Measures of Frequency and Effect in Clinical Research

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Overview of this Session

- Study Design
  - Clinical trial
  - Cohort study
  - Case-control study
- Frequency measures
  - Incidence
  - Prevalence
- Measures of Association and Effect
  - Attributable Risk
  - Relative Risk
  - Odds Ratio
  - Correlation
  - Analysis of paired data (measure of change)

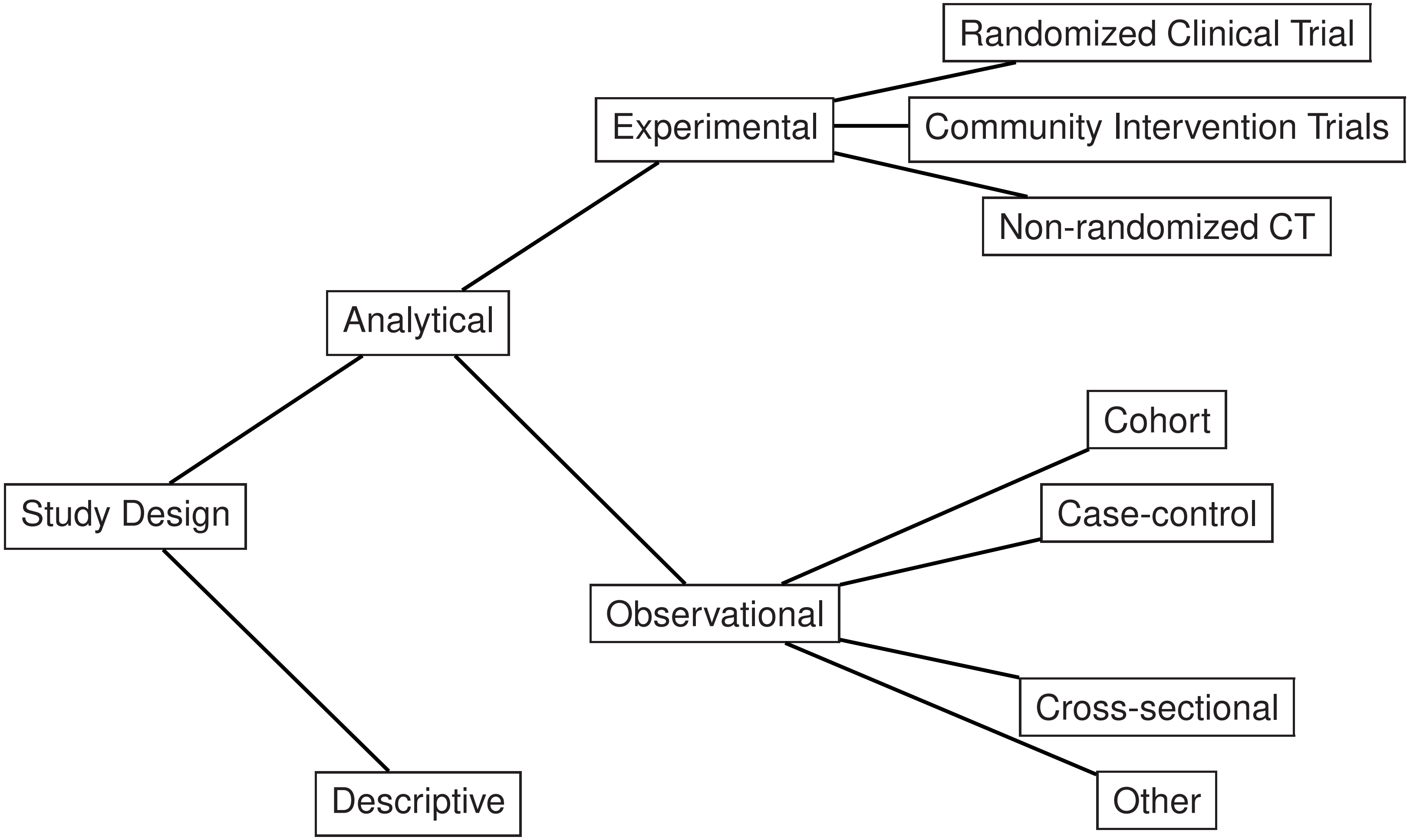
Study Design

- Descriptive Studies (a.k.a., hypothesis screening studies)
  - Used to study variation in disease frequency by demographic characteristics, place and time
  - Lack a hypothesis specified in advance $\Rightarrow$ hypothesis generating
  - Relatively low cost studies using pre-existing data
- Analytic studies
  - Researcher has a pre-specified hypothesis in mind
  - Experimental vs. observational

Study Design: Analytic Studies

- Experimental studies
  - An experiment is a set of observations conducted under controlled conditions, where the researcher manipulates conditions to ascertain what effect the manipulation will have.
  - In general, experimental studies are those in which the researchers manipulate exposure.
- Observational or non-experimental studies
  - A study that does not involve intervention
  - Observe natural course of events where changes in one characterstic is studied in association with changes in other characterstics
  - Often necessary when unethical or infeasible to manipulate exposure

Study Design Taxonomy



Randomized Clinical Trials (RCT)

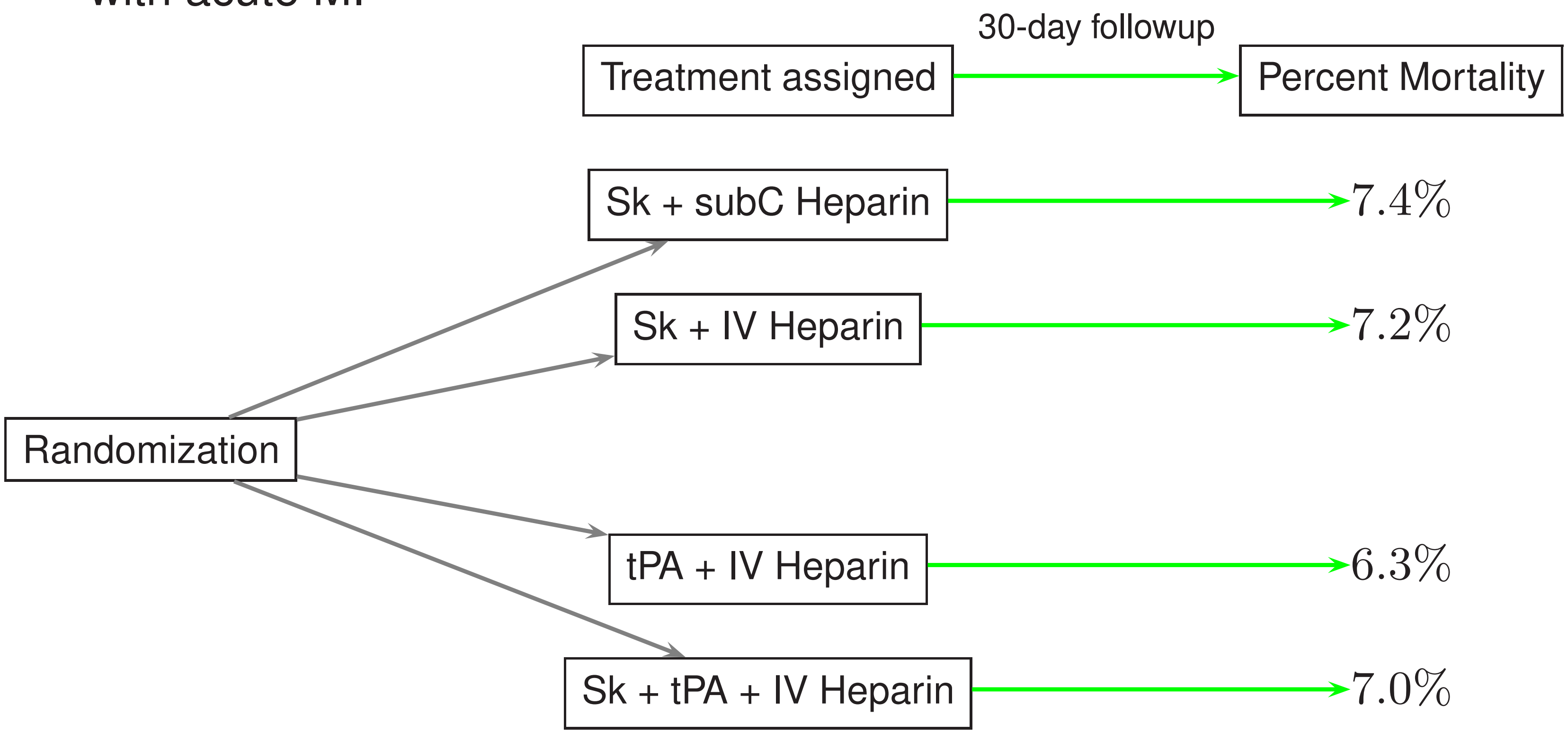
- In their simplest implementation:
  1. Subject enrolled into the study...
  2. randomly assigned to one of ≥ 2 treatments...
  3. followed up until the outcome measure is obtained
- Using a prespecified effect measure, outcome comparisons made among various treatment groups
- The key is that a random assignment determines subject's treatment
- Strongest study design to establish causal relationships (superior control over confounding factors including those that are difficult or impossible to measure)
- It may be beneficial to blind subjects and / or researchers to treatment assignment (avoid sources of bias)
- Variations of this design include crossover studies

Randomized Clinical Trials (RCTs)

- Situations favoring use of RCTs
  - Exposure status is modifiable (subjects willing to relinquish control)
  - Legitimate uncertainty exists about effect of alternative interventions (e.g., the study is ethical)
    - Reasonable to believe benefits of new treatment outweigh risks
  - Outcome of interest is reasonably common or effect of intervention on a rare outcome is important enough to justify a large study
- Factors to consider when recruiting / enrolling subjects
  - Potential for benefit and/or risks of interventions
  - Internal validity: Subjects who will be reliable and compliant
  - External validity: Do results generalize to the broader population?
  - Power enhancement: high risk subjects

Clinical Trial Examples

- GUSTO 1: 41,021 patients in 1081 hospitals in 15 countries present with acute MI



- P-value for tPA versus either Sk group 0.001
- Significantly higher hemorrhagic strokes in tPA versus Sk

Clinical Trials

- Advantages
  - Strong claims for causal effects
  - Optimal control over confounding factors
- Challenges
  - Very expensive
  - Time consuming
  - Ethical problems
  - Selection bias

Cohort Studies (Follow-up Studies)

- In a classical cohort study
  1. Study sample is identified...
  2. exposure group status at the beginning of the study period is measured...
  3. subjects are followed...
  4. outcome status at the end of the study period is determined...
- Compare outcome status among various exposure groups.
- Useful when clinical trials are infeasible
  - For ethical reasons (e.g., when an exposure is thought to be harmful)
  - When exposure cannot be controlled (e.g., smoking, drug use, diet)
- Frequently implemented when exposure is rare in the population
  - By selecting a group of people who experience exposure variation we are able to detect exposure effects

Cohort Studies

- Exposure not randomly assigned, only assessed
  - Minimize confounding through study sample selection and through analysis
- For this design to be useful, we need a sufficient number of subjects experiencing events
- Prospective cohort studies
  - Outcome events occur after study initiation
- Retrospective cohort studies
  - Outcomes have occurred by the time study is initiated
  - “Reconstruct” a prospective cohort study which has already occurred
  - Requires good exposure data on subjects at some time in the past

Cohort Studies Example

Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR; *COX-2 selective non-steroidal and anti-inflammatory drugs and risk of serious coronary heart disease*, The Lancet, 2002.

- Study sample: 50-84 year olds participating in TennCare from January 1999 through June 2001 with no life-threatening non-cardiovascular disease
  - $\approx$ 200,000 nonusers of NSAIDS
  - $\approx$ 24,000 Rofecoxib users
  - $\approx$ 150,000 other NSAIDs users
- Rate at which CHD occurred

	per 1000 person-years	Adjusted Relative Rate
Non-users of NSAIDS	13.0	1
High dose Rofecoxib users	21.0	1.70 (0.98-2.95; p=0.06)
New high dose Rofecoxib users	24.0	1.93 (1.09-3.42; p=0.02)

Cohort Studies

- Advantages
  - Efficient for rare exposures
  - Can study numerous outcomes / responses
  - Useful when clinical trials are infeasible
- Challenges
  - No control over risk factor
  - Not efficient for rare outcomes
  - Potential for loss to followup
  - Expensive relative to other observational studies

Case-Control Studies

- Subjects are identified based on disease (outcome) status and exposure status is assessed retrospectively
  - Cases - those with disease
  - Controls - those without disease
- In case-control studies we:
  1. Identify cases...
  2. Identify comparable controls...
  3. Retrospectively determine prior exposure in cases and controls...
- Control identification
  - Control group may be substantially different from cases
  - Must account for all differences between cases and controls that could explain the relationship between exposure and case status.

Case-Control Studies: The Control Group

- Function of the control group: to estimate the exposure that would have taken place in cases in the absence of an exposure-disease association.
  - Can the exposure-disease relationship be attributed to other differences between cases and controls?
- Sources of controls
  - Probability sample of non-cases from same population as cases
    - Cases: Females ≥ 50 years in TennCare with breast cancer (BC)
    - Controls: Random sample of females ≥ 50 in TennCare without BC
    - Such controls are best but such a design may be difficult and expensive
  - Hospital or clinic-based
    - Cases: Females ≥ 50 years seeking treatment at Vanderbilt for BC
    - Controls: Females ≥ 50 years seeking health care at Vanderbilt for non-BC related conditions
    - Challenge: May not be representative of study base (selection bias)

- Relatives, friends or neighbors
  * Controls: Women living in the same block as BC cases, siblings of BC cases
  * Challenge: may be overmatched on genetic / demographic / occupational / behavioral / environmental predictors

Case-Control Studies (cont.)

- Problems with exposure recall
  - Cases and controls may not report exposure precisely (guessing exposure leads to issues with measurement error)
  - Recall bias: potentially problematic if cases recall exposure differently than controls
    - Mother of a child with a birth defect may recall events that occurred during pregnancy that other mothers would not remember (e.g., respiratory infection)
- CC studies are most useful when
  - Disease is rare even among exposed subjects
  - Latency period from exposure to disease is very long

Case-Control Studies

- Advantages
  - Efficient for rare outcomes
  - Efficient for long latency periods
  - Can study numerous exposures
  - Optimal when cohort study is infeasible and RCT is unethical
- Challenges
  - Inefficient for rare exposures
  - Control identification
  - Confounding
  - Recall

Study Design Summary

- Randomized Clinical Trial
  - Optimal design for asserting a causal relationship between exposure and outcome
- Cohort Study when...
  - RCT is not possible or ethical
  - Exposure is rare
- Case-Control Study when...
  - Outcome is rare among all exposure groups
  - Biological latency period is long

Frequency Measures

Incidence

- A measure of new events
- Incidence Rate:
  - The rate of occurence of an outcome event
  - Number of events divided by person-time at risk of becoming diseased

$$IR = \frac{\text{\# new events}}{\text{person-time at risk}}$$

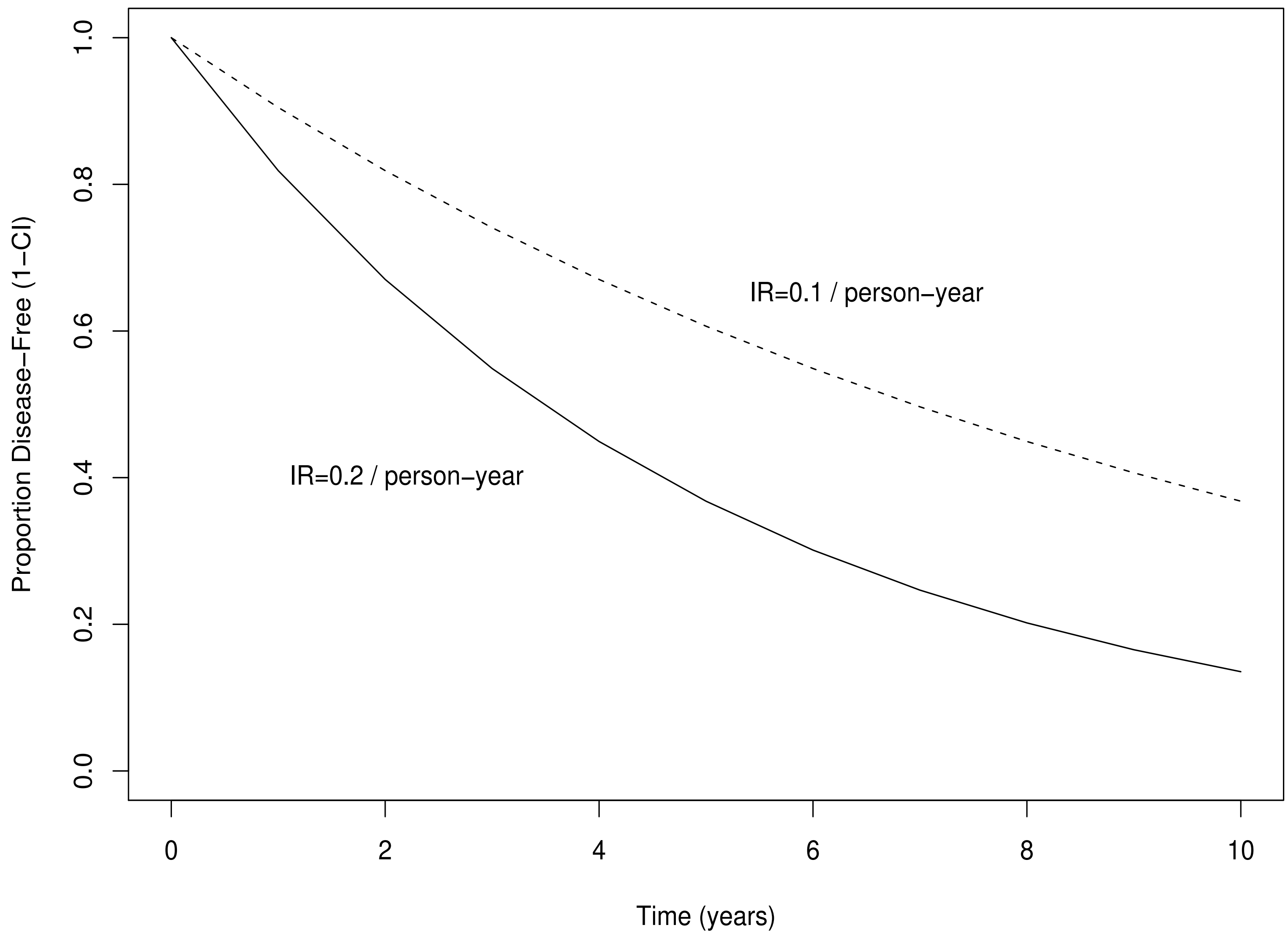
  - a.k.a., Incidence density
  - a.k.a., Hazard rate or force of morbidity (mortality) as person-time $\longrightarrow 0$.
  - For rare diseases *IR* is usually multiplied by some constant
    * In the UK the *IR* of prostate cancer is 74.3 per 100,000 men-years.

Incidence (cont.)

- Cumulative Incidence or Risk
  - Probability of a new event for individuals in a population over a specified time period

$$CI = \frac{\text{\# new events in a population}}{\text{size of population at risk}}$$

  - a.k.a., Incidence fraction
  - With CI time period is implicit, as opposed to IR where it is explicit
    - e.g., the longer the observation time, the greater the risk
- Note: Constant IR implies non-constant increases in (additive) risk over time



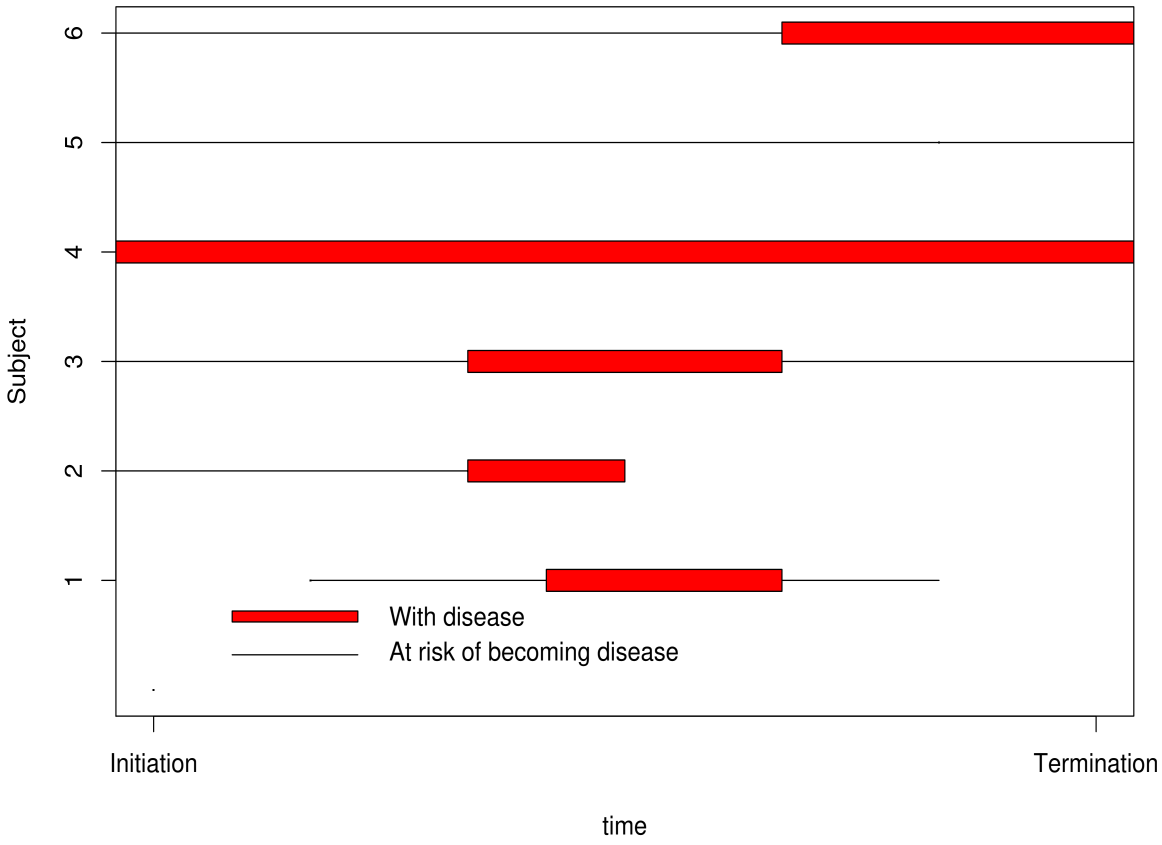
1.0
0.8
0.6
0.4
0.2
0.0
Proportion Disease−Free (1−CI)
IR=0.1 / person−year
IR=0.2 / person−year
0
2
4
6
8
10
Time (years)

Prevalence

- A measure of status
- Proportion of the population with disease at a given time point

$$\text{Prevalence} = \frac{\text{\# existing cases}}{\text{population at risk of having disease}}$$

- Prevalence per 1000 = Prevalence $\times$ 1,000
- Point prevalence:
  - Denominator is the population at risk at a given point in time
- Period prevalence:
  - Numerator is the number of people who had disease at any point during the observation period
  - Denominator is the population at risk (usually) at the midpoint of the observation time
- Effected by: Immigration, emigration, birth, death, and length of disease



- Point prevalence at initiation:
- Period prevalence:
- CI:
- IR: $\dfrac{}{\text{total person-time at risk of becoming diseased}}$

Measures of Association

Measures of Association

- Risk (R): probability than an event will occur in an individual during the observation period
  - We generally use the observed CI to estimate R
    * CI is actually an estimate of average R
  - $R_{\overline{E}}$: risk for an individual in the unexposed group
  - R_E: risk for an individual in exposed group
- Relative Risk (RR): Ratio of the risk of an event among those who are exposed to E to the risk among those who are not exposed to E

$$RR = R_E / R_{\overline{E}}.$$

  - a.k.a., risk ratio
  - Multiplicative measure of excess risk (e.g. a “fold increase”)
  - Rate ratio if interested in IR not CI (Vioxx study presented earlier)

Measures of Association

- Risk Difference, Absolute Risk Reduction, Attributable Risk (AR): Difference in risk between exposed and unexposed subjects

$$AR = R_E - R_{\overline{E}}$$

  - A measure of the (absolute) reduction in risk that would occur in the exposed group if exposure is removed

- Relative Risk Reduction, Attributable Risk Percent (AR$\%$): Percentage of disease in exposed individuals caused by (??) exposure

$$AR\% = 100 \times (R_E - R_{\overline{E}})/R_E.$$

  - A measure of $\%$ reduction in risk of disease for exposed subjects if exposure is removed

Smoking and CHD: A Hypothetical Cohort Study of 3,000 Smokers and 5,000 Non-Smokers with 2 years of followup

	Develop CHD	Do Not Develop CHD	Total
Smoke	84	2,916	3,000
Do Not Smoke	87	4,913	5,000

- Risk among smokers: $R_S = \frac{84}{3000} = 0.028$ or 28 per 1000
- Risk among non-smokers: $R_{NS} = \frac{87}{5000} = 0.0174$ or 17.4 per 1000
- Relative risk: $RR = \frac{0.028}{0.0174} \approx 1.61$
- Attributable Risk: $AR = 0.028 - 0.0174 = 0.0106$ or 10.6 per 1000
- Attributable Risk Percent: $AR\% = 100 \times (0.028 - 0.174)/0.028 \approx 38\%$

Interpretations: Additive versus Multiplicative Effects

- $RR > 1 \Leftrightarrow AR > 0$: Exposed subjects are more likely to experience the outcome than unexposed subjects
- AR vs. RR
  - AR is a measure of the additive excess risk due to exposure
    - Easily translated directly into $\$$
    - Answers public health questions directly
  - RR is a measure of multiplicative excess risk due to exposure
- Relationship between these measures and the relevance of each depends upon baseline risk (e.g., the risk among unexposed subjects)

$$AR = R_E - R_{\overline{E}} = RR \times R_{\overline{E}} - R_{\overline{E}} = R_{\overline{E}} \times (RR - 1)$$

Example: Impact of Baseline Risk on Measures of Excess Risk

	Scenario 1	Scenario 2	Scenario 3
$R_{\overline{E}}$	$\frac{50}{1000} = 0.05$	$\frac{200}{1000} = 0.2$	$\frac{2}{1000} = 0.002$
R_E	$\frac{150}{1000} = 0.15$	$\frac{300}{1000} = 0.3$	$\frac{3}{1000} = 0.003$
RR	$\frac{0.15}{0.05} = 3$	$\frac{0.3}{0.2} = 1.5$	$\frac{0.003}{0.002} = 1.5$
AR%	$100\frac{(0.15-0.05)}{0.15} = 67$	$100\frac{(0.3-0.2)}{0.3} = 33$	$100\frac{0.003-0.002}{0.003} = 33$
AR	$0.15 - 0.05 = 0.1$	$0.3 - 0.2 = 0.1$	$0.003 - 0.002 = 0.001$
NNT	$\frac{1}{0.1} = 10$	$\frac{1}{0.1} = 10$	$\frac{1}{0.001} = 1000$

GUSTO 1

Treatment Group	30-day Mortality	AR	RR
Sk + SubC Hep	7.4%	0	1
SK + IV Hep	7.2%	-0.2	0.97
tPA + IV Hep	6.3%	-1.1	0.85
tPA + Sk + IV Hep	7.0%	-0.4	0.95

Reference group is Sk + SubC Hep

The Odds Ratio

- Odds: The probability that an event occurs divided by the probability that it does not occur
- Odds of disease for those exposed to E

$$Odds_{D|E} = \frac{P(D|E)}{P(\overline{D}|E)} \equiv \frac{p_E}{1 - p_E}$$

- Odds of disease for those **NOT** exposed to E

$$Odds_{D|\overline{E}} = \frac{P(D|\overline{E})}{P(\overline{D}|\overline{E})} \equiv \frac{p_{\overline{E}}}{1 - p_{\overline{E}}}$$

- Odds ratio of disease from exposure E: Odds of disease for those exposed to E divided by the odds of disease for those **NOT** exposed to E

$$OR_{D|E} = \frac{p_E}{1 - p_E} \Bigg/ \frac{p_{\overline{E}}}{1 - p_{\overline{E}}}$$

The Odds Ratio

	D	$\overline{D}$	Total
E	A	B	A+B
$\overline{E}$	C	D	C+D
Total	A+C	B+D	A+B+C+D

$$P(D|E) = \frac{A}{A+B} = \frac{P(D \text{ and } E)}{P(E)}$$

- $Odds_{D|E} = \frac{A/(A+B)}{B/(A+B)} = \frac{A}{B}$
- $Odds_{D|\overline{E}} = \frac{C/(C+D)}{D/(C+D)} = \frac{C}{D}$
- $OR_{D|E} = \frac{A}{B} / \frac{C}{D} = \frac{A \cdot D}{B \cdot C}$
- $OR_{E|D} = \frac{A}{C} / \frac{B}{D} = \frac{A \cdot D}{B \cdot C}$

Key Mathematical Property of the Odds Ratio

- Reversibility
- This property comes from the Bayes' Theorem:

$$P(X|Y) = \frac{P(Y \text{ and } X)}{P(Y)} = \frac{P(Y|X) \cdot P(X)}{P(Y)}$$

- Applied to the disease - exposure model:

$$OR_{D|E} = \frac{\frac{P(D|E)}{P(\overline{D}|E)}}{\frac{P(D|\overline{E})}{P(\overline{D}|\overline{E})}} = \underbrace{\frac{P(D|E)}{P(\overline{D}|E)} \cdot \frac{P(\overline{D}|\overline{E})}{P(D|\overline{E})}}_{\text{Apply Bayes now}}$$

$$= \frac{P(E|D)}{P(\overline{E}|D)} \cdot \frac{P(\overline{E}|\overline{D})}{P(E|\overline{D})} = OR_{E|D}$$

- Makes evaluation of case-control studies possible
- More transportable than RR (RR=2 can only apply if $p_{\overline{E}} \leq 0.5$)

Odds Ratio and Case-Control Studies

- In CC studies, we collect information retrospectively but analyze it as if data were collected prospectively
- Possible because logistic regression use to analyze case-control data

$$I(Exposed) = \begin{cases} 1 & \text{Exposed} \\ 0 & \text{Not Exposed} \end{cases}$$

$$\begin{aligned} log\left(\frac{p}{1-p}\right) =& \beta_0 + \beta_1 \cdot I(Exposed) + \text{confounders} \\ \Rightarrow \beta_1 =& log\left(\frac{p_E}{1-p_E}\right) - log\left(\frac{p_{\overline{E}}}{1-p_{\overline{E}}}\right) = log\left[\frac{p_E}{1-p_E} \Big/ \frac{p_{\overline{E}}}{1-p_{\overline{E}}}\right] \\ \Rightarrow e^{\beta_1} =& \frac{p_E}{1-p_E} \Big/ \frac{p_{\overline{E}}}{1-p_{\overline{E}}} \end{aligned}$$

- Since our responses are (log) odds ratios, we can make prospective inference with a retrospective study
- What is β_0 in CC studies?

OR (RR) as an estimate of RR (OR) in Rare Diseases

	Diseased	Total
Exposed	50	10,000
Not Exposed	20	10,000

- $R_E = \frac{50}{10{,}000} = 0.005$
- $R_{\overline{E}} = \frac{20}{10{,}000} = 0.002 \Rightarrow RR = 2.5$
- $Odds_{D|E} = \frac{50}{9{,}950} \approx 0.005$
- $Odds_{D|\overline{E}} = \frac{20}{9{,}980} \approx 0.002 \Rightarrow OR \approx 2.5$
- $OR \approx RR$
- OR commonly called RR with rare diseases, but unlike RR, OR is valid for the entire risk spectrum

Correlation ρ

- A measure of the **linear** association between two continuous random variables X and Y

$$\rho = \frac{E\left[(X - E(X)) \times (Y - E(Y))\right]}{\sqrt{Var(X) \times Var(Y)}}$$

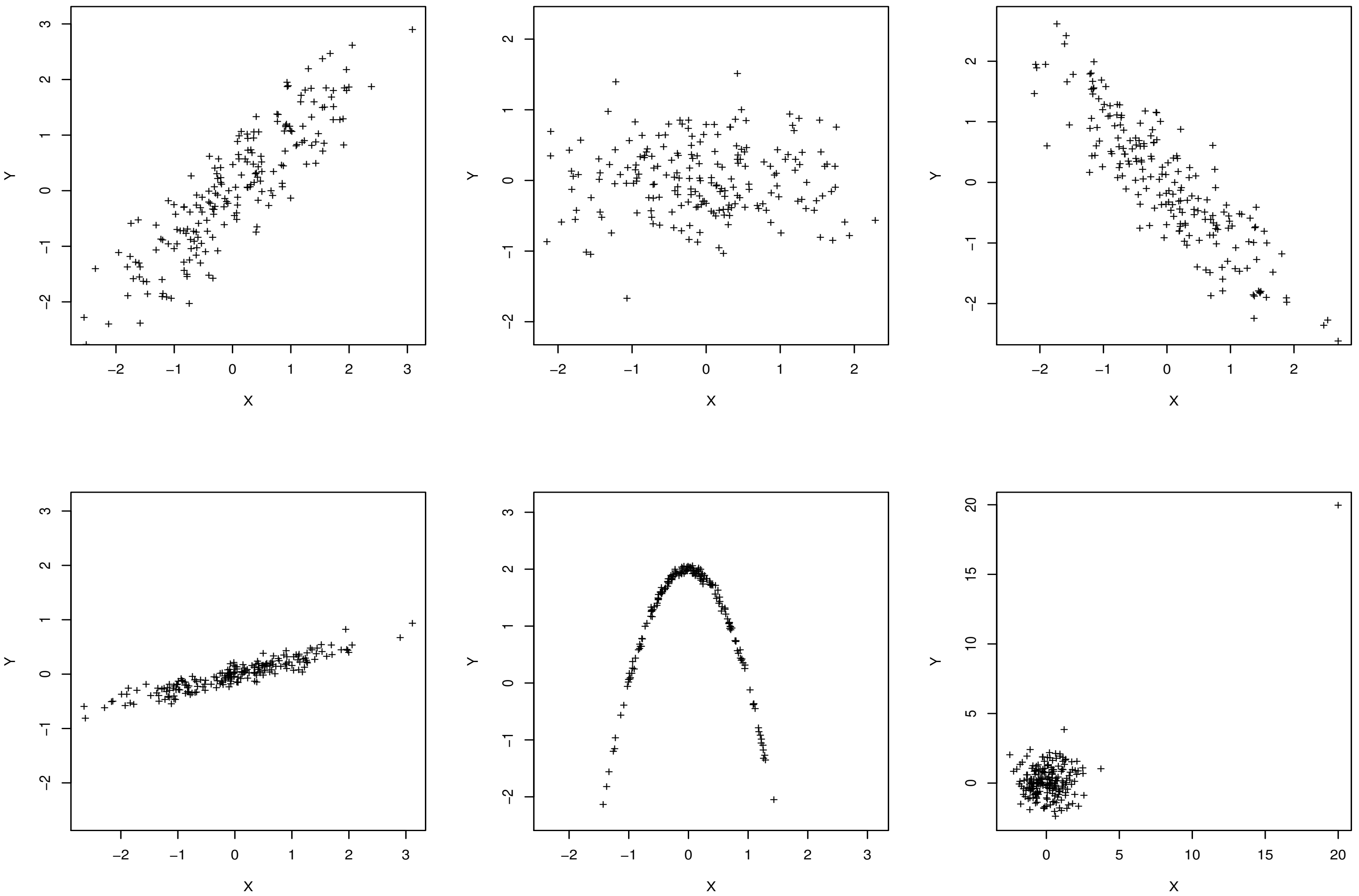
- Estimated with the Pearson correlation coefficient

$$r = \frac{\sum_{i=1}^{N}(x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum_{i=1}^{N}(x_i - \overline{x})^2 \cdot \sum_{i=1}^{N}(y_i - \overline{y})^2}}$$

- $-1 \leq \rho \leq 1$

- Simple linear regression model

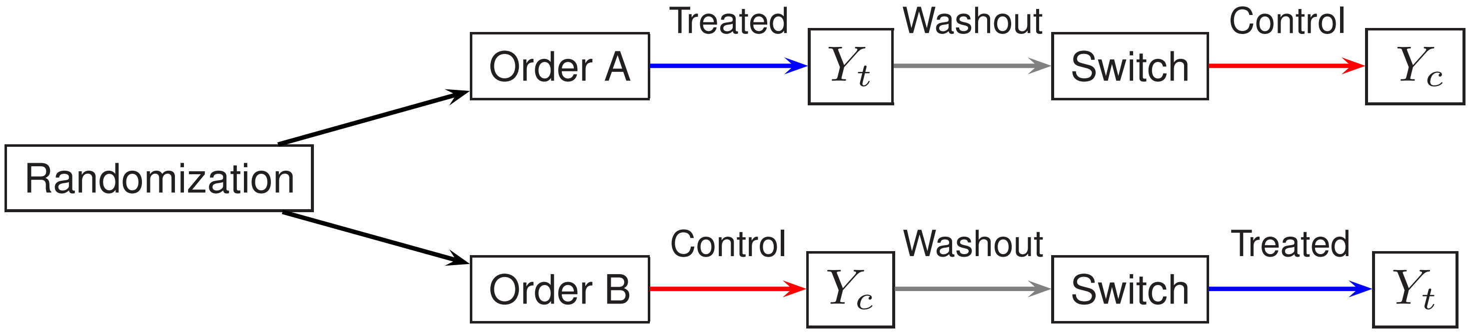
$$E(Y|X) = \beta_0 + \beta_1 X = \beta_0 + \frac{\rho\sqrt{Var(Y)}}{\sqrt{Var(X)}} \times X$$



X
Y

Analysis of Paired Observations

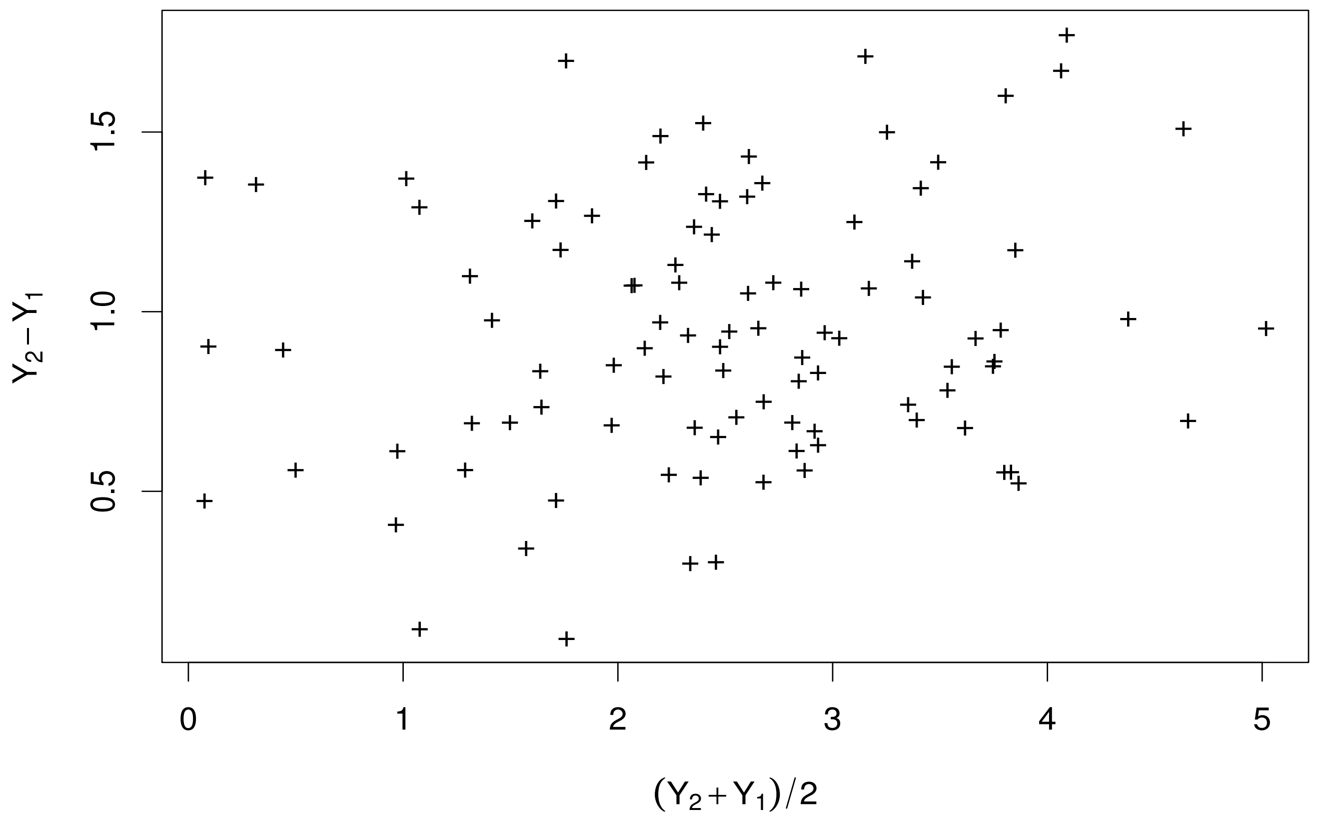
- In many types of experiments we measure multiple observations on an individual
- Pre-post Analysis
  - A baseline (pre-treatment) measurement is observed, treatment is administered, a followup (post-treatment) is observed
- Cross-over Clinical Trial
  - Subjects are randomized to a treatment order



Paired Data: Choosing an Effect Measure

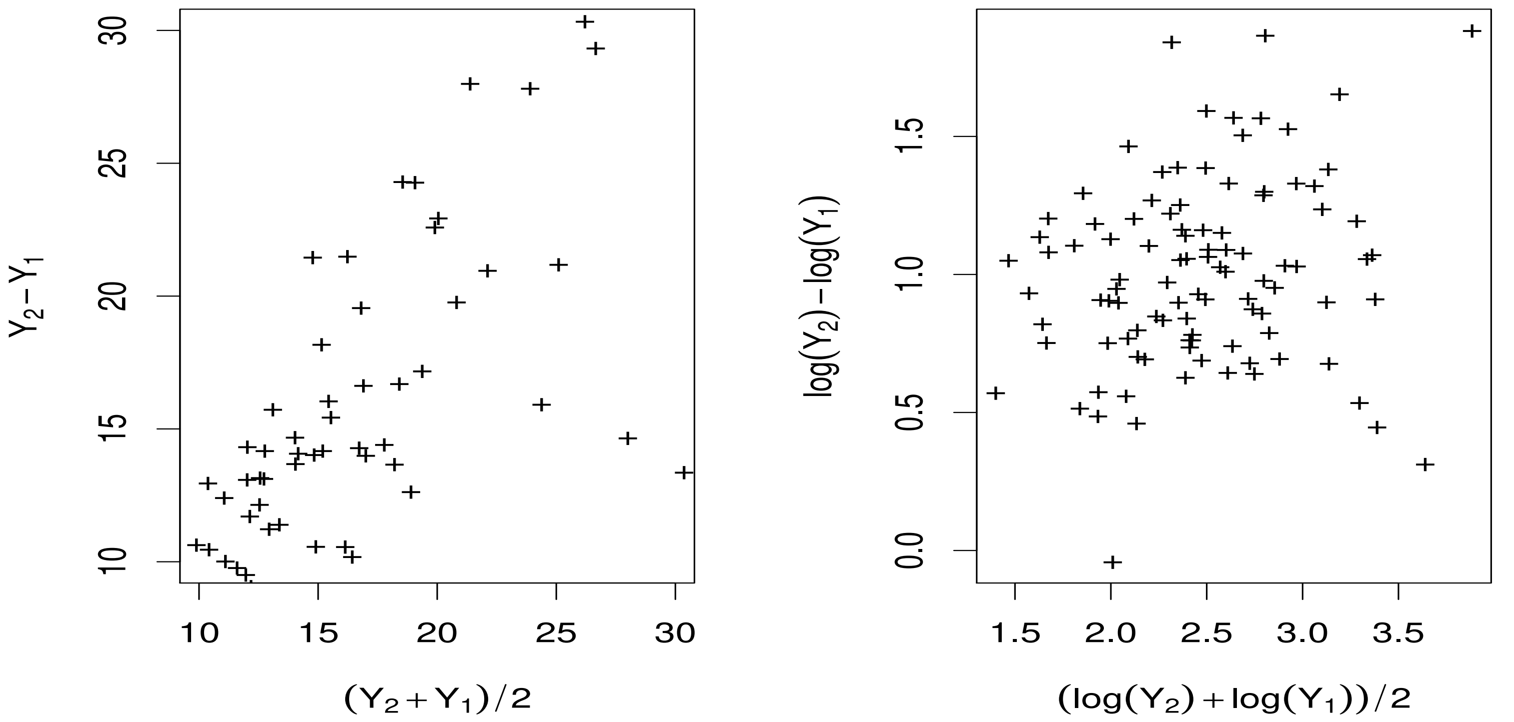
- Additive vs. multiplicative effects
- Key consideration: Effect of treatment should not depend on the baseline value
- Objective method for choosing an effect measure with paired data
- Plot $(Y_2 + Y_1)/2$ vs $Y_2 - Y_1$
  - If there is no trend between the average (or baseline) value and the difference, then the treatment effect does not depend on the baseline value and use the difference as an effect measure
  - If you see trends consider a transformation

Paired Data: Scenario 1



- Consider testing $H_0 : median(Y_2 - Y_1) = 0$ using a Wilcoxon signed-rank test

Paired Data: Scenario 2



- Consider a test such as $H_0 : median\,[log(Y_2) - log(Y_1)] = 0$ using a Wilcoxon signed-rank test
- Note: $med\,(log(Y_2) - log(Y_1)) \equiv med\left[log\left(\frac{Y_2}{Y_1}\right)\right] \equiv log\left[med\left(\frac{Y_2}{Y_1}\right)\right]$

Review

- Study design
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