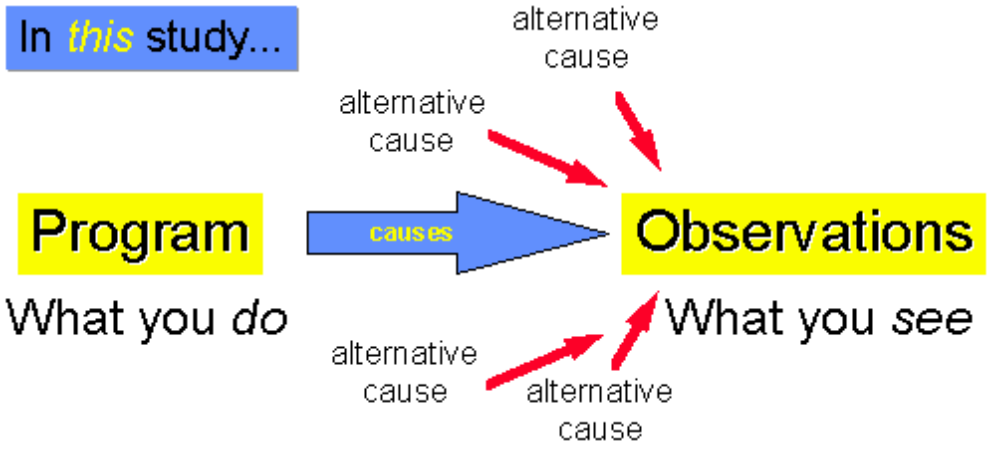


Burns N, Grove SK. *The Practice of Nursing Research: Appraisal, Synthesis and Generation of Evidence. 6th ed.* St. Louis: Saunders Elsevier, 2009.

Internal Validity

Definition

- The extent to which the effects detected in the study are a true reflection of reality, rather than being the result of the effects of extraneous variables (Burns and Grove)



www.socialresearchmethods.net/kb/intval.php

Internal Validity

Threats to internal validity

- Selection Bias: baseline differences between the control and intervention groups
  - Known factors (confounding variables) that may have an effect on the outcome being measured (eg. age, education or income level)
  - Unknown factors
- Differences in details of the intervention between groups
- Non-random dropout from the study
- Bias due to conscious and unconscious prejudice for or against the intervention on the part of participants, providers or evaluators

Internal Validity

Ways non-randomized study designs can increase internal validity

- Blinding
  - Blind participants so they do not know whether they are in the intervention group or the control group
  - Blind providers so they do not know which participants are in the intervention group
  - Blind evaluators so they do not know which participants are in the intervention group
- Statistically control confounding variables

CAUTION: Due to lack of randomizaton, differences between the groups that are present before the intervention may affect the outcome of the study, thus limiting the conclusions regarding cause and effect.

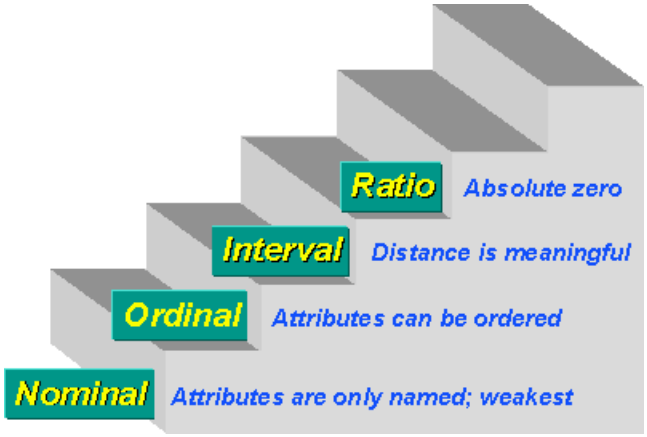
Results

- Establish whether control and intervention groups are equivalent
- Compare baseline characteristics between groups
  - Are differences statistically significant?
    - If yes: may indicate systematic bias in group assignment
    - If no:
      a) Groups are not different or
      b) If sample size is too small to provide adequate statistical power to detect a difference, groups may not be equivalent
  - Are differences clinically significant?
    - If yes: potential confounders exist
    - If no: : due to nonrandom assignment, unknown confounders are still a threat to internal validity

Non-Randomized Trial (NRT)

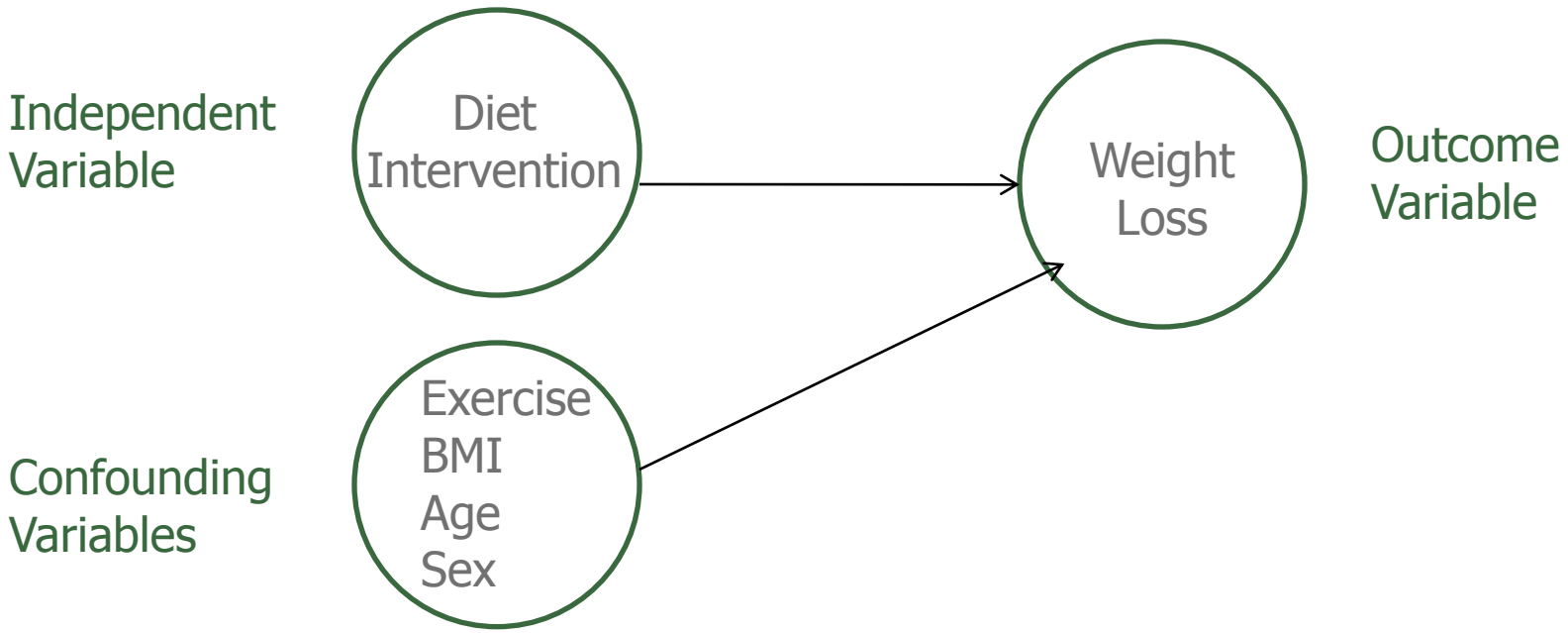
Are differences in the outcome variable between the control group and intervention group(s) significant?

- Outcome variables are measured quantitatively (ordinal, interval or ratio)
  - Four levels of measurement
    - Nominal: the numerical values just "name" the attribute uniquely
    - Ordinal: the attributes can be ranked in order
    - Interval: the distance between attributes has meaning
    - Ratio: there is an absolute zero
- Level of measurement affects which statistical tests are appropriate



www.socialresearchmethods.net/kb/measlevl.php

Were Data Adjusted for Confounders?



Confounding Variables: characteristics that differ between groups and may affect the results of the study

Typical Statistics

- Parametric statistics are used for normally* distributed data measured on the interval or ratio scales
  - T-test: compares means of two groups
  - Analysis of variance (ANOVA): compares means of three or more groups
  - Multivariate analysis (e.g. MANOVA): analyzes relationships among three or more variables
  - Logistic regression: predicts odds of a dichotomous outcome
- Nonparametric statistics are used for data measured on the nominal or ordinal scales that do not meet certain assumptions about population parameters such as a normal distribution
  - Chi-square test: compares observed frequencies within categories to frequencies expected by chance

*normal distribution: a symmetrical bell-shaped theoretical distribution that has defined properties

Key Points

- Appropriate when randomization not feasible
- No random assignment into groups
- Conclusions must take into account potential biases
- Can show associations and trends, but cannot test cause-and-effect hypotheses

Resources

- Schwartz RP, Hamre R, Dietz, WH, et al. Office-Based Motivational Interviewing to Prevent Childhood Obesity. Arch Pediatr Adolesc Med. 2007;161:495-501.

  http://archpedi.ama-assn.org/cgi/content/full/161/5/495