Epidemiology VHM 811 Course
Fall 2008, Atlantic Veterinary College, PEI
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# Index of Lecture 11a

# Practical Information

Webpage news:

- home assignment posted,
- link to paper on paradoxes added (supplementary reading).

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 next week:

- start in Faculty Lounge, 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 $\sim$ 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 $\approx 2$, and crude OR $\approx 2$
  $\Rightarrow$ 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):

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

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

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

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

[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.

How does it work?

- example given in VER (Ex. 13.10) 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, 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).

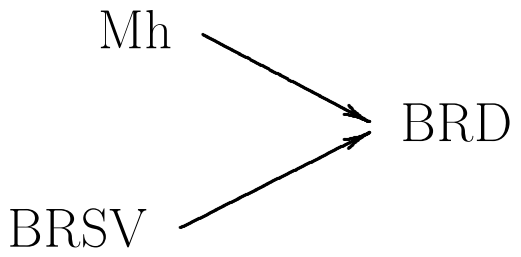
[6] We caution that inferring causal structure from data has some limitations; see Thompson (1991) paper referred in VER.

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

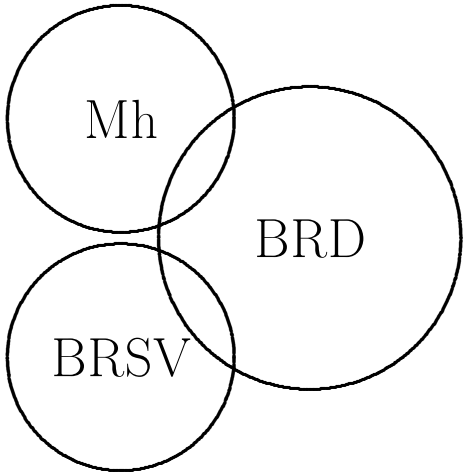
## Exposure–Independent Variable $Z$

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).

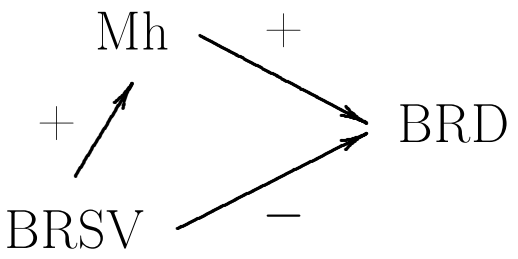
Implications for (statistical) modelling:

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

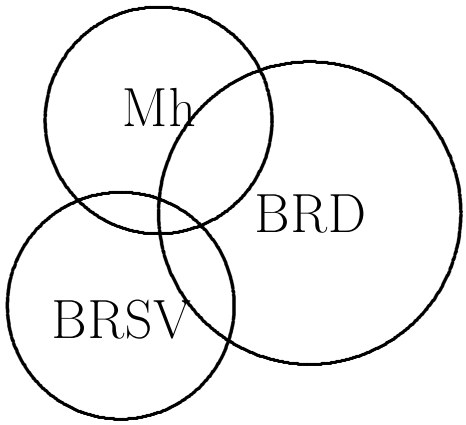
# Distorter Variable $Z$

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:

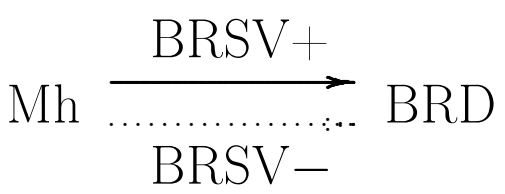
- control for confounding by BRSV required,
  - will usually increase the strength of association,
  - may change the direction of association from negative to positive (or vice versa, for different distribution of + and −),
- for an artificial data example, see Problem 13.2.

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

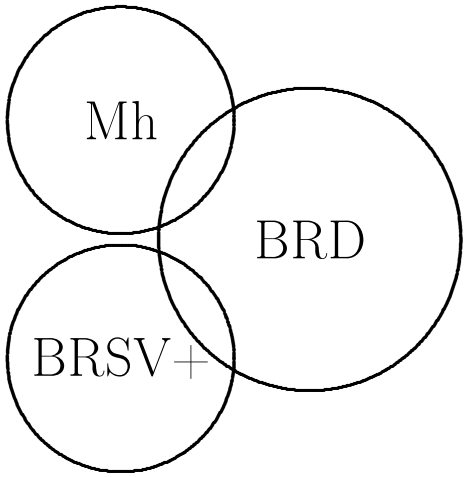
# Moderator Variable $Z$

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).

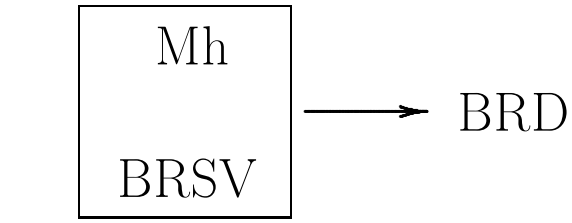
Implications for (statistical) modelling:

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

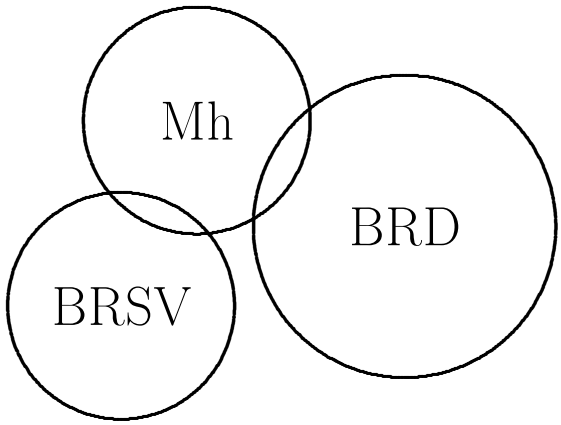
# Suppressor Variable $Z$

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 ($X^2_{\text{hom}}$) for homogeneity of 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).