Confounding and Bias in Pharmacoepidemiology

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ISPE

Learning Objectives

- Describe threats to our ability to estimate population value of parameters of interest
- Understand confounding, how to address
- Identify potential biases with different study designs

Outline

- Definition of confounding
- Options to address confounding
  - Identifying effect modifier vs. confounder
- Bias in study design

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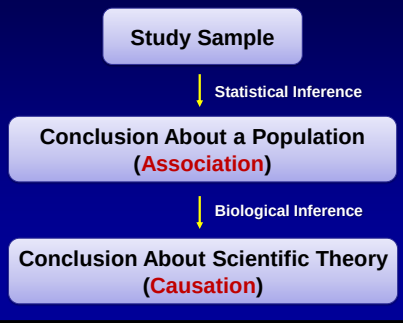
Causal Pathway

- We develop conceptual model
- Explain how exposure *causes* outcome

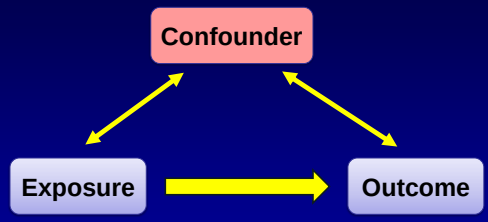
Overview of the Scientific Method



Criteria Supporting Causal Nature of an Association

- Coherence with existing information
- Time sequence
- Specificity
- Consistence
- Strength of association
  - Quantitative strength
  - Dose-response relationship
  - Study design

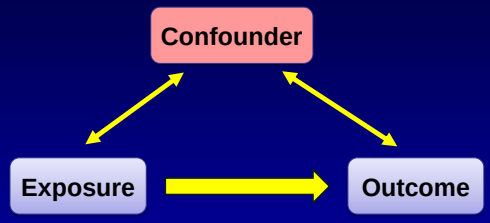
Confounding of an Association



Confounder:

- Independently assoc. with exposure and outcome
- Not in causal pathway

Confounding of an Association



Failure to account for confounding will result in inaccurate estimate of measure of association

Selecting Potential Confounders

- Must select potential confounders to measure before starting study
  - Ensure data on factors will be available
  - Ensure accurate measurement of factors

Study Question

- Is alcohol a risk factor for oral cancer?
- Study designs to answer question:
  - Randomized controlled trial
    - May be unethical to randomize alcohol use
  - Cohort study: OK
  - Case-control study: OK

What Else May Affect Risk of Oral Cancer?

- Age
- Sex
- Tobacco use
- Mouthwash use

Risk of Oral Cancer With Alcohol

- Cohort study: alcohol users more likely to develop oral cancer
- Smoking more common in alcohol users
- How will we know if ↑ risk of oral cancer was due to alcohol or, in part, smoking?
- Answer: Must control for confounding

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Options for Controlling Confounding in Observational Studies

Design Stage	Analysis Stage
Restriction	Stratification
Matching	Adjustment (Modeling)

Restriction

- Restriction of inclusion criteria
- Controls for confounding by assuring that no patients are exposed to the potential confounder

Restriction in Study of Alcohol and Oral Cancer

- Limit study to non-smokers
  - If observe relationship between alcohol and oral cancer → not due to smoking
  - Advantages:
    - Complete control
    - Convenient
    - Inexpensive
    - Easy analysis

Matching in a Cohort Study

Match Group	Alcohol Drinker Group	Non-Drinker Group
1	Smoker	Smoker
2	Smoker	Smoker
3	Non-smoker	Non-smoker
4	Smoker	Smoker
5	Non-smoker	Non-smoker
…1,0000		

Matching in a Cohort Study

- Proportion of smokers is same in alcohol and non-alcohol groups
- Thus, smoking cannot account for differences in oral cancer in groups
- But, cannot match on all confounders!

Stratification

- Can reduce or eliminate confounding
- Evaluates effect of exposure in strata of confounding variable
- Confounding exists when "crude" estimate of exposure-disease relationship differs from estimate "adjusted" for factor
  - How much should it differ? 15%

You examine if chronic renal insufficiency is associated with death in your ICU. You perform a case-control study and stratify on infection status. Is infection a confounder?

```
. cc status chr_renal, by(infection)

    0/1=probable |      OR       [95% Conf. Interval]    M-H Weight
-----------------+-------------------------------------------------
               0 |   2.238095      .2002529    14.11748      .7241379  (exact)
               1 |   3.666667      .8087737     16.8891      1.071429  (exact)
-----------------+-------------------------------------------------
           Crude |   3.386364      1.081399    10.04129               (exact)
     M-H combined |   3.090535       1.11603    8.558381
-----------------+-------------------------------------------------
Test of homogeneity (M-H)       chi2(1) =     0.21  Pr>chi2 = 0.6504

                Test that combined OR = 1:
                        Mantel-Haenszel chi2(1) =      4.91
                                 Pr>chi2 =     0.0267
```

The "crude" OR is 3.39 and "adjusted" OR is 3.09, a 9% difference. Since this is <15%, infection is not a confounder.

Confounder Must Be a Risk Factor

- To be a confounder, variable must be:
  - Risk factor for outcome of interest
  - Risk factor for exposure of interest
  - Not be part of causal pathway
- Never adjust for variables in causal pathway → will adjust away association

We can confirm that infection is not a confounder via 2x2 table analysis.

Infection is a risk factor for death but not renal insufficiency. This is further evidence that infection is not a confounder in the association between renal insufficiency and death.

```
. ta infection chr_renal, chi2

0/1=probab |       0/1=yes
        le |         0          1 |     Total
-----------+----------------------+----------
         0 |       108          8 |       116
         1 |        73         11 |        84
-----------+----------------------+----------
     Total |       181         19 |       200

          Pearson chi2(1) =   2.1774   Pr = 0.140

. tab infection status, chi2

0/1=probab |       0/1=died
        le |         0          1 |     Total
-----------+----------------------+----------
         0 |       100         16 |       116
         1 |        60         24 |        84
-----------+----------------------+----------
     Total |       160         40 |       200

          Pearson chi2(1) =   6.6502   Pr = 0.010
```

Effect Modifier (Interaction)

- Variable that alters magnitude of relationship between exposure and disease
- Within different strata, association between exposure and outcome is different
- If effect modification is identified, report only stratum-specific measures of effect

A prospective cohort study evaluated the effect of a new antiviral drug on cure of chronic hepatitis C virus infection.

Is disease stage an effect modifier in the association between the new therapy and cure? Is it a confounder?

```
. cs cure tx [fweight = count], by(stage)

      stage |        RR       [95% Conf. Interval]    M-H Weight
------------+------------------------------------------------
          1 |  3.298969   .9367269    11.61832      1.507772
          2 |   .969697   .5580333    1.685047      10.15385
          3 |         .5  .2874207    .8698052            15
------------+------------------------------------------------
      Crude |   .837544   .5827012    1.203842
M-H combined |  .8371678   .5843798    1.199305
------------+------------------------------------------------
Test of homogeneity (M-H)       chi2(2) =     8.159  Pr>chi2 = 0.0169
```

The test of homogeneity is significant (p=0.02), so disease stage is an effect modifier.

Thus, we have detected an interaction between drug therapy and disease stage.

```
. cs cure tx [fweight = count], by(stage)

      stage |        RR       [95% Conf. Interval]    M-H Weight
------------+------------------------------------------------
          1 |  3.298969   .9367269    11.61832      1.507772
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```

The results should therefore be reported separately, by disease stage. Reporting a combined RR is not appropriate.

Note that for those with stage 3 (severe disease), the new drug treatment was significantly associated with failure.

```
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```

Effect Modification

- **Finding of potential clinical and public health importance**
- **Can lead to further insight into biology**
- **Important to discover, describe effect modifiers**

Confounder vs. Effect Modifier

Confounder	Effect Modifier
Associated with exposure and outcome	Alters magnitude of association between exposure and disease
Within strata of confounder, assoc. between exposure and outcome is ≈ equal	Within strata of confounder, assoc. between exposure and outcome is different
Report adjusted association	Report only stratum-specific relationships

Mathematical Modeling

- **Multivariable regression can adjust for a number of potential confounders**
  - **Linear (continuous outcome)**
  - **Logistic (dichotomous outcome)**
  - **Poisson (rates of dichotomous outcomes)**
  - **Cox (time to event)**

Adjusting for Confounding: Example

- Case-control study of alcohol drinking and oral cancer

Association	Group	Odds Ratio
Alcohol-Oral Ca	Smokers	2.0
Alcohol-Oral Ca	Non-smokers	2.0
Alcohol-Oral Ca	Crude (All Patients)	2.8
Alcohol-Oral Ca	Adjusted for Smoking	2.0

- Adjusted OR is weighted average of stratum specific ORs

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Bias

- Systematic difference between study groups in collecting or interpreting data
- Can lead to over-estimation or under-estimation of measure of association
- Different types of bias:
  - Selection
  - Information
  - Misclassification

Selection Bias

- Distortion in estimate of effect resulting from manner in which subject are selected
- Selection bias in case-control study:
  - Selection of cases or controls is related to probability of exposure

Information Bias

- Distortion in estimate of effect resulting from measurement error
- Information bias in cohort study:
  - Hepatitis C patients may present with less advanced stage of liver cancer because they are screened more frequently than uninfected

Misclassification Bias

- Distortion in estimate of effect resulting from inaccuracy of measurement
- Can affect exposure or outcome
- Differential or non-differential between groups
- Misclassification in cohort study:
  - Lack of validation of algorithm for outcome can lead to inaccurate estimation of effect

Direction of Bias

- Null effect: RR or OR = 1
- Bias toward the null: underestimate effect
- Bias toward the null: overestimate effect
- Switchover: misestimate magnitude, direction of effect

Implication of Direction of Bias

Study Effect	Direction of Bias	Implication
Yes	Toward the null	Real effect even stronger
No	Toward the null	Might have missed real effect
Yes	Away from the null	Spurious conclusion
No	Away from the null	Nothing going on

Statistics Will Not Fix Bias

- Potential for bias must be addressed in design of study to minimize its effects
- Cannot fix bias after data are collected
- Bias may occur if question is unclear

Sources of Bias: Case-Control Studies

- Selection bias
  - Selection dependent on exposure of interest
  - Sampling frame
  - Non-response
  - Selective survival (depletion of susceptible)
- Information bias: recall
- Misclassification

Sources of Bias: Cohort Studies

- Selection bias
  - Non-participation, loss to follow-up
- Information bias:
  - Ascertainment of disease pursued more vigorously in one group
- Misclassification
  - Errors in measuring exposure/outcome are made differently in the groups

Summary

- Confounder: associated with exposure and outcome
- Failure to account for confounder can yield inaccurate estimates of association
- Effect modifier alters magnitude of assoc. between exposure and outcomes
- Minimize bias in study design