Confounding in health research

Part 2: adjustment and control

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Confounding: 4 ways to understand it!

1. “Mixing of effects”
2. “Classical” approach based on *a priori* criteria
3. Collapsibility and data-based criteria
4. “Counterfactual” and non-comparability approaches

Control of confounding: Outline

- Control at the design stage
  - Randomization
  - Restriction
  - Matching

- Control at the analysis stage
  - Conventional approaches
    - Stratified analyses
    - Multivariate analyses
  - Newer approaches **[EPIB 610 Advanced Methods: Causal Inference]**
    - Graphical approaches using DAGs
    - Propensity scores
    - Instrumental variables
    - Marginal structural models

Control of confounding: at the design stage

- Options at the design stage:
  - Randomization
    - Reduces potential for confounding by generating groups that are fairly comparable with respect to known and unknown confounding variables (attempts to simulate a counterfactual contrast)
  - Restriction
    - Eliminates variation in the confounder (e.g. only recruiting males into the study will eliminate confounding by sex)
  - Matching
    - Involves selection of a comparison group that is forced to resemble the index group with respect to the distribution of one or more potential confounders

Randomization

- Randomization
  - Useful only for intervention studies
  - Definition: random assignment of study subjects to exposure categories (this breaks any links between exposure and confounders)
  - The special strength of randomization is its ability to control/reduce the effect of confounding variables about which the investigator is unaware (i.e. both known and unknown confounders get distributed evenly because of randomization)
  - But this will happen provided:
    - Trial is sufficiently large
    - Concealment of allocation is correctly done

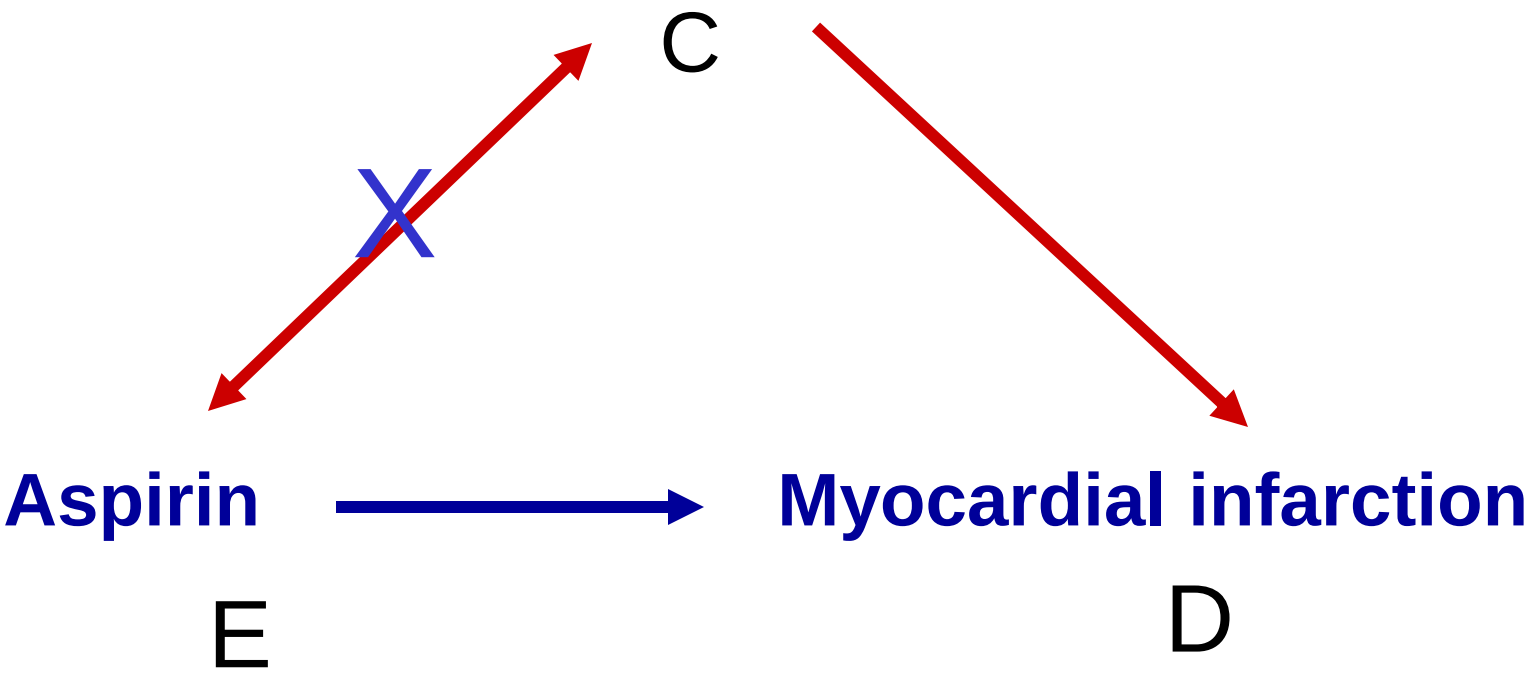
Randomization

- Randomization
  - Randomization does not always eliminate confounding
    - Covariate imbalance after randomization can occur in small trials
    - If there is “maldistribution” of potentially confounding variables after randomization (the reason for the classic “Table I: Baseline characteristics” in the randomized trial) then other confounding control options (see below) are applied (e.g. multivariate analysis to adjust for confounding)
    - If allocation concealment is not well done, then treatment allocation can be biased (randomization can be subverted)

Randomization breaks any links between treatment and prognostic factors

Example: aspirin to prevent MI

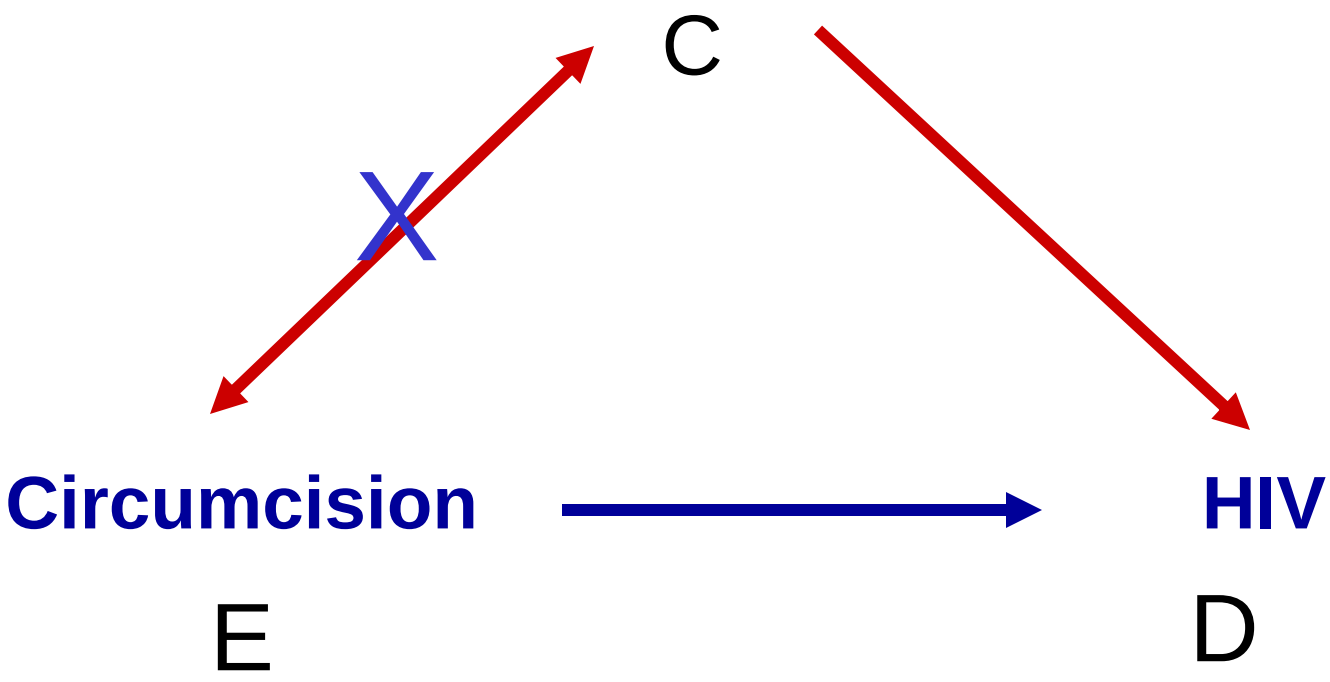
Confounders: Obesity, smoking, family history of heart disease, etc



In a RCT, there can be no association between aspirin and confounders (because intervention is randomly allocated)

Example: circumcision to prevent HIV

Confounders: religion, sexual behavior, etc



In a RCT, there can be no association between circumcision and confounders (because intervention is randomly allocated)

Randomization results in groups with comparable distribution of confounders
Example: First RCT on circumcision and HIV

Table 2. Baseline Characteristics of HIV-Negative Men Enrolled in the Trial

Background Characteristics		Control $n = 1,582$	Intervention $n = 1,546$
Age	Less than or equal to 21 y	52.4%	48.6%
	More than 21 y	47.6%	51.4%
Primary level of education completed		98.4%	98.3%
Religion	African traditional	47.0%	51.6%
	Protestant or Catholic	11.1%	11.9%
	Other religion	41.8%	36.5%
Ethnic group	Sotho	47.3%	49.0%
	Zulu	38.1%	32.8%
	Other	14.6%	18.2%
Drank alcohol in the past month		41.9%	42.2%
Reported sexual behaviour			
Have had first sexual experience		90.5%	91.8%
Median (IQR) age at first sex (years)[a]		16.6 (15.2–18.4)	16.8 (15.4–18.5)
Median (IQR) number of lifetime sex partners[b]		4 (2–7)	4 (3–7)
Used a condom at first sex[b]		13.4%	15.2%
Ever used a condom[b]		81.2%	82.3%
At-risk behaviour[c,d]		46.7%	46.8%
Married or living as married[d]		1.8%	1.8%
Mean (IQR) number of non-spousal partners[e]		1.4 (0–2)	1.4 (0–2)
At least one sexual partnership with only one sexual contact[e]		29.8%	30.7%
Mean (IQR) number of sexual contacts[e]		8.0 (0–8)	8.7 (1–8)
Attended a clinic for a health problem related to the genital area[e]		10.0%	9.6%

Randomization resulted in highly comparable distribution of potential confounders; so confounding is not an issue!

Restriction

- Confounding cannot occur if the distribution of the potential confounding factors do not vary across exposure or disease categories
  - Implication of this is that an investigator may restrict study subjects to only those falling with specific level(s) of a confounding variable
    - Extreme example: an investigator only selects subjects of exactly the same age or same sex.
- Advantages of restriction
  - straightforward, convenient, inexpensive
  - but, reduces recruitment!

Restriction

- Disadvantages
  - Will limit number of eligible subjects
  - Will limit ability to generalize the study findings (e.g. study of only males may not directly apply to all women)
  - Residual confounding may persist if restriction categories not sufficiently narrow (e.g. “decade of age” might be too broad)
  - Not possible to evaluate the relationship of interest at different levels of the confounder
    - E.g. if only elderly males are included, then effect of age and sex can no longer be evaluated

Matching

- Matching is commonly used in case-control studies (where each case is matched to a control)
- For example, if age and sex are the matching variables, then a 35 year old male case is matched to a 35 year old male control
- Types:
  - Pair matching (one to one individual matching)
  - Frequency matching
- The use of matching usually requires special analysis techniques (e.g. matched pair analyses and conditional logistic regression)
  - Same approach as in paired tests of statistical significance (e.g. paired t-test)

Matching

Advantages	Disadvantages
Gain precision and gain study efficiency	Additional cost and time (difficulty in finding matches)
Control for variables difficult to measure	Cases with no matching controls may need to be excluded
Can match on time to get time comparability	Cannot study the effect of matching variable
	Overmatching can introduce new bias
	Matching on weak risk factors may lose precision
	Can adjust for confounding even without matching
	Matching does not control for confounding by factors other than that used to match
	Data analysis is more complex (i.e. matched analysis)

Matching

- Disadvantages of matching
  - Matching is most often used in case- control studies because in a large cohort study the cost of matching may be prohibitive
    - In a case-control study, matching may introduce confounding rather than eliminate confounding!
    - *Très compliqué* and will be covered briefly here, but more in intermediate epi (EPIB603)

Matching in a case control study

- Why can matching introduce confounding in a case-control study?
  - The purpose of the control series in a case-control study is to permit an estimate of the person-time distribution of exposure in the source population (study base) from which cases arose
  - In other words, controls selected for a case-control study are supposed to reflect the distribution of exposure in the source population.
  - If controls are selected to match the cases for a factor that is correlated with exposure, this will change the distribution of the control population away from the distribution in the source population
    - then the crude exposure odds in controls is distorted in the direction of similarity to that of the cases (e.g. friend controls of the same age and sex).
  - This will introduce a selection bias that is very similar to confounding.
  - If the matching factor were perfectly correlated with the exposure, the exposure distribution of controls would be identical to cases, and the crude OR estimate would be 1.0

Matching in case control studies

- So, matching (whose well-meaning goal is to reduce confounding) does not attain that objective in case-control studies
  - It substitutes a new confounding structure for the old one
  - At times, it will introduce new confounding where none previously existed
  - So, use matching with caution
  - If you must match, then match on a strong confounder

- The confounding introduced by matching into a case-control study is not irremediable
  - The proper form of analysis is needed in matched studies in order to reduce the confounding introduced by matching
    - Matched Odds Ratios
    - Conditional logistic regression
    - General rule: paired data must be treated as such in the analysis (do not break up the pairs!)

Matched odds ratio

		Control	
		Exposed	Not exposed
Case	Exposed	a	b
	Not exposed	c	d

Matched OR (mOR) = b/c

Definition: OR in a matched case-control study is defined as the ratio of the number of pairs a case was exposed and the control was not to the number of ways the control was exposed and the case was not

The pairs in cells A and D do not contribute any information since they are concordant

Control of confounding: at the analysis stage

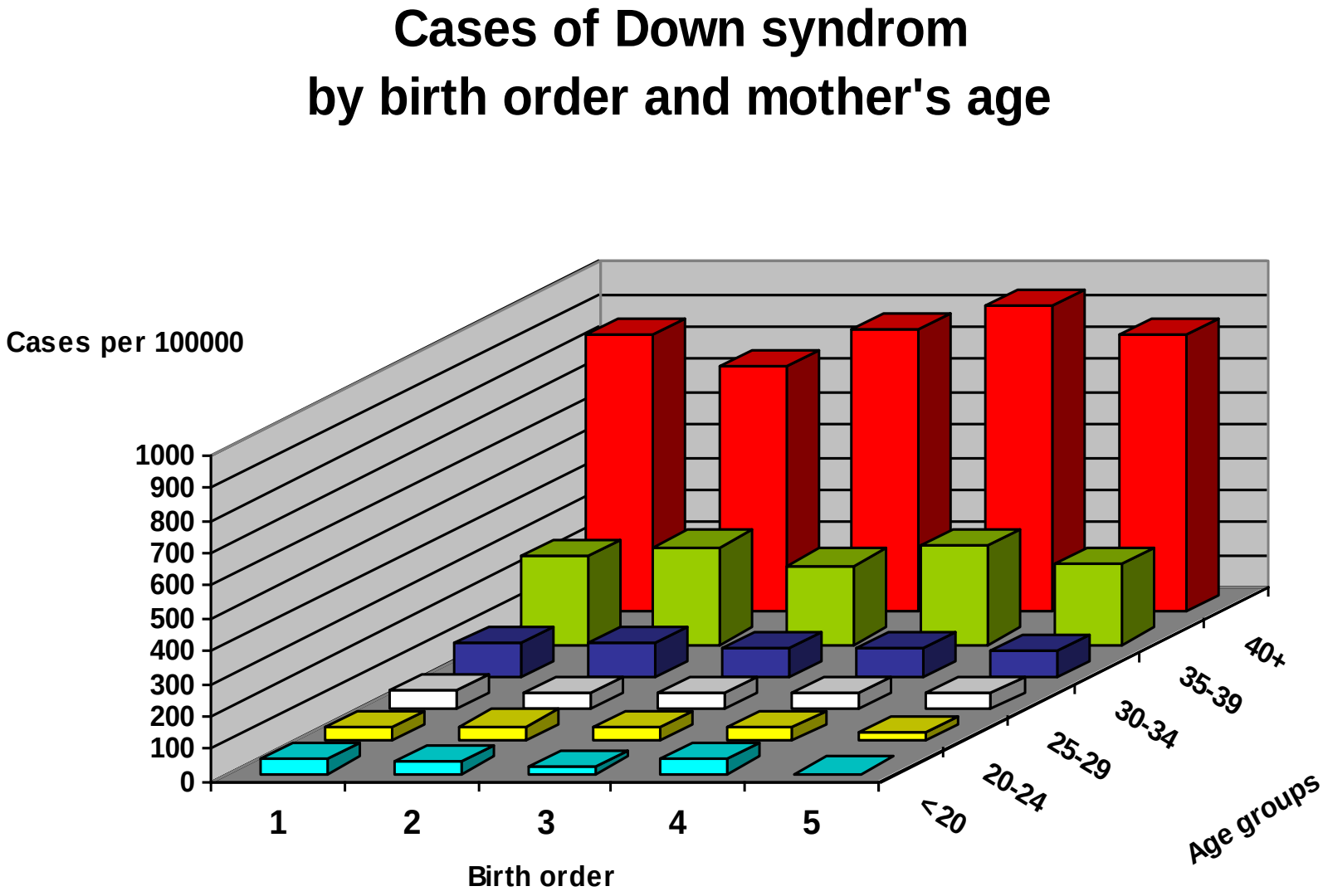
- Unlike selection and information bias, confounding is one type of bias that can be, to a large extent, adjusted in the analysis
- Options at the analysis stage:
  - Stratification
  - Multivariate methods
- To control for confounding in the analyses, one must measure the confounders in the study!
  - Investigators usually do this by collecting data on all known, previously identified confounders
  - A sound knowledge of disease biology will help decide what to measure
  - Drawing a DAG before a study is done will help decide on what minimum set of covariates need to be measured

Stratification

- Objective of stratified analysis is to “fix” the level of the confounding variable and produce groups within which the confounder does not vary
  - This is also called “conditioning on the confounder”
- Then evaluate the exposure-disease association within each stratum of the confounder
- Within each stratum, the confounder cannot confound because it does not vary

- Question: Who is an epidemiologist?
- Answer: A physician broken down by age and sex!

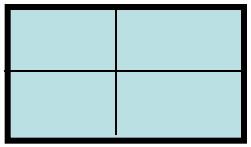
Stratified Analysis: graphic approach



Source: www.epiet.org

Stratified Analysis

Crude

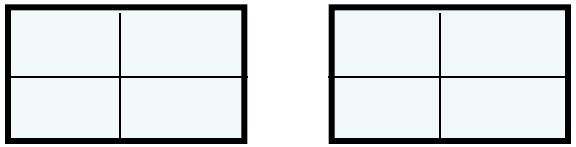


OR_{Crude}

Crude 2 x 2 table
Calculate Crude OR (or RR)

Stratify by Confounder

Stratum 1 Stratum 2



Calculate OR's
for each stratum

OR_1 OR_2

If stratum-specific OR's are similar,
calculate adjusted OR (e.g. M-H)

If Crude OR =/= Adjusted OR, confounding is likely

If Crude OR = Adjusted OR, confounding is unlikely

What are adjusted effect estimates?

- Simply put, they are “weighted averages” of the stratum-specific effect measures
  - There are many methods
    - M-H is one of the commonest and easiest, but there are other techniques as well (e.g. Peto method, Inverse-variance method)
- Same as a “meta-analysis” which computes weighted averages of effects across trials

Mantel-Haenszel (M-H) estimators of adjusted effects from stratified data

Case-Control Study:

$$OR_{MH} = \frac{\sum(ad / T)_i}{\sum(bc / T)_i}$$

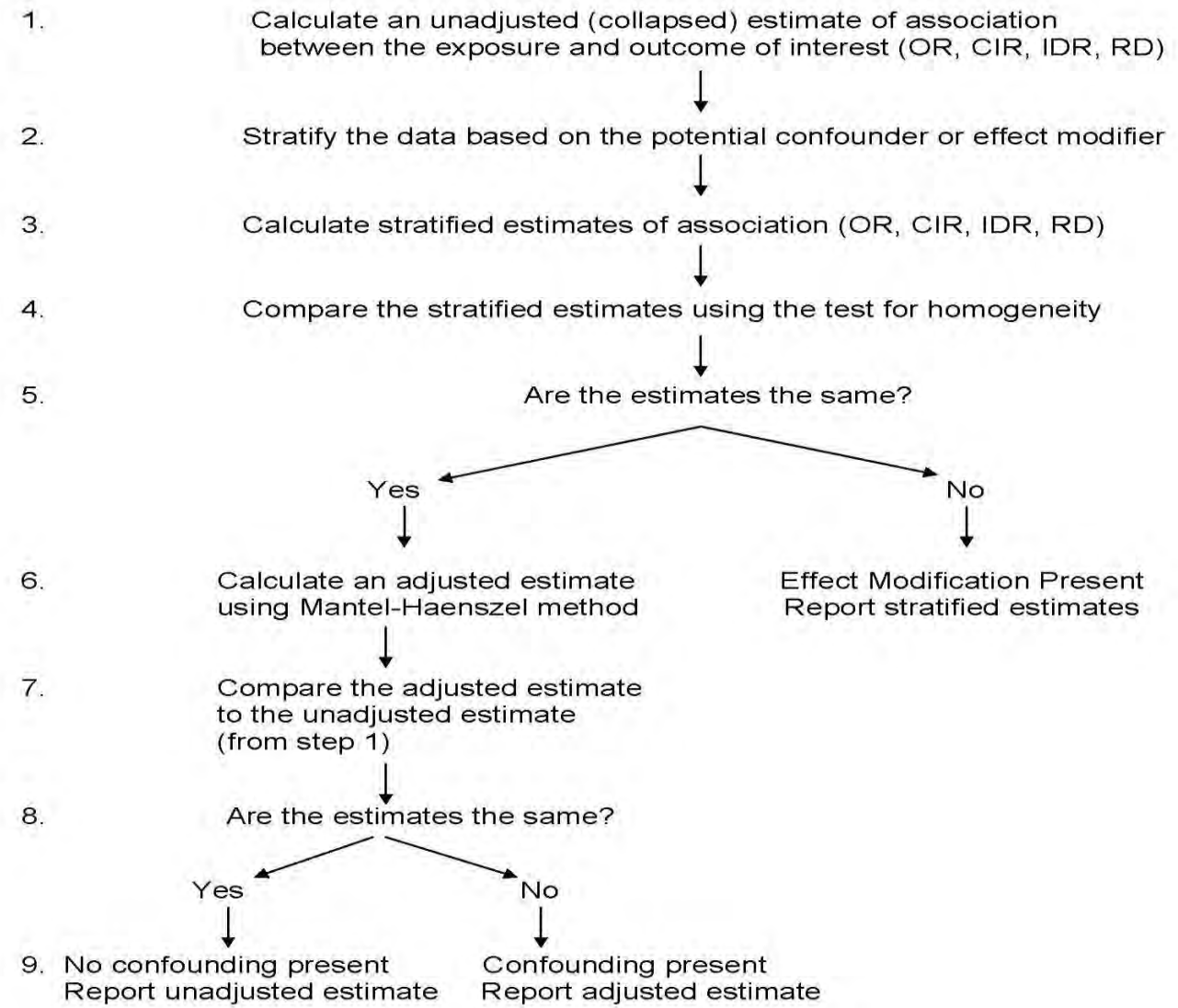
Cohort Study with Count Denominators:

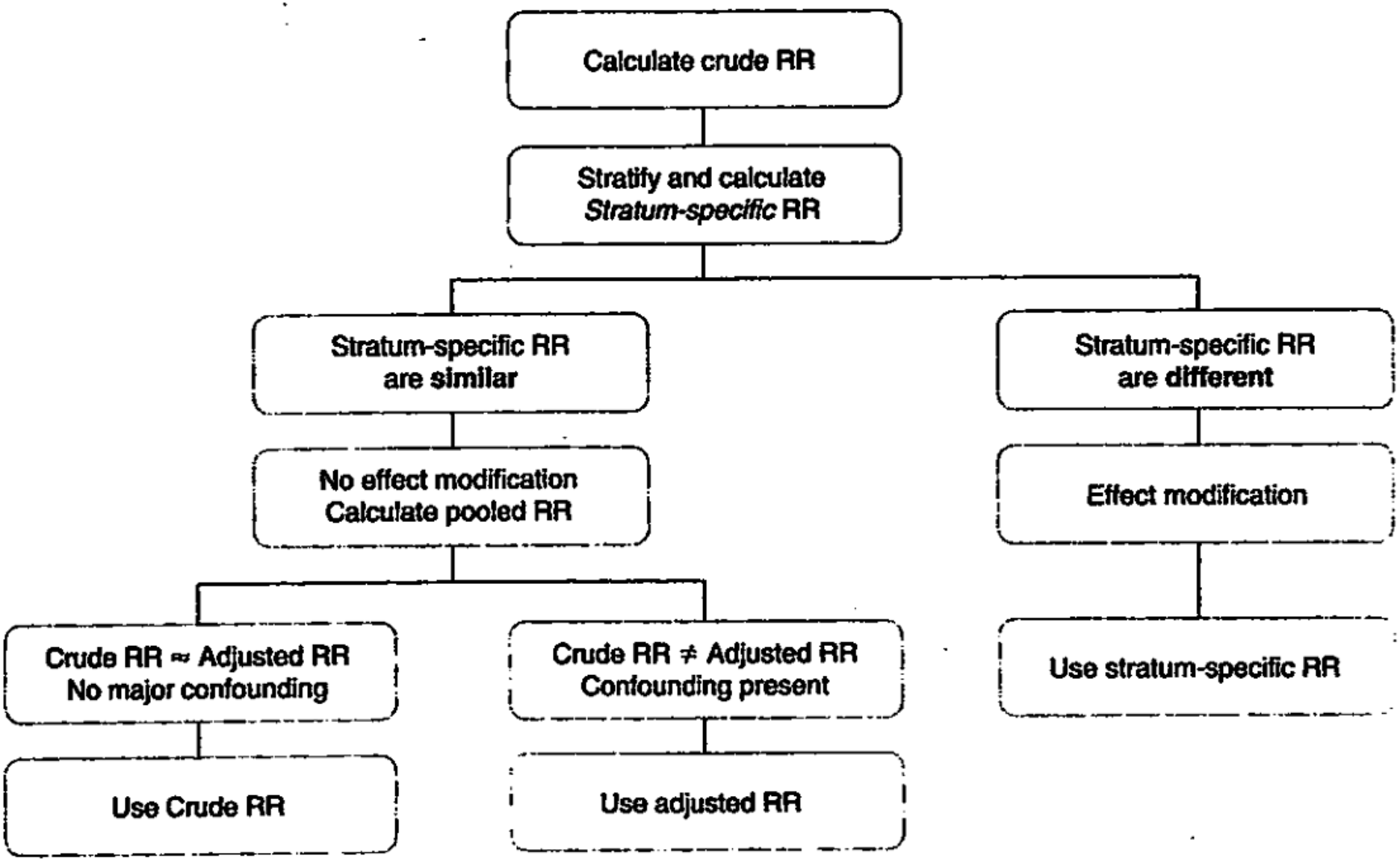
$$RR_{MH} = \frac{\sum\{a(c + d) / T\}_i}{\sum\{c(a + b) / T\}_i}$$

Cohort Study with Person-years Denominators:

$$RR_{MH} = \frac{\sum\{a(PY_0) / T\}_i}{\sum\{b(PY_1) / T\}_i}$$

Decision tree for evaluating confounding and effect modification





Webb. Essential Epidemiology, Cambridge Univ Press.

Observational Study on Vit E and Coronary Heart Disease

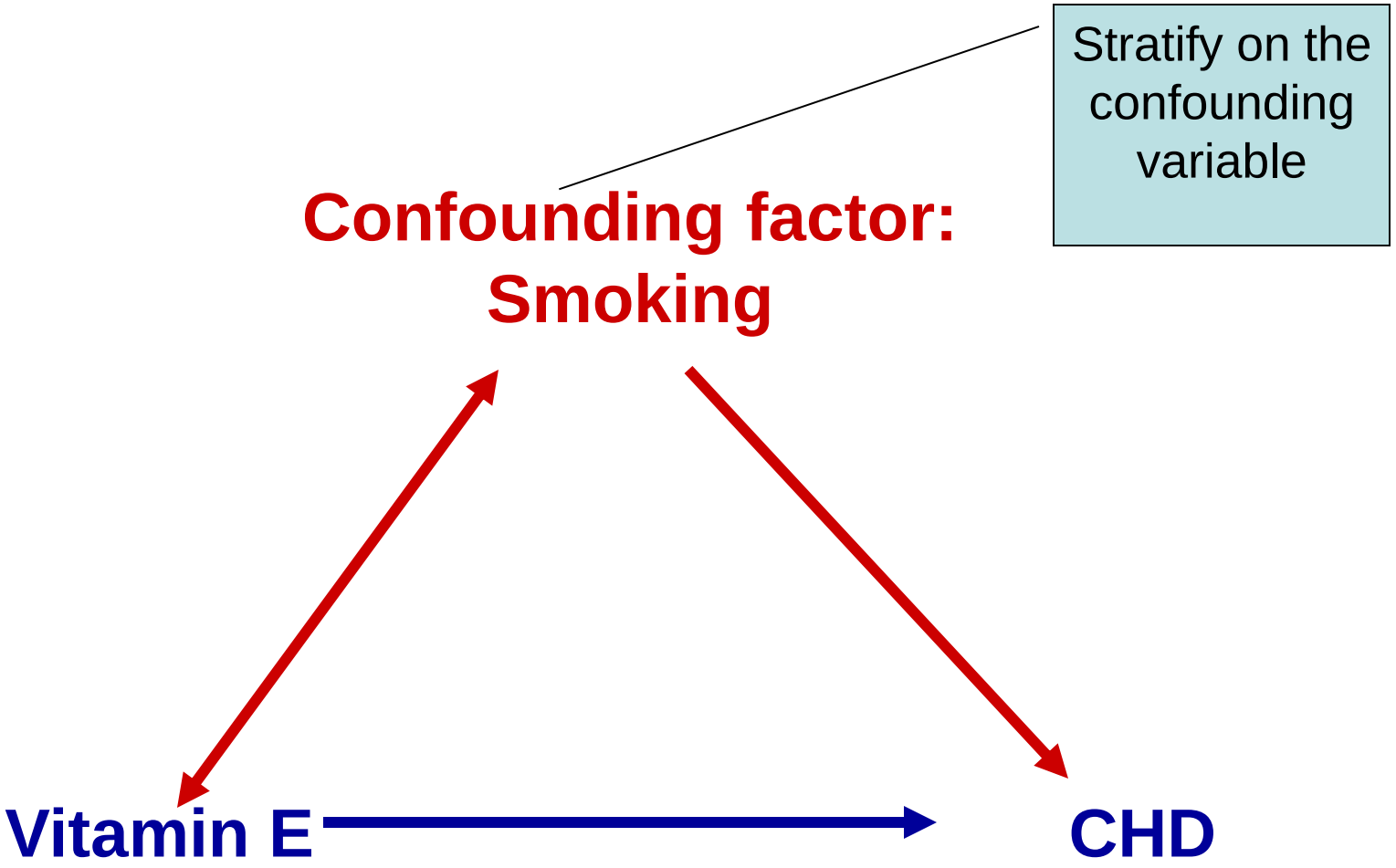
Vitamin E Supplement	CHD: Present	CHD: Absent
Yes	50	501
No	65	384

Crude OR = (50)(384)/(501)(65) = 0.59

Are there potential confounders that can explain this crude OR?

Fitzmaurice, 2004

Could reduced smoking among Vit E users partly explain the observed protective effect?



Stratified Analyses (by smoking status)

Smokers:

Vitamin E Supplement	CHD Present	CHD Absent
Yes	11	40
No	49	200

Stratum 1: smokers

OR (smokers) = (11)(200)/(40)(49) = 1.12

Non-Smokers:

Vitamin E Supplement	CHD Present	CHD Absent
Yes	39	461
No	16	184

Stratum 2: non-smokers

OR (non-smokers) = (39)(184)/(461)(16) = 0.97

Fitzmaurice, 2004

Inference

- Before adjusting for smoking, Vit E had a strong protective effect (Crude OR=0.59)
- After stratification, there is little evidence of an association between vitamin E and CHD after controlling for smoking (Stratum-specific ORs 1.1 & 0.97)
- Why is there an apparent contradiction with the results obtained from the crude data?
- Vitamin E group contains considerably fewer smokers (9.3% versus 55.5%), thereby decreasing this group's apparent risk of CHD
  - In other words, Vit E users probably had a healthier lifestyle

Fitzmaurice, 2004

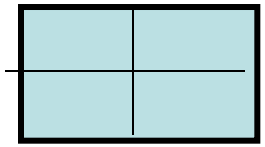
Direction of Confounding Bias

- Confounding "distorts" the observed association away from the true association
  - It can either exaggerate/over-estimate the true association (positive confounding, away from the null)
    - Example
      - $RR_{causal} = 1.0$
      - $RR_{observed} = 3.0$

    or
  - It can hide/under-estimate the true association (negative confounding, towards the null)
    - Example
      - $RR_{causal} = 3.0$
      - $RR_{observed} = 1.0$

Limitations of Stratified Analyses

Crude



OR_{Crude}

Confounder 1

Stratum 1

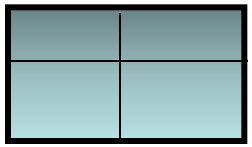
OR_1

Stratum 2

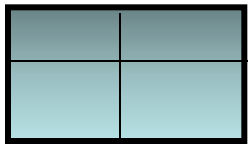
OR_2

Confounder 2

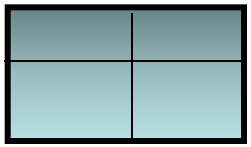
Stratum 1



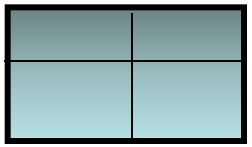
Stratum 2



Stratum 1



Stratum 2



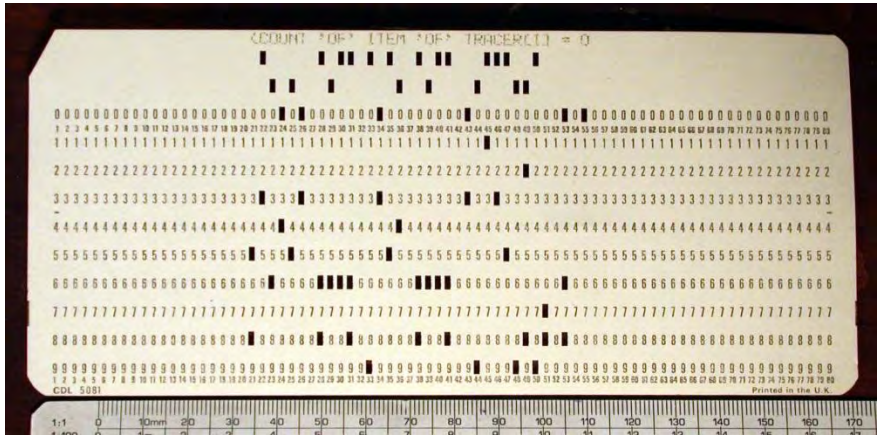
"Sparseness of data" problem
Computational and interpretational difficulties

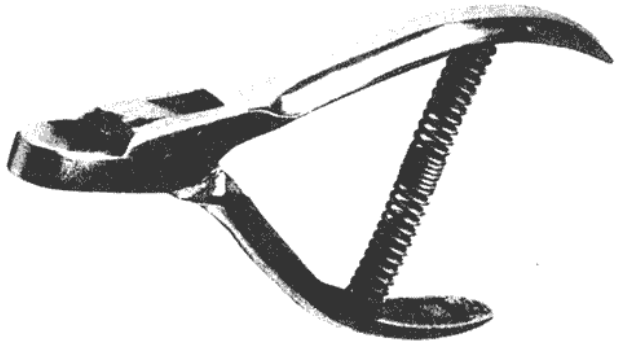
Multivariate Analysis

- Stratified analysis works best when there are few strata (i.e. if only 1 or 2 confounders have to be controlled)

- If the number of potential confounders is large, multivariate analyses offer the only real solution
  - Can handle large numbers of confounders (covariates) simultaneously (e.g. in the Vit E example, one could control for smoking, alcohol, physical activity, diet, in the same analysis)
  - Based on statistical regression “models”
    - E.g. logistic regression, multiple linear regression
  - Always done with statistical software packages (e.g. SAS, Stata)
    - Multivariate analysis was a nightmare before the advent of microcomputers and software options!

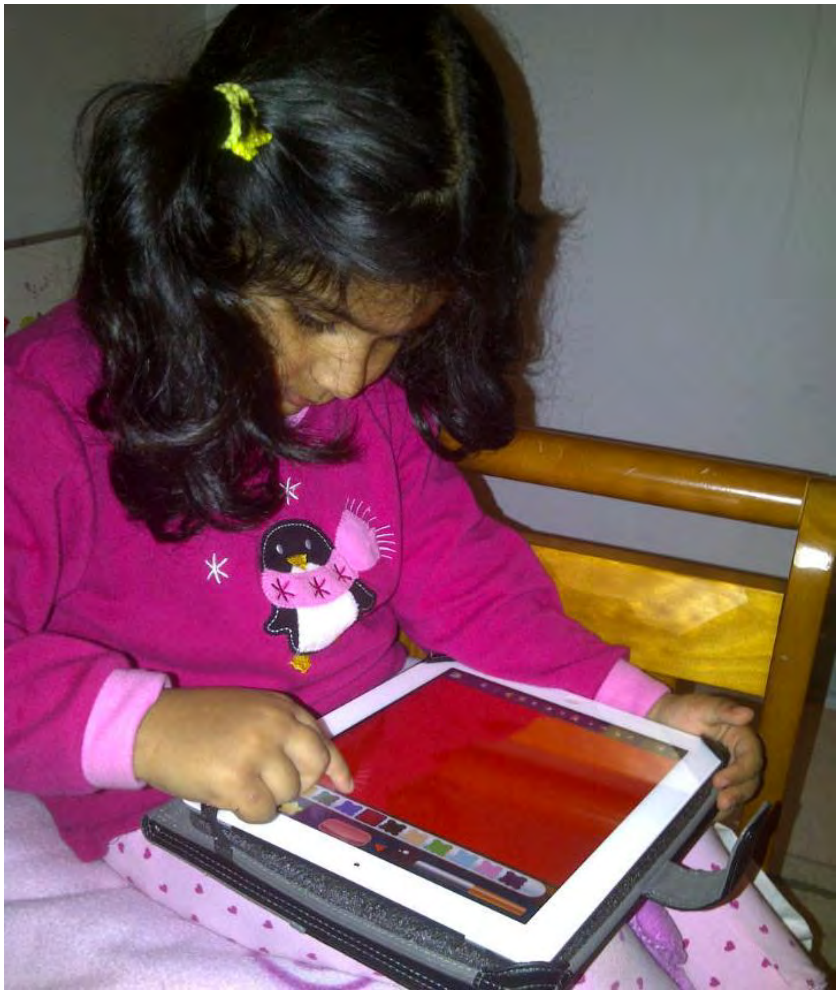
Computing has come a long way!





Thanks to guys like these…

3 year olds today have more computing power than entire universities had not too long ago!



Multivariate Analysis: Demo

- Example: Association between preterm labor and low birth weight
- N = 189 subjects
- Outcome: low birth weight **[low]** (yes=1; no=0)
- Main exposure of interest: History of preterm labor **[ptl]** (yes=1; no=0)
- Covariates:
  - Smoking status of mother **[smoke]** (yes=1; no=0)
  - **Age** (mother's age in years)
  - **Race** (0=white; 1=black/others)

	ID	low	age	smoke	ptl	race
1	4	1	28	1	1	1
2	10	1	29	0	0	0
3	11	1	34	1	0	1
4	13	1	25	0	1	1
5	15	1	25	0	0	1

Data adapted from Hosmer & Lemeshow. Applied Logistic Regression, Wiley, 2000

Bivariate analysis: Preterm labor and low birth weight

- Outcome: low birth weight **[low]** (yes=1; no=0)
- Main exposure of interest: History of premature labor **[ptl]** (yes=1; no=0)
- 59/189 (31%) were low birth weight
- Crude association: OR = 4.31

```
. cc low ptl

                                                      Proportion
                |    Exposed    Unexposed |      Total   Exposed
----------------+------------------------+------------------------
          Cases |         18           41 |         59      0.3051
       Controls |         12          118 |        130      0.0923
----------------+------------------------+------------------------
          Total |         30          159 |        189      0.1587
                |                        |
                |   Point estimate       |  [95% Conf. Interval]
----------------+------------------------+------------------------
     Odds ratio |       4.317073         |   1.777511    10.65589 (exact)
Attr. frac. ex. |        .7683616        |    .4374155   .9061552 (exact)
Attr. frac. pop |        .2344154        |
----------------+------------------------+------------------------
                          chi2(1) =    13.76  Pr>chi2 = 0.0002
```

Stratified analysis (by smoking status)

Preterm labor and low birth weight

Mantel-Haenszel adjusted OR:

```
. cc low ptl, by(smoke)

      smoke |      OR   [95% Conf. Interval]    M-H Weight
------------+-------------------------------------------------
          0 |  3.478261   .8320418    14.22408         1.2  (exact)
          1 |  4.222222    1.20591    15.76105    1.459459  (exact)
------------+-------------------------------------------------
      Crude |  4.317073   1.777511    10.65589              (exact)
M-H combined |  3.886532   1.697176    8.900158
------------+-------------------------------------------------
Test of homogeneity (M-H)       chi2(1) =     0.05  Pr>chi2 = 0.8191

                 Test that combined OR = 1:
                         Mantel-Haenszel chi2(1) =    10.97
                                         Pr>chi2 =   0.0009
```

Crude OR = 4.31
OR (smokers) = 4.22
OR (non-smokers) = 3.47
M-H (adjusted) OR = 3.88

Multivariate analysis: Preterm labor and low birth weight

Model 1: Logistic regression model with no covariates (unadjusted)

```
. logistic low ptl

Logistic regression                               Number of obs   =        189
                                                  LR chi2(1)      =      12.77
                                                  Prob > chi2     =     0.0004
Log likelihood = -110.94888                       Pseudo R2       =     0.0544

------------------------------------------------------------------------------
         low | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ptl |   4.317073   1.789132     3.53   0.000     1.916128    9.72645
------------------------------------------------------------------------------
```

OR is the same as we got from a simple 2 x 2 table

Multivariate analysis: Preterm labor and low birth weight

Model 2: Logistic regression model with covariates (adjusted)

- ORs are adjusted for only smoking

```
. logistic low ptl smoke

Logistic regression                               Number of obs   =        189
                                                  LR chi2(2)      =      15.34
                                                  Prob > chi2     =     0.0005
Log likelihood = -109.66445                       Pseudo R2       =     0.0654

------------------------------------------------------------------------------
         low | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ptl |   3.863837   1.628601     3.21   0.001     1.69137    8.826711
       smoke |   1.709971   .5702925     1.61   0.108     .8894148   3.287554
------------------------------------------------------------------------------
```

After adjusting for smoking, the
OR is significant and strong, but less than the crude OR

Adjusted OR is similar to what we got via M-H method

Multivariate analysis: Preterm labor and low birth weight

Model 3: Logistic regression model with all covariates (adjusted)

- ORs are adjusted for age, race and smoking

```
. logistic low ptl age race smoke

Logistic regression                               Number of obs   =        189
                                                  LR chi2(4)      =      26.25
                                                  Prob > chi2     =     0.0000
Log likelihood = -104.21339                       Pseudo R2       =     0.1118

------------------------------------------------------------------------------
         low | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ptl |   4.099114   1.817752     3.18   0.001     1.718798    9.775868
         age |   .9459476   .0340036    -1.55   0.122     .8815953    1.014997
        race |   2.620422   1.006873     2.51   0.012     1.233971    5.564648
       smoke |   2.477854   .9507154     2.36   0.018     1.168107    5.256165
------------------------------------------------------------------------------
```

After adjusting for age, race and smoking, the
OR is significant and strong, but less than the crude OR;
Smoking and race also appear to be independent risk factors for low birth weight

Logistic regression equation

- General:
  - ln (odds of disease) = $a + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4$
  - Where, a is the intercept; b_1 b_2 etc are the beta coefficients; and X_1, X_2, etc are covariates in the model

- Low birth weight study:
  - ln (odds of low birth wt) = $a + b_1$(preterm labor) + b_2(age) + b_3(race) + b_4(smoking)
  - From the final model, we can get ORs for each covariate by generating the exponential of the beta coefficients (i.e. e^b)

More on this in EPIB621

Residual confounding

- Confounding can persist, even after adjustment
- Why?
  - All confounders were not adjusted for (unmeasured confounding)
  - Some variables were actually not confounders!
  - Confounders were measured with error (misclassification of confounders)
  - Categories of the confounding variable are improperly defined (e.g. age categories were too broad)

Residual confounding: a case study

ORIGINAL ARTICLE

Tobacco smoking and pulmonary tuberculosis

C Kolappan, P G Gopi

Thorax 2002;**57**:964–966

See end of article for authors' affiliations

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Background: The prevalence of tuberculosis in adult men in India is 2–4 times higher than in women. Tobacco smoking is prevalent almost exclusively among men, so it is possible that tobacco smoking may be a risk factor for developing pulmonary tuberculosis. A nested case control study was carried out to study the association between tobacco smoking and pulmonary tuberculosis.

Methods: A tuberculosis disease survey was carried out in two Panchayat unions in the Tiruvallur district of Tamil Nadu in India. Eighty five men aged 20–50 years with bacteriological tuberculosis (smear and/or culture positive) were selected as cases and 459 age matched men without tuberculosis were selected randomly as controls. Information on smoking status, type of tobacco smoked, quantity of tobacco smoked, and duration of tobacco smoking was collected from cases and controls using a questionnaire.

Results: The estimated crude odds ratio (OR) of the association between tobacco smoking and bacillary tuberculosis was 2.48 (95% confidence interval (CI) 1.42 to 4.37), $p<0.001$.The age adjusted OR (Mantel-Hanszel estimate) was 2.24.(95% CI 1.27 to 3.94), $p<0.05$. The ORs for mild (1–10 cigarettes/day), moderate (11–20/day), and heavy (>20/day) smokers were 1.75, 3.17, and 3.68, respectively ($p<0.0001$ test for linear trend). The ORs for smokers with <10 years, 11–20 years, and >20 years of smoking were 1.72, 2.45, and 3.23, respectively ($p<0.0001$ test for linear trend).

Conclusion: There is a positive association between tobacco smoking and pulmonary (bacillary) tuberculosis (OR 2.5). The association also shows a strong dose-response relationship.

Residual confounding: a case study

Smoking and Tuberculosis among the Elderly in Hong Kong

Chi C. Leung, Teresa Li, Tai H. Lam, Wing W. Yew, Wing S. Law, Cheuk M. Tam, Wai M. Chan, Chi K. Chan, Kin S. Ho, and Kwok C. Chang

TB and Chest Service; Elderly Health Service, Department of Health; Department of Community Medicine, The University of Hong Kong; and the TB and Chest Unit, Grantham Hospital, Hong Kong, China

TABLE 4. ADJUSTED HAZARD RATIOS OF TUBERCULOSIS-RELATED OUTCOMES BY SMOKING STATUS IN COX PROPORTIONAL HAZARDS ANALYSIS

	Ex-smokers Versus Never-smokers			Current Smokers Versus Never-smokers			p Value
Outcome	HR*	95% CI		HR*	95% CI	p Value	for Trend
Active TB	1.41	1.02–1.95	0.04	2.63	1.87–3.70	< 0.001	< 0.001
Culture-confirmed TB	1.68	1.13–2.50	0.01	2.80	1.82–4.31	< 0.001	< 0.001
TB > 3 mo	1.48	1.04–2.10	0.03	2.39	1.63–3.50	< 0.001	< 0.001
Culture-confirmed TB > 3 mo	1.73	1.13–2.67	0.01	2.36	1.45–3.86	0.001	< 0.001
New TB	1.44	1.01–2.04	0.04	2.61	1.80–3.80	< 0.001	< 0.001
Retreatment TB cases	1.16	0.49–2.73	0.74	2.48	1.04–5.89	0.04	< 0.05
Pulmonary TB	1.39	0.98–1.97	0.06	2.87	2.00–4.11	< 0.001	< 0.001
Extrapulmonary TB	1.32	0.57–3.05	0.52	1.04	0.33–3.30	0.95	0.79
Extrapulmonary TB only	1.77	0.72–4.35	0.22	0.73	0.16–3.46	0.70	0.86

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; TB = tuberculosis.

* Adjusted hazard ratio, adjusted for sex, age, alcohol use, language, marital status, education, housing, working status, public financial assistance status, monthly expenditure, participation in social activities, self-rated health status, hospital admission within 12 months, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, heart disease, and cerebrovascular disease, with categories as listed in Table 1.

AJRCCM 2004

Residual confounding: a case study

- In the observational component of the Multiple Risk Factor Intervention Trial, subjects were followed to determine whether changes in risk behaviour (e.g. smoking cessation) reduces the risk of coronary heart disease
- A coincidental finding was an increased risk of suicide among smokers.
- After adjustment for a large number of confounding factors, compared with non-smokers, the RRs of suicide for those who smoked 1–19, 20–39, 40–59 and ≥60 cigarettes per day were 1.4, 1.9, 2.3 and 3.4, respectively (significant trend).

- One explanation is that depressed people tend to smoke and also to commit suicide.
- That is, depression confounded the association; it produced a statistically significant, but nevertheless spurious, dose-response relationship
- The confounding effect of depression could not be eliminated because it was not adequately defined or measured.

J Fam Plann Reprod Health Care 2008; **34**(3): 185–190
Lancet. 1992 Sep 19;340(8821):709-12.

Overadjustment and unnecessary adjustment

Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies

Enrique F. Schisterman,[a] *Stephen R. Cole,*[b] *and Robert W. Platt*[c]

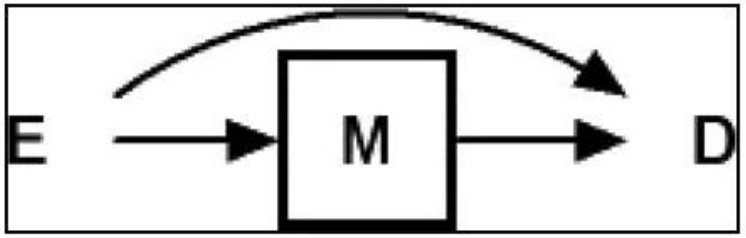
Abstract: Overadjustment is defined inconsistently. This term is meant to describe control (eg, by regression adjustment, stratification, or restriction) for a variable that either increases net bias or decreases precision without affecting bias. We define overadjustment bias as control for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome. We define unnecessary adjustment as control for a variable that does not affect bias of the causal relation between exposure and outcome but may affect its precision. We use causal diagrams and an empirical example (the effect of maternal smoking on neonatal mortality) to illustrate and clarify the definition of overadjustment bias, and to distinguish overadjustment bias from unnecessary adjustment. Using simulations, we quantify the amount of bias associated with overadjustment. Moreover, we show that this bias is based on a different causal structure from confounding or selection biases. Overadjustment bias is not a finite sample bias, while inefficiencies due to control for unnecessary variables are a function of sample size.

(*Epidemiology* 2009;20: 488–495)

confounding[1] and selection biases[2,3] have been discussed extensively in the epidemiologic literature, the concept of "overadjustment" has had relatively little attention. The definition of overadjustment remains vague and the causal structure of this concept has not been well described.

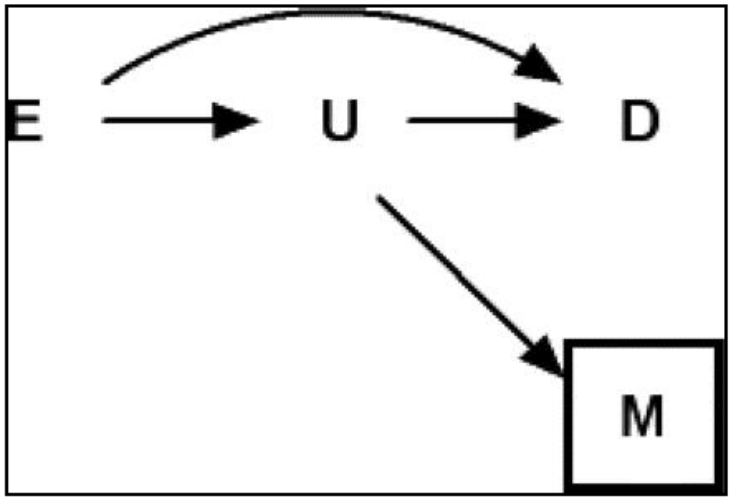
The Dictionary of Epidemiology[4] cites a seminal paper by Breslow[5] in broadly defining overadjustment as "Statistical adjustment by an excessive number of variables or parameters, uninformed by substantive knowledge (eg, lacking coherence with biologic, clinical, epidemiological, or social knowledge). It can obscure a true effect or create an apparent effect when none exists." Rothman and Greenland[6] discuss overadjustment in the context of intermediate variables: "Intermediate variables, if controlled in an analysis, would usually bias results towards the null. . . . . Such control of an intermediate may be viewed as a form of overadjustment." One also finds reference to the term overadjustment in settings with unnecessary control for variables.[7] In summary, overadjustment sometimes means control (eg, by regression

Overadjustment bias is control for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome



Example: mediating role of triglycerides (M) in the association between prepregnancy body mass index (E) and preeclampsia (D)

If M is adjusted for, then the causal effect will be biased towards null



Example: adjusting for prior history of spontaneous abortion (M); an underlying abnormality in the endometrium (U) is the unmeasured intermediate caused by smoking (E), and is a cause of prior (M) and current (D) spontaneous abortion. M is a “descending” proxy for the intermediate variable U.

If U is adjusted for, the observed association between the exposure E and outcome D will typically be biased toward the null with respect to the total causal effect

Schisterman E et al. Epidemiology 2009

Content area expertise is important for evaluation of confounding

American Journal of Epidemiology
Vol. 155, No. 2
Printed in U.S.A.

Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology

Miguel A. Hernán,[1] Sonia Hernández-Díaz,[2] Martha M. Werler,[2] and Allen A. Mitchell[2]

Common strategies to decide whether a variable is a confounder that should be adjusted for in the analysis rely mostly on statistical criteria. The authors present findings from the Slone Epidemiology Unit Birth Defects Study, 1992–1997, a case-control study on folic acid supplementation and risk of neural tube defects. When statistical strategies for confounding evaluation are used, the adjusted odds ratio is 0.80 (95% confidence interval: 0.62, 1.21). However, the consideration of a priori causal knowledge suggests that the crude odds ratio of 0.65 (95% confidence interval: 0.46, 0.94) should be used because the adjusted odds ratio is invalid. Causal diagrams are used to encode qualitative a priori subject matter knowledge. *Am J Epidemiol* 2002;155:176–84.

Know your field!

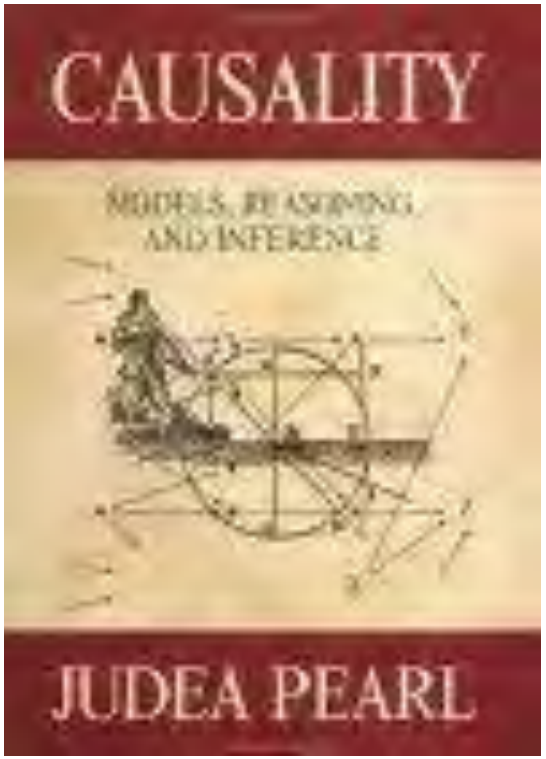
Do a systematic review on your research topic

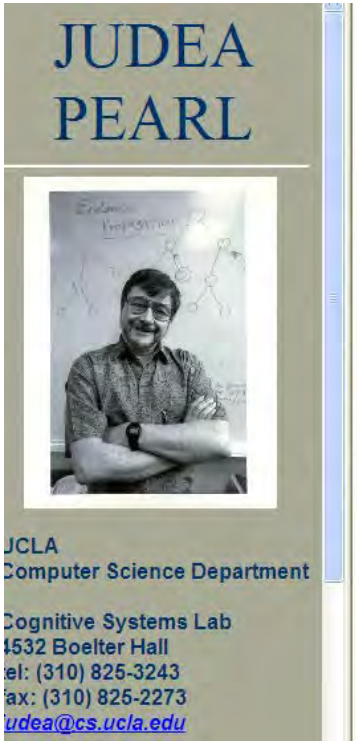
Newer approaches to address confounding [covered in EPIB610]

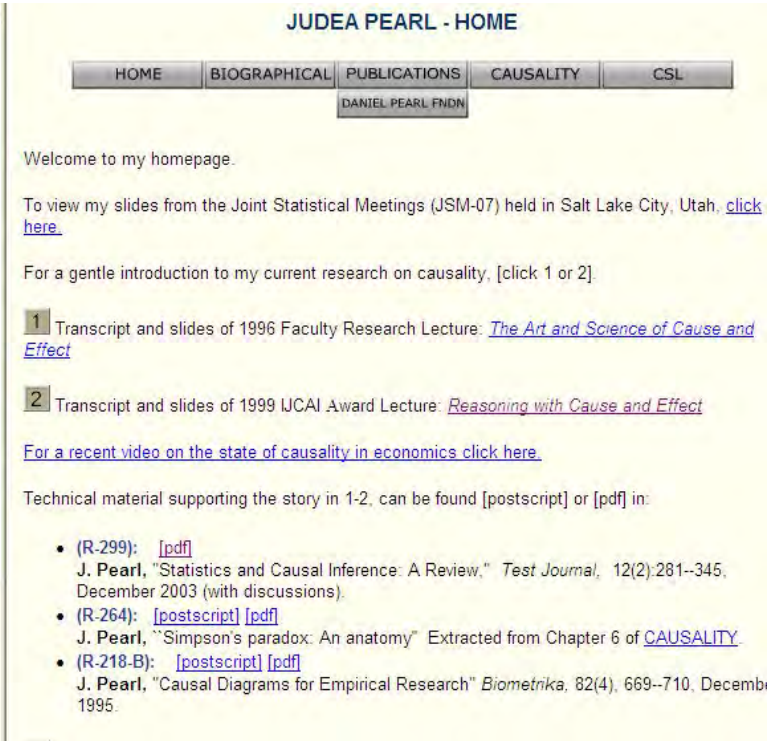
- Mostly based on the counterfactual causality model
  - Causal graphs (Directed Acyclic Graphs) [Pearl 2000]
  - Marginal structural models (Robins 2000)
  - Propensity score analysis (Rubin 1974; Rosenbaum & Rubin 1983)

You are not responsible for this material

Graphical solutions to the adjustment problem (based on directed acyclic graphs [DAG])



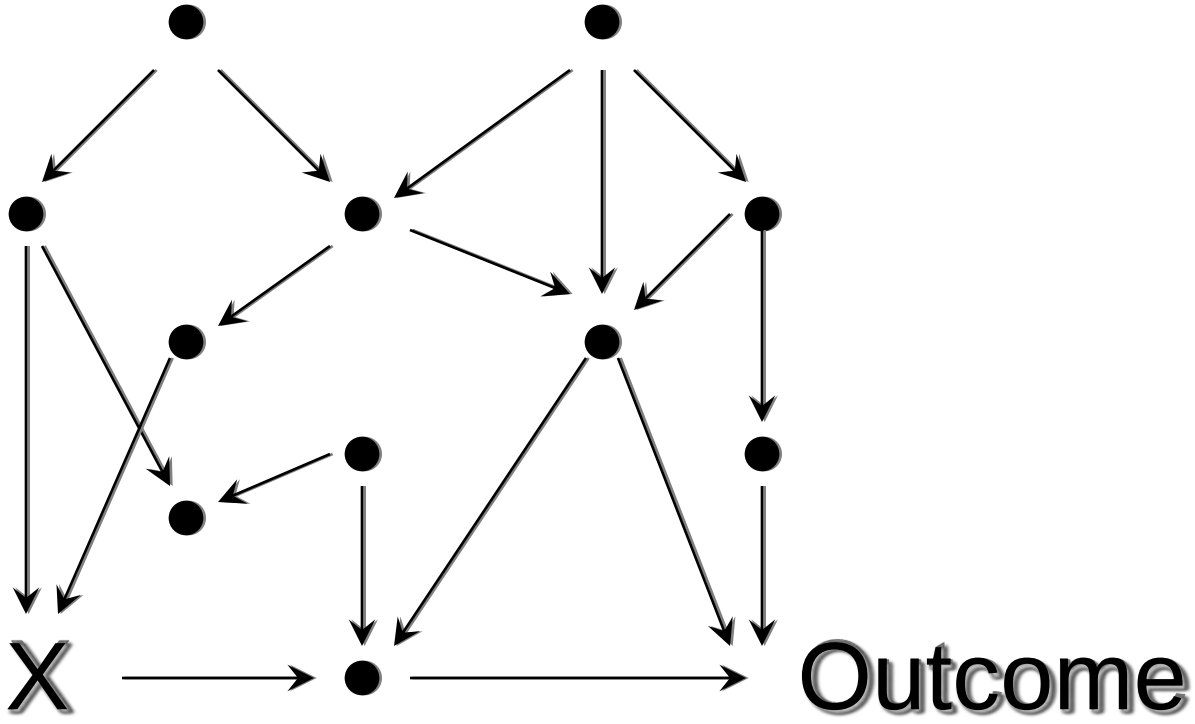




Pearl J. Causality: models, reasoning and inference. Cambridge: Cambridge University Press, 2000

Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10(1):37-48.

Graphical solutions to the adjustment problem

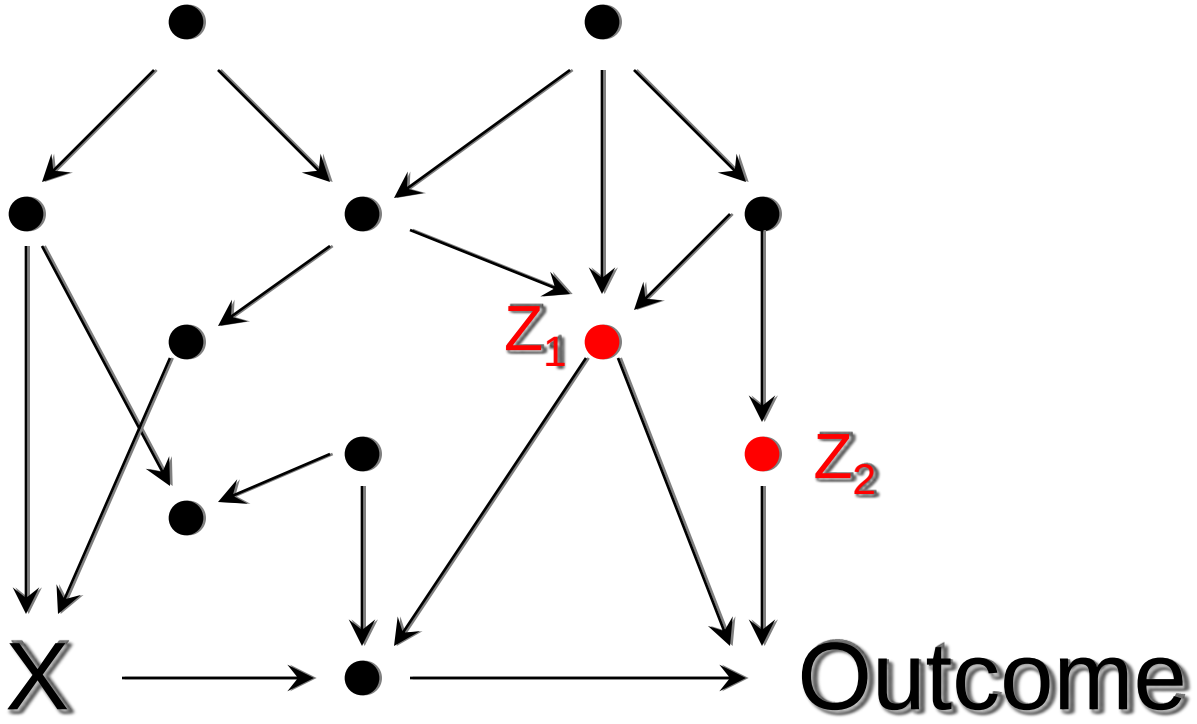


Which measurements should be included in the model if we are interested in the relation between X and Outcome?

Slide: Shrier, I

Pearl J. Causality: models, reasoning and inference. Cambridge: Cambridge University Press, 2000

Graphical solutions to the adjustment problem

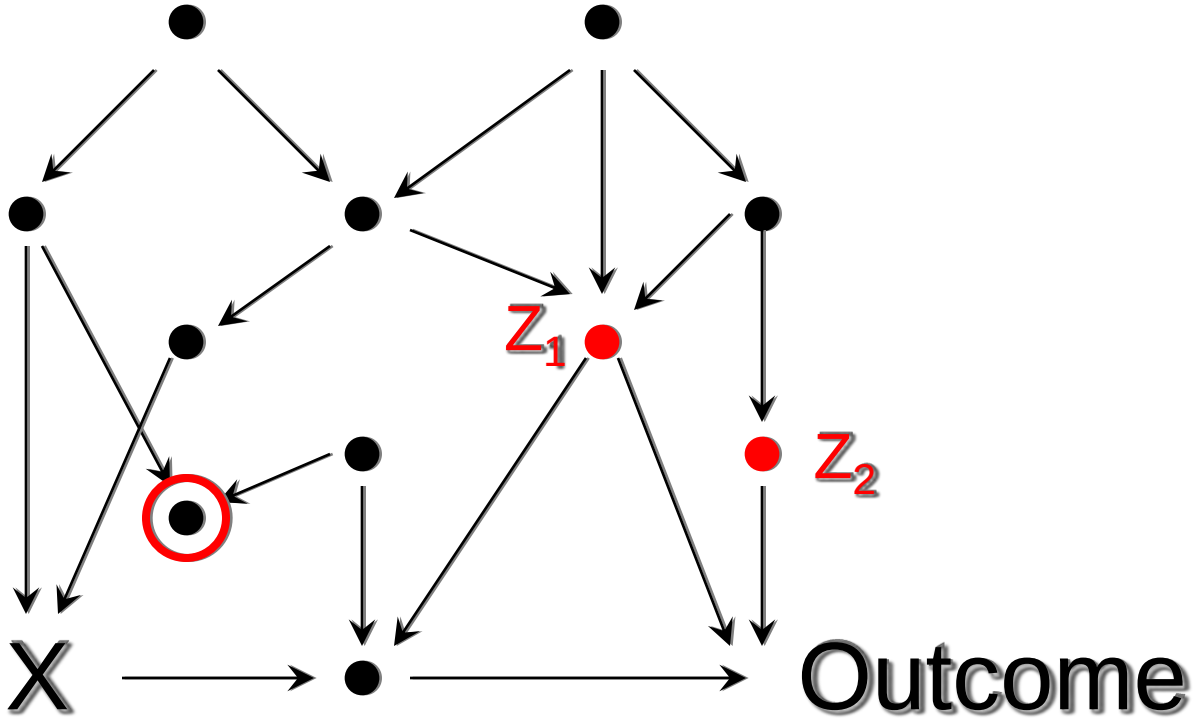


Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Slide: Shrier, I

Pearl J. Causality: models, reasoning and inference. Cambridge: Cambridge University Press, 2000

Graphical solutions to the adjustment problem



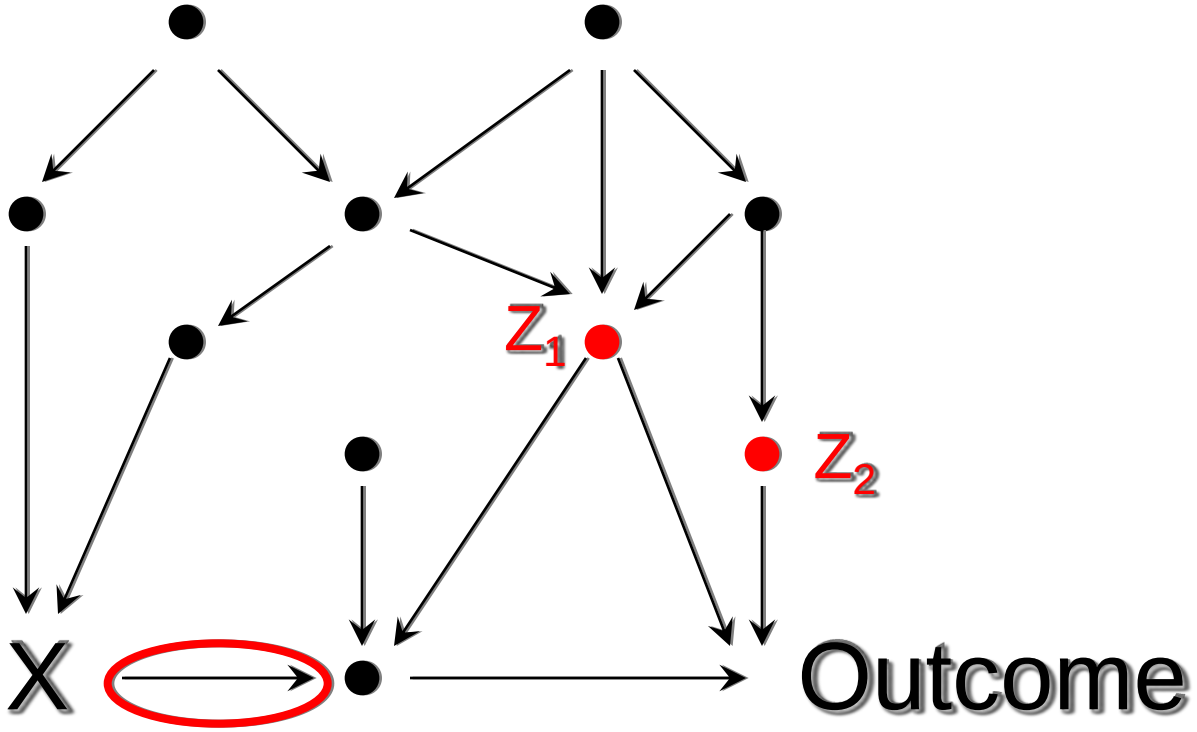
Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Step 1: Z_1 and Z_2 should not be descendents of X.

Step 2: Delete all non-ancestors of {X, Outcome, Z_1 and Z_2}.

Slide:
Shrier, I

Graphical solutions to the adjustment problem



Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Step 3: Delete all arcs emanating from X.

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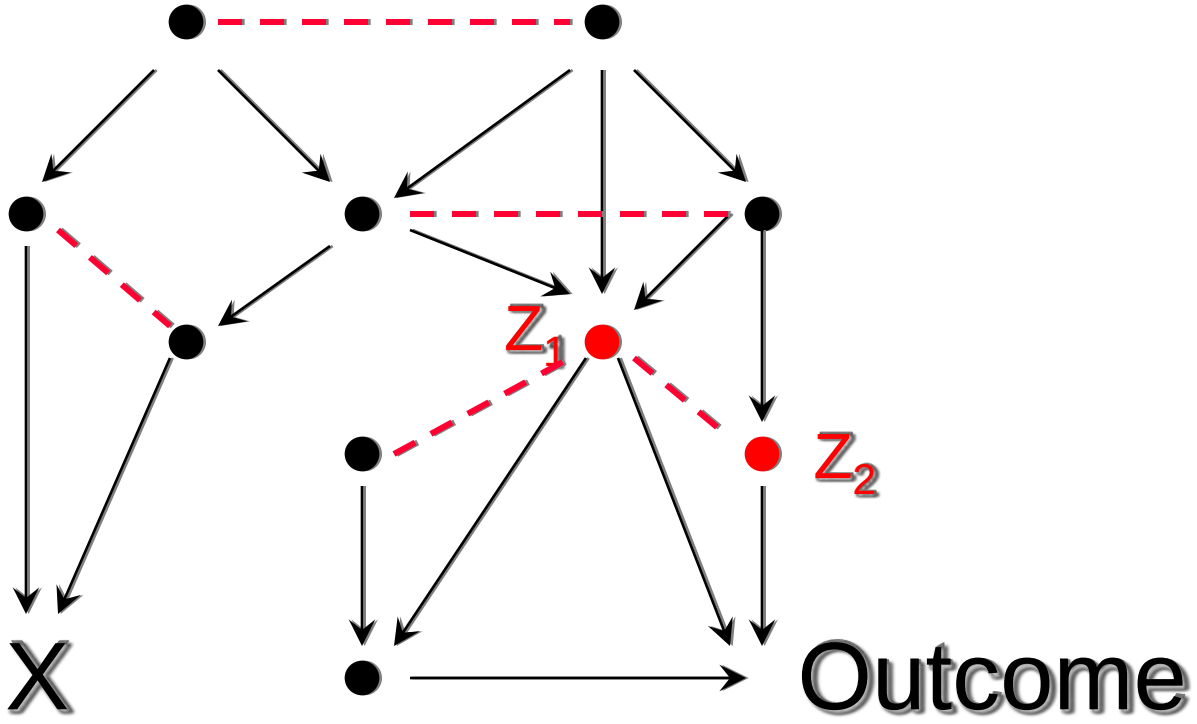
Shrier, I

Graphical solutions to the adjustment problem



Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Step 4: Connect any two parents sharing a common child.

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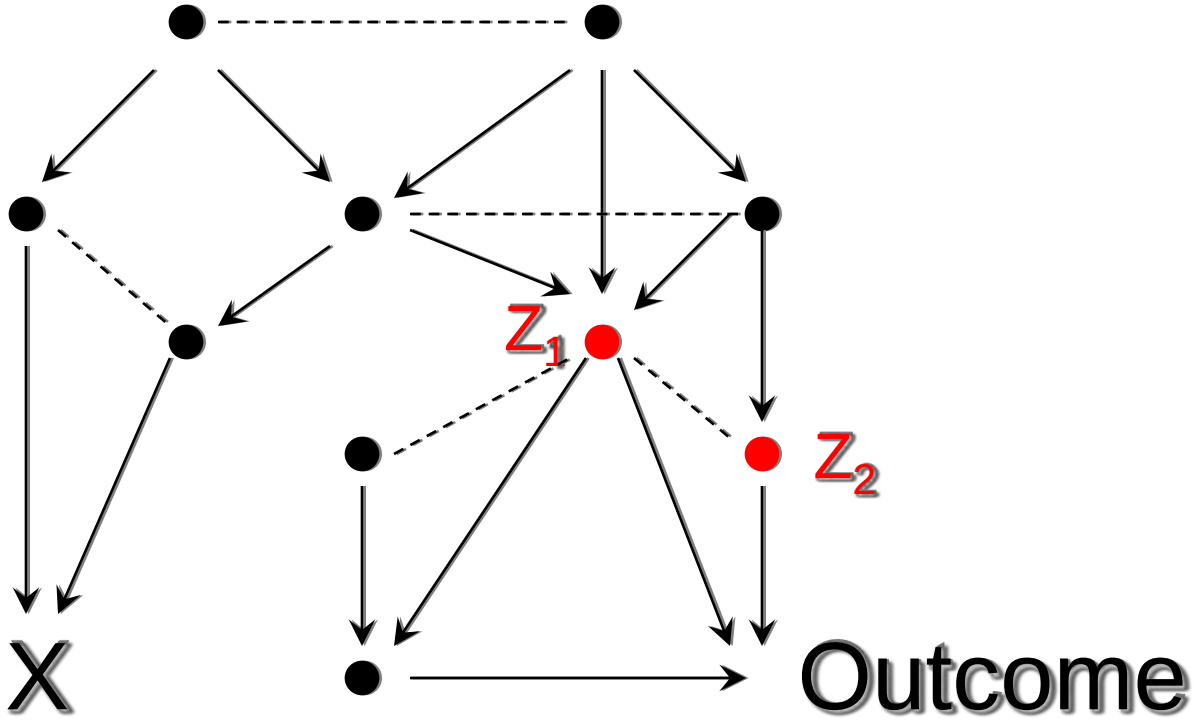
Shrier, I

Graphical solutions to the adjustment problem

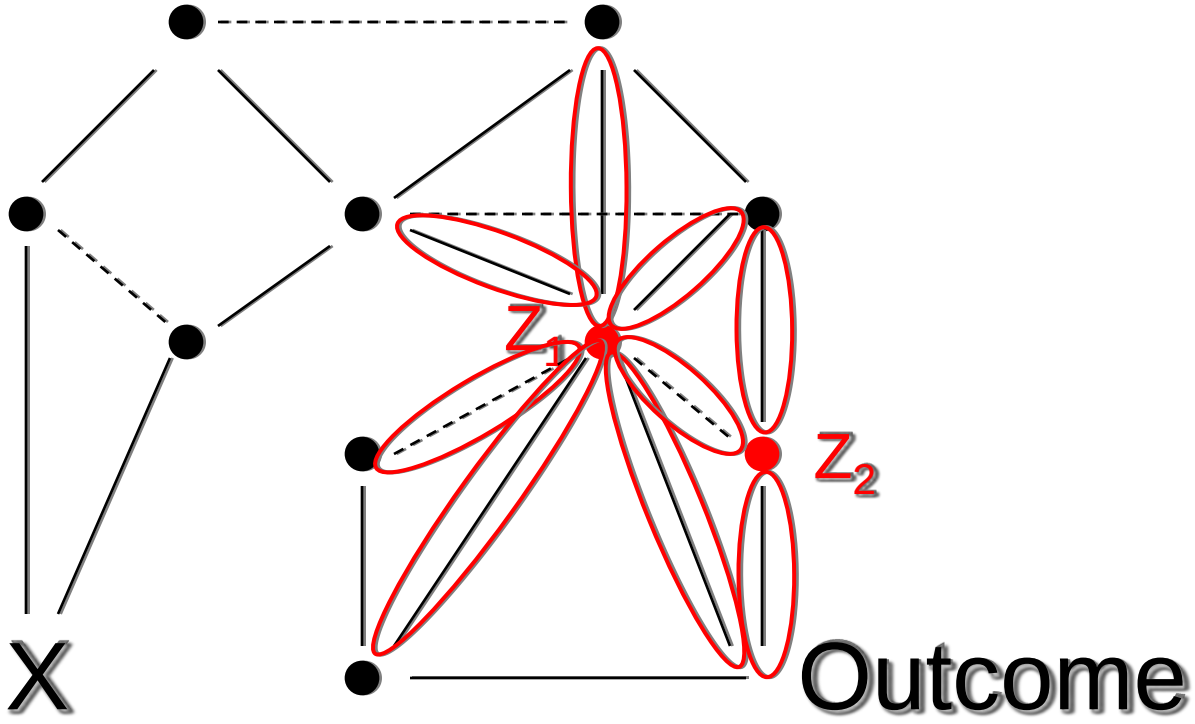


Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Step 5: Strip arrow-heads from all edges.

Slide:
Shrier, I

Graphical solutions to the adjustment problem



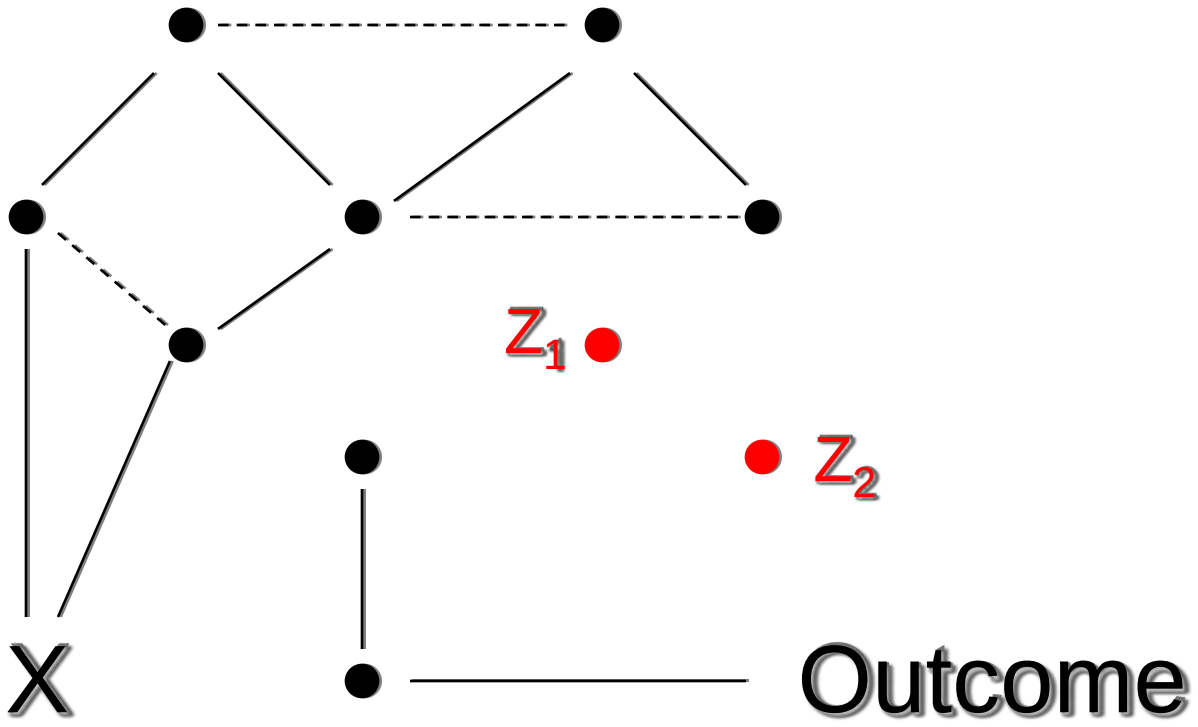
Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Step 5: Strip arrow-heads from all edges.

Step 6: Delete all lines from Z_1 and Z_2.

Slide:
Shrier, I

Graphical solutions to the adjustment problem



Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

If X is disconnected from Outcome, then there is no confounding

Slide: Shrier, I

Pearl J. Causality: models, reasoning and inference. Cambridge: Cambridge University Press, 2000

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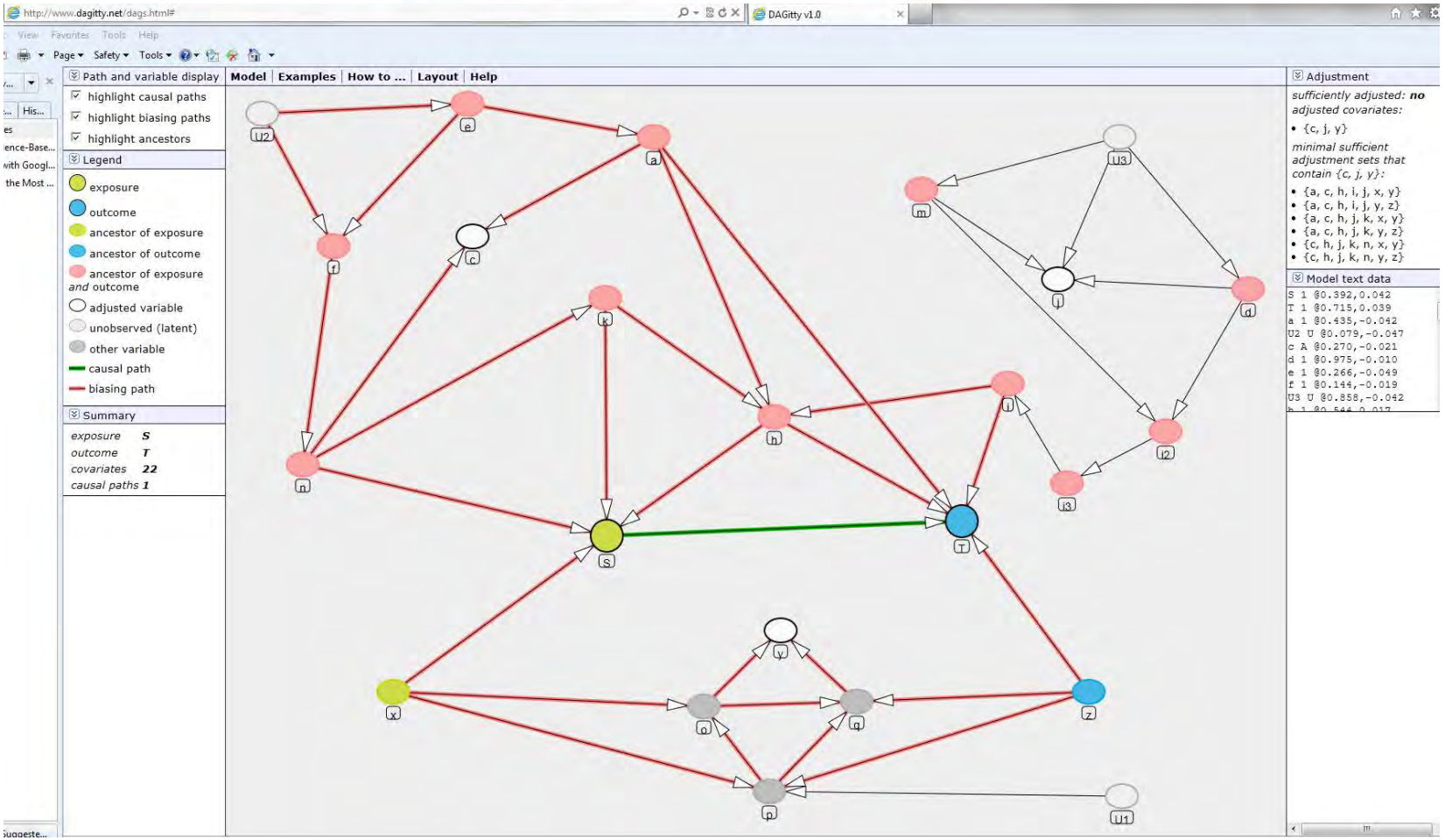

http://www.dagitty.net/

Reducing bias through directed acyclic graphs

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Email: Ian Shrier* - ian.shrier@mcgill.ca; Robert W Platt - robert.platt@mcgill.ca

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Abstract

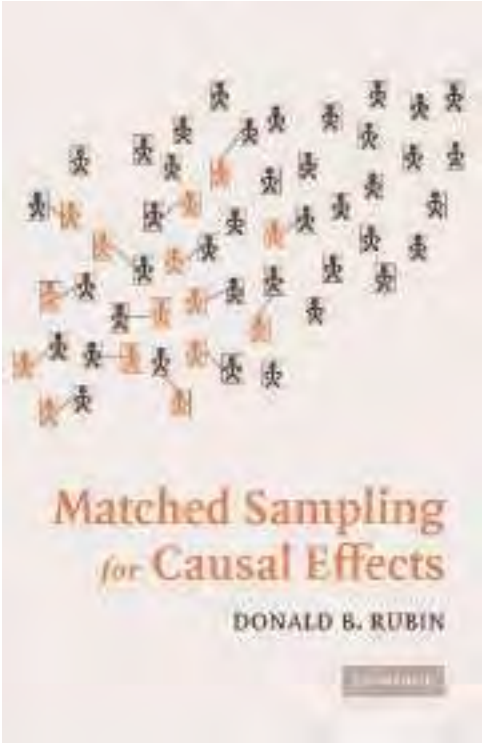
Background: The objective of most biomedical research is to determine an unbiased estimate of effect for an exposure on an outcome, i.e. to make causal inferences about the exposure. Recent developments in epidemiology have shown that traditional methods of identifying confounding and adjusting for confounding may be inadequate.

Discussion: The traditional methods of adjusting for "potential confounders" may introduce conditional associations and bias rather than minimize it. Although previous published articles have discussed the role of the causal directed acyclic graph approach (DAGs) with respect to confounding, many clinical problems require complicated DAGs and therefore investigators may continue to use traditional practices because they do not have the tools necessary to properly use the DAG approach. The purpose of this manuscript is to demonstrate a simple 6-step approach to the use of DAGs, and also to explain why the method works from a conceptual point of view.

Summary: Using the simple 6-step DAG approach to confounding and selection bias discussed is likely to reduce the degree of bias for the effect estimate in the chosen statistical model.

Newer analytical methods to address confounding

- Marginal structural models & propensity scores
  - Build on previously used methods such as “multivariate confounder scores” (Miettinen 1976) and “propensity scores” (Rosenbaum & Rubin)
  - Use a new class of estimators, the inverse-probability-of-treatment weighted estimators
  - Particularly helpful for observational studies with exposures (or treatments) that vary over time and are affected by time-dependent confounders



Robins et al. Epidemiology. 2000 Sep;11(5):550-60

Rosenbaum PR, Rubin DB. Biometrika (1983) 70:41–55

HEALTH CARE

The *Best* Medicine

A quiet revolution in comparative effectiveness research just might save us from soaring medical costs

By Sharon Begley

IN BRIEF

Soaring bill: U.S. health care costs are expected to top $2.7 trillion in 2011 and are growing at an unsustainable rate. One way to save money is to pay only for the most effective treatments.

Roadblock: Proving which treatments work best can be expensive and time-consuming. Randomized controlled trials, the most scientifically rigorous, often require hundreds of millions of dollars.

Sensible solution: Analyzing information found in the medical records of large health networks could reveal which treatments are most effective at a fraction of the cost of standard clinical trials.

Political reality: Many Americans fear that talk about cost-cutting in health care will lead to rationing. But who wants to spend money on something that does not work?

TEN COMMANDMENTS FOR DEALING WITH CONFOUNDING

I. Always worry about confounding in your research, especially at the design/protocol stage. Try to use design elements (e.g. randomization) that will help reduce potential confounding.

II. Prior to the study, review the literature and consider the underlying causal mechanisms (e.g. draw causal diagrams such as directed acyclic graphs [DAGs]). Then make sure you collect data on all potential confounders; otherwise you will not be able to adjust for them in your analyses.

III. Know your field or collaborate with an expert who does! Subject-matter knowledge is important to recognize (e.g. draw causal diagrams) and adjust for confounding.

IV. Use *a priori* and data-based methods to check if the potential confounders are indeed confounders that should be adjusted for.

V. Use stratified analyses and multivariable methods to handle confounding at the analysis stage. Choose the multivariate model that best suits the type of data (e.g. dichotomous vs. continuous) you collected and the design you employed (e.g. case-control vs. cohort).

VI. Do not adjust for covariates that may be intermediate causes (on the causal pathway between the exposure and disease). Do not adjust for covariates that may not be genuine confounders. And beware of time-varying covariates that will need special approaches.

VII. Use matching with great caution. Use analytic methods that are appropriate for the design used; for example, if matching was done, use methods that take matching into account (e.g. conditional logistic regression, matched pairs analyses).

VIII. Always consider effect measure modification, but perform and interpret subgroup analyses with caution. The subgroup analysis should be one of a small number of hypotheses tested, and the hypothesis should precede rather than follow the analysis (i.e. subgroups must be pre-specified).

IX. Always remember that adjustment for confounding can be inadequate due to residual confounding because of unmeasured confounders, misclassification of confounders, and inadequate adjustment procedures (e.g. model misspecification, categorization of continuous covariates).

X. If conventional methods prove to be inadequate, consider using newer approaches such as propensity scores, matched sampling, instrumental variables and marginal structural models. However, make sure you work with statisticians who understand these new methods (not many do).

When all else fails, pray! If prayer fails, consider changing professions!!

Readings for this lecture

- Rothman text:
  Chapter 8

- Gordis text:
  Chapters 15

Grades Don't Matter, Sources Say

Palo Alto, CA (AP) - Documents obtained by the Associated Press indicate that grades achieved in post-graduate classes have no effect on future prospects for students enrolled in academic institutions.

According to interviews with several current and past graduate students, "grades don't count," said former grad student and now billionaire Jerry Yang, co-founder of Yahoo! Inc. "I got mostly B's in grad school, which at Stanford was really really bad."

A poll conducted by the Los Angeles Times showed that over 85% of first year grads believe getting high marks "is worth the effort" and "a valuable way to spend my time". Fewer than 10% of fifth year students felt the same way.

In reality, neither employers nor your parents appear to care if you get an A or a B in your advanced Nonlinear Optimization class. "I'm just glad I don't have to pay for tuition any more," said a mother who wished to remain anonymous.

Reaction among graduate TA's was mixed, with some expressing shock that their late hours grading amount to nothing, while others showed visible relief that losing a student's final exam will not really ruin their life.

Sources close to academic faculty reveal that this fact is well known among professors. "Of course grades don't matter," said Prof. Smith, "we only care about the lab work." Grades only serve to "feed the ego of the smart students, and break the spirit of the mediocre ones."

NOW you tell me?? A grad student expresses frustration over the revelation

Continued on page A23