Monday, Apr 24

Fixed Effects Approach

The fixed effects approach is to specify the many-leveled factor as we might normally do with a factor with fewer levels. The term "fixed effects" is used to distinguish it from the "random effects" approach which we will discuss later. The question then is if and how having such a factor compromises inferences.

Example: Consider again the `baserun` data.

```
library(dplyr)
library(tidyr)
baselong <- trtools::baserun %>% mutate(player = factor(letters[1:n()])) %>%
  pivot_longer(cols = c(round, narrow, wide), names_to = "route", values_to = "time")
head(baselong)
```

```
# A tibble: 6 x 3
  player route   time
  <fct>  <chr>  <dbl>
1 a      round   5.4
2 a      narrow  5.5
3 a      wide    5.55
4 b      round   5.85
5 b      narrow  5.7
6 b      wide    5.75
```

Consider a fixed effects model with an effect for player (but no interaction with route).

```
m.fix <- lm(time ~ route + player, data = baselong)
summary(m.fix)$coefficients
```

```
              Estimate Std. Error    t value  Pr(>|t|)
(Intercept)  5.505e+00    0.05205  1.058e+02 1.320e-52
routeround   9.091e-03    0.02603  3.493e-01 7.286e-01
routewide   -7.500e-02    0.02603 -2.882e+00 6.208e-03
playerb      2.833e-01    0.07048  4.020e+00 2.366e-04
playerc     -5.000e-02    0.07048 -7.094e-01 4.820e-01
playerd      3.192e-15    0.07048  4.529e-14 1.000e+00
playere      3.333e-01    0.07048  4.729e+00 2.550e-05
playerf      5.000e-02    0.07048  7.094e-01 4.820e-01
playerg     -1.000e-01    0.07048 -1.419e+00 1.633e-01
playerh     -5.000e-02    0.07048 -7.094e-01 4.820e-01
playeri     -3.500e-01    0.07048 -4.966e+00 1.189e-05
playerj      3.000e-01    0.07048  4.256e+00 1.140e-04
playerk     -3.000e-01    0.07048 -4.256e+00 1.140e-04
playerl      6.667e-02    0.07048  9.459e-01 3.496e-01
playerm     -1.667e-02    0.07048 -2.365e-01 8.142e-01
playern     -4.833e-01    0.07048 -6.858e+00 2.323e-08
playero     -1.667e-02    0.07048 -2.365e-01 8.142e-01
playerp      1.667e-02    0.07048  2.365e-01 8.142e-01
playerq      2.866e-15    0.07048  4.067e-14 1.000e+00
```

```
playerr      1.667e-02    0.07048  2.365e-01 8.142e-01
players     -8.333e-02    0.07048 -1.182e+00 2.437e-01
playert      6.667e-02    0.07048  9.459e-01 3.496e-01
playeru      1.500e-01    0.07048  2.128e+00 3.923e-02
playerv      8.000e-01    0.07048  1.135e+01 2.238e-14
```

For comparison, we will also consider the marginal model using GEE, which should produce fairly accurate inferences.

```
library(geepack)
m.gee <- geeglm(time ~ route, data = baselong,
  id = player, corstr = "exchangeable")
trtools::lincon(m.gee) # easy way to get something like summary(m.gee)$coefficients
```

```
             estimate      se    lower    upper   tvalue df    pvalue
(Intercept)  5.534091 0.05411  5.42597  5.64221 102.2809 63 9.591e-72
routeround   0.009091 0.02564 -0.04215  0.06033   0.3546 63 7.241e-01
routewide   -0.075000 0.01839 -0.11176 -0.03824  -4.0775 63 1.301e-04
```

Here are the inferences for the expected time for each route, and the differences in the expected time between routes.

```
library(emmeans)
# Note: The player we choose does not matter.
pairs(emmeans(m.fix, ~route, at = list(player = "a")), infer = TRUE, adjust = "none")
```

```
 contrast       estimate    SE df lower.CL upper.CL t.ratio p.value
 narrow - round -0.00909 0.026 42  -0.0616   0.0434  -0.349  0.7286
 narrow - wide   0.07500 0.026 42   0.0225   0.1275   2.882  0.0062
 round - wide    0.08409 0.026 42   0.0316   0.1366   3.231  0.0024

Confidence level used: 0.95
```

```
pairs(emmeans(m.gee, ~route), infer = TRUE, adjust = "none")
```

```
 contrast       estimate     SE  df asymp.LCL asymp.UCL z.ratio p.value
 narrow - round -0.00909 0.0256 Inf   -0.0593    0.0412  -0.355  0.7229
 narrow - wide   0.07500 0.0184 Inf    0.0389    0.1110   4.077  <.0001
 round - wide    0.08409 0.0307 Inf    0.0239    0.1443   2.737  0.0062

Confidence level used: 0.95
```

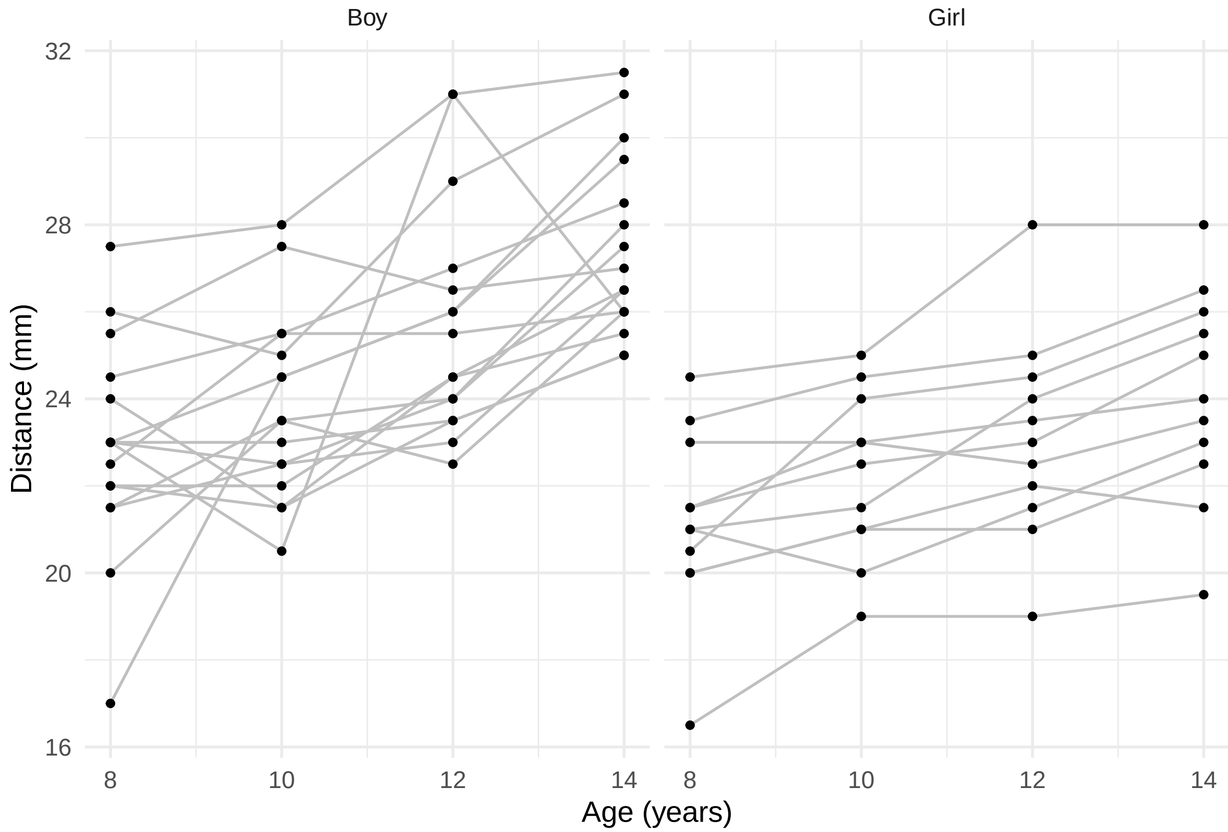
In *linear* models a fixed effects approach where the factor does not interact with other explanatory variables can produce valid inferences. But some inferences for explanatory variables that are confounded with the factor are not possible.

Example: Consider the following data on orthodontic measurements on children over time.

```
library(bayeslongitudinal)
head(Dental)
```

```
  gender id gencode distance age
1   Girl  1       1     21.0   8
2   Girl  1       1     20.0  10
3   Girl  1       1     21.5  12
4   Girl  1       1     23.0  14
5   Girl  2       1     21.0   8
6   Girl  2       1     21.5  10
```

```r
p <- ggplot(Dental, aes(x = age, y = distance)) +
  geom_line(aes(group = id), color = grey(0.75)) +
  geom_point(size = 1) + facet_wrap(~ gender) +
  labs(x = "Age (years)", y = "Distance (mm)") + theme_minimal()
plot(p)
```



Age could be treated as a quantitative or categorical variable here. But the problem with the fixed effects approach is inferences for differences in expected distance between male and female children.

```r
m.fix <- lm(distance ~ id + age + gender, data = Dental)
summary(m.fix)$coefficients
```

```
            Estimate Std. Error t value  Pr(>|t|)
(Intercept) 18.71963    1.52595 12.2675 6.228e-22
id          -0.05194    0.05356 -0.9698 3.344e-01
age          0.66019    0.09779  6.7513 8.587e-10
genderGirl  -3.02227    0.84903 -3.5597 5.613e-04
```

Notice that there is no indicator variable of gender! The `lm` function recognized that it is confounded with subject and removed it. We can see this if we construct a table of the number of observations by subject and sex.

```r
with(Dental, table(id, gender))
```

```
    gender
id   Boy Girl
  1    0    4
  2    0    4
  3    0    4
```

```
  4   0   4
  5   0   4
  6   0   4
  7   0   4
  8   0   4
  9   0   4
  10  0   4
  11  0   4
  12  4   0
  13  4   0
  14  4   0
  15  4   0
  16  4   0
  17  4   0
  18  4   0
  19  4   0
  20  4   0
  21  4   0
  22  4   0
  23  4   0
  24  4   0
  25  4   0
  26  4   0
  27  4   0
```

These factors are *nested* (i.e., the variable `id` is nested in the variable `gender`).

By changing the order of the explanatory variables we can get sex in the model but then we lose a subject indicator variable.

```
m.fix <- lm(distance ~ age * gender + id, data = Dental)
summary(m.fix)$coefficients
```

```
               Estimate Std. Error t value  Pr(>|t|)
(Intercept)    17.35354    1.75589  9.8830 1.347e-16
age             0.78437    0.12620  6.2155 1.102e-08
genderGirl      0.33085    2.33265  0.1418 8.875e-01
id             -0.05194    0.05321 -0.9762 3.312e-01
age:genderGirl -0.30483    0.19771 -1.5418 1.262e-01
```

If we wanted to compare the boys and girls, we could *in principle* estimate the average expected response for each sex, and the difference in these average expected responses (at a given age).

```
emmeans(m.fix, ~ gender, at = list(age = 14))
```

```
 gender emmean    SE  df lower.CL upper.CL
 Boy      27.6 0.555 103     26.5     28.7
 Girl     23.7 0.711 103     22.3     25.1

Confidence level used: 0.95
```

```
pairs(emmeans(m.fix, ~ gender, at = list(age = 14)))
```

```
 contrast   estimate   SE  df t.ratio p.value
 Boy - Girl     3.94 1.03 103   3.818  0.0002
```

But there is maybe a limitation of such inferences — they are *for these particular children* (i.e., these 16 boys and 11 girls). We will see if/how we can generalize these inferences to other boys and girls of a given sex or age.

We also have a problem if we specify an interaction involving subject.

```
m.fix <- lm(distance ~ id*age + gender*age, data = Dental)
summary(m.fix)$coefficients
```

```
                 Estimate Std. Error t value  Pr(>|t|)
(Intercept)    19.236375     5.4206  3.5488 0.0005868
id             -0.148500     0.2682 -0.5536 0.5810510
age             0.613208     0.4829  1.2698 0.2070315
genderGirl     -0.972648     4.2520 -0.2287 0.8195226
id:age          0.008778     0.0239  0.3673 0.7141351
age:genderGirl -0.186330     0.3788 -0.4919 0.6238531
```

Note that there are no terms for gender

Fixed Effects and Nonlinear Models

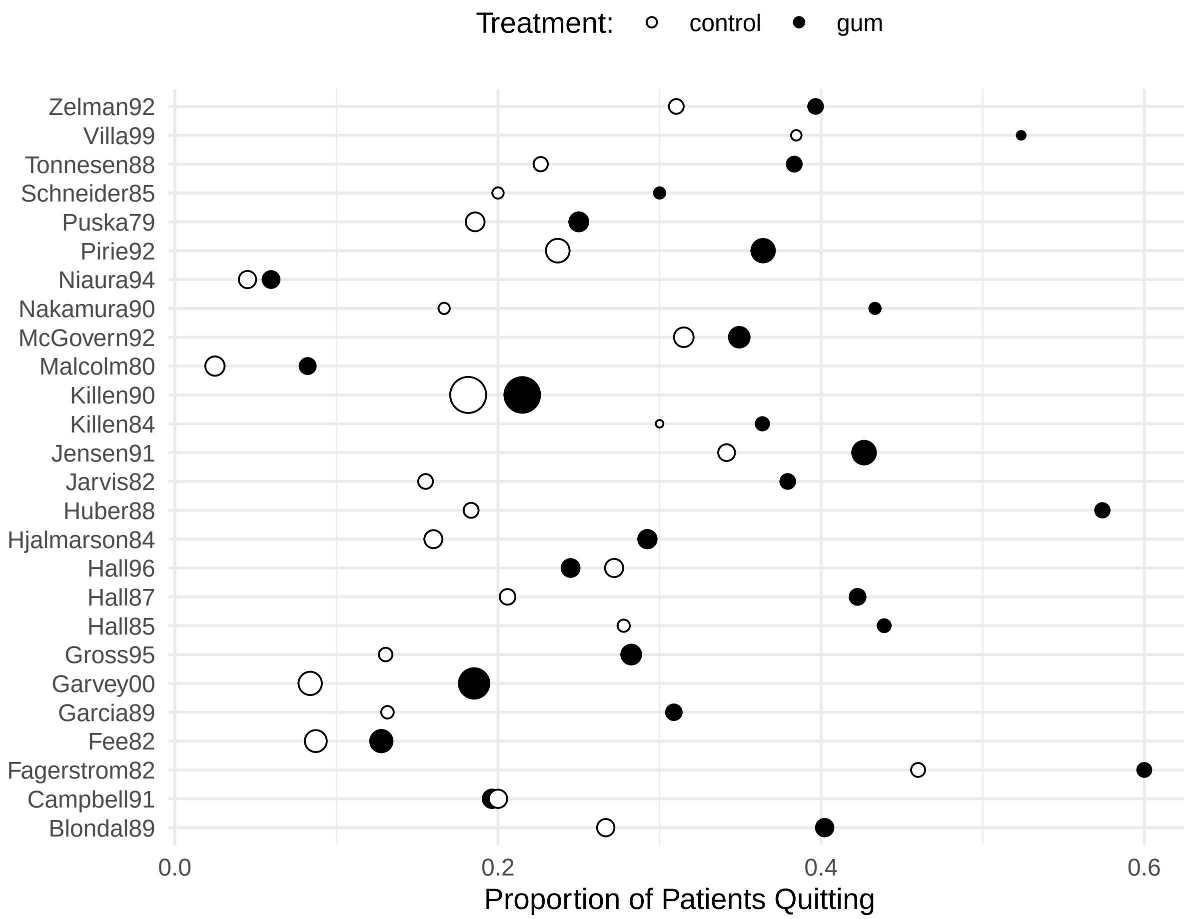
Fixed effects *can* produce valid inferences for nonlinear models (including generalized linear models), but not necessarily. It depends, in part, on the *number of parameters* relative to the number of observations.

Example: Recall the meta-analysis of 26 studies of the effect of nicotine gum on smoking cessation.

```
library(dplyr)
library(tidyr)
quitsmoke <- HSAUR3::smoking
quitsmoke$study <- rownames(quitsmoke)
quitsmoke.quits <- quitsmoke %>% dplyr::select(study, qt, qc) %>%
  rename(gum = qt, control = qc) %>%
  pivot_longer(cols = c(gum,control), names_to = "treatment", values_to = "quit")
quitsmoke.total <- quitsmoke %>% dplyr::select(study, tt, tc) %>%
  rename(gum = tt, control = tc) %>%
  pivot_longer(cols = c(gum,control), names_to = "treatment", values_to = "total")
quitsmoke <- full_join(quitsmoke.quits, quitsmoke.total) %>% mutate(study = factor(study)) %>% arrange(
head(quitsmoke)
```

```
# A tibble: 6 x 4
  study        treatment  quit total
  <fct>        <chr>     <int> <int>
1 Blondal89    gum          37    92
2 Blondal89    control      24    90
3 Campbell91   gum          21   107
4 Campbell91   control      21   105
5 Fagerstrom82 gum          30    50
6 Fagerstrom82 control      23    50
```

```
p <- ggplot(quitsmoke, aes(x = study, y = quit/total,
    size = total, fill = treatment)) +
  geom_point(pch = 21) + coord_flip() + guides(size = "none") +
  scale_fill_manual(values = c("White","Black")) + theme_minimal() +
  labs(x = "", y = "Proportion of Patients Quitting", fill = "Treatment:") +
  theme(legend.position = "top")
plot(p)
```



Here is a fixed-effects logistic regression model.

```
m <- glm(cbind(quit, total-quit) ~ treatment + study,
  family = binomial, data = quitsmoke)
summary(m)$coefficients
```

```
                  Estimate Std. Error z value  Pr(>|z|)
(Intercept)       -0.95611    0.16223 -5.8935 3.782e-09
treatmentgum       0.51478    0.06571  7.8337 4.738e-15
studyCampbell91   -0.72182    0.23458 -3.0771 2.090e-03
studyFagerstrom82  0.82087    0.25660  3.1990 1.379e-03
studyFee82        -1.44471    0.23392 -6.1760 6.575e-10
studyGarcia89     -0.51371    0.27679 -1.8560 6.346e-02
studyGarvey00     -1.13119    0.19513 -5.7970 6.750e-09
studyGross95      -0.57476    0.23716 -2.4235 1.537e-02
studyHall85        0.11322    0.28635  0.3954 6.926e-01
studyHall87       -0.08874    0.24238 -0.3661 7.143e-01
studyHall96       -0.36356    0.22648 -1.6052 1.084e-01
studyHjalmarson84 -0.54554    0.23002 -2.3717 1.771e-02
studyHuber88       0.16466    0.25162  0.6544 5.128e-01
studyJarvis82     -0.32539    0.26384 -1.2333 2.175e-01
studyJensen91      0.18524    0.19887  0.9314 3.516e-01
studyKillen84     -0.05394    0.30863 -0.1748 8.613e-01
studyKillen90     -0.71634    0.17393 -4.1186 3.812e-05
studyMalcolm80    -2.28969    0.37670 -6.0784 1.214e-09
```

```
studyMcGovern92   -0.02349    0.20432 -0.1150 9.085e-01
studyNakamura90   -0.16186    0.32479 -0.4984 6.182e-01
studyNiaura94     -2.22602    0.37765 -5.8945 3.759e-09
studyPirie92      -0.15991    0.19132 -0.8358 4.033e-01
studyPuska79      -0.59867    0.22560 -2.6536 7.963e-03
studySchneider85  -0.41647    0.33913 -1.2281 2.194e-01
studyTonnesen88   -0.13127    0.25883 -0.5072 6.120e-01
studyVilla99       0.50932    0.33548  1.5182 1.290e-01
studyZelman92      0.08506    0.25163  0.3380 7.353e-01
```

We can estimate the odds ratio for the effect of treatment as follows.

```r
rbind(pairs(emmeans(m, ~ treatment | study, type = "response"),
  reverse = TRUE), adjust = "none")
```

```
 study        contrast      odds.ratio   SE  df null z.ratio p.value
 Blondal89    gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Campbell91   gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Fagerstrom82 gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Fee82        gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Garcia89     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Garvey00     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Gross95      gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Hall85       gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Hall87       gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Hall96       gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Hjalmarson84 gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Huber88      gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Jarvis82     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Jensen91     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Killen84     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Killen90     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Malcolm80    gum / control       1.67 0.11 Inf    1   7.834  <.0001
 McGovern92   gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Nakamura90   gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Niaura94     gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Pirie92      gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Puska79      gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Schneider85  gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Tonnesen88   gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Villa99      gum / control       1.67 0.11 Inf    1   7.834  <.0001
 Zelman92     gum / control       1.67 0.11 Inf    1   7.834  <.0001

Tests are performed on the log odds ratio scale
```

Note that using `rbind` makes the output a bit more compact. Here is how we can do that using `contrast` from **trtools**.

```r
trtools::contrast(m,
  a = list(treatment = "gum", study = unique(quitsmoke$study)),
  b = list(treatment = "control", study = unique(quitsmoke$study)),
  tf = exp, cnames = unique(quitsmoke$study))
```

```
             estimate lower upper
Blondal89       1.673 1.471 1.903
Campbell91      1.673 1.471 1.903
```

```
Fagerstrom82    1.673 1.471 1.903
Fee82           1.673 1.471 1.903
Garcia89        1.673 1.471 1.903
Garvey00        1.673 1.471 1.903
Gross95         1.673 1.471 1.903
Hall85          1.673 1.471 1.903
Hall87          1.673 1.471 1.903
Hall96          1.673 1.471 1.903
Hjalmarson84    1.673 1.471 1.903
Huber88         1.673 1.471 1.903
Jarvis82        1.673 1.471 1.903
Jensen91        1.673 1.471 1.903
Killen84        1.673 1.471 1.903
Killen90        1.673 1.471 1.903
Malcolm80       1.673 1.471 1.903
McGovern92      1.673 1.471 1.903
Nakamura90      1.673 1.471 1.903
Niaura94        1.673 1.471 1.903
Pirie92         1.673 1.471 1.903
Puska79         1.673 1.471 1.903
Schneider85     1.673 1.471 1.903
Tonnesen88      1.673 1.471 1.903
Villa99         1.673 1.471 1.903
Zelman92        1.673 1.471 1.903
```

Since the odds ratio is assumed to be the same for each study, we can just pick an arbitrary study.

```r
pairs(emmeans(m, ~ treatment | study, type = "response",
  at = list(study = "Blondal89")), adjust = "none", reverse = TRUE)
```

```
study = Blondal89:
 contrast      odds.ratio   SE  df null z.ratio p.value
 gum / control       1.67 0.11 Inf    1   7.834  <.0001

Tests are performed on the log odds ratio scale
```

```r
trtools::contrast(m,
  a = list(treatment = "gum", study = "Blondal89"),
  b = list(treatment = "control", study = "Blondal89"),
  tf = exp)
```

```
 estimate lower upper
    1.673 1.471 1.903
```

Here is a model where the effect of nicotine gum varies over study.

```r
m <- glm(cbind(quit, total-quit) ~ treatment * study,
  family = binomial, data = quitsmoke)
summary(m)$coefficients
```

```
                                Estimate Std. Error   z value  Pr(>|z|)
(Intercept)                    -1.011601     0.2384 -4.243904 2.197e-05
treatmentgum                    0.615186     0.3194  1.925966 5.411e-02
studyCampbell91                -0.374693     0.3411 -1.098520 2.720e-01
studyFagerstrom82               0.851258     0.3706  2.297064 2.162e-02
studyFee82                     -1.336595     0.3604 -3.709126 2.080e-04
studyGarcia89                  -0.875469     0.5358 -1.633834 1.023e-01
```

```
studyGarvey00                    -1.380932     0.3479 -3.969605 7.199e-05
studyGross95                     -0.885519     0.4985 -1.776429 7.566e-02
studyHall85                       0.056089     0.4419  0.126927 8.990e-01
studyHall87                      -0.338326     0.3831 -0.883128 3.772e-01
studyHall96                       0.026317     0.3254  0.080884 9.355e-01
studyHjalmarson84                -0.646627     0.3622 -1.785045 7.425e-02
studyHuber88                     -0.482324     0.4100 -1.176276 2.395e-01
studyJarvis82                    -0.682995     0.4340 -1.573798 1.155e-01
studyJensen91                     0.354821     0.3332  1.064752 2.870e-01
studyKillen84                     0.164303     0.5431  0.302551 7.622e-01
studyKillen90                    -0.494459     0.2602 -1.899981 5.744e-02
studyMalcolm80                   -2.660471     0.6314 -4.213818 2.511e-05
studyMcGovern92                   0.234572     0.3055  0.767904 4.425e-01
studyNakamura90                  -0.597837     0.5448 -1.097331 2.725e-01
studyNiaura94                    -2.044756     0.5644 -3.622682 2.916e-04
studyPirie92                     -0.157780     0.2881 -0.547567 5.840e-01
studyPuska79                     -0.465665     0.3396 -1.371344 1.703e-01
studySchneider85                 -0.374693     0.5149 -0.727661 4.668e-01
studyTonnesen88                  -0.217065     0.4056 -0.535119 5.926e-01
studyVilla99                      0.541597     0.4683  1.156483 2.475e-01
studyZelman92                     0.213093     0.3706  0.574934 5.653e-01
treatmentgum:studyCampbell91     -0.638716     0.4699 -1.359285 1.741e-01
treatmentgum:studyFagerstrom82   -0.049378     0.5156 -0.095762 9.237e-01
treatmentgum:studyFee82          -0.187742     0.4742 -0.395873 6.922e-01
treatmentgum:studyGarcia89        0.466259     0.6334  0.736093 4.617e-01
treatmentgum:studyGarvey00        0.295743     0.4273  0.692111 4.889e-01
treatmentgum:studyGross95         0.349557     0.5756  0.607252 5.437e-01
treatmentgum:studyHall85          0.095203     0.5827  0.163387 8.702e-01
treatmentgum:studyHall87          0.422366     0.4997  0.845244 3.980e-01
treatmentgum:studyHall96         -0.755913     0.4542 -1.664447 9.602e-02
treatmentgum:studyHjalmarson84    0.159542     0.4712  0.338590 7.349e-01
treatmentgum:studyHuber88         1.177232     0.5377  2.189539 2.856e-02
treatmentgum:studyJarvis82        0.586934     0.5539  1.059684 2.893e-01
treatmentgum:studyJensen91       -0.254387     0.4191 -0.607000 5.439e-01
treatmentgum:studyKillen84       -0.327504     0.6621 -0.494666 6.208e-01
treatmentgum:studyKillen90       -0.404172     0.3504 -1.153314 2.488e-01
treatmentgum:studyMalcolm80       0.643954     0.7908  0.814266 4.155e-01
treatmentgum:studyMcGovern92     -0.460208     0.4107 -1.120609 2.625e-01
treatmentgum:studyNakamura90      0.725988     0.6912  1.050312 2.936e-01
treatmentgum:studyNiaura94       -0.318839     0.7592 -0.419943 6.745e-01
treatmentgum:studyPirie92        -0.003513     0.3863 -0.009096 9.927e-01
treatmentgum:studyPuska79        -0.236532     0.4544 -0.520520 6.027e-01
treatmentgum:studySchneider85    -0.076189     0.6849 -0.111241 9.114e-01
treatmentgum:studyTonnesen88      0.138056     0.5294  0.260782 7.943e-01
treatmentgum:studyVilla99        -0.049872     0.6749 -0.073900 9.411e-01
treatmentgum:studyZelman92       -0.236532     0.5046 -0.468741 6.393e-01
```

```
rbind(pairs(emmeans(m, ~ treatment | study, type = "response"),
  reverse = TRUE), adjust = "none")
```

```
 study        contrast      odds.ratio    SE  df null z.ratio p.value
 Blondal89    gum / control      1.850 0.591 Inf    1   1.926  0.0541
 Campbell91   gum / control      0.977 0.337 Inf    1  -0.068  0.9456
 Fagerstrom82 gum / control      1.761 0.713 Inf    1   1.398  0.1622
 Fee82        gum / control      1.533 0.537 Inf    1   1.219  0.2227
```

```
 Garcia89     gum / control      2.949 1.613 Inf    1    1.977  0.0480
 Garvey00     gum / control      2.487 0.706 Inf    1    3.209  0.0013
 Gross95      gum / control      2.624 1.257 Inf    1    2.015  0.0440
 Hall85       gum / control      2.035 0.992 Inf    1    1.458  0.1449
 Hall87       gum / control      2.822 1.085 Inf    1    2.700  0.0069
 Hall96       gum / control      0.869 0.281 Inf    1   -0.436  0.6629
 Hjalmarson84 gum / control      2.170 0.752 Inf    1    2.236  0.0253
 Huber88      gum / control      6.004 2.597 Inf    1    4.144  <.0001
 Jarvis82     gum / control      3.327 1.506 Inf    1    2.657  0.0079
 Jensen91     gum / control      1.434 0.389 Inf    1    1.330  0.1836
 Killen84     gum / control      1.333 0.773 Inf    1    0.496  0.6198
 Killen90     gum / control      1.235 0.178 Inf    1    1.464  0.1433
 Malcolm80    gum / control      3.522 2.548 Inf    1    1.740  0.0818
 McGovern92   gum / control      1.168 0.301 Inf    1    0.600  0.5482
 Nakamura90   gum / control      3.824 2.344 Inf    1    2.188  0.0287
 Niaura94     gum / control      1.345 0.926 Inf    1    0.430  0.6670
 Pirie92      gum / control      1.844 0.400 Inf    1    2.816  0.0049
 Puska79      gum / control      1.460 0.472 Inf    1    1.172  0.2414
 Schneider85  gum / control      1.714 1.039 Inf    1    0.890  0.3737
 Tonnesen88   gum / control      2.124 0.897 Inf    1    1.784  0.0744
 Villa99      gum / control      1.760 1.046 Inf    1    0.951  0.3416
 Zelman92     gum / control      1.460 0.571 Inf    1    0.969  0.3324

Tests are performed on the log odds ratio scale
```

The `contrast` function will let you estimate the *average* odds ratio (using the delta method).

```r
trtools::contrast(m,
  a = list(treatment = "gum", study = unique(quitsmoke$study)),
  b = list(treatment = "control", study = unique(quitsmoke$study)),
  tf = function(x) mean(exp(x)))
```

```
 estimate    se lower upper tvalue  df    pvalue
     2.14 0.228 1.693 2.587  9.383 Inf 6.431e-21
```

These inferences are probably fine because while there can be a relatively large number of parameters, there are many observations per study as well. Where we can get into trouble is when there are only a few observations per level of the many-leveled factor.

The Incidental Parameter Problem and Fixed Effects Models

Example: Consider simulated data for a logistic regression model where we observe m observations of a binary response variable for each of n subjects. If we include a fixed effect for subject, the number of parameters is $1 + n$ and the number of binary observations is nm (m per subject). We will use a relatively large total sample size of $nm = 1000$, which *should* produce good estimates of the parameter for the effect of the explanatory variable, which has a value of $\beta_1 = 1$.

Here we have $n = 1000$ subjects with $m = 2$ observations per subject (1001 parameters).

```r
set.seed(101)
n <- 1000
m <- 2
d <- data.frame(x = runif(n*m, -3, 3), z = rep(rnorm(n), each = m))
d$y <- rbinom(n*m, 1, plogis(d$x + d$z))
d$subject <- rep(1:n, each = m)

m <- glm(y ~ x + factor(subject), family = binomial, data = d)
```

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

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

```
                  Estimate Std. Error   z value  Pr(>|z|)
(Intercept)          3.550  2.190e+00  1.620793 1.051e-01
x                    2.026  1.264e-01 16.031488 7.702e-58
factor(subject)2   -26.387  1.246e+04 -0.002117 9.983e-01
factor(subject)3   -21.415  1.247e+04 -0.001718 9.986e-01
factor(subject)4   -24.302  1.135e+04 -0.002141 9.983e-01
factor(subject)5    -4.570  2.634e+00 -1.735034 8.273e-02
```

Here we have $n = 100$ subjects with $m = 20$ observations per subject (21 parameters).

```r
set.seed(101)
n <- 100
m <- 20
d <- data.frame(x = runif(n*m, -3, 3), z = rep(rnorm(n), each = m))
d$y <- rbinom(n*m, 1, plogis(d$x + d$z))
d$subject <- rep(1:n, each = m)

m <- glm(y ~ x + factor(subject), family = binomial, data = d)
head(summary(m)$coefficients)
```

```
                  Estimate Std. Error z value   Pr(>|z|)
(Intercept)         0.5058    0.56849  0.8898  3.736e-01
x                   1.0706    0.04924 21.7399 8.601e-105
factor(subject)2   -4.0151    1.00050 -4.0131  5.994e-05
factor(subject)3   -0.9076    0.78983 -1.1492  2.505e-01
factor(subject)4    0.5687    0.92331  0.6159  5.379e-01
factor(subject)5   -1.5492    0.86751 -1.7858  7.413e-02
```

Having too many parameters relative to the number of observations causes problems.

Conditional Maximum Likelihood

In some models (namely logistic and Poisson regression), we can handle the incidental parameter problem if it only involves a "main effect" by using what is called a *conditional likelihood* which in a sense removes the effect of the factor. Consider again our data with $n = 1000$ subjects and $m = 2$ binary observations per subject.

```r
set.seed(101)
n <- 1000
m <- 2
d <- data.frame(x = runif(n*m, -3, 3), z = rep(rnorm(n), each = m))
d$y <- rbinom(n*m, 1, plogis(d$x + d$z))
d$subject <- rep(1:n, each = m)

library(survival) # for the clogit function
m <- clogit(y ~ x + strata(subject), data = d)
summary(m)
```

```
Call:
coxph(formula = Surv(rep(1, 2000L), y) ~ x + strata(subject),
    data = d, method = "exact")

  n= 2000, number of events= 982
```

```
    coef exp(coef) se(coef)    z Pr(>|z|)
x 1.0132    2.7544   0.0894 11.3   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

  exp(coef) exp(-coef) lower .95 upper .95
x      2.75      0.363      2.31      3.28

Concordance= 0.861  (se = 0.023 )
Likelihood ratio test= 335  on 1 df,   p=<2e-16
Wald test            = 128  on 1 df,   p=<2e-16
Score (logrank) test = 255  on 1 df,   p=<2e-16
```

The `clogit` function requires that the response is *binary*, so to apply it to the smoking cessation data we would need to reformat the data.

```r
quitsmoke <- quitsmoke %>% mutate(noquit = total - quit) %>% dplyr::select(-total) %>%
  pivot_longer(cols = c(quit, noquit), names_to = "outcome", values_to = "count")
head(quitsmoke)
```

```
# A tibble: 6 x 4
  study      treatment outcome count
  <fct>      <chr>     <chr>   <int>
1 Blondal89  gum       quit       37
2 Blondal89  gum       noquit     55
3 Blondal89  control   quit       24
4 Blondal89  control   noquit     66
5 Campbell91 gum       quit       21
6 Campbell91 gum       noquit     86
```

```r
quitsmoke <- quitsmoke %>% uncount(count) %>% mutate(y = ifelse(outcome == "quit", 1, 0))
head(quitsmoke)
```

```
# A tibble: 6 x 4
  study     treatment outcome     y
  <fct>     <chr>     <chr>   <dbl>
1 Blondal89 gum       quit        1
2 Blondal89 gum       quit        1
3 Blondal89 gum       quit        1
4 Blondal89 gum       quit        1
5 Blondal89 gum       quit        1
6 Blondal89 gum       quit        1
```

```r
m <- clogit(y ~ treatment + strata(study), data = quitsmoke)
summary(m)
```

```
Call:
coxph(formula = Surv(rep(1, 5846L), y) ~ treatment + strata(study),
    data = quitsmoke, method = "exact")

  n= 5846, number of events= 1394

               coef exp(coef) se(coef)    z Pr(>|z|)
treatmentgum 0.5123    1.6691   0.0656 7.81  5.5e-15 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
             exp(coef) exp(-coef) lower .95 upper .95
treatmentgum      1.67      0.599      1.47       1.9

Concordance= 0.545  (se = 0.011 )
Likelihood ratio test= 62.3  on 1 df,   p=3e-15
Wald test            = 61.1  on 1 df,   p=6e-15
Score (logrank) test = 61.7  on 1 df,   p=4e-15
```

Poisson regression is an interesting special case when using either a fixed effects approach or conditional maximum likelihood. Here the two approaches produce the same results.

Example: Consider the following data from a case-control study that compared the number of *naevi* between children with (`case`) and without (`control`) spina bifida.

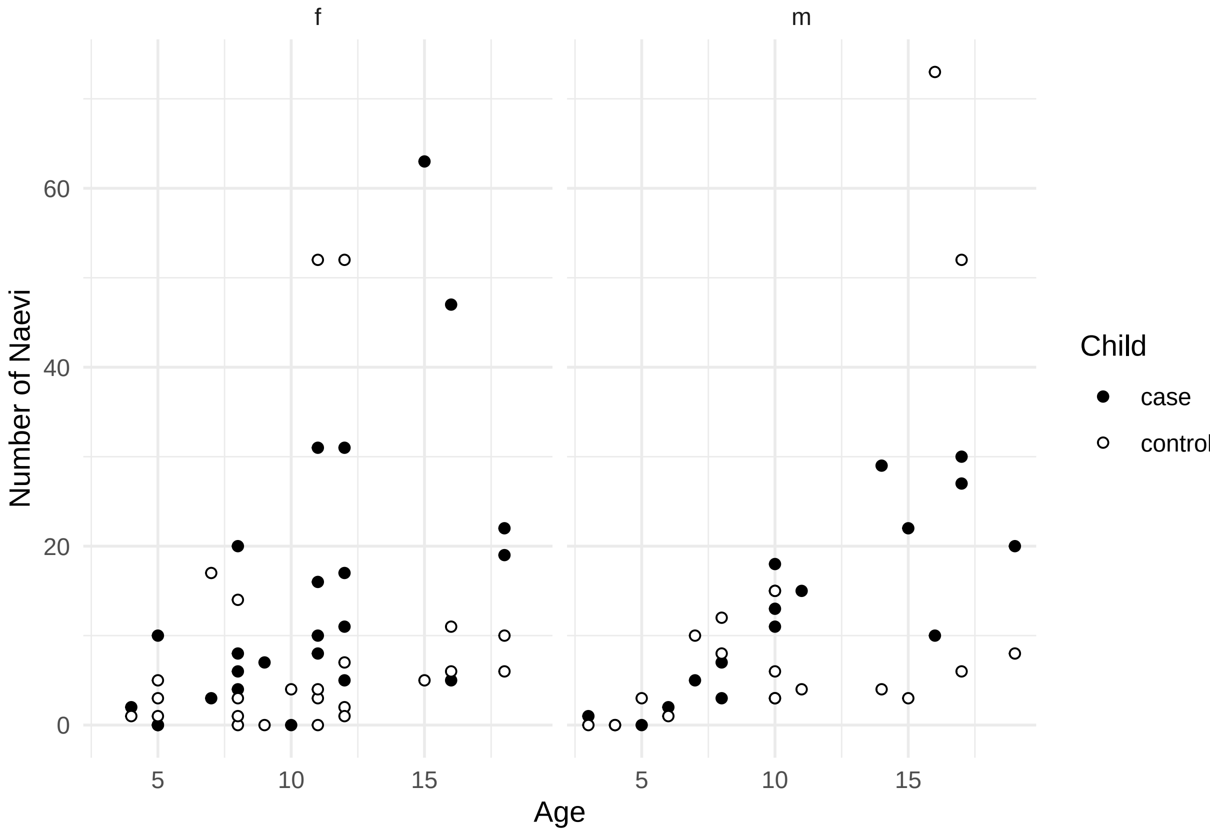
```
library(dplyr)
library(tidyr)
library(trtools) # for the naevi data
naevi$set <- factor(1:nrow(naevi)) # data frame naevi is from trtools package
head(naevi)
```

```
  sex age case control set
1   f  16    5       6   1
2   f   5    0       3   2
3   m  10   15      15   3
4   m   6    2       1   4
5   f  12   11       7   5
6   f  18   22       6   6
```

```
naevilong <- naevi %>% pivot_longer(cols = c(case, control),
  names_to = "child", values_to = "count")
head(naevilong)
```

```
# A tibble: 6 x 5
  sex     age set   child   count
  <fct> <int> <fct> <chr>   <int>
1 f        16 1     case        5
2 f        16 1     control     6
3 f         5 2     case        0
4 f         5 2     control     3
5 m        10 3     case       15
6 m        10 3     control    15
```

```
p <- ggplot(naevilong, aes(x = age, y = count, fill = child)) +
  facet_wrap(~ sex) + geom_point(shape = 21) +
  scale_fill_manual(values = c("black","white")) +
  labs(x = "Age", y = "Number of Naevi", fill = "Child") + theme_minimal()
plot(p)
```



The children have been matched by age and sex. But there may be other variables that are correlated with age and sex that are also related to the number of naevi, and these will potential cause a "set effect" on the counts. There are several ways we could handle this.

```
m <- glm(count ~ child + set, family = poisson, data = naevilong)
head(summary(m)$coefficients)
```

```
             Estimate Std. Error z value  Pr(>|z|)
(Intercept)    1.8491    0.30273   6.108 1.009e-09
childcontrol  -0.3130    0.06428  -4.870 1.118e-06
set2          -1.2993    0.65134  -1.995 4.607e-02
set3           1.0033    0.35248   2.846 4.422e-03
set4          -1.2993    0.65134  -1.995 4.607e-02
set5           0.4925    0.38271   1.287 1.982e-01
```

Note that we omit age and sex since those variables vary between but not within sets and are thus "redundant" with the effect of set (if you include them it will not change inferences concerning the effect of child). Let's estimate the effect of being a case.

```
trtools::contrast(m, tf = exp,
  a = list(child = "case", set = "1"),
  b = list(child = "control", set = "1"))
```

```
 estimate lower upper
    1.368 1.206 1.551
```

Note that the set does not matter.

There is a trick to using conditional maximum likelihood here. It can be done by using logistic regression.

```r
m <- glm(cbind(case, control) ~ 1, family = binomial, data = naevi)
summary(m)$coefficients
```

```
            Estimate Std. Error z value  Pr(>|z|)
(Intercept)    0.313    0.06428    4.87 1.118e-06
```

Strange model. But look at this.

```r
trtools::lincon(m, tf = exp)
```

```
            estimate lower upper
(Intercept)    1.368 1.206 1.551
```

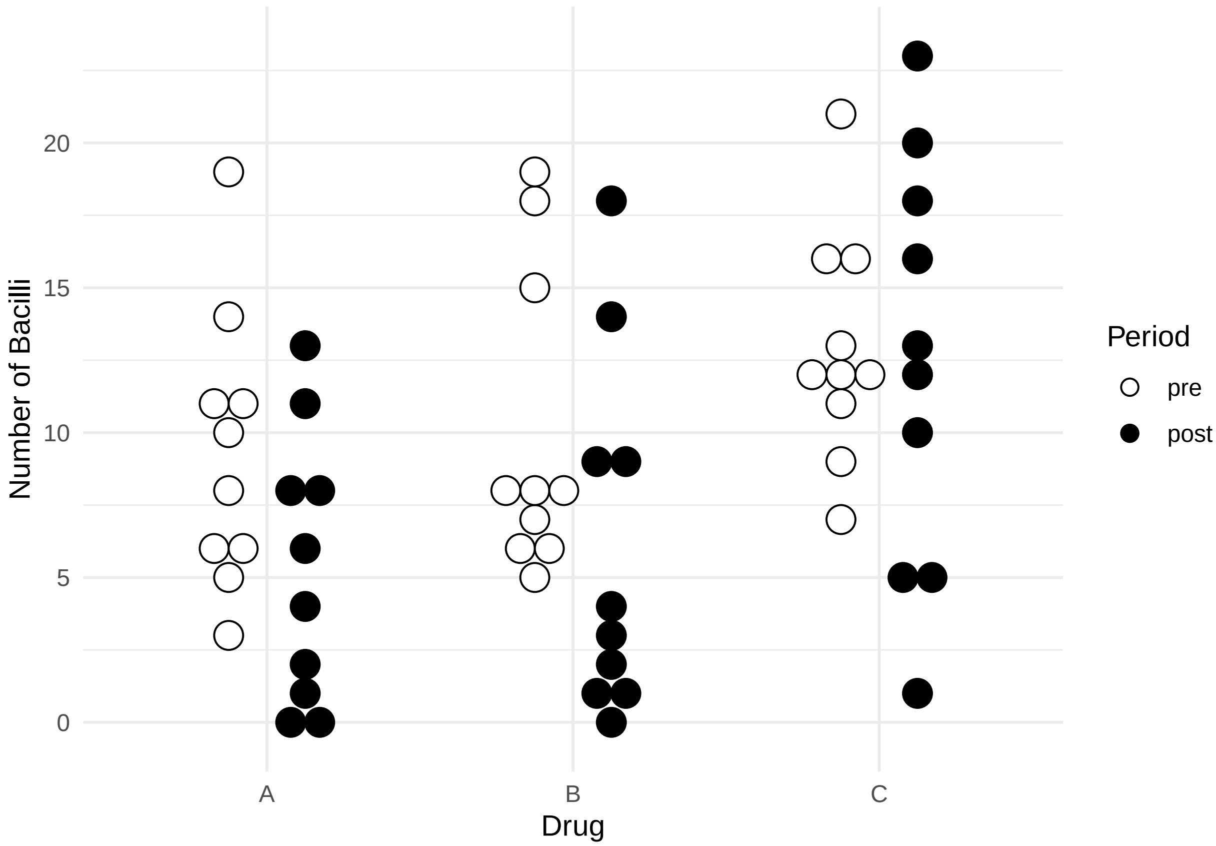
There's maybe no real advantage to using conditional maximum likelihood here via logistic regression except that in problems with *many* levels it is computationally faster.

Example: Consider data from a study of the effect of three antibiotics on leprosy bacilli. Note that if you want to install **ALA** you will need to use `install.packages("ALA", repos = "http://R-Forge.R-project.org")` because it is not kept on the default repository.

```r
library(ALA)
head(leprosy)
```

```
   id drug period nBacilli
1   1    A    pre       11
31  1    A   post        6
2   2    B    pre        6
32  2    B   post        0
3   3    C    pre       16
33  3    C   post       13
```

```r
p <- ggplot(leprosy, aes(x = drug, y = nBacilli, fill = period)) +
  geom_dotplot(binaxis = "y", method = "histodot",
    stackdir = "center", binwidth = 1,
    position = position_dodge(width = 0.5)) +
  scale_fill_manual(values = c("white","black")) +
  labs(x = "Drug", y = "Number of Bacilli", fill = "Period") +
  theme_minimal()
plot(p)
```



First a fixed effects approach.

```
m <- glm(nBacilli ~ factor(id) + drug*period, family = poisson, data = leprosy)
summary(m)$coefficients
```

```
              Estimate Std. Error  z value  Pr(>|z|)
(Intercept)    2.38221     0.2505  9.51158 1.878e-21
factor(id)2   -1.06668     0.4829 -2.20896 2.718e-02
factor(id)3    0.31547     0.3178  0.99269 3.209e-01
factor(id)4   -0.75377     0.4287 -1.75809 7.873e-02
factor(id)5   -0.77900     0.4376 -1.78006 7.507e-02
factor(id)6    0.08367     0.3316  0.25229 8.008e-01
factor(id)7   -0.88730     0.4491 -1.97579 4.818e-02
factor(id)8   -0.55586     0.4081 -1.36218 1.731e-01
factor(id)9    0.31547     0.3178  0.99269 3.209e-01
factor(id)10   0.25783     0.3229  0.79843 4.246e-01
factor(id)11  -0.66122     0.4215 -1.56888 1.167e-01
factor(id)12  -0.41277     0.3714 -1.11137 2.664e-01
factor(id)13   0.56798     0.3036  1.87099 6.135e-02
factor(id)14   0.72508     0.3071  2.36126 1.821e-02
factor(id)15   0.73237     0.2987  2.45163 1.422e-02
factor(id)16  -0.53063     0.3985 -1.33147 1.830e-01
factor(id)17  -0.37353     0.3871 -0.96495 3.346e-01
factor(id)18   0.28038     0.3197  0.87694 3.805e-01
factor(id)19   0.30228     0.3198  0.94508 3.446e-01
factor(id)20   0.63807     0.3112  2.05063 4.030e-02
factor(id)21  -0.21861     0.3540 -0.61750 5.369e-01
factor(id)22  -0.88730     0.4491 -1.97579 4.818e-02
```

```
factor(id)23     -0.02523     0.3540 -0.07126 9.432e-01
factor(id)24      0.28038     0.3197  0.87694 3.805e-01
factor(id)25      0.11123     0.3338  0.33316 7.390e-01
factor(id)26     -1.06668     0.4829 -2.20895 2.718e-02
factor(id)27     -0.97238     0.4376 -2.22198 2.628e-02
factor(id)28     -1.73460     0.6262 -2.76994 5.607e-03
factor(id)29      0.31961     0.3289  0.97173 3.312e-01
factor(id)30      0.41391     0.3127  1.32381 1.856e-01
periodpost       -0.56231     0.1721 -3.26721 1.086e-03
drugB:periodpost  0.06801     0.2367  0.28736 7.738e-01
drugC:periodpost  0.51468     0.2133  2.41279 1.583e-02
```

Now we can estimate the rate ratio for the effect of period for each drug.

```
pairs(emmeans(m, ~ period | drug, type = "response"),
  reverse = TRUE, infer = TRUE)
```

```
drug = A:
 contrast   ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 post / pre 0.570 0.0981 Inf     0.407     0.798    1  -3.267  0.0011

drug = B:
 contrast   ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 post / pre 0.610 0.0991 Inf     0.444     0.839    1  -3.043  0.0023

drug = C:
 contrast   ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 post / pre 0.954 0.1202 Inf     0.745     1.221    1  -0.378  0.7055

Results are averaged over the levels of: id
Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

Interestingly for this particular model we could actually drop `factor(id)` from the model entirely as it is nested with drug. We would obtain the same inferences! But do not assume that this is the case in general.

Note how `rbind` makes the output a bit more compact. Nice feature.

```
rbind(pairs(emmeans(m, ~ period | drug, type = "response"),
  reverse = TRUE, infer = TRUE), adjust = "none")
```

```
 drug contrast   ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 A    post / pre 0.570 0.0981 Inf     0.407     0.798    1  -3.267  0.0011
 B    post / pre 0.610 0.0991 Inf     0.444     0.839    1  -3.043  0.0023
 C    post / pre 0.954 0.1202 Inf     0.745     1.221    1  -0.378  0.7055

Results are averaged over some or all of the levels of: id
Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

How do we compare the rate ratios between drugs? Here are a couple of approaches.

```
pairs(pairs(emmeans(m, ~ period | drug, type = "response"),
  reverse = TRUE), by = NULL, adjust = "none")
```

```
 contrast                         ratio    SE  df null z.ratio p.value
```

```
 (post / pre A) / (post / pre B) 0.934 0.221 Inf    1  -0.287  0.7738
 (post / pre A) / (post / pre C) 0.598 0.128 Inf    1  -2.413  0.0158
 (post / pre B) / (post / pre C) 0.640 0.132 Inf    1  -2.172  0.0298

Results are averaged over the levels of: id
Tests are performed on the log scale
```

```
pairs(rbind(pairs(emmeans(m, ~ period | drug, type = "response"),
  reverse = TRUE)), adjust = "none")
```

```
 contrast                        ratio    SE  df null z.ratio p.value
 (A post / pre) / (B post / pre) 0.934 0.221 Inf    1  -0.287  0.7738
 (A post / pre) / (C post / pre) 0.598 0.128 Inf    1  -2.413  0.0158
 (B post / pre) / (C post / pre) 0.640 0.132 Inf    1  -2.172  0.0298

Results are averaged over some or all of the levels of: id
Tests are performed on the log scale
```

Now consider conditional maximum likelihood using logistic regression.

```
leprosylong <- leprosy %>%
  pivot_wider(names_from = "period", values_from = "nBacilli")
head(leprosylong)
```

```
# A tibble: 6 x 4
  id    drug    pre  post
  <fct> <fct> <int> <int>
1 1     A        11     6
2 2     B         6     0
3 3     C        16    13
4 4     A         8     0
5 5     B         6     2
6 6     C        13    10
```

```
m <- glm(cbind(post, pre) ~ drug, family = binomial, data = leprosylong)
summary(m)$coefficients
```

```
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.56231     0.1721 -3.2672 0.001086
drugB        0.06801     0.2367  0.2874 0.773834
drugC        0.51468     0.2133  2.4128 0.015831
```

Our estimates of the "odds" of a bacilli in the post period equals the estimated rate ratio for the effect of a drug.

```
trtools::contrast(m, tf = exp,
  a = list(drug = c("A","B","C")), cnames = c("A","B","C"))
```

```
  estimate  lower  upper
A   0.5699 0.4067 0.7985
B   0.6100 0.4437 0.8387
C   0.9535 0.7448 1.2206
```

When there are more than two observations per level, conditional maximum likelihood can be done using a multinomial logistic regression model. But there's no advantage to using conditional maximum likelihood here either since we can get the same results using a more straightforward fixed effects approach.

Limitations of the Fixed Effects Approach

1. Some inferences may be impossible. Meaningful inferences are largely limited to variables that vary *within* the levels of the fixed effect.
2. Possibly poor inferences in nonlinear or generalized linear models.
3. More computationally intensive (although there are workarounds).