Stat 525 Homework 4

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1. *For 2×2 tables show that $\widehat{RR} = 1$ when computed using the estimated expected counts $\widehat{E}_{ij}$. That is, show that the expected counts satisfy the null hypothesis of independence. You can assume population based sampling with the total sample size fixed.*

   Generally,

   $$\widehat{RR} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}.$$

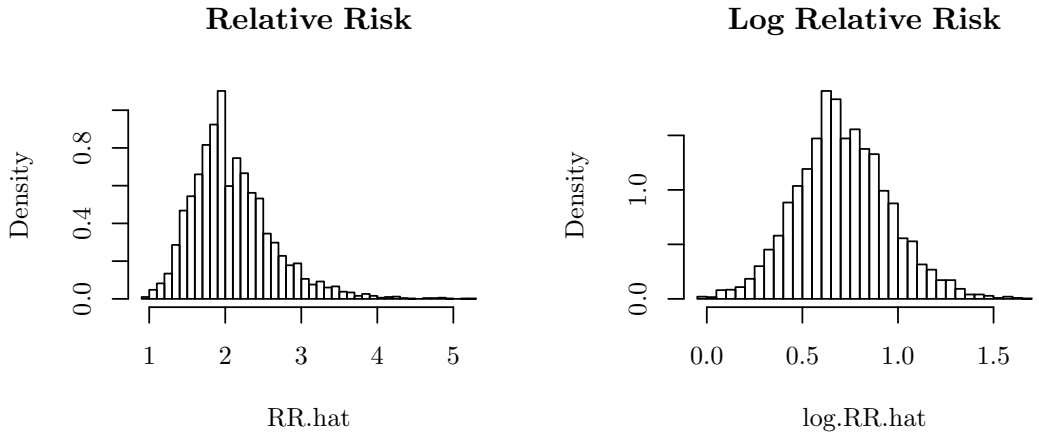
   Replacing the cell counts with their expectations under independence,

   $$\begin{aligned}
   \widehat{RR} &= \frac{\frac{\widehat{E}_{11}}{\widehat{E}_{11}+\widehat{E}_{12}}}{\frac{\widehat{E}_{21}}{\widehat{E}_{21}+\widehat{E}_{22}}} \\
   &= \frac{\frac{n\widehat{P}(D)\widehat{P}(E)}{n\widehat{P}(D)\widehat{P}(E)+n\widehat{P}(\overline{D})\widehat{P}(E)}}{\frac{n\widehat{P}(D)\widehat{P}(\overline{E})}{n\widehat{P}(D)\widehat{P}(\overline{E})+n\widehat{P}(\overline{D})\widehat{P}(\overline{E})}} \\
   &= \frac{\frac{\widehat{P}(D)}{\widehat{P}(D)+\widehat{P}(\overline{D})}}{\frac{\widehat{P}(D)}{\widehat{P}(D)+\widehat{P}(\overline{D})}} \\
   &= 1.
   \end{aligned}$$

2. *We will examine the skewness of the estimator of relative risk and how the log transformation helps via simulation. For the simulation $RR = 0.4/0.2 = 2$. We will simulate 5000 values of $\widehat{p}_1$ and $\widehat{p}_2$ based on samples of size 100.*

   (a) *The R-code below will do this for us and plot the results. Discuss.*

   ```
   p1.hat <- rbinom(5000, 100, 0.4) / 100
   p2.hat <- rbinom(5000, 100, 0.2) / 100
   RR.hat <- p1.hat / p2.hat
   log.RR.hat <- log(RR.hat)
   par(mfrow = c(1, 2))
   hist(RR.hat, prob = TRUE, main = 'Relative Risk', breaks = 50)
   hist(log.RR.hat, prob = TRUE, main = 'Log Relative Risk', breaks = 50)
   ```



The distribution of $\widehat{RR}$ values has a noticeable long right tail, so even for this large of a sample, the normal distribution is a poor approximation of the sampling distribution. In constrast, the distribution of $\log\left(\widehat{RR}\right)$ values is much more symmetric (although the right tail is heavier than the left). If we want to use the normal distribution to create an approximate confidence interval or make inference, we get a better approximation by working on the log scale.

(b) *Compute the variance of the 5000 simulated values of* $\log(\widehat{RR})$ *you got in part (a) and compare to the Delta Method approximate variance formula. Discuss.*

```
var(log.RR.hat)
```

```
[1] 0.05920074
```

The variance of the simulated values is 0.0592 which is slightly larger than the delta-method approximation,

$$\begin{aligned}
\text{Var}\left(\log\left(\widehat{RR}\right)\right) &= \text{Var}\left(\log\left(\widehat{p_1}\right)\right) + \text{Var}\left(\log\left(\widehat{p_2}\right)\right) \\
&= \frac{1-p_1}{n_E p_1} + \frac{1-p_2}{n_{\overline{E}} p_2} \\
&= \frac{1-0.4}{100 \times 0.4} + \frac{1-0.2}{100 \times 0.2} \\
&= 0.055,
\end{aligned}$$

but the difference is probably not large enough to affect our inferences.

3. *This example involves hypothetical data collected in a case-control design.*

   (a) *A 2×2 table giving the relationship between exposure and disease is shown below.*

	D	$\overline{D}$	
E	30	12	42
$\overline{E}$	70	88	158
	100	100	200

   Estimate the ratio of the odds of disease given exposure to the odds given no exposure (give me both the point estimate and an approximate 95% CI).

```
DE <- cbind(D = c(E = 30, E.bar =  70), D.bar = c(E = 12, E.bar = 88))
twoby2(DE, alpha = 0.05)

2 by 2 table analysis:
------------------------------------------------------
Outcome   : D
Comparing : E vs. E.bar

       D D.bar    P(D) 95% conf. interval
E     30    12  0.7143    0.5614   0.8300
E.bar 70    88  0.4430    0.3676   0.5213

                                  95% conf. interval
            Relative Risk: 1.6122    1.2442   2.0892
         Sample Odds Ratio: 3.1429    1.5004   6.5832
Conditional MLE Odds Ratio: 3.1250    1.4299   7.2184
    Probability difference: 0.2712    0.1023   0.4078

             Exact P-value: 0.0029
        Asymptotic P-value: 0.0024
------------------------------------------------------
```

   The odds of disease given exposure are estimated to be 3.14 times larger than the odds of disease given no exposure. An approximate 95% Wald confidence interval for the true odds ratio is (1.50, 6.58).

   (b) *Below are two tables: one showing the distribution of cases and controls by age and one showing the distribution of exposed and unexposed by age. Investigate the association between age and exposure status and age and disease status. Again give point estimates and approximate 95% CIs for odds ratios.*

	D	$\overline{D}$	
< 40	50	80	130
≥ 40	50	20	70
	100	100	200

	E	$\overline{E}$	
< 40	12	118	130
≥ 40	30	40	70
	42	158	200

Disease and age:

```
D.age <- cbind(D = c(`< 40` = 50, `>= 40` =  50), D.bar = c(`< 40` = 80, `>= 40` = 20))
twoby2(D.age, alpha = 0.05)

2 by 2 table analysis:
------------------------------------------------------
Outcome   : D
Comparing : < 40 vs. >= 40

       D D.bar    P(D) 95% conf. interval
< 40  50    80  0.3846    0.3051   0.4709
>= 40 50    20  0.7143    0.5981   0.8077

                                    95% conf. interval
            Relative Risk:  0.5385    0.4139   0.7005
         Sample Odds Ratio:  0.2500    0.1335   0.4682
Conditional MLE Odds Ratio:  0.2518    0.1263   0.4880
    Probability difference: -0.3297   -0.4514  -0.1864

            Exact P-value: 0
        Asymptotic P-value: 0
------------------------------------------------------
```

The odds of disease given that the person is under 40 are estimated to be 0.250 times the odds of disease given that the person is at least 40, with an approximate 95% CI of (0.136, 0.468).

Exposure and age:

```
E.age <- cbind(E = c(`< 40` = 12, `>= 40` =  30), E.bar = c(`< 40` = 118, `>= 40` = 40))
twoby2(E.age, alpha = 0.05)

2 by 2 table analysis:
------------------------------------------------------
Outcome   : E
Comparing : < 40 vs. >= 40

       E E.bar    P(E) 95% conf. interval
< 40  12   118  0.0923    0.0532   0.1555
>= 40 30    40  0.4286    0.3184   0.5463

                                    95% conf. interval
            Relative Risk:  0.2154    0.1178   0.3937
         Sample Odds Ratio:  0.1356    0.0634   0.2898
Conditional MLE Odds Ratio:  0.1372    0.0580   0.3064
    Probability difference: -0.3363   -0.4592  -0.2106

            Exact P-value: 0
        Asymptotic P-value: 0
------------------------------------------------------
```

The odds of exposure given that the person is under 40 are estimated to be 0.136 times the odds of exposure given that the person is at least 40, with an approximate 95% CI of (0.0634, 0.290).

(c) *Stratifying on age yields the two table below. Analyze these separately. Report the estimated odds ratios and associated 95% CIs.*

Age < 40

	D	$\overline{D}$	
E	5	6	11
$\overline{E}$	45	74	119
	50	80	130

Age ≥ 40

	D	$\overline{D}$	
E	25	6	31
$\overline{E}$	25	14	39
	50	20	70

Age $<$ 40:

```
DE.under40 <- cbind(D = c(E = 5, E.bar =  45), D.bar = c(E = 6, E.bar = 74))
twoby2(DE.under40, alpha = 0.05)

2 by 2 table analysis:
------------------------------------------------------
Outcome   : D
Comparing : E vs. E.bar

       D D.bar    P(D) 95% conf. interval
E      5     6  0.4545    0.2028   0.7319
E.bar 45    74  0.3782    0.2957   0.4683

                                  95% conf. interval
            Relative Risk: 1.2020    0.6046   2.3896
          Sample Odds Ratio: 1.3704    0.3953   4.7512
Conditional MLE Odds Ratio: 1.3669    0.3109   5.7260
    Probability difference: 0.0764   -0.1815   0.3541

            Exact P-value: 0.7483
       Asymptotic P-value: 0.6194
------------------------------------------------------
```

For individuals under 40, the odds of disease given exposure are estimated to be 1.37 times the odds of disease given no exposure, with an approximate 95% CI of (0.395, 4.75).

Age $\geq$ 40:

```
DE.atleast40 <- cbind(D = c(E = 25, E.bar =  25), D.bar = c(E = 6, E.bar = 14))
twoby2(DE.atleast40, alpha = 0.05)

2 by 2 table analysis:
------------------------------------------------------
Outcome   : D
Comparing : E vs. E.bar
```

```
       D D.bar    P(D) 95% conf. interval
E     25     6  0.8065    0.6309   0.9104
E.bar 25    14  0.6410    0.4814   0.7745

                                  95% conf. interval
            Relative Risk: 1.2581    0.9401   1.6836
         Sample Odds Ratio: 2.3333    0.7725   7.0478
Conditional MLE Odds Ratio: 2.3056    0.6927   8.5633
    Probability difference: 0.1654   -0.0489   0.3523

             Exact P-value: 0.1837
       Asymptotic P-value: 0.133
------------------------------------------------------
```

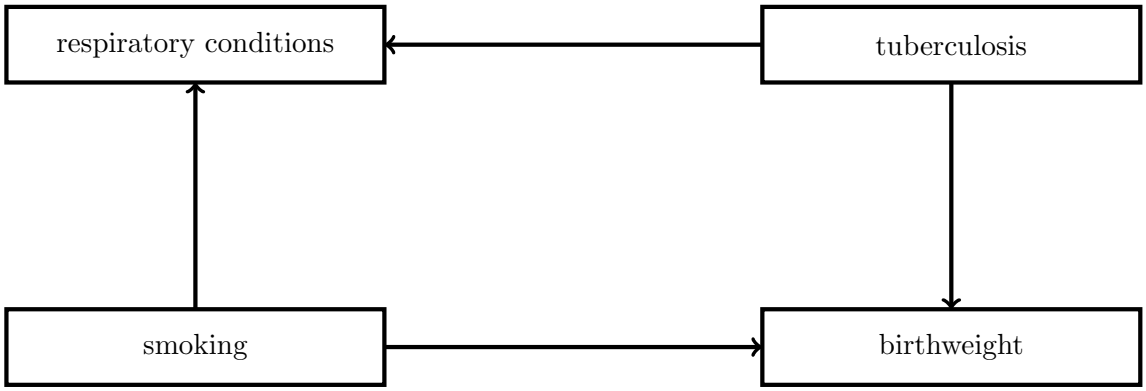
For individuals who are at least 40, the odds of disease given exposure are estimated to be 2.33 times the odds of disease given no exposure, with an approximate 95% CI of (0.773, 7.05).

(d) *Is there evidence of confounding? Why or why not?*

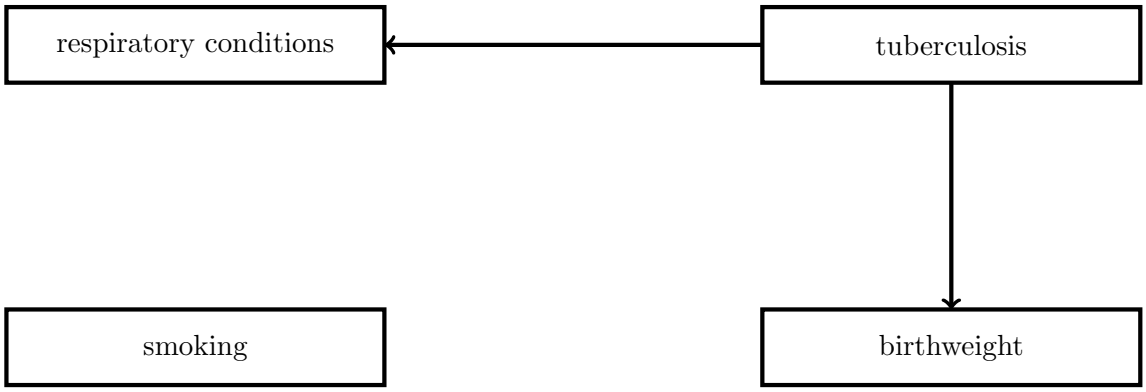
There is evidence of confounding. Age appears to be related to both disease and exposure because the confidence intervals in (b) do not include 1. Furthermore the pooled results disagree with the results from stratifying by age – in part (a) there appeared to be an association between exposure and disease, but this association disappears in part (c) when conditioning on age.

4. *Problem 8.3 on page 119.*

Assuming no direct effect of respiratory conditions on birthweight:

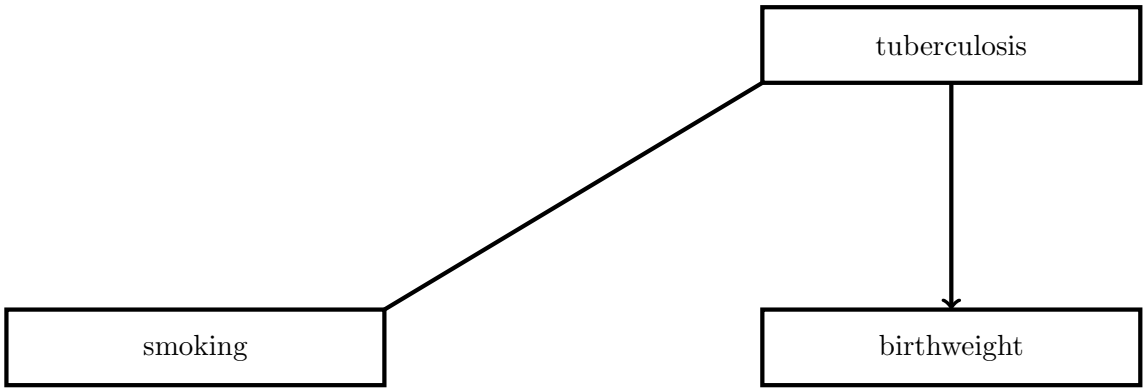


Removing the paths leaving smoking:



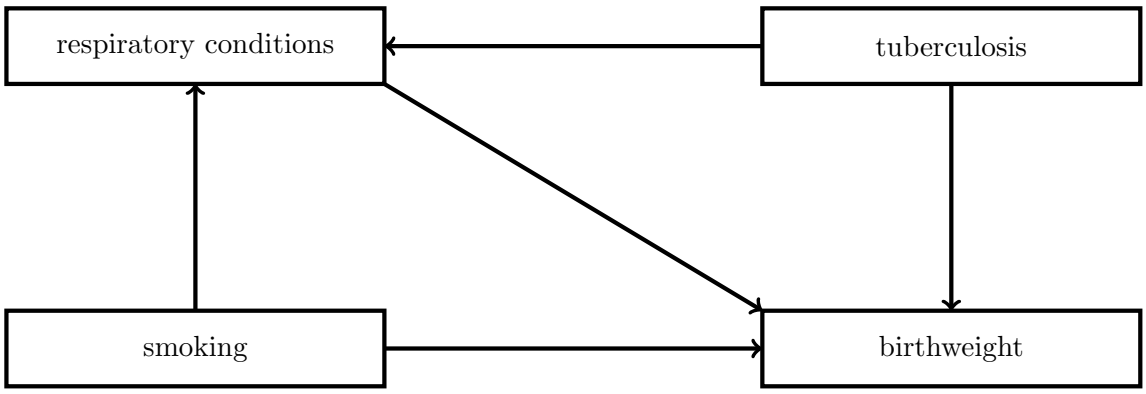
There are no unblocked backdoor paths from birthweight to smoking so the association is not confounded.

Stratifying on respiratory conditions:

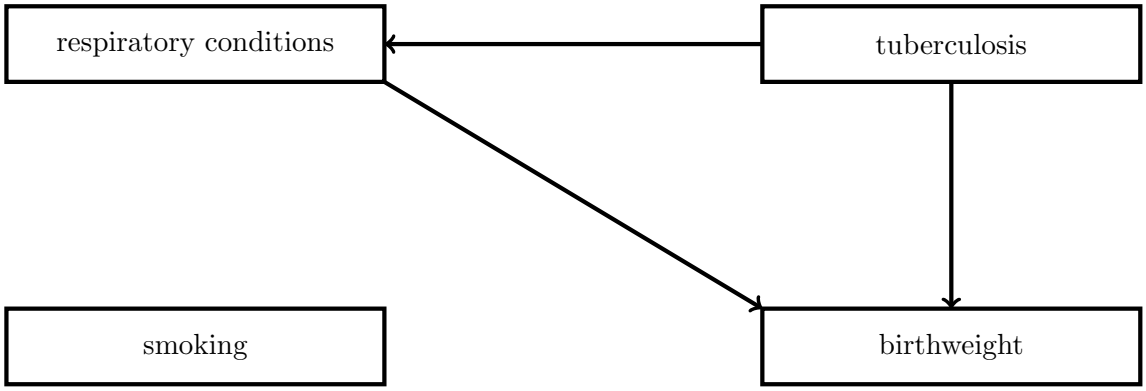


Respiratory conditions was a collider in the original graph, so stratifying on respiratory conditions results in tuberculosis becoming a confounder.

Assuming a direct effect of respiratory conditions on birthweight:

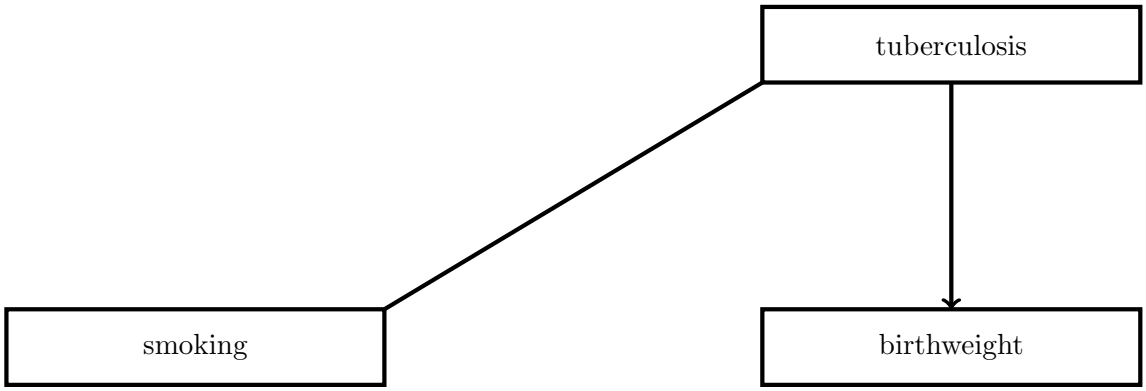


Removing the paths leaving smoking:



There are no unblocked backdoor paths from birthweight to smoking so that association is not confounded by another variable. Note however that tuberculosis confounds the association between respiratory conditions and birthweight.

Stratifying on respiratory conditions:



Again, stratifying on respiratory conditions leads to confounding of smoking with tuberculosis. To avoid confounding, we would need to condition on tuberculosis as well.

5. *STAT 525 Students: Using the Delta Method confirm the variance formula for* $\log\left[\widehat{OR}\right]$.

First, note that

$$\begin{aligned}\frac{d}{dp}\left[\log\left(\frac{\widehat{p}}{1-\widehat{p}}\right)\right] &= \frac{d}{dp}\left[\log\left(\widehat{p}\right) - \log\left(1-\widehat{p}\right)\right] \\ &= \frac{1}{\widehat{p}} + \frac{1}{1-\widehat{p}} \\ &= \frac{1}{\widehat{p}\left(1-\widehat{p}\right)},\end{aligned}$$

so

$$\begin{aligned}\widehat{\text{Var}}\left[\log\left(\frac{\widehat{p}}{1-\widehat{p}_1}\right)\right] &\approx \left(\frac{1}{\widehat{p}\,(1-\widehat{p})}\right)^2 \widehat{\text{Var}}\,(\widehat{p}) \\ &= \left(\frac{1}{\widehat{p}\,(1-\widehat{p})}\right)^2 \frac{\widehat{p}\,(1-\widehat{p})}{n} \\ &= \frac{1}{n\widehat{p}\,(1-\widehat{p})}.\end{aligned}$$

Then

$$\begin{aligned}\widehat{\text{Var}}\left[\log\left(\widehat{OR}\right)\right] &= \widehat{\text{Var}}\left[\log\left(\frac{\widehat{p_1}}{1-\widehat{p_1}}\right)\right] + \widehat{\text{Var}}\left[\log\left(\frac{\widehat{p_2}}{1-\widehat{p_2}}\right)\right] \\ &= \frac{1}{n_E\widehat{p_1}\,(1-\widehat{p_1})} + \frac{1}{n_{\overline{E}}\widehat{p_2}\,(1-\widehat{p_2})} \\ &= \frac{1}{(a+b)\left(\frac{a}{a+b}\right)\left(\frac{b}{a+b}\right)} + \frac{1}{(c+d)\left(\frac{c}{c+d}\right)\left(\frac{d}{c+d}\right)} \\ &= \frac{a+b}{ab} + \frac{c+d}{cd} \\ &= \frac{b}{ab} + \frac{a}{ab} + \frac{d}{cd} + \frac{c}{cd} \\ &= \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}.\end{aligned}$$

6. *STAT 525 Students: We saw one version of the formula for X^2 as*

$$X^2 = \sum_{i=1}^{I}\sum_{j=1}^{J} \frac{\left(n_{ij} - \widehat{E}_{ij}\right)^2}{\widehat{E}_{ij}}$$

This can be reexpressed as

$$X^2 = n\left[\sum_{i=1}^{I}\sum_{j=1}^{J} \frac{\left(\frac{n_{ij}}{n} - \frac{n_D n_E}{n^2}\right)^2}{\frac{n_D n_E}{n^2}}\right]$$

Discuss the implications of this as n increases while all n_{ij}/n remain constant.

Note that

$$\frac{n_D n_E}{n^2} = \left(\frac{n_{11}}{n} + \frac{n_{21}}{n}\right)\left(\frac{n_{11}}{n} + \frac{n_{12}}{n}\right)$$

so the terms inside the summation depend only on the n_{ij}/n. Thus the sum is constant, so X^2 is proportional to n. This means that, as n increases, it becomes easier to reject the null hypothesis of independence, so with very large samples we should expect to find evidence of an association.