Lecture 3: Measures of effect: Risk Difference Attributable Fraction Risk Ratio and Odds Ratio

Dankmar Böhning

Southampton Statistical Sciences Research Institute
University of Southampton, UK

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Measures of differences in disease occurrence

Risk difference

Choosing an Effect Measure and Public Health Impact

Attributable Fraction

Risk Ratio

Odds Ratio

Odds ratio and study type

We have seen earlier how to measure diseases and their distributions using prevalence and incidence.

Now we are concerned with differences in disease occurrence in different populations.

Common measures are

1. risk difference (RD)
2. relative risk difference or attributable fraction (AF)
3. risk ratio (RR)
4. odds ratio (OR)

In this lecture we will look at the first two.

The risk ratio and odds ratio will be covered in the next lecture.

The **Risk Difference** (RD) is the difference between disease risk in an **exposed** population and risk in an **non-exposed** population.

Let p_1 = disease risk in an **exposed** population

p_0 = disease risk in an **non-exposed** population.

$$RD = p_1 - p_0$$

RD is a number between -1 and 1.

Example 1

In a study of two toothpastes, 10 out of 100 caries-free children using a new toothpaste (exposure) develop caries after 1 year. In another group of 100 caries-free children using a standard toothpaste, 25 develop caries.

$$\widehat{RD} = \frac{10}{100} - \frac{25}{100} = -0.15$$

Example 2

In a group of 1000 persons with heavy sun-exposure, there are 40 cases of skin cancer. In a comparative, equally sized, non-exposed group there are 10 cases of skin cancer.

$$\widehat{RD} = \frac{40}{1000} - \frac{10}{1000} = 0.03$$

Exercise 1

In a cohort study evaluating radiation exposures, 52 tumours developed among 2872 exposed individuals and 6 tumours developed among 5049 unexposed individuals within the observation period.
What is the risk difference?

$$\widehat{RD} = \hat{p}_1 - \hat{p}_0 =$$

Distribution of number of diseased

Suppose that in a cohort study,

Y_1 out of n_1 exposed individuals and

Y_0 out of n_0 non-exposed individuals

developed the disease.

Assume that the probability p_1 of developing the disease is the **same** for everyone in the exposed group

Similarly, assume that the probability p_0 of developing the disease is the **same** for everyone in the non-exposed group

Then $Y_1 \sim B(n_1, p_1)$ distribution

And $Y_0 \sim B(n_0, p_0)$ distribution

Variance of RD

A reasonable estimate for the RD is

$$\widehat{RD} = \hat{p}_1 - \hat{p}_0 = \frac{Y_1}{n_1} - \frac{Y_0}{n_0}$$

From which we get,

$$\begin{aligned} Var(\widehat{RD}) &= Var\left(\frac{Y_1}{n_1} - \frac{Y_0}{n_0}\right) \\ &= Var\left(\frac{Y_1}{n_1}\right) + Var\left(\frac{Y_0}{n_0}\right) \end{aligned}$$

and since both Y_1 and Y_2 follow binomial distributions,

$$Var(\widehat{RD}) = \frac{p_1(1-p_1)}{n_1} + \frac{p_0(1-p_0)}{n_0}$$

A confidence interval for RD

$$SD(\widehat{RD}) = \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_0(1-p_0)}{n_0}}$$

Estimating p_1 and p_0 by $\hat{p}_1 = Y_1/n_1$ and $\hat{p}_0 = Y_0/n_0$

A 95% confidence interval for RD is

$$\widehat{RD} \pm 2SD(\widehat{RD})$$

$$= \widehat{RD} \pm 2\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_0(1-\hat{p}_0)}{n_0}})$$

Example 1 (revisited)

Here we had that 10 children out of 100 using a new toothpaste developed caries while 25 out of 100 using the standard toothpaste developed caries.
The estimated RD was shown to be $\widehat{RD} = \frac{10}{100} - \frac{25}{100} = -0.15$
A $95\% CI$ for RD is $\widehat{RD} \pm 2SD(\widehat{RD})$

$$= \widehat{RD} \pm 2\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_0(1-\hat{p}_0)}{n_0}})$$

$$= -0.15 \pm 2\sqrt{\frac{0.1(1-0.1)}{100} + \frac{.25(1-0.25)}{100}})$$

$$= -0.15 \pm 2\sqrt{0.002775}$$

$$= -0.15 \pm 2 \times 0.0526783 = (-0.255, -0.045)$$

Exercise 1 (revisited)

Here we had a cohort study on radiation exposure where 52 tumours developed among 2872 exposed and 6 tumours developed among 5049 unexposed individuals.
The risk difference was $\widehat{RD} = \hat{p}_1 - \hat{p}_0 =$
A 95% CI for the risk difference is:

$$\widehat{RD} \pm 2\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_0(1-\hat{p}_0)}{n_0})}$$

$$=$$

Interpretation:

Choosing an Effect Measure and Public Health Impact

An illustration

case A): $p_1 = 1/10$, $p_0 = 1/100$
$RR = 10$, $RD = 0.1 - 0.01 = 0.09 \sim 0.1$

case B): $p_1 = 1/100$, $p_0 = 1/1000$
$RR = 10$, $RD = 0.01 - 0.001 = 0.009 \sim 0.01$

the risk ratio is independent of the absolute disease occurrence, whereas the risk difference is containing this!

NNT or NNE

the **number needed to be exposed** NNE is defined as the number of people needed to be exposed to get **one case more** than under non-exposure:

$$NNE = \frac{1}{p_1 - p_0}$$

motivation:

np_1 expected number of cases under exposure

np_0 expected number of cases under non-exposure

$$np_1 - np_0 = 1?$$

$$n(= NNE) = \frac{1}{p_1 - p_0}$$

illustration

case A): $p_1 = 1/10$, $p_0 = 1/100$
$RR = 10$, $RD = 0.1 - 0.01 = 0.09 \sim 0.1$

$$NNE = 10$$

case B): $p_1 = 1/100$, $p_0 = 1/1000$
$RR = 10$, $RD = 0.01 - 0.001 = 0.009 \sim 0.01$

$$NNE = 100$$

interpretation:

the smaller the *NNE* the higher the public health impact of the exposure.

Attributable Fraction (AF):

The attributable fraction (AF) or **relative risk difference** is a measure that **combines** RD and prevalence

AF due to exposure: Assume that exposure **increases** risk.

That is assume $p_1 > p_0$.

$$AF = \frac{RD}{p_1} = \frac{p_1 - p_0}{p_1}$$

interpretation: Let n be the total number of cases and controls

$$AF = \frac{np_1 - np_0}{np_1}$$

$$= \frac{(\#\text{ cases if everyone exposed}) - (\#\text{ cases if everyone non-exposed})}{\#\text{ cases if everyone exposed}}$$

$$AF = \text{ proportion of cases due to exposure}$$
$$= \text{ proportion of avoidable cases due to exposure}$$

AF is a relative measure:

Effects with similar risks will have similar attributable fractions.

Scenario A): $p_1 = 1/10$, $p_0 = 1/100$
$RD = 0.1 - 0.01 = 0.09 \sim 0.1$

$$AF = 0.09/0.1 = 0.90$$

Scenario B): $p_1 = 1/100$, $p_0 = 1/1000$

$RD = 0.01 - 0.001 = 0.009 \sim 0.01$

$$AF = 0.009/0.01 = 0.90$$

Preventive fraction

If exposure **decreases** risk the preventive fraction is instead calculated:

$$\frac{p_0 - p_1}{p_0}$$

Population attributable fraction (PAF)

This is the proportion of cases occurring in the total population which can be explained by the exposure

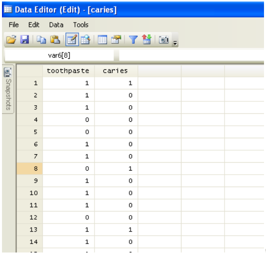
Let the proportion exposed be p

$$PAF = \frac{p(p_1 - p_0)}{pp_1 + (1 - p)p_0}$$

In STATA

Example 1: Caries Study

Data in rectangular format:

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. cs caries toothpaste

                 | toothpaste             |
                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |        10          25  |         35
        Noncases |        90          75  |        165
-----------------+------------------------+------------
           Total |       100         100  |        200
                 |                        |
            Risk |        .1         .25  |       .175
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |             -.15       |   -.2532475   -.0467525
      Risk ratio |               .4       |    .2028594    .7887236
 Prev. frac. ex. |               .6       |    .2112764    .7971406
 Prev. frac. pop |               .3       |
                 +-------------------------------------------------
                               chi2(1) =     7.79  Pr>chi2 = 0.0052
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```

csi 10 25 90 75

Risk ratio (RR):

The risk ratio or **relative risk** is the ratio of disease risk in an **exposed** to disease risk in an **non-exposed** population.

$$RR = \frac{p_1}{p_0}$$

where p_1 is disease risk in **exposed** and p_0 is disease risk in **non-exposed** population.

- RR is a number between 0 and ∞.

Interpretation:

For example, RR=2 means that disease occurrence is 2 times more likely in exposure group than in non-exposure group.

RR=1 means **no effect** of exposure.

Example 1

In a study of two toothpastes, 10 out of 100 caries-free children using a new toothpaste (exposure) develop caries after 1 year. In another group of 100 caries-free children using a standard toothpaste, 25 develop caries.

$$\widehat{RR} = \frac{10}{100} / \frac{25}{100} = 0.40$$

Example 2

In a group of 1000 persons with heavy sun-exposure, there are 40 cases of skin cancer. In a comparative, equally sized, non-exposed group there are 10 cases of skin cancer.

$$\widehat{RR} = \frac{40}{1000} / \frac{10}{1000} = 40$$

Exercise 1

In a cohort study evaluating radiation exposures, 52 tumours developed among 2872 exposed individuals and 6 tumours developed among 5049 unexposed individuals within the observation period.
What is the risk ratio?

$$\widehat{RR} = \frac{\hat{p}_1}{\hat{p}_0} =$$

Estimator of RR

Suppose that in a cohort study,

Y_1 out of n_1 exposed individuals and

Y_0 out of n_0 non-exposed individuals

developed the disease.

Assume that the probability p_1 of developing the disease is the **same** for everyone in the exposed group

Similarly, assume that the probability p_0 of developing the disease is the **same** for everyone in the non-exposed group

Then a plausible **estimator of the risk ratio** is

$$\widehat{RR} = \frac{\frac{Y_1}{n_1}}{\frac{Y_0}{n_0}} = \frac{Y_1 n_0}{Y_0 n_1}$$

Variance of RR

Technically it is easier to work with the logarithm of the risk ratio.

$$\log(RR) = \log(p_1) - \log(p_0)$$

Applying the δ **method**, an approximate variance is

$$\begin{aligned} Var\left(\widehat{\log RR}\right) &= \begin{pmatrix} \frac{1}{p_1} & \frac{1}{p_0} \end{pmatrix} \begin{pmatrix} Var(\hat{p}_1) & 0 \\ 0 & Var(\hat{p}_0) \end{pmatrix} \begin{pmatrix} \frac{1}{p_1} \\ \frac{1}{p_0} \end{pmatrix} \\ &= \frac{1}{p_1^2}\frac{p_1(1-p_1)}{n_1} + \frac{1}{p_0^2}\frac{p_0(1-p_0)}{n_0} \end{aligned}$$

Estimating p_1 by Y_1/n_1 and p_0 by Y_0/n_0 and simplifying, we get

$$Var\left(\widehat{\log RR}\right) = \frac{1}{Y_1} - \frac{1}{n_1} + \frac{1}{Y_0} - \frac{1}{n_0}$$

A confidence interval for RR

$$SD(\widehat{\log RR}) = \sqrt{\frac{1}{Y_1} - \frac{1}{n_1} + \frac{1}{Y_0} - \frac{1}{n_0}}$$

Consequently, a 95% confidence interval for the **log relative risk** is

$$\widehat{\log RR} \pm 2SD(\widehat{\log RR})$$
$$= \widehat{\log RR} \pm 2\sqrt{\frac{1}{Y_1} - \frac{1}{n_1} + \frac{1}{Y_0} - \frac{1}{n_0}}$$

and back on the **relative risk scale**, a 95% CI for RR is

$$\exp\left(\widehat{\log RR} \pm 2\sqrt{\frac{1}{Y_1} - \frac{1}{n_1} + \frac{1}{Y_0} - \frac{1}{n_0}}\right)$$

Example 1 (revisited)

Here we had that 10 children out of 100 using a new toothpaste developed caries while 25 out of 100 using the standard toothpaste developed caries.
The estimated RR was shown to be

$$\widehat{RR} = \frac{10}{100} \Big/ \frac{25}{100} = 0.4$$

A 95% CI for $\log(RR)$ is

$$\widehat{\log RR} \pm 2\sqrt{\frac{1}{Y_1} - \frac{1}{n_1} + \frac{1}{Y_0} - \frac{1}{n_0}}$$

$$= \log 0.4 \pm 2\sqrt{\frac{1}{10} - \frac{1}{100} + \frac{1}{25} - \frac{1}{100}}$$

$$= -0.92 \pm 2\sqrt{0.12}$$
$$= -0.92 \pm 2 \times 0.3464 = (-1.6128, -0.2272)$$

Hence a 95%CI for the **risk ratio** is

$$(\exp(-1.6128), \exp(-0.2272)) = (0.1993, 0.7968)$$

This shows that the new toothpaste **significantly** reduces the risk of developing caries.

Exercise 1 (revisited)

Here we had a cohort study on radiation exposure where 52 tumours developed among 2872 exposed and 6 tumours developed among 5049 unexposed individuals.
The risk ratio was $\widehat{RR} = \frac{\hat{p}_1}{\hat{p}_0}$

A 95% CI for RR is:

Interpretation:

AF and RR:

Assume that $p_1 > p_0$:

$$AF = RD/p_1 = \frac{p_1 - p_0}{p_1}$$
$$= 1 - \frac{p_0}{p_1}$$
$$= 1 - \frac{1}{RR}$$

Hence an **estimate of AF is available if an estimate of RR** is available.

Estimator of RR for person-time data

Suppose that in a cohort study people are under risk with different person-times

Y_1 events in T_1 person time units in the exposed group

and

Y_0 events in T_0 person tme units in the non-exposed group

Assume that the probability p_1 (p_0) of developing the disease is the **same** for everyone in the exposed (non-exposed) group

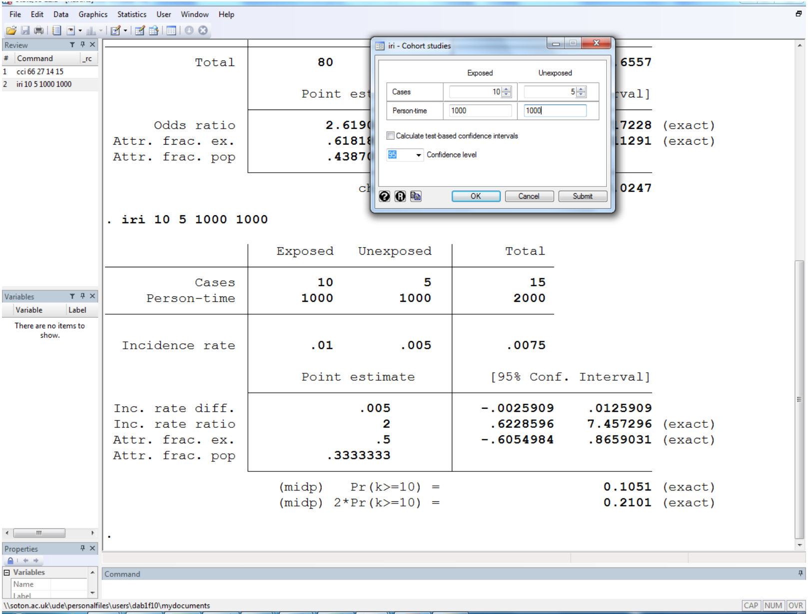
Then a plausible **estimator of the risk ratio** is ratio of the incidence densities

$$\widehat{RR} = \frac{\frac{Y_1}{T_1}}{\frac{Y_0}{T_0}} = \frac{Y_1 T_0}{Y_0 T_1}$$

Example

A cohort study is conducted to evaluate the relationship between dietary fat intake and the development in prostate cancer in men. In the study, 100 men with high fat diet are compared with 100 men who are on low fat diet. Both groups start at age 65 and are followed for 10 years. During the follow-up period, 10 men in the high fat intake group are diagnosed with prostate cancer and 5 men in the low fat intake group develop prostate cancer.
The incidence density is $\widehat{ID} = 10/(1,000) = 0.01$ in the high fat intake group and $\widehat{ID} = 5/(1,000) = 0.005$ in the low fat intake group.
Hence

$$\widehat{RR} = \frac{Y_1/T_1}{Y_0/T_0} = 0.01/0.005 = 2$$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Exposed Unexposed
Cases 10 5
Person-time 1000 1000
Calculate test-based confidence intervals
95 Confidence level
OK Cancel Submit
Total 80
Point est
Odds ratio 2.619
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7228 (exact)
1291 (exact)
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Exposed Unexposed Total
Cases 10 5 15
Person-time 1000 1000 2000
Incidence rate .01 .005 .0075
Point estimate [95% Conf. Interval]
Inc. rate diff. .005 -.0025909 .0125909
Inc. rate ratio 2 .6228596 7.457296 (exact)
Attr. frac. ex. .5 -.6054984 .8659031 (exact)
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Odds

The odds of an outcome is the number of times the outcome occurs to the number of times it does not.

Suppose that p is the probability of the outcome, then

$$odds = \frac{p}{1-p}$$

It follows that $p = \frac{odds}{odds+1}$

Examples

- $p = 1/2 \Rightarrow odds = 1$
- $p = 1/4 \Rightarrow odds = 1/3$
- $p = 3/4 \Rightarrow odds = 3/1 = 3$

Odds Ratio

$$OR = \frac{odds(\text{ in exposure })}{odds(\text{ in non-exposure })} = \frac{p_1/(1-p_1)}{p_0/(1-p_0)}$$

Properties of Odds Ratio

- $0 < OR < \infty$
- $OR = 1$ if and only if $p_1 = p_0$

Examples

$$\text{risk} = \begin{cases} p_1 = 1/4 \\ p_0 = 1/8 \end{cases} \quad \text{effect measure} = \begin{cases} OR = \frac{p_1/(1-p_1)}{p_0/(1-p_0)} = \frac{1/3}{1/7} = 2.33 \\ RR = \frac{p_1}{p_0} = 2 \end{cases}$$

$$\text{risk} = \begin{cases} p_1 = 1/100 \\ p_0 = 1/1000 \end{cases} \quad \text{eff. meas.} = \begin{cases} OR = \frac{1/99}{1/999} = 10.09 \\ RR = \frac{p_1}{p_0} = 10 \end{cases}$$

Fundamental Theorem of Epidemiology

$$p_0 \text{ small } \Rightarrow OR \approx RR$$

benefit: OR is interpretable as RR which is easier to deal with

Example: Radiation Exposure and Tumor Development

	cases	non-cases	
E	52	2820	2872
NE	6	5043	5049

odds and *OR*

odds for disease given exposure:

$$\frac{52/2872}{2820/2872} = 52/2820$$

odds for disease given non-exposure:

$$\frac{6/5049}{5043/5049} = 6/5043$$

Example, cont'd

	cases	non-cases	
E	52	2820	2872
NE	6	5043	5049

odds ratio for disease :

$$OR = \frac{52/2820}{6/5043} = \frac{52 \times 5043}{6 \times 2820} = 15.49$$

or, $\log OR = \log 15.49 = 2.74$
for comparison

$$RR = \frac{52/2872}{6/5049} = 15.24$$

	cases	non-cases
E	a	b
NE	c	d

$$OR = \frac{a/b}{c/d} = \frac{ad}{bc}$$

CI for OR: Using

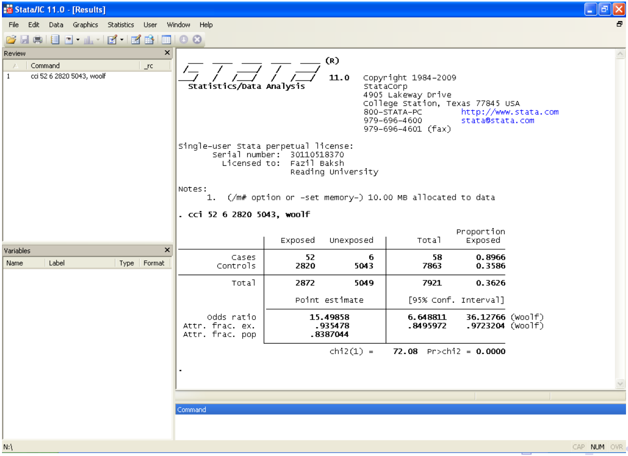
$$Var(\log OR) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

A 95% CI for log OR is $\log OR \pm 2\sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

As for RR, the exponent of these limits will provide the CI for OR

In STATA

Example: Radiation Exposure and Tumor Development



OR and study type cohort/CT

	case	non-case	
exposed	p_1	$1 - p_1$	n_1
non-exposed	p_0	$1 - p_0$	n_0

odds ratio for disease:

$$OR = \frac{p_1/(1 - p_1}{p_0/(1 - p_0)}$$

for comparison, relative risk for disease:

$$RR = \frac{p_1}{p_0}$$

OR and study type case-control

	case	non-case	
exposed	q_1	q_0	
non-exposed	$1 - q_1$	$1 - q_0$	
	m_1	m_0	

relative risk for disease is not estimable:

$$RR = \frac{p_1}{p_0}$$

relative risk for exposure is estimable but not of interest:

$$RR_e = \frac{q_1}{q_0}$$

since unfortunately

$$RR \neq RR_e$$

Illustration

	case	non-case	
exposed	500	199,500	200,000
non-exposed	500	799,500	800,000
	1,000	999,000	1,000,000

relative risk for disease:

$$RR = \frac{p_1}{p_0} = 4$$

relative risk for exposure:

$$RR_e = \frac{q_1}{q_0} = \frac{5/10}{1,955/9990} = 2.5 \neq RR$$

Odds Ratio for disease

$$OR = \frac{p_1/(1-p_1)}{p_0/(1-p_0)}$$

notations:

$$P(D|E) = p_1, P(D|NE) = p_0$$

$$P(E|D) = q_1, P(E|ND) = q_0, P(D) = p$$

then

$$\begin{aligned} p_1 = P(D|E) &= \frac{P(E|D)P(D)}{P(E)} = \frac{P(E|D)P(D)}{P(E|D)P(D)+P(E|ND)P(ND)} \\ &= \frac{q_1 p}{q_1 p + q_0(1-p)} \\ p_1/(1-p_1) &= \frac{q_1 p}{q_1 p + q_0(1-p)} \Big/ \left(1 - \frac{q_1 p}{q_1 p + q_0(1-p)}\right) = \frac{q_1 p}{q_0(1-p)} \quad (1) \end{aligned}$$

notations:

$$P(D|E) = p_1, P(D|NE) = p_0$$

$$P(E|D) = q_1, P(E|ND) = q_0, P(D) = p$$

then

$$\begin{aligned}
p_0 = P(D|NE) &= \frac{P(NE|D)P(D)}{P(NE)} = \frac{P(NE|D)P(D)}{P(NE|D)P(D)+P(NE|ND)P(ND)} \\
&= \frac{(1-q_1)p}{(1-q_1)p+(1-q_0)(1-p)} \\
p_0/(1-p_0) &= \frac{(1-q_1)p}{(1-q_1)p+(1-q_0)(1-p)} \Big/ \left(1 - \frac{(1-q_1)p}{(1-q_1)p+(1-q_0)(1-p)}\right) \\
&= \frac{(1-q_1)p}{(1-q_0)(1-p)} \qquad (2)
\end{aligned}$$

Odds Ratio

$$
\begin{aligned}
OR = \quad & \frac{p_1/(1-p_1)}{p_0/(1-p_0)} \\
& = \frac{(1)}{(2)} \\
& = \left(\frac{q_1 p}{q_0(1-p)}\right) / \left(\frac{(1-q_1)p}{(1-q_0)(1-p)}\right) \\
& = \frac{q_1/(1-q_1)}{q_0/(1-q_0)} = OR_e
\end{aligned}
$$

disease odds ratio = exposure odds ratio

Illustration

	case	non-case	
exposed	500	199,500	200,000
non-exposed	500	799,500	800,000
	1,000	999,000	1,000,000

odds ratio for disease:

$$OR = \frac{5/1995}{5/7995} = 4.007$$

odds ratio for exposure:

$$OR_e = \frac{5/5}{1995/7995} = 4.007$$

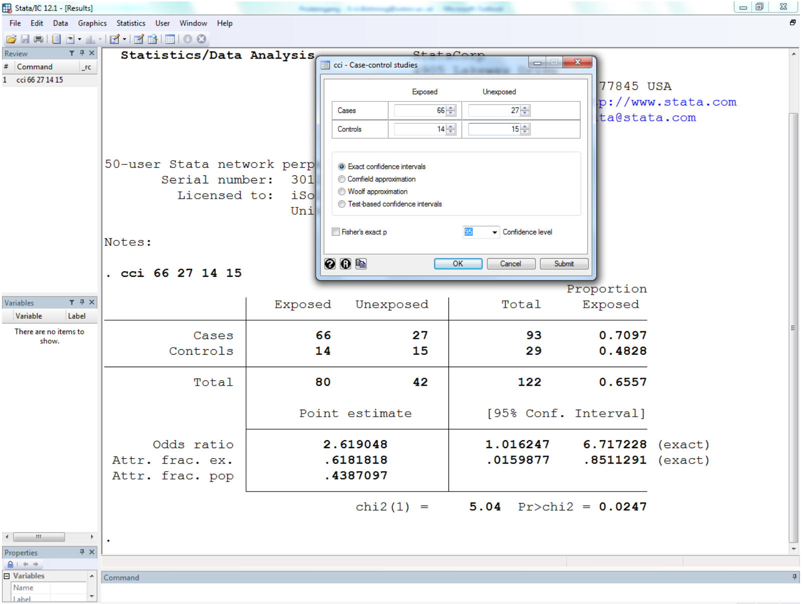
also, if disease occurrence is low (low prevalence): $OR \approx RR$

Sun exposure and lip cancer occurrence

a case-control study was done in a population of 50-69 year old men

	case	non-case	
exposed	500	199,500	200,000
non-exposed	66	14	80
	27	15	42
	93	29	122

$$OR = \frac{66/27}{14/15} = \frac{66 \times 15}{27 \times 14}$$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Exact confidence intervals
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Test-based confidence intervals
Fisher's exact p
95
Confidence level
OK
Cancel
Submit
Proportion
Exposed Unexposed Total Exposed
Cases 66 27 93 0.7097
Controls 14 15 29 0.4828
Total 80 42 122 0.6557
Point estimate [95% Conf. Interval]
Odds ratio 2.619048 1.016247 6.717228 (exact)
Attr. frac. ex. .6181818 .0159877 .8511291 (exact)
Attr. frac. pop .4387097
chi2(1) = 5.04 Pr>chi2 = 0.0247
Variables
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