Understanding and Evaluating Quantitative Research

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What is a Hypothesis?

- Quantitative
- Testable
- Needs a change in outcome
  - OR a comparison
  - OR both

What are Outcomes?

- Primary
- Secondary
- Composite
- Patient Centred Outcomes

Patient Population, Eligibility Criteria

- Patient Population
  - Every Study is a sample of a population vs Study is a collection of data
  - Effect size same but P value different
  - Generalisability
- Inclusion Criteria
- Exclusion Criteria
- Internal Validity

What is an Randomised Control Trial?

- Balancing Confounders
- Treatment A vs Best Practice (Not Placebo)
- Non-Inferiority
- Equivalence
- Crossover
- Factorial
- Multiple Arms
- Pragmatic

Randomisation Techniques

- Simple
- Fixed
- Blocking
- Stratified
- Adaptive

Sample Size

- Detectable Effect Size
- Alpha
- Power (1-Beta)
- Cross Over Rates
- Drop Out Rates
- Non-Compliance

Hypothesis Testing

- Null Hypothesis
- Alternative Hypothesis
- Alpha
- Beta
- Type 1 Error
- Type 2 Error

HYPOTHESIS TESTING OUTCOMES

Research	Reality: The Null Hypothesis Is True	Reality: The Alternative Hypothesis is True
The Null Hypothesis Is True	Accurate $1 - \alpha$	Type II Error β
The Alternative Hypothesis is True	Type I Error α	Accurate $1 - \beta$

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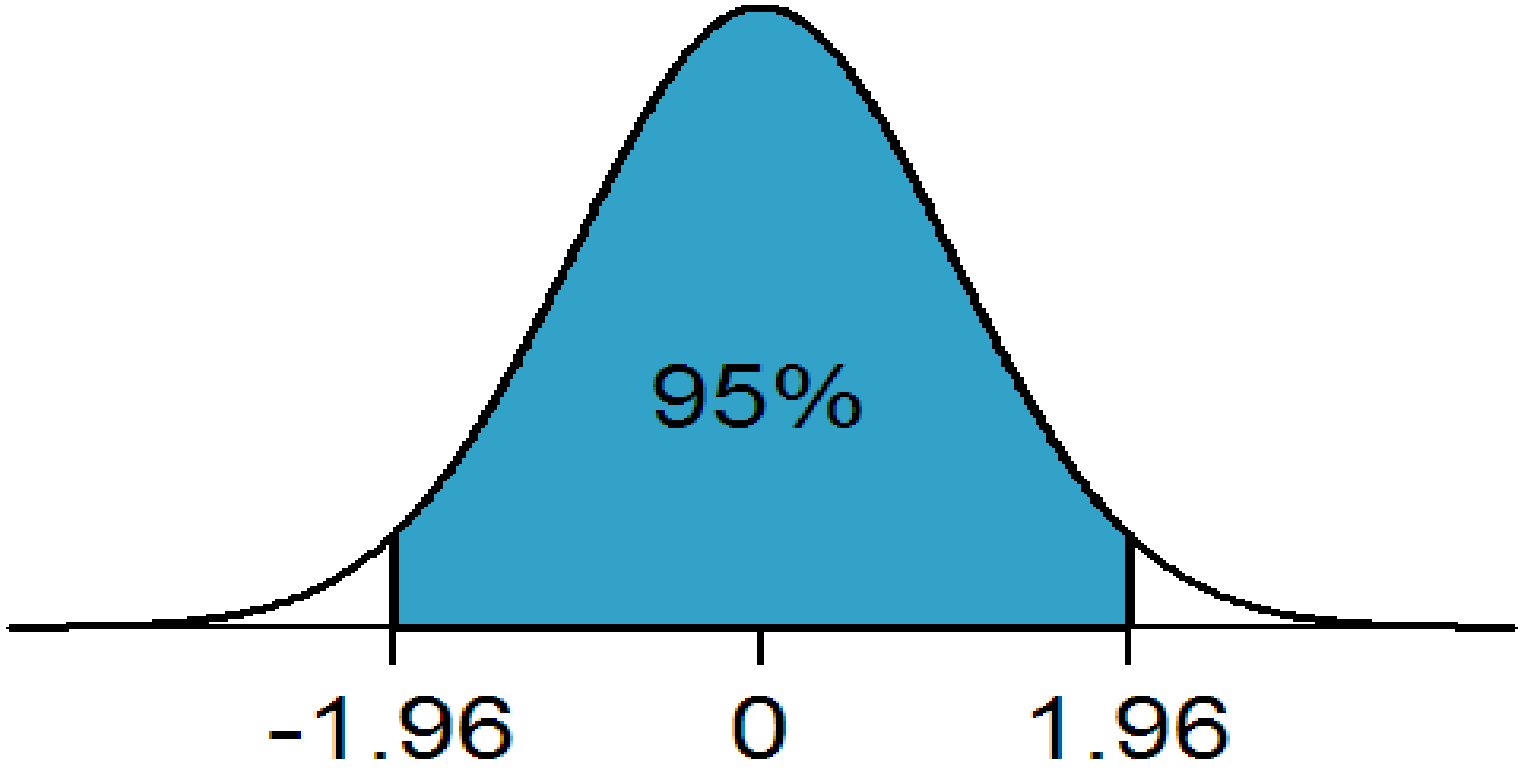
Source: http://allpsych.com/researchmethods/errors/

P Value and 95% Confidence Interval



http://en.wikipedia.org/wiki/1.96

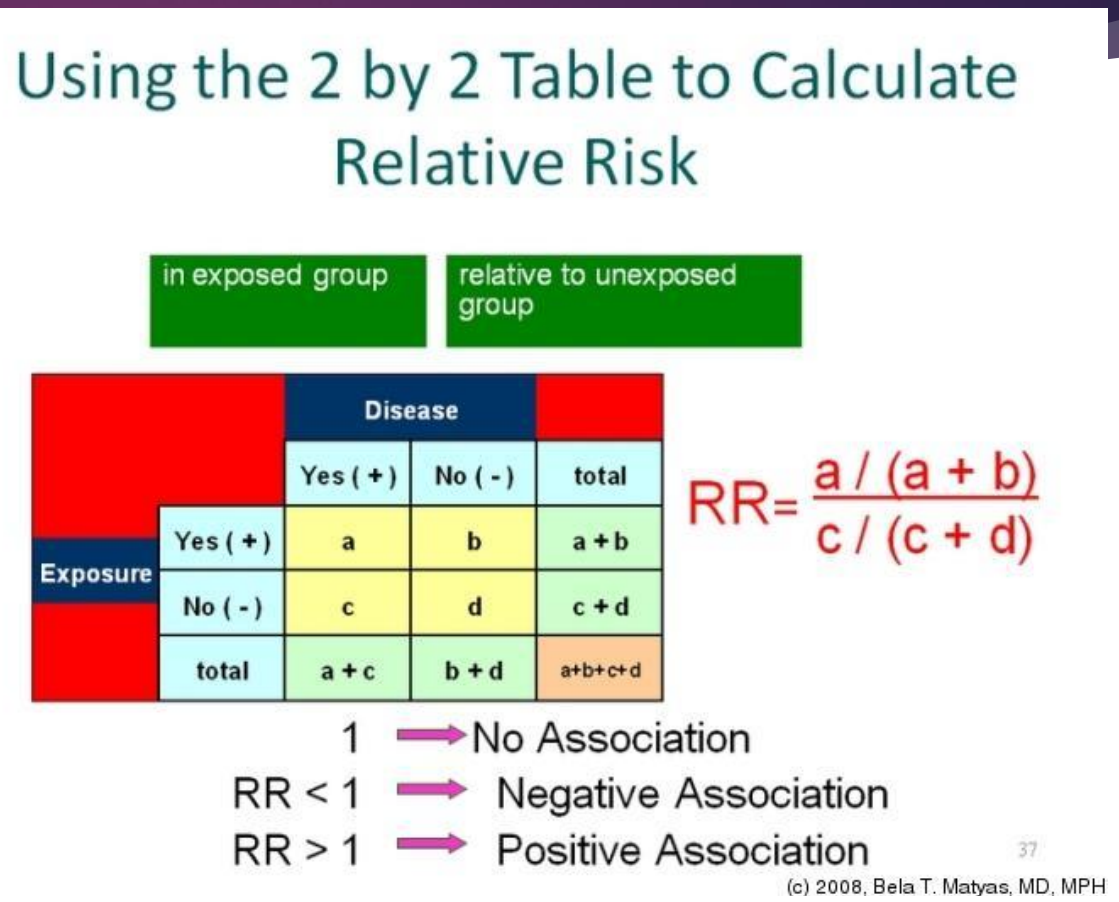
Analysing Trial Data

- Who to Include, who not to include?
- Intention to Treat
- As Treated
- Per Protocol

Study Designs – Cross sectional

Study Designs – Cohort

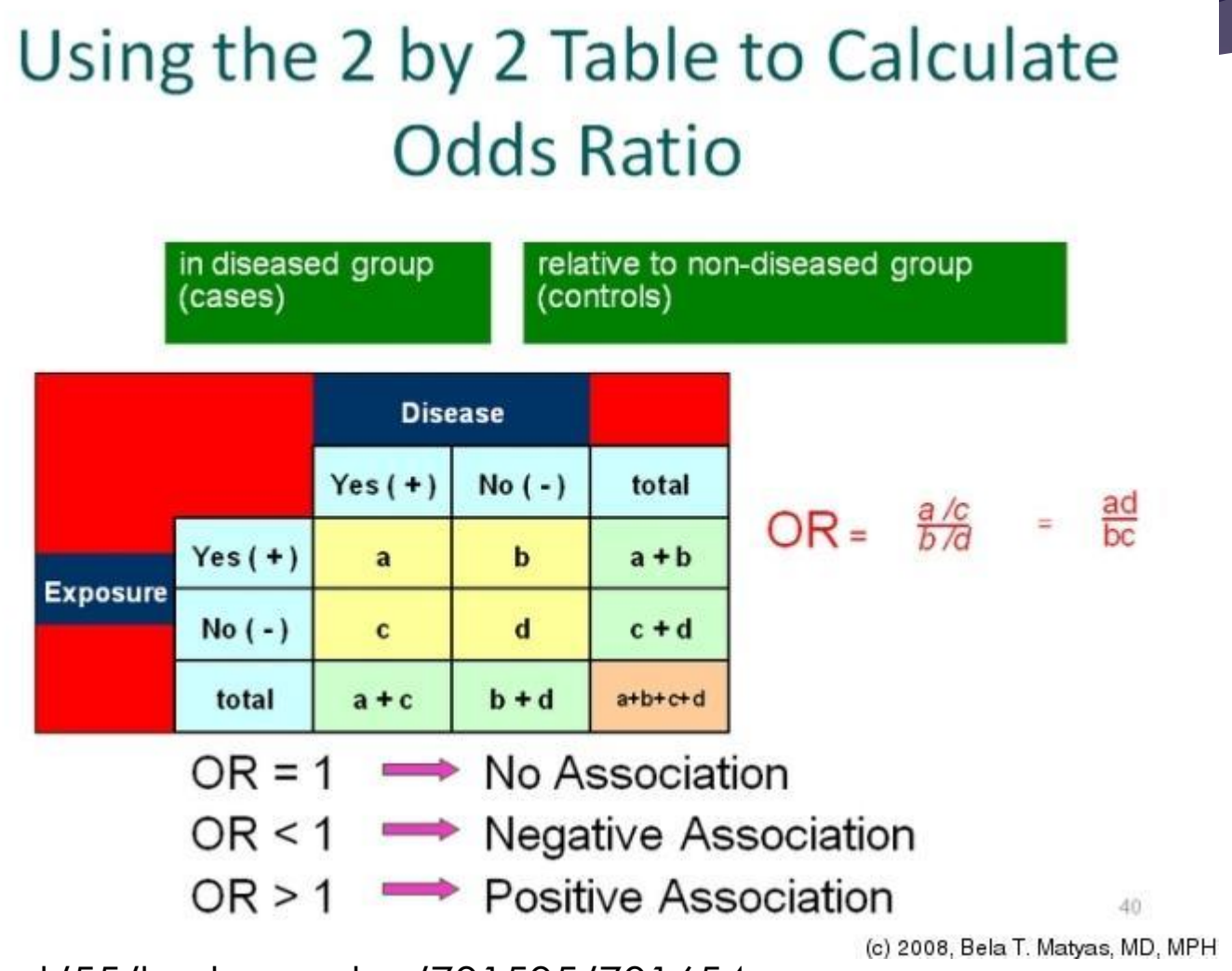
- Uses Relative Risk



Source: http://ocw.tufts.edu/Content/55/lecturenotes/701505/701650

Study Design – Case Control

- Use for rare cases.
- Use Odds Ratio



Source: http://ocw.tufts.edu/Content/55/lecturenotes/701505/701654

Odds Ratio vs Relative Risk

- RR is more fashionable as it is simpler to understand.
- The wording:
- RR – Smoking is 10 times more likely to kill you.
- OR – The odds of dying is 10 times higher in smokers than non-smokers.
- Nested Case Controls can be used to calculate RR.
  - Using the control as a case once they develop the disease.

How does the Data Look (OR/RR)?

- Death Smoker

1	1
1	0
1	1
0	0
0	0
0	1

Linear Regression – Coefficient

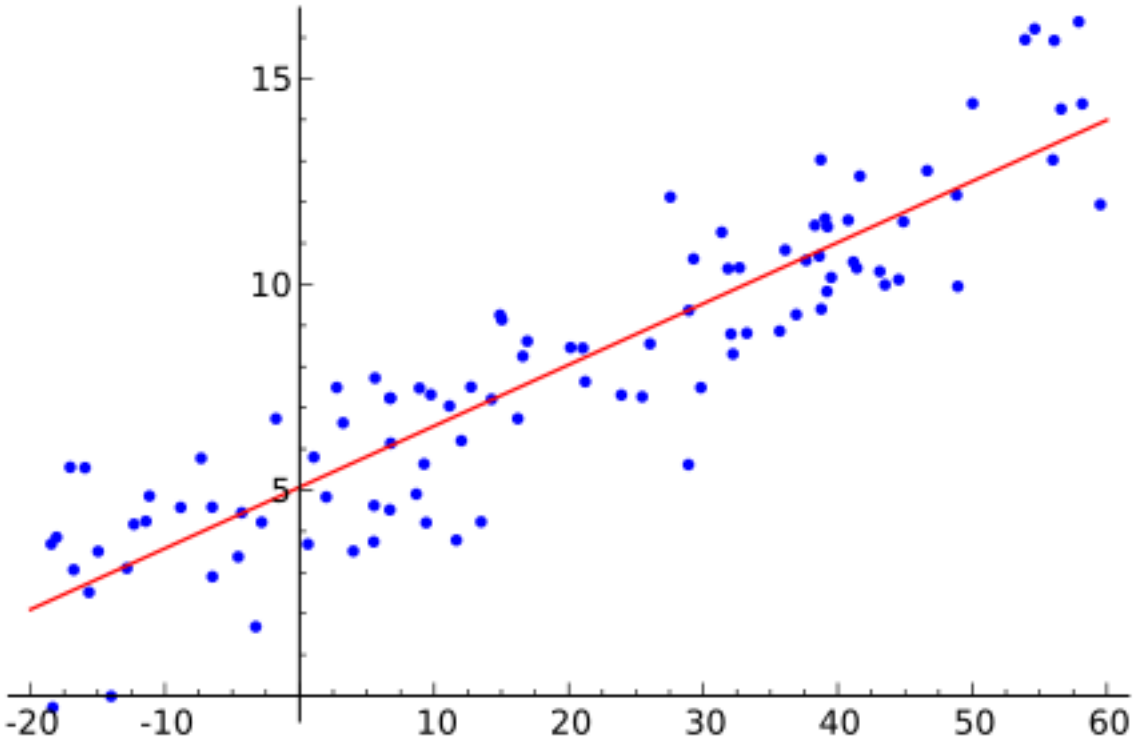
- Useful in Snapshots, should not be used in measurements with repeated data.

Y = mx+ b

What is b and What is m?

Assumptions

1. Y has to be normally distributed.
2. Linear Relationship
3. Spread of Errors is constant
   (residual vs predicted)

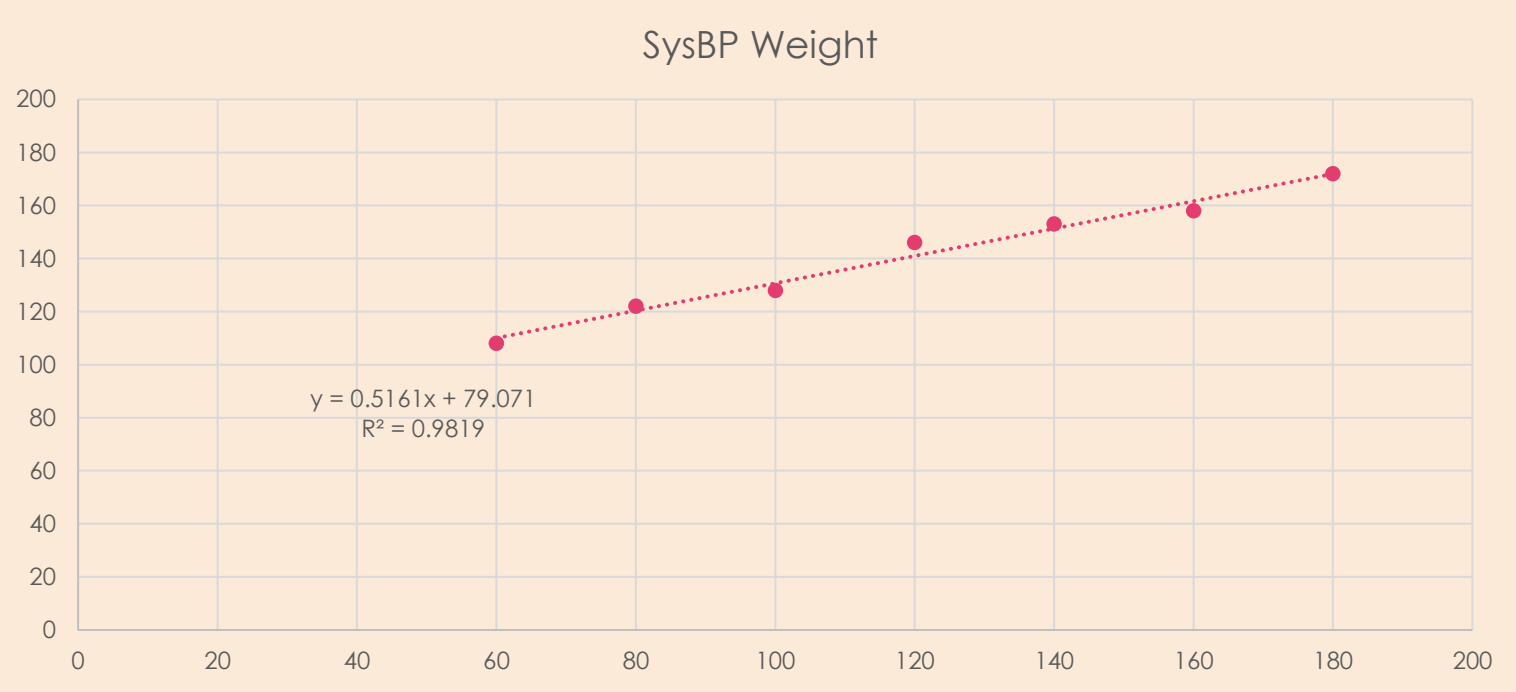


How does the Data Look (Linear Regression)?

SysBP(y)	Weight(x)
108	60
122	80
128	100
146	120
153	140
158	160
172	180

$y = 0.5161x + 79.071$

$R^2 = 0.9819$



Poisson Regression – Incidence Rate Ratio

- The outcome is a rate.
- Usually the number of events for a given time period (eg Incidence)
- It can be any rate.
- If Annual Incidence, then the exposure relates to events happening that year.

<u>Assumption</u>

1. Two rates of different time intervals should be independent
2. Over-dispersion (if so use negative binomial model)

   (Variance fitted by model > Variance of Observed Rate)

How does the Data Look (Poisson)?

Example

Year	STI Notification Rate	Percent of Youth aged 15-24
2000	6/100,000	10%
2001	10/100,000	12%
2002	14/100,000	14%
2003	20/100,000	15%
2004	30/100,000	16%
2005	35/100,000	20%

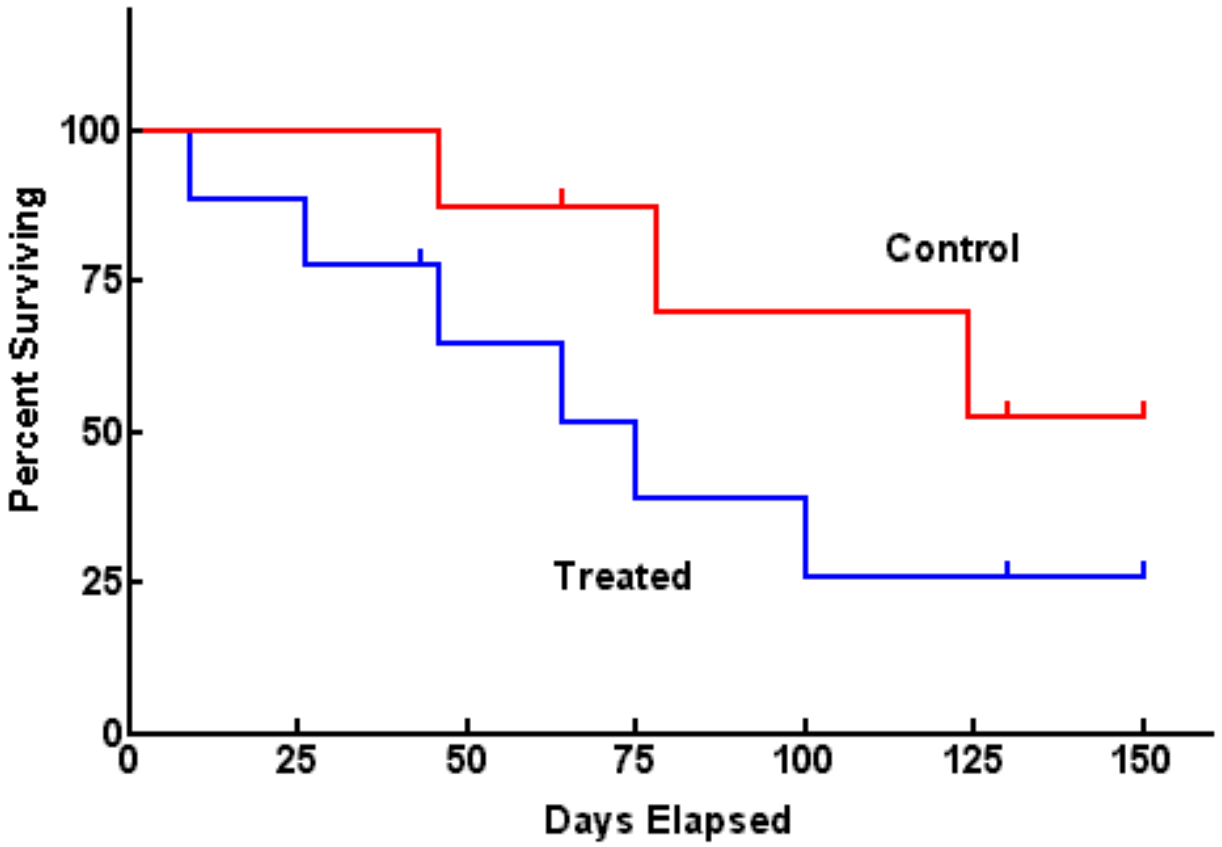
- STI notification rate (per 100,000) per year in WA ***(Outcome)***
- Percent of WA aged between 15-24 in *that year.*
- ***Effect Size: Incidence Rate Ratio. For each extra percent increase in youth there is 10% increase in STI notification rate.***

Survival Analysis

- Modelling Time to Event *Hazard Ratio is just like Relative Risk*
  - Time to Death (Survival)
  - Time to recurrence of Cancer
  - Time to heart attack
  - Time to hospitalisation (Recurrent Event)
  - Time to getting Cancer, independent of dying from something else (Competing Risk)
- Assumption:
  - Proportional Hazards: The Hazard Ratio or Relative Risk of a smoker's risk of dying from cancer to a non-smoker's risk of dying from cancer does not change over time.

Survival Analysis – How does the data look like?

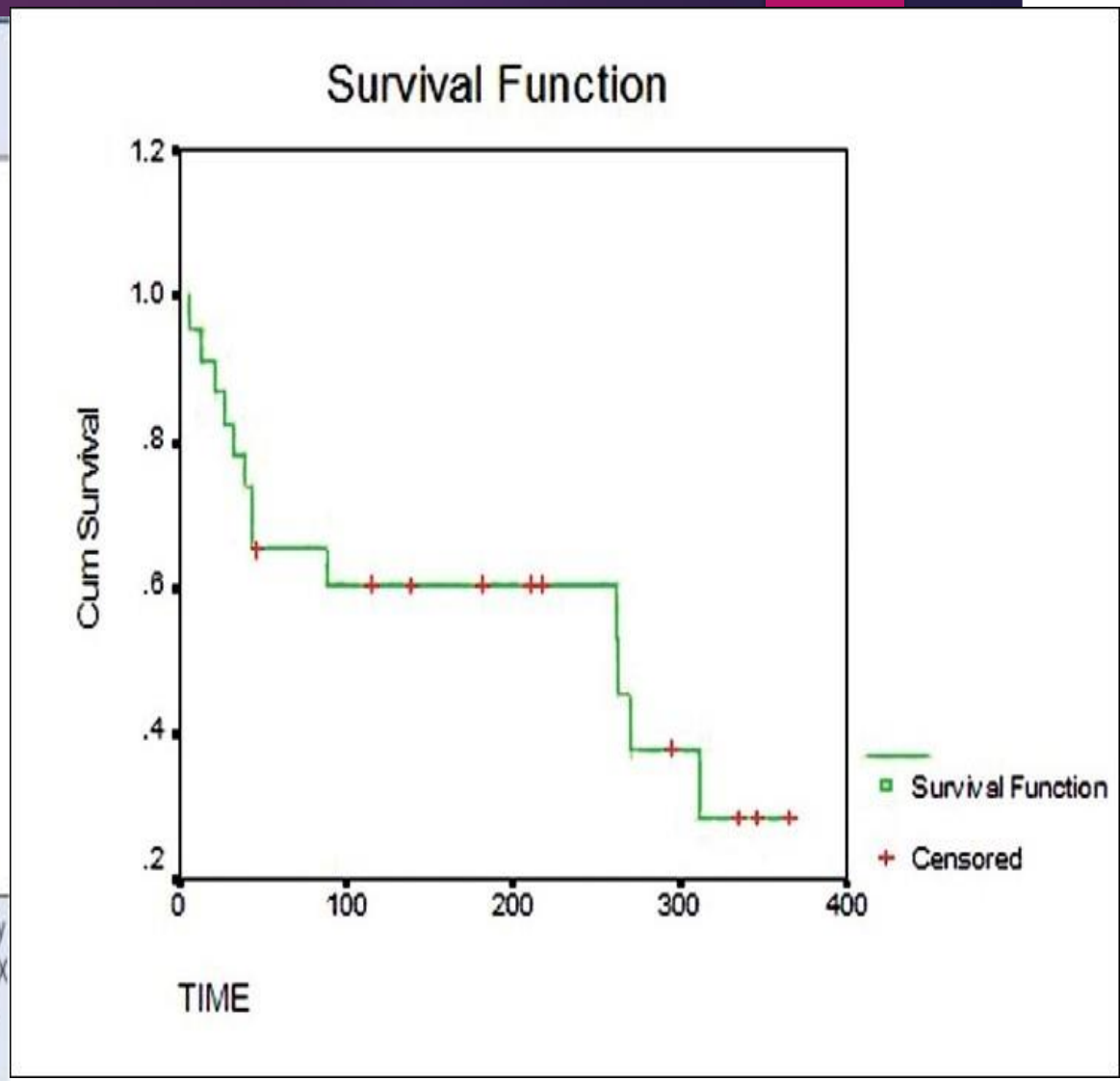
Followup time	Death	ACE Inhibitor
20	1	1
15	1	0
10	0	0
18	1	1
5	0	1
10	1	0
4	0	0
25	1	1



Kaplan Meier Curve

Time of event (t)	No. of Pt. died (d)	Live at the start of the day (n)	Estimated probability		Probability of survivors at the end of time (L)
			death (d/n)	survival (1 - d/n)	
6	1	23	0.0435	0.9565	0.9565
12	1	22	0.0455	0.9545	0.9565 × 0.9545 = 0.9130
21	1	21	0.0476	0.9524	0.9130 × 0.9523 = 0.8695
27	1	20	0.0500	0.9500	0.8695 × 0.9500 = 0.8260
32	1	19	0.0526	0.9474	0.7826
39	1	18	0.0556	0.9444	0.7391
43	2	17	0.1176	0.8824	0.6522
89	1	14	0.0714	0.9286	0.6056
261	1	8	0.125	0.875	0.5299
263	1	7	0.1429	0.8571	0.4542
270	1	6	0.1667	0.8333	0.3785
311	1	4	0.25	0.75	0.2839

The time 't' for which the value of 'L' i.e. total probability of survival at the end of a particular time is 0.50 is called as median survival time. The estimates obtained are invariably expressed in graphical form. The graph plotted between estimated survival probabilities/estimated survival percentages (on Y axis) and time past after entry into the study (on X axis) consists of horizontal and vertical lines.[4] The survival curve is drawn as a step function: the proportion surviving remains unchanged between the events, even if there are some intermediate censored observations. It is incorrect to join the calculated points by sloping lines (Figure 1).



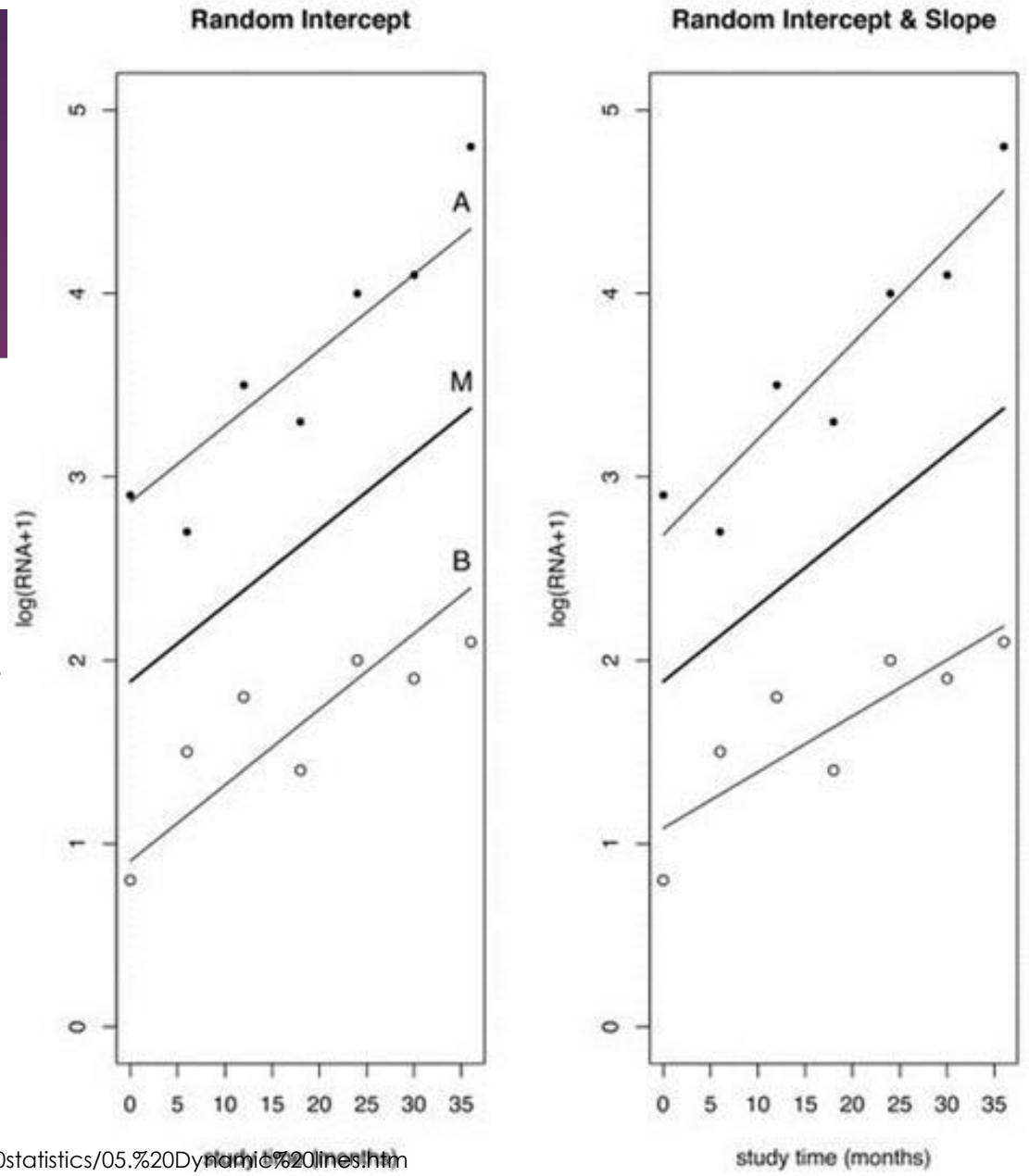
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059453/

Correlated Data and Longitudinal Data (Data over Time) -

- Errors not independent
- Marginal Models (Specifying how the errors correlate and accounting for them via a variance-covariance matrix)
- Random Effects and Fixed Effects
- Multilevel Modelling
- Similar coefficients to linear regression but different P values as there is increased error if errors are not independent.

Random Effects

- Fixed Effects is the difference in Effects between the treatment Groups over time.
- Random Effects is the difference i Effects within an individual over time.
  - Random Intercept
  - Random Intercept and Slope



Source: http://intranet.tdmu.edu.ua/data/kafedra/internal/distance/classes_stud/English/1course/Medical%20statistics/05.%20Dynamic%20lines.htm

Multilevel Modelling

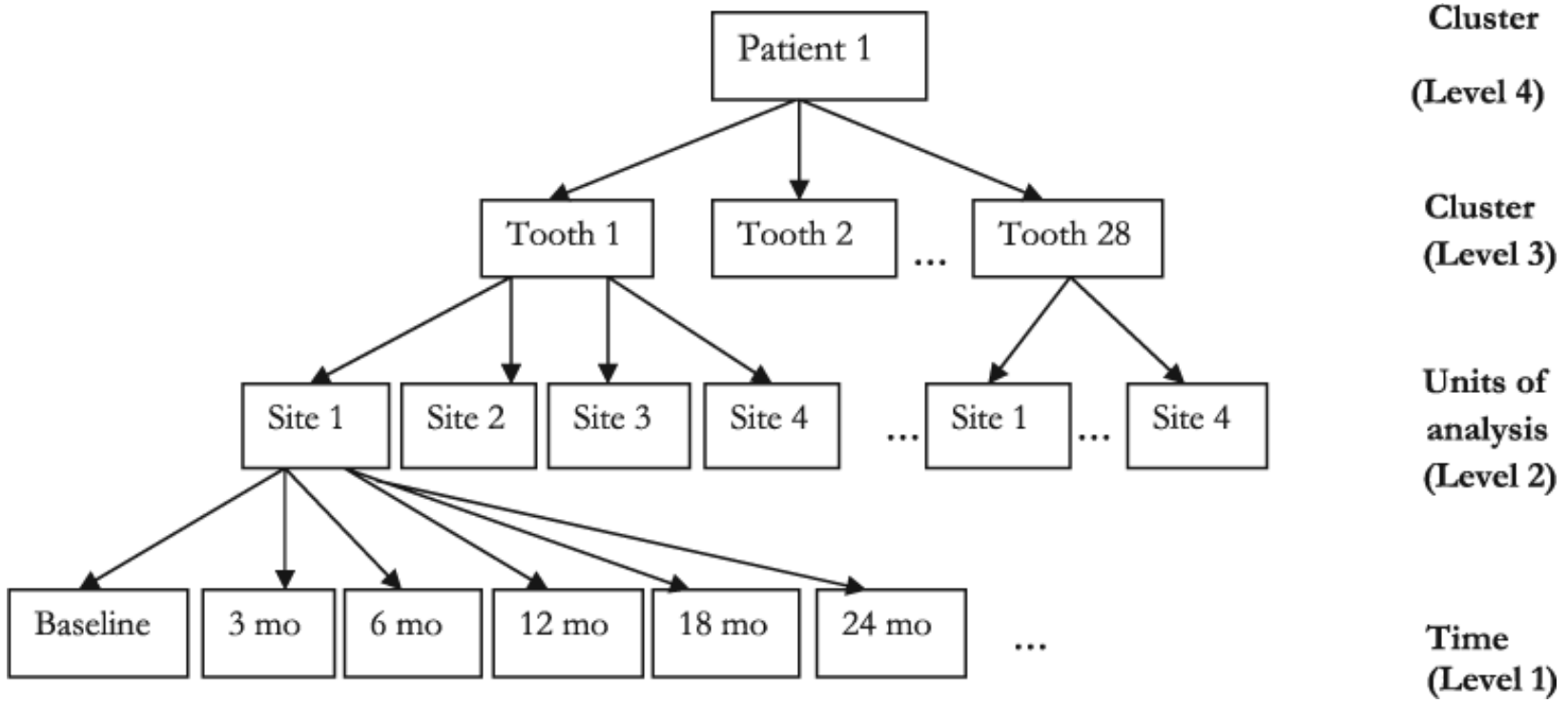
Patient followed up over time

with in a Postcode

within a town

with in a region

within a state.



Source: http://www.journaloforalmicrobiology.net/index.php/jom/article/view/17535

The three types of Bias

- Selection Bias
- Measurement or Misclassification Bias
- Confounding

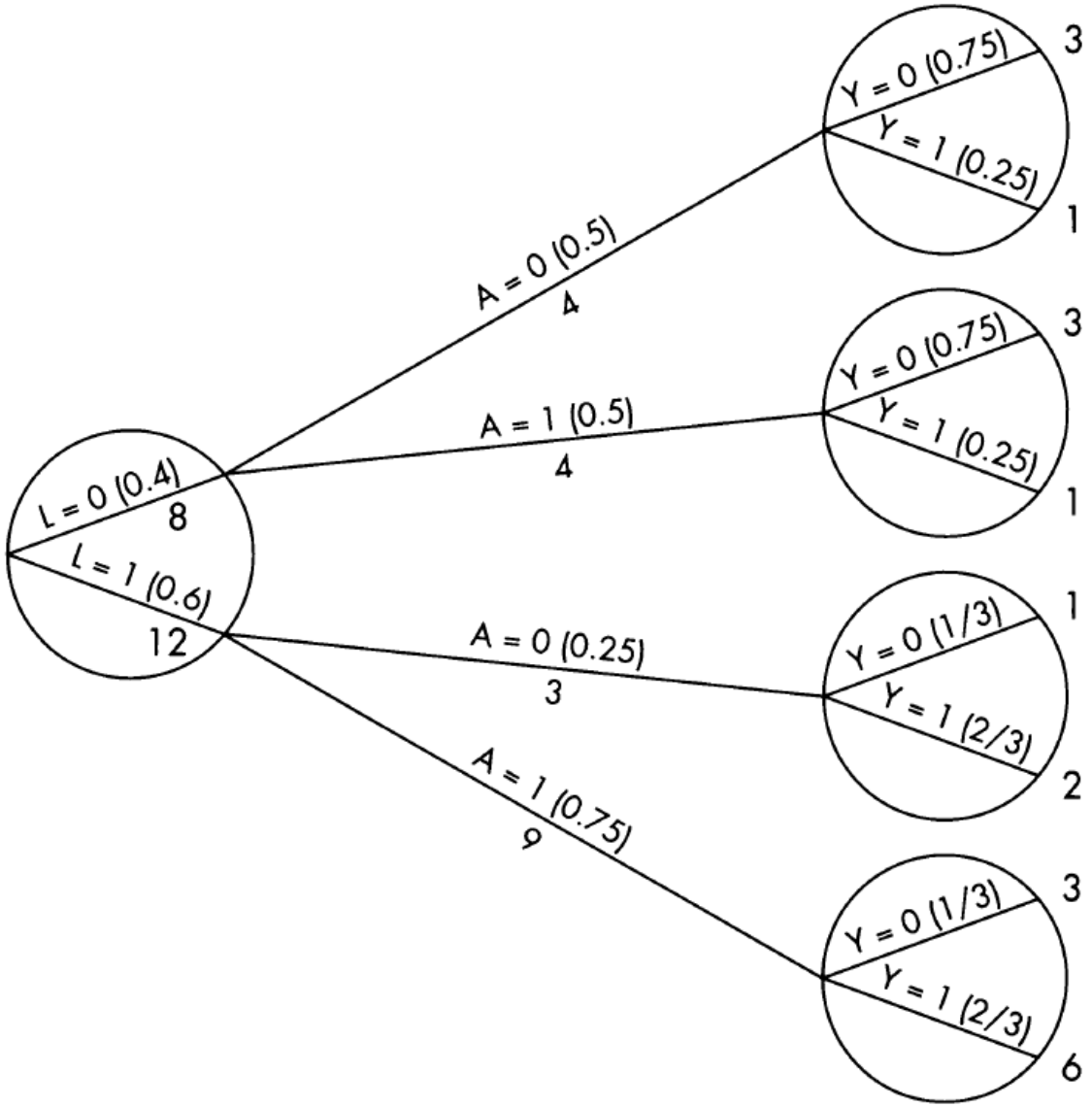
Confounding Bias – AKA Causal Inference – Still no consensus.

- Measured Confounding:
  - Propensity Scores,
  - Inverse Probability Treatment Weights,
  - Matching,
  - G-computation
- Unmeasured Confounding:
  - Instrumental Variable,
  - Mendelian Randomisation,
  - Regression Discontinuity,
  - Difference In Difference,
  - Cross-Over Studies

Propensity Scores

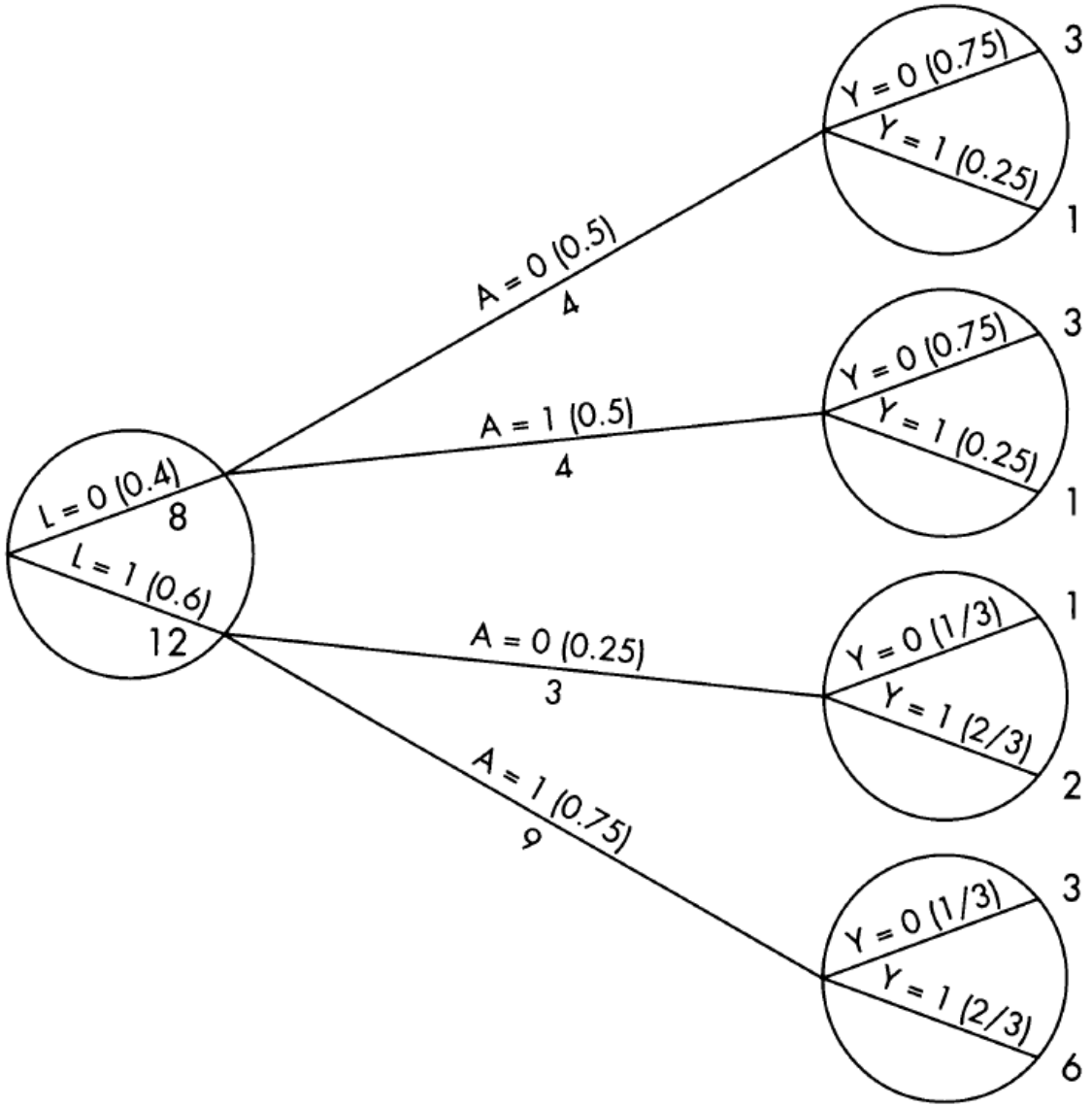
- Determining the Propensity Score
  - Probability of Getting a Treatment(x)
    - $X(1|0) = a_1z_1 + a_2z_2 + a_2z_2 \ldots\ldots a_kz_k + a_0$
  - z_1 to z_k are all the confounders
- Adjusting Via the Propensity Score
- $Y = m_1x + b_0$
- $Y = m_2x + m_3(\text{Prob:X=1}) + b_1$
- m_1 is biased and m_2 remove allocation bias by measured confounders.
- Matching via the Propenstiy Score
- Use the propensity score to match patients and do an analysis like a Case-Control Study

Inverse Probability Treatment Weights



L is the confounder.
A is the treatment.
Y is Died (Y=1) and Alive (Y=0)
L=0 (8 patients) and A=0 is 1/4 → (By IPTW) 2/8
L=1 (12 patients) and A=0 is 2/3 → (By IPTW) 8/12
Untreated risk of death: 10/20

Inverse Probability Treatment Weights



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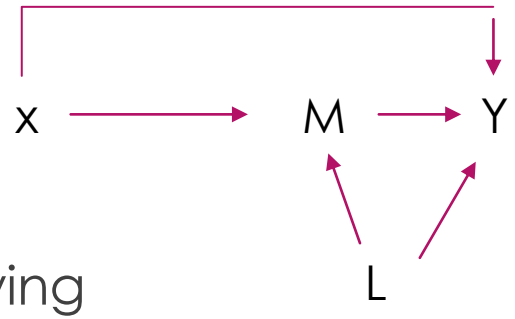
Untreated risk of death: 10/20

L=0 (8 patients) and A=1 is 1/4 → (By IPTW) 2/8
L=1 (12 patients) and A=1 is 6/9 → (By IPTW) 8/12
Treated risk of death: 10/20

Treatment vs No Treatment: 10/20 vs 10/20
RR=1
Therefore no difference.

G Computation

- Uses to deal with:
  - time varying confounding
  - Time varying exposures
  - time varying exposures changing or effecting time varying confounders
  - Another complex confounding scenario when Exposure (X) acts on Outcome (Y) through a Mediator(M) and directly on Y outside of M. Here a confounder L acts on M working on Y, but also L is affected by X.
- G Computation does separate models for each time point and then summarises the effect to get a RCT type estimate



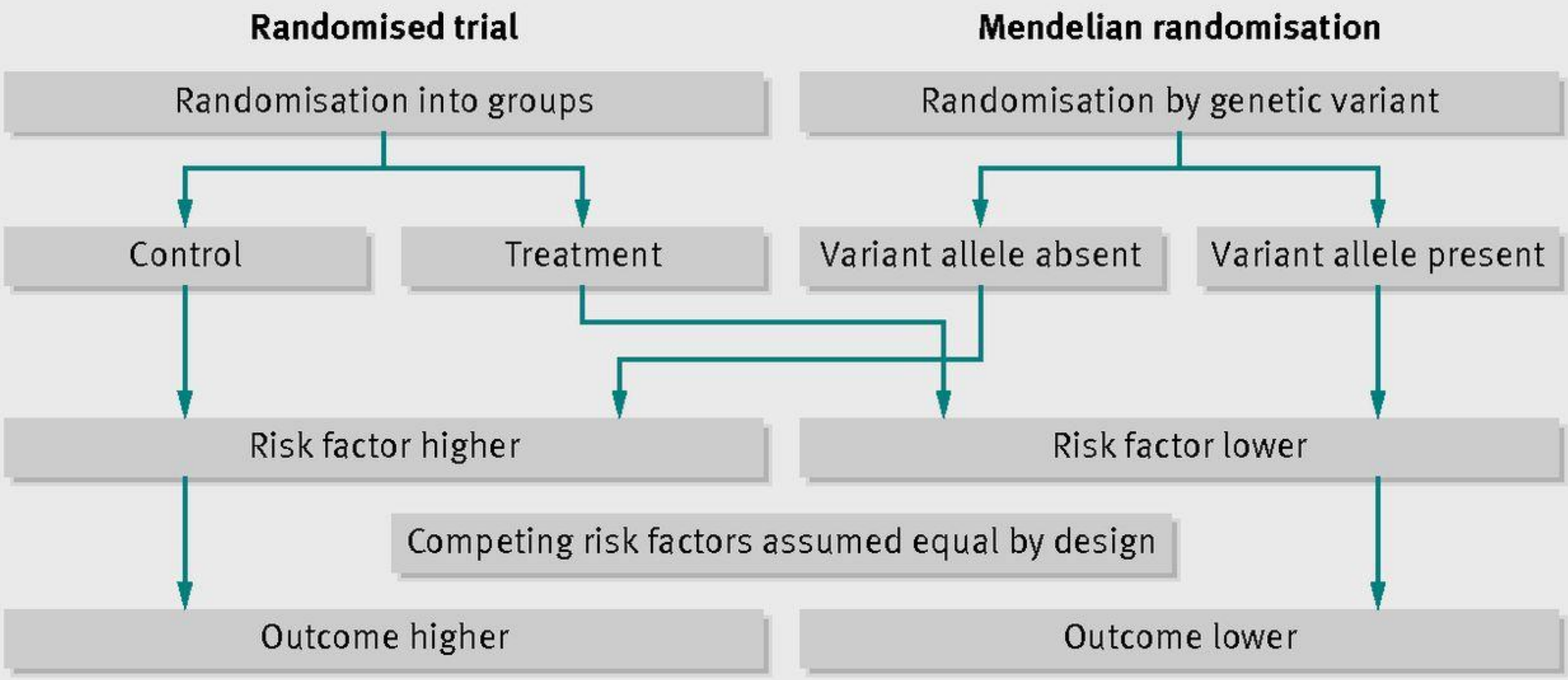
Instrumental Variables

- Confounder Z is exclusively linked to Outcome Y via Treatment X.

- $Y = m_0x + b_0$
- $X = m_1z + b_1$
- $X_{fitted} = m_1z + b_1$
- $Y = m_2X_{fitted} + b_2$

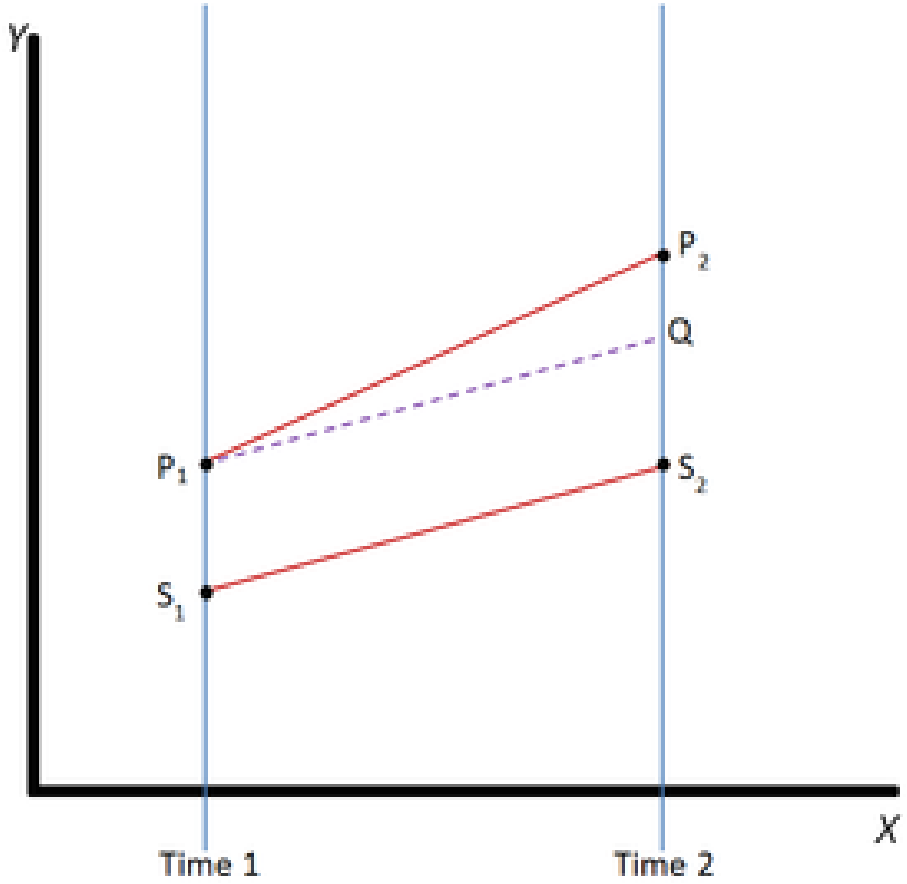
- m_1 is the biased treatment effect of X.
- m_2 is the true treatment effect of X and is a good approximation of the RCT result.

Mendelian Randomization



Source: http://www.bmj.com/content/345/bmj.e7325

Difference in Difference



Source: http://en.wikipedia.org/wiki/Difference_in_differences

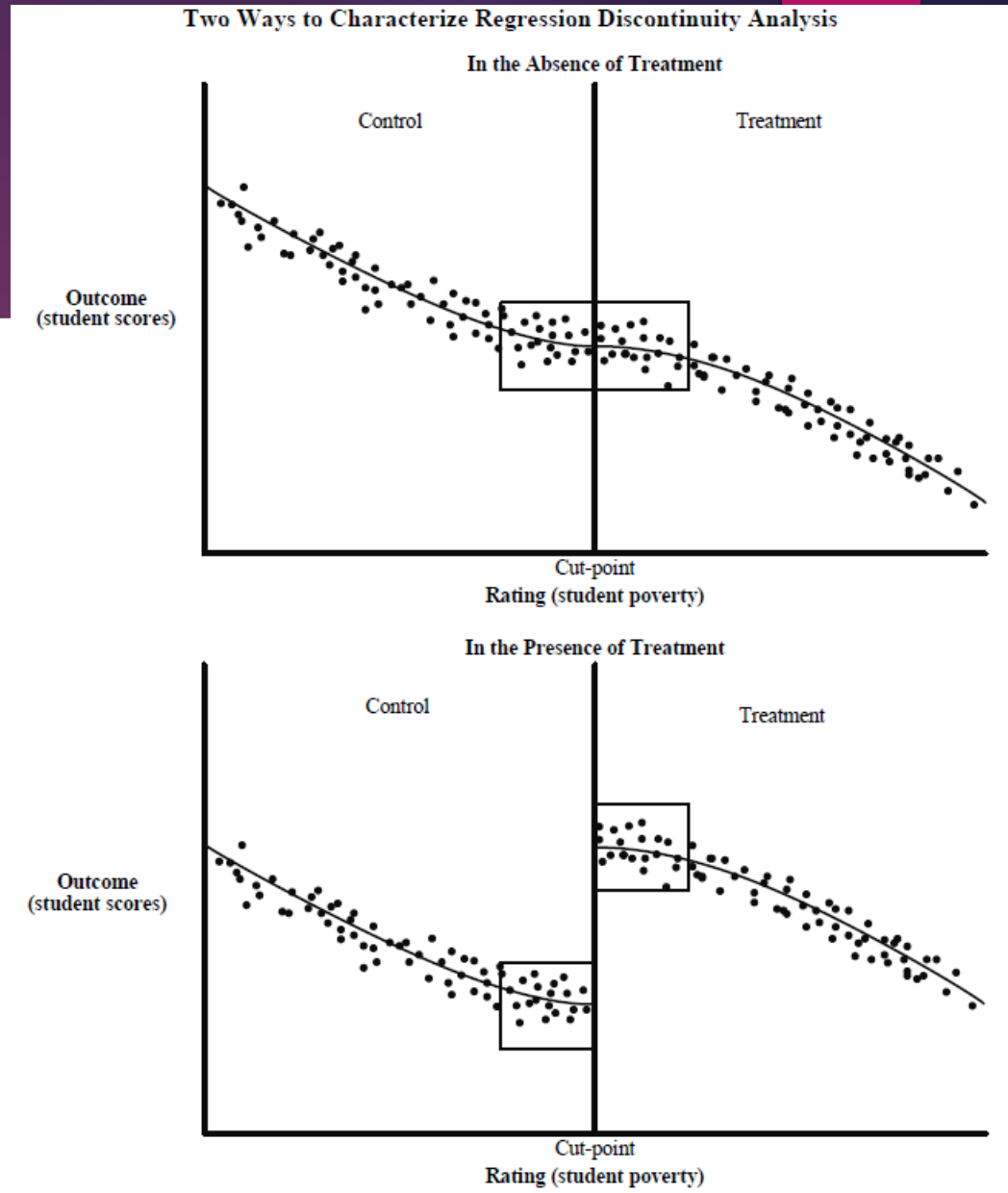
Cross-Over Studies

Cross-Over Studies

- Measures an effect that wears off
- Uses a treatment that does not have a carry over effect
- Need to be able to go through both treatments
- Cannot measure non-reversible events like death.
- Subject should be stable in other respects, eg they cant suddenly start smoking.

Regression Discontinuity

- If treatment is assigned based on a cutoff of a variable.
  - Panadol given to people who have fever greater that 38°C
  - School gets Academic Intervention if average test score is lower than 60%.
- Those who just miss the cutoff and make the cut off are similar so either will have balanced confounding.
- Difference are equivalent to randomised estimate.



Summary

- Study Design (Cross-Sectional, Case-Control, Cohort, RCT)
- Statistical Methods
  - Hypothesis Testing (Type I&II Error, P Value, 95%Confidence Intervals)
  - Linear Regression, Poisson, OR/RR,
  - Survival Analysis: HR & K-M Plot,
  - Corelated Data: Mixed Effect, Marginal, Multilevel
- Bias (Selection, Measurement, Confounding)
- Causal Inference
  - Measured Confounding – (Propensity Scores, IPTW, Matching)
  - Unmeasured Confounding – (IV, Mendelian Randomisation, Crossover, Difference in Difference, Regression Discontinuity)

Any Questions??