Age, BMI, Number of Cigarettes per day and Cholesterol Levels

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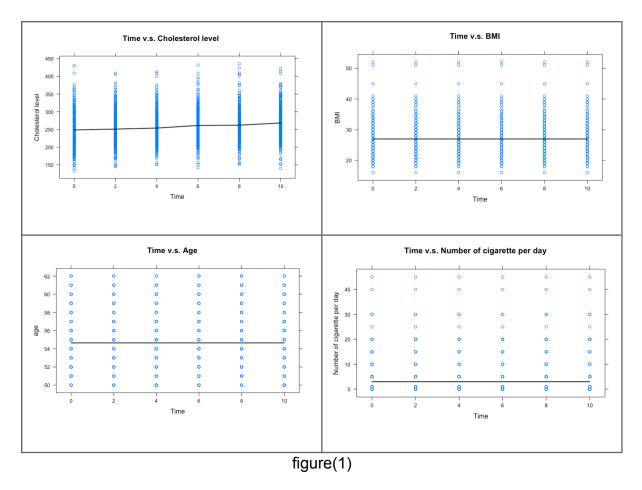
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1.0 Introduction

Cardiovascular disease is now found to be closely related to cholesterol levels. It is commonly believed that the higher the cholesterol level, the more likely one is to develop cardiovascular disease. During annual physical exams, people pay special attention to their cholesterol levels and trends. This article discusses the factors that influence the cholesterol level for females who are over 50 years old, in the city of Framingham, Massachusetts. As a direct outcome of this research, we would know how these factors affect cholesterol levels; thus, help people to adjust their lifestyle. By Lowering their cholesterol level, the public can reduce their chances of developing cardiovascular disease.

The Framingham Heart Study is a long-term, ongoing cardiovascular cohort study of residents of the city of Framingham since 1948. Little was known about cardiovascular before the data from this study, but now more than 3,000 peer-reviewed scientific papers on the Framingham Heart Study have been published. The data set herein was collected and combined by Framingham Heart Study every 2 years in a total duration of 10 year, which consists of anonymous information such as the baseline age (are all over 50 years old), baseline BMI (Body mass index), number of cigarette consumption per day and cholesterol level for every subject. We can see that the explanatory variables: baseline age and BMI are continuous, cigarette consumption per day is discrete. The outcome variable cholesterol level is continuous as well. I downloaded the data set from LEARN, a study platform of the University of Waterloo.

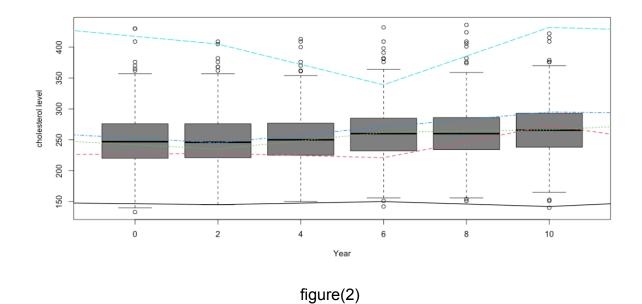


The figure above provides an overview of the pattern that the explanatory variables and response variable change over time.

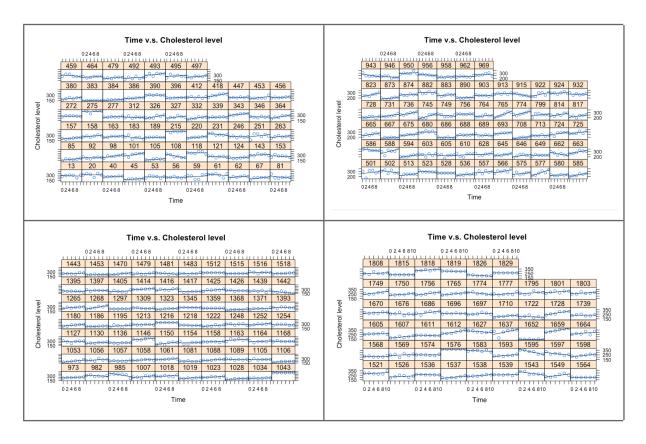
The report is organized as follows, section 2 discusses the statistical methods to be used in detail and the model-building process. Section 3 describes the main results from R-output with graphs. Section 4 is the conclusion and discussion.

2.0 Methods

Often the first step in analysis is the data quality assurance, it is essential to ensure proper and efficient data modeling. Firstly, I drew a boxplot for cholesterol level over time, and figured out there were some extremely large values.



It suggested that the data contained outliers, and we needed to drop them in the later modeling. Also, it demonstrated the likely model was in linear effect. Then I investigated variation among individuals, for the first half of the subjects in the data set.



figure(3)

From the graph, there was not too much variation in estimated intercepts and slopes, then I ruled out the linear mixed effects models. Also, the outcome variable here was continuous, not discrete, so I would choose a marginal linear model rather than a generalized estimating equation.

I fit the full model as the marginal linear model with unstructured correlation. From the summary of the regression result (Appendix), notice that the coefficient estimates of BMI, age, and age and BMI interaction is insignificant according to the Wald test (p-value=0.0.8833, 0.7410 and 0.8370 > 0.05), I was motivated to drop these terms to obtain a more accurate model.

Next I fit model2 with linear terms: number of cigarettes per day, 2-way interaction terms BMI:number of cigarettes per day, age:number of cigarettes per day and a 3-way interaction term BMI:age:number of cigarettes per day with unstructured correlation using maximum likelihood method. By comparing AIC and BIC values between these two models, model 2 has lower AIC and BIC values than model 1(Appendix). Considering a simpler model is more attractive, then I tried to omit the 3-way interaction term BMI:age:number of cigarettes per day, and fit model 3. The AIC and BIC values are pretty much similar for each other, therefore, I concluded that the marginal linear model 3 is preferred.

In the next step of choosing models, the correlation structure should be determined. I fit the model into independent correlation, exchangeable correlation, exponential correlation and gaussian correlation and then applied likelihood ratio test between these models and the unstructured correlation model respectively. Based on the

likelihood ratio test (as this is a nested model situation), all of their p-values < 0.05 (Appendix), thus I conclude that these correlations do not fit as well as unstructured.

As a result, the final model I would use is model 3 with an unstructured variance-covariance pattern. In terms of estimation, restricted maximum likelihood is more preferable, so I updated the MLE by substituting those parameters with their REML estimates.

3.0 Results

3.1 Coefficients Estimates

The following table shows the estimated value of each coefficient, and their standard error.

	Value <chr></chr>	Std.Error <chr></chr>	t-value <chr></chr>	p-value <chr></chr>
(Intercept)	256.54593	2.158829	118.83567	0.0000
numcigpd	7.44935	5.267136	1.41431	0.1574
numcigpd:age	-0.11017	0.093851	-1.17384	0.2406
numcigpd:BMI	-0.05649	0.045362	-1.24542	0.2131

figure(4)

3.11 Impact of number of cigarettes per day

Observe that smoking influences cholesterol in a negative aspect, if someone smokes one more cigarette a day, then her cholesterol level will rise by 7.44935mg/dL every 2 years, with 95% confidence interval [-2.87423, 17.77294].

- 3.12 Impact of age and number of cigarettes per day interaction term

 With the same number of cigarettes per day, the older the age, the lower the
 cholesterol level. For every one year old increases, the cholesterol level decreases

 0.11017 mg/dL every 2 years, with a 95% confidence interval [-0.29411, 0.07378].
- 3.13 Impact of BMI and number of cigarettes per day interaction term

 Similarly, for the same number of cigarettes smoked per day, the higher BMI, the
 lower the cholesterol level, with estimates 0.05649 mg/dL every 2 years, with a 95%
 confidence interval [-0.14658, 0.03359]. But compared to the mean cholesterol level,
 this does not influence it too much, not even 1 mg/dL.

3.2 Correlation coefficients

The restricted maximum likelihood estimation of pairwise correlation is in the following table.

	1	2	3	4	5
2	0.730				
3	0.659	0.722			
4	0.655	0.675	0.773		
5	0.645	0.653	0.754	0.820	
6	0.583	0.590	0.696	0.794	0.810

figure(5)

4.0 Discussion

This paper aims to investigate the effect of BMI, age and number of cigarettes per day on cholesterol levels. In order to accurately model the changes in the cholesterol over time, I eliminate the strange outliers in the data set, who experienced extremely higher cholesterol levels than others. By considering the type of variables and heterogeneity among individuals, I applied a marginal linear model to fit the data. I obtain the estimated values of the number of cigarettes per day effect, and the interaction effect of the number of cigarettes per day and age/BMI every two year on cholesterol level, respectively as 7.44935, -0.11017,-0.05649, which indicates a statistically significant impact of smoking on cholesterol levels. Smoking creates a bad impression of cholesterol, which leads to a greater susceptibility to cardiovascular disease.

However, this experiment has its limitations. Here, I dropped the information for a subject once an outlier is found. It could be dangerous if the data set with a small population. The dataset in this study only contains 382 subjects, which might cause bias for the estimation. Also, in the model, I found out that age is insignificant. The reason for this might be: baseline age is similar to each subject, and are all around 50-60 years old. Hence, with such a small age gap, the effect of age on cholesterol levels is not reflected. If we compare young people, such as adding a significant proportion of 20-year-old girls' information in the data set. Fit the model again, we might come to a different conclusion.

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Appendix

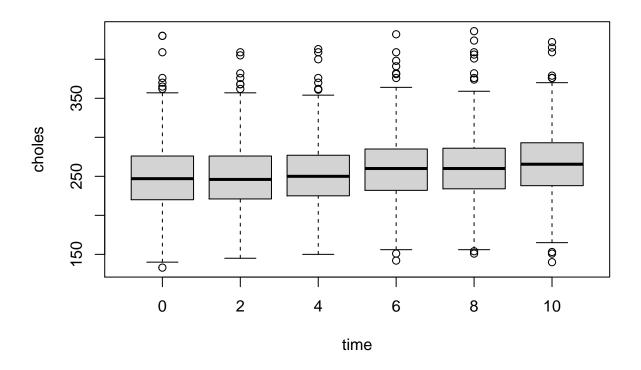
```
# read data file
fram <- read.table ("fram.dat", col.names = c("ID","time","age","BMI","numcigpd","choles"))</pre>
unique(fram[c("numcigpd")])
##
        numcigpd
## 1
              15
## 25
## 49
              20
## 73
               5
## 169
               1
## 385
              10
## 781
              25
              45
## 847
              40
## 859
## 1171
              30
unique(fram[c("age")])
##
        age
## 1
         53
## 7
         54
## 13
         55
## 19
         50
## 31
         52
## 61
         57
## 67
         59
## 73
         56
## 121
         51
## 151
         60
## 157
         58
## 415
         61
## 1489 62
```

Detect and eliminate outliers

```
# number of subjects in the data
n = length(unique(fram$ID))
aux = sort(tapply(fram$choles, fram$ID, median))

# identify the subjects benchmark the quantiles of medians
loc = c(1, round((1:4)*n/4))
newid = as.numeric(names(aux[loc]))

# boxplot of cholesterol level against time
Outvar = boxplot(choles~time, data=fram)$out
```



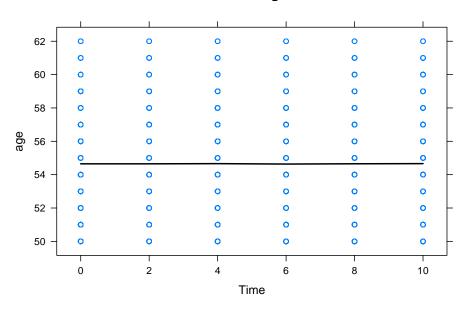
```
x = rep(0,51)
for (i in 1:51){
    x[i] = fram$ID[fram$choles==Outvar[i]]
}
unique(x)
```

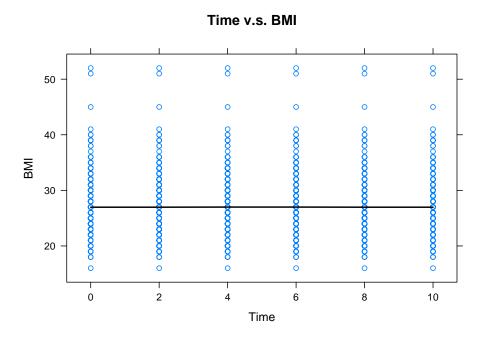
[1] 118 215 383 985 1043 588 1146 275 2171 2496 1163 1652 1659 1442 85

```
framnew = subset(fram,fram$ID!=c(118,215,383,985,1041,588,1146,275,
2171,2496,1163,1652,1659,1442,85))
```

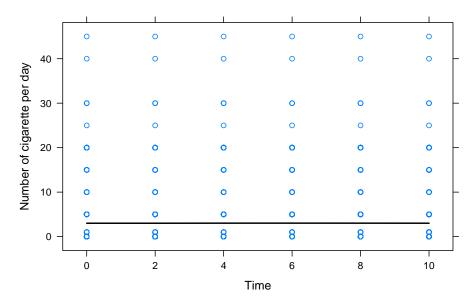
Group means over time

Time v.s. Age

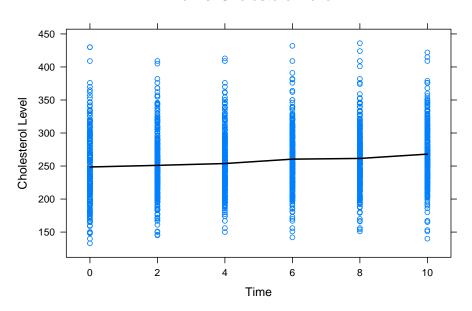




Time v.s. Number of cigarette per day

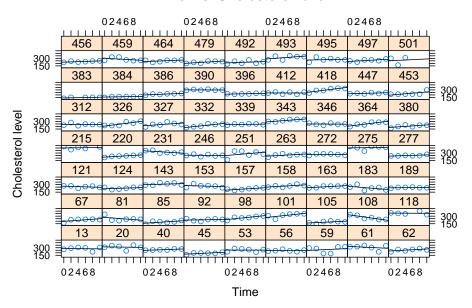


Time v.s. Cholesterol Level

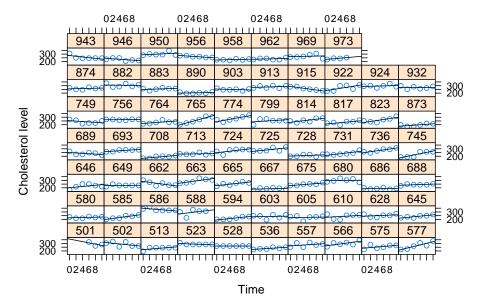


Variation among individuals

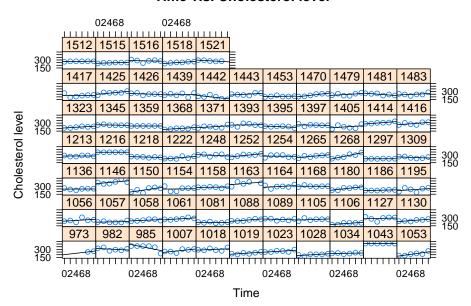
Time v.s. Cholesterol level



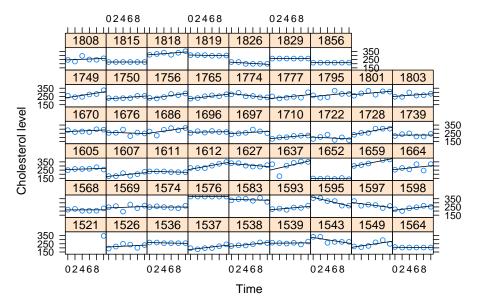
Time v.s. Cholesterol level



Time v.s. Cholesterol level



Time v.s. Cholesterol level



Fit marginal linear models

Generalized least squares fit by REML

1. fit the model as the marginal linear model with unstructured correlation:

```
library(nlme)
fit1u=gls(choles~BMI*age*numcigpd, data=framnew,correlation=corSymm(form=~1|ID))
summary(fit1u)
```

```
##
     Model: choles ~ BMI * age * numcigpd
##
     Data: framnew
##
          AIC
                   BIC
                           logLik
     21951.03 22088.56 -10951.52
##
##
## Correlation Structure: General
    Formula: ~1 | ID
##
    Parameter estimate(s):
##
    Correlation:
##
     1
                              5
## 2 0.733
## 3 0.663 0.725
## 4 0.659 0.680 0.777
## 5 0.649 0.657 0.757 0.823
## 6 0.588 0.595 0.700 0.797 0.812
##
## Coefficients:
##
                        Value Std.Error
                                            t-value p-value
## (Intercept)
                    199.17986 210.92693
                                          0.9443074
                                                     0.3451
## BMI
                      1.12017
                                 7.62848
                                                     0.8833
                                          0.1468407
## age
                      1.27106
                                 3.84498
                                         0.3305765
                                                     0.7410
## numcigpd
                    -20.05011 25.81401 -0.7767142 0.4374
```

```
## BMI:age
                    -0.02863
                               0.13909 -0.2058013 0.8370
## BMI:numcigpd
                     1.09640 0.98640 1.1115196 0.2665
## age:numcigpd
                     0.38886
                               0.47675 0.8156462 0.4148
## BMI:age:numcigpd -0.02099
                               0.01825 -1.1496590 0.2504
   Correlation:
##
                   (Intr) BMI
                                        nmcgpd BMI:ag BMI:nm ag:nmc
                                 age
                   -0.986
## BMI
## age
                   -0.998 0.984
                   -0.385 0.373 0.386
## numcigpd
## BMI:age
                    0.984 -0.998 -0.986 -0.374
## BMI:numcigpd
                    0.346 -0.346 -0.348 -0.977
                                                0.348
## age:numcigpd
                    0.380 -0.368 -0.382 -0.999 0.371 0.976
## BMI:age:numcigpd -0.341 0.341 0.344 0.974 -0.345 -0.999 -0.977
## Standardized residuals:
##
                                               QЗ
                                  Med
                                                          Max
## -2.78808658 -0.64878550 -0.04217512 0.58986239
                                                   3.88205164
## Residual standard error: 44.90856
## Degrees of freedom: 2284 total; 2276 residual
```

From the table we see that the coefficient of BMI, age, and age and BMI interaction is insignificant according to the Wald test (p-value=0.0.8874, 0.7518 and 0.8405 > 0.05), we try to drop these terms in the model.

fit2=gls(choles~numcigpd+BMI:numcigpd+age:numcigpd+BMI:age:numcigpd, data=framnew,correlation=corSymm(f
summary(fit2)

```
## Generalized least squares fit by maximum likelihood
##
    Model: choles ~ numcigpd + BMI:numcigpd + age:numcigpd + BMI:age:numcigpd
##
     Data: framnew
##
         AIC
                  BIC
                          logLik
     21934.77 22055.17 -10946.38
##
##
## Correlation Structure: General
## Formula: ~1 | ID
## Parameter estimate(s):
## Correlation:
##
   1
           2
                             5
## 2 0.730
## 3 0.659 0.722
## 4 0.655 0.675 0.773
## 5 0.645 0.653 0.754 0.820
## 6 0.583 0.590 0.696 0.794 0.810
## Coefficients:
                        Value Std.Error
                                         t-value p-value
## (Intercept)
                    256.62763 2.154691 119.10185 0.0000
## numcigpd
                    -24.40630 23.610731 -1.03370 0.3014
## numcigpd:BMI
                     1.21125 0.917074
                                         1.32078 0.1867
## numcigpd:age
                     0.47984 0.436498
                                          1.09930 0.2718
## numcigpd:BMI:age -0.02350 0.016980 -1.38406 0.1665
##
```

```
## Correlation:
##
                    (Intr) nmcgpd nm:BMI nmcgp:
## numcigpd
                    -0.036
                     0.030 -0.977
## numcigpd:BMI
## numcigpd:age
                     0.029 -0.999 0.976
## numcigpd:BMI:age -0.028  0.975 -0.999 -0.977
## Standardized residuals:
           Min
                        Q1
                                   Med
                                                QЗ
                                                           Max
## -2.77092362 -0.65181865 -0.05327856 0.56916578 3.93070256
## Residual standard error: 44.61604
## Degrees of freedom: 2284 total; 2279 residual
fit3 = gls(choles~numcigpd+numcigpd:age+numcigpd:BMI,data=framnew,
           correlation=corSymm(form=~1|ID),method="ML")
summary(fit3)
## Generalized least squares fit by maximum likelihood
##
    Model: choles ~ numcigpd + numcigpd:age + numcigpd:BMI
##
    Data: framnew
##
          AIC
                          logLik
                  BIC
     21934.68 22049.35 -10947.34
##
##
## Correlation Structure: General
## Formula: ~1 | ID
## Parameter estimate(s):
## Correlation:
##
   1
           2
                3
                             5
## 2 0.731
## 3 0.660 0.723
## 4 0.656 0.677 0.774
## 5 0.646 0.654 0.755 0.821
## 6 0.584 0.592 0.697 0.795 0.810
##
## Coefficients:
##
                    Value Std.Error
                                      t-value p-value
## (Intercept) 256.54593 2.158829 118.83567 0.0000
## numcigpd
                 7.44935 5.267136
                                     1.41431 0.1574
                                    -1.17384 0.2406
## numcigpd:age -0.11017 0.093851
## numcigpd:BMI -0.05649 0.045362 -1.24542 0.2131
##
## Correlation:
##
                (Intr) nmcgpd nmcgp:
## numcigpd
                -0.037
## numcigpd:age 0.007 -0.972
## numcigpd:BMI 0.035 -0.279 0.053
##
## Standardized residuals:
##
                        Q1
                                   Med
                                                0.3
## -2.76370550 -0.66093834 -0.03458217 0.58854079 3.92488365
##
## Residual standard error: 44.703
```

Degrees of freedom: 2284 total; 2280 residual

```
anova(fit3,fit2)
                      AIC
##
        Model df
                               BIC
                                      logLik
                                               Test L.Ratio p-value
## fit3
            1 20 21934.68 22049.35 -10947.34
## fit2
            2 21 21934.77 22055.17 -10946.38 1 vs 2 1.913807 0.1665
fit1 = update(fit1u, method="ML")
anova(fit3,fit1)
        Model df
                      AIC
                               BIC
                                      logLik
                                               Test L.Ratio p-value
            1 20 21934.68 22049.35 -10947.34
## fit3
            2 24 21939.15 22076.76 -10945.58 1 vs 2 3.52706 0.4738
## fit1
Correlation structure selection
  1. fit the model as the marginal linear model with independent correlation:
fit3i = gls(choles~numcigpd+BMI:numcigpd+age:numcigpd, data=framnew,method = 'ML')
summary(fit3i)
## Generalized least squares fit by maximum likelihood
##
    Model: choles ~ numcigpd + BMI:numcigpd + age:numcigpd
##
    Data: framnew
##
          AIC
                   BIC
                          logLik
     23772.26 23800.93 -11881.13
##
##
## Coefficients:
##
                    Value Std.Error t-value p-value
## (Intercept) 256.96030 1.0080767 254.90154 0.0000
            8.34864 2.4552897
## numcigpd
                                      3.40027 0.0007
## numcigpd:BMI -0.05647 0.0211455 -2.67050 0.0076
## numcigpd:age -0.12628 0.0437490 -2.88642 0.0039
##
##
   Correlation:
##
                (Intr) nmcgpd nm:BMI
## numcigpd
                -0.037
## numcigpd:BMI 0.035 -0.279
## numcigpd:age 0.007 -0.972 0.053
##
## Standardized residuals:
           Min
                        Q1
                                   Med
                                                           Max
## -2.82075377 -0.68175569 -0.04460732 0.57801140 3.98308056
## Residual standard error: 43.94581
## Degrees of freedom: 2284 total; 2280 residual
  • unstructured v.s. independent
```

anova(fit3i,fit3)

```
## Model df AIC BIC logLik Test L.Ratio p-value ## fit3i 1 5 23772.26 23800.93 -11881.13 ## fit3 2 20 21934.68 22049.35 -10947.34 1 vs 2 1867.58 <.0001
```

Based on LRT (as this is a nested model situation) p - value < 0.005, we conclude that independent correlation does not fit as well as unstructured.

2. fit the model as the marginal linear model with exchange correlation:

```
fit3e = gls(choles~numcigpd+BMI:numcigpd+age:numcigpd, data=framnew,method = 'ML',correlation=corCompSys
summary(fit3e)
```

```
## Generalized least squares fit by maximum likelihood
    Model: choles ~ numcigpd + BMI:numcigpd + age:numcigpd
##
##
    Data: framnew
         AIC
                  BIC
                         logLik
     22105.32 22139.72 -11046.66
##
##
## Correlation Structure: Compound symmetry
## Formula: ~1 | ID
  Parameter estimate(s):
##
##
        Rho
## 0.6961436
##
## Coefficients:
##
                    Value Std.Error
                                     t-value p-value
## (Intercept) 257.19203 2.141516 120.09811 0.0000
                 8.32791 5.225971
## numcigpd
                                      1.59356 0.1112
## numcigpd:BMI -0.05630 0.045007
                                    -1.25093 0.2111
## numcigpd:age -0.12621 0.093118 -1.35540 0.1754
##
##
   Correlation:
##
                (Intr) nmcgpd nm:BMI
               -0.037
## numcigpd
## numcigpd:BMI 0.035 -0.279
## numcigpd:age 0.007 -0.972 0.053
## Standardized residuals:
          Min
                                   Med
                                                Q3
                                                           Max
                        Q1
## -2.81050722 -0.68325581 -0.04960645 0.57306492 3.95596270
##
## Residual standard error: 44.18848
## Degrees of freedom: 2284 total; 2280 residual
```

• unstructured v.s. exchangeable

anova(fit3e,fit3)

Based on LRT (as this is a nested model situation) p-value < 0.005, we conclude that exchangable correlation does not fit as well as unstructured.

3. fit the model as the marginal linear model with exponential correlation:

```
fit3exp = gls(choles~numcigpd+BMI:numcigpd+age:numcigpd,data=framnew,
              correlation=corExp(form=~1|ID),method = 'ML')
summary(fit3exp)
## Generalized least squares fit by maximum likelihood
##
    Model: choles ~ numcigpd + BMI:numcigpd + age:numcigpd
##
     Data: framnew
##
          AIC
                  BIC
                         logLik
     22128.81 22163.21 -11058.4
##
##
## Correlation Structure: Exponential spatial correlation
   Formula: ~1 | ID
   Parameter estimate(s):
##
##
     range
## 3.839014
##
## Coefficients:
                                      t-value p-value
                    Value Std.Error
## (Intercept) 257.65073 1.950767 132.07662 0.0000
                 7.58202 4.756588
## numcigpd
                                     1.59400 0.1111
## numcigpd:BMI -0.05793 0.040965
                                    -1.41418 0.1574
## numcigpd:age -0.11186 0.084754 -1.31986 0.1870
##
##
   Correlation:
##
                (Intr) nmcgpd nm:BMI
                -0.037
## numcigpd
## numcigpd:BMI 0.035 -0.279
## numcigpd:age 0.007 -0.972 0.053
##
## Standardized residuals:
##
           Min
                        Q1
                                   Med
                                                QЗ
                                                           Max
## -2.79408773 -0.68704635 -0.05941701 0.56457931 3.90809708
## Residual standard error: 44.61232
## Degrees of freedom: 2284 total; 2280 residual
```

• unstructured v.s. exponential

```
anova(fit3exp,fit3)
```

```
## Model df AIC BIC logLik Test L.Ratio p-value ## fit3exp 1 6 22128.81 22163.21 -11058.40 ## fit3 2 20 21934.68 22049.35 -10947.34 1 vs 2 222.1279 <.0001
```

Based on LRT (as this is a nested model situation) p-value < 0.005, we conclude that exponential correlation does not fit as well as unstructured.

4. fit the model as the marginal linear model with Gaussian correlation:

```
fit3g = gls(choles~numcigpd+BMI:numcigpd+age:numcigpd, data=framnew,
            correlation=corGaus(form=~1|ID),method = 'ML')
summary(fit3g)
## Generalized least squares fit by maximum likelihood
##
     Model: choles ~ numcigpd + BMI:numcigpd + age:numcigpd
##
     Data: framnew
         AIC
##
                  BIC
                         logLik
##
     22749.16 22783.56 -11368.58
##
## Correlation Structure: Gaussian spatial correlation
  Formula: ~1 | ID
##
   Parameter estimate(s):
##
     range
## 1.239159
##
## Coefficients:
##
                    Value Std.Error t-value p-value
## (Intercept) 257.34862 1.298733 198.15362 0.0000
                                      2.57358 0.0101
## numcigpd
                 8.14367 3.164335
## numcigpd:BMI -0.05807 0.027252 -2.13089 0.0332
## numcigpd:age -0.12196 0.056383 -2.16298 0.0306
##
##
   Correlation:
                (Intr) nmcgpd nm:BMI
                -0.037
## numcigpd
## numcigpd:BMI 0.035 -0.279
## numcigpd:age 0.007 -0.972 0.053
##
## Standardized residuals:
##
          Min
                        Q1
                                  Med
                                                Q3
                                                           Max
## -3.00660877 -0.73379516 -0.05678685 0.61044561 4.22287281
## Residual standard error: 41.35843
## Degrees of freedom: 2284 total; 2280 residual
```

• unstructured v.s. Gaussian

```
anova(fit3g,fit3)
```

```
## Model df AIC BIC logLik Test L.Ratio p-value ## fit3g 1 6 22749.16 22783.56 -11368.58 ## fit3 2 20 21934.68 22049.35 -10947.34 1 vs 2 842.4829 <.0001
```

Based on LRT (as this is a nested model situation) p-value < 0.005, we conclude that Gaussian correlation does not fit as well as unstructured.

```
library(knitr)
Value = fit3$coefficients[2:4]
Std.Error = c(5.267136,0.093851,0.045962)
```

```
ci_upper = rep(0,3)
ci_lower = rep(0,3)
for (i in 1:3){
    ci_upper[i]=Value[i]+1.96*Std.Error[i]
    ci_lower[i]=Value[i]-1.96*Std.Error[i]
}
Results = as.matrix(cbind(Value, Std.Error,ci_lower,ci_upper))
kable(Results, digits = 5)
```

	Value	Std.Error	ci_lower	ci_upper
numcigpd	7.44935	5.26714	-2.87423	17.77294
numcigpd:age	-0.11017	0.09385	-0.29411	0.07378
numcigpd:BMI	-0.05649	0.04596	-0.14658	0.03359