Case Study #1

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0: Abstract

1: Introduction

We study how DDE (Dichlorodiphenyldichloroethylene) and PCBs (Polychlorinated Biphenyls) relate to risk of pre-mature delivery, which is associated with high risk of morbidity and mortality for the child. We use a sample of 2,380 women and children provided by Longnecker, et al. (2001) and initially provided by the National Collaborative Perinatal Project. DDE and PCBs have been used to treat crops, in order to limit their predation, and, as a result, are present in the environment and expose humans. These chemicals build up in fat in human tissues, and can have an impact on human health, including risk of pre-mature delivery.

The data include various demographic variables (race, age, and socioeconomic index), smoking status, concentration doses of DDE and PCBs due to exposure, and cholesterol and triglycerides levels. We define pre-term pregnancy with a cut-off of 36 weeks or fewer, which tends to be the region around which there begins higher risk of morbidity and mortality for the child.

2: Materials & Methods

Since linear model assumptions (namely, normality of residuals) were not satisfied in this dataset, we instead chose to implement a logistic model. To satisfy the assumptions needed for logistic models, we modified our data. The model predicts whether an observation is pre-term (<=36 weeks) or around normal (>36 weeks), so the dependent variable, gestational age, is changed to be binary. Our observations are assumed to be independent from one another, and we use Bayesian Model Averaging (described later) to get rid of multicollinearity. We finally check that each predictor has a linear relationship with the logit function (this will be done later!! TODO).

We first used Bayesian Model Averaging for generalized linear models to explore variable importance. Key variables with significant probabilities of inclusion were triglycerides, race, and DDE, and the noninclusion of other variables like maternal age and smoking status were corroborated by running a full naive GLM model. From our EDA analysis showing differences in gestational ages but similar racial trends across centers, we decided to add a random-effect intercept to the logistic model based on centers. Because the goal of this analysis was to assess effects of DDE and PCB on gestational age, we also included the average of the PCB variates as a covariate in our model. Our final model that we implemented was a logistic model with a random-effect intercept:

MODEL HERE

We evaluate model fit using BIC and AIC.

- 3: Results
- 3.1: Exploratory Data Analysis
- 3.2: Main Results
- 3.3: Sensitivity Analysis

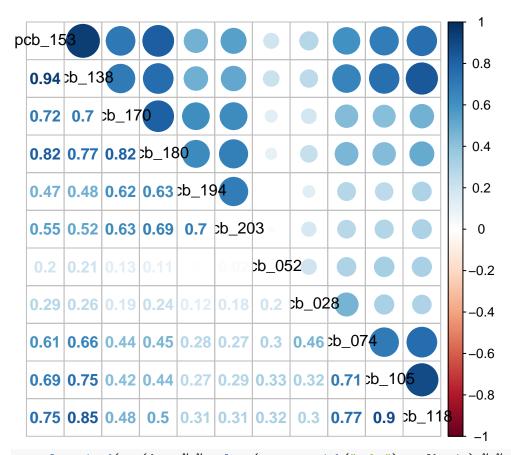
4: Discussion

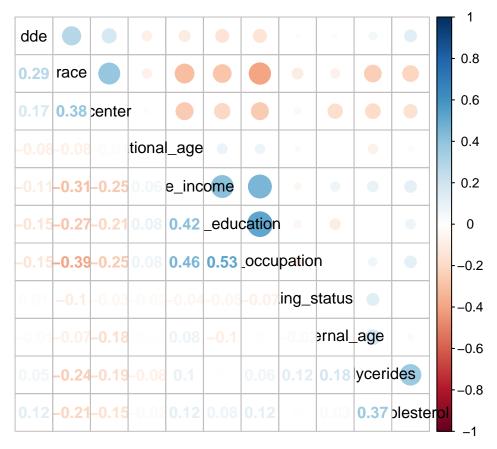
Our results find that the effect for average PCB is not significant, meaning there is no evidence of an association between PCB exposure and risk of pre-term delivery. However, higher DDE exposure is associated with higher risk of pre-term delivery. A one unit increase in DDE is associated with decreasing the expected odds of having a full-term pregnancy by approximately a factor of 2 (0.72 decrease in the expected log odds), holding everything else fixed. In addition, we find several other interesting pieces of insight. Higher triglycerides are associated with a higher risk of preterm delivery, as are being a non-white mother.

TODO: advantages/disadvantages

These results are consistent with some of the trends we saw in our exploratory plots and with current literature surrounding pre-term deliveries. Future directions for analysis include (1) sensitivity analysis on the number of weeks that defines a pre-term birth, (2) multiple category outcome model using Bayesian GLMM, and (3) accounting for natural ordering in outcome via a proportional odds model.

5: Appendix

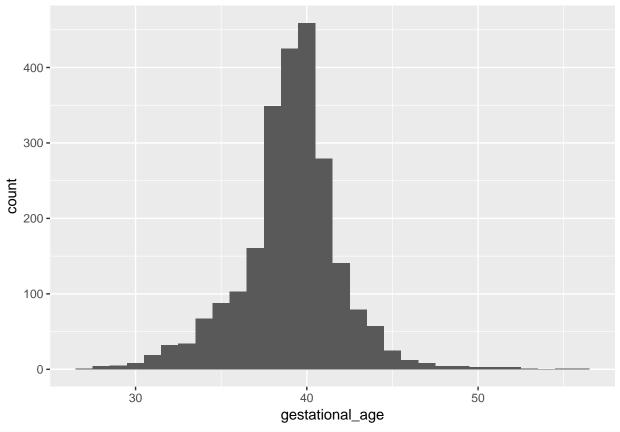




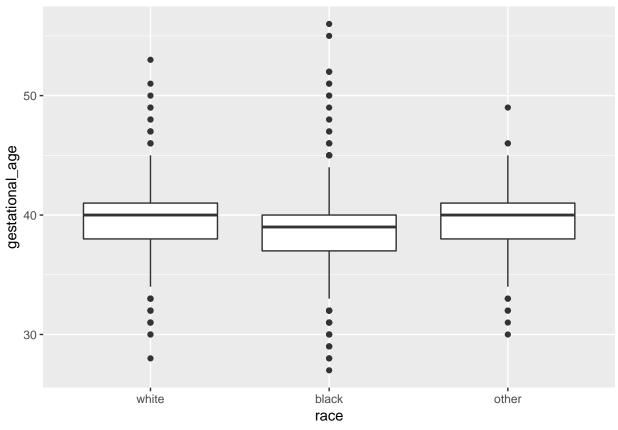
We observe that PCB variations are positively correlated with one another, and that certain groups of variables are also correlated (education, occupation, and income; triglycerides and cholesterol; race and center; race and DDE; maternal age and triglycerides, etc.).

```
# histogram of gestational age
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(gestational_age)) + geom_histogram()
```

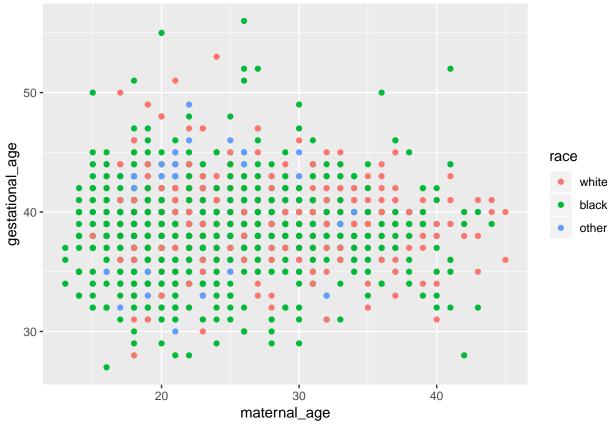
`stat_bin()` using `bins = 30`. Pick better value with `binwidth`.



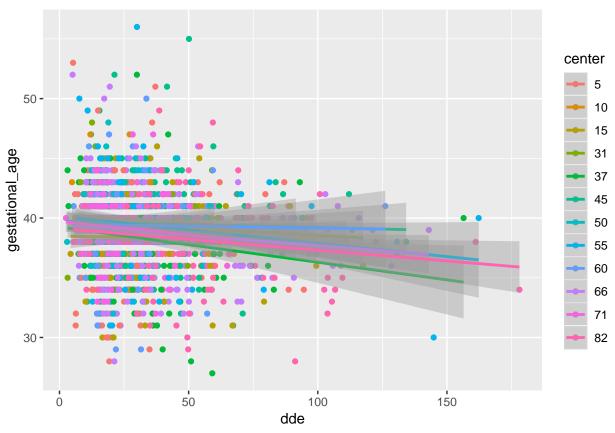
```
# boxplot of outcome by race
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=race, y=gestational_age)) + geom_boxplot()
```



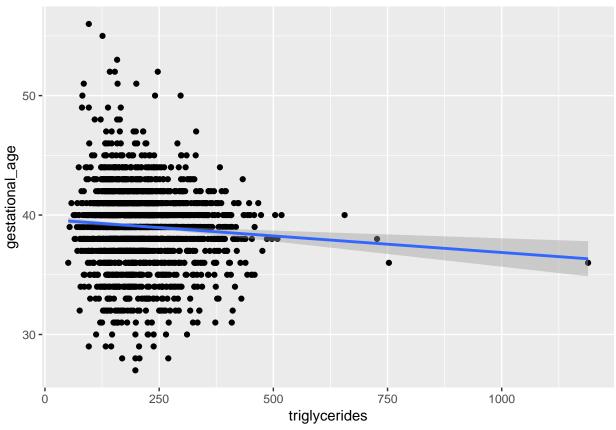
```
# maternal age by outcome
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=maternal_age, y=gestational_age, color=race)) + geom_point()
```



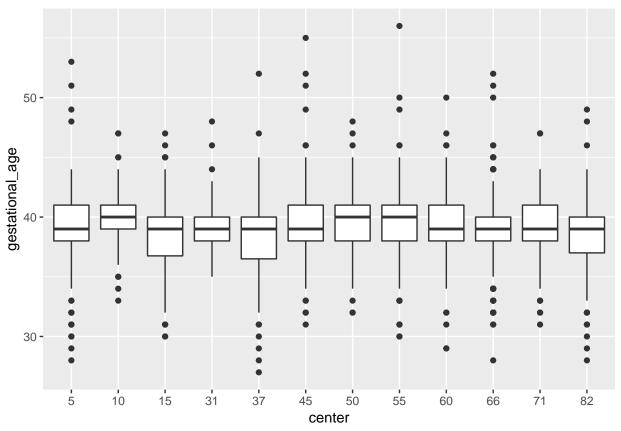
```
# dde by outcome & colored by centers
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=dde, y=gestational_age, color=center)) + geom_point() +
  geom_smooth(method="lm", formula=y ~ x)
```



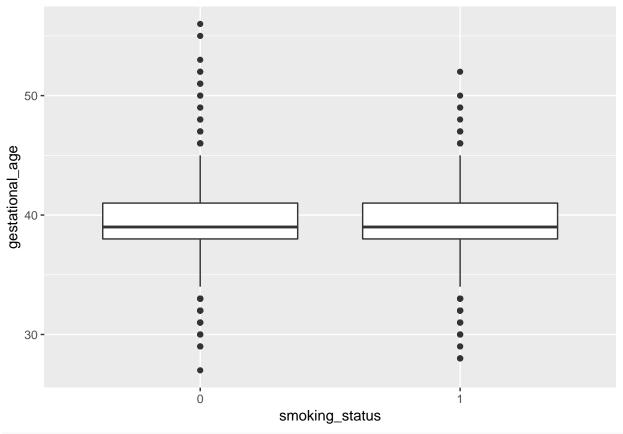
```
# triglycerides by outcome
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=triglycerides, y=gestational_age)) +geom_point() +
  geom_smooth(method="lm", formula=y ~ x)
```



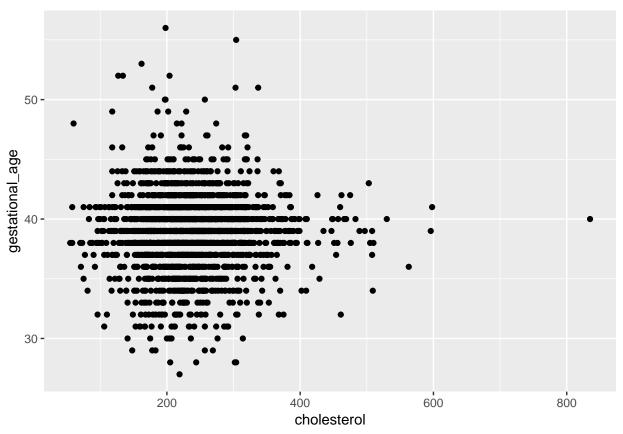
```
# boxplot of outcome by center
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=center, y=gestational_age)) + geom_boxplot()
```



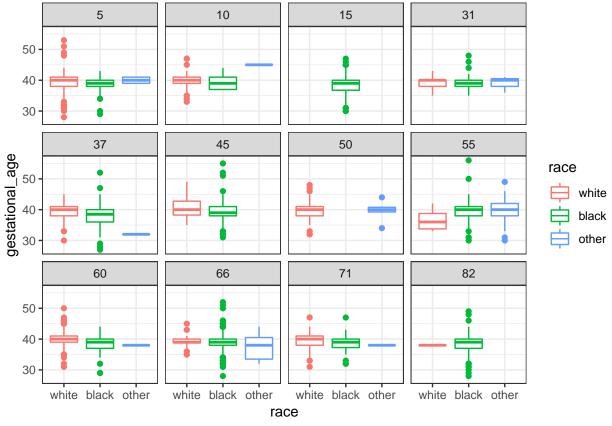
```
# boxplot of outcome by smoking indicator
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=smoking_status, y=gestational_age)) + geom_boxplot()
```



```
# cholesteral by outcome
data %>%
  filter(gestational_age < 60) %>%
  ggplot(., aes(x=cholesterol, y=gestational_age)) + geom_point()
```



```
# boxplot of race by outcome by center
data %>%
  filter(gestational_age < 60) %>%
  ggplot(aes(x=race, y=gestational_age, color=race)) +
  geom_boxplot() +
  facet_wrap(.~center) +
  theme_bw()
```

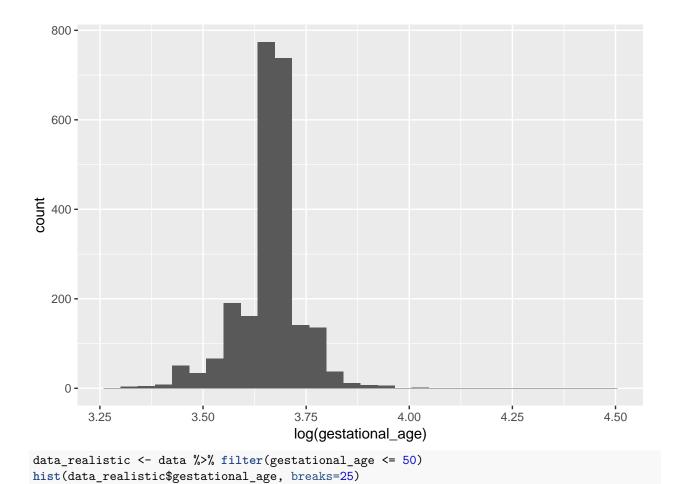


```
# number of races per center
data %>%
  group_by(race, center) %>%
  summarise(n_race=n())
```

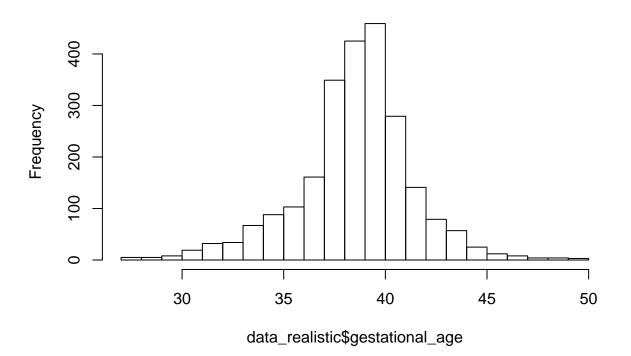
```
## # A tibble: 31 x 3
## # Groups:
               race [?]
##
      race center n_race
##
      <fct> <fct>
                     <int>
##
    1 white 5
                       431
##
    2 white 10
                       122
    3 white 31
##
                        21
    4 white 37
                        46
##
##
    5 white 45
                        30
    6 white 50
                       141
##
    7 white 55
                         8
    8 white 60
                        86
##
## 9 white 66
                        28
## 10 white 71
## # ... with 21 more rows
```

```
# log transform of outcoome
data %>%
    ggplot(aes(log(gestational_age))) + geom_histogram()
```

`stat_bin()` using `bins = 30`. Pick better value with `binwidth`.

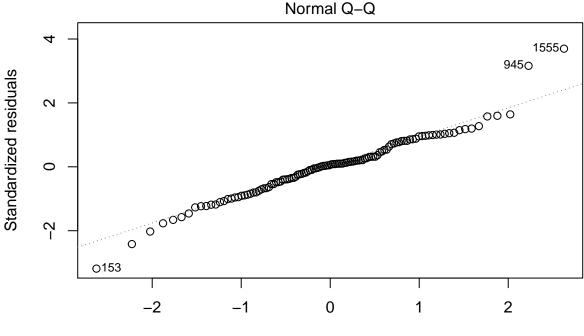


Histogram of data_realistic\$gestational_age

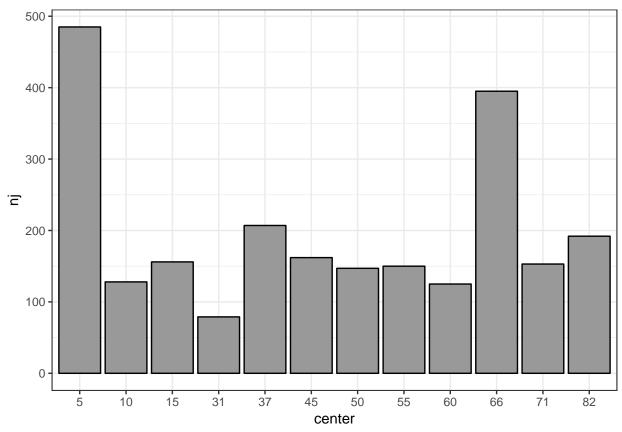


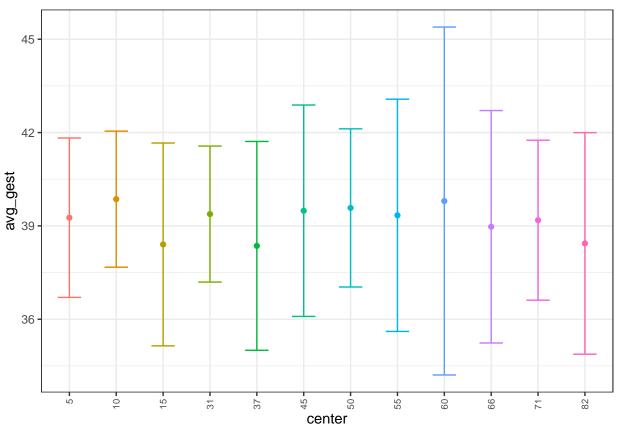
```
lm_model <- lm(gestational_age ~ ., data_realistic)
plot(lm_model, which=2)</pre>
```

Warning: not plotting observations with leverage one:
103, 104

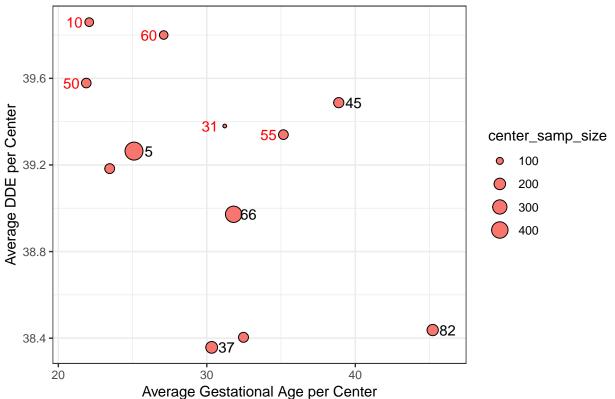


Theoretical Quantiles Im(gestational_age ~ .)

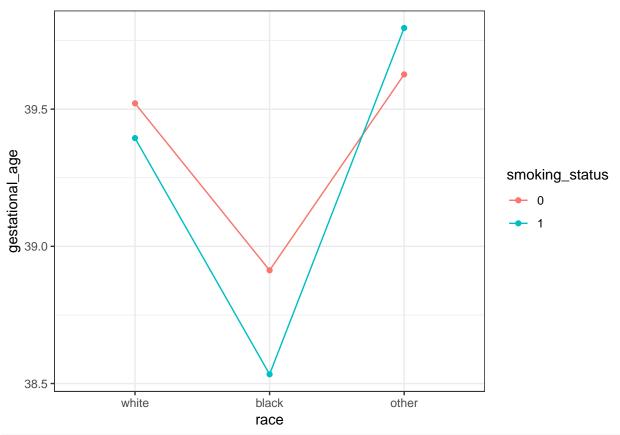


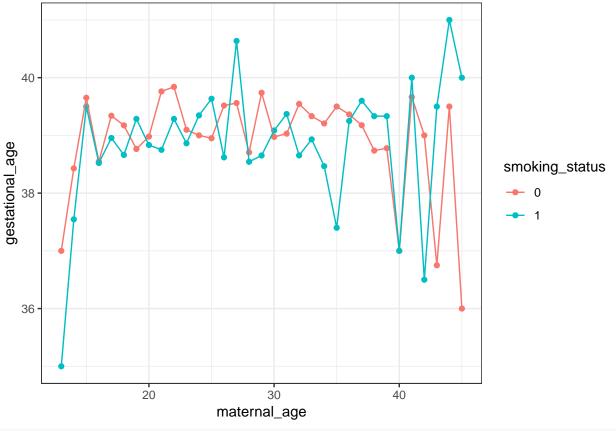


Average DDE versus Average Gestational Age per Center



```
# relationship between race and smoking status
# no constant (or parallel), so indicates interactive effect
data %>% ggplot() +
   aes(x=race, color=smoking_status, group=smoking_status, y=gestational_age) +
   stat_summary(fun.y=mean, geom="point") +
   stat_summary(fun.y=mean, geom="line") +
   theme_bw()
```





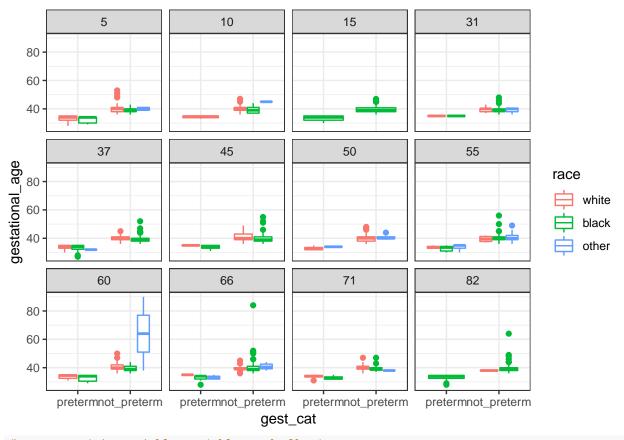
```
# relationship between race and age
# no constant (or parallel), so indicates interactive effect
data %>% ggplot() +
   aes(x=maternal_age, color=race, group=race, y=gestational_age) +
   stat_summary(fun.y=mean, geom="point") +
   stat_summary(fun.y=mean, geom="line") +
   theme_bw()
```

```
45.0
destational_age
                                                                                    race
                                                                                     white
                                                                                         black
                                                                                         other
   37.5
                        20
                                             30
                                                                  40
                                     maternal_age
# transform gestational age to multi-class variable
# ncbi.nlm.nih.gov/books/NBK279571/ (cutoffs for pre-term pregnancies)
data <- data %>%
  rowwise() %>%
                       pcb 203),
```

Warning: Grouping rowwise data frame strips rowwise nature

```
## # A tibble: 31 x 3
               center [?]
## # Groups:
##
      center race n_cat
##
      <fct> <fct> <int>
   1 5
##
             white
                     431
##
   2 5
             black
                      50
   3 5
             other
                       4
##
##
   4 10
             white
                     122
##
  5 10
             black
                       5
##
   6 10
             other
                       1
   7 15
##
             black
                     156
## 8 31
             white
                      21
```

```
## 9 31
              black
                        39
## 10 31
              other
                        19
## # ... with 21 more rows
data %>% ggplot(aes(x=gest_cat, y=gestational_age)) + geom_boxplot() +
  facet_wrap(.~center) +
  theme_bw()
                5
                                      10
                                                            15
                                                                                   31
   80
   60
   40
                37
                                      45
                                                            50
                                                                                   55
gestational_age
                60
                                      66
                                                            71
                                                                                   82
   80
   60
   40
                               preterm not_preterm
                                                     preterm not_preterm
         preterm not_preterm
                                                                            preterm not_preterm
                                              gest_cat
data %>% ggplot(aes(x=gest_cat, y=gestational_age, color=race)) + geom_boxplot() +
  facet_wrap(.~center) +
  theme_bw()
```



```
##
## bic.glm.data.frame(x = data_realistic %% select(-gestational_age),
                                                                             y = data_realistic$gestation
##
##
##
    Posterior probabilities(%):
##
              dde triglycerides
                                            race
                                                   maternal_age smoking_status
##
             86.9
                            92.3
                                             0.0
                                                            0.0
                                                                            2.7
      cholesterol
##
                          center
                                             pcb
##
             31.6
                           100.0
                                            46.3
##
   Coefficient posterior expected values:
```

```
##
       (Intercept)
                                dde
                                       triglycerides
                                                            raceblack
##
         2.9678380
                         -0.0090611
                                          -0.0024392
                                                            0.0000000
                     maternal age smoking status1
                                                          cholesterol
##
         raceother
        0.0000000
                          0.0000000
##
                                          -0.0054254
                                                            0.0007984
##
         center10
                           center15
                                            center31
                                                             center37
                        -1.1510422
                                           0.3574178
                                                           -1.0916218
##
        1.0481124
##
         center45
                          center50
                                           center55
                                                             center60
                                                           -0.4842138
##
        -0.4843342
                          0.0724230
                                          -0.7918955
##
          center66
                          center71
                                            center82
                                                                  pcb
        -0.6084895
                                          -0.8150424
                                                           -0.0473818
##
                         -0.1297061
# model w/ random intercept for centers
m1 <- lmer(gestational_age ~ dde + triglycerides + smoking_status*maternal_age + race + min_pcb +
           max pcb + avg pcb + (1|center), data=data, REML=FALSE)
summary(m1)
# model w/ random slope for race
m2 <- lmer(gestational_age ~ dde + triglycerides + smoking_status*maternal_age + min_pcb + max_pcb +
           avg_pcb + (0 + race|center), data=data, REML=FALSE)
summary(m2)
# model w/ random slope for race and random intercept for centers
m3 <- lmer(gestational_age ~ dde + triglycerides + smoking_status*maternal_age + min_pcb + max_pcb +
           avg_pcb + (1 + race|center), data=data, REML=FALSE,
           control=lmerControl(optimizer="Nelder_Mead"))
summary(m3) # might be overfitting
# simple linear regression model
m4 <- lm(gestational_age ~ dde + triglycerides + smoking_status*maternal_age + race + min_pcb +
         max_pcb + avg_pcb + cholesterol, data=data)
summary(m4)
# simple linear regression model using BMA variable selection
m5 <- lm(gestational_age ~ triglycerides + race + center + dde + max_pcb + min_pcb + avg_pcb, data=data
summary(m5)
# model fits
BIC(m1); BIC(m2); BIC(m3); BIC(m4); BIC(m5)
# residual plots
plot(m1); plot(m2); plot(m3); plot(m4); plot(m5)
# model w/ random intercept for centers
m1 <- glmer(gest_cat ~ I(triglycerides/100) + I(dde/100) + avg_pcb + race + (1|center), family=binomial,
            control=glmerControl(optimizer="bobyqa", optCtrl=list(maxfun=2e5)), data=data)
summary(m1)
## Generalized linear mixed model fit by maximum likelihood (Laplace
    Approximation) [glmerMod]
## Family: binomial (logit)
## Formula: gest_cat ~ I(triglycerides/100) + I(dde/100) + avg_pcb + race +
##
       (1 | center)
##
      Data: data
## Control:
## glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e+05))
```

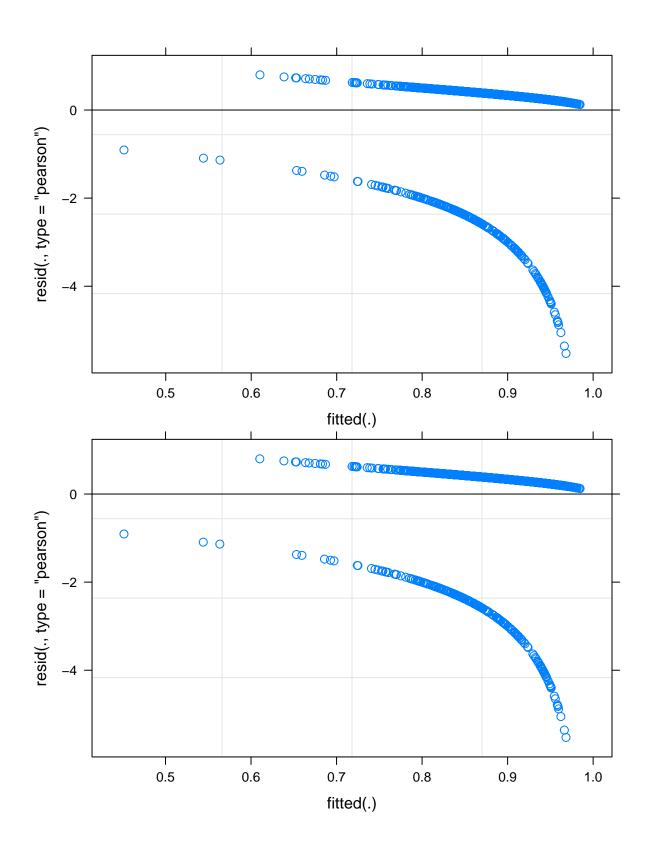
```
##
##
        ATC
                BIC
                       logLik deviance df.resid
                      -788.5
##
     1590.9
             1631.3
                               1576.9
##
## Scaled residuals:
               1Q Median
##
      Min
                                3Q
                                      Max
## -5.2415 0.2370 0.3077 0.3912 0.7713
##
## Random effects:
## Groups Name
                       Variance Std.Dev.
## center (Intercept) 0.2037 0.4514
## Number of obs: 2379, groups: center, 12
## Fixed effects:
##
                        Estimate Std. Error z value Pr(>|z|)
## (Intercept)
                         3.2405
                                    0.3009 10.768
                                                     <2e-16 ***
## I(triglycerides/100)
                        -0.1670
                                    0.0857 -1.948
                                                     0.0514 .
## I(dde/100)
                         -0.7191
                                    0.3226 - 2.229
                                                     0.0258 *
## avg_pcb
                        -0.5232
                                    0.4952 -1.057
                                                     0.2907
## raceblack
                         -0.4776
                                    0.2329 - 2.051
                                                     0.0403 *
## raceother
                        -0.8142
                                    0.3527 -2.309
                                                     0.0210 *
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
## Correlation of Fixed Effects:
               (Intr) I(t/100) I(d/100) avg_pc rcblck
## I(trgl/100) -0.642
## I(dde/100) -0.109 -0.086
              -0.188 -0.131
## avg_pcb
                              -0.311
## raceblack
                                        -0.128
              -0.465 0.238
                              -0.141
              -0.307 0.049
## raceother
                              -0.054
                                        0.072 0.414
# model w/ random slope for race
m2 <- glmer(gest_cat ~ I(triglycerides/100) + I(dde/100) + avg_pcb + race + (0 + race|center),
            family=binomial, control=glmerControl(optimizer="bobyqa", optCtrl=list(maxfun=2e5)),
            data=data)
summary(m2)
## Generalized linear mixed model fit by maximum likelihood (Laplace
     Approximation) [glmerMod]
## Family: binomial (logit)
## Formula: gest_cat ~ I(triglycerides/100) + I(dde/100) + avg_pcb + race +
       (0 + race | center)
##
##
     Data: data
## Control:
  glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e+05))
##
##
##
                       logLik deviance df.resid
        ATC
                BIC
##
     1596.2
             1665.5
                       -786.1
                               1572.2
                                           2367
##
## Scaled residuals:
               1Q Median
      Min
                                3Q
                                      Max
## -5.5263 0.2302 0.3102 0.3939 0.7992
##
## Random effects:
```

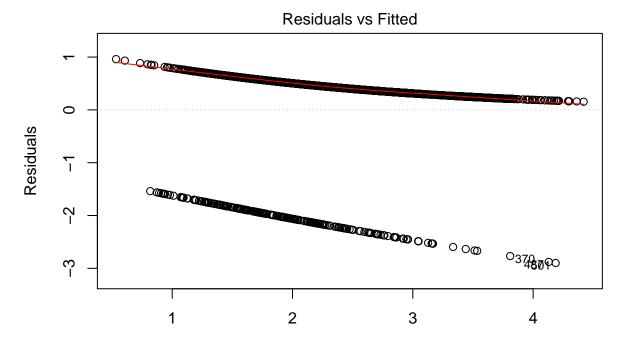
```
## Groups Name
                    Variance Std.Dev. Corr
##
   center racewhite 0.4123
                             0.6421
                             0.3186
##
          raceblack 0.1015
                                      1.00
          raceother 2.7310 1.6526 0.65 0.71
##
## Number of obs: 2379, groups: center, 12
##
## Fixed effects:
                       Estimate Std. Error z value Pr(>|z|)
##
## (Intercept)
                        3.20535
                                   0.33783
                                             9.488
                                                     <2e-16 ***
## I(triglycerides/100) -0.17257
                                   0.08554 -2.017
                                                     0.0437 *
## I(dde/100)
                       -0.73408
                                   0.32215 -2.279
                                                     0.0227 *
## avg_pcb
                       -0.46293
                                   0.49803 -0.930
                                                     0.3526
## raceblack
                       -0.52115
                                   0.25714 -2.027
                                                     0.0427 *
                       -0.63470
                                   0.78647 -0.807
                                                     0.4196
## raceother
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
               (Intr) I(t/100) I(d/100) avg_pc rcblck
## I(trgl/100) -0.580
## I(dde/100) -0.117 -0.078
## avg pcb
              -0.137 -0.136
                              -0.317
## raceblack
             -0.638 0.222
                              -0.113
                                       -0.144
## raceother
              -0.046 0.035
                              -0.019
                                        0.032 0.013
# model w/ random slope for race and random intercept for centers
m3 <- glmer(gest_cat ~ I(triglycerides/100) + I(dde/100) + avg_pcb + race + (race|center),
            family=binomial, control=glmerControl(optimizer="bobyqa", optCtrl=list(maxfun=2e5)),
            data=data)
summary(m3)
## Generalized linear mixed model fit by maximum likelihood (Laplace
     Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: gest_cat ~ I(triglycerides/100) + I(dde/100) + avg_pcb + race +
##
       (race | center)
##
      Data: data
## Control:
  glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e+05))
##
        AIC
                BIC
                      logLik deviance df.resid
                      -786.1
##
     1596.2
             1665.5
                               1572.2
##
## Scaled residuals:
##
      Min
               1Q Median
                               30
## -5.5257 0.2302 0.3102 0.3940 0.7991
##
## Random effects:
                       Variance Std.Dev. Corr
## Groups Name
##
   center (Intercept) 0.4119 0.6418
          raceblack
                      0.1055
                               0.3248
                                        -1.00
                                         0.33 -0.27
##
                      1.7542
                               1.3245
          raceother
## Number of obs: 2379, groups: center, 12
## Fixed effects:
```

```
##
                       Estimate Std. Error z value Pr(>|z|)
                                             9.490
## (Intercept)
                        3.20534
                                   0.33776
                                                     <2e-16 ***
## I(triglycerides/100) -0.17257
                                   0.08554 - 2.017
                                                      0.0436 *
                       -0.73410
## I(dde/100)
                                   0.32214 -2.279
                                                     0.0227 *
## avg_pcb
                       -0.46286
                                   0.49803 -0.929
                                                     0.3527
## raceblack
                       -0.52128
                                   0.25710 -2.028
                                                     0.0426 *
## raceother
                       -0.63325
                                   0.78667 - 0.805
                                                     0.4208
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
               (Intr) I(t/100) I(d/100) avg_pc rcblck
##
## I(trgl/100) -0.580
## I(dde/100) -0.117 -0.078
              -0.137 -0.136
## avg_pcb
                              -0.317
## raceblack
               -0.638 0.222
                               -0.113
                                        -0.144
## raceother
              -0.046 0.035
                              -0.019
                                        0.032 0.013
# simple model
m4 <- glm(gest_cat ~ 1 + I(triglycerides/100) + I(dde/100) + center + avg_pcb + race, family=binomial,
          data=data)
summary (m4)
##
## glm(formula = gest_cat ~ 1 + I(triglycerides/100) + I(dde/100) +
##
       center + avg_pcb + race, family = binomial, data = data)
##
## Deviance Residuals:
##
      Min
                 10
                     Median
                                   3Q
                                          Max
## -2.8991
                     0.4249
            0.3055
                              0.5391
                                       0.9607
##
## Coefficients:
##
                       Estimate Std. Error z value Pr(>|z|)
## (Intercept)
                        3.48915
                                 0.30715 11.360 < 2e-16 ***
## I(triglycerides/100) -0.17109
                                   0.08697 -1.967 0.049159 *
## I(dde/100)
                       -0.66357
                                   0.32650 -2.032 0.042112 *
## center10
                        0.78060
                                   0.54220
                                             1.440 0.149957
## center15
                       -1.12647
                                   0.35216 -3.199 0.001380 **
## center31
                       1.29480
                                   0.76492
                                             1.693 0.090507 .
## center37
                                   0.29690 -3.657 0.000255 ***
                       -1.08576
## center45
                       -0.24803
                                   0.36195 -0.685 0.493183
## center50
                                            1.203 0.229039
                        0.59741
                                   0.49666
## center55
                       -0.61866
                                   0.39722 -1.557 0.119356
                                   0.36072 -1.582 0.113761
## center60
                       -0.57048
## center66
                       -0.46342
                                   0.30453
                                            -1.522 0.128076
## center71
                       -0.46932
                                   0.33171 -1.415 0.157109
## center82
                       -0.86720
                                   0.35056 -2.474 0.013369 *
                       -0.72921
                                   0.50486
                                            -1.444 0.148633
## avg_pcb
## raceblack
                       -0.23779
                                   0.23843 -0.997 0.318609
## raceother
                       -0.72770
                                   0.39654 -1.835 0.066489 .
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
## (Dispersion parameter for binomial family taken to be 1)
```

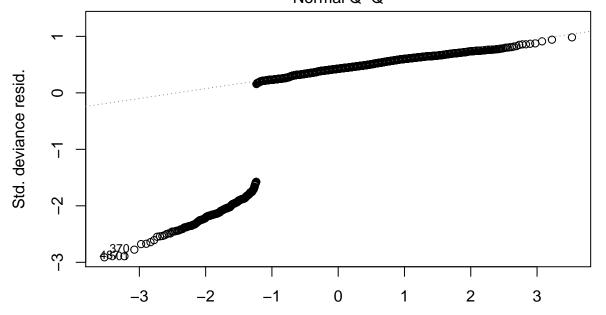
```
##
##
       Null deviance: 1633.2 on 2378 degrees of freedom
## Residual deviance: 1544.0 on 2362 degrees of freedom
## AIC: 1578
## Number of Fisher Scoring iterations: 6
# model fits
BIC(m1); BIC(m2); BIC(m3); BIC(m4)
## [1] 1631.35
## [1] 1665.54
## [1] 1665.54
## [1] 1676.19
# residual plots
plot(m1); plot(m2); plot(m3); plot(m4)
      1
             0
                     0
                          0
resid(., type = "pearson")
     -1
                             0 00000
                         0
                                        -2
     -3
     -5
                          0.7
                                             8.0
                                                                0.9
```

fitted(.)

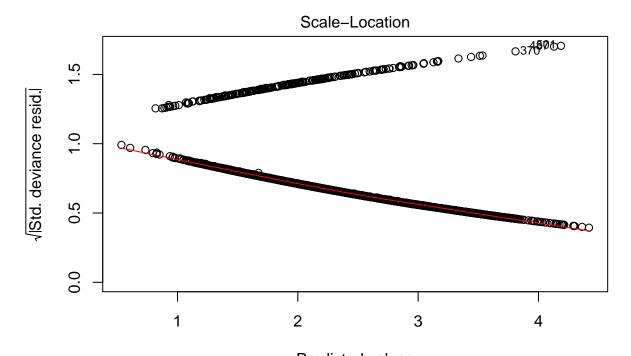




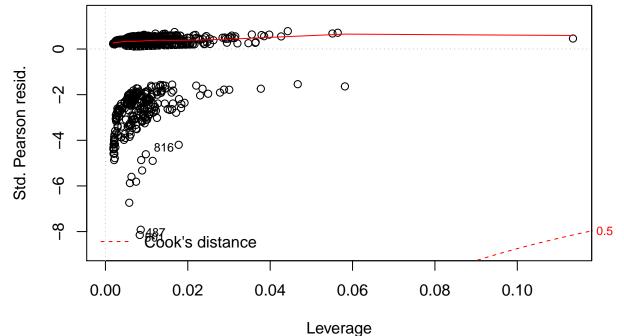
Predicted values $glm(gest_cat \sim 1 + I(triglycerides/100) + I(dde/100) + center + avg_pcb + r \dots \\ Normal Q-Q$



Theoretical Quantiles
glm(gest_cat ~ 1 + I(triglycerides/100) + I(dde/100) + center + avg_pcb + r ...



Predicted values
glm(gest_cat ~ 1 + I(triglycerides/100) + I(dde/100) + center + avg_pcb + r ...
Residuals vs Leverage



glm(gest_cat ~ 1 + I(triglycerides/100) + I(dde/100) + center + avg_pcb + r ...