CASE-CONTROL STUDIES

1. Introduction:

☞ In a **cohort** study, the relationship between exposure and disease incidence is investigated by **following** the entire cohort and measuring the **rate of occurrence** of new cases in the **different exposure groups**.

☞ The follow-up allows the investigator to register those subjects who develop the disease during the study period and to identify those who remain free of the disease.

☞ In a **case-control** study the **subjects who develop the disease** are registered by some other mechanism than follow-up and a group of healthy subjects (the **controls**) is used to represent the subjects who did not develop the disease.

☞ ☞ Therefore a case-control study recruits some people because **they have** the disease (or outcome of interest) and some people because **they do not** have it.

☞ This approach has two advantages:

It removes the need to follow people over time, waiting to see who falls ill and who does not, and

It reduces the number of people without the outcome of interest that need to be studied (very important with very rare diseases).

2. Analysis of case-control studies

☞ *The retrospective approach*

Compare **the distribution of exposure between cases and controls** – since the distribution **of the outcome is fixed by design** we study the distribution of exposure (the other way round to the study of cohort studies)

The proportion of cases who smoke compared to controls

The proportion of cases who were vaccinated compared to controls

The mean age of cases compared to controls (continuous exposure)

☞ *The prospective approach*

Compare the case/control ratio between exposed and not exposed

Example:

William Guy’s study of TB (perhaps the 1st case-control study!)

Level of physical activity (PA) in occupation	Tuberculosis (cases, D)	Other diseases (Controls, H)	Case/Control ratio
0 = Little	125	385	0.325
1 = Varied	41	136	0.301
2 = More	142	630	0.225
3 = Great	33	167	0.198

Retrospective: mean level of PA is 1.243 for cases and 1.439 for controls (p=0.0021), i.e., We compare the distribution of PA in occupation across cases and controls.

We see that people who did not develop the disease share a higher level of PA in occupation compared to people who developed tuberculosis.

Prospective: the prospective approach is given in the last column of the table:

We see that the case/control ratio decreases as we go from the first level of PA in occupation (little) to the last one (great) – the odds of being a case are less for people with high PA in occupation compared to those with little PA – there is a steady increase in the odds of failure with decreasing level of PA

Conclusion : the level of physical activity is inversely associated with developing tuberculosis.

Example:

William Guy's study of TB (perhaps the 1st case-control study!)

Level of physical activity (PA) in occupation	Tuberculosis (cases, D)	Other diseases (Controls, H)	Odds
0 = Little	37%	29%	0.325
1 = Varied	12%	10%	0.301
2 = More	42%	48%	0.225
3 = Great	10%	13%	0.198

Odds ratio σε μελέτες case-control

- $OR = Odds\ Ratio(disease|exposure\ status) = \frac{odds(disease|exposed)}{odds(disease|unexposed)}$

- Σε μια μελέτη ασθενών- μαρτύρων δεν μπορούμε να εκτιμήσουμε αυτά τα odds απευθείας, διότι:
  - Στη μελέτη *επιλέγουμε* ποιοι είναι cases και ποιοι controls
  - Τα δεδομένα μας είναι δεδομένης της κατάστασης ως προς τη νόσο (***conditioned on disease status***).

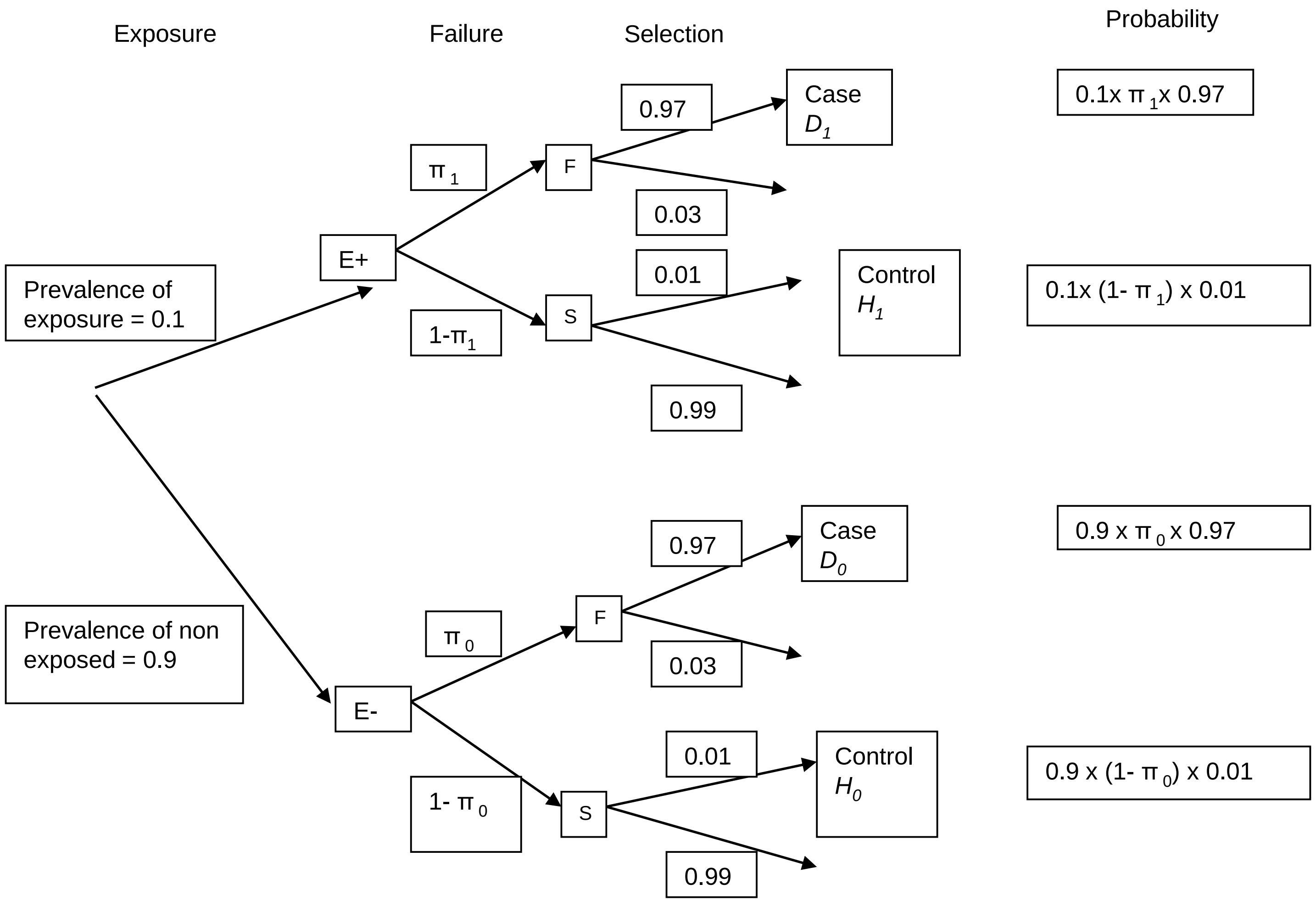
- Εναλλακτικά, **εκτιμάμε τα odds της έκθεσης**
- $OR^* = Odds\ Ratio(exposure|disease\ status) = \frac{odds(exposed|case)}{odds(exposed|control)}$

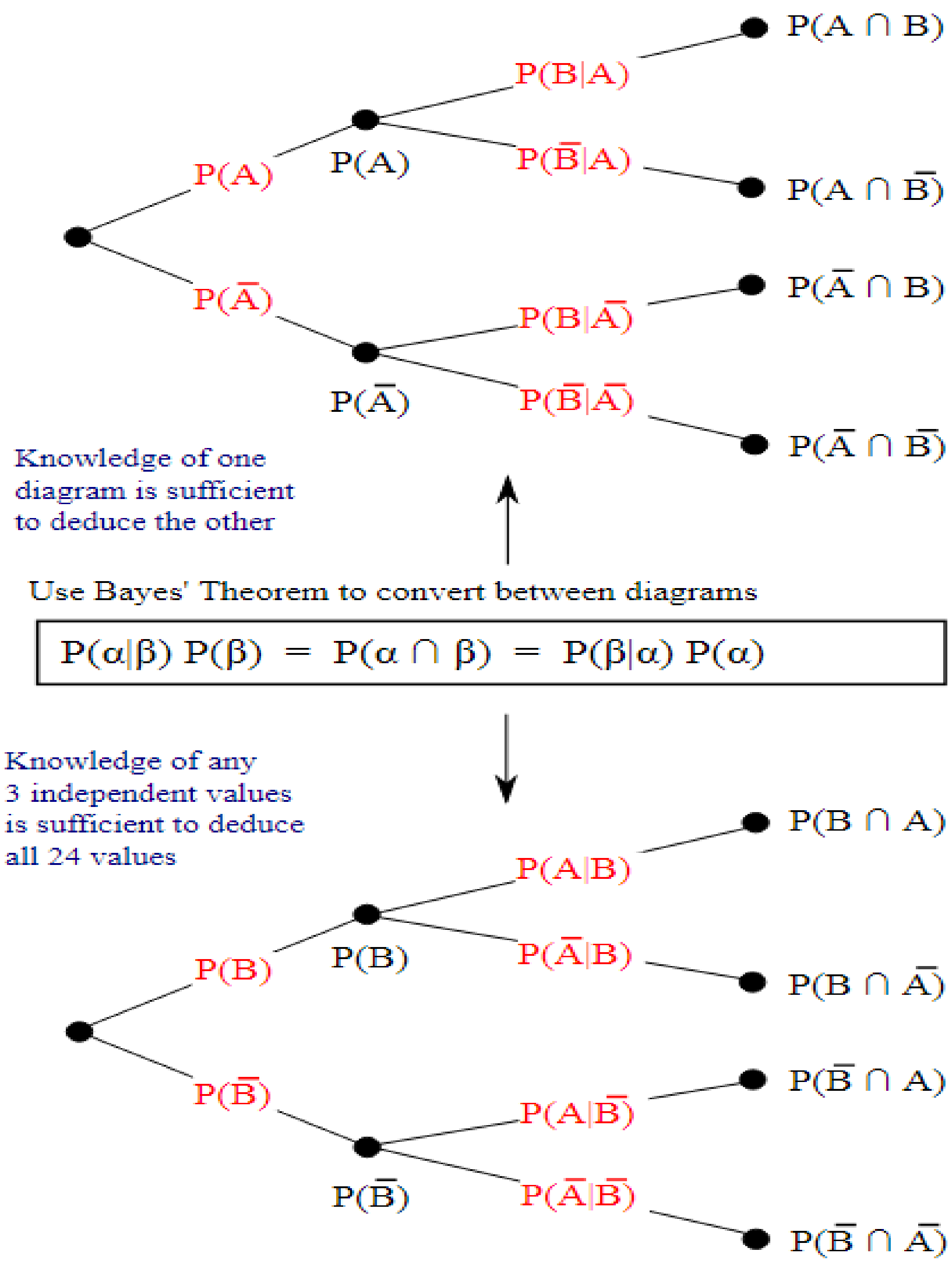
3. The probability model in the population

☞ Every case control study of incidence can be seen within the context of an underlying cohort (*study base*) which supplies the cases on which the case-control study is based.

π_1 = probability of being a case having been exposed

π_0 = probability of being a case not having been exposed.





Knowledge of one diagram is sufficient to deduce the other

Use Bayes' Theorem to convert between diagrams

$$\boxed{P(\alpha|\beta)\,P(\beta) = P(\alpha \cap \beta) = P(\beta|\alpha)\,P(\alpha)}$$

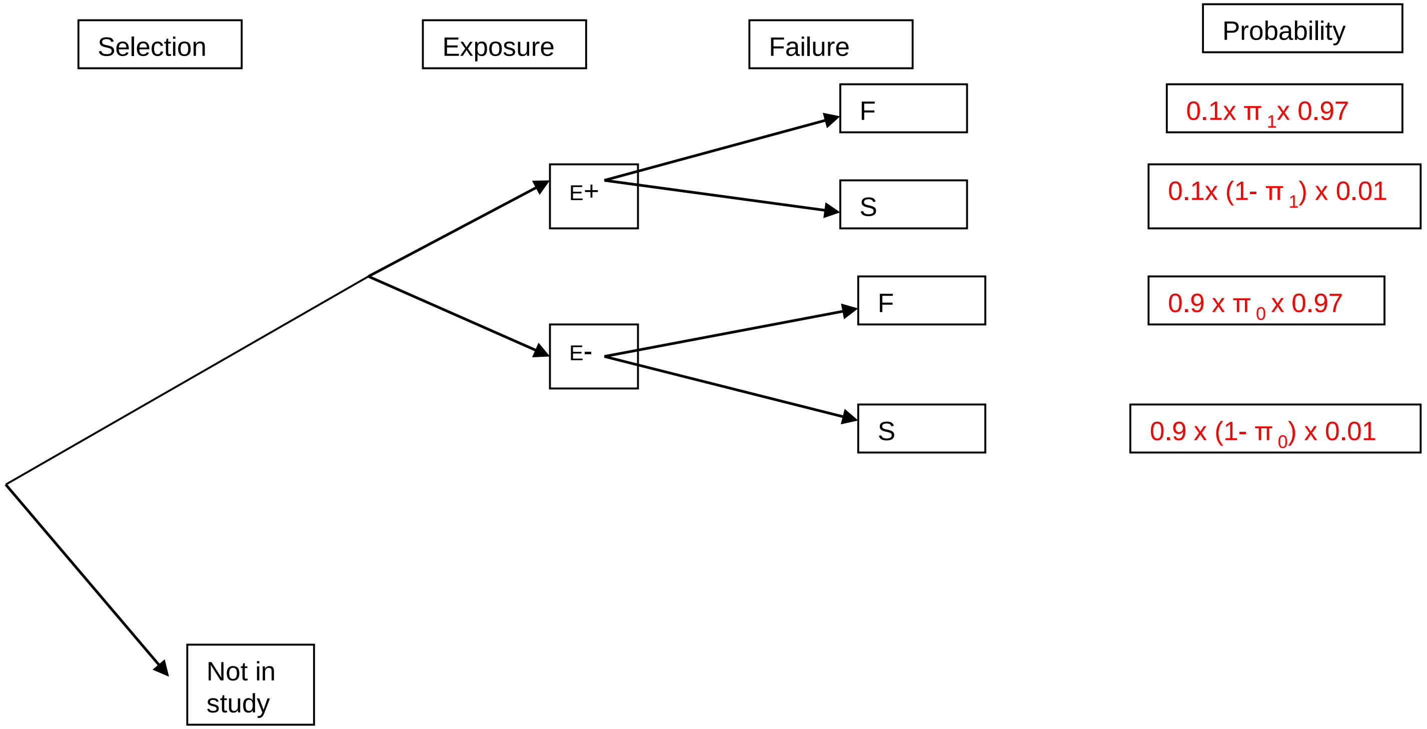
Knowledge of any 3 independent values is sufficient to deduce all 24 values

Chain rule:
$P(A,B,C)=P(C|A,B)*P(A,B)=P(C|A,B)*P(B|A)*P(A)$

$P(\text{exposure,case,selected})=P(S|E,C)P(E,C)=$
$P(S|E,C)P(C|E)P(E)$

where
$P(\text{exposure})=0.1$
$P(\text{case}|\text{exposure})=\pi_1$
$P(\text{selection}|\ \text{exposure,case})=0.97$

4. The prospective model



Selection

Exposure

Failure

Probability

E+

F

S

E-

F

S

Not in study

$0.1 \times \pi_1 \times 0.97$

$0.1 \times (1-\pi_1) \times 0.01$

$0.9 \times \pi_0 \times 0.97$

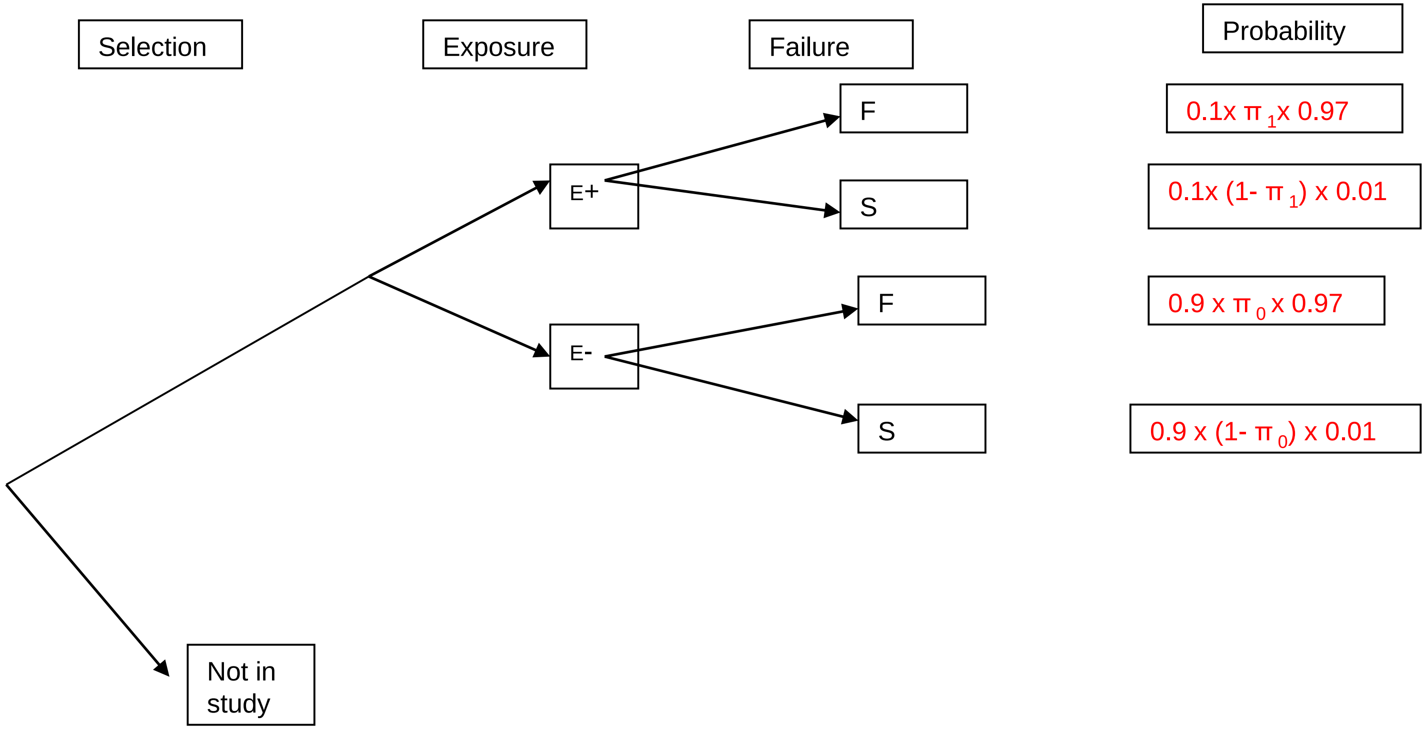
$0.9 \times (1-\pi_0) \times 0.01$

Conditioning for the exposure status:

odds(disease|**exposure**)
odds(disease|**non exposed**)

Assumes we know the exposure status prior to the disease status

4. The prospective model



The odds of being a case

☞ Let ω_1 be the odds **in the study** that an **exposed** subject **is a case**. Then

$$\omega_1 = \frac{0.1\times\pi_1\times0.97}{0.1\times(1-\pi_1)\times0.01} = \frac{0.97}{0.01}\times\frac{\pi_1}{1-\pi_1}$$

☞ Let ω_0 be the odds **in the study** that an un**exposed** subject **is a case**. Then

$$\omega_0 = \frac{0.9\times\pi_0\times0.97}{0.9\times(1-\pi_0)\times0.01} = \frac{0.97}{0.01}\times\frac{\pi_0}{1-\pi_0}$$

☞ The odds ratio in the study is then

$$\frac{\omega_1}{\omega_0} = \frac{\pi_1 / (1-\pi_1)}{\pi_0 / (1-\pi_0)}$$

i.e., the “true” odds ratio can be estimated by the study odds ratio

5. ESTIMATION

☞ D_1 / H_1 estimates ω_1 and D_0 / H_0 estimates ω_0. Then

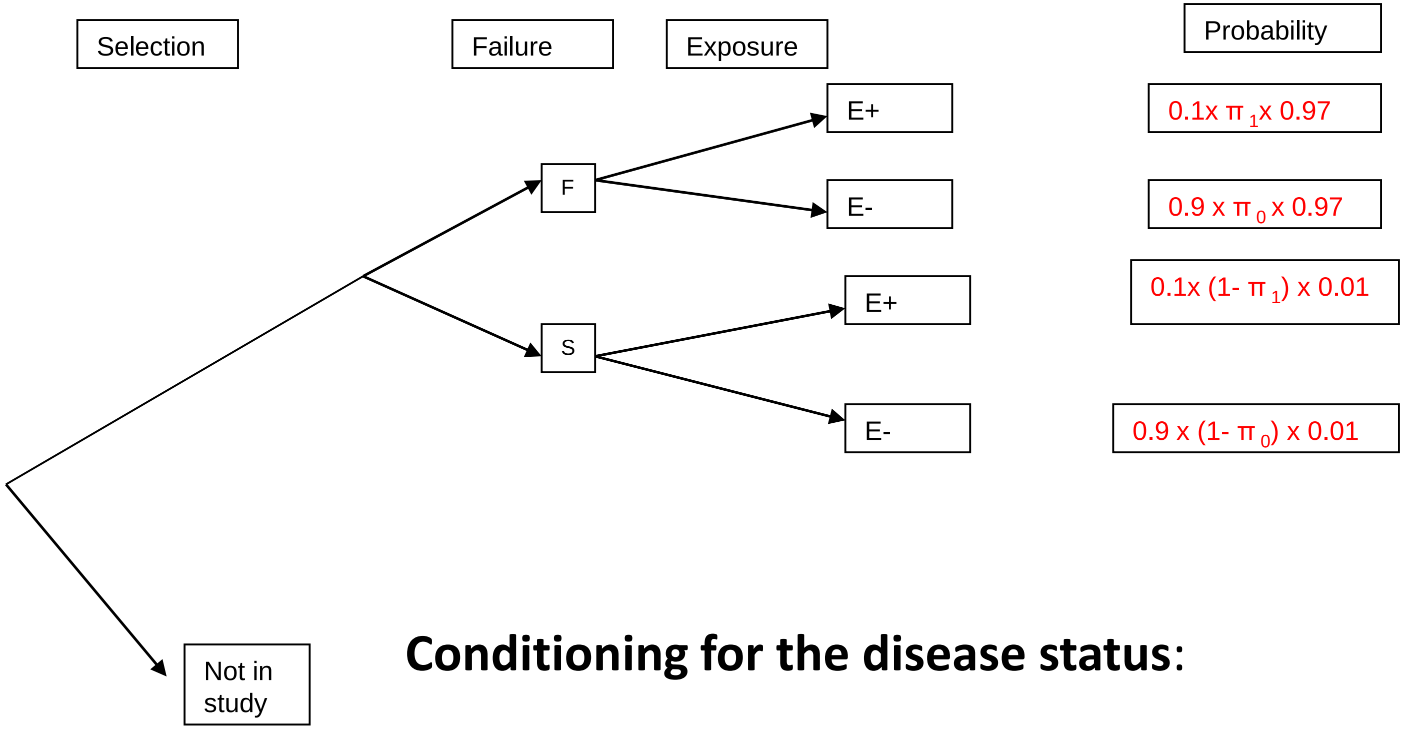
$$\frac{\omega_1}{\omega_0} = \frac{\pi_1 / (1-\pi_1)}{\pi_0 / (1-\pi_0)} = \frac{\frac{D_1/N}{H_1/N}}{\frac{D_0/N}{H_0/N}} = \frac{D_1 / H_1}{D_0 / H_0} = \frac{D_1 H_0}{D_0 H_1}$$

estimates the odds ratio.

☞ *Thus although it is not possible to estimate π_1 and π_0 separately from a case control study, it is possible to estimate the odds ratio.*

6. The retrospective model

☞ We define a model for the conditional probabilities of exposure, given that the subject was a case (F) or a control (S) in our STUDY.



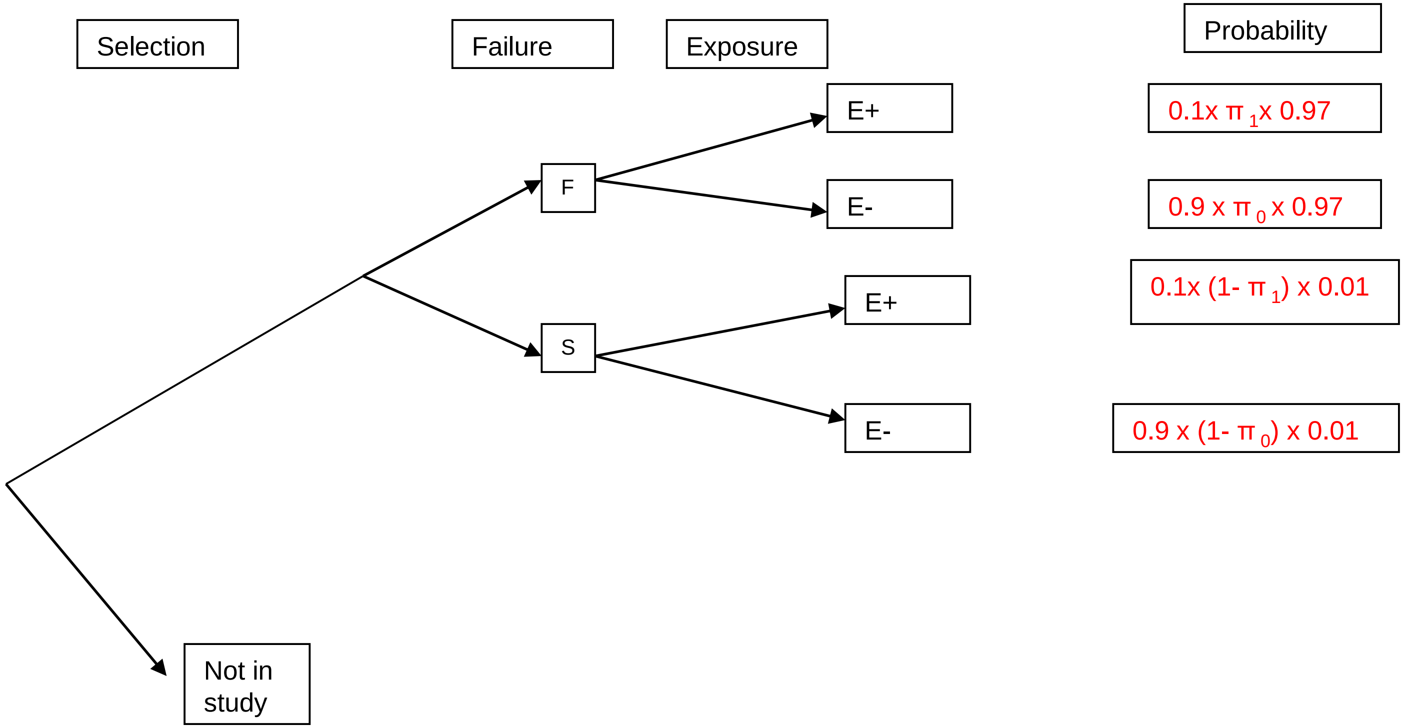
Conditioning for the disease status:

odds(exposure|**diseased**)
odds(exposure|**diseased**)

In reality we know the disease status prior to the exposure status

6. The retrospective model

☞ We define a model for the conditional probabilities of exposure, given that the subject was a case (F) or a control (S) in our STUDY.



Let Ω_1 (and Ω_0) be the odds of having been exposed for a case (or for control). From the figure Ω_1 and Ω_0 are given as

$$\Omega_1 = \frac{0.1\times\pi_1\times 0.97}{0.9\times\pi_0\times 0.97} = \frac{0.1}{0.9}\times\frac{\pi_1}{\pi_0} \quad \Omega_0 = \frac{0.1\times(1-\pi_1)\times 0.01}{0.9\times(1-\pi_0)\times 0.01} = \frac{0.1}{0.9}\times\frac{1-\pi_1}{1-\pi_0} \qquad \frac{\Omega_1}{\Omega_0} = \frac{\pi_1/(1-\pi_1)}{\pi_0/(1-\pi_0)}$$

☞ The value of Ω_1 can be estimated by D_1/D_0, i.e., the ratio of the exposed to unexposed cases, and Ω_0 by H_1/H_0, i.e., the ratio of exposed to unexposed controls. Thus the odds ratio of disease in the population can be estimated by the odds rario of exposure from the case control study

$$\frac{\Omega_1}{\Omega_0} = \frac{\pi_1/\pi_0}{(1-\pi_1)/(1-\pi_0)} = \frac{\frac{D_1/N}{D_0/N}}{\frac{H_1/N}{H_0/N}} = \frac{D_1/D_0}{H_1/H_0}$$

☞ *You see that estimation of the true odds ratio is the same whether we adopt the prospective or the retrospective approach.*

8. What is the «odds ratio»?

Note that when the disease of interest is rare, π is small and π / (1-π) is approximately equal to π [because (1-π) is almost 1]. So:

$$\text{«disease odds ratio»} = \frac{\pi_1}{(1-\pi_1)} \div \frac{\pi_0}{(1-\pi_0)}$$

$$= \pi_1 \div \pi_0$$

which is the risk ratio.

When the disease under investigation is rare, the cross-product ratio from a case-control study provides an estimate of the risk ratio. Traditionally, this has been the approach to the interpretation of case-control studies and is often referred to as the «rare disease assumption».

A more general result states that when the disease is rare (in the population under study, over the period of the study), the odds ratio, risk ratio and rate ratio are, for all practical purposes, equal.

More recently it has been shown that, when the disease is not rare, which of these three measures is estimated by the (cross-product) odds ratio depends on the way in which controls are selected.

In general terms, we can state that **the cross-product ratio** obtained from a case-control study provides an estimate of **how much more (or less) common the disease / outcome is among the exposed compared with the unexposed**.

9. The likelihood for a model for a case-control study

☞ We are now interested to investigate the likelihood of a case-control study

- Therefore we must calculate the **likelihood for a model for the odds ratio** since this is the only parameter which can be estimated from such a study.
- The likelihood depends on which approach we have adopted to analyze the data - prospective or retrospective.
  - Fortunately it can be shown that the results are exactly the same regarding the odds ratio estimate and its variance.
- Here we will show only **the prospective approach** since it is the one that is used for setting up **logistic regression models** (described below).
  - The likelihood for the retrospective approach can be found in Clayton and Hills, page 166 where you can also see that the two approaches end up to identical results.

9.1 The prospective likelihood

☞ Imagine the following case-control study

Exposure	Cases	Controls	Total subjects
Exposed	D_1	H_1	$N_1 = D_1 + H_1$
Unexposed	D_0	H_0	$N_0 = D_0 + H_0$
Total	D	H	N = D + H

Recall that ω_1 the odds of being a case for the exposed given that the subject is in the study, where p_1 is the probability of being a case for the exposed given that the subject is in the study.

Similarly ω_0 the odds of being a case for the unexposed given that the subject is in the study, where p_0 is the probability of being a case for the unexposed given that the subject is in the study.

In addition define $\theta = \omega_1 / \omega_0$

[Reminder]

- The **Likelihood function** describes the plausibility of a model parameter value, given specific observed data.
- the **Likelihood** of a set of parameter values given the observed outcomes is the probability of some observed outcomes given the set of parameter.
- Δίνεται από το γινόμενο των συναρτήσεων πιθανότητας για συγκεκριμένες τιμές δεδομένων (X) για κάθε άτομο του δείγματος
- Εκφράζει πόσο πιθανές είναι οι τιμές της παραμέτρου θ δεδομένου του δείγματος (δηλαδή δεδομένων των συγκεκριμένων τιμών-δεδομένων που έχουμε)

Logistic model Likelihood

- To find the likelihood function recall that the data here *are binary responses* (case vs. control)
- Recall that for a Bernoulli distribution with N subjects and D successes, where π is the probability of success, the likelihood function is given by
  - Likelihood = $\pi^{D}(1-\pi)^{N-D}$, where π^{D} the contribution of a case, $(1-\pi)^{N-D}$ the contribution of a control

Likelihood = $\pi^D(1-\pi)^{N-D}$

Thus the log-likelihood is:

log-likelihood = D log(π) + (N-D) log(1- π)

Recall that the odds of success , say $\omega = \dfrac{\pi}{(1-\pi)}$, and $1-\pi = \dfrac{1}{(1+\omega)}$

So that the log-likelihood can be expressed as a function of ω, that is:

log-likelihood = D log(ω(1-π)) + (N-D) log(1- π)

= Dlog(ω) + Dlog(1-π) + Nlog(1-π) – Dlog(1-π)

= Dlog(ω) + Nlog(1-π)

= Dlog(ω) + Nlog(1/(1+ω))

= Dlog(ω) - Nlog(1+ω) (1)

Thus, for a Bernoulli distribution with N subjects and D successes:

$$\text{log-likelihood} = D\log(\omega) - N\log(1+\omega)$$

In a case control study the data come from **two independent Bernoulli distributions** one for the exposed and one for the unexposed. Under the prospective approach the log likelihood for the data will then be

log-likelihood = $D_1 \log(p_1) + (N_1-D_1) \log(1- p_1) + D_0 \log(p_0) + (N_0-D_0) \log(1- p_0)$ and from (1) above it follows that

log-likelihood $= D_1\log(\omega_1) – N_1\log(1+\omega_1) + D_0 \log(\omega_0) -N_0 \log(1+\omega_0)$, and

by substituting $\omega_1 = \theta\, \omega_0$: $D_0 \log(\omega_0) -N_0 \log(1+\omega_0) \quad + \quad D_1 \log(\theta\omega_0) -N_1 \log(1+\theta\omega_0)$

MATCHED CASE-CONTROL STUDIES

1. Introduction:

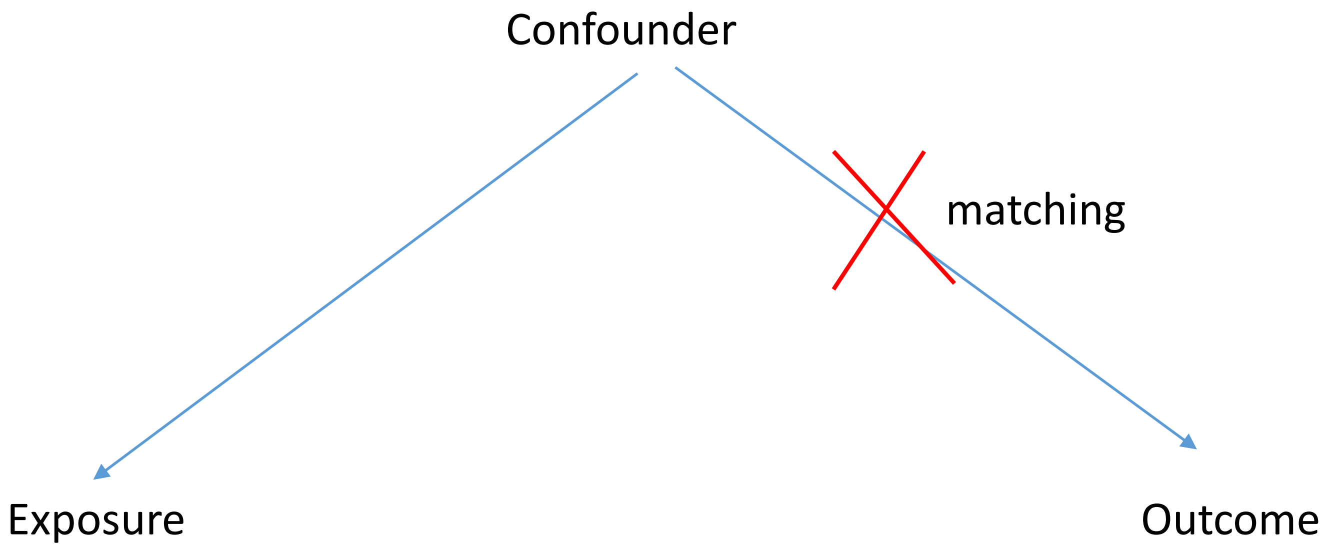
- In case-control studies, the sample of controls may be randomly selected from the population of individuals free from the condition that defines the cases.
- Controls can be “matched” to cases with respect to factors that are expected to be related to the risk of disease.
- Variables that are usually used for matching are age, sex, place of recruitment and time of recruitment.
- Due to the special design, matched case control studies require special analyses.

2. Why match?

- Matching is a technique of selecting control subjects for the control of confounding at the design stage
- *Idea:* Place constraints on selection of controls to make two groups similar at least with respect to confounding variables. In matched case-control studies, for each case or a fixed size group of cases, a fixed (or even variable) number of controls are identified who match the cases on a set of characteristics.
- The distribution of these characteristics will be the same (or at least similar) between cases and controls, so no associations are possible *by design*.
- During the analysis of the results: Post-stratification analysis
- Advantage of using stratification in design: avoid the inefficiencies resulting from some strata with a gross imbalance of cases and controls.

2. Why match?

- Balance cases/controls within strata to improve efficiency
- Test a particular pathway
- Deal with bias due to confounding
- Matching on *Confounder (C)* forces no association between *C* and Disease (*D)*, so *C* cannot confound.


Confounder
matching
Exposure
Outcome

More on matching

- Controls can be individually matched or frequency matched.
- **Individual matching:** Search for one (or more) controls who have the required matching criteria. Paired or triplet matching is when there is one or two controls individually matched to each case.
- **Frequency matching:** select a population of controls such that the overall characteristics of the group match the overall characteristics of the cases. e.g. if 15% of cases are under age 20, 15% of the controls are also.
- Obtain power by matching more than one control per case. In general, N of controls should be < 4, because there is no further gain of power above four controls per case.

2.1. Example

Consider the following example: The BCG vaccination and leprosy:

New cases of leprosy examined for presence or absence of the BCG scar. Say we identified 260 cases of leprosy. Assume we use 1000 controls for the 260 cases. After stratification by age:

	BCG scar			
	Cases		Controls	
Age	Absent	Present	Absent	Present
0-4	1	1	101	137
5-9	11	14	91	115
10-14	28	22	82	101
15-19	16	28	28	87
20-24	20	19	25	69
25-29	36	11	63	21
30-34	47	6	56	24

Not very efficient! There are 238 controls for the 2 cases in the 0 - 4 age group!

2.2 Group matching

The optimal strategy is to maintain the same ratio of controls to cases in different age strata

For example in the previous study we could maintain the 1:4 case/control ratio as shown below

	BCG scar			
	Cases		Controls	
Age	Absent	Present	Absent	Present
0-4	1	1	3	5
5-9	11	14	48	52
10-14	28	22	67	133
15-19	16	28	46	130
20-24	20	19	50	106
25-29	36	11	126	62
30-34	47	6	174	38

This is a group-matched case-control study.

Caution!

- Controls are no longer representative of source population

➢ **Matching introduces bias**!

2.3 Can we ignore matching in the analysis?

Indeed it was thought that matching is an alternative way of controlling for confounding - **this is not true**; see the example below:

	Cases		Controls		Odds ratio
Stratum	**exposed**	**unexposed**	**exposed**	**unexposed**	
1	89	11	80	20	2
2	67	33	50	50	2
3	33	67	20	80	2
Total	189	111	150	150	1.7

Odds ratio is biased towards 1, i.e., towards the null. This turns out to be a general result!

A case-control study introduces a new confounding structure in place of the original structure and this is why the estimate from an analysis that ignores matching is biased towards the null. Remember:

Matched design =======> «Matched» analysis

3. Advantages of a matched design

Precision / efficiency in a matched case-control

When the analysis of a study involves stratification on the basis of some confounding variable, usually **the precision of the study will be maximal if the ratio of cases to controls is approximately the same across strata**. We can succeed on this by a matched design.

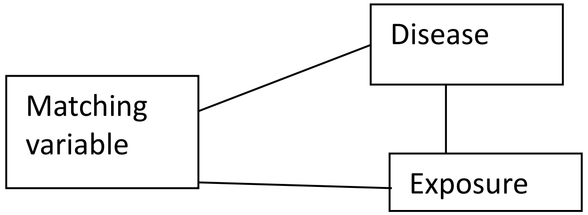
Study 1 case: control ratio = 1:4

	Exposed	Unexposed	Total	
Cases	30	10	40	= 3.0
Controls	80	80	160	(1.30,7.07)
	100	90	200	

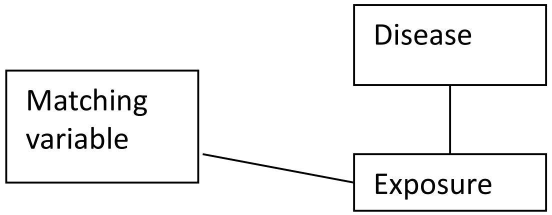
Study 2 case: control ratio = 1:1

	Exposed	Unexposed	Total	
Cases	75	25	100	= 3.0
Controls	50	50	100	(1.58,5.72)
	125	75	200	

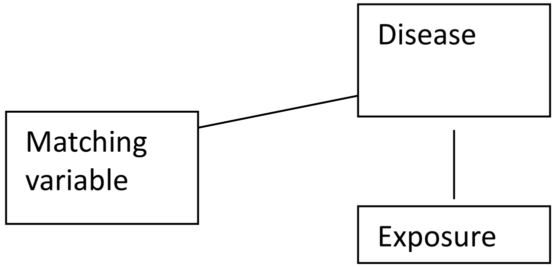
The **power** of a case-control study of total sample N to detect a difference in exposure rates between cases and controls is **greatest if number of cases equals number of controls**.



Matching variable is a confounder – matching will gain us precision in the exposure/disease relationship

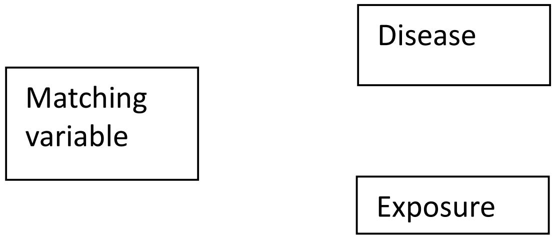


Overmatching – precision is lost



UNNECASSARY MATCHING: Matching can be ignored in the analysis since its effect is neutral

If analysis with stratification→ reduction of power



UNNECASSARY MATCHING: Matching can be ignored in the analysis since its effect is neutral

If analysis with stratification→ reduction of power

Overmatching

- **Matching on a variable which is associated with exposure but not with disease** should be avoided because this in practice will reduce power – the more the association with exposure the more the reduction will be.

- In general it is only worthwhile matching on variables which are strong confounders.

- And do not forget that:
    - Matching must be taken into account in the *analysis*.
    - Attempting to match for more than a few variables usually inefficient.

4. Disadvantages of matched studies

- The association of the matching variable with the outcome cannot be studied: By definition the distribution of a matching variable is the same (or similar) in the case and control groups
- Logistically more difficult
- Data may be more difficult to present and analyze.
- May be difficult to find suitable matches. May reduce available sample size – many potential cases may be excluded because no match can be found
- Possibility of «overmatching»-> Power loss.

Matching on a mediator

- Matching on variable in causal pathway will introduce bias: the **“post-treatment bias”** ή **“overcontrol bias”**.
- O mediator είναι **μεταβλητή που προκαλείται από** την έκθεση.

Κάνοντας matching σε κάτι που εξαρτάται από την έκθεση:

- Δημιουργούνται τεχνητές εξαρτήσεις (collider bias)
- Μπλοκάρονται μονοπάτια που είναι στην πραγματικότητα αιτιολογικά.
- **Παρεμβαίνουμε στο ίδιο το φαινόμενο που προσπαθούμε να μετρήσουμε, δηλαδή στον τρόπο μέσω του οποίου επιδρά η έκθεση**.

Matching on a mediator- Παράδειγμα

- Έστω ότι θέλουμε να εκτιμήσουμε την επίδραση του καπνίσματος στην εμφάνιση καρδιακής νόσου:
- X=κάπνισμα, M= αρτηριακή πίεση, Y=καρδιακή νόσος
- Αν κάνουμε matching ως προς M (δηλ. συγκρίνουμε καπνιστές και μη καπνιστές με ίδια πίεση),
  τότε *αφαιρούμε* το κομμάτι της επίδρασης του καπνίσματος που περνάει μέσω της πίεσης
- Υποτιμάς την πραγματική επίδραση του καπνίσματος στο Y.
  ->biased estimate

5. Analysis of grouped matched case-control studies

Stratification method

Logistic regression

Matching variables should be in the logistic regression model in order to get unbiased estimates of the effects of interest.

Example: Consider the previous example on leprosis and say we matched for age with age being a categorical variable with k levels.

The model

$$\log(\text{odds}_i) = \alpha + \Sigma\, \beta_{1k}\, \text{age}_{i\kappa} + \beta_2\, \text{BCG}_i$$

Parameter	Estimate	SD
Cons	-1.07	0.8
Age(1)	-0.04	0.83
Age(2)	0.012	0.81
Age(3)	0.07	0.8
Age(4)	0.024	0.82
Age(5)	-0.16	0.81
Age(6)	-0.24	0.81
BCG	-0.53	0.16

Note that because of matching the age effects are small and not interpretable. But can we remove age from the model?

Example (continued):

Removing age :

BCG scar	Leprosy cases	Controls
Present	101	526
Absent	159	514

The odds ratio is (101 x 514) / (159 x 526) = 0.621, so that the log of odds is -0.477 i.e, biased towards the null.

Note that the age parameters are really nuisance parameters but they are still estimated.

In case of many of nuisance parameters -- this approach does not work

e.g. when we match *individually*, which is effectively the perfect matching!

6. Matched pairs (1 : 1)

Suppose we have n matched pairs. **Each pair can be thought of as a stratum.** For each stratum (pair) there are four possible outcomes as follows:

	Exposure								Total
	+	-	+	-	+	-	+	-	
Case	1	0	1	0	0	1	0	1	
Control	1	0	0	1	1	0	0	1	
	2	0	1	1	1	1	0	2	
Total no. of pairs of each kind	n_{11}		n_{10}		n_{01}		n_{00}		n

Where n_{ij} corresponds to the number of pairs with exposure status i (0=unexposed, 1=exposed) for the case and j (0=unexposed, l=exposed) for the control.

The results of an 1:1 matched, case-control study can therefore be presented in a table of the form:

	Control		
		Exposed	Unexposed
Case	Exposed	n_{11}	n_{10}
	Unexposed	n_{01}	n_{00}

From this table we can easily obtain the following table that contains *individuals.*

	Exposure		Total
	+	-	
Case	$n_{11} + n_{10}$	$n_{00} + n_{01}$	n
Control	$n_{11} + n_{01}$	$n_{00} + n_{10}$	n

Let’s see this in detail:

Exposure

	+	-	+	-	+	-	+	-	Total
Case	1	0	1	0	0	1	0	1	1
Control	1	0	0	1	1	0	0	1	1
Total	2	0	1	1	1	1	0	2	2
# of such tables	n_{11}		n_{10}		n_{01}		n_{00}		

Each of these pairs will contribute to the mantel-haenzel estimate:

Contribution to the numerator $D_{1j}H_{0j}/N_j = \#$ Exposed cases*# Unexposed controls/Total individuals in pair j

Contribution to the denominator $= D_{0j}H_{1j}/N_j = \#$ Unexposed cases*# Exposed controls/Total individuals in pair j

6.1 Estimating the odds ratio from a 1:1 matched case control

Thus, the Mantel-Haenszel estimate considering each stratum=matched pair is:

$$\boldsymbol{MHOR} = \frac{\Sigma \boldsymbol{D}_{1\boldsymbol{j}} \boldsymbol{H}_{0\boldsymbol{j}} / \boldsymbol{N}_{\boldsymbol{j}}}{\Sigma \boldsymbol{D}_{0\boldsymbol{j}} \boldsymbol{H}_{1\boldsymbol{j}} / \boldsymbol{N}_{\boldsymbol{j}}} = \frac{\boldsymbol{Q}}{\boldsymbol{R}} = \frac{[(\mathrm{n}_{11}\mathrm{x}0) + (\mathrm{n}_{10}\mathrm{x}1) + (\mathrm{n}_{01}\mathrm{x}0) + \mathrm{n}_{00}\mathrm{x}0)]/2}{[(\mathrm{n}_{11}\mathrm{x}0) + (\mathrm{n}_{10}\mathrm{x}0) + (\mathrm{n}_{01}\mathrm{x}1) + (\mathrm{n}_{00}\mathrm{x}0)]/2} = \frac{\boldsymbol{n}_{10}}{\boldsymbol{n}_{01}}$$

D_{1j}: Number of exposed cases in pair j

D_{0j}: Number of unexposed cases in pair j

H_{1j}: Number of exposed controls in pair j

H_{0j}: Number of unexposed controls in pair j

N_{0j}: Number of individuals in pair j

Pairs with case and control being both exposed or unexposed do not contribute to the odds ratio estimate.

Example

Suppose a matched case control study has been conducted to investigate **risk factors for infant death from diarrhoea** (Clayton and Hills).

Cases were defined as infants dying from diarrhoea at less than 1 year of age.
Cases were matched with 1 ***neighborhood*** control who had to be the same **age group** (0-2, 3-5, ≥6 months) as the case also (two matching variables).
The study included 86 cases and 86 controls.
Among other variables, information on social and environmental factors, birth weight and feeding mode were also collected.
See in the following table this case control study with **exposure being the breastfeeding mode**:

		Control	
	Feeding mode	Breast fed	Not breast fed
Case	Breast fed	24	6
	Not breast fed	29	27

MH odds ratio from the matched table: 6/29 = 0.21

Example:

Ignoring matching

		Control	
	Feeding mode	Breast Fed	No Breast Fed
Case	Breast fed	30	56
	Not breast fed	53	33

Odds ratio ignoring matching (30*33)/(56*53) = 0.33 bias towards the null

6.2. Confidence interval for the MHOR for the 1:1 matched case control study

An approximate 95% confidence interval for the odds ratio may be calculated as follows:

$$\boldsymbol{EF} = \exp(1.96\boldsymbol{xS}) \qquad \boldsymbol{where\ S}^2 = \frac{\boldsymbol{V}}{\boldsymbol{QR}}$$

Note that:

$$\boldsymbol{Q} = \frac{\boldsymbol{n}_{10}}{2}, \quad \boldsymbol{R} = \frac{\boldsymbol{n}_{01}}{2}, \quad \boldsymbol{V} = \frac{\boldsymbol{n}_{10}}{4} + \frac{\boldsymbol{n}_{01}}{4},$$

$S^2 = 1/n_{10} + 1/n_{01}$

$$\boldsymbol{EF} = \exp[1.96\sqrt{(1/\boldsymbol{n}_{10} + 1/\boldsymbol{n}_{01})}]$$

concordant pairs contribute nothing to the confidence interval.

This approximation brakes down when the number of discordant pairs is small (e.g. less than 20)→ «exact» 95% confidence intervals

6.3. Test of the null hypothesis that the true MHOR = 1

A test of the null hypothesis that the true odds ratio is 1 is based only on the discordant pairs.

When the true odds ratio is 1 the probability of a discordant pair to be of either type, should be 0.5→ $E(n_{10}) = (n_{10}+n_{01})/2$.

Test whether n_{10} differs from its expected value under the null hypothesis.

For large numbers of discordant pairs (> 20) → Normal approximation to the Binomial distribution

Under the null hypothesis p=0.5, $var(n_{10}) = np(1-p) = (n_{10}+n_{01})/4$

Using the Normal approximation on the Binomial distribution gives:

$$\boldsymbol{x}^2 = \frac{(\boldsymbol{n}_{10} - \boldsymbol{E}(\boldsymbol{n}_{10}))^2}{\boldsymbol{Var}(\boldsymbol{n}_{10})} = \frac{(\boldsymbol{n}_{10} - (\boldsymbol{n}_{10} + \boldsymbol{n}_{01})/2)^2}{(\boldsymbol{n}_{10} + \boldsymbol{n}_{01})/4} = \frac{(n_{10} - n_{01})^2}{(n_{10} + n_{01})}$$

On 1 DF

McNemar's test for matched pairs = MH χ^2 test, using pairs as strata.

No of discordant pairs ≤ 20 (say) → exact test based upon the Binomial distribution
Table of cumulative probabilities of the Binomial distribution with a value of p = 0.5
(null hypothesis value).

6 .4. Testing for heterogeneity of the odds ratio

Matching variable -- confounding variable.

Test whether matching factor is an effect modifier of the association of exposure with the outcome of interest.

Straight forward for group-matching variables.

1:1 matched study: levels of the matching factor (e.g. age groups) and estimate the odds ratio by the pairs in each subgroup.

Wide groups for the matching factor → enough number of discordant pairs in each

For example, the pairs may be closely matched for age (e.g. ± one year), but the subgroups may be defined by 10-year age groups.

	Matching factor						
	1	2	3	i		k	Total
No of Pairs with Case exposed and Control unexposed							
No of Pairs with Case unexposed and Control exposed							

χ^2 test for a 2 x k table → tests whether the odds ratio estimates vary according to the level of the matching factor.

If matching factor is on an ordinal scale then a test for trend can also be used.

Example (cont)

Say we want to assess the effect of birth weight (low vs. normal) on risk of death from diarrhoea. Look below the crude estimate of the odds ratio.

		Control	
	Birth weight	Low	Normal
Case	Low	12	25
	Normal	18	31

OR = 25/18 = 1.39 (0.76, 2.55)

We have matched for age because age is a confounding variable but we want to check whether low birth weight has a greater effect on the risk of death from diarrhea among younger infants than among older infants. Since the data are matched for age, we may stratify the pairs into three age groups as follows:

OR_1 = 7/6 = 1.17

OR_2 = 12/7 = 1.71

OR_3 = 6/5 = 1.20

		Age					
		0-2 months		3-5 months		≥ 6 months	
		Control		Control		Control	
	Birth weight	Low	Normal	Low	Normal	Low	Normal
Case	Low	4	7	4	12	4	6
	Normal	6	8	7	15	5	8

χ^2 = 0.35 on 2 df, p>0.5 → no evidence for a modifying effect of age on the odds ratios. Odds ratio of 1.39 is the association of low birth weight on the risk of death from diarrhoea adjusted for both neighborhood and age.

7. The analysis of 1:k matched case control studies

>1 controls per case recruited the number of possible outcomes increases.

E.g. 2 controls per case there are six possible outcomes for each triplet

Previous methods can be extended to the general case of 1:k matched case control studies.

$$\text{OR} = \frac{\text{Total no. of unexposed controls who hove an exposed case}}{\text{Total no. of exposed controls who have an unexposed case}}$$

Formulas for these situations and approximate confidence intervals have also been established.

8. Adjustment for other factors

NOT POSSIBLE through stratification since the data are already stratified into pairs of cases and controls so that no further stratification is possible.

Use statistical modeling techniques.

8. Analysis of matched case-control studies using statistical models

Use logistic regression with a separate parameter for each case-control set:

$$\log(\boldsymbol{odds}_i) = \boldsymbol{a} + \sum_{j=1}^{m} \boldsymbol{\gamma}_{\mathbf{j}}\, \mathbf{z}_{\mathbf{ij}} + \sum_{k=1}^{p} \boldsymbol{\beta}_{\mathbf{k}}\, \mathbf{x}_{\mathbf{ik}}$$

x_{ik} are the exposure and possible confounders, and z_{ij} are dummies with 1 if subject *i* is in matched set *j*, and 0 otherwise.

β_k are still interpreted as estimates of the population odds ratios associated wit certain levels of the x_{ik} variables.

For large number of sets usual properties of MLEs do not apply; parameter estimates will not be consistent:

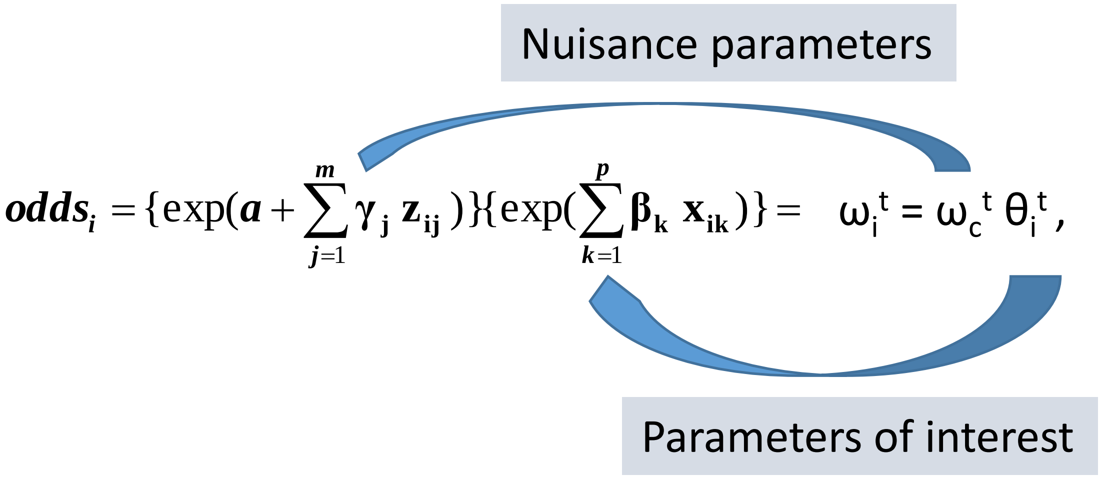
1) Assume that the matched set parameters γ_j are themselves a sample from some distribution - i.e, set up a *mixed (random effects) model*, or,

2) Perform conditional logistic regression

The model for conditional logistic regression

$$1st\ part = a + \sum_{j=1}^{m} \gamma_j\, \mathbf{z}_{ij} \qquad 2nd\ \ part = \sum_{k=1}^{p} \boldsymbol{\beta}_k\ \mathbf{x}_{ik}$$

Or,



Nuisance parameters

$$odds_i = \{\exp(a + \sum_{j=1}^{m} \gamma_j\, \mathbf{z}_{ij})\}\{\exp(\sum_{k=1}^{p} \boldsymbol{\beta}_k\ \mathbf{x}_{ik})\} = \ \omega_i^{t} = \omega_c^{t}\ \theta_i^{t}\ ,$$

Parameters of interest

Eliminate nuisance parameters using the *conditional likelihood:* the pair of the control/case matched set is used as the unit for the analysis.

Only β_k are estimated and reported
α is not estimated and not reported

1:1 matched studies - Parameters

odds(disease)=$\omega_P\vartheta_i$

P(disease)=$\omega_P\vartheta_i\,/\,(1+\omega_P\vartheta_i)$, **P(no disease)=$1\,/\,(1+\omega_P\vartheta_i)$**

ω_P : baseline odds of pair *P*

Specific of each pair because of matching.

ϑ_i : covariate effects for subject *i* (a function of covariate values for subject *i*).

Disease odds for subject 1: $\omega_P\vartheta_1 = \omega_1$

Disease odds for subject 2: $\omega_P\vartheta_2 = \omega_2$

ln[odds(disease)]=ln[ω_P] + ln[ϑ_i]

= Corner$_P$ + ln(OR)

One parameter per pair, i.e. number of parameters =~ N/2.

Profile likelihood breaks down.

Solution: Conditional likelihood.

Probability of data, *conditional* on design, i.e. on 1 case and 1 control per set.

Distribution of covariates for case and control contains the information.

1:1 matched studies – Conditional likelihood

Conditional on the design one case and one control in each set, a set would contribute:

L = P(subj. 1 case | 1 case, 1 control)

To the likelihood

Taking into account

1. P(1 **case**, 1 control |subj. 1 case)=P(subj 2 control)
2. P(disease)=$\omega_P\vartheta_i\,/\,(1+\omega_P\vartheta_i)$, P(no disease)=$1\,/\,(1+\omega_P\vartheta_i)$
3. P(A|B)=P(B|A)*P(A)/(P(B|A)*P(A)+P(B|A-)*P(A-))

1:1 matched studies – Conditional likelihood

Conditional on one case and one control in each set,

L = P(subj. 1 case | 1 case, 1 control)=

$$\frac{P(1\ case, 1\ control|subj.1\ case\ ) * P(subj.1\ case)}{(P(1\ case, 1\ control|subj.1\ case\ ) * P(subj.1\ case) + P(1\ case, 1\ control|subj.1\ control\ ) * P(subj.1\ control}$$

$$\frac{P(subj\ 2\ control) * P(subj.1\ case)}{(P(subj\ 2\ control) * P(subj.1\ case) + P(subj.2\ case\ ) * P(subj.1\ control))}$$

1:1 matched studies – Conditional likelihood

$$L=\frac{(\omega_P\vartheta_1 / (1+\omega_P\vartheta_1))\ast(1/ (1+\omega_P\vartheta_2))}{[(\omega_P\vartheta_1 / (1+\omega_P\vartheta_1))\ast1 / (1+\omega_P\vartheta_2)+(\omega_P\vartheta_2 / (1+\omega_P\vartheta_2))\ast1 / (1+\omega_P\vartheta_1)}=$$

$$\frac{(\omega_1 / (1+\omega_1))\ast(1/ (1+\omega_2))}{(\omega_1 / (1+\omega_1))\ast(1 / (1+\omega_2))+((\omega_2 / (1+\omega_2))\ast(1 / (1+\omega_1))}=$$

$$\frac{(\omega_1 / (1+\omega_1) \ast(1+\omega_2))}{(\omega_1 +\omega_2)/(1+\omega_1) \ast(1+\omega_2))} \quad =$$

$$\omega_P\vartheta_1 / (\omega_P\vartheta_1+\omega_P\vartheta_2)$$

$$= \vartheta_1 / (\vartheta_1+\vartheta_2)$$

Log-likelihood contribution from one matched pair is:

$$\ln[\vartheta_{\text{case}}/(\vartheta_{\text{case}}+ \vartheta_{\text{control}})]$$

Independent of the corner parameters!

1:M matching

Odds for disease on one matched set:

subject 1: $\omega_P \vartheta_1 = \omega_1$

subject 2: $\omega_P \vartheta_2 = \omega_2$

subject *m*+1: $\omega_P \vartheta_{m+1} = \omega_{m+1}$

Probability that subject 1 is the case and the others are the controls:

$[\omega_1/(1+\omega_1)]*[1/(1+\omega_2)]*\ldots*[1/(1+\omega_{m+1})]$

Probability to have 1 case and *m* controls:

$\Sigma_i\{\omega_i/[(1+\omega_1)*(1+\omega_2)*\ldots*(1+\omega_{m+1})]\}$

$= \Sigma_i\omega_i/[(1+\omega_1)*(1+\omega_2)*\ldots*(1+\omega_{m+1})]$

Conditional probability that subject 1 is the case and subjects 2, 3, …, *m*+1 are the controls, *given* one case and *m* controls:

$$\omega_1/(\omega_1+\omega_2+\ldots+\omega_{m+1}) = \vartheta_1/(\vartheta_1+\vartheta_2+\ldots+\vartheta_{m+1})$$

1:M matching

Log-likelihood contribution from one matched set:

$$l = \ln\left(\frac{\theta_{case}}{\sum_{i \in cases \& controls} \theta_i} \right)$$

Log-likelihood for the total study:

$$l = \sum_{matched\ sets} \ln\left(\frac{\theta_{case}}{\sum_{i \in cases \& controls} \theta_i} \right)$$

The conditional log-likelihood for a 1:M matched CC study looks like a Cox-log-likelihood:

$$l = \sum_{failuretimes} \ln\left(\frac{\theta_{case}}{\sum_{i \in Risk\ set} \theta_i} \right)$$

The matched CC likelihood is of this form if at each death time, the case dies and only controls of the same set are at risk.

Analysis of conditional likelihood by ordinary logistic regression

Likelihood contribution from one matched pair is:

$$\vartheta_{\text{case}}/(\vartheta_{\text{case}}+\vartheta_{\text{control}})=(\vartheta_{\text{case}}/\vartheta_{\text{control}})/(1+\vartheta_{\text{case}}/\vartheta_{\text{control}})=\omega/(1+\omega)$$

This is the likelihood contribution from one binary observation with odds of success $\omega = \vartheta_{\text{case}}/\vartheta_{\text{control}}$

Linear model for $\ln(\vartheta)$

$$\log(\boldsymbol{odds_i}) = \boldsymbol{a} + \sum_{j=1}^{m} \boldsymbol{\gamma}_{\mathbf{j}}\, \mathbf{z}_{\mathbf{ij}} + \sum_{k=1}^{p} \boldsymbol{\beta}_{\mathbf{k}}\, \mathbf{x}_{\mathbf{ik}}$$

$\ln(\vartheta_{\text{case}})$ = Corner+Set+A_{case}

leads to (for one matched pair)

$\ln(\omega) = \boldsymbol{\ln(\vartheta_{\text{case}} / \vartheta_{\text{control}})} = \ln(\vartheta_{\text{case}}) - \ln(\vartheta_{\text{control}})$

= (Corner+Set+A_{case}) - (Corner+Set+A_{control})

= $A_{\text{case}} - A_{\text{control}}$

Corresponds to logistic regression without intercept.

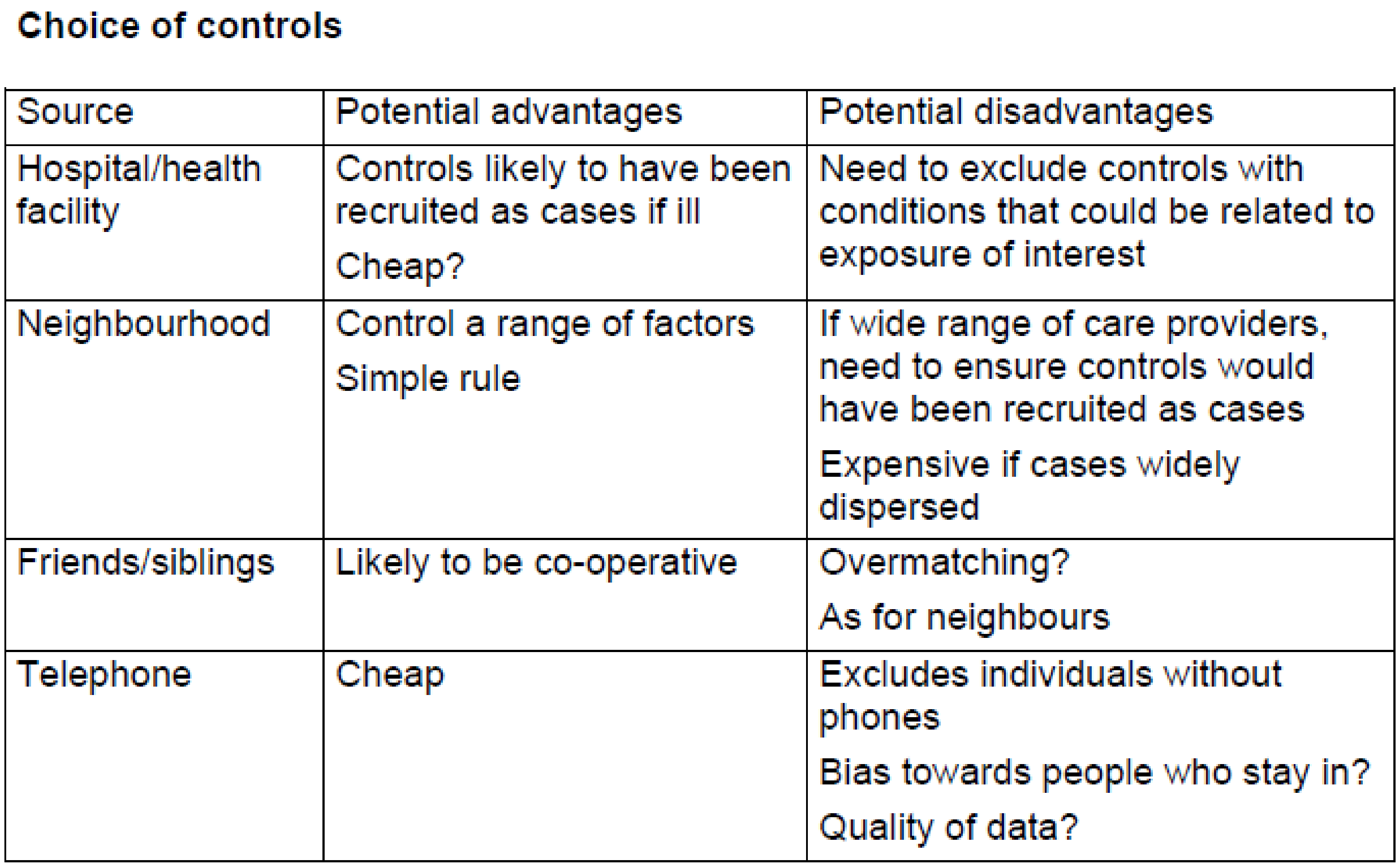
One observation per matched set.

Covariates are: covariate-value for case – covariate-value for control

Logistic regression without intercept. “Through the origin”.

1:1 matched studies by ordinary logistic regression

- The information is in the covariates:
- Continuous covariate: $\text{Age}_{\text{case}} - \text{Age}_{\text{control}}$.
- Differences between dummies, value for case minus value for control.
- Categorical covariate, dummies replaced by variables with values -1, 0 or 1:
  - if case and control belong to the same category all are = 0
  - if case and control belong to different categories:
  - 1 for the category where the case is.
  - -1 for the category where the control is.
  - 0 for the other categories.
- ONLY possible for 1:1 matched studies.



Choice of controls

Source	Potential advantages	Potential disadvantages
Hospital/health facility	Controls likely to have been recruited as cases if ill Cheap?	Need to exclude controls with conditions that could be related to exposure of interest
Neighbourhood	Control a range of factors Simple rule	If wide range of care providers, need to ensure controls would have been recruited as cases Expensive if cases widely dispersed
Friends/siblings	Likely to be co-operative	Overmatching? As for neighbours
Telephone	Cheap	Excludes individuals without phones Bias towards people who stay in? Quality of data?