Wednesday, Mar 6

Using the emmeans Package for Poisson and Logistic Regression

The **emmeans** package can be used to produce many of the same inferences that are obtained using `contrast` with respect to estimated expected rates/probabilities as well as rate/odds ratios.

Example: Consider the following Poisson regression model for the `ceriodaphniastrain` data.

```
fleas <- trtools::ceriodaphniastrain
fleas$strain <- factor(fleas$strain, levels = c(1,2), labels = c("a","b"))
m <- glm(count ~ concentration * strain, family = poisson, data = fleas)
summary(m)$coefficients
```

```
                     Estimate Std. Error z value   Pr(>|z|)
(Intercept)            4.4811    0.04350 103.008  0.000e+00
concentration         -1.5979    0.06244 -25.592 1.862e-144
strainb               -0.3367    0.06704  -5.022  5.114e-07
concentration:strainb  0.1253    0.09385   1.336  1.817e-01
```

We can compute the expected count for a concentration of two for each strain using `contrast`.

```
trtools::contrast(m, tf = exp,
  a = list(strain = c("a","b"), concentration = 2))
```

```
 estimate lower upper
    3.616 2.970 4.402
    3.318 2.671 4.122
```

And we can do it using `emmeans` if we specify `type = "response"` and use the `at` argument to specify the value of any quantitative explanatory variables.

```
library(emmeans)
emmeans(m, ~ strain, type = "response", at = list(concentration = 2))
```

```
 strain rate    SE  df asymp.LCL asymp.UCL
 a      3.62 0.363 Inf      2.97      4.40
 b      3.32 0.367 Inf      2.67      4.12

Confidence level used: 0.95
Intervals are back-transformed from the log scale
```

```
emmeans(m, ~ strain|concentration, type = "response", at = list(concentration = c(1,2,3)))
```

```
concentration = 1:
 strain   rate    SE  df asymp.LCL asymp.UCL
 a      17.872 0.815 Inf    16.343     19.54
 b      14.467 0.725 Inf    13.113     15.96

concentration = 2:
 strain   rate    SE  df asymp.LCL asymp.UCL
 a       3.616 0.363 Inf     2.970      4.40
 b       3.318 0.367 Inf     2.671      4.12
```

```
concentration = 3:
 strain   rate    SE  df asymp.LCL asymp.UCL
 a       0.732 0.118 Inf     0.534      1.00
 b       0.761 0.136 Inf     0.537      1.08

Confidence level used: 0.95 
Intervals are back-transformed from the log scale 
```

```r
emmeans(m, ~ concentration|strain, type = "response", at = list(concentration = c(1,2,3)))
```

```
strain = a:
 concentration   rate    SE  df asymp.LCL asymp.UCL
             1 17.872 0.815 Inf    16.343     19.54
             2  3.616 0.363 Inf     2.970      4.40
             3  0.732 0.118 Inf     0.534      1.00

strain = b:
 concentration   rate    SE  df asymp.LCL asymp.UCL
             1 14.467 0.725 Inf    13.113     15.96
             2  3.318 0.367 Inf     2.671      4.12
             3  0.761 0.136 Inf     0.537      1.08

Confidence level used: 0.95 
Intervals are back-transformed from the log scale 
```

```r
emmeans(m, ~ concentration*strain, type = "response", at = list(concentration = c(1,2,3)))
```

```
 concentration strain   rate    SE  df asymp.LCL asymp.UCL
             1 a      17.872 0.815 Inf    16.343     19.54
             2 a       3.616 0.363 Inf     2.970      4.40
             3 a       0.732 0.118 Inf     0.534      1.00
             1 b      14.467 0.725 Inf    13.113     15.96
             2 b       3.318 0.367 Inf     2.671      4.12
             3 b       0.761 0.136 Inf     0.537      1.08

Confidence level used: 0.95 
Intervals are back-transformed from the log scale 
```

Note that `emmeans` does produce a valid standard error on the scale of the expected count/rate which `trtools::contrast` does not (by default), and that `trtools::contrast` will show the test statistic and p-value on the log scale if we omit the `tf = exp` argument.

We can compute the rate ratio to compare the two strains at a given concentration.

```r
trtools::contrast(m, tf = exp,
  a = list(strain = "a", concentration = 2),
  b = list(strain = "b", concentration = 2))
```

```
 estimate  lower upper
     1.09 0.8132  1.46
```

```r
pairs(emmeans(m, ~ strain, type = "response",
  at = list(concentration = 2)), infer = TRUE)
```

```
 contrast ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b     1.09 0.163 Inf     0.813      1.46    1   0.576  0.5648
```

```
Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```r
pairs(emmeans(m, ~ strain|concentration, type = "response",
  at = list(concentration = c(1,2,3))), infer = TRUE)
```

```
concentration = 1:
 contrast ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b    1.235 0.0837 Inf     1.082      1.41    1   3.118  0.0018

concentration = 2:
 contrast ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b    1.090 0.1628 Inf     0.813      1.46    1   0.576  0.5648

concentration = 3:
 contrast ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b    0.961 0.2308 Inf     0.601      1.54    1  -0.164  0.8698

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

If we apply `pairs` when using `*` we will get all possible pairwise comparisons.

```r
pairs(emmeans(m, ~ strain*concentration, type = "response",
  at = list(concentration = c(1,2,3))), infer = TRUE)
```

```
 contrast                                 ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a concentration1 / b concentration1  1.235 0.084 Inf     1.018      1.50    1   3.118  0.0225
 a concentration1 / a concentration2  4.942 0.309 Inf     4.137      5.90    1  25.592  <.0001
 a concentration1 / b concentration2  5.386 0.645 Inf     3.830      7.58    1  14.068  <.0001
 a concentration1 / a concentration3 24.428 3.050 Inf    17.114     34.87    1  25.592  <.0001
 a concentration1 / b concentration3 23.486 4.323 Inf    13.900     39.68    1  17.149  <.0001
 b concentration1 / a concentration2  4.001 0.449 Inf     2.906      5.51    1  12.362  <.0001
 b concentration1 / b concentration2  4.360 0.306 Inf     3.571      5.32    1  21.015  <.0001
 b concentration1 / a concentration3 19.775 3.330 Inf    12.237     31.96    1  17.721  <.0001
 b concentration1 / b concentration3 19.012 2.664 Inf    12.752     28.34    1  21.015  <.0001
 a concentration2 / b concentration2  1.090 0.163 Inf     0.712      1.67    1   0.576  0.9926
 a concentration2 / a concentration3  4.942 0.309 Inf     4.137      5.90    1  25.592  <.0001
 a concentration2 / b concentration3  4.752 0.972 Inf     2.652      8.51    1   7.617  <.0001
 b concentration2 / a concentration3  4.535 0.885 Inf     2.600      7.91    1   7.746  <.0001
 b concentration2 / b concentration3  4.360 0.306 Inf     3.571      5.32    1  21.015  <.0001
 a concentration3 / b concentration3  0.961 0.231 Inf     0.485      1.91    1  -0.164  1.0000

Confidence level used: 0.95
Conf-level adjustment: tukey method for comparing a family of 6 estimates
Intervals are back-transformed from the log scale
P value adjustment: tukey method for comparing a family of 6 estimates
Tests are performed on the log scale
```

To force `pairs` to only do pairwise comparisons within each value of concentration use `by = "concentration"`.

```r
pairs(emmeans(m, ~ strain*concentration, type = "response",
  at = list(concentration = c(1,2,3)), by = "concentration", infer = TRUE)
```

```
concentration = 1:
```

```
 contrast ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b    1.235 0.0837 Inf     1.082      1.41    1   3.118  0.0018

concentration = 2:
 contrast ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b    1.090 0.1628 Inf     0.813      1.46    1   0.576  0.5648

concentration = 3:
 contrast ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 a / b    0.961 0.2308 Inf     0.601      1.54    1  -0.164  0.8698

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

What about the rate ratio for the effect of concentration?

```r
trtools::contrast(m, tf = exp,
  a = list(strain = c("a","b"), concentration = 2),
  b = list(strain = c("a","b"), concentration = 1))
```

```
 estimate  lower  upper
   0.2023 0.1790 0.2287
   0.2293 0.1999 0.2631
```

```r
emmeans(m, ~concentration|strain,
  at = list(concentration = c(2,1)), type = "response")
```

```
strain = a:
 concentration  rate    SE  df asymp.LCL asymp.UCL
             2  3.62 0.363 Inf      2.97      4.40
             1 17.87 0.815 Inf     16.34     19.54

strain = b:
 concentration  rate    SE  df asymp.LCL asymp.UCL
             2  3.32 0.367 Inf      2.67      4.12
             1 14.47 0.725 Inf     13.11     15.96

Confidence level used: 0.95
Intervals are back-transformed from the log scale
```

```r
pairs(emmeans(m, ~concentration|strain,
  at = list(concentration = c(2,1)), type = "response"))
```

```
strain = a:
 contrast                        ratio     SE  df null z.ratio p.value
 concentration2 / concentration1 0.202 0.0126 Inf    1 -25.592  <.0001

strain = b:
 contrast                        ratio     SE  df null z.ratio p.value
 concentration2 / concentration1 0.229 0.0161 Inf    1 -21.015  <.0001

Tests are performed on the log scale
```

```r
pairs(emmeans(m, ~concentration*strain,
  at = list(concentration = c(2,1)), type = "response"), by = "strain")
```

```
strain = a:
 contrast                          ratio     SE  df null z.ratio p.value
 concentration2 / concentration1 0.202 0.0126 Inf    1 -25.592  <.0001

strain = b:
 contrast                          ratio     SE  df null z.ratio p.value
 concentration2 / concentration1 0.229 0.0161 Inf    1 -21.015  <.0001

Tests are performed on the log scale
```

What if we want to know if the rate ratios are significantly different?

```r
emtrends(m, ~strain, var = "concentration")
```

```
 strain concentration.trend     SE  df asymp.LCL asymp.UCL
 a                    -1.60 0.0624 Inf     -1.72     -1.48
 b                    -1.47 0.0701 Inf     -1.61     -1.34

Confidence level used: 0.95
```

```r
pairs(emtrends(m, ~strain, var = "concentration"))
```

```
 contrast estimate     SE  df z.ratio p.value
 a - b      -0.125 0.0939 Inf  -1.335  0.1817
```

Note that these are essentially slopes but for the log of the expected response But the tests are still useful.

Example: Consider the following logistic regression model for the `insecticide data`.

```r
m <- glm(cbind(deaths, total-deaths) ~ insecticide * deposit,
  family = binomial, data = trtools::insecticide)
summary(m)$coefficients
```

```
                        Estimate Std. Error  z value  Pr(>|z|)
(Intercept)             -2.81091    0.35845 -7.84177 4.442e-15
insecticideboth          1.22575    0.67176  1.82468 6.805e-02
insecticideDDT          -0.03893    0.50722 -0.07676 9.388e-01
deposit                  0.62207    0.07786  7.98986 1.351e-15
insecticideboth:deposit  0.37010    0.20897  1.77109 7.655e-02
insecticideDDT:deposit  -0.14143    0.10376 -1.36301 1.729e-01
```

We can use `trtools::contrast` or `emmeans` to produce estimates of the probability of death for a given insecticide at a given deposit value.

```r
trtools::contrast(m, tf = plogis,
  a = list(insecticide = c("g-BHC","both","DDT"), deposit = 5),
  cnames = c("g-BHC","both","DDT"))
```

```
      estimate  lower  upper
g-BHC   0.5743 0.5027 0.6429
both    0.9669 0.9212 0.9865
DDT     0.3902 0.3289 0.4550
```

```r
emmeans(m, ~ insecticide, type = "response", at = list(deposit = 5))
```

```
 insecticide  prob     SE  df asymp.LCL asymp.UCL
 g-BHC       0.574 0.0360 Inf     0.503     0.643
 both        0.967 0.0149 Inf     0.921     0.987
 DDT         0.390 0.0323 Inf     0.329     0.455
```

```
Confidence level used: 0.95
Intervals are back-transformed from the logit scale
```

Again, `emmeans` produces a valid standard error on the probability scale while `trtools::contrast` does not, and `trtools::contrast` will produce test statistics and p-values on the logit scale when the `tf = plogis` argument is omitted.

We can compute odds ratios to compare the insecticides at a given deposit.

```r
pairs(emmeans(m, ~ insecticide, type = "response",
  at = list(deposit = 5)), adjust = "none", infer = TRUE)
```

```
 contrast       odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.05  0.023 Inf     0.018      0.12    1  -6.275  <.0001
 (g-BHC) / DDT        2.11  0.423 Inf     1.424      3.12    1   3.724  0.0002
 both / DDT          45.71 22.260 Inf    17.600    118.72    1   7.849  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log odds ratio scale
Tests are performed on the log odds ratio scale
```

```r
trtools::contrast(m, tf = exp,
  a = list(insecticide = c("g-BHC","g-BHC","both"), deposit = 5),
  b = list(insecticide = c("both","DDT","DDT"), deposit = 5),
  cnames = c("g-BHC / both", "g-BHC / DDT", "both / DDT"))
```

```
             estimate    lower    upper
g-BHC / both  0.04613  0.01765   0.1206
g-BHC / DDT   2.10871  1.42385   3.1230
both / DDT   45.71097 17.59954 118.7243
```

We can flip/reverse the odds ratios if desired (which can also be done with rate ratios).

```r
pairs(emmeans(m, ~ insecticide, type = "response",
  at = list(deposit = 5)), adjust = "none", reverse = TRUE, infer = TRUE)
```

```
 contrast       odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 both / (g-BHC)     21.677 10.628 Inf     8.293     56.67    1   6.275  <.0001
 DDT / (g-BHC)       0.474  0.095 Inf     0.320      0.70    1  -3.724  0.0002
 DDT / both          0.022  0.011 Inf     0.008      0.06    1  -7.849  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log odds ratio scale
Tests are performed on the log odds ratio scale
```

```r
trtools::contrast(m, tf = exp,
  a = list(insecticide = c("both","DDT","DDT"), deposit = 5),
  b = list(insecticide = c("g-BHC","g-BHC","both"), deposit = 5),
  cnames = c("both / g-BHC", "DDT / g-BHC", "DDT / both"))
```

```
             estimate    lower    upper
both / g-BHC 21.67723 8.292521 56.66581
DDT / g-BHC   0.47422 0.320208  0.70232
DDT / both    0.02188 0.008423  0.05682
```

We can estimate the odds ratios at several values of deposit.

```r
pairs(emmeans(m, ~ insecticide|deposit, type = "response",
  at = list(deposit = c(4,5,6))), adjust = "none", infer = TRUE)
```

```
deposit = 4:
 contrast       odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.07  0.02 Inf     0.035      0.13    1  -8.239  <.0001
 (g-BHC) / DDT        1.83  0.37 Inf     1.234      2.72    1   3.004  0.0027
 both / DDT          27.41  9.12 Inf    14.274     52.62    1   9.947  <.0001

deposit = 5:
 contrast       odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.05  0.02 Inf     0.018      0.12    1  -6.275  <.0001
 (g-BHC) / DDT        2.11  0.42 Inf     1.424      3.12    1   3.724  0.0002
 both / DDT          45.71 22.26 Inf    17.600    118.72    1   7.849  <.0001

deposit = 6:
 contrast       odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.03  0.02 Inf     0.008      0.12    1  -5.080  <.0001
 (g-BHC) / DDT        2.43  0.60 Inf     1.495      3.95    1   3.584  0.0003
 both / DDT          76.24 51.04 Inf    20.529    283.13    1   6.474  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log odds ratio scale
Tests are performed on the log odds ratio scale
```

```r
pairs(emmeans(m, ~ insecticide*deposit, type = "response",
  at = list(deposit = c(4,5,6))), by = "deposit", adjust = "none", infer = TRUE)
```


```
deposit = 4:
 contrast       odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.07  0.02 Inf     0.035      0.13    1  -8.239  <.0001
 (g-BHC) / DDT        1.83  0.37 Inf     1.234      2.72    1   3.004  0.0027
 both / DDT          27.41  9.12 Inf    14.274     52.62    1   9.947  <.0001

deposit = 5:
 contrast       odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.05  0.02 Inf     0.018      0.12    1  -6.275  <.0001
 (g-BHC) / DDT        2.11  0.42 Inf     1.424      3.12    1   3.724  0.0002
 both / DDT          45.71 22.26 Inf    17.600    118.72    1   7.849  <.0001

deposit = 6:
 contrast       odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 (g-BHC) / both       0.03  0.02 Inf     0.008      0.12    1  -5.080  <.0001
 (g-BHC) / DDT        2.43  0.60 Inf     1.495      3.95    1   3.584  0.0003
 both / DDT          76.24 51.04 Inf    20.529    283.13    1   6.474  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log odds ratio scale
Tests are performed on the log odds ratio scale
```


Here is how we can estimate the odds ratios for the effect of deposit.

```r
emmeans(m, ~deposit|insecticide, at = list(deposit = c(2,1)), type = "response") # probability
```

```
insecticide = g-BHC:
 deposit   prob     SE  df asymp.LCL asymp.UCL
       2 0.1727 0.0318 Inf    0.1190     0.244
       1 0.1008 0.0261 Inf    0.0599     0.165
```

```
insecticide = both:
 deposit   prob     SE  df asymp.LCL asymp.UCL
       2 0.5985 0.0566 Inf    0.4844     0.703
       1 0.3560 0.0892 Inf    0.2049     0.542

insecticide = DDT:
 deposit   prob     SE  df asymp.LCL asymp.UCL
       2 0.1314 0.0271 Inf    0.0867     0.194
       1 0.0856 0.0232 Inf    0.0497     0.143

Confidence level used: 0.95
Intervals are back-transformed from the logit scale
```

```r
pairs(emmeans(m, ~deposit|insecticide, at = list(deposit = c(2,1)),
  type = "response"), infer = TRUE) # odds ratios
```

```
insecticide = g-BHC:
 contrast            odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 deposit2 / deposit1       1.86 0.145 Inf      1.60      2.17    1   7.990  <.0001

insecticide = both:
 contrast            odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 deposit2 / deposit1       2.70 0.523 Inf      1.84      3.94    1   5.116  <.0001

insecticide = DDT:
 contrast            odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 deposit2 / deposit1       1.62 0.111 Inf      1.41      1.85    1   7.007  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log odds ratio scale
Tests are performed on the log odds ratio scale
```

We can also compare the odds ratios.

```r
pairs(pairs(emmeans(m, ~deposit|insecticide, at = list(deposit = c(2,1)))), by = NULL)
```

```
 contrast                                              estimate    SE  df z.ratio p.value
 (deposit2 - deposit1 g-BHC) - (deposit2 - deposit1 both)   -0.370 0.209 Inf  -1.771  0.1794
 (deposit2 - deposit1 g-BHC) - (deposit2 - deposit1 DDT)     0.141 0.104 Inf   1.363  0.3605
 (deposit2 - deposit1 both) - (deposit2 - deposit1 DDT)      0.511 0.206 Inf   2.487  0.0344

Results are given on the log odds ratio (not the response) scale.
P value adjustment: tukey method for comparing a family of 3 estimates
```

For odds ratios for a quantitative variable you can also compare using `emtrends`.

```r
pairs(emtrends(m, ~insecticide, var = "deposit"))
```

```
 contrast       estimate    SE  df z.ratio p.value
 (g-BHC) - both   -0.370 0.209 Inf  -1.771  0.1794
 (g-BHC) - DDT     0.141 0.104 Inf   1.363  0.3605
 both - DDT        0.511 0.206 Inf   2.487  0.0344

P value adjustment: tukey method for comparing a family of 3 estimates
```

Here I have left off `type = "response"`. Including it will give ratios of odds ratios, which is a bit confusing, but if all we care about is whether the odds ratios are significantly different this is sufficient. Note that to avoid controlling for family-wise Type I error rate include the option `adjust = "none"` as an argument to `pairs`.

Relationship Between Poisson and Logistic Regression

Suppose C_i has a binomial distribution with parameters p_i and m_i so that

$$P(C_i = c) = \binom{m_i}{c} p_i^y (1 - p_i)^{m_i - c}.$$

Define the expected count as $E(C_i) = m_i p_i = \lambda_i$. Then $p_i = \lambda_i / m_i$ so we can write

$$P(C_i = c) = \binom{m_i}{c} \left(\frac{\lambda_i}{m_i}\right)^y \left(1 - \frac{\lambda_i}{m_i}\right)^{c-y}.$$

Then it can be shown that

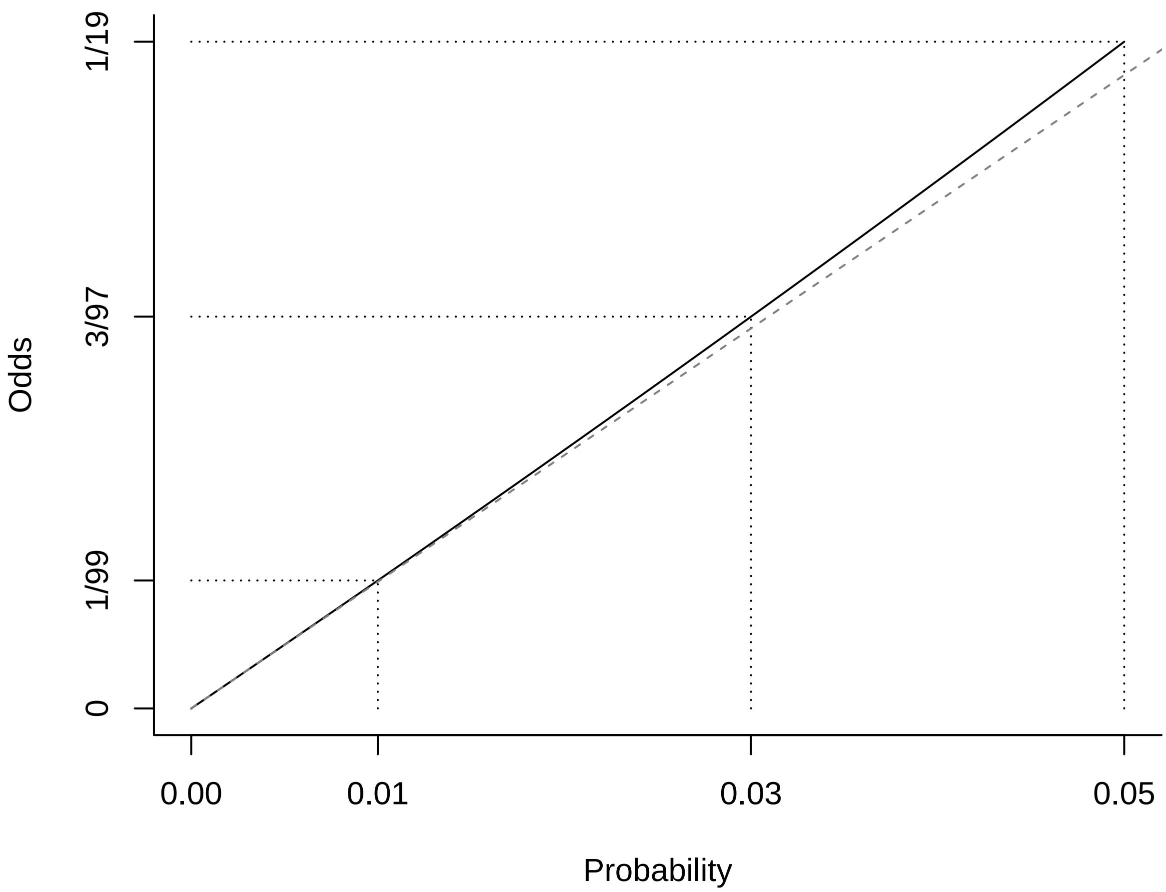
$$\lim_{m_i \to \infty} \binom{m_i}{c} \left(\frac{\lambda_i}{m_i}\right)^y \left(1 - \frac{\lambda_i}{m_i}\right)^{m_i - y} = \frac{e^{\lambda_i} \lambda_i^y}{y!},$$

which is the Poisson distribution.

Thus *in practice* if p_i is small relative to m_i we can *approximate a binomial distribution with a Poisson distribution*. Furthermore there is a close relationship between the model parameters. In logistic regression we have

$$O_i = \exp(\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_k x_{ik}),$$

where $O_i = p_i/(1 - p_i)$ is the odds of the event. But when p_i is very small then $O_i \approx p_i$.



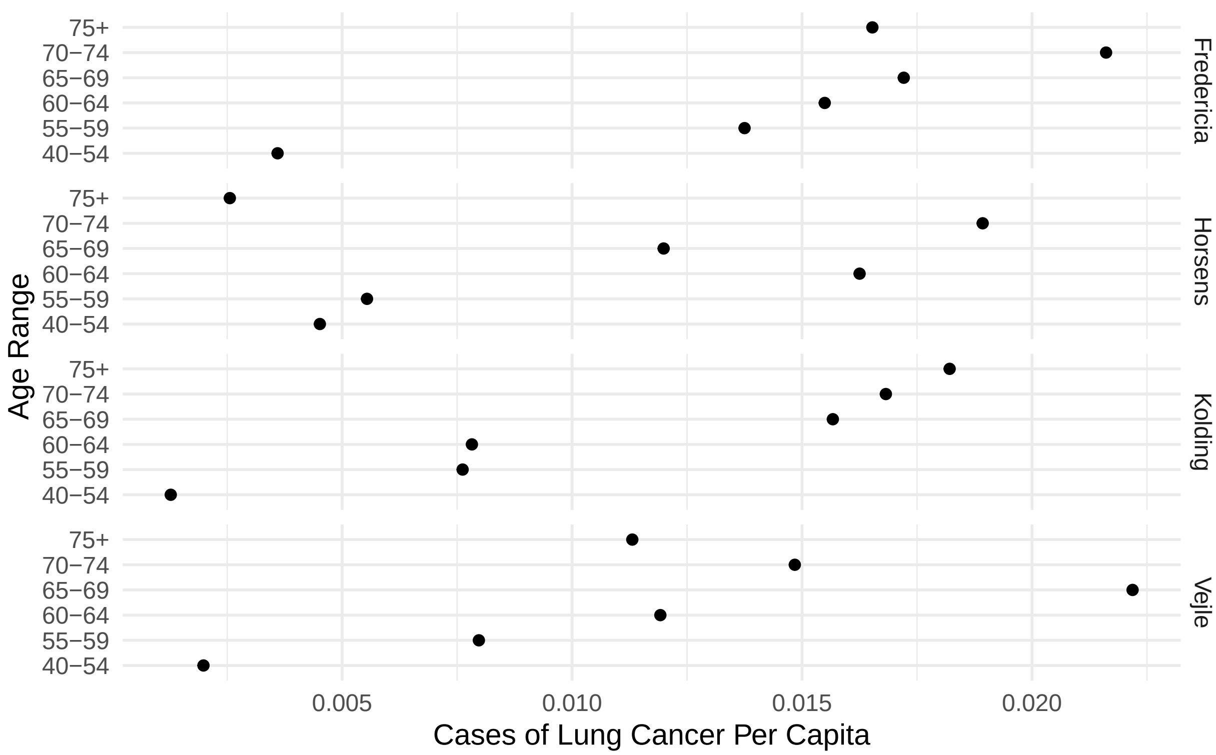
So then
$$p_i \approx \exp(\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_k x_{ik}),$$
and because $E(C_i) = m_i p_i$,
$$E(C_i) \approx \exp(\log m_i + \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_k x_{ik}),$$
where $\log m_i$ is used as an offset in a Poisson regression model. That is, we can model a proportion (approximately) as a rate in a Poisson regression model for events that are rare and when m_i (i.e., the denominator of the proportion) is relatively large. This is relatively common in large-scale observational studies.

Example: Consider the following data on the incidence of lung cancer in four Danish cities.

```r
library(ISwR) # for eba1977 data
head(eba1977)
```

```
        city   age  pop cases
1 Fredericia 40-54 3059    11
2    Horsens 40-54 2879    13
3    Kolding 40-54 3142     4
4      Vejle 40-54 2520     5
5 Fredericia 55-59  800    11
6    Horsens 55-59 1083     6
```

```r
p <- ggplot(eba1977, aes(x = age, y = cases/pop)) +
  geom_point() + facet_grid(city ~ .) + coord_flip() +
  labs(x = "Age Range", y = "Cases of Lung Cancer Per Capita") +
  theme_minimal()
plot(p)
```



Consider both a logistic and Poisson regression models to compare the cities while controlling for age.

```r
m.b <- glm(cbind(cases, pop-cases) ~ city + age, family = binomial, data = eba1977)
cbind(summary(m.b)$coefficients, confint(m.b))
```

```
             Estimate Std. Error z value   Pr(>|z|)   2.5 %    97.5 %
(Intercept)  -5.6262     0.2008 -28.021 9.132e-173 -6.0385 -5.249799
cityHorsens  -0.3345     0.1827  -1.830  6.719e-02 -0.6946  0.023561
cityKolding  -0.3764     0.1890  -1.991  4.646e-02 -0.7504 -0.007412
cityVejle    -0.2760     0.1891  -1.459  1.444e-01 -0.6503  0.093162
age55-59      1.1070     0.2490   4.445  8.771e-06  0.6159  1.596828
age60-64      1.5291     0.2325   6.577  4.812e-11  1.0760  1.991225
age65-69      1.7819     0.2305   7.732  1.061e-14  1.3335  2.240675
age70-74      1.8727     0.2365   7.918  2.415e-15  1.4105  2.341695
age75+        1.4289     0.2512   5.688  1.289e-08  0.9328  1.922467
```

```r
m.p <- glm(cases ~ offset(log(pop)) + city + age, family = poisson, data = eba1977)
cbind(summary(m.p)$coefficients, confint(m.p))
```

```
             Estimate Std. Error z value   Pr(>|z|)   2.5 %    97.5 %
(Intercept)  -5.6321     0.2003 -28.125 4.911e-174 -6.0433 -5.256725
cityHorsens  -0.3301     0.1815  -1.818  6.899e-02 -0.6878  0.025582
cityKolding  -0.3715     0.1878  -1.978  4.789e-02 -0.7432 -0.004967
cityVejle    -0.2723     0.1879  -1.450  1.472e-01 -0.6441  0.094356
age55-59      1.1010     0.2483   4.434  9.230e-06  0.6114  1.589441
age60-64      1.5186     0.2316   6.556  5.528e-11  1.0672  1.979110
age65-69      1.7677     0.2294   7.704  1.314e-14  1.3213  2.224503
age70-74      1.8569     0.2353   7.891  3.005e-15  1.3970  2.323556
age75+        1.4197     0.2503   5.672  1.408e-08  0.9254  1.911381
```

The expected proportion/rate of cases in Fredericia appears to be the highest. Let's compare that city with the others while controlling for age.

```r
trtools::contrast(m.b,
  a = list(city = "Fredericia", age = "40-54"),
  b = list(city = c("Horsens","Kolding","Vejle"), age = "40-54"),
  cnames = c("vs Horsens","vs Kolding","vs Vejle"), tf = exp)
```

```
           estimate  lower upper
vs Horsens    1.397 0.9766 1.999
vs Kolding    1.457 1.0059 2.110
vs Vejle      1.318 0.9097 1.909
```

```r
trtools::contrast(m.p,
  a = list(city = "Fredericia", age = "40-54", pop = 1),
  b = list(city = c("Horsens","Kolding","Vejle"), age = "40-54", pop = 1),
  cnames = c("vs Horsens","vs Kolding","vs Vejle"), tf = exp)
```

```
           estimate  lower upper
vs Horsens    1.391 0.9746 1.985
vs Kolding    1.450 1.0035 2.095
vs Vejle      1.313 0.9086 1.897
```

Note that since there is no interaction in the model, contrasts for city will not depend on the age group. We can also compute the estimated expected proportion (i.e., probability) or expected rate for each model.

```r
trtools::contrast(m.b, a = list(city = levels(eba1977$city), age = "40-54"), tf = plogis)
```

```
 estimate    lower    upper
 0.003589 0.002424 0.005311
```

```
 0.002571 0.001701 0.003885
 0.002466 0.001625 0.003741
 0.002726 0.001787 0.004155
```

```r
trtools::contrast(m.p, a = list(city = levels(eba1977$city), age = "40-54", pop = 1), tf = exp)
```

```
 estimate    lower    upper
 0.003581 0.002419 0.005303
 0.002574 0.001704 0.003890
 0.002470 0.001628 0.003747
 0.002727 0.001789 0.004158
```

```r
d <- expand.grid(city = levels(eba1977$city), age = levels(eba1977$age))
cbind(d, trtools::glmint(m.b, newdata = d))
```

```
         city   age      fit      low      upp
1  Fredericia 40-54 0.003589 0.002424 0.005311
2     Horsens 40-54 0.002571 0.001701 0.003885
3     Kolding 40-54 0.002466 0.001625 0.003741
4       Vejle 40-54 0.002726 0.001787 0.004155
5  Fredericia 55-59 0.010780 0.007192 0.016129
6     Horsens 55-59 0.007739 0.005135 0.011648
7     Kolding 55-59 0.007424 0.004884 0.011270
8       Vejle 55-59 0.008201 0.005378 0.012487
9  Fredericia 60-64 0.016348 0.011360 0.023473
10    Horsens 60-64 0.011755 0.008104 0.017024
11    Kolding 60-64 0.011278 0.007702 0.016489
12      Vejle 60-64 0.012454 0.008520 0.018170
13 Fredericia 65-69 0.020952 0.014654 0.029876
14    Horsens 65-69 0.015086 0.010513 0.021604
15    Kolding 65-69 0.014476 0.009925 0.021069
16      Vejle 65-69 0.015979 0.010956 0.023252
17 Fredericia 70-74 0.022898 0.015845 0.032986
18    Horsens 70-74 0.016496 0.011299 0.024025
19    Kolding 70-74 0.015830 0.010679 0.023407
20      Vejle 70-74 0.017471 0.011844 0.025703
21 Fredericia   75+ 0.014812 0.009872 0.022169
22    Horsens   75+ 0.010646 0.007042 0.016065
23    Kolding   75+ 0.010214 0.006661 0.015633
24      Vejle   75+ 0.011280 0.007368 0.017232
```

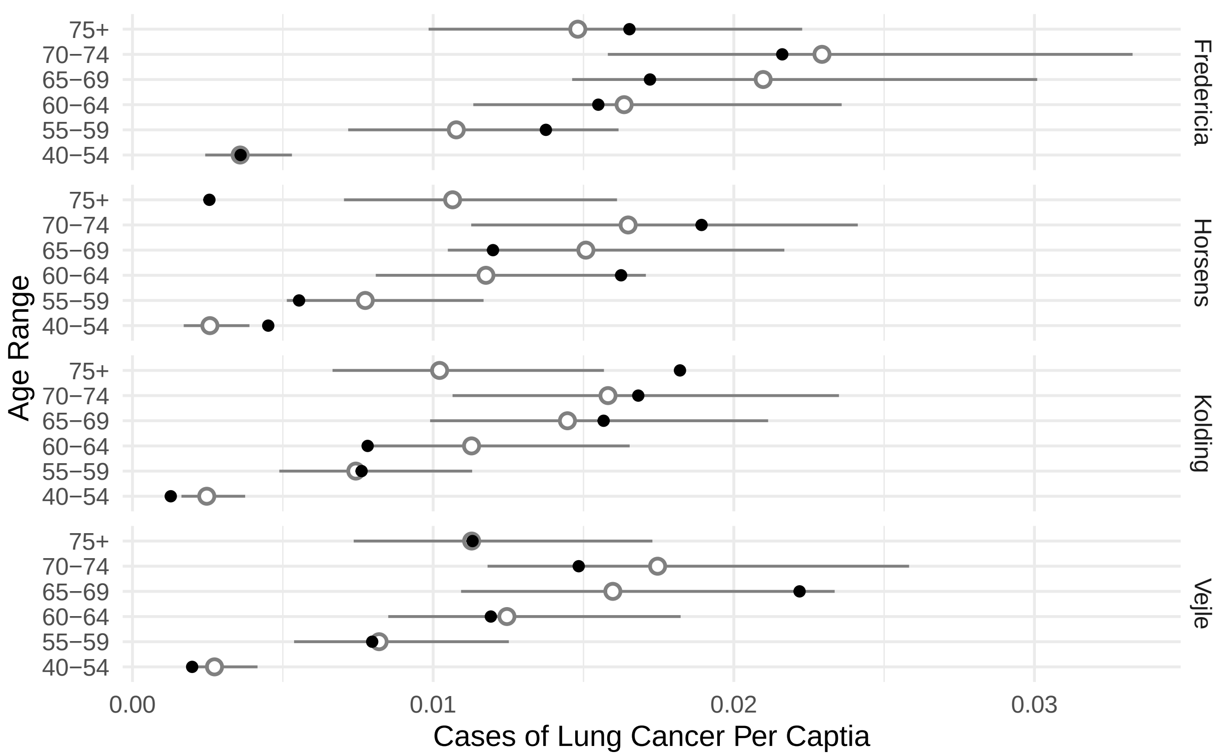
```r
d <- expand.grid(city = levels(eba1977$city), age = levels(eba1977$age), pop = 1)
cbind(d, trtools::glmint(m.p, newdata = d))
```

```
         city   age pop      fit      low      upp
1  Fredericia 40-54   1 0.003581 0.002419 0.005303
2     Horsens 40-54   1 0.002574 0.001704 0.003890
3     Kolding 40-54   1 0.002470 0.001628 0.003747
4       Vejle 40-54   1 0.002727 0.001789 0.004158
5  Fredericia 55-59   1 0.010769 0.007174 0.016167
6     Horsens 55-59   1 0.007742 0.005133 0.011676
7     Kolding 55-59   1 0.007427 0.004883 0.011297
8       Vejle 55-59   1 0.008202 0.005375 0.012517
9  Fredericia 60-64   1 0.016351 0.011335 0.023587
10    Horsens 60-64   1 0.011755 0.008092 0.017075
11    Kolding 60-64   1 0.011277 0.007690 0.016536
```

```
12       Vejle 60-64   1 0.012453 0.008506 0.018231
13 Fredericia 65-69   1 0.020976 0.014623 0.030090
14     Horsens 65-69   1 0.015080 0.010488 0.021681
15     Kolding 65-69   1 0.014467 0.009899 0.021141
16       Vejle 65-69   1 0.015976 0.010929 0.023354
17 Fredericia 70-74   1 0.022932 0.015810 0.033263
18     Horsens 70-74   1 0.016486 0.011266 0.024123
19     Kolding 70-74   1 0.015816 0.010646 0.023497
20       Vejle 70-74   1 0.017466 0.011810 0.025830
21 Fredericia   75+   1 0.014811 0.009848 0.022273
22     Horsens   75+   1 0.010647 0.007034 0.016116
23     Kolding   75+   1 0.010214 0.006654 0.015681
24       Vejle   75+   1 0.011280 0.007358 0.017292
```

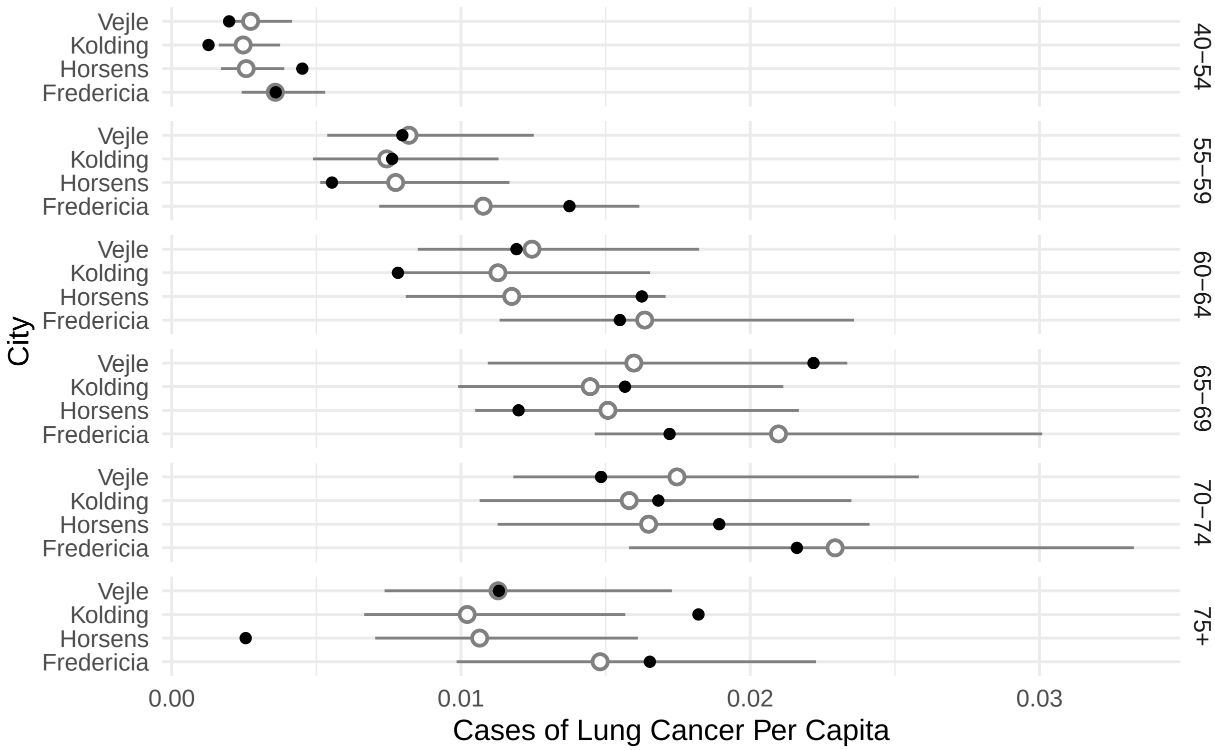
We can use this to make some helpful plots of the estimated rates (or probabilities) of lung cancer.

```r
d <- expand.grid(age = levels(eba1977$age), city = levels(eba1977$city), pop = 1)
d <- cbind(d, trtools::glmint(m.p, newdata = d))
p <- ggplot(eba1977, aes(x = age, y = cases/pop)) +
  geom_pointrange(aes(y = fit, ymin = low, ymax = upp),
    shape = 21, fill = "white", data = d, color = grey(0.5)) +
  geom_point() + facet_grid(city ~ .) + coord_flip() +
  labs(x = "Age Range", y = "Cases of Lung Cancer Per Captia") +
  theme_minimal()
plot(p)
```




```r
p <- ggplot(eba1977, aes(x = city, y = cases/pop)) +
  geom_pointrange(aes(y = fit, ymin = low, ymax = upp),
    shape = 21, fill = "white", data = d, color = grey(0.5)) +
  geom_point() + facet_grid(age ~ .) + coord_flip() +
  labs(x = "City", y = "Cases of Lung Cancer Per Capita") +
```

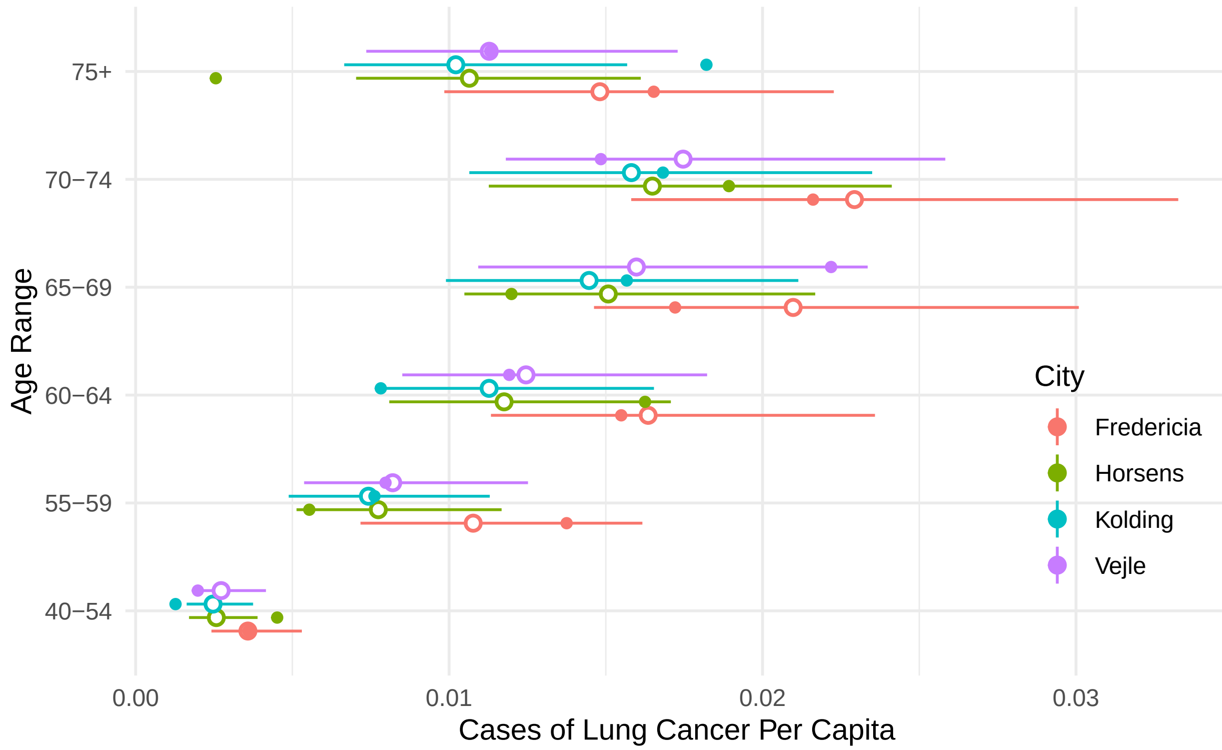
```r
  theme_minimal()
plot(p)
```




```r
p <- ggplot(eba1977, aes(x = age, y = cases/pop, color = city)) +
  geom_pointrange(aes(y = fit, ymin = low, ymax = upp),
    shape = 21, fill = "white", data = d,
      position = position_dodge(width = 0.5)) +
  geom_point(position = position_dodge(width = 0.5)) +
  coord_flip() +
  labs(x = "Age Range", y = "Cases of Lung Cancer Per Capita",
       color = "City") +
  theme_minimal() + theme(legend.position = c(0.9,0.3))
```

```
Warning: A numeric `legend.position` argument in `theme()` was deprecated in ggplot2 3.5.0.
i Please use the `legend.position.inside` argument of `theme()` instead.
This warning is displayed once every 8 hours.
Call `lifecycle::last_lifecycle_warnings()` to see where this warning was generated.
```

```r
plot(p)
```



Separation and Infinite Parameter Estimates

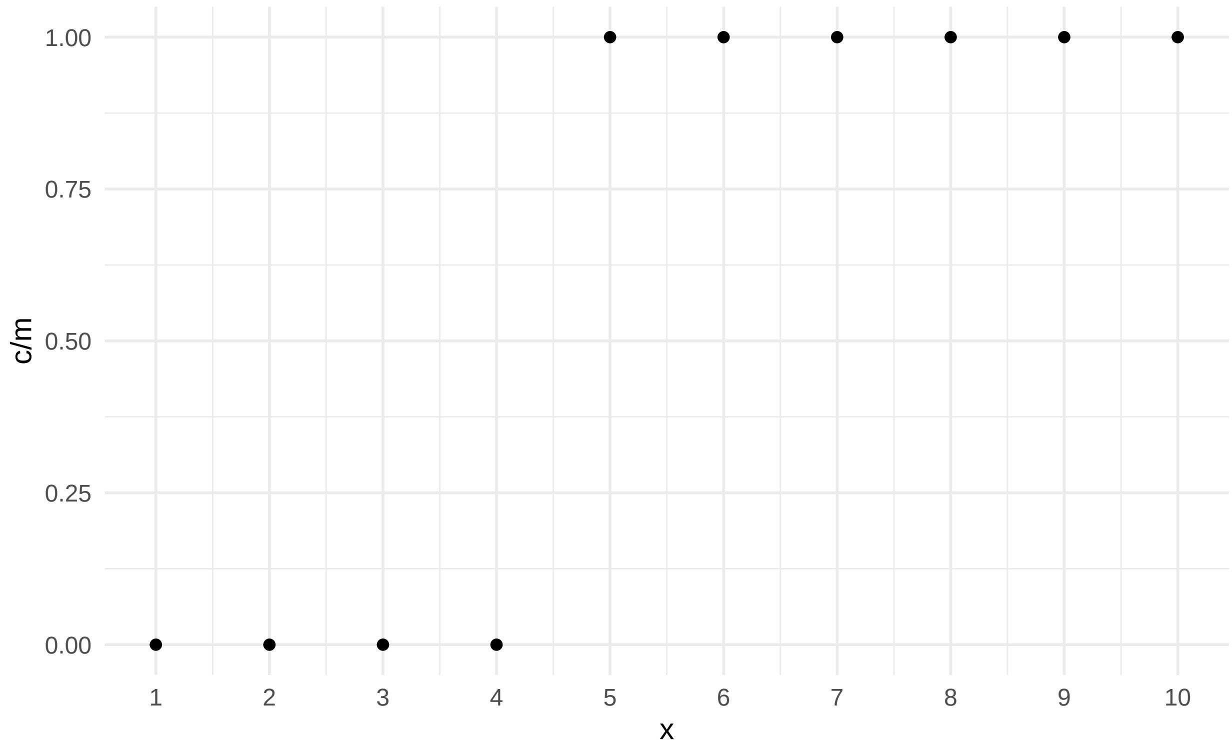
Some GLMs are prone to numerical problems due to (nearly) infinite parameter estimates.

Example: Consider the following data.

```r
mydata <- data.frame(m = rep(20, 10), c = rep(c(0,20), c(4,6)), x = 1:10)
mydata
```

```
    m  c  x
1  20  0  1
2  20  0  2
3  20  0  3
4  20  0  4
5  20 20  5
6  20 20  6
7  20 20  7
8  20 20  8
9  20 20  9
10 20 20 10
```

```r
p <- ggplot(mydata, aes(x = x, y = c/m)) + theme_minimal() +
  geom_point() + scale_x_continuous(breaks = 1:10)
plot(p)
```



If we try to estimate a logistic regression model we get errors and some extreme estimates, standard errors, and confidence intervals.

```
m <- glm(cbind(c,m-c) ~ x, family = binomial, data = mydata)
```

```
Warning: glm.fit: algorithm did not converge

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
```

```
summary(m)$coefficients
```

```
            Estimate Std. Error   z value Pr(>|z|)
(Intercept)  -212.11     114489 -0.001853   0.9985
x              47.12      25082  0.001879   0.9985
```

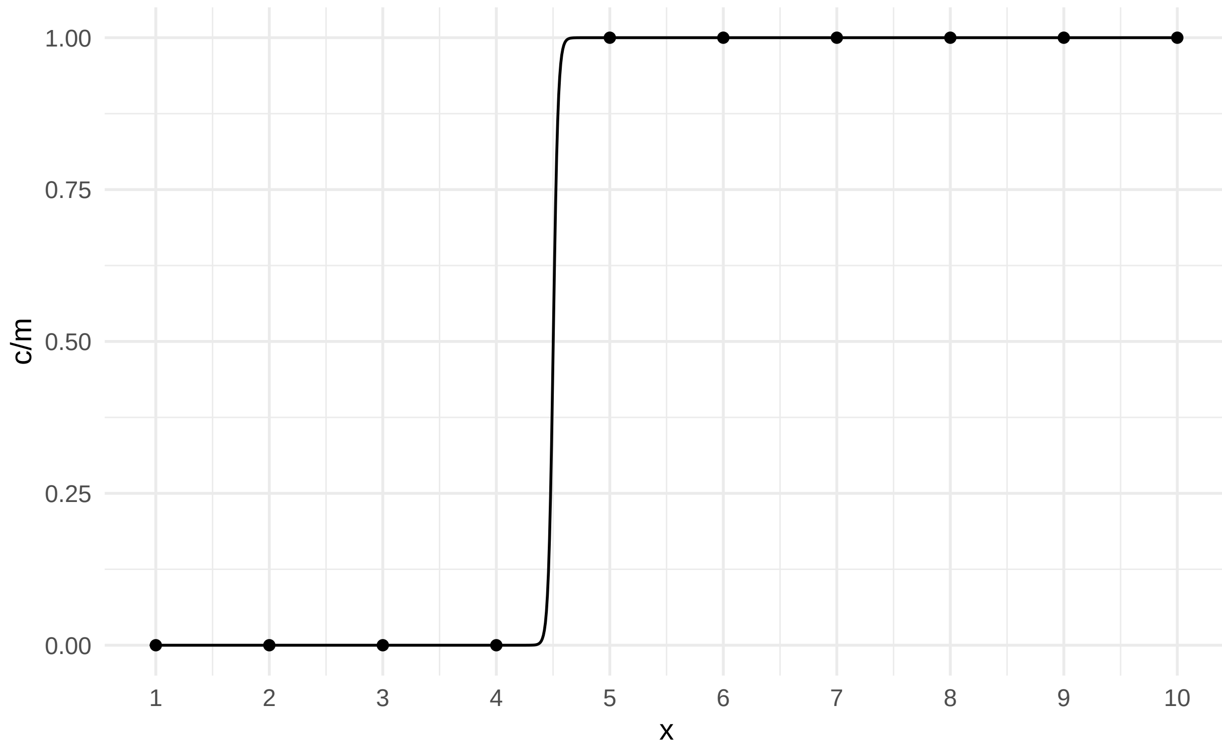
```
confint(m)
```

```
Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: algorithm did not converge

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
```

```
             2.5 % 97.5 %
(Intercept) -29559 -28057
x             7969   1966
```

But we can still plot the model.

```r
d <- data.frame(x = seq(1, 10, length = 1000))
d$yhat <- predict(m, newdata = d, type = "response")
p <- p + geom_line(aes(y = yhat), data = d)
plot(p)
```



The problem is that the estimation procedure "wants" the curve to be a step function, but that only occurs as $\beta_1 \to \infty$, and the value of x where the estimated expected response is 0.5 equals $-\beta_0/\beta_1$, and for the step function that would be 4.5, so the estimation procedure "wants" the estimate of β_0 to be $-\beta_1 5.5 = -\infty$. This is called *separation*. It is fairly obvious with a single explanatory variable, but much less so with multiple explanatory variables. The example above shows *complete separation* because we can separate the values of y based on the values of x. *Quasi-separation* occurs when this is almost true as in the following example.

```r
mydata <- data.frame(m = rep(20, 50), x = seq(1, 10, length = 50),
  c = rep(c(0,20,0,20), c(24,1,1,24)))

m <- glm(cbind(c,m-c) ~ x, family = binomial, data = mydata)
```

```
Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
```

```r
summary(m)$coefficients
```

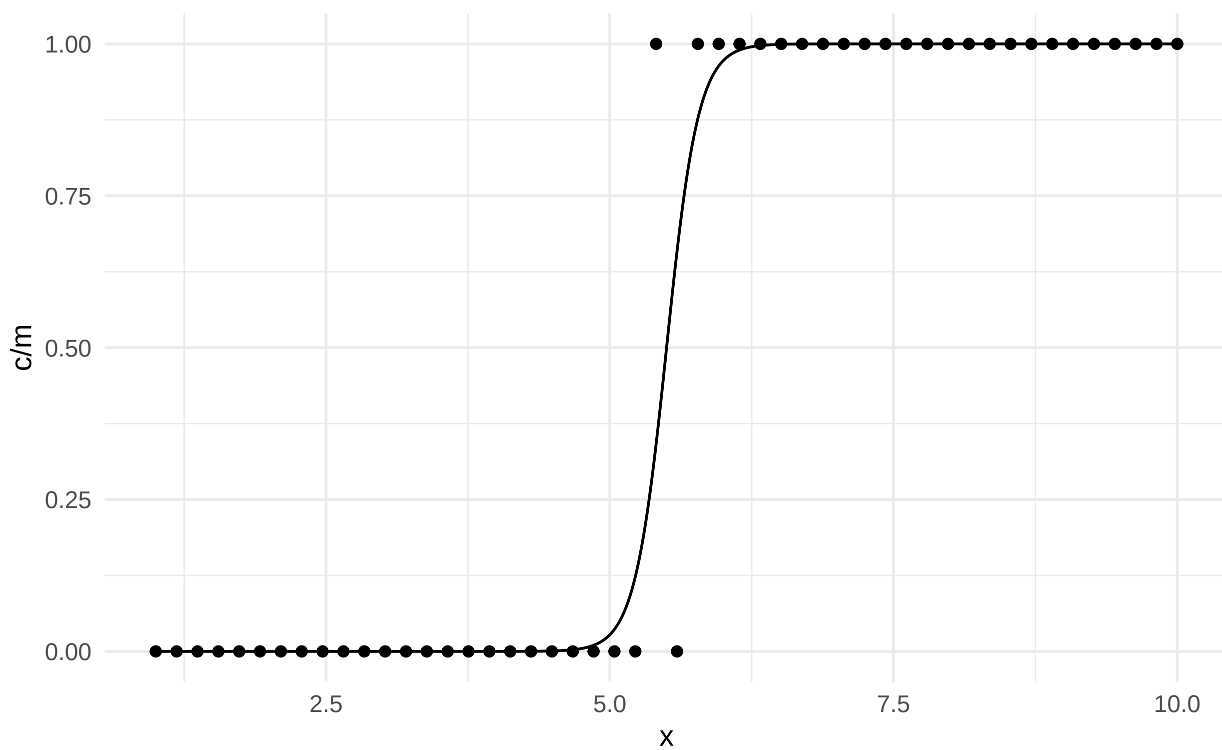
```
            Estimate Std. Error z value  Pr(>|z|)
(Intercept)  -39.231      5.542  -7.079 1.448e-12
x              7.133      1.006   7.087 1.371e-12
```

```r
confint(m)
```

```
Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
```

```
Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
              2.5 %  97.5 %
(Intercept) -51.696 -29.767
x             5.414   9.397
```

```
d <- data.frame(x = seq(1, 10, length = 10000))
d$yhat <- predict(m, newdata = d, type = "response")

p <- ggplot(mydata, aes(x = x, y = c/m)) + theme_minimal() +
  geom_point() + geom_line(aes(y = yhat), data = d)
plot(p)
```



Example: Consider the following data.

```
mydata <- data.frame(m = c(100,100), c = c(25,100), group = c("control","treatment"))
mydata
```

```
    m   c     group
1 100  25   control
2 100 100 treatment
```

```
m <- glm(cbind(c,m-c) ~ group, family = binomial, data = mydata)
summary(m)$coefficients
```

```
               Estimate Std. Error     z value  Pr(>|z|)
(Intercept)      -1.099  2.309e-01 -4.7571308 1.964e-06
grouptreatment   28.410  5.169e+04  0.0005496 9.996e-01
```

```
confint(m)
```

```
Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
                      2.5 %     97.5 %
```

```
(Intercept)       -1.571    -0.6611
grouptreatment -1849.427 18872.0265
```

A similar problem can happen in Poisson regression where the observed count or rate in a category is zero.

Example: Consider the following data and model.

```r
mydata <- data.frame(y = c(20, 10, 50, 15, 0), x = letters[1:5])
mydata
```

```
   y x
1 20 a
2 10 b
3 50 c
4 15 d
5  0 e
```

```r
m <- glm(y ~ x, family = poisson, data = mydata)
summary(m)$coefficients
```

```
            Estimate Std. Error    z value  Pr(>|z|)
(Intercept)   2.9957  2.236e-01 13.3973220 6.268e-41
xb           -0.6931  3.873e-01 -1.7896983 7.350e-02
xc            0.9163  2.646e-01  3.4632534 5.337e-04
xd           -0.2877  3.416e-01 -0.8422469 3.996e-01
xe          -25.2983  4.225e+04 -0.0005988 9.995e-01
```

```r
confint(m)
```

```
Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred
```

```
Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred

Warning: glm.fit: fitted rates numerically 0 occurred
Error: no valid set of coefficients has been found: please supply starting values
```

There are some solutions to this problem, depending on the circumstances.

1. In simple cases such as the logistic regression example with a control and treatment group, a nonparametric approach could be used for a significance test (e.g., Fisher's exact test).
2. In some cases with a categorical explanatory variable, we can omit the level(s) where the observed count is zero (in Poisson regression), or the observed proportion is 0 or 1 (in logistic regression). Clearly this precludes inferences concerning that level or its relationship with other levels.
3. For logistic regression (or similar models) a "penalized" or "bias-reduced" estimation method can be used for quasi-separation (see the **logistf** and **brglm** packages).