Matched and nested case-control studies

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Program
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Program

9:15–10:00 Recap of case-control studies.
Frequency-matched studies.

10:00–10:45 Nested case-control studies.

10:45–12:00 Analysis of matched studies.

13:00–14:00 Discussion of article.

14:00–15:30 Practicals.

Case-control studies
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Relationship between follow–up studies and case–control studies

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.

Relationship between follow–up studies and case–control studies

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

Rationale behind case-control studies I

- In a follow-up study, rates among exposed and non-exposed are estimated by:

$$\frac{D_1}{Y_1} \qquad \frac{D_0}{Y_0}$$

and the rate ratio by:

$$\frac{D_1}{Y_1} \Big/ \frac{D_0}{Y_0} = \frac{D_1}{D_0} \Big/ \frac{Y_1}{Y_0}$$

Rationale behind case-control studies II

- Case-control study: same cases but controls represent the distribution of risk time

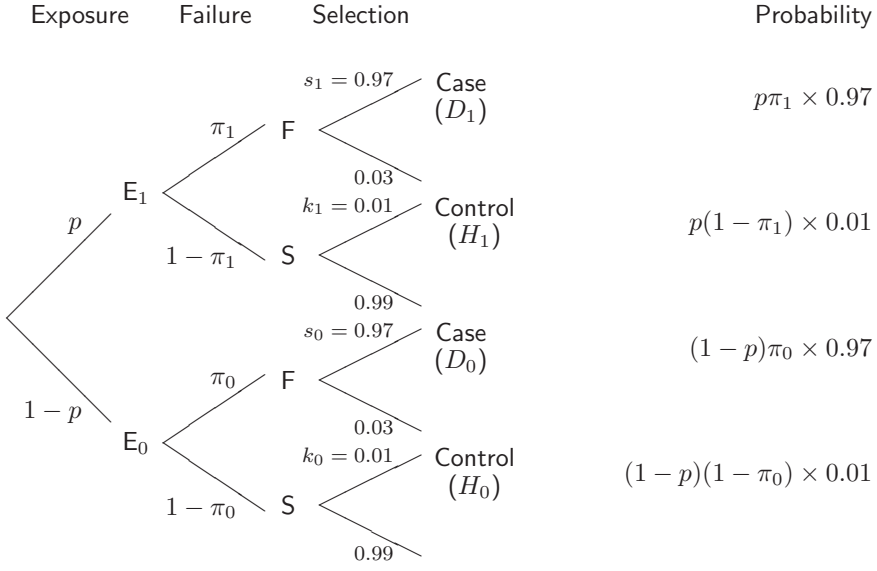
$$\frac{H_1}{H_0} \approx \frac{Y_1}{Y_0}$$

Therefore the rate ratio is estimated by:

$$\frac{D_1}{D_0} \Big/ \frac{H_1}{H_0}$$

- Controls represent **risk time**, **not** disease-free persons.

Case–control probability tree



What is estimated by the case-control ratio?

$$\frac{D_1}{H_1} = \frac{0.97}{0.01} \times \frac{\pi_1}{1-\pi_1} = \left(\frac{s_1}{k_1} \times \frac{\pi_1}{1-\pi_1}\right)$$

$$\frac{D_0}{H_0} = \frac{0.97}{0.01} \times \frac{\pi_0}{1-\pi_0} = \left(\frac{s_0}{k_0} \times \frac{\pi_0}{1-\pi_0}\right)$$

$$\frac{D_1/H_1}{D_0/H_0} = \frac{\pi_1/(1-\pi_1)}{\pi_0/(1-\pi_0)} = \mathrm{OR}_{\text{population}}$$

— but only for equal sampling fractions:

$$s_1/k_1 = s_0/k_0$$

.

Estimation from case-control study I

Odds-ratio of disease between exposed and unexposed *given inclusion*:

$$\mathrm{OR} = \frac{\omega_1}{\omega_0} = \frac{\pi_1}{1-\pi_1} \Big/ \frac{\pi_0}{1-\pi_0}$$

odds-ratio of disease (for a small interval)

between exposed and unexposed *in the study* is the same as odds-ratio for disease between exposed and unexposed in the "study base",

Estimation from case-control study II

under the assumption that:

- inclusion probability is the same for exposed and unexposed cases.
- inclusion probability is the same for exposed and unexposed controls.

The selection mechanism can **only** depend on case/control status.

Log-likelihood for case-control studies I

The **observations** in a case-control study are

- Response: case/control status
- Covariates: exposure status, etc.

The **parameters** possible to estimate are **odds** of disease *conditional* on inclusion into the study.

The log-likelihood is a binomial likelihood with odds of being a case (conditional on being included) ω_0 (unexposed) and ω_1 (exposed)
— or the odds ω_0 and the odds-ratio $\theta = \omega_1/\omega_0$.

Log-likelihood for case-control studies I

Binomial outcome (case/control) and binary exposure $(0/1)$

$$D_0\ln(\omega_0) - N_0\ln(1+\omega_0) + D_1\ln(\theta\omega_0) - N_1\ln(1+\theta\omega_0)$$

Odds-ratio (θ) is the ratio of ω_1 to ω_0, so:

$$\ln(\theta) = \ln(\omega_1) - \ln(\omega_0)$$

Estimates of $\ln(\omega_1)$ and $\ln(\omega_0)$ are:

$$\ln\left(\frac{D_1}{H_1}\right) \quad \text{and} \quad \ln\left(\frac{D_0}{H_0}\right)$$

Log-likelihood for case-control studies II

with standard errors:

$$\sqrt{\frac{1}{D_1} + \frac{1}{H_1}} \quad \text{and} \quad \sqrt{\frac{1}{D_0} + \frac{1}{H_0}}$$

Exposed and unexposed form two independent bodies of data, so the estimate of $\ln(\theta) \quad [= \ln(\mathrm{OR})]$ is

$$\ln\left(\frac{D_1}{H_1}\right) - \ln\left(\frac{D_0}{H_0}\right), \quad \text{s.e.} = \sqrt{\frac{1}{D_1} + \frac{1}{H_1} + \frac{1}{D_0} + \frac{1}{H_0}}$$

BCG vaccination and leprosy

New cases of leprosy were examined for presence or absence of the BCG scar. During the same period, a 100% survey of the population of this area, which included examination for BCG scar, had been carried out.

BCG scar	Leprosy cases	Population survey
Present	101	46 028
Absent	159	34 594

The tabulated data refer only to subjects under 35.

Confidence interval for the odds ratio

$$\text{OR} = \frac{D_1/H_1}{D_0/H_0} = \frac{101/46028}{159/34594} = 0.48$$

$$\begin{aligned}\text{s.e.}(\ln[\text{OR}]) &= \sqrt{\frac{1}{D_1} + \frac{1}{H_1} + \frac{1}{D_0} + \frac{1}{H_0}} \\ &= \sqrt{\frac{1}{101} + \frac{1}{46028} + \frac{1}{159} + \frac{1}{34594}} \\ &= 0.127\end{aligned}$$

$$\text{erf} = \exp(1.96 \times 0.127) = 1.28$$

$$\text{OR} \overset{\times}{\div} \text{erf} = 0.48 \overset{\times}{\div} 1.28 = (0.37, 0.61) \quad \text{(95\% c.i.)}$$

Unmatched study with 1000 controls

BCG scar	Leprosy cases	Controls
Present	101	554
Absent	159	446

$$\text{OR} = \frac{101/554}{159/446} = \frac{0.1823}{0.3565} = 0.51$$

$$\text{s.e.}(\ln[\text{OR}]) = \sqrt{1/101 + 1/554 + 1/159 + 1/446} = 0.1$$

$$\text{erf} = \exp(1.96\text{s.e.}(\ln[\text{OR}])) = 1.32$$

95% c.i.: $0.51 \overset{\times}{\div} \text{erf} = (0.39, 0.68)$

Frequency matched studies
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Age-stratified odds-ratio: BCG data

Exposure: BCG

Potential confounder: age

- Age and BCG-scar correlated.
- Age is associated with leprosy.
- Bias in the estimation of the relationship between BCG-scar and leprosy.

Now, stratify the analysis by age:

	cases		population		Odds ratio
BCG	−	+	−	+	estimate
Age					
0–4	1	1	7593	11719	0.65
5–9	11	14	7143	10184	0.89
10–14	28	22	5611	7561	0.58
15–19	16	28	2208	8117	0.48
20–24	20	19	2438	5588	0.41
25–29	36	11	4356	1625	0.82
30–34	47	6	5245	1234	0.54
				Overall	0.58

Simulated cc-study, stratified by age

	cases		population	
BCG	−	+	−	+
Age				
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

Matching and efficiency

- If some strata have many controls per case and other only few, there is a tendency to "waste"
  - controls in strata with many controls
  - cases in strata with few controls
- The solution is to *match* or *stratify* the study; i.e make sure that the ratio of cases to controls is approximately the same in all strata (e.g. age-groups).

Simulated cc-study (group-matched) I

	cases		population	
BCG	−	+	−	+
Age				
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

Simulated cc-study (group-matched) II

- **Not** possible to estimate effect of age.
- Age **must** be included in model.
  But the estimates do not have any meaning.
  Testing of the age-effect is irrrelevant.
- If a variable is used for matching (stratified sampling) it **must** be included in the model.

Matching: BIAS!

- If the study is stratified on a variable, this variable **must** enter in the analysis too:

	Cases		Controls		Odds
Stratum	+	−	+	−	ratio
1	89	11	80	20	2.0
2	67	33	50	50	2.0
3	33	67	20	80	2.0
Total	189	111	150	150	1.7

- The bias from ignoring matching will always be towards 1.

Interaction with the matching variable

Age-effect cannot be estimated from a stratified study, i.e. how age influences the risk of leprocy cannot be estimated from an age-matched study.

But the exposure×age interaction **can** be estimated: i.e.: how the does the effect of BCG-scar vary with age.

- The OR of leprosy between BGC yes/no is not same in all age-classes.
- The OR of leprosy between BGC yes/no decreses from age-class to age-class.

Recall confounding

Exposure effect estimated wrongly because a factor is associated both with exposure and disease.

Age and sex are the most common confounders.

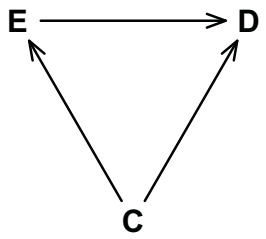
Confounder characteristics:

- Associated to exposure
- Risk factor in it self (associated to disease).

Associated to exposure only: Irrelevant

Associated to disease only: Independent Risk Factor

Confounding and causal chain:



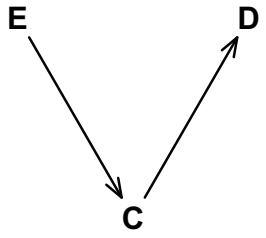
Confounding:

Ignoring **C** gives biased estimate of the effect of **E**.

Control of the confounding effect of **C** is necessary.

BMI — Age — DM
Should we match on **C**?
If we do should it be included in analysis?

Confounding and causal chain:



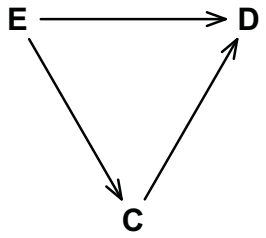
Intermediate variable:

Control of the effect of **C** is not wanted:

C is a stage in the development of **D**.

Genotype — BMI — Insulin resistance
Should we match on **C**?
If we do should it be included in analysis?

Confounding and causal chain:



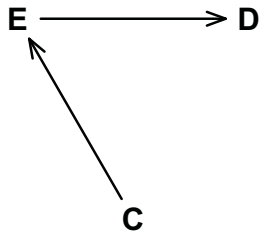
Intermediate variable **and** and direct effect of **E**:

Control of the effect of **C** is not wanted:

Cannot be destinguished from confounding.

Genotype — BMI — Insulin resistance
Should we match on **C**?
If we do should it be included in analysis?

Confounding and causal chain:



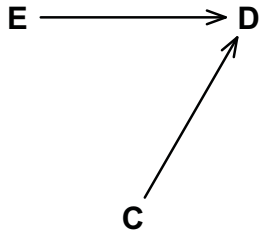
Preceeding exposure:

Control of the effect of **C** is not necessary.

It will just decrease the precision of the effect estimate.

BMI effect on occurrence of DM.
Should we match on **C**?
If we do should it be included in analysis?

Confounding and causal chain:



Separate risk factor (independent of **E**):

Control of the effect of **C** is not necessary.

But it will probably be useful to estimate the effect of both **E** and **C**.

Should we match on **C**?
If we do should it be included in analysis?

Analysis by logistic regression

- Assuming the odds ratio, θ, to be constant over strata, each stratum adds a separate contribution to the log likelihood function for θ.
- The log likelihood can be analysed in a model where odds is a product of age-effect and exposure effect.
- This is a **logistic regression** model:

$$\text{case-control odds}(a) = \mu_a \times \theta$$

— a multiplicative model for **odds**.

Recall the sampling fractions:

What is estimated by the case-control ratio?

$$\frac{D_1}{H_1} = \frac{0.97}{0.01} \times \frac{\pi_1}{1-\pi_1} = \left(\frac{s_1}{k_1} \times \frac{\pi_1}{1-\pi_1}\right)$$

$$\frac{D_0}{H_0} = \frac{0.97}{0.01} \times \frac{\pi_0}{1-\pi_0} = \left(\frac{s_0}{k_0} \times \frac{\pi_0}{1-\pi_0}\right)$$

$$\frac{D_1/H_1}{D_0/H_0} = \frac{\pi_1/(1-\pi_1)}{\pi_0/(1-\pi_0)} = \text{OR}_{\text{population}}$$

— only for equal samping fractions:
$s_1/k_1 = s_0/k_0 = s/k$.

Logistic regression for case-control studies I

- Model for the population:

$$\ln\left[\frac{\pi}{1-\pi}\right] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

- Model for the observed data:

$$\begin{aligned}\ln[\text{odds(case|incl.)}] =& \ln\left[\frac{\pi}{1-\pi}\right] + \ln\left[\frac{s}{k}\right] \\ =& \left(\ln\left[\frac{s}{k}\right] + \beta_0\right) \\ &+ \beta_1 x_1 + \beta_2 x_2\end{aligned}$$

Logistic regression for case-control studies II

- Analysis of $\mathrm{P}\{\text{case} \mid \text{inclusion}\}$ — i.e. binary observations:

$$Y = \begin{cases} 1 & \sim \text{case} \\ 0 & \sim \text{control} \end{cases}$$

- Effect of covariates is estimated correctly.
- Intercept is meaningless.
  Depends on the sampling fractions for cases, s, and controls, k, which are usually not known.

Parameter interpretation in logistic regression I

Model for persons with covariates x_A, x_B:

$$\ln[\text{odds}(\text{case} \mid x_A)] = \left(\ln\left[\frac{s}{k}\right] + \beta_0\right) + \beta_1 x_{1A} + \beta_2 x_{2A}$$
$$\ln[\text{odds}(\text{case} \mid x_B)] = \left(\ln\left[\frac{s}{k}\right] + \beta_0\right) + \beta_1 x_{1B} + \beta_2 x_{2B}$$

$$\ln[\mathrm{OR}_{x_A \text{ vs. } x_B}] = \beta_1(x_{1A} - x_{1B}) + \beta_2(x_{2A} - x_{2B})$$

$\exp(\beta_1)$ is OR for a change of 1 in x_1
$\exp(\beta_2)$ is OR for a change of 1 in x_2

SAS commands — random sample of controls

```
proc genmod  data = a1 ;
  class alder bcg ;
  model cases / rtotal = alder bcg
        / dist = bin
          link = logit
         type3 ;
  estimate "+bcg" bcg  1 -1 / exp ;
  estimate "-bcg" bcg -1  1 / exp ;
run;
```

Random sample of controls

Deviance		6	6.6268	1.1045

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Std Err	ChiSquare
INTERCEPT		1	-4.5008	0.7138	39.7577
ALDER	1	1	4.2062	0.7333	32.9008
ALDER	2	1	4.0452	0.7345	30.3339
ALDER	3	1	3.9700	0.7363	29.0739
ALDER	4	1	3.9233	0.7333	28.6209
ALDER	5	1	3.4711	0.7282	22.7200
ALDER	6	1	2.6685	0.7414	12.9538
ALDER	7	0	0.0000	0.0000	
BCG	0	1	-0.5475	0.1604	11.6557
BCG	1	0	0.0000	0.0000	

LR Statistics For Type 3 Analysis:

Source	DF	Chi-Square	Pr > ChiSq
alder	6	149.73	<.0001
bcg	1	11.78	0.0006

Contrast Estimate Results

Label	Estimate	Standard Error	Conf. Limits		Chi-Square
+bcg	-0.5475	0.1604	-0.8619	-0.2332	11.66
Exp(+bcg)	0.5784	0.0928	0.4224	0.7920	
-bcg	0.5475	0.1604	0.2332	0.8619	11.66
Exp(-bcg)	1.7290	0.2773	1.2626	2.3676	

Matched sample of controls I

Deviance		6	4.4399	0.7400

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Std Err	ChiSquare
INTERCEPT		1	-1.0667	0.7998	1.7786
ALDER	1	1	-0.2380	0.8129	0.0857
ALDER	2	1	-0.1628	0.8136	0.0400
ALDER	3	1	0.0244	0.8160	0.0009
ALDER	4	1	0.0713	0.8139	0.0077
ALDER	5	1	0.0119	0.8116	0.0002
ALDER	6	1	-0.0421	0.8271	0.0026
ALDER	7	0	0.0000	0.0000	
BCG	0	1	-0.5721	0.1547	13.6790
BCG	1	0	0.0000	0.0000	

Matched sample of controls II

LR Statistics For Type 3 Analysis

Source	DF	Chi-Square	Pr > ChiSq
alder	6	2.33	0.8867
bcg	1	13.89	0.0002

Contrast Estimate Results

Label	Estimate	Standard Error	Conf. Limits		Chi-Square
+bcg	-0.5721	0.1547	-0.8752	-0.2689	13.68
Exp(+bcg)	0.5644	0.0873	0.4168	0.7642	
-bcg	0.5721	0.1547	0.2689	0.8752	13.68
Exp(-bcg)	1.7719	0.2741	1.3085	2.3994	

Matched sample of controls III

Standard deviation of $\ln(\mathrm{OR})$ shrinks from 0.160 to 0.155 by age-matching.

The age-BCG and the age-leprocy associations are not very strong.

Remember the matching variable

With age in the model:

+bcg	-0.5721	0.1547	-0.8752	-0.2689	13.68
Exp(+bcg)	0.5644	0.0873	0.4168	0.7642	

Without age in the model (**wrong!**—OR biased towards 1):

+bcg	-0.4769	0.1416	-0.7543	-0.1994	11.35
Exp(+bcg)	0.6207	0.0879	0.4703	0.8192	

Odds-ratio and rate ratio

- If the disease probability, π, in the study period (length of period: T) is small:

  π = cumulative risk $\approx$ cumulative rate $= \lambda T$

- For small π, $1 - \pi \approx 1$, so:

$$\mathrm{OR} = \frac{\pi_1/(1-\pi_1)}{\pi_0/(1-\pi_0)} \approx \frac{\pi_1}{\pi_0} \approx \frac{\lambda_1}{\lambda_0} = \mathrm{RR}$$

  π small $\Rightarrow$ OR estimate of RR.

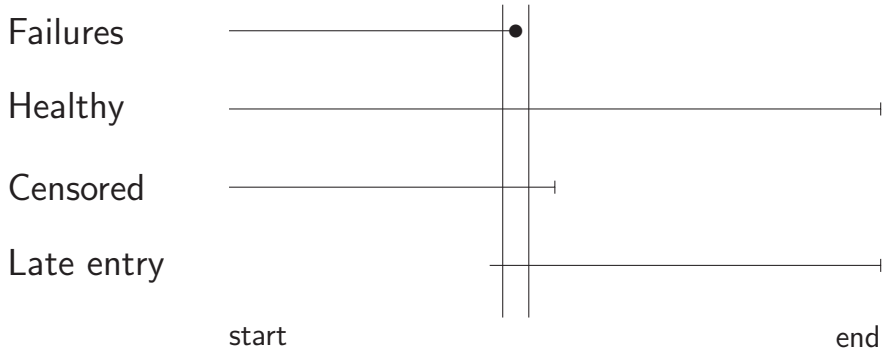
Important assumption behind rate ratio interpretation

The entire "study base" must have been available throughout:

- no censorings.
- no delayed entries.

This will clearly not always be the case, but it may be achieved in carefully designed studies.

Choice of controls (I)



Instead, choose controls from members of the source population who are in the study and healthy, at the times the cases are registered.
This is called **incidence density sampling**.

Incidence density sampling

- The method is equivalent to sampling observation time from vertical bands drawn to enclose each case.
  This is how controls are chosen to represent risk time. ($H \propto Y$).
- New case-control study in each time band.
- No delayed entry or censoring.
- If the fraction of exposed does not vary much over time, all the small studies can be analysed together as one.
- This is effectively matching on calendar time.

Nested case-control study

Case-control study nested in cohort:

Controls are chosen from a cohort from which the cases arise. Controls are chosen among those at risk of becoming cases at the time of diagnosis of each case.

Nested case-control study

Reasons to use nested case-control study:

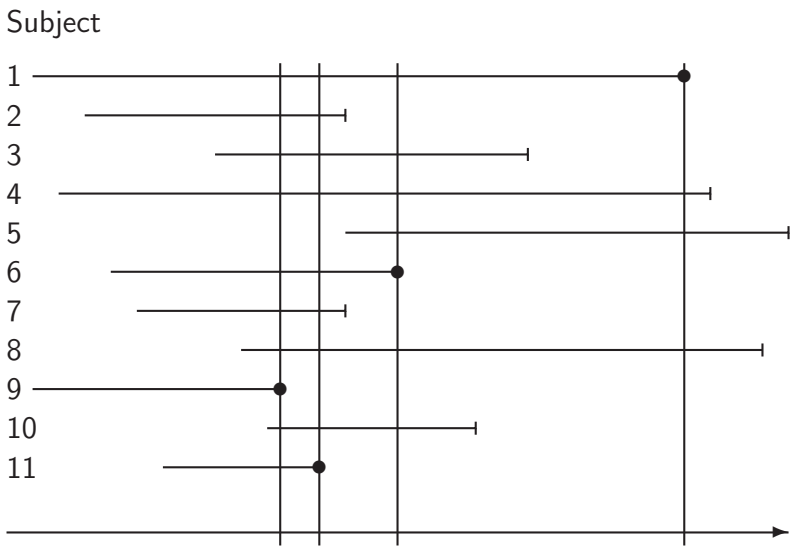
- Cost saving by collecting data on controls only instead of the entire cohort at risk at each failure time (=diagnosis of case).
- Collection of data to elucidate an unmeasured covariate in a cohort study.
  Restricted only to Cases and matched controls.

Note that any cohort study can be used as basis for generating a nested case-control study.

Nested case-control study

The technical term is to *sample the risk set*, i.e. instead of collecting exposure information on all individuals in the risk set, we only do it for a subsample of them.

Sampling the risk set



The risk sets

Defined at each event time (•):

Event	Risk set	Sample
1		
2		
3		
4		

How many controls per case?

The standard deviation of $\ln(\mathrm{OR})$:

Equal number of cases and controls:

$$\sqrt{\frac{1}{D_1}+\frac{1}{H_1}+\frac{1}{D_0}+\frac{1}{H_0}} \approx \sqrt{\frac{1}{D_1}+\frac{1}{D_1}+\frac{1}{D_0}+\frac{1}{D_0}}$$

$$= \sqrt{\left(\frac{1}{D_1}+\frac{1}{D_0}\right)\times(1+1)}$$

Twice as many:

$$\sqrt{\frac{1}{D_1}+\frac{1}{H_1}+\frac{1}{D_0}+\frac{1}{H_0}} \approx \sqrt{\frac{1}{D_1}+\frac{1}{2D_1}+\frac{1}{D_0}+\frac{1}{2D_0}}$$

$$= \sqrt{\left(\frac{1}{D_1}+\frac{1}{D_0}\right)\times(1+1/2)}$$

m times as many:

$$\sqrt{\frac{1}{D_1}+\frac{1}{H_1}+\frac{1}{D_0}+\frac{1}{H_0}} \approx \sqrt{\left(\frac{1}{D_1}+\frac{1}{D_0}\right)\times(1+1/m)}$$

- The standard deviation of the $\ln[\mathrm{OR}]$ is (approximately)

$$\sqrt{1+\frac{1}{m}}$$

  times larger in a case-control study, compared to the corresponding cohort-study.
- Therefore, 5 controls per case is normally sufficient. (Only relevant if controls are "cheap" compared to cases).
- **But** if cases and controls cost the same, and are available the most efficient is to have the same number of cases and controls.

Individually matched studies
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Individually matched study

If strata are defined so finely that there is only one case in each, we have an individually matched study.

The reason for this may be:

- Comparability between cases and controls.
- Control for ill-defined factors.
- Convenience in sampling.
- Controlling for age, calendar time (incidence density sampling).

Individually matched study I

Pitfall in design:

- Overmatching (cases and controls are identical on some risk factors).

Consequence in analysis:

- Conventional method for analysis (logistic regression) breaks down, because we get one parameter per set
(which means one per case)!

Individually matched study II

- If matching is on a well-defined variable as e.g. age, then broader stata may be formed *post hoc*, and age included in the model.
- If matching is on "soft" variables (neighborhood, occupation, ...) the original matching cannot be ignored:
  Matched analysis.

Salmonalla Manhattan study

Telephone interview concerning the food items ingested during the last three days:

- Case: Verified infection with *S.* Manhattan
- Control: Person from same geographical area.
- 16 matched pairs — 1:1 matched study.
- Exposure: Eaten sliced saxony ham (hamburgerryg)

OBS	PARNR	KONTROL	HAMBURG
1	1	0	0
2	1	1	0
3	3	0	1
4	3	1	0
5	4	0	1
6	4	1	0
7	5	0	1
8	5	1	1
9	7	0	1
10	7	1	0
11	8	0	0
12	8	1	1
13	9	0	0
14	9	1	0
15	11	0	1
16	11	1	1

OBS	PARNR	KONTROL	HAMBURG
17	12	0	0
18	12	1	0
19	14	0	1
20	14	1	0
21	16	0	0
22	16	1	0
23	17	0	1
24	17	1	0
25	18	0	0
26	18	1	1
27	19	0	1
28	19	1	1
29	20	0	1
30	20	1	1
31	23	0	1
32	23	1	0

1:1 matched studies — Tabulation

1:1 matched case-control study can be tabulated as:

No. of matched pairs		Control exposure +	Control exposure −	
Case exposure	+	a	b	$a+b$
	−	c	d	$c+d$
		$a+c$	$b+d$	N

Table of **pairs**.

Remember: Exposure OR = Disease OR:

$$\text{OR} = \omega = \frac{\text{P}\left\{\text{E}+|\text{case}\right\}\text{P}\left\{\text{E}-|\text{control}\right\}}{\text{P}\left\{\text{E}-|\text{case}\right\}\text{P}\left\{\text{E}+|\text{control}\right\}}$$

estimated by:

$$\hat{\omega} = \frac{b}{c}$$

Standard error on the log-scale:

$$\text{s.e.}[\ln(\hat{\omega})] = \sqrt{\frac{1}{b} + \frac{1}{c}}$$

Salmonalla Manhattan study

Exercise: Tabulate the *Salmonella* data:

No. of matched pairs		Control exposure +	Control exposure −	
Case exposure	+			
	−			

OR estimated by:

$$\hat{\omega} = \frac{b}{c} =$$

Standard error on the log-scale:

$$\text{s.e.}[\ln(\hat{\omega})] = \sqrt{\frac{1}{b} + \frac{1}{c}} =$$

Find approximate 95% c.i. for the OR:

1:1 matched studies: — Test I

No. of pairs		Control exposure +	Control exposure −	
Case exposure	+	a	b	$a+b$
	−	c	d	$c+d$
		$a+c$	$b+d$	N

- McNemar's test of OR$= 1$ compares b og c:

$$\frac{(b-c)^2}{b+c} \sim \chi^2(1)$$

1:1 matched studies: — Test II

- McNemar's test with continuity correction:

$$\frac{(|b-c|-1)^2}{b+c} \sim \chi^2(1)$$

1:1 matched studies: Parameters

$$\text{odds(disease)} = \omega_P \theta_i \quad \Longleftrightarrow \quad \mathrm{P}\{\text{disease}\} = \frac{\omega_P \theta_i}{1 + \omega_P \theta_i}$$

- ω_P — baseline odds for pair P
- θ_i — covariate effects for subject i.
- subject 1: $\omega_P \theta_1 = \omega_1$
- subject 2: $\omega_P \theta_2 = \omega_2$

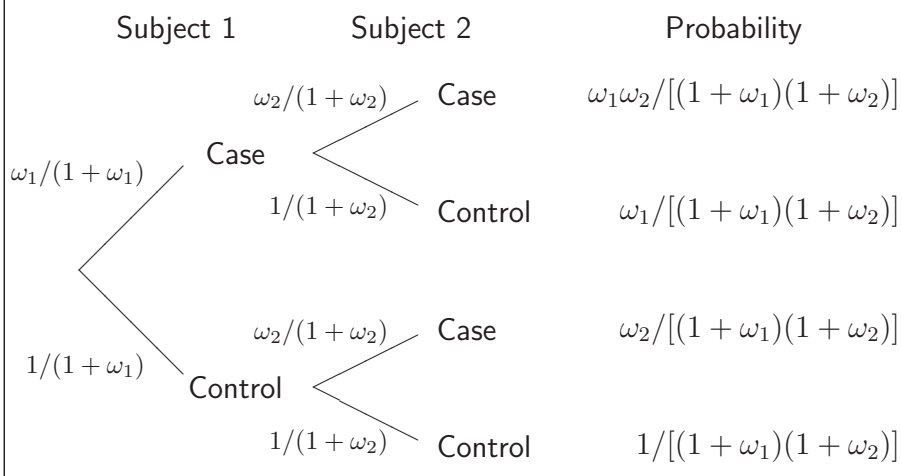
1:1 matched studies: Likelihood

$$\text{odds(disease)} = \omega_P \theta_i$$
$$\ln[\text{odds(disease)}] = \ln[\omega_P] + \ln[\theta_i] = \boxed{\text{Cnr}_P} + \ln(\text{OR})$$

One parameter per pair, i.e. number of parameters $\approx N/2$. Profile likelihood approach breaks down. Solution:

- 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.

A set with 2 subjects



Only the middle two outcomes need be considered.

Likelihood from one matched pair

$$L = \mathrm{P}\{\text{subj. 1 case} \mid \text{1 case, 1 control}\}$$

$$= \frac{\omega_1}{\omega_1 + \omega_2} = \frac{\omega_P \theta_1}{\omega_P \theta_1 + \omega_P \theta_2} = \frac{\theta_1}{\theta_1 + \theta_2}$$

Log-likelihood contribution from one matched pair:

$$\log\left(\frac{\theta_{\text{case}}}{\theta_{\text{case}} + \theta_{\text{control}}}\right)$$

Independent of the parameters ω_P.

$1 : m$ matching

Odds for disease in one matched set:

$$\begin{array}{lll} \text{subject } 1: & \omega_P \theta_1 & = \omega_1 \\ \text{subject } 2: & \omega_P \theta_2 & = \omega_2 \\ & \cdots & \\ \text{subject } m+1: & \omega_P \theta_{m+1} & = \omega_{m+1} \end{array}$$

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

$$\frac{\omega_1}{1+\omega_1} \times \frac{1}{1+\omega_2} \times \cdots \times \frac{1}{1+\omega_{m+1}}$$

Probability of 1 case and m controls:

$$\sum_i \frac{\omega_i}{(1+\omega_1) \times (1+\omega_2) \times \cdots (1+\omega_{m+1})}$$

$$= \frac{\sum_i \omega_i}{(1+\omega_1) \times (1+\omega_2) \times \cdots (1+\omega_{m+1})}$$

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

$$\frac{\omega_1}{\omega_1 + \omega_2 + \cdots + \omega_{m+1}} = \frac{\theta_1}{\theta_1 + \theta_2 + \cdots + \theta_{m+1}}$$

$1 : m$ matching

Log-likelihood contribution from one matched set:

$$\ell = \log\left(\frac{\theta_{\text{case}}}{\sum_{i \in \text{ cases \& controls}} \theta_i}\right)$$

Log-likelihood for the total study:

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

$1 : m$ matching

- Number of controls can vary between sets.
- If a variable is constant *within* matched sets, it is *impossible* to estimate a multiplicative effect:

$$\frac{\beta\theta_{\text{case}}}{\sum_i \beta\theta_i} = \frac{\theta_{\text{case}}}{\sum_i \theta_i}$$

  Beware of overmatching!
- *Interactions* between such variables and other variable *can* be estimated.

$1 : m$ matching

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

$$\ell = \sum_{\text{failure times}} \ln\left(\frac{\theta_{\text{case}}}{\sum_{i \in \text{ Risk set}} \theta_i}\right)$$

The matched case-control likelihood is of this form if at each death time:

- The case dies.
- Only controls from the same set are at risk.

Use of Proc Phreg

- Input is a dataset with one observation per person.
- "Survival time" for controls $>$ for cases.
- Cases events, controls censorings.
- Matched set variable required for `strata`-command.
- Ties handling = `discrete`.
  (not really necessary if only one case per matched set).

This is what traditionally is recommended for programs that can handles a stratified Cox-model.

Use of Proc Phreg I

```
proc phreg  data = manh11 ;
  model kontrol * kontrol (1) = hamb / ties = discrete ;
  strata parnr ;
run ;

The PHREG Procedure

 Model Information
Data Set                  WORK.MANH11
Dependent Variable        kontrol
Censoring Variable        kontrol
Censoring Value(s)        1
Ties Handling             DISCRETE

          Summary of the Number of Event and Censored Values
                                                                 Perc
Stratum    parnr          Total       Event    Censored        Censo

      1    1                  2           1           1           50
      2    3                  2           1           1           50
```


Use of Proc Phreg II

```
      3    4                  2           1           1           50
      4    5                  2           1           1           50
      5    7                  2           1           1           50
      6    8                  2           1           1           50
      7    9                  2           1           1           50
      8   11                  2           1           1           50
      9   12                  2           1           1           50
     10   14                  2           1           1           50
     11   16                  2           1           1           50
     12   17                  2           1           1           50
     13   18                  2           1           1           50
     14   19                  2           1           1           50
     15   20                  2           1           1           50
     16   23                  2           1           1           50
-------------------------------------------------------------------
  Total                      32          16          16           50

 Testing Global Null Hypothesis: BETA=0
Test                 Chi-Square       DF     Pr > ChiSq
Likelihood Ratio         2.0930        1         0.1480
Score                    2.0000        1         0.1573
Wald                     1.8104        1         0.1785
```

Use of Proc Phreg III

Analysis of Maximum Likelihood Estimates

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr>ChiSq	Haza Rat
hamb	1.09861	0.81650	1.8104	0.1785	3.0

How the *S.* Manhattan study REALLY was

PARNR	KONTROL 0	KONTROL 1
1	1	2
3	1	2
4	1	1
5	1	3
7	1	3
8	1	2
9	1	3
10	.	2
11	1	3
12	1	3
14	1	3
16	1	3
17	1	3
18	1	3
19	1	3
20	1	3
22	.	2
23	1	3

```
proc phreg  data = manh ;
  model kontrol * kontrol (1) = hamb
        / ties = discrete ;
  strata parnr ;
run ;
```


The PHREG Procedure

Model Information

Data Set	WORK.MANH
Dependent Variable	kontrol
Censoring Variable	kontrol
Censoring Value(s)	1
Ties Handling	DISCRETE

Number of Observations Read	63
Number of Observations Used	63

Summary of the Number of Event and Censored Values

Stratum	parnr	Total	Event	Censored	Perc Censored
1	1	3	1	2	66.67
2	3	3	1	2	66.67
3	4	2	1	1	50.00

4	5	4	1	3	75.00
5	7	4	1	3	75.00
6	8	3	1	2	66.67
7	9	4	1	3	75.00
8	10	2	0	2	100.00
9	11	4	1	3	75.00
10	12	4	1	3	75.00
11	14	4	1	3	75.00
12	16	4	1	3	75.00
13	17	4	1	3	75.00
14	18	4	1	3	75.00
15	19	4	1	3	75.00
16	20	4	1	3	75.00
17	22	2	0	2	100.00
18	23	4	1	3	75.00
Total		63	16	47	74.60

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	5.8323	1	0.0157
Score	5.6749	1	0.0172
Wald	4.9411	1	0.0262

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
hamb	1	1.52985	0.68824	4.9411	0.0262

Using `proc logistic` I

```
proc logistic  data = manh ;
  class parnr hamb(ref="0") ;
  model kontrol = hamb ;
  strata parnr ;
run ;
```

...

Strata Summary

Response Pattern	kontrol 0	kontrol 1	Number of Strata	Frequency
1	0	2	2	4
2	1	1	1	2
3	1	2	3	9
4	1	3	12	48

...

Using `proc logistic` II

```
                Analysis of Maximum Likelihood Estimates
                                        Standard          Wald
Parameter       DF    Estimate          Error     Chi-Square    Pr >
hamb       1     1      0.7649         0.3441         4.9411         0


The LOGISTIC Procedure
 Conditional Analysis

              Odds Ratio Estimates
                   Point          95% Wald
Effect           Estimate      Confidence Limits

hamb 1 vs 0         4.617        1.198      17.792
```


Matched studies in practice

- Think of the scenario where extensive follow-up and measurements were available for all persons in the cohort.
- Use "history" of a peron as predictor of mortality.
- Definition of "history":
  - Original treatment allocation.
  - Profile of measurements over time.
  - Genotype.
  - ...

Definition of history

- Is the entire profile of measurements relevant:
  - Only the most recent.
  - Only measurements older than 1 year, say (latency).
  - Cumulative measures?
- What is the relevant summary measure(s) of history.
- Age. (current age, age at entry)
- Calendar time. (current or at entry).

Selecting controls: Incidence density sampling

- Timescale.
  Controls should be alive when the correspondig case dies.
- More than one time-scale:
  Age and calendar time:
  Match on date of exit (calendar time) and date of birth.
- Measurements should be of the same "age" for case and control.
  Comparability of covariates within matched sets.

Sampling from the cohort

Matched / incidence density sampled case-control studies are money-saving sampling plans for a survival study.

The design allows estimation of the same parameters as do a total follow up of the entire cohort.
Albeit with less precision.

Another possible sampling scheme allowing this is the **case-cohort** design. This design allows analysis of several types of event using the same "contols".

Case-cohort design

Select a sub-cohort from the original cohort. Collect covariateinformation on these persons.

Take all persons with events of the type(s) of interest, and collect covariate information on these.

The analysis of these data allows estimation of rate-ratios for different event types.

Case-cohort design vs. case-control

Analysis of different event types would require separate nested case-control studies.

The price to be paid for the simpler sampling in case-cohort studies is a more is a complicated statistical analysis.

Implemented in many standard packages, and detailed guides are available.