Epidemiology VHM 811 Course
Fall 2009, Atlantic Veterinary College, PEI
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Index of Lecture 11a

Practical Information

Home assignment news:

- now posted, deadline Nov 27,
- same rules as in VHM 801.

Today's session:

- matching in cohort and case-control studies,
- note on dealing with unmeasured confounders,
- review-type material:
  - different causation scenarios,
  - operational summary of confounding & interaction,
- problem: home assignment 2007:1–4.

Last session on Friday:

- start in 1003N, later move to small computer lab (225N),
- homework for you:
  - Problem 13.9,
  - Problem on matching (webpage),
  - prepare a causation scenario (L11a–9),
- questions/discussion of Chapter 13 material,
- work on remaining problems for Chapter 13 (webpage).

Introduction to Matching

Matching

= idea/principle for study design, to account for potential effect of confounder(s) Z for exposure/treatment variable(s) E:

> confounding can be eliminated (reduced) by making the E-groups being compared as equal as possible with respect to Z,

i.e., matching attempts to eliminate association between Z and E,

- varies in its implementation in different study designs,
  - ∗ experiments/randomised trials: matching ∼ blocking by strata of Z (treatments are randomised within blocks),
  - ∗ observational studies discussed on following slides,
- individual matching: individuals are selected in pairs (or clusters, if not 1-1 matching) with the same value of Z,
- frequency matching: treatment/exposure groups have the same distribution of Z,
- caliper-matching: for a continuous Z, define groups/ranges for Z to perform the matching on.

Matching — "a double-edged sword",

- can have both strong advantages and disadvantages,
- some disagreement among epidemiologists on how much to use it,
- will be treated in more detail in VHM 812 (Winter semester).

Frequency Matching in Cohort Studies

Matching procedure:

1. select random sample among exposed individuals,
2. select sample among unexposed individuals subject to the restriction:
   distribution of confounder(s) should be same as for exposed individuals (observed/theoretically),

— illustrated on next slide in our BRD–Mh–BRSV causal complex and with constructed data.

Notes:

- if succesful, the matching eliminates confounding and bias (crude and stratified risk measures are the same),
- (additional) analytic control for the confounder may still be produce a smaller variance estimate,
- the matching is undertaken at study onset, and is therefore independent of the outcome,
- examples of commonly used matching variables:
  age, breed, sex, farm, region/neighbourhood; also stage of disease has been used.

Example 13.2 — Matching in Cohort Study

Aim: study design with 500 Mh+ and 500 Mh−, and frequency matching of Mh− group to distribution of BRSV in Mh+ group:

- prev. of BRSV among Mh+: 0.85 (5500/6500, Ex. 13.1),
- expected no. of BRSV+ individuals in Mh+ group: $0.85 \cdot 500 = 425$,
- need to have also 425 BRSV+ indiv. in Mh− group[1],
- expected counts (based on BRD risks, Ex. 13.1):

BRSV (Z)	BRD (Y)	Mh (E) +	Mh (E) −	total
+	1			
	0			
total		425	425	850

BRSV (Z)	BRD (Y)	Mh (E) +	Mh (E) −	total
−	1			
	0			
total		75	75	150

- stratum-specific OR ≈ 2, and crude OR ≈ 2
  $\Rightarrow$ no confounding bias.

[1] In general, we need to have the same prevalence, but as the $E+$ and $E-$ groups are of the same size, the numbers are also the same.

Frequency Matching in Case-Control Studies

Matching procedure:

1. select random sample among cases (possibly all cases),
2. select sample among controls subject to the restriction: distribution of confounder(s) should be same as for cases (observed/theoretically),

— illustrated on next slide in our BRD–Mh–BRSV causal complex and with constructed data.

Notes:

- if successful, the matching eliminates confounding but will introduce selection bias for the exposure:
  - bias for association $E \rightarrow Y$ in the direction of the null,
  - increases with source population strength of $E - Z$ association,
  - intuitive explanation: the matching of controls by Z will make distribution of E among controls more similar to that of E among the cases (because of the $E - Z$ association) $\Rightarrow$ reduced effect of E,
- analytic control for the confounder is necessary (and eliminates the selection bias).

Ex. 13.3 — Matching in Case-Control Study

Aim: study design with 280 BRD cases[2] and 280 controls, and frequency matching of controls to distribution of BRSV among cases:

- prev. of BRSV among cases: 0.82 (230/280, Ex. 13.1),
- expected no. of BRSV+ individuals among cases: 230,[3]
- need to have also 230 BRSV+ indiv. among controls[4],
- expected counts (based on BRD risks, Ex. 13.1):

		Mh (E)	
BRSV (Z)	BRD (Y)	+ −	total
+	1		230
	0		230

		Mh (E)	
BRSV (Z)	BRD (Y)	+ −	total
−	1		50
	0		50

- stratum-spec. and M-H OR ≈ 2.1; crude OR ≈ 1.6 $\Rightarrow$ adjustment for Z required,
- selection bias for Mh:

$$\begin{aligned} \text{study}: &\quad p(\text{Mh}+|\text{BRD}-) = 0.79 \quad ((210{+}12)/280), \\ \text{popul.}: &\quad p(\text{Mh}+|\text{BRD}-) = 0.64 \quad (6260/9720), \\ \text{cases}: &\quad p(\text{Mh}+|\text{BRD}+) = 0.86 \quad (240/280). \end{aligned}$$

[2] All cases in entire population.

[3] Number in total population because all cases included in study; in general, prevalence times no. of cases.

[4] In general, we need to have the same prevalence, but as the case and control groups are of the same size, the numbers are also the same.

Pros/Cons of Matching

Advantages:

- may lead to gain in efficiency when random sampling would lead to highly unbalanced and/or sparse data,
- matching on broad variables like farm or neighbourhood may provide efficient adjustment for largely unmeasurable factors,
- matching on convenient variables like closest case may facilitate the logistics of data collection,
- does not preclude analytic control for (additional) confounders (so matching is only for strongest confounders).

Disadvantages:

- effect of matched factor(s) on the outcome is lost (but interactions are possible),
- low efficiency for factors with strong link to matching variable (possible *overmatching*),
- can be difficult/costly to find appropriate subjects,
- for pair-matching in a case-control design, the matched analysis may have very low efficiency.

Recommendation against matching on

- factors whose confounding effect is uncertain or weak,
- intervening variables (!), and uncertain/weak risk factors.

Adjusting for Unmeasured Confounder

yes, it *is* possible, but requires strong external information:

(i) assume confounding effect (but no interaction) of Z,

(ii) assume known distribution of Z in exposed and non-exposed groups,

(iii) assume known assocation between Z and Y after adjustment for exposure,

- information for (ii) and (iii) can perhaps be found in literature and assumed valid for actual study,
- approach invites sensitivity analysis: to try a range of different values for (ii) and (iii), and note the impact on results (note: `episens` package for Stata).

How does it work?

- example given in VER (Ex. 13.13) for case-control study and dichotomous confounder[5], (constructed data)
- step 1: assumed prevalences of confounder allow calculation of expected no. of non-cases (within E groups),
- step 2: assumed OR for association (Z, Y) within strata of E allows calculation of expected no. cases (within E),
- compute quantities of interest from constructed tables.

[5] Rothman & Greenland (1998), Chapter 19, gives more detail, including extensions to other study designs and multiple-category confounders.

Causation Scenarios — Introduction

Purpose: to provide an overview of different relationships between variables, in order to

- aid in interpretation of findings in the data analysis[6],
- clarify terminology[7] and concepts.

Methods:

- causal diagrams: single- and double-headed arrows, line (non-headed arrow (!)), absence of arrow,
- Venn diagrams: circles representing factors, amount of overlap indicating strength of association (zero to total),

both with a temporal dimension (from left to right).

List of scenarios: (Y=BRD, E=Mh, Z=BRSV)

1. Exposure-independent variable — next slide,
2. Simple antecedent variable,
3. Explan. antecedent variable – complete confounding,
4. Explan. antecedent variable – incomplete confounding,
5. Intervening variable,

6.–8. Distorter, Suppressor and Moderator variables — following slides.

Idea: Scenarios 2–5 are for student preparation (Friday).

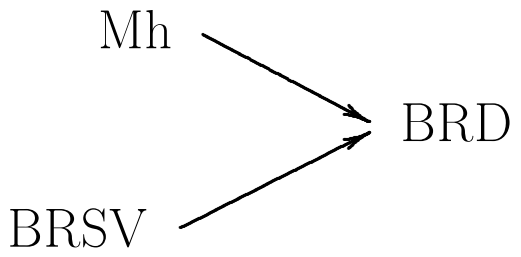
[6] We caution that inferring causal structure from data has some limitations; see Thompson (1991) paper referred in VER.

[7] Terminology is from VER, and not all is in general use in epidemiology.

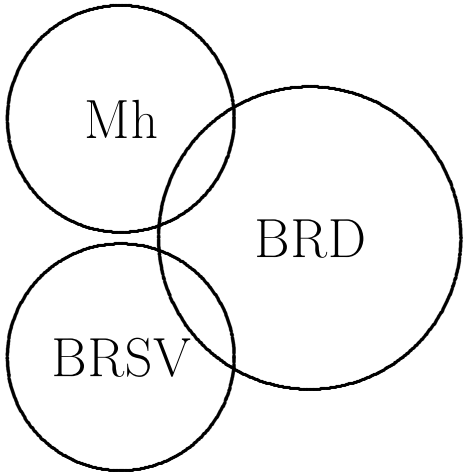
Exposure–Independent Variable Z

Assumption:
no relation between BRSV and Mh:

Causal model:



Statistical model:



* independence of BRSV and Mh: no connecting arrow (left), disjoint circles (right),
* associations of Mh and BRSV with BRD: directed arrows (left), overlapping circles (right).

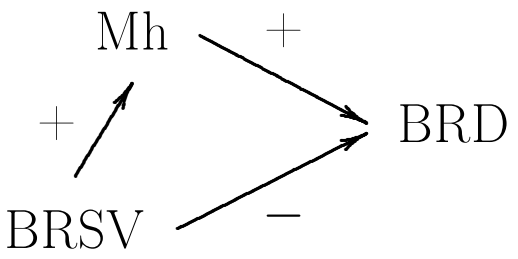
Implications for (statistical) modelling:

- crude and stratified estimates for Mh should be similar,
- inclusion of BRSV in model may reduce residual variation $\Rightarrow$ improve estimation precision.

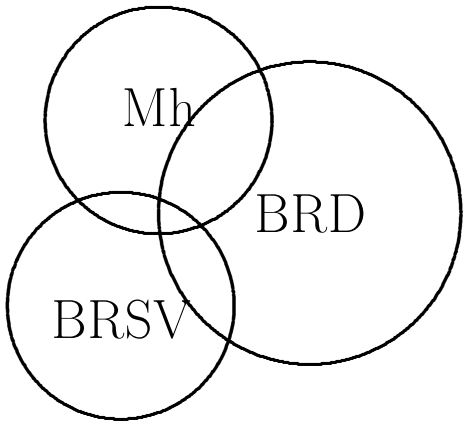
Distorter Variable Z

Assumption:
confounding by Z (BRSV), and different directions (signs) on some of the causal relations:

Causal model:



Statistical model:



* positive associations (Mh,BRD) and (BRSV,Mh), but negative association (BRSV,BRD)[8].

Implications for (statistical) modelling:

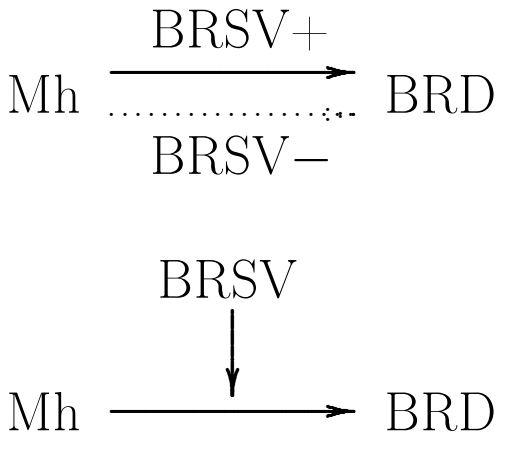
- control for confounding by BRSV required,
  - will usually increase the strength of association,
  - may change the direction of association from negative to positive (or vice versa, for different distribution of + and −),
- for an artificial data example, see Problem 13.2.

[8] Similar effects are produced by other sign-reversed relations, e.g. a positive association (BRSV,BRD) and a negative association (BRSV,Mh).

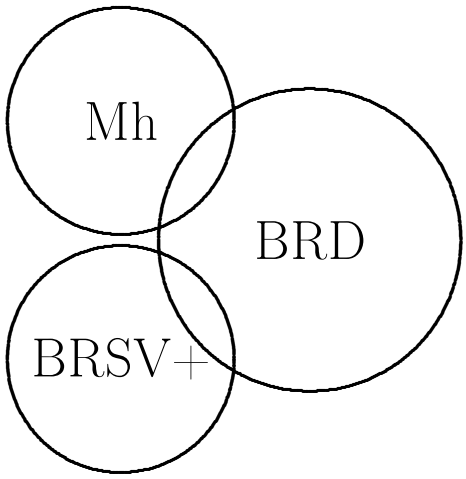
Moderator Variable Z

Assumption:
interaction between Z (BRSV) and E (Mh):

Causal model:



Statistical model:



* positive association (Mh,BRD) only for BRSV+,
* statistical model for BRSV− (not shown): no association between Mh and BRD (disjoint circles),
* other interaction effects possible, but would not be called moderator effects (in VER terminology).

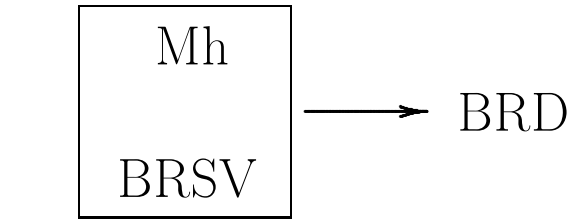
Implications for (statistical) modelling:

- statistical model needs to include BRSV+ (either as single term, or as part of the interaction BRSV $*$ Mh),
- test for homogeneity (X^2_{hom}) statistically significant,
- Mh effect reported separately for BRSV+ and BRSV−.

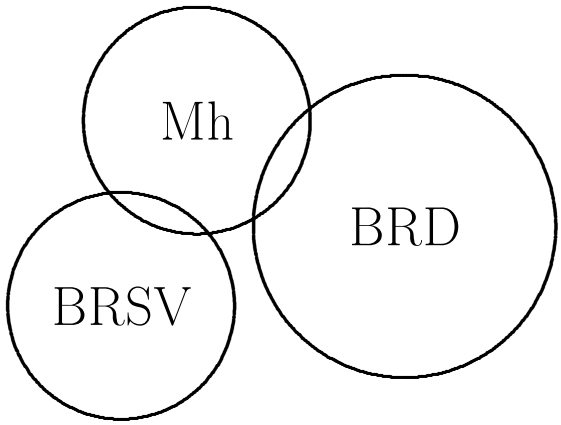
Suppressor Variable Z

Assumptions:
no relation between BRSV and BRD, but Mh and BRSV measured only via "proxy variable":

Causal model:



Statistical model:



* indirect measurement of BRSV and Mh by proxy variable (in the example, cattle contact).

Implications for (statistical) modelling:

- need to refine measurement of predictors whereby the (irrelevant) BRSV component is eliminated,
- statistical association of proxy variable with BRD will increase by removal of BRSV,
- note: suppresion of outcome possible as well (e.g., by including multiple reasons of mortality of which only one is of interest).

Confounding & Interaction Summary

Setting: risk outcome Y, binary/categorical exposure E, binary/categorical potential confounder Z.

Approach of Chapter 13 (without multivariable modelling):

1. Is interaction $Z * E$ present?
   - $*$ subjective assessment: compare stratum-specific estimates for $E \rightarrow Y$ (RD, RR, OR, IRR),
   - $*$ statistical assessment: compute chi-square test (X^2_{hom}) for homogeneity across strata,

   1a. interaction present: report stratum-specific point estimates instead of a single estimate,

   1b. interaction absent: compute stratified estimate (Mantel-Haenszel estimate), and proceed to Question 2,

2. Is Z a confounder for the relation $E \rightarrow Y$?
   - $*$ check necessary conditions for confounding (using graphical approach), and use the data to assess the relations between Z and both E and Y (recall slightly different approaches for $Z - E$ relation in cohort and case-control studies),
   - $*$ assess the relative difference between the crude estimate and M-H estimate for the association $E \rightarrow Y$ ("20-30% rule"),

   2a. confounding present: report the M-H estimate and the evidence obtained for confounding,

   2b. confounding absent: report the crude estimate, and note that Z was not found to be a confounder (perhaps only in cases where a confounding effect might have been expected).

Stata Do-file for Home Assignment 3 (2007)

```
* crude associations
cc case aircirc [fw=n]
tabulate case hsize [fw=n], chi2 expected
* odds-ratios against baseline category
cci 23 6 48 34
cci 20 6 29 34
cci 9 6 9 34
cci 58 6 13 34
* odds-ratios at a cutpoint
gen hsize200=hsize>=2
gen hsize300=hsize>=3
gen hsize400=hsize>=4
gen hsize500=hsize>=5
cc case hsize200 [fw=n]
cc case hsize300 [fw=n]
cc case hsize400 [fw=n]
cc case hsize500 [fw=n]

* Mantel-Haenszel estimate for aircirc
cc case aircirc [fw=n], by(hsize)
* association with outcome among exposure-negative
tabulate case hsize if aircirc==0 [fw=n], chi2 expected exact
cc case hsize200 if aircirc==0 [fw=n]
cc case hsize300 if aircirc==0 [fw=n]
cc case hsize400 if aircirc==0 [fw=n]
cc case hsize500 if aircirc==0 [fw=n]
* association with exposure among controls
tabulate aircirc hsize if case==0 [fw=n], chi2 expected

* frequency distribution of farm size among cases
tabulate case hsize [fw=n], row
```