Monday, April 21

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)  5.51e+00     0.0521  1.06e+02 1.32e-52
routeround   9.09e-03     0.0260  3.49e-01 7.29e-01
routewide   -7.50e-02     0.0260 -2.88e+00 6.21e-03
playerb      2.83e-01     0.0705  4.02e+00 2.37e-04
playerc     -5.00e-02     0.0705 -7.09e-01 4.82e-01
playerd      1.18e-15     0.0705  1.67e-14 1.00e+00
playere      3.33e-01     0.0705  4.73e+00 2.55e-05
playerf      5.00e-02     0.0705  7.09e-01 4.82e-01
playerg     -1.00e-01     0.0705 -1.42e+00 1.63e-01
playerh     -5.00e-02     0.0705 -7.09e-01 4.82e-01
playeri     -3.50e-01     0.0705 -4.97e+00 1.19e-05
playerj      3.00e-01     0.0705  4.26e+00 1.14e-04
playerk     -3.00e-01     0.0705 -4.26e+00 1.14e-04
playerl      6.67e-02     0.0705  9.46e-01 3.50e-01
playerm     -1.67e-02     0.0705 -2.36e-01 8.14e-01
playern     -4.83e-01     0.0705 -6.86e+00 2.32e-08
playero     -1.67e-02     0.0705 -2.36e-01 8.14e-01
playerp      1.67e-02     0.0705  2.36e-01 8.14e-01
playerq      8.79e-16     0.0705  1.25e-14 1.00e+00
```

```
playerr      1.67e-02     0.0705  2.36e-01 8.14e-01
players     -8.33e-02     0.0705 -1.18e+00 2.44e-01
playert      6.67e-02     0.0705  9.46e-01 3.50e-01
playeru      1.50e-01     0.0705  2.13e+00 3.92e-02
playerv      8.00e-01     0.0705  1.14e+01 2.24e-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)  5.53409 0.0541  5.4260  5.6422 102.281 63 9.59e-72
routeround   0.00909 0.0256 -0.0421  0.0603   0.355 63 7.24e-01
routewide   -0.07500 0.0184 -0.1118 -0.0382  -4.077 63 1.30e-04
```

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

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

```
 contrast       estimate    SE df lower.CL upper.CL t.ratio p.value
 narrow - round  -0.0091 0.026 42  -0.0616   0.0434  -0.350  0.7290
 narrow - wide    0.0750 0.026 42   0.0225   0.1275   2.880  0.0060
 round - wide     0.0841 0.026 42   0.0316   0.1366   3.230  0.0020

Results are averaged over the levels of: player
Confidence level used: 0.95
```

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

```
 contrast       estimate     SE df lower.CL upper.CL t.ratio p.value
 narrow - round  -0.0091 0.0256 63  -0.0603   0.0421  -0.350  0.7240
 narrow - wide    0.0750 0.0184 63   0.0382   0.1118   4.080  <.0001
 round - wide     0.0841 0.0307 63   0.0227   0.1455   2.740  0.0080

Confidence level used: 0.95
```

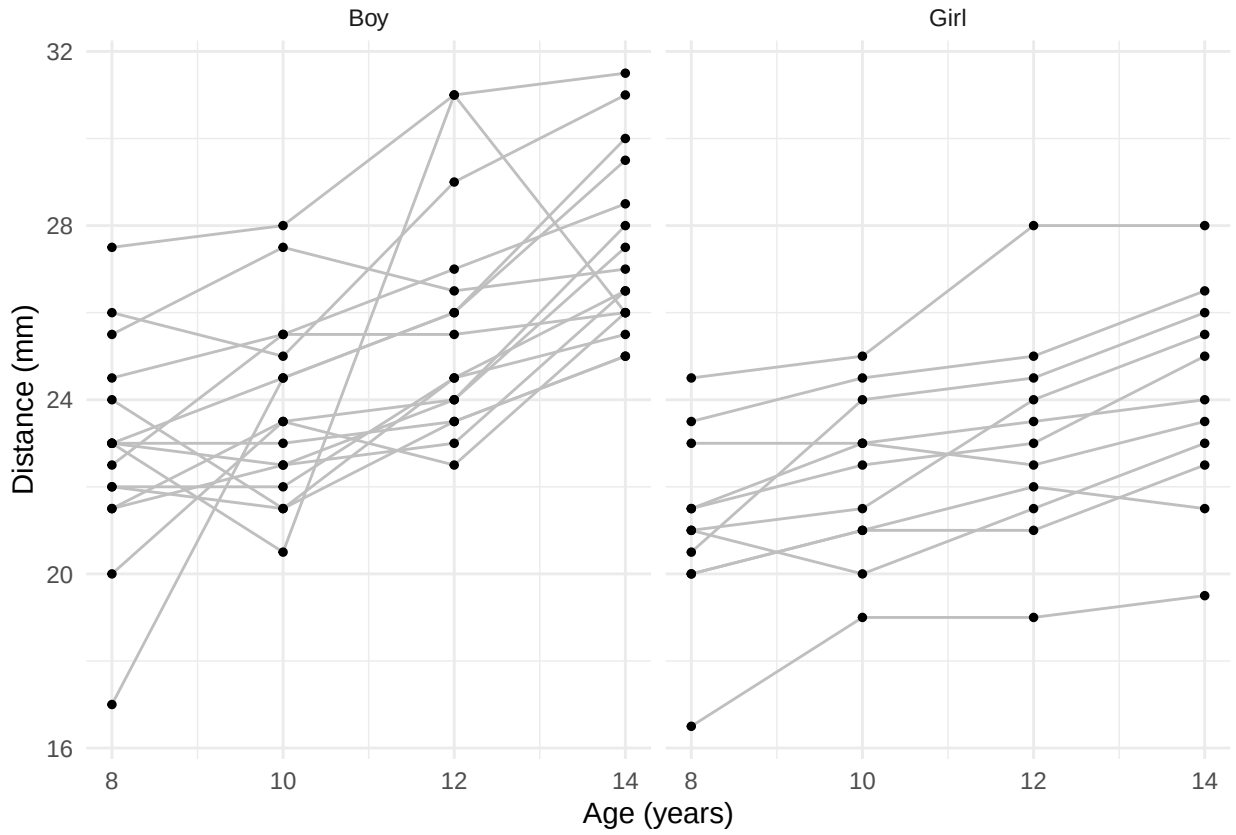
In *linear* models a fixed effects approach where the factor does not interact with other explanatory variables can produce valid inferences. But some inferences for explanatory variables that are confounded with the factor are not possible.

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
```

```
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.

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

```
             Estimate Std. Error t value Pr(>|t|)
(Intercept)     14.11     0.9857  14.318 8.88e-24
factor(id)2      1.62     1.0123   1.605 1.12e-01
factor(id)3      2.37     1.0123   2.346 2.14e-02
factor(id)4      3.50     1.0123   3.458 8.76e-04
factor(id)5      1.25     1.0123   1.235 2.21e-01
factor(id)6     -0.25     1.0123  -0.247 8.06e-01
factor(id)7      1.62     1.0123   1.605 1.12e-01
factor(id)8      2.00     1.0123   1.976 5.16e-02
factor(id)9     -0.25     1.0123  -0.247 8.06e-01
factor(id)10    -2.88     1.0123  -2.840 5.72e-03
factor(id)11     5.00     1.0123   4.939 4.22e-06
factor(id)12     6.38     1.0123   6.298 1.53e-08
factor(id)13     2.00     1.0123   1.976 5.16e-02
factor(id)14     2.88     1.0123   2.840 5.72e-03
```

```
factor(id)15     5.25     1.0123   5.186 1.58e-06
factor(id)16     1.62     1.0123   1.605 1.12e-01
factor(id)17     5.00     1.0123   4.939 4.22e-06
factor(id)18     2.37     1.0123   2.346 2.14e-02
factor(id)19     2.50     1.0123   2.470 1.57e-02
factor(id)20     3.75     1.0123   3.704 3.88e-04
factor(id)21     8.12     1.0123   8.026 7.18e-12
factor(id)22     2.25     1.0123   2.223 2.91e-02
factor(id)23     2.87     1.0123   2.840 5.72e-03
factor(id)24     2.87     1.0123   2.840 5.72e-03
factor(id)25     3.50     1.0123   3.458 8.76e-04
factor(id)26     4.50     1.0123   4.445 2.80e-05
factor(id)27     1.62     1.0123   1.605 1.12e-01
age              0.66     0.0616  10.716 3.95e-17
```

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.

```
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 + factor(id), data = Dental)
summary(m.fix)$coefficients
```

```
              Estimate Std. Error   t value Pr(>|t|)
(Intercept)   1.57e+01     0.9857  1.60e+01 1.36e-26
age           6.60e-01     0.0616  1.07e+01 3.95e-17
genderGirl   -1.62e+00     1.0123 -1.61e+00 1.12e-01
factor(id)2   1.62e+00     1.0123  1.61e+00 1.12e-01
factor(id)3   2.37e+00     1.0123  2.35e+00 2.14e-02
factor(id)4   3.50e+00     1.0123  3.46e+00 8.76e-04
factor(id)5   1.25e+00     1.0123  1.23e+00 2.21e-01
factor(id)6  -2.50e-01     1.0123 -2.47e-01 8.06e-01
factor(id)7   1.62e+00     1.0123  1.61e+00 1.12e-01
factor(id)8   2.00e+00     1.0123  1.98e+00 5.16e-02
factor(id)9  -2.50e-01     1.0123 -2.47e-01 8.06e-01
factor(id)10 -2.88e+00     1.0123 -2.84e+00 5.72e-03
factor(id)11  5.00e+00     1.0123  4.94e+00 4.22e-06
factor(id)12  4.75e+00     1.0123  4.69e+00 1.10e-05
factor(id)13  3.75e-01     1.0123  3.70e-01 7.12e-01
factor(id)14  1.25e+00     1.0123  1.23e+00 2.21e-01
factor(id)15  3.63e+00     1.0123  3.58e+00 5.86e-04
factor(id)16  6.96e-16     1.0123  6.87e-16 1.00e+00
factor(id)17  3.37e+00     1.0123  3.33e+00 1.30e-03
factor(id)18  7.50e-01     1.0123  7.41e-01 4.61e-01
factor(id)19  8.75e-01     1.0123  8.64e-01 3.90e-01
factor(id)20  2.12e+00     1.0123  2.10e+00 3.90e-02
factor(id)21  6.50e+00     1.0123  6.42e+00 8.97e-09
factor(id)22  6.25e-01     1.0123  6.17e-01 5.39e-01
factor(id)23  1.25e+00     1.0123  1.23e+00 2.21e-01
factor(id)24  1.25e+00     1.0123  1.23e+00 2.21e-01
factor(id)25  1.87e+00     1.0123  1.85e+00 6.77e-02
factor(id)26  2.87e+00     1.0123  2.84e+00 5.72e-03
```

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      26.9 0.257 80     26.4     27.5
 Girl     24.6 0.284 80     24.1     25.2

Results are averaged over the levels of: id
Confidence level used: 0.95
```

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

```
 contrast   estimate   SE df t.ratio p.value
 Boy - Girl     2.32 0.28 80   8.280  <.0001

Results are averaged over the levels of: id
```

But there is maybe a limitation of such inferences — they are *for these particular children* (i.e., these 16 boys and 11 girls). We are literally basing inferences on the average response across *the children in this study*.

```
rbind(emmeans(m.fix, ~gender|id, at = list(age = 14)), adjust = "none")
```

```
 gender id emmean    SE df lower.CL upper.CL
 Boy    12   29.7 0.739 80     28.3     31.2
 Boy    13   25.4 0.739 80     23.9     26.8
 Boy    14   26.2 0.739 80     24.8     27.7
 Boy    15   28.6 0.739 80     27.1     30.1
 Boy    16   25.0 0.739 80     23.5     26.5
 Boy    17   28.4 0.739 80     26.9     29.8
 Boy    18   25.7 0.739 80     24.3     27.2
 Boy    19   25.9 0.739 80     24.4     27.3
 Boy    20   27.1 0.739 80     25.6     28.6
 Boy    21   31.5 0.739 80     30.0     33.0
 Boy    22   25.6 0.739 80     24.1     27.1
 Boy    23   26.2 0.739 80     24.8     27.7
 Boy    24   26.2 0.739 80     24.8     27.7
 Boy    25   26.9 0.739 80     25.4     28.3
 Boy    26   27.9 0.739 80     26.4     29.3
 Boy    27   25.0 0.739 80     23.5     26.5
 Girl   1    23.4 0.739 80     21.9     24.8
 Girl   2    25.0 0.739 80     23.5     26.5
 Girl   3    25.7 0.739 80     24.3     27.2
 Girl   4    26.9 0.739 80     25.4     28.3
 Girl   5    24.6 0.739 80     23.1     26.1
 Girl   6    23.1 0.739 80     21.6     24.6
 Girl   7    25.0 0.739 80     23.5     26.5
 Girl   8    25.4 0.739 80     23.9     26.8
 Girl   9    23.1 0.739 80     21.6     24.6
 Girl   10   20.5 0.739 80     19.0     22.0
 Girl   11   28.4 0.739 80     26.9     29.8

Confidence level used: 0.95
```

Now suppose we specify an interaction between age and gender, so that the growth rate is different for boys and girls.

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

```
               Estimate Std. Error t value Pr(>|t|)
(Intercept)      16.100     1.2400 12.9837 2.74e-21
factor(id)2       1.625     0.9803  1.6576 1.01e-01
factor(id)3       2.375     0.9803  2.4227 1.77e-02
factor(id)4       3.500     0.9803  3.5703 6.11e-04
factor(id)5       1.250     0.9803  1.2751 2.06e-01
factor(id)6      -0.250     0.9803 -0.2550 7.99e-01
factor(id)7       1.625     0.9803  1.6576 1.01e-01
factor(id)8       2.000     0.9803  2.0402 4.47e-02
factor(id)9      -0.250     0.9803 -0.2550 7.99e-01
factor(id)10     -2.875     0.9803 -2.9327 4.39e-03
factor(id)11      5.000     0.9803  5.1004 2.27e-06
factor(id)12      3.022     1.6568  1.8239 7.19e-02
factor(id)13     -1.353     1.6568 -0.8167 4.17e-01
factor(id)14     -0.478     1.6568 -0.2886 7.74e-01
factor(id)15      1.897     1.6568  1.1449 2.56e-01
```

```
factor(id)16     -1.728     1.6568 -1.0431 3.00e-01
factor(id)17      1.647     1.6568  0.9940 3.23e-01
factor(id)18     -0.978     1.6568 -0.5904 5.57e-01
factor(id)19     -0.853     1.6568 -0.5149 6.08e-01
factor(id)20      0.397     1.6568  0.2395 8.11e-01
factor(id)21      4.772     1.6568  2.8802 5.11e-03
factor(id)22     -1.103     1.6568 -0.6658 5.07e-01
factor(id)23     -0.478     1.6568 -0.2886 7.74e-01
factor(id)24     -0.478     1.6568 -0.2886 7.74e-01
factor(id)25      0.147     1.6568  0.0887 9.30e-01
factor(id)26      1.147     1.6568  0.6922 4.91e-01
factor(id)27     -1.728     1.6568 -1.0431 3.00e-01
age               0.784     0.0775 10.1208 6.44e-16
age:genderGirl   -0.305     0.1214 -2.5105 1.41e-02
```

We can estimate the growth rates and compare them.

```
pairs(emmeans(m.fix, ~age|gender, at = list(age = c(10,9))))
```

```
gender = Boy:
 contrast     estimate     SE df t.ratio p.value
 age10 - age9    0.784 0.0775 79  10.120  <.0001

gender = Girl:
 contrast     estimate     SE df t.ratio p.value
 age10 - age9    0.480 0.0935 79   5.130  <.0001

Results are averaged over the levels of: id
```

```
pairs(pairs(emmeans(m.fix, ~age|gender, at = list(age = c(10,9)))), by = NULL)
```

```
 contrast                                estimate    SE df t.ratio p.value
 (age10 - age9 Boy) - (age10 - age9 Girl)    0.305 0.121 79   2.511  0.0141

Results are averaged over the levels of: id
```

But now suppose we want to have a different growth rate for each child.

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

```
                Estimate Std. Error   t value Pr(>|t|)
(Intercept)      1.72e+01      3.288  5.25e+00 2.67e-06
factor(id)2     -3.05e+00      4.650 -6.56e-01 5.15e-01
factor(id)3     -2.85e+00      4.650 -6.13e-01 5.43e-01
factor(id)4      2.40e+00      4.650  5.16e-01 6.08e-01
factor(id)5      2.35e+00      4.650  5.05e-01 6.15e-01
factor(id)6     -2.50e-01      4.650 -5.38e-02 9.57e-01
factor(id)7     -3.00e-01      4.650 -6.45e-02 9.49e-01
factor(id)8      4.20e+00      4.650  9.03e-01 3.70e-01
factor(id)9      8.50e-01      4.650  1.83e-01 8.56e-01
factor(id)10    -3.70e+00      4.650 -7.96e-01 4.30e-01
factor(id)11     1.70e+00      4.650  3.66e-01 7.16e-01
factor(id)12     5.00e-02      4.650  1.08e-02 9.91e-01
factor(id)13    -2.40e+00      4.650 -5.16e-01 6.08e-01
factor(id)14    -1.25e+00      4.650 -2.69e-01 7.89e-01
factor(id)15     7.45e+00      4.650  1.60e+00 1.15e-01
```

```
factor(id)16     -3.60e+00      4.650 -7.74e-01 4.42e-01
factor(id)17      1.70e+00      4.650  3.66e-01 7.16e-01
factor(id)18     -2.30e+00      4.650 -4.95e-01 6.23e-01
factor(id)19      2.50e+00      4.650  5.38e-01 5.93e-01
factor(id)20     -2.85e+00      4.650 -6.13e-01 5.43e-01
factor(id)21      4.00e+00      4.650  8.60e-01 3.93e-01
factor(id)22      2.80e+00      4.650  6.02e-01 5.50e-01
factor(id)23     -4.00e+00      4.650 -8.60e-01 3.93e-01
factor(id)24     -1.44e+01      4.650 -3.11e+00 3.01e-03
factor(id)25      1.85e+00      4.650  3.98e-01 6.92e-01
factor(id)26     -3.75e+00      4.650 -8.06e-01 4.24e-01
factor(id)27     -3.00e-01      4.650 -6.45e-02 9.49e-01
age               3.75e-01      0.293  1.28e+00 2.06e-01
factor(id)2:age   4.25e-01      0.414  1.03e+00 3.10e-01
factor(id)3:age   4.75e-01      0.414  1.15e+00 2.57e-01
factor(id)4:age   1.00e-01      0.414  2.41e-01 8.10e-01
factor(id)5:age  -1.00e-01      0.414 -2.41e-01 8.10e-01
factor(id)6:age  -1.64e-14      0.414 -3.97e-14 1.00e+00
factor(id)7:age   1.75e-01      0.414  4.22e-01 6.74e-01
factor(id)8:age  -2.00e-01      0.414 -4.83e-01 6.31e-01
factor(id)9:age  -1.00e-01      0.414 -2.41e-01 8.10e-01
factor(id)10:age  7.50e-02      0.414  1.81e-01 8.57e-01
factor(id)11:age  3.00e-01      0.414  7.24e-01 4.72e-01
factor(id)12:age  5.75e-01      0.414  1.39e+00 1.71e-01
factor(id)13:age  4.00e-01      0.414  9.66e-01 3.39e-01
factor(id)14:age  3.75e-01      0.414  9.05e-01 3.69e-01
factor(id)15:age -2.00e-01      0.414 -4.83e-01 6.31e-01
factor(id)16:age  4.75e-01      0.414  1.15e+00 2.57e-01
factor(id)17:age  3.00e-01      0.414  7.24e-01 4.72e-01
factor(id)18:age  4.25e-01      0.414  1.03e+00 3.10e-01
factor(id)19:age -5.60e-15      0.414 -1.35e-14 1.00e+00
factor(id)20:age  6.00e-01      0.414  1.45e+00 1.53e-01
factor(id)21:age  3.75e-01      0.414  9.05e-01 3.69e-01
factor(id)22:age -5.00e-02      0.414 -1.21e-01 9.04e-01
factor(id)23:age  6.25e-01      0.414  1.51e+00 1.37e-01
factor(id)24:age  1.57e+00      0.414  3.80e+00 3.67e-04
factor(id)25:age  1.50e-01      0.414  3.62e-01 7.19e-01
factor(id)26:age  7.50e-01      0.414  1.81e+00 7.58e-02
factor(id)27:age  1.75e-01      0.414  4.22e-01 6.74e-01
```

Note that there are no terms for gender.

```
pairs(emmeans(m.fix, ~age|gender, at = list(age = c(10,9))))
```

```
gender = Boy:
 contrast     estimate     SE df t.ratio p.value
 age10 - age9    0.784 0.0732 54  10.710  <.0001

gender = Girl:
 contrast     estimate     SE df t.ratio p.value
 age10 - age9    0.480 0.0883 54   5.430  <.0001

Results are averaged over the levels of: id
```

```
pairs(pairs(emmeans(m.fix, ~age|gender, at = list(age = c(10,9)))), by = NULL)
```

```
 contrast                                estimate    SE df t.ratio p.value
 (age10 - age9 Boy) - (age10 - age9 Girl)    0.305 0.115 54   2.657  0.0104

Results are averaged over the levels of: id
```

These are are based on averaging the estimated rates of change across the *subjects in this study*.

In general, the fixed effects approach does not permit proper inferences for explanatory variables that have a fixed effects variable nested within them. We are limited to inferences that are *crossed* with the fixed effect. Also, we are not able to properly model interactions involving the fixed effects.

Fixed Effects and Nonlinear Models

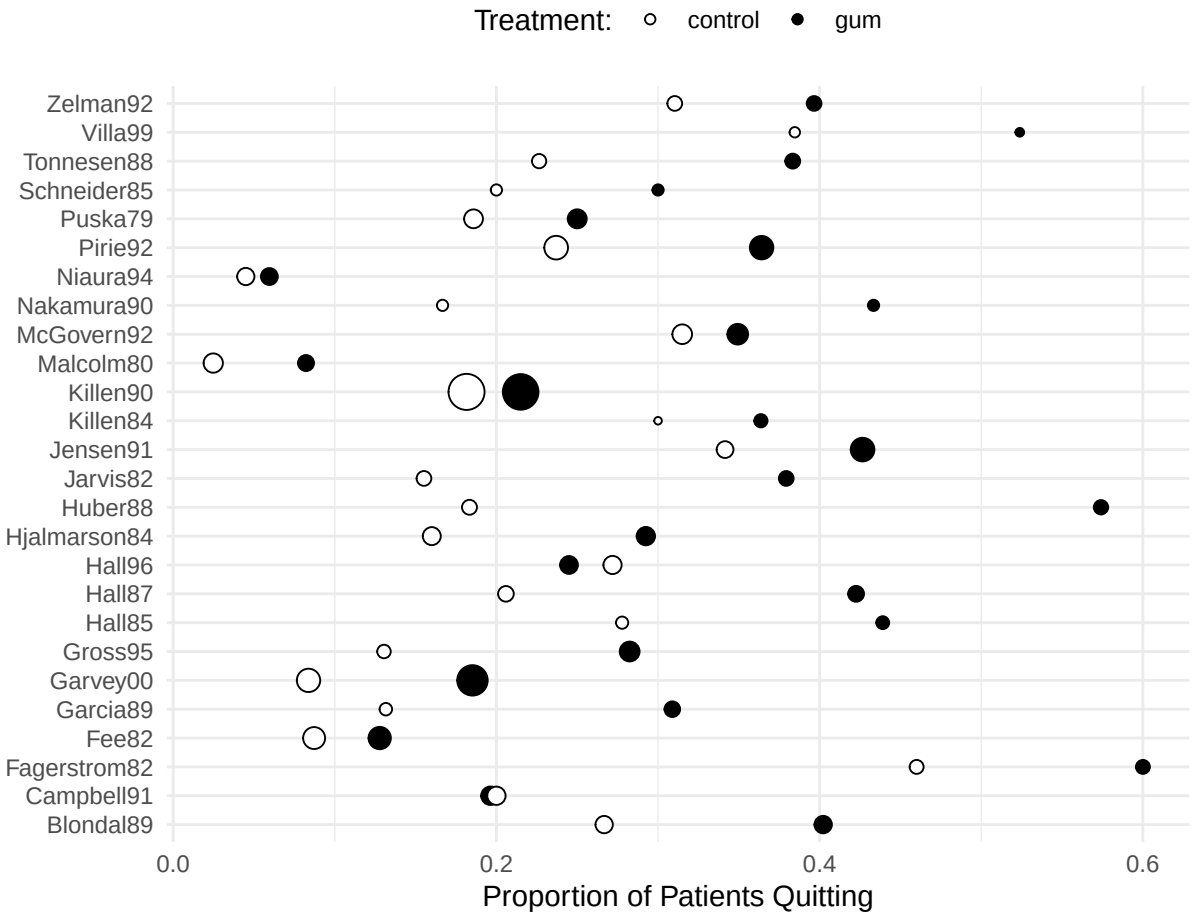
Fixed effects *can* produce valid inferences for nonlinear models (including generalized linear models), but not necessarily. It depends, in part, on the *number of parameters* relative to the number of observations.

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(st
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)       -0.9561     0.1622  -5.893 3.78e-09
treatmentgum       0.5148     0.0657   7.834 4.74e-15
studyCampbell91   -0.7218     0.2346  -3.077 2.09e-03
studyFagerstrom82  0.8209     0.2566   3.199 1.38e-03
studyFee82        -1.4447     0.2339  -6.176 6.57e-10
studyGarcia89     -0.5137     0.2768  -1.856 6.35e-02
studyGarvey00     -1.1312     0.1951  -5.797 6.75e-09
studyGross95      -0.5748     0.2372  -2.424 1.54e-02
studyHall85        0.1132     0.2863   0.395 6.93e-01
studyHall87       -0.0887     0.2424  -0.366 7.14e-01
studyHall96       -0.3636     0.2265  -1.605 1.08e-01
studyHjalmarson84 -0.5455     0.2300  -2.372 1.77e-02
studyHuber88       0.1647     0.2516   0.654 5.13e-01
studyJarvis82     -0.3254     0.2638  -1.233 2.17e-01
studyJensen91      0.1852     0.1989   0.931 3.52e-01
studyKillen84     -0.0539     0.3086  -0.175 8.61e-01
studyKillen90     -0.7163     0.1739  -4.119 3.81e-05
```

```
studyMalcolm80     -2.2897     0.3767  -6.078 1.21e-09
studyMcGovern92    -0.0235     0.2043  -0.115 9.08e-01
studyNakamura90    -0.1619     0.3248  -0.498 6.18e-01
studyNiaura94      -2.2260     0.3776  -5.894 3.76e-09
studyPirie92       -0.1599     0.1913  -0.836 4.03e-01
studyPuska79       -0.5987     0.2256  -2.654 7.96e-03
studySchneider85   -0.4165     0.3391  -1.228 2.19e-01
studyTonnesen88    -0.1313     0.2588  -0.507 6.12e-01
studyVilla99        0.5093     0.3355   1.518 1.29e-01
studyZelman92       0.0851     0.2516   0.338 7.35e-01
```

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

```
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   7.830  <.0001
 Campbell91   gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Fagerstrom82 gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Fee82        gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Garcia89     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Garvey00     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Gross95      gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Hall85       gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Hall87       gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Hall96       gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Hjalmarson84 gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Huber88      gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Jarvis82     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Jensen91     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Killen84     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Killen90     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Malcolm80    gum / control       1.67 0.11 Inf    1   7.830  <.0001
 McGovern92   gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Nakamura90   gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Niaura94     gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Pirie92      gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Puska79      gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Schneider85  gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Tonnesen88   gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Villa99      gum / control       1.67 0.11 Inf    1   7.830  <.0001
 Zelman92     gum / control       1.67 0.11 Inf    1   7.830  <.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**.

```
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        1.67  1.47   1.9
```

```
Campbell91       1.67  1.47   1.9
Fagerstrom82     1.67  1.47   1.9
Fee82            1.67  1.47   1.9
Garcia89         1.67  1.47   1.9
Garvey00         1.67  1.47   1.9
Gross95          1.67  1.47   1.9
Hall85           1.67  1.47   1.9
Hall87           1.67  1.47   1.9
Hall96           1.67  1.47   1.9
Hjalmarson84     1.67  1.47   1.9
Huber88          1.67  1.47   1.9
Jarvis82         1.67  1.47   1.9
Jensen91         1.67  1.47   1.9
Killen84         1.67  1.47   1.9
Killen90         1.67  1.47   1.9
Malcolm80        1.67  1.47   1.9
McGovern92       1.67  1.47   1.9
Nakamura90       1.67  1.47   1.9
Niaura94         1.67  1.47   1.9
Pirie92          1.67  1.47   1.9
Puska79          1.67  1.47   1.9
Schneider85      1.67  1.47   1.9
Tonnesen88       1.67  1.47   1.9
Villa99          1.67  1.47   1.9
Zelman92         1.67  1.47   1.9
```

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

```
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   7.830  <.0001

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

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

```
 estimate lower upper
     1.67  1.47   1.9
```

Or we can omit `study` when using the **emmeans** package, causing it to average over study.

```
pairs(emmeans(m, ~ treatment, type = "response"), infer = TRUE, reverse = TRUE)
```

```
 contrast      odds.ratio   SE  df asymp.LCL asymp.UCL null z.ratio p.value
 gum / control       1.67 0.11 Inf      1.47       1.9    1   7.830  <.0001

Results are averaged over the levels of: study
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 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)                 -1.01160      0.238 -4.2439 2.20e-05
treatmentgum                 0.61519      0.319  1.9260 5.41e-02
studyCampbell91             -0.37469      0.341 -1.0985 2.72e-01
studyFagerstrom82            0.85126      0.371  2.2971 2.16e-02
studyFee82                  -1.33659      0.360 -3.7091 2.08e-04
studyGarcia89               -0.87547      0.536 -1.6338 1.02e-01
studyGarvey00               -1.38093      0.348 -3.9696 7.20e-05
studyGross95                -0.88552      0.498 -1.7764 7.57e-02
studyHall85                  0.05609      0.442  0.1269 8.99e-01
studyHall87                 -0.33833      0.383 -0.8831 3.77e-01
studyHall96                  0.02632      0.325  0.0809 9.36e-01
studyHjalmarson84           -0.64663      0.362 -1.7850 7.43e-02
studyHuber88                -0.48232      0.410 -1.1763 2.39e-01
studyJarvis82               -0.68299      0.434 -1.5738 1.16e-01
studyJensen91                0.35482      0.333  1.0648 2.87e-01
studyKillen84                0.16430      0.543  0.3026 7.62e-01
studyKillen90               -0.49446      0.260 -1.9000 5.74e-02
studyMalcolm80              -2.66047      0.631 -4.2138 2.51e-05
studyMcGovern92              0.23457      0.305  0.7679 4.43e-01
studyNakamura90             -0.59784      0.545 -1.0973 2.72e-01
studyNiaura94               -2.04476      0.564 -3.6227 2.92e-04
studyPirie92                -0.15778      0.288 -0.5476 5.84e-01
studyPuska79                -0.46567      0.340 -1.3713 1.70e-01
studySchneider85            -0.37469      0.515 -0.7277 4.67e-01
studyTonnesen88             -0.21706      0.406 -0.5351 5.93e-01
studyVilla99                 0.54160      0.468  1.1565 2.47e-01
studyZelman92                0.21309      0.371  0.5749 5.65e-01
treatmentgum:studyCampbell91   -0.63872      0.470 -1.3593 1.74e-01
treatmentgum:studyFagerstrom82 -0.04938      0.516 -0.0958 9.24e-01
treatmentgum:studyFee82        -0.18774      0.474 -0.3959 6.92e-01
treatmentgum:studyGarcia89      0.46626      0.633  0.7361 4.62e-01
treatmentgum:studyGarvey00      0.29574      0.427  0.6921 4.89e-01
treatmentgum:studyGross95       0.34956      0.576  0.6073 5.44e-01
treatmentgum:studyHall85        0.09520      0.583  0.1634 8.70e-01
treatmentgum:studyHall87        0.42237      0.500  0.8452 3.98e-01
treatmentgum:studyHall96       -0.75591      0.454 -1.6644 9.60e-02
treatmentgum:studyHjalmarson84  0.15954      0.471  0.3386 7.35e-01
treatmentgum:studyHuber88       1.17723      0.538  2.1895 2.86e-02
treatmentgum:studyJarvis82      0.58693      0.554  1.0597 2.89e-01
treatmentgum:studyJensen91     -0.25439      0.419 -0.6070 5.44e-01
treatmentgum:studyKillen84     -0.32750      0.662 -0.4947 6.21e-01
treatmentgum:studyKillen90     -0.40417      0.350 -1.1533 2.49e-01
treatmentgum:studyMalcolm80     0.64395      0.791  0.8143 4.15e-01
treatmentgum:studyMcGovern92   -0.46021      0.411 -1.1206 2.62e-01
treatmentgum:studyNakamura90    0.72599      0.691  1.0503 2.94e-01
treatmentgum:studyNiaura94     -0.31884      0.759 -0.4199 6.75e-01
treatmentgum:studyPirie92      -0.00351      0.386 -0.0091 9.93e-01
treatmentgum:studyPuska79      -0.23653      0.454 -0.5205 6.03e-01
treatmentgum:studySchneider85  -0.07619      0.685 -0.1112 9.11e-01
```

```
treatmentgum:studyTonnesen88    0.13806      0.529  0.2608 7.94e-01
treatmentgum:studyVilla99      -0.04987      0.675 -0.0739 9.41e-01
treatmentgum:studyZelman92     -0.23653      0.505 -0.4687 6.39e-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       1.85 0.591 Inf    1   1.930  0.0540
 Campbell91   gum / control       0.98 0.337 Inf    1  -0.070  0.9460
 Fagerstrom82 gum / control       1.76 0.713 Inf    1   1.400  0.1620
 Fee82        gum / control       1.53 0.538 Inf    1   1.220  0.2230
 Garcia89     gum / control       2.95 1.610 Inf    1   1.980  0.0480
 Garvey00     gum / control       2.49 0.706 Inf    1   3.210  0.0010
 Gross95      gum / control       2.62 1.260 Inf    1   2.010  0.0440
 Hall85       gum / control       2.03 0.992 Inf    1   1.460  0.1450
 Hall87       gum / control       2.82 1.080 Inf    1   2.700  0.0070
 Hall96       gum / control       0.87 0.280 Inf    1  -0.440  0.6630
 Hjalmarson84 gum / control       2.17 0.752 Inf    1   2.240  0.0250
 Huber88      gum / control       6.00 2.600 Inf    1   4.140  <.0001
 Jarvis82     gum / control       3.33 1.510 Inf    1   2.660  0.0080
 Jensen91     gum / control       1.43 0.389 Inf    1   1.330  0.1840
 Killen84     gum / control       1.33 0.773 Inf    1   0.500  0.6200
 Killen90     gum / control       1.23 0.178 Inf    1   1.460  0.1430
 Malcolm80    gum / control       3.52 2.550 Inf    1   1.740  0.0820
 McGovern92   gum / control       1.17 0.301 Inf    1   0.600  0.5480
 Nakamura90   gum / control       3.82 2.340 Inf    1   2.190  0.0290
 Niaura94     gum / control       1.34 0.926 Inf    1   0.430  0.6670
 Pirie92      gum / control       1.84 0.400 Inf    1   2.820  0.0050
 Puska79      gum / control       1.46 0.472 Inf    1   1.170  0.2410
 Schneider85  gum / control       1.71 1.040 Inf    1   0.890  0.3740
 Tonnesen88   gum / control       2.12 0.897 Inf    1   1.780  0.0740
 Villa99      gum / control       1.76 1.050 Inf    1   0.950  0.3420
 Zelman92     gum / control       1.46 0.570 Inf    1   0.970  0.3320

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

We can estimate the *average* odds ratio across studies (using the delta method).

```
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  1.69  2.59   9.38 Inf 6.43e-21
```

Note that the following will also "average" over study, but the averaging is done on the log odds scale, so the result is not actually the average odds ratio but instead the average logarithm of the odds ratio to which we have applied the exponential function, for which the interpretation is not clear.

```
pairs(emmeans(m, ~ treatment, type = "response"), infer = TRUE, reverse = TRUE)
```

```
 contrast      odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 gum / control       1.93 0.169 Inf      1.62      2.29    1   7.490  <.0001

Results are averaged over the levels of: study
```

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

To estimate the average odds ratio with the **emmeans** package we need to usse `regrid`.

```
tmp <- pairs(emmeans(m, ~ treatment|study, type = "response"), reverse = TRUE)
emmeans(regrid(tmp), ~1)
```

```
 1       odds.ratio    SE  df asymp.LCL asymp.UCL
 overall       2.14 0.228 Inf      1.69      2.59

Results are averaged over the levels of: study
Confidence level used: 0.95
```

This does the same thing as using `tf = function(x) mean(exp(x))` with the `contrast` function.

These inferences are probably fine because while there can be a relatively large number of parameters, there are many observations per study as well. The data are *aggregated*. But we should note that when including the interaction the average odds ratio is *just for those studies*.

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).

```
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
```

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

```
                 Estimate Std. Error  z value Pr(>|z|)
(Intercept)          3.55   2.19e+00  1.62079 1.05e-01
x                    2.03   1.26e-01 16.03149 7.70e-58
factor(subject)2   -26.39   1.25e+04 -0.00212 9.98e-01
factor(subject)3   -21.41   1.25e+04 -0.00172 9.99e-01
factor(subject)4   -24.30   1.13e+04 -0.00214 9.98e-01
factor(subject)5    -4.57   2.63e+00 -1.73503 8.27e-02
```

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

```
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)         0.506     0.5685   0.890  3.74e-01
x                   1.071     0.0492  21.740 8.60e-105
factor(subject)2   -4.015     1.0005  -4.013  5.99e-05
factor(subject)3   -0.908     0.7898  -1.149  2.50e-01
factor(subject)4    0.569     0.9233   0.616  5.38e-01
factor(subject)5   -1.549     0.8675  -1.786  7.41e-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 only 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.

```
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.

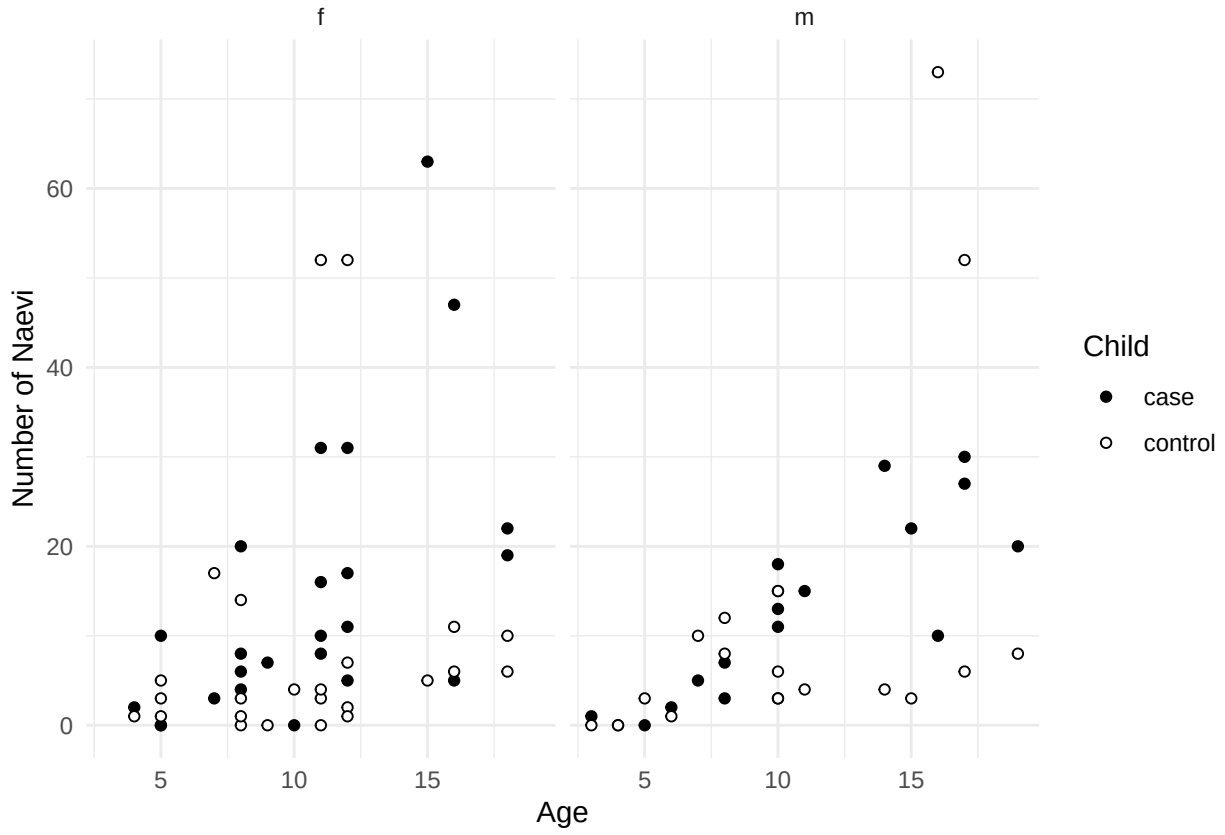
```r
library(dplyr)
library(tidyr)
library(trtools) # for the naevi data
naevi$set <- factor(1:nrow(naevi)) # data frame naevi is from trtools package
head(naevi)
```

```
  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
```

```r
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
```

```r
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)     1.849     0.3027    6.11 1.01e-09
childcontrol   -0.313     0.0643   -4.87 1.12e-06
set2           -1.299     0.6513   -1.99 4.61e-02
set3            1.003     0.3525    2.85 4.42e-03
set4           -1.299     0.6513   -1.99 4.61e-02
set5            0.492     0.3827    1.29 1.98e-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
     1.37  1.21  1.55
```

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.

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

```
            Estimate Std. Error z value Pr(>|z|)
(Intercept)    0.313     0.0643    4.87 1.12e-06
```

Strange model. But look at this.

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

```
            estimate lower upper
(Intercept)     1.37  1.21  1.55
```

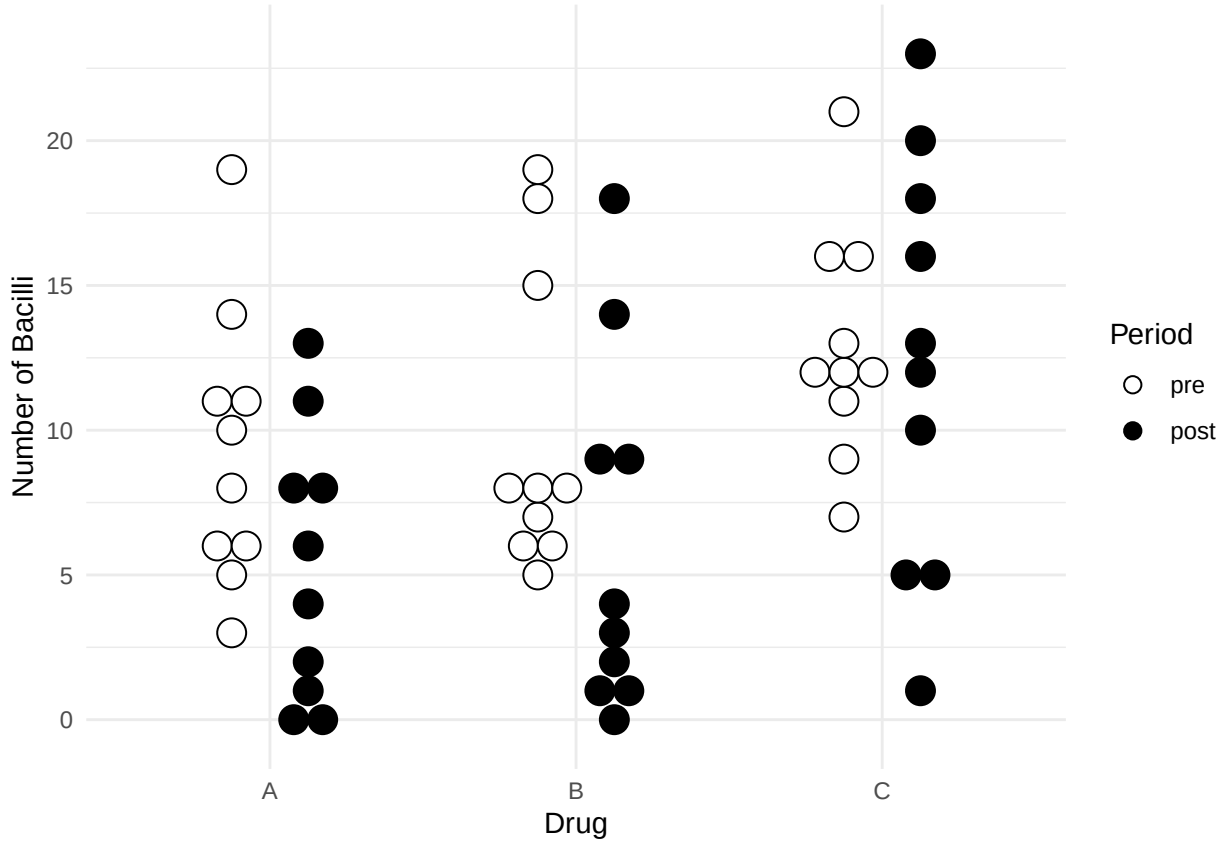
There's maybe no real advantage to using conditional maximum likelihood here via logistic regression except that in problems with *many* levels it is computationally faster.

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.

```
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
```

```
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)       2.3822      0.250  9.5116 1.88e-21
factor(id)2      -1.0667      0.483 -2.2090 2.72e-02
factor(id)3       0.3155      0.318  0.9927 3.21e-01
factor(id)4      -0.7538      0.429 -1.7581 7.87e-02
factor(id)5      -0.7790      0.438 -1.7801 7.51e-02
factor(id)6       0.0837      0.332  0.2523 8.01e-01
factor(id)7      -0.8873      0.449 -1.9758 4.82e-02
factor(id)8      -0.5559      0.408 -1.3622 1.73e-01
factor(id)9       0.3155      0.318  0.9927 3.21e-01
factor(id)10      0.2578      0.323  0.7984 4.25e-01
factor(id)11     -0.6612      0.421 -1.5689 1.17e-01
factor(id)12     -0.4128      0.371 -1.1114 2.66e-01
factor(id)13      0.5680      0.304  1.8710 6.13e-02
factor(id)14      0.7251      0.307  2.3613 1.82e-02
factor(id)15      0.7324      0.299  2.4516 1.42e-02
factor(id)16     -0.5306      0.399 -1.3315 1.83e-01
factor(id)17     -0.3735      0.387 -0.9649 3.35e-01
factor(id)18      0.2804      0.320  0.8769 3.81e-01
factor(id)19      0.3023      0.320  0.9451 3.45e-01
factor(id)20      0.6381      0.311  2.0506 4.03e-02
factor(id)21     -0.2186      0.354 -0.6175 5.37e-01
```

```
factor(id)22      -0.8873      0.449 -1.9758 4.82e-02
factor(id)23      -0.0252      0.354 -0.0713 9.43e-01
factor(id)24       0.2804      0.320  0.8769 3.81e-01
factor(id)25       0.1112      0.334  0.3332 7.39e-01
factor(id)26      -1.0667      0.483 -2.2090 2.72e-02
factor(id)27      -0.9724      0.438 -2.2220 2.63e-02
factor(id)28      -1.7346      0.626 -2.7699 5.61e-03
factor(id)29       0.3196      0.329  0.9717 3.31e-01
factor(id)30       0.4139      0.313  1.3238 1.86e-01
periodpost        -0.5623      0.172 -3.2672 1.09e-03
drugB:periodpost   0.0680      0.237  0.2874 7.74e-01
drugC:periodpost   0.5147      0.213  2.4128 1.58e-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     0.799    1  -3.270  0.0010

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  -3.040  0.0020

drug = C:
 contrast   ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 post / pre 0.953 0.1200 Inf     0.745     1.221    1  -0.380  0.7050

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     0.799    1  -3.270  0.0010
 B    post / pre 0.610 0.0991 Inf     0.444     0.839    1  -3.040  0.0020
 C    post / pre 0.953 0.1200 Inf     0.745     1.221    1  -0.380  0.7050

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  0.7740
 (post / pre A) / (post / pre C) 0.598 0.128 Inf    1  -2.413  0.0160
 (post / pre B) / (post / pre C) 0.640 0.132 Inf    1  -2.172  0.0300

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  0.7740
 (A post / pre) / (C post / pre) 0.598 0.128 Inf    1  -2.413  0.0160
 (B post / pre) / (C post / pre) 0.640 0.132 Inf    1  -2.172  0.0300

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)   -0.562      0.172  -3.267  0.00109
drugB          0.068      0.237   0.287  0.77383
drugC          0.515      0.213   2.413  0.01583
```

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    0.570 0.407 0.799
B    0.610 0.444 0.839
C    0.953 0.745 1.221
```

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 explanatory variables that are *crossed* with the fixed effect.
2. Possibly poor/invalid inferences in nonlinear or generalized linear models.
3. More computationally intensive (although there are solutions).