CIMT study
Ultrasound and metabolic data

SDC / LLCh
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Contents

Chapter 1

Construction of data

First we read the ultrasound data for *all* participants. Note that some of the numerical variables are with "." as decimal separator, even if we have a file from a Danish Locale:

```
> options( width=90 )
> imt <- read.csv2("./data/imt.csv")
> str( imt )
```

```
'data.frame':        1544 obs. of  20 variables:
 $ subjid           : int  10002 70032 10002 10002 91089 60001 60001 80010 91081 91118 ...
 $ visit            : Factor w/ 2 levels "1a","7a": 1 2 1 2 1 1 1 2 1 1 ...
 $ cca_side         : Factor w/ 2 levels "L","R": 1 1 2 2 1 1 2 2 2 1 ...
 $ datescanned      : Factor w/ 805 levels "2008/05/06 - 10:45:19",..: 24 726 24 320 177 8 8 569 147
 $ mean_fimtavg     : Factor w/ 85 levels "0.44","0.46",..: 56 38 39 31 43 40 31 14 64 61 ...
 $ mean_fimtmin     : num  0.91 0.69 0.68 0.58 0.63 0.69 0.6 0.45 0.94 0.86 ...
 $ mean_fimtmax     : num  1.14 0.94 1 0.93 1.08 0.99 0.97 0.71 1.28 1.23 ...
 $ minvesseldia     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ maxvesseldia     : Factor w/ 368 levels "","10","10.03",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ vesselareal      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ lumenareal       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ imtareal         : Factor w/ 1120 levels "","10.27300798",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ systolicpressure : int  115 163 115 140 119 145 145 151 145 124 ...
 $ diastolicpressure: int  69 84 69 72 73 89 89 97 68 69 ...
 $ ddpct            : num  NA NA NA NA NA NA NA NA NA NA ...
 $ csdpct           : num  NA NA NA NA NA NA NA NA NA NA ...
 $ dc               : num  NA NA NA NA NA NA NA NA NA NA ...
 $ csc1             : num  NA NA NA NA NA NA NA NA NA NA ...
 $ csc2             : num  NA NA NA NA NA NA NA NA NA NA ...
 $ iem              : num  NA NA NA NA NA NA NA NA NA NA ...
```

```
> names( imt )[c(5,9,12)]
```

```
[1] "mean_fimtavg" "maxvesseldia" "imtareal"
```

```
> for( i in c(5,9,12) ) imt[,i] <- as.numeric(as.character(imt[,i]))
> imt$datescanned <- as.Date( substr(imt$datescanned,1,10) )
> str(imt)
```

```
'data.frame':        1544 obs. of  20 variables:
 $ subjid           : int  10002 70032 10002 10002 91089 60001 60001 80010 91081 91118 ...
 $ visit            : Factor w/ 2 levels "1a","7a": 1 2 1 2 1 1 1 2 1 1 ...
 $ cca_side         : Factor w/ 2 levels "L","R": 1 1 2 2 1 1 2 2 2 1 ...
 $ datescanned      : Date, format: "2008-09-23" "2011-12-09" ...
```

```
 $ mean_fimtavg     : num  1.01 0.83 0.84 0.76 0.88 0.85 0.76 0.59 1.09 1.06 ...
 $ mean_fimtmin     : num  0.91 0.69 0.68 0.58 0.63 0.69 0.6 0.45 0.94 0.86 ...
 $ mean_fimtmax     : num  1.14 0.94 1 0.93 1.08 0.99 0.97 0.71 1.28 1.23 ...
 $ minvesseldia     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ maxvesseldia     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ vesselareal      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ lumenareal       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ imtareal         : num  NA NA NA NA NA NA NA NA NA NA ...
 $ systolicpressure : int  115 163 115 140 119 145 145 151 145 124 ...
 $ diastolicpressure: int  69 84 69 72 73 89 89 97 68 69 ...
 $ ddpct            : num  NA NA NA NA NA NA NA NA NA NA ...
 $ csdpct           : num  NA NA NA NA NA NA NA NA NA NA ...
 $ dc               : num  NA NA NA NA NA NA NA NA NA NA ...
 $ csc1             : num  NA NA NA NA NA NA NA NA NA NA ...
 $ csc2             : num  NA NA NA NA NA NA NA NA NA NA ...
 $ iem              : num  NA NA NA NA NA NA NA NA NA NA ...
```

```
> addmargins( with( imt, table(visit,cca_side) ) )
```

```
     cca_side
visit    L    R  Sum
  1a   411  427  838
  7a   343  363  706
  Sum  754  790 1544
```

```
> with( imt, table( table( subjid ) ) )
```

```
  1   2   3   4
  5  81  15 333
```

The we read the randomization codes for those actually randomized:

```
> rnd <- read.csv2("./data/PTNR_MetforminCode_InsulinTypeCode.csv" )
> str( rnd )
```

```
'data.frame':        412 obs. of  3 variables:
 $ PTNR           : int  70002 70001 70004 70005 70006 70007 70010 70008 70009 70011 ...
 $ MetforminCode  : int  1 1 0 0 0 0 0 1 0 0 ...
 $ InsulinTypeCode: int  3 3 3 2 2 3 2 2 2 1 ...
```

By merging with `all.y=TRUE`, we ensure that only those from the randomization set are included:

```
> dim( imt )
```

```
[1] 1544   20
```

```
> rimt <- merge( imt, rnd, by.x="subjid", by.y="PTNR", all.y=TRUE )
> dim( rimt )
```

```
[1] 1498   22
```

```
> str( rimt )
```

```
'data.frame':        1498 obs. of  22 variables:
 $ subjid           : int  10001 10001 10001 10001 10002 10002 10002 10003 10003 10003 ...
 $ visit            : Factor w/ 2 levels "1a","7a": 1 2 2 1 1 1 2 2 1 2 ...
 $ cca_side         : Factor w/ 2 levels "L","R": 2 1 2 1 1 2 2 1 2 2 ...
 $ datescanned      : Date, format: "2008-09-22" "2010-03-22" ...
 $ mean_fimtavg     : num  0.8 0.84 0.88 0.85 1.01 0.84 0.76 0.88 1.04 1.02 ...
 $ mean_fimtmin     : num  0.54 0.63 0.71 0.65 0.91 0.68 0.58 0.7 0.87 0.86 ...
 $ mean_fimtmax     : num  1 1.03 1.03 0.96 1.14 1 0.93 1.03 1.21 1.2 ...
 $ minvesseldia     : num  NA 10.8 NA 10.9 NA ...
 $ maxvesseldia     : num  NA 11.5 NA 11.5 NA ...
 $ vesselareal      : num  NA 104 NA 103 NA ...
 $ lumenareal       : num  NA 76 NA 74.8 NA ...
 $ imtareal         : num  NA 28.2 NA 28.3 NA ...
 $ systolicpressure : int  142 124 124 142 115 115 140 154 153 154 ...
 $ diastolicpressure: int  86 73 73 86 69 69 72 85 95 85 ...
 $ ddpct            : num  NA 7.05 NA 5.51 NA NA NA 5.39 3.89 5.57 ...
 $ csdpct           : num  NA 14.6 NA 11.3 NA ...
 $ dc               : num  NA 0.0149 NA 0.0107 NA NA NA 0.00633 0.00608 0.00693 ...
 $ csc1             : num  NA 0.26 NA 0.19 NA NA NA 0.0829 0.0883 0.0961 ...
 $ csc2             : num  NA 0.00286 NA 0.00202 NA NA NA 0.0016 0.00137 0.00166 ...
 $ iem              : num  NA 1914 NA 2680 NA ...
 $ MetforminCode    : int  1 1 1 1 0 0 0 0 0 0 ...
 $ InsulinTypeCode  : int  3 3 3 3 3 3 3 1 1 1 ...
```

```
> with( rimt, table(table(subjid)) )
```

```
  1   2   3   4
  5  60  15 332
```

Fishily enough there is one person with 4 observations in `imt` that is not randomized:

```
> tt <- with( imt, table( subjid ) )
> has4i <- names( tt[tt==4] )
> isrnd <- rnd$PTNR
> setdiff( has4i, isrnd )
```

```
[1] "91218"
```

```
> with( rimt, pairs( cbind( avg = as.numeric(as.character(mean_fimtavg)),
+                           min = mean_fimtmin,
+                           max = mean_fimtmax,
+                            mn = (mean_fimtmin+mean_fimtmax)/2 ),
+                   gap=0, pch=16, cex=0.5 ) )
```

We now take the average for left and right-sided measurements, but also merge in as separate variables the left and right side measurements:

```
> what <- 5:22
> names( rimt )[what]
```

```
 [1] "mean_fimtavg"      "mean_fimtmin"      "mean_fimtmax"      "minvesseldia"
 [5] "maxvesseldia"      "vesselareal"       "lumenareal"        "imtareal"
 [9] "systolicpressure"  "diastolicpressure" "ddpct"             "csdpct"
[13] "dc"                "csc1"              "csc2"              "iem"
[17] "MetforminCode"     "InsulinTypeCode"
```

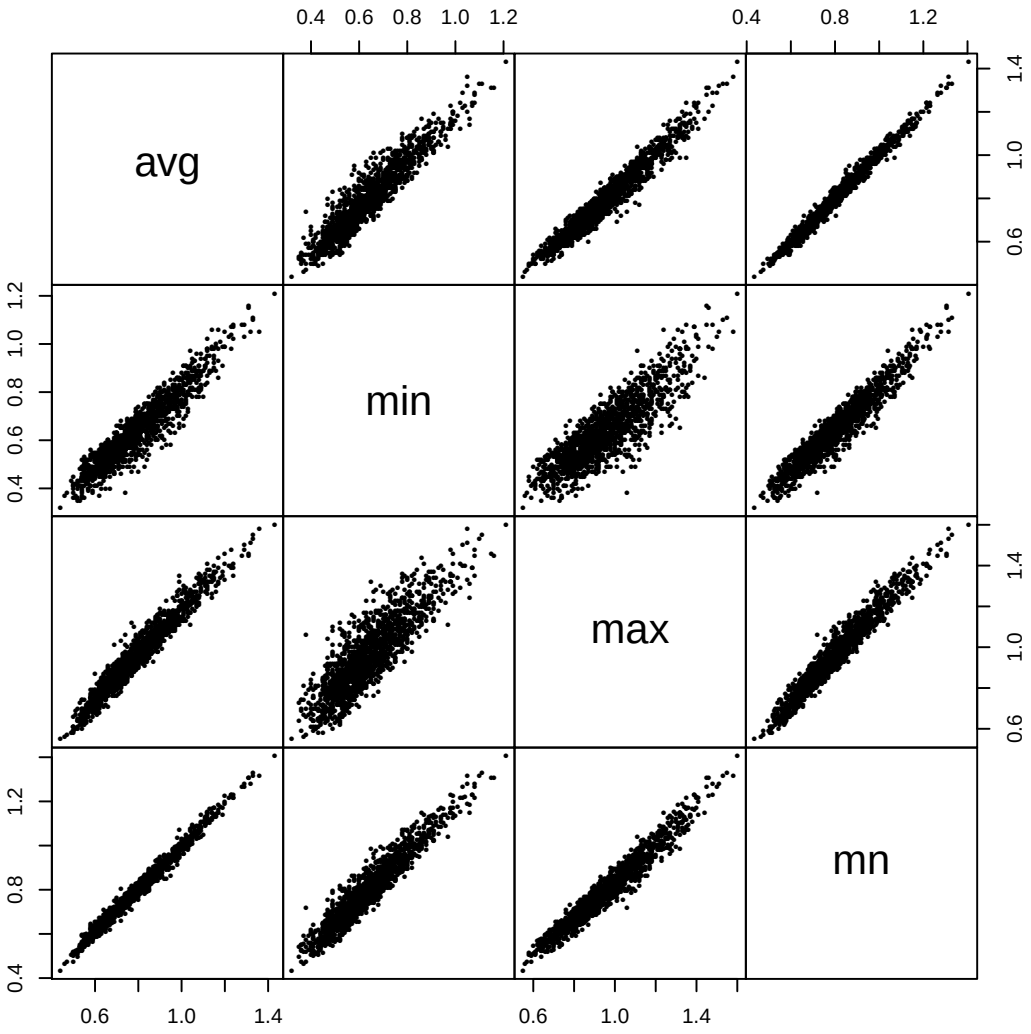

Figure 1.1: *Pairwise comparison of far wall intima media thickness as the average, min, max and the mean of min and max.*

```
> mimt <- aggregate( rimt[,what], list( subjid=rimt$subjid,
+                                       visit=rimt$visit),
+                    FUN=mean, na.rm=TRUE )
> wh <- c(1,2,5:12,18:20)
> names( imt )[wh]
```

```
 [1] "subjid"       "visit"        "mean_fimtavg" "mean_fimtmin" "mean_fimtmax"
 [6] "minvesseldia" "maxvesseldia" "vesselareal"  "lumenareal"   "imtareal"
[11] "csc1"         "csc2"         "iem"
```

```
> Limt <- subset( rimt, cca_side=="L" )[,wh]
> Rimt <- subset( rimt, cca_side=="R" )[,wh]
> names( Limt ) <- gsub( "mean_", "", names( Limt ) )
> names( Rimt ) <- gsub( "mean_", "", names( Rimt ) )
> names( Limt )[-(1:2)] <- paste( "left_" , names( Limt )[-(1:2)], sep="" )
> names( Rimt )[-(1:2)] <- paste( "right_", names( Rimt )[-(1:2)], sep="" )
> mimt <- merge( merge( mimt, Limt, all.x=TRUE ), Rimt, all.x=TRUE )
> head( mimt )
```

```
  subjid visit mean_fimtavg mean_fimtmin mean_fimtmax minvesseldia maxvesseldia
1  10001    1a        0.825        0.595        0.980       10.860       11.460
2  10001    7a        0.860        0.670        1.030       10.760       11.520
3  10002    1a        0.925        0.795        1.070          NaN          NaN
4  10002    7a        0.760        0.580        0.930          NaN          NaN
5  10003    1a        0.940        0.725        1.105        8.610        8.960
6  10003    7a        0.950        0.780        1.115        8.345        8.805
  vesselareal lumenareal imtareal systolicpressure diastolicpressure ddpct csdpct      dc
1   103.14760   74.81514 28.33245              142                86 5.510 11.330 0.01070
2   104.23050   76.04665 28.18386              124                73 7.050 14.600 0.01490
3         NaN        NaN      NaN              115                69   NaN    NaN     NaN
4         NaN        NaN      NaN              140                72   NaN    NaN     NaN
5    63.21921   39.42228 23.79694              153                95 4.095  8.355 0.00606
6    60.94144   37.45741 23.48403              154                85 5.480 11.260 0.00663
     csc1    csc2      iem MetforminCode InsulinTypeCode left_fimtavg left_fimtmin
1 0.19000 0.00202 2680.310             1               3         0.85         0.65
2 0.26000 0.00286 1913.970             1               3         0.84         0.63
3     NaN     NaN      NaN             0               3         1.01         0.91
4     NaN     NaN      NaN             0               3           NA           NA
5 0.08365 0.00144 3520.270             0               1         0.84         0.58
6 0.08950 0.00163 3080.515             0               1         0.88         0.70
  left_fimtmax left_minvesseldia left_maxvesseldia left_vesselareal left_lumenareal
1         0.96             10.86             11.46        103.14760        74.81514
2         1.03             10.76             11.52        104.23050        76.04665
3         1.14                NA                NA               NA              NA
4           NA                NA                NA               NA              NA
5         1.00              8.15              8.50         56.74502        36.53075
6         1.03              8.11              8.55         57.41457        36.21008
  left_imtareal left_csc1 left_csc2 left_iem right_fimtavg right_fimtmin right_fimtmax
1      28.33245    0.1900   0.00202  2680.31          0.80          0.54          1.00
2      28.18386    0.2600   0.00286  1913.97          0.88          0.71          1.03
3            NA        NA        NA       NA          0.84          0.68          1.00
4            NA        NA        NA       NA          0.76          0.58          0.93
5      20.21426    0.0790   0.00151  3262.22          1.04          0.87          1.21
6      21.20449    0.0829   0.00160  3099.45          1.02          0.86          1.20
  right_minvesseldia right_maxvesseldia right_vesselareal right_lumenareal right_imtareal
1                 NA                 NA                NA               NA             NA
2                 NA                 NA                NA               NA             NA
3                 NA                 NA                NA               NA             NA
4                 NA                 NA                NA               NA             NA
5               9.07               9.42          69.69341         42.31380       27.37961
6               8.58               9.06          64.46831         38.70474       25.76357
  right_csc1 right_csc2 right_iem
```

```
1         NA         NA        NA
2         NA         NA        NA
3         NA         NA        NA
4         NA         NA        NA
5     0.0883    0.00137   3778.32
6     0.0961    0.00166   3061.58
```

```
> subset( rimt, subjid==10001 )
```

```
  subjid visit cca_side datescanned mean_fimtavg mean_fimtmin mean_fimtmax minvesseldia
1  10001    1a        R  2008-09-22         0.80         0.54         1.00           NA
2  10001    7a        L  2010-03-22         0.84         0.63         1.03        10.76
3  10001    7a        R  2010-03-22         0.88         0.71         1.03           NA
4  10001    1a        L  2008-09-22         0.85         0.65         0.96        10.86
  maxvesseldia vesselareal lumenareal imtareal systolicpressure diastolicpressure ddpct
1           NA          NA         NA       NA              142                86    NA
2        11.52    104.2305   76.04665 28.18386              124                73  7.05
3           NA          NA         NA       NA              124                73    NA
4        11.46    103.1476   74.81514 28.33245              142                86  5.51
  csdpct     dc csc1    csc2     iem MetforminCode InsulinTypeCode
1     NA     NA   NA      NA      NA             1               3
2  14.60 0.0149 0.26 0.00286 1913.97             1               3
3     NA     NA   NA      NA      NA             1               3
4  11.33 0.0107 0.19 0.00202 2680.31             1               3
```

```
> subset( mimt, subjid==10001 )
```

```
  subjid visit mean_fimtavg mean_fimtmin mean_fimtmax minvesseldia maxvesseldia
1  10001    1a        0.825        0.595         0.98        10.86        11.46
2  10001    7a        0.860        0.670         1.03        10.76        11.52
  vesselareal lumenareal imtareal systolicpressure diastolicpressure ddpct csdpct     dc
1    103.1476   74.81514 28.33245              142                86  5.51  11.33 0.0107
2    104.2305   76.04665 28.18386              124                73  7.05  14.60 0.0149
  csc1    csc2     iem MetforminCode InsulinTypeCode left_fimtavg left_fimtmin
1 0.19 0.00202 2680.31             1               3         0.85         0.65
2 0.26 0.00286 1913.97             1               3         0.84         0.63
  left_fimtmax left_minvesseldia left_maxvesseldia left_vesselareal left_lumenareal
1         0.96             10.86             11.46         103.1476        74.81514
2         1.03             10.76             11.52         104.2305        76.04665
  left_imtareal left_csc1 left_csc2 left_iem right_fimtavg right_fimtmin right_fimtmax
1      28.33245      0.19   0.00202  2680.31          0.80          0.54          1.00
2      28.18386      0.26   0.00286  1913.97          0.88          0.71          1.03
  right_minvesseldia right_maxvesseldia right_vesselareal right_lumenareal right_imtareal
1                 NA                 NA                NA               NA             NA
2                 NA                 NA                NA               NA             NA
  right_csc1 right_csc2 right_iem
1         NA         NA        NA
2         NA         NA        NA
```

Finally we attach the stratification variables, and grom the variable names to something slightly more handy:

```
> st <- read.csv2( "./data/strata.csv" )[,-2]
> names( st )[2:4] <- c("o.65","pre.ins","SDC")
> mimt <- merge( mimt, st, by.x="subjid", by.y="ptnr" )
> names( mimt ) <- gsub( "mean_", "", names(mimt) )
```

The resulting data set has one observation per visit among the randomized patients:

```
> mimt <- transform( mimt, subjid = factor(subjid),
+                            met = factor(MetforminCode,labels=c("Plc","Met")),
+                            ins = factor(InsulinTypeCode,labels=c("NR+Lv","Lv","NM30")) )
> with( mimt, table(MetforminCode, met ))
```

```
             met
MetforminCode Plc Met
            0 388   0
            1   0 395
```

```
> with( mimt, table(InsulinTypeCode,ins))
```

```
               ins
InsulinTypeCode NR+Lv  Lv NM30
              1   263   0    0
              2     0 257    0
              3     0   0  263
```

```
> with( mimt, ftable(addmargins(table(Met=met, Ins=ins, visit ))) )
```

```
          visit  1a  7a Sum
Met Ins
Plc NR+Lv        73  66 139
    Lv           66  55 121
    NM30         67  61 128
    Sum         206 182 388
Met NR+Lv        65  59 124
    Lv           71  65 136
    NM30         70  65 135
    Sum         206 189 395
Sum NR+Lv       138 125 263
    Lv          137 120 257
    NM30        137 126 263
    Sum         412 371 783
```

Finally for the benefit of the client, we write it both an `Rda` format and as a SAS data-file with corresponding script:

```
> save( mimt, file="./data/mimt.Rda" )
> write.foreign( mimt,
+             datafile = "./sas/mimt.dat",
+             codefile = "./sas/mimt.sas",
+              package = "SAS" )
```

Chapter 2

Primary outcome (CIMT)

2.1 Analysis as repeated measures

We reload the data and the two necessary packages from R, and convert the subject indicator to a factor as is needed for use in `lmer`:

```
> library( lme4 )
> library( Epi )
> load( file="./data/mimt.Rda" )
```

2.1.1 Model with baseline difference

We analyze data with a random effects model, for the CIMT-mean y_{it} on individual i at time $t = 1, 7$ (`mean_fimtavg`), randomized to treatment $m = M, P$ using subject as random, and with a separate metformin by time (`visit`) interaction:

$$\begin{aligned} y_{it} &= \mu + \beta_t + \gamma_{mt} \\ &\quad + \alpha_1 \texttt{o.65} + \alpha_2 \texttt{per.ins} + \alpha_1 \texttt{SDC} \\ &\quad + a_i + e_{it}, \quad t = 1, 7 \\ a_i &\sim \mathcal{N}(0, \tau^2), \quad e_{it} \sim \mathcal{N}(0, \sigma^2), \quad \text{all independent} \end{aligned} \tag{2.1}$$

The model states that persons have an average baseline level of CIMT depending on randomization and stratification group; the mean at baseline and follow-up are:

$$\begin{aligned} \text{baseline:} \quad & \mu + \beta_1 + \gamma_{m1} + \alpha_1 \texttt{o.65} + \alpha_2 \texttt{per.ins} + \alpha_3 \texttt{SDC} \\ \text{follow-up:} \quad & \mu + \beta_7 + \gamma_{m7} + \alpha_1 \texttt{o.65} + \alpha_2 \texttt{per.ins} + \alpha_3 \texttt{SDC} \\ \text{change:} \quad & \beta_7 - \beta_1 + (\gamma_{m7} - \gamma_{m1}) \end{aligned}$$

So in the changes in CIMT are:

$$\begin{aligned} \text{metformin:} \quad & \beta_7 - \beta_1 + (\gamma_{\text{met7}} - \gamma_{\text{met1}}) \\ \text{placebo:} \quad & \beta_7 - \beta_1 + (\gamma_{\text{plc7}} - \gamma_{\text{plc1}}) \end{aligned}$$

The model as stated here is grossly overparametrized, it can be identified if all parameters relation to baseline or placebo were set to 0, the changes in CIMT over the follow-up are

$$\begin{aligned} \text{metformin:} \quad & \beta_7 + \gamma_{\text{met7}} \\ \text{placebo:} \quad & \beta_7 \\ \text{difference:} \quad & \gamma_{\text{met7}} \end{aligned}$$

These three parameters are those of interest which should be extracted.

The model is a random effects model that is very close to using the baseline (y_{i1}) as covariate in an analysis of the follow-up (y_{i7}) as outcome:

```
> m0 <- lmer( fimtavg ~ -1 + visit:met + o.65 + pre.ins + SDC +(1|subjid),
+             data = mimt )
> summary( m0 )


Linear mixed model fit by REML
Formula: fimtavg ~ -1 + visit:met + o.65 + pre.ins + SDC + (1 | subjid)
   Data: mimt
   AIC   BIC logLik deviance REMLdev
 -1365 -1323  691.5    -1436   -1383
Random effects:
 Groups   Name        Variance  Std.Dev.
 subjid   (Intercept) 0.0144863 0.120359
 Residual             0.0026388 0.051369
Number of obs: 783, groups: subjid, 412

Fixed effects:
                Estimate Std. Error t value
o.65            0.089748   0.013846    6.48
pre.ins        -0.006157   0.013800   -0.45
SDC            -0.014061   0.012718   -1.11
visit1a:metPlc  0.785330   0.014019   56.02
visit7a:metPlc  0.771776   0.014117   54.67
visit1a:metMet  0.773305   0.014082   54.91
visit7a:metMet  0.772499   0.014178   54.48

Correlation of Fixed Effects:
            o.65   pre.ns SDC    vst1:P vst7:P vst1:M
pre.ins     -0.075
SDC         -0.031 -0.204
vist1:mtPlc -0.208 -0.566 -0.302
vist7:mtPlc -0.206 -0.560 -0.302  0.927
visit1:mtMt -0.221 -0.569 -0.295  0.579  0.574
visit7:mtMt -0.220 -0.566 -0.294  0.576  0.571  0.931


> round( ee <- ci.lin( m0, subset="visit" ), 4 )


               Estimate StdErr       z P   2.5%  97.5%
visit1a:metPlc   0.7853 0.0140 56.0180 0 0.7579 0.8128
visit7a:metPlc   0.7718 0.0141 54.6710 0 0.7441 0.7994
visit1a:metMet   0.7733 0.0141 54.9139 0 0.7457 0.8009
visit7a:metMet   0.7725 0.0142 54.4843 0 0.7447 0.8003


> C0 <- rbind(diag(4),c(0,0,-1,1),
+                     c(-1,1,0,0),
+                     c(1,-1,-1,1))
> row.names(C0) <- c("Plc 1a","Plc 7a",
+                    "Met 1a","Met 7a",
+                    "Met 7a-1a",
+                    "Plc 7a-1a",
+                    "dMet - dPlc" )
> colnames(C0) <- row.names(ee)
> C0
```

```
            visit1a:metPlc visit7a:metPlc visit1a:metMet visit7a:metMet
Plc 1a                   1              0              0              0
Plc 7a                   0              1              0              0
Met 1a                   0              0              1              0
Met 7a                   0              0              0              1
Met 7a-1a                0              0             -1              1
Plc 7a-1a               -1              1              0              0
dMet - dPlc              1             -1             -1              1
```

```
> round( e0 <- ci.lin( m0, subset="visit", ctr.mat=C0 ), 4 )
```

```
            Estimate StdErr       z      P    2.5%   97.5%
Plc 1a        0.7853 0.0140 56.0180 0.0000  0.7579  0.8128
Plc 7a        0.7718 0.0141 54.6710 0.0000  0.7441  0.7994
Met 1a        0.7733 0.0141 54.9139 0.0000  0.7457  0.8009
Met 7a        0.7725 0.0142 54.4843 0.0000  0.7447  0.8003
Met 7a-1a    -0.0008 0.0053 -0.1529 0.8785 -0.0111  0.0095
Plc 7a-1a    -0.0136 0.0054 -2.5283 0.0115 -0.0241 -0.0030
dMet - dPlc   0.0127 0.0075  1.6963 0.0898 -0.0020  0.0275
```

```
> elab <- c("Metformin 18m - baseline",
+           "Placebo 18m - baseline",
+           "Metformin vs. Placebo change")
> rownames( e0 )[5:7] <- elab
> round( e0, 4 )
```

```
                            Estimate StdErr       z      P    2.5%   97.5%
Plc 1a                        0.7853 0.0140 56.0180 0.0000  0.7579  0.8128
Plc 7a                        0.7718 0.0141 54.6710 0.0000  0.7441  0.7994
Met 1a                        0.7733 0.0141 54.9139 0.0000  0.7457  0.8009
Met 7a                        0.7725 0.0142 54.4843 0.0000  0.7447  0.8003
Metformin 18m - baseline     -0.0008 0.0053 -0.1529 0.8785 -0.0111  0.0095
Placebo 18m - baseline       -0.0136 0.0054 -2.5283 0.0115 -0.0241 -0.0030
Metformin vs. Placebo change  0.0127 0.0075  1.6963 0.0898 -0.0020  0.0275
```

2.1.2 Assuming identical mean baseline

If we want to fit a model where we do not allow different baseline means between randomization groups, we must hand-code the interaction at the follow-up visit:

```
> mm <- model.matrix( ~ visit:met-1, data = mimt )
> m7 <- mm[,xx <- grep("7a",colnames(mm))]
> head( m7 )
```

```
  visit7a:metPlc visit7a:metMet
1              0              0
2              0              1
3              0              0
4              1              0
5              0              0
6              1              0
```

The model matrix thus generated only has the indicators of randomization group at follow-up, so we need the intercept in this model to take care of the overall mean:

```
> m1 <- lmer( fimtavg ~ m7 + o.65 + pre.ins + SDC +(1|subjid),
+             data = mimt )
> summary( m1 )
```

```
Linear mixed model fit by REML
Formula: fimtavg ~ m7 + o.65 + pre.ins + SDC + (1 | subjid)
   Data: mimt
   AIC   BIC logLik deviance REMLdev
 -1373 -1336  694.5    -1435   -1389
Random effects:
 Groups   Name        Variance  Std.Dev.
 subjid   (Intercept) 0.0144816 0.120340
 Residual             0.0026387 0.051369
Number of obs: 783, groups: subjid, 412

Fixed effects:
                   Estimate Std. Error t value
(Intercept)        0.779381   0.012482   62.44
m7visit7a:metPlc -0.012628   0.005268   -2.40
m7visit7a:metMet -0.001732   0.005173   -0.33
o.65               0.089549   0.013843    6.47
pre.ins           -0.006222   0.013798   -0.45
SDC               -0.013985   0.012716   -1.10

Correlation of Fixed Effects:
            (Intr) m7v7:P m7v7:M o.65   pre.ns
m7vst7:mtPl -0.101
m7vst7:mtMt -0.094  0.036
o.65        -0.242  0.006 -0.005
pre.ins     -0.639  0.007 -0.004 -0.075
SDC         -0.336 -0.006 -0.003 -0.031 -0.204
```

```
> round( ee <- ci.lin( m1, subset=1:3 ), 4 )
```

```
                 Estimate StdErr       z      P    2.5%   97.5%
(Intercept)        0.7794 0.0125 62.4412 0.0000  0.7549  0.8038
m7visit7a:metPlc  -0.0126 0.0053 -2.3971 0.0165 -0.0230 -0.0023
m7visit7a:metMet  -0.0017 0.0052 -0.3348 0.7378 -0.0119  0.0084
```

```
> C1 <- cbind(apply(C0,1,sum),C0[,xx])
> colnames(C1) <- row.names(ee)
> C1
```

```
            (Intercept) m7visit7a:metPlc m7visit7a:metMet
Plc 1a                1                0                0
Plc 7a                1                1                0
Met 1a                1                0                0
Met 7a                1                0                1
Met 7a-1a             0                0                1
Plc 7a-1a             0                1                0
dMet - dPlc           0               -1                1
```

```
> round( e1 <- ci.lin( m1, subset=1:3, ctr.mat=C1 ), 4 )
```

```
            Estimate StdErr       z      P    2.5%   97.5%
Plc 1a        0.7794 0.0125 62.4412 0.0000  0.7549  0.8038
Plc 7a        0.7668 0.0130 58.7693 0.0000  0.7412  0.7923
Met 1a        0.7794 0.0125 62.4412 0.0000  0.7549  0.8038
Met 7a        0.7776 0.0131 59.5600 0.0000  0.7521  0.8032
Met 7a-1a    -0.0017 0.0052 -0.3348 0.7378 -0.0119  0.0084
Plc 7a-1a    -0.0126 0.0053 -2.3971 0.0165 -0.0230 -0.0023
dMet - dPlc   0.0109 0.0072  1.5032 0.1328 -0.0033  0.0251
```

```
> rownames( e1 )[5:7] <- elab
> round( e1, 4 )
```

```
                            Estimate StdErr       z      P    2.5%   97.5%
Plc 1a                        0.7794 0.0125 62.4412 0.0000  0.7549  0.8038
Plc 7a                        0.7668 0.0130 58.7693 0.0000  0.7412  0.7923
Met 1a                        0.7794 0.0125 62.4412 0.0000  0.7549  0.8038
Met 7a                        0.7776 0.0131 59.5600 0.0000  0.7521  0.8032
Metformin 18m - baseline     -0.0017 0.0052 -0.3348 0.7378 -0.0119  0.0084
Placebo 18m - baseline       -0.0126 0.0053 -2.3971 0.0165 -0.0230 -0.0023
Metformin vs. Placebo change  0.0109 0.0072  1.5032 0.1328 -0.0033  0.0251
```

We can compare the estimated changes within groups under the two different assumptions:

```
> round( cbind( e0[,1:2], e1[,1:2] ), 4 )
```

```
                            Estimate StdErr Estimate StdErr
Plc 1a                        0.7853 0.0140   0.7794 0.0125
Plc 7a                        0.7718 0.0141   0.7668 0.0130
Met 1a                        0.7733 0.0141   0.7794 0.0125
Met 7a                        0.7725 0.0142   0.7776 0.0131
Metformin 18m - baseline     -0.0008 0.0053  -0.0017 0.0052
Placebo 18m - baseline       -0.0136 0.0054  -0.0126 0.0053
Metformin vs. Placebo change  0.0127 0.0075   0.0109 0.0072
```

If we are going to present the effect measure as derived from the conditional model (*i.e.* using baseline as covariate, then we should use the estimated changes from the model `m1` without allowance for baseline imbalance.

2.1.3 Plotting results

We first produce an overview of the estimates of the absolute levels (in this case in the reference group):

```
> pclr <- c("limegreen","blue","orange","black")
> ppclr <- rgb( t(col2rgb(pclr)+255)/2, max=255 )
> matplot( c(1,7), cbind(e0[3:4,1],e0[1:2,1]),
+         type="o", lty=1, lwd=3, pch=1, col=ppclr[1:2], cex=1.5,
+       xlim=c(0,8), xaxt="n", xlab="Visit",
+       ylim=c(0.76,0.79), yaxs="i", ylab="CIMT",
+       las=2, bty="n" )
> matlines(  c(1,7), cbind(e1[3:4,1],e1[1:2,1]),
+         type="o", lty=1, lwd=3, pch=16, col=pclr[1:2], cex=1.5 )
> mtext( paste(c(1,7)), at=c(1,7), line=1, side=1 )
> text( rep(7,7), 0.785-0:1/400, c("Metformin","Placebo"),
+       col=pclr[1:2], adj=1 )
> sd0 <- as.numeric( VarCorr( m0 )$subjid )
> sd1 <- as.numeric( VarCorr( m1 )$subjid )
> lines( c(0.52,0.52), 0.78+c(-1,1)*sd0/2, lwd=3, col=gray(0.5) )
> lines( c(0.45,0.45), 0.78+c(-1,1)*sd1/2, lwd=3, col=gray(0.5) )
> text( 0.25, 0.78, "Between person SD", col=gray(0.5), srt=90 )
```

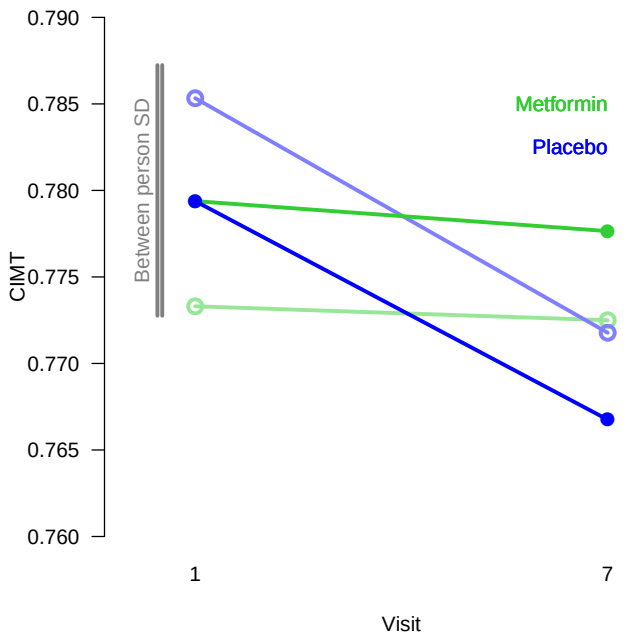

Figure 2.1: *Estimated CIMT levels at baseline and follow-up (in the reference group), using a model allowing different means (pale colors open symbols) and assuming common mean (full colors, full symbols). Note that the dramatically looking differences are of the same magnitude as the between person variation. The two lines represent the between-person SD from the two different models.*

From the figure 2.1 it is clear that the changes in each group (and hence the difference between the changes) are pretty simular under the two models, it is the absolute levels in the groups that differ.

```
> par( mar=c(3,1,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( e0[5:7,c(1,5,6)], lwd=4, cex=1.5,
+          xlab="", col=ppclr, vref=0, y=3:1+0.1,
+          restore.par=FALSE )
> linesEst( e1[5:7,c(1,5,6)], lwd=4, lty=3, cex=1.5,
+           xlab="", col=pclr, vref=0, y=3:1-0.1,
+           restore.par=FALSE )
> axis( side=1 )
> mtext( "Carotid intima-media thickness (mm)", side=1, line=3/1.6, col=pclr[4] )
```

For the sake of plotting effects in slides we start out by defining the colors to be used for Metformin, Placebo, differences and the axes etc. on the transparent plots:

```
> eclr <- c("green","yellow","orange","white")


> win.metafile( "forest1.emf", width=10, height=5, pointsize=24 )
> par( mar=c(3,1,1,1), mgp=c(3,1,0)/1.6,
+      bg=#"black",
+         "transparent",
+      col.axis=eclr[4], col.lab=eclr[4] )
> plotEst( e0[5:7,c(1,5,6)], lwd=7,cex=1.5,
+          xlab="", col.txt="transparent", col=eclr,
+          restore.par=FALSE )
> for( i in 1:3 ) axis( side=2, at=4-i, labels=elab[i], col="transparent",
+                       col.axis= eclr[i], las=1 )
> abline( v=0, col=eclr[4] )
> axis( side=1, col=eclr[4] )
> mtext( "Carotid intima-media thickness (mm)", side=1, line=3/1.6, col=eclr[4] )
> dev.off()


null device
          1
```

2.2 Analysis using baseline as covariate

Another way of looking at the analysis is to use the measurement at the second occasion using the baseline measurement as covariate. In section **??** is a brief account of the relationship between the two approaches.

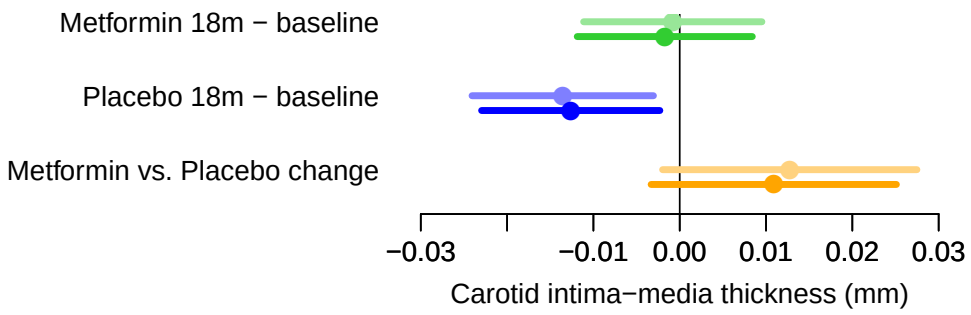

Figure 2.2: *Estimeated changes and treatment effect on CIMT, full colors are from the model assuming common means at baseline, pale colors from the model allowing baseline imbalance.*

2.2.1 Model

The main difference is that the absolute change in the response from baseline to follow-up in each of the groups does not appear as a parameter in this approach. The model is (for 7—follow-up and 1—baseline):

$$\begin{aligned} y_{i7} &= \mu + \theta y_{i1} + \gamma_m \\ &\quad + \alpha_1 \texttt{o.65} + \alpha_2 \texttt{per.ins} + \alpha_1 \texttt{SDC} \\ &\quad + e_i, \\ e_i &\sim \mathcal{N}(0, \sigma^2) \end{aligned} \tag{2.2}$$

In order to use this approach we restructure the data set so that we have only one row per person with follow-up and baseline as separate variables:

```
> names( mimt )
```

```
 [1] "subjid"             "visit"              "fimtavg"            "fimtmin"
 [5] "fimtmax"            "minvesseldia"       "maxvesseldia"       "vesselareal"
 [9] "lumenareal"         "imtareal"           "systolicpressure"   "diastolicpressure"
[13] "ddpct"              "csdpct"             "dc"                 "csc1"
[17] "csc2"               "iem"                "MetforminCode"      "InsulinTypeCode"
[21] "left_fimtavg"       "left_fimtmin"       "left_fimtmax"       "left_minvesseldia"
[25] "left_maxvesseldia"  "left_vesselareal"   "left_lumenareal"    "left_imtareal"
[29] "left_csc1"          "left_csc2"          "left_iem"           "right_fimtavg"
[33] "right_fimtmin"      "right_fimtmax"      "right_minvesseldia" "right_maxvesseldia"
[37] "right_vesselareal"  "right_lumenareal"   "right_imtareal"     "right_csc1"
[41] "right_csc2"         "right_iem"          "o.65"               "pre.ins"
[45] "SDC"                "met"                "ins"
```

```
> wimt <- reshape( mimt[,c("fimtavg","visit","subjid",
+                          "met","o.65","pre.ins","SDC")],
+                  direction = "wide",
+                    v.names = "fimtavg",
+                    timevar = "visit",
+                      idvar = "subjid" )
> subset( mimt[,c("fimtavg","visit","subjid",
+                          "MetforminCode","o.65","pre.ins","SDC")],
+         subjid=="10002" )
```

```
  fimtavg visit subjid MetforminCode o.65 pre.ins SDC
3   0.925    1a  10002             0    1       0   0
4   0.760    7a  10002             0    1       0   0
```

```
> subset( wimt, subjid=="10002" )
```

```
  subjid met o.65 pre.ins SDC fimtavg.1a fimtavg.7a
3  10002 Plc    1       0   0      0.925       0.76
```

We now have a dataset with the relevant variables, where we can estimate the difference in changes between the two groups:

```
> mf <- lm( fimtavg.7a ~ fimtavg.1a + met + o.65 + pre.ins + SDC,
+           data = wimt )
> summary( mf )
```

```
Call:
lm(formula = fimtavg.7a ~ fimtavg.1a + met + o.65 + pre.ins +
    SDC, data = wimt)

Residuals:
      Min        1Q    Median        3Q       Max
-0.246178 -0.039118  0.000996  0.042370  0.218314

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.111079   0.023192   4.790 2.43e-06
fimtavg.1a   0.839373   0.027631  30.378  < 2e-16
metMet       0.010418   0.007252   1.437   0.1517
o.65         0.020962   0.008412   2.492   0.0132
pre.ins      0.005352   0.008056   0.664   0.5069
SDC         -0.011232   0.007432  -1.511   0.1316

Residual standard error: 0.06966 on 365 degrees of freedom
  (41 observations deleted due to missingness)
Multiple R-squared:  0.7439,        Adjusted R-squared:  0.7404
F-statistic:   212 on 5 and 365 DF,  p-value: < 2.2e-16
```

```
> mm <- lm( fimtavg.7a ~ fimtavg.1a + met,
+           data = wimt )
> summary( mm )
```

```
Call:
lm(formula = fimtavg.7a ~ fimtavg.1a + met, data = wimt)

Residuals:
      Min        1Q    Median        3Q       Max
-0.259533 -0.038533  0.000097  0.042784  0.218626

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 0.098472   0.021941   4.488 9.63e-06
fimtavg.1a  0.859657   0.026706  32.190  < 2e-16
metMet      0.011424   0.007296   1.566    0.118

Residual standard error: 0.07018 on 368 degrees of freedom
  (41 observations deleted due to missingness)
Multiple R-squared:  0.7379,        Adjusted R-squared:  0.7365
F-statistic: 518.1 on 2 and 368 DF,  p-value: < 2.2e-16
```

```
> round( cf <- ci.lin( mf, subset=c("fimt","Met") ), 4 )
```

```
           Estimate StdErr       z      P    2.5%  97.5%
fimtavg.1a   0.8394 0.0276 30.3782 0.0000  0.7852 0.8935
metMet       0.0104 0.0073  1.4366 0.1508 -0.0038 0.0246
```

```
> round( cm <- ci.lin( mm, subset=c("fimt","Met") ), 4 )
```

```
           Estimate StdErr       z      P    2.5%  97.5%
fimtavg.1a   0.8597 0.0267 32.1899 0.0000  0.8073 0.9120
metMet       0.0114 0.0073  1.5658 0.1174 -0.0029 0.0257
```

These estimates can now be compared with those from the random effects model:

```
> round( e0, 4 )
```

```
                            Estimate StdErr       z      P    2.5%   97.5%
Plc 1a                        0.7853 0.0140 56.0180 0.0000  0.7579  0.8128
Plc 7a                        0.7718 0.0141 54.6710 0.0000  0.7441  0.7994
Met 1a                        0.7733 0.0141 54.9139 0.0000  0.7457  0.8009
Met 7a                        0.7725 0.0142 54.4843 0.0000  0.7447  0.8003
Metformin 18m - baseline     -0.0008 0.0053 -0.1529 0.8785 -0.0111  0.0095
Placebo 18m - baseline       -0.0136 0.0054 -2.5283 0.0115 -0.0241 -0.0030
Metformin vs. Placebo change  0.0127 0.0075  1.6963 0.0898 -0.0020  0.0275
```

The relevant quantities to compare are the additive effects of treatment:

```
> round( rbind( "Simple" = cm[2,],
+               "Contrl" = cf[2,],
+           "RanEff-dif" = e0[7,],
+           "RanEff-eql" = e1[7,] ), 4 )
```

```
           Estimate StdErr      z      P    2.5%  97.5%
Simple       0.0114 0.0073 1.5658 0.1174 -0.0029 0.0257
Contrl       0.0104 0.0073 1.4366 0.1508 -0.0038 0.0246
RanEff-dif   0.0127 0.0075 1.6963 0.0898 -0.0020 0.0275
RanEff-eql   0.0109 0.0072 1.5032 0.1328 -0.0033 0.0251
```

Clearly, the conclusion for the models are not substantially different; CIMT difference is some 0.01 mm larger between the groups at follow-up; in favor of the Placebo group.

```
> par( mar=c(3,1,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( e0[5:7,c(1,5,6)], lwd=4, cex=1.5,
+          xlab="", col=ppclr, vref=0, y=3:1+0.1,
+          restore.par=FALSE )
> linesEst( e1[5:7,c(1,5,6)], lwd=4, lty=3, cex=1.5,
+           xlab="", col=pclr, vref=0, y=3:1-0.1 )
> linesEst( cf[2,c(1,5,6),drop=FALSE], lwd=4, lty=3, cex=1.5,
+           xlab="", col=pclr[3], vref=0, y=1-0.3 )
> axis( side=1 )
> mtext( "Carotid intima-media thickness (mm)", side=1, line=3/1.6, col=eclr[4] )
```

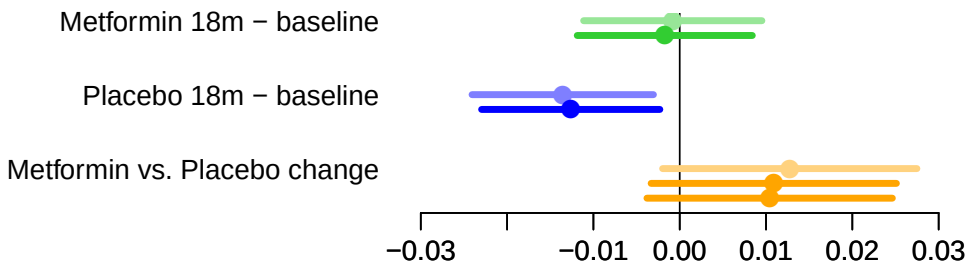

Figure 2.3: *Estimeated changes and treatment effect on CIMT, full colors are from the model assuming common means at baseline, pale colors from the model allowing baseline imbalance. The bottom estimate is the effect estimate from the conditional model using the baseline as covariate.*

2.3 Using multiple imputation

We see that there are some missing values in the follow-up values. Therefore we want to make a multiple imputation using a rich model to predict the outcome for additional analyses.

Hence we are using the multiple imputation on the wide dataset:

```
> summary( wimt )
```

```
     subjid     met           o.65          pre.ins           SDC
 10001  :  1   Plc:206   Min.   :0.000   Min.   :0.0000   Min.   :0.0000
 10002  :  1   Met:206   1st Qu.:0.000   1st Qu.:0.0000   1st Qu.:0.0000
 10003  :  1             Median :0.000   Median :1.0000   Median :0.0000
 10004  :  1             Mean   :0.284   Mean   :0.6917   Mean   :0.4927
 10005  :  1             3rd Qu.:1.000   3rd Qu.:1.0000   3rd Qu.:1.0000
 10006  :  1             Max.   :1.000   Max.   :1.0000   Max.   :1.0000
 (Other):406
   fimtavg.1a       fimtavg.7a
 Min.   :0.4850   Min.   :0.5200
 1st Qu.:0.6950   1st Qu.:0.6850
 Median :0.7850   Median :0.7700
 Mean   :0.7936   Mean   :0.7849
 3rd Qu.:0.8712   3rd Qu.:0.8700
 Max.   :1.2800   Max.   :1.1850
                  NA's   :41
```

We start by reading the data set with all the variables to be used for imputation, except the outcomes variables CIMT:

```
> library( mice )
> library( foreign )
> llch <- read.ssd( "./data", "mi" )
> names( llch ) <- tolower( gsub("_",".",names(llch)) )
> Wimt <- merge( wimt, llch )
> Wimt <- transform( Wimt, sex = factor( sex     , labels=c("F","M") ), # code 0/1 !
+                          ami = factor( ami     , labels=c("No","Yes") ),
+                     heartsur = factor( heartsur, labels=c("No","Yes") ),
+                        apopl = factor( apopl    , labels=c("No","Yes") ),
+                          tci = factor( tci     , labels=c("No","Yes") ),
+                          sdc = factor( sdc     , labels=c("no","yes") ),
+                         o.65 = factor( o.65    , labels=c("no","yes") ),
+                      pre.ins = factor( pre.ins , labels=c("no","yes") ),
+                     metformi = factor( metformi, labels=c("Plc","Met") ) )
> Wimt <- Wimt[,c(1,42,43,41,3,4,6:40,44:47)]
> cbind( 1:ncol(Wimt), t( apply( Wimt, 2,
+                                function(x) c(sum(is.na(x)),
+                                              length(unique(x))) ) ) )
```

```
           [,1] [,2] [,3]
subjid        1    0  412
metformi      2    0    2
insulint      3    0    3
sdc           4    0    2
o.65          5    0    2
pre.ins       6    0    2
fimtavg.1a    7    0  118
fimtavg.7a    8   41  105
sex           9    0    2
ami          10    0    2
heartsur     11    1    3
apopl        12    1    3
tci          13    0    2
```

```
microalb     14   10    3
age          15    0   45
nonsever     16    1   49
severehy     17    1    4
hba1c.b1     18    0   49
hba1c.b2     19   32   61
hba1c.b3     20   45   57
hba1c.b4     21   53   55
hba1c.b5     22   64   54
hba1c.b6     23   83   46
hba1c.b7     24   39   56
weight.b     25    0  299
weight.2     26   32  269
weight.3     27   42  273
weight.4     28   54  278
weight.5     29   65  263
weight.6     30   79  265
weight.7     31   43  286
bmi.1a       32    0  404
bmi.7a       33   43  366
chol.1a      34    0   46
trig.1a      35    0  228
ldl.1a       36   14   43
hdlc.1a      37    0  129
chol.7a      38   42   52
trig.7a      39   42  214
ldl.7a       40   55   40
hdlc.7a      41   42  118
natualb1     42   19  354
natualb2     43   22  361
natualb3     44   32  358
avgnatua     45   14  398
```

```
> ftable( addmargins( xtabs( cbind( "Baseline"=!is.na(fimtavg.1a),
+                                   "FU18mth"=!is.na(fimtavg.7a),
+                                     "Diff."=!is.na(fimtavg.1a)-
+                                             !is.na(fimtavg.7a),
+                                 "MissingFU"= is.na(fimtavg.7a) ) ~ sex + metformi,
+                           data=Wimt ),
+                     margin=1:2 ) )
```

```
              Baseline FU18mth Diff. MissingFU
sex metformi
F   Plc             65      55    10        10
    Met             66      59     7         7
    Sum            131     114    17        17
M   Plc            141     127    14        14
    Met            140     130    10        10
    Sum            281     257    24        24
Sum Plc            206     182    24        24
    Met            206     189    17        17
    Sum            412     371    41        41
```

So we see that there is about 10% missing follow-up measurements (41 out of 412). The pattern of missing values is:

```
> zz <- md.pattern( Wimt )
> t( zz )
```

```
           261   1   1   7   3   1   3   1   3   1   4   3   3   2  12   1   6   1   2
subjid       1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
metformi     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
```

insulint	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sdc	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
o.65	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
pre.ins	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
fimtavg.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sex	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ami	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
tci	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
age	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hba1c.b1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.b	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
bmi.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
chol.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
trig.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hdlc.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
heartsur	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
apopl	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
nonsever	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
severehy	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
microalb	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ldl.1a	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0
avgnatua	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
natualb1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1
natualb2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
hba1c.b2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.2	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
natualb3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
hba1c.b7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
fimtavg.7a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
chol.7a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
trig.7a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hdlc.7a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
bmi.7a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
hba1c.b3	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hba1c.b4	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.4	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
ldl.7a	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0
hba1c.b5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.5	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
weight.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
hba1c.b6	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1
	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2
	1	1	2	1	1	1	1	1	1	1	10	2	1	8	1	1	5	2	1
subjid	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
metformi	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
insulint	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sdc	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
o.65	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
pre.ins	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
fimtavg.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
sex	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ami	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
tci	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
age	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hba1c.b1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
weight.b	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
bmi.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
chol.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
trig.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
hdlc.1a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
heartsur	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
apopl	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
nonsever	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
severehy	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

```
microalb     1   1   1   1   1   1   1   1   1   1   1   1   1   1   0   1   1   1   1
ldl.1a       0   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1   1   1
avgnatua     1   1   1   1   1   1   1   1   1   1   1   1   1   0   1   1   1   0   0
natualb1     1   0   1   1   1   1   1   1   0   1   1   1   1   0   1   1   1   0   0
natualb2     0   0   0   1   1   1   1   1   1   1   1   1   1   0   0   1   1   1   0   0
hba1c.b2     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
weight.2     1   1   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1   1   1
natualb3     1   1   0   1   1   1   1   1   1   0   1   1   0   0   1   1   1   0   0
hba1c.b7     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
fimtavg.7a   1   1   1   0   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
weight.3     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
chol.7a      1   1   1   1   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
trig.7a      1   1   1   1   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
hdlc.7a      1   1   1   1   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
weight.7     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   0
bmi.7a       1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   0
hba1c.b3     1   1   1   1   1   0   1   1   1   1   1   1   1   1   1   1   1   1   1   1
hba1c.b4     1   1   1   1   0   1   1   1   1   1   1   1   1   1   1   1   1   0   1   1
weight.4     1   1   1   1   1   0   1   1   1   1   1   1   1   1   1   1   1   0   1   1
ldl.7a       1   1   1   1   1   0   0   0   0   0   1   0   1   1   1   0   1   1   1
hba1c.b5     1   1   1   1   1   1   0   1   1   1   0   1   1   1   0   0   0   1   1
weight.5     1   1   1   1   1   1   0   1   1   1   0   1   1   1   0   0   0   1   1
weight.6     1   1   1   0   0   1   1   0   1   1   0   1   0   1   0   0   0   0   1
hba1c.b6     1   1   1   0   0   1   1   0   1   1   0   1   0   1   0   0   0   0   1
             2   2   2   3   3   3   3   3   3   3   4   4   4   4   5   5   6   6   6
             1   1   1   3   3   6   1   2   1   1   1   1   2   4   1   2  17   1   2
subjid       1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
metformi     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
insulint     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
sdc          1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
o.65         1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
pre.ins      1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
fimtavg.1a   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
sex          1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
ami          1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
tci          1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
age          1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
hba1c.b1     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
weight.b     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
bmi.1a       1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
chol.1a      1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
trig.1a      1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
hdlc.1a      1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
heartsur     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
apopl        1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
nonsever     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
severehy     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
microalb     1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1
ldl.1a       1   1   1   1   1   1   0   1   1   1   1   1   1   1   1   0   1   0   0
avgnatua     1   1   0   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
natualb1     1   1   0   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
natualb2     1   1   0   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
hba1c.b2     1   1   1   1   1   0   0   1   1   1   1   0   1   1   0   1   0   0   0
weight.2     1   1   1   1   1   0   1   1   1   1   1   0   1   1   0   1   0   1   0
natualb3     1   0   0   1   1   1   1   1   1   1   0   1   1   1   1   1   1   1   1
hba1c.b7     1   1   1   1   0   1   1   0   0   0   0   1   0   0   1   0   0   0   0
fimtavg.7a   1   1   1   1   0   1   1   0   0   0   0   0   0   0   1   0   0   0   0
weight.3     1   1   1   0   1   0   0   1   1   1   1   0   1   0   0   0   0   0   0
chol.7a      1   1   1   1   0   1   1   0   0   0   0   1   0   0   0   0   0   0   0
trig.7a      1   1   1   1   0   1   1   0   0   0   0   1   0   0   0   0   0   0   0
hdlc.7a      1   1   1   1   0   1   1   0   0   0   0   1   0   0   0   0   0   0   0
weight.7     1   1   1   1   0   1   1   0   0   0   0   0   0   0   0   0   0   0   0
bmi.7a       1   1   1   1   0   1   1   0   0   0   0   0   0   0   0   0   0   0   0
hba1c.b3     1   1   1   0   1   0   0   1   1   1   1   0   1   0   0   0   0   0   0
hba1c.b4     0   0   1   0   1   0   0   1   0   1   1   0   0   0   0   0   0   0   0
weight.4     0   0   1   0   1   0   0   1   1   1   1   0   0   0   0   0   0   0   0
```

```
ldl.7a       0   1   0   1   0   1   1   0   0   0   0   1   0   0   0   0   0   0   0
hba1c.b5     0   0   1   0   1   0   0   1   1   0   1   0   0   0   0   0   0   0   0
weight.5     0   0   1   0   1   0   0   1   1   0   1   0   0   0   0   0   0   0   0
weight.6     0   0   0   0   1   0   0   0   0   0   1   0   0   0   0   0   0   0   0
hba1c.b6     0   0   0   0   1   0   0   0   0   0   1   0   0   0   0   0   0   0   0
             7   7   7   8   8  10  10  10  11  12  12  13  14  16  16  17  18  18  19
             1   1   1
subjid       1   1   1   0
metformi     1   1   1   0
insulint     1   1   1   0
sdc          1   1   1   0
o.65         1   1   1   0
pre.ins      1   1   1   0
fimtavg.1a   1   1   1   0
sex          1   1   1   0
ami          1   1   1   0
tci          1   1   1   0
age          1   1   1   0
hba1c.b1     1   1   1   0
weight.b     1   1   1   0
bmi.1a       1   1   1   0
chol.1a      1   1   1   0
trig.1a      1   1   1   0
hdlc.1a      1   1   1   0
heartsur     1   1   1   1
apopl        1   1   1   1
nonsever     0   1   1   1
severehy     0   1   1   1
microalb     1   0   0  10
ldl.1a       1   1   1  14
avgnatua     1   1   0  14
natualb1     1   1   0  19
natualb2     1   0   0  22
hba1c.b2     0   0   0  32
weight.2     0   0   0  32
natualb3     1   0   0  32
hba1c.b7     0   0   0  39
fimtavg.7a   0   0   0  41
weight.3     0   0   0  42
chol.7a      0   0   0  42
trig.7a      0   0   0  42
hdlc.7a      0   0   0  42
weight.7     0   0   0  43
bmi.7a       0   0   0  43
hba1c.b3     0   0   0  45
hba1c.b4     0   0   0  53
weight.4     0   0   0  54
ldl.7a       0   0   0  55
hba1c.b5     0   0   0  64
weight.5     0   0   0  65
weight.6     0   0   0  79
hba1c.b6     0   0   0  83
            20  21  23 1011
```

```
> pairs( Wimt[,c(7,8,15,16:24)], gap=0, pch=16, cex=0.2 )
```

```
> pairs( Wimt[,25:36], gap=0, pch=16, cex=0.2 )
```

```
> pairs( Wimt[,37:45], gap=0, pch=16, cex=0.2 )
```

We see from figure 2.4 that non-severe hypoglycemia, `nonsever` is quite skew so we will include it as log-transformed in the imputation. In figure 2.5 it is evident that the weight

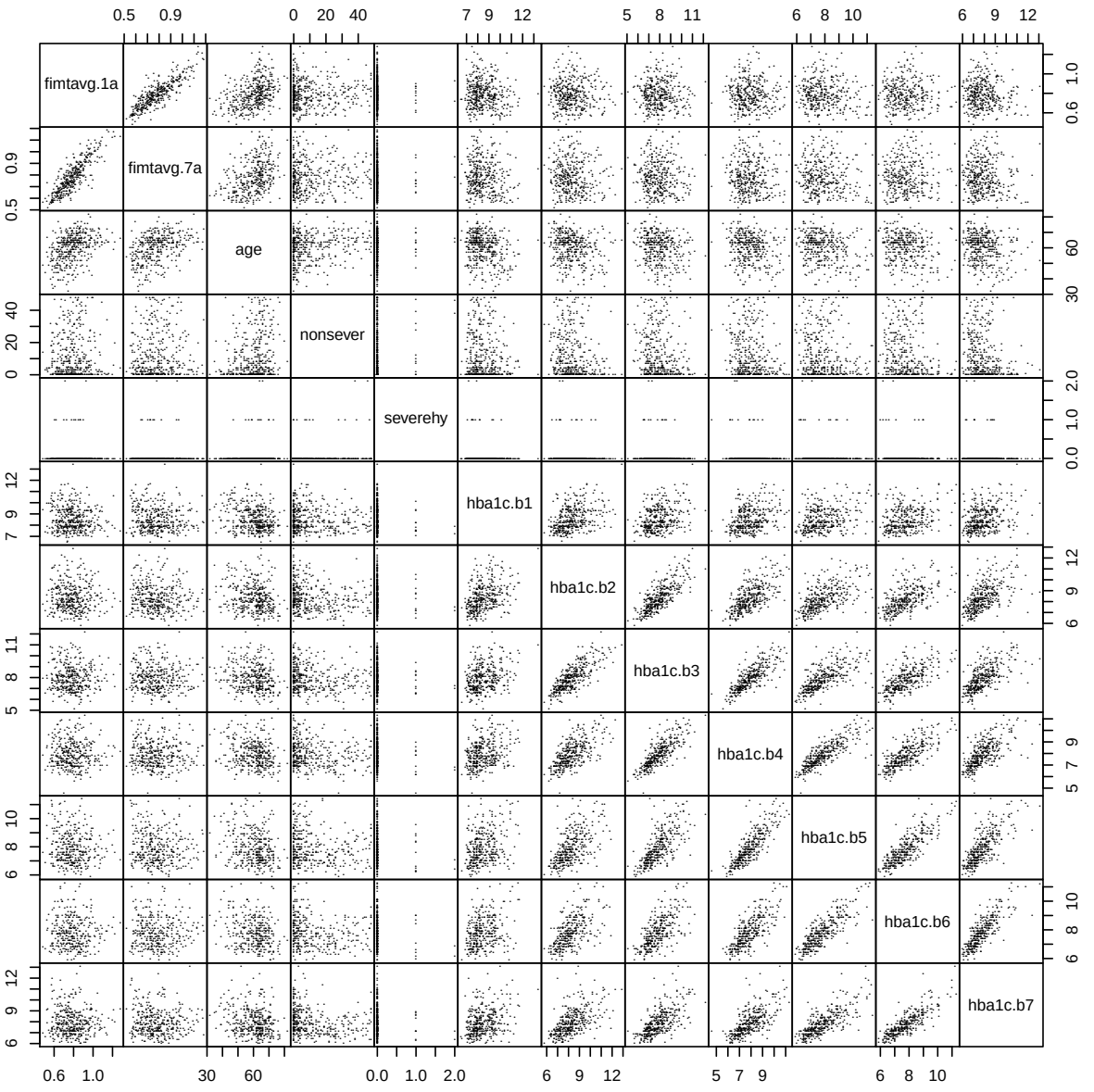

Figure 2.4: *Pairwise marginal distributions of the variables in the dataset* `Wimt`.

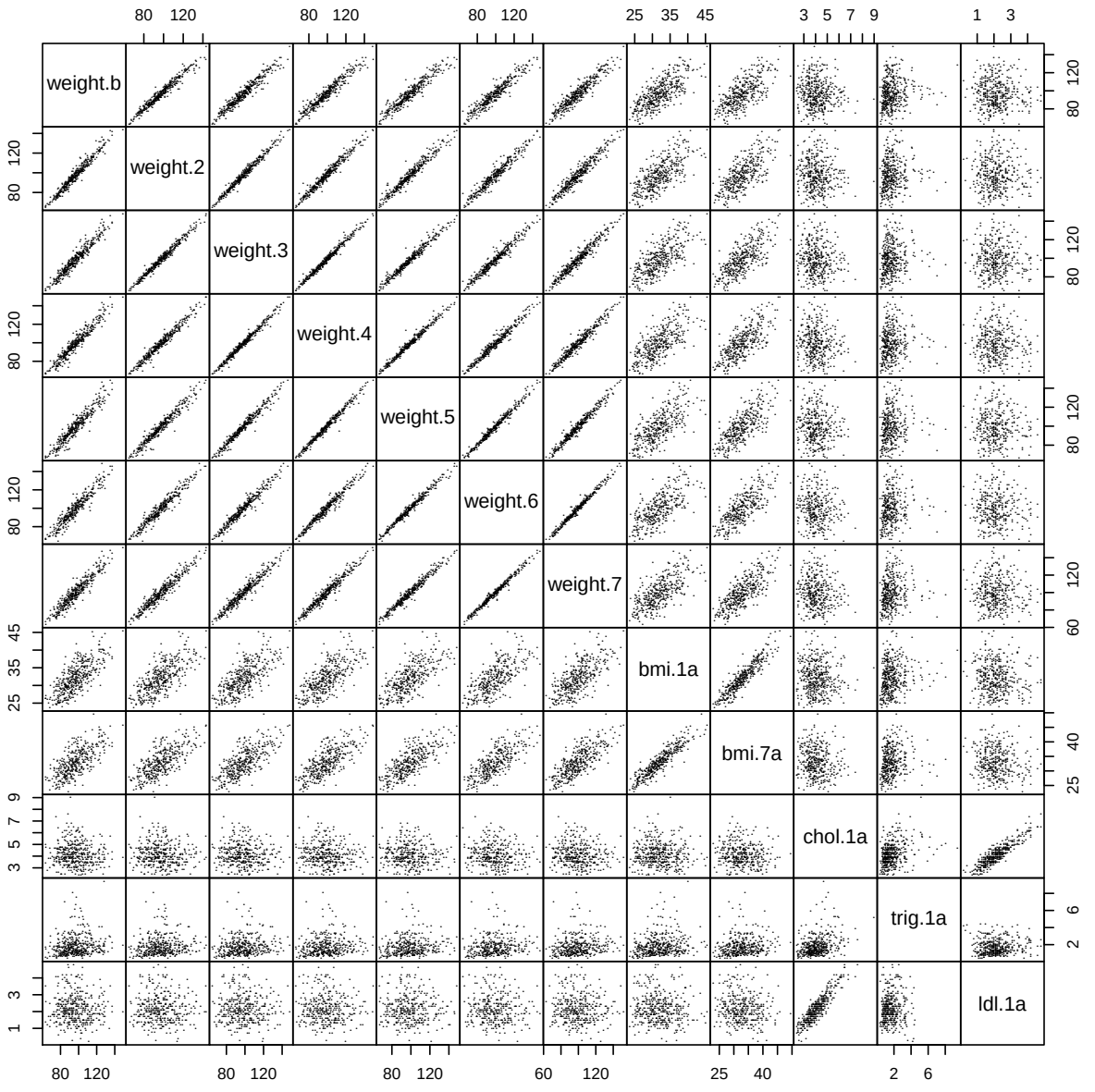

Figure 2.5: *Pairwise marginal distributions of the variables in the dataset* `Wimt`.

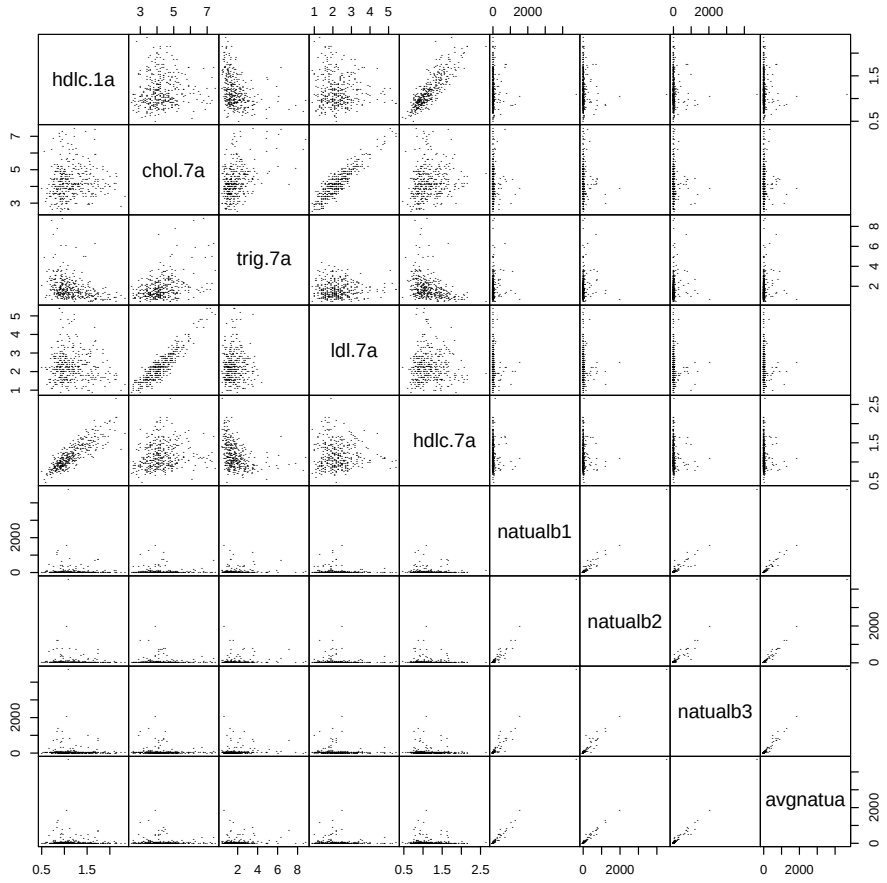

Figure 2.6: *Pairwise marginal distributions of the variables in the dataset* `Wimt`.

measurements very closely correlated, so we include only the baseline and the visit7 values. Finally from figure 2.6 we see that the albumin measurements are both correlated and very skewed, so we include only the log-transform of the average (`avgnatua`). With this in the model we do not include microalbuminuria:

```
> mimimt <- transform( Wimt, l.alb  = log( avgnatua ),
+                            l.nsev = log( nonsever ) )[,-c(14,16,26:30,42:45)][c(1:15,36,16:35)]
> names( mimimt )
```

```
 [1] "subjid"     "metformi"   "insulint"   "sdc"        "o.65"       "pre.ins"
 [7] "fimtavg.1a" "fimtavg.7a" "sex"        "ami"        "heartsur"   "apopl"
[13] "tci"        "age"        "severehy"   "l.nsev"     "hba1c.b1"   "hba1c.b2"
[19] "hba1c.b3"   "hba1c.b4"   "hba1c.b5"   "hba1c.b6"   "hba1c.b7"   "weight.b"
[25] "weight.7"   "bmi.1a"     "bmi.7a"     "chol.1a"    "trig.1a"    "ldl.1a"
[31] "hdlc.1a"    "chol.7a"    "trig.7a"    "ldl.7a"     "hdlc.7a"    "l.alb"
```

```
> save( mimimt, file="./data/mimimt.Rda" )
```

```
> pairs( mimimt[,7:21], gap=0, pch="." )
```



```
> pairs( mimimt[,22:36], gap=0, pch="." )
```


With this in place we can now make a multiple imputation of the missing values, including those on the outcome variable:

```
> set.seed( 876528358 )
> tt <- system.time( imp <- mice( mimimt[,2:36], m=100 ) )
```

```
> tt
> save( imp, file="./data/imp" )
```

Once we have done the imputation we can make the imputation analysis:

```
> load( file="./data/imp" )
> class( imp )
```

```
[1] "mids"
```

```
> i.mf <- with( imp, lm( fimtavg.7a ~ fimtavg.1a +
+                        metformi + o.65 + pre.ins + sdc ) )
> round( smf <- summary( pool(i.mf) ), 4 )
```

```
               est     se       t       df Pr(>|t|)   lo 95  hi 95 nmis    fmi lambda
(Intercept)  0.1060 0.0231  4.5847 360.8125   0.0000  0.0605 0.1515   NA 0.0886 0.0836
fimtavg.1a   0.8436 0.0276 30.5281 359.2179   0.0000  0.7893 0.8980    0 0.0913 0.0862
metformi2    0.0113 0.0072  1.5585 357.6867   0.1200 -0.0030 0.0255   NA 0.0938 0.0887
o.652        0.0212 0.0084  2.5375 361.4973   0.0116  0.0048 0.0377   NA 0.0875 0.0825
pre.ins2     0.0052 0.0081  0.6386 347.8272   0.5235 -0.0107 0.0211   NA 0.1097 0.1046
sdc2        -0.0094 0.0075 -1.2550 347.0198   0.2103 -0.0240 0.0053   NA 0.1110 0.1059
```

```
> i.mm <- with( imp, lm( fimtavg.7a ~ fimtavg.1a + metformi ) )
> round( smm <- summary( pool( i.mm ) ), 4 )
```

```
               est     se       t       df Pr(>|t|)   lo 95  hi 95 nmis    fmi lambda
(Intercept) 0.0944 0.0217  4.3447 371.7383   0.0000  0.0517 0.1371   NA 0.0747 0.0697
fimtavg.1a  0.8642 0.0266 32.4679 364.2013   0.0000  0.8118 0.9165    0 0.0873 0.0823
metformi2   0.0119 0.0073  1.6315 361.5280   0.1037 -0.0024 0.0262   NA 0.0917 0.0867
```

With the estimate for the metformin effect in `smm` (which is the relevant one) we can now re-do the forest plot using the "old" estimates of the corrected changes estimated from the random-effects model:

```
> par( mar=c(3,1,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( rbind(e0[5:6,c(1,5,6)],smm[3,c("est","lo 95","hi 95")]),
+          txt=rownames(e0)[5:7], lwd=7,cex=1.5,
+          restore.par=FALSE )
> abline( v=0 )
> axis( side=1 )
> mtext( "Carotid intima-media thickness (mm)", side=1, line=3/1.6 )


> eclr <- c("green","yellow","orange")
> win.metafile( "forest2.emf", width=10, height=6, pointsize=20 )
> par( mar=c(3,1,1,1), mgp=c(3,1,0)/1.6,
+      bg="transparent",
+      col.axis=eclr[4], col.lab=eclr[4] )
> plotEst( rbind(e0[5:6,c(1,5,6)],smm[3,c("est","lo 95","hi 95")]),
+          ylim=c(0,3),
+          txt=rownames(e0)[5:7], lwd=7,cex=1.5,
+          xlab="", col.txt="transparent", col=eclr,
+          restore.par=FALSE )
> for( i in 1:3 ) axis( side=2, at=4-i, labels=elab[i], col="transparent",
+                       col.axis= eclr[i], las=1 )
> abline(v=0,col=eclr[4])
> axis( side=1, col=eclr[4] )
> text( c(e0[5:6,1],smm[3,"est"]), 0.7+2:0,
+       paste( "P =", formatC( c(e0[5:6,"P"],smm[3,"Pr(>|t|)"]),
+                              format="f", digits=3 ) ),
+       col=eclr[4] )
> text( -0.03, 0.2, "Improvement"  , adj=0, col=eclr[4], cex=0.8 )
> text(  0.03, 0.2, "Deterioration", adj=1, col=eclr[4], cex=0.8 )
> mtext( "Carotid intima-media thickness (mm)", side=1, line=3/1.6, col=eclr[4] )
> dev.off()


null device
          1
```

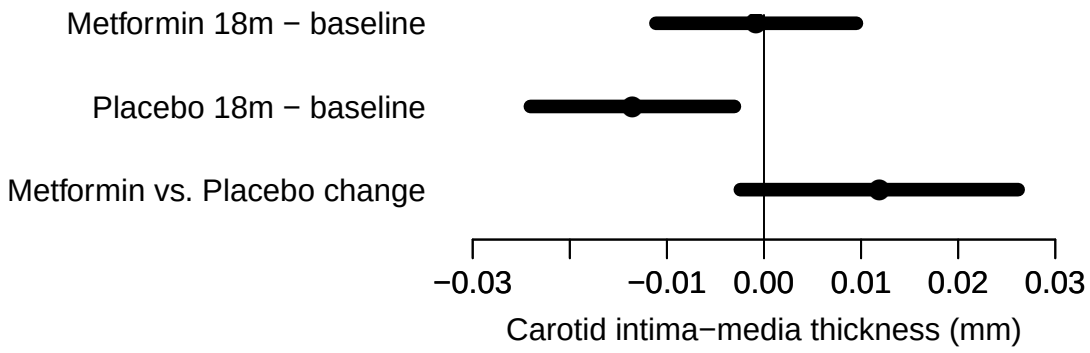

Figure 2.7: *Estimated contrasts from the random effects model. The difference is the estimate from the model with baseline as covariate, using multiply imputed data.*

2.4 Relationship between approaches

This section is a digression alien to the main analysis in the report; it aims at explaining the relationship between the random effects model and the conditional model.

The usual approach to analysis repeated measures with a baseline and one follow-up measurement is to use the baseline as covariate, as done in the latter analysis above. This is a corollary of the basic statistical principle that inference should be made in the conditional distribution given the sufficient statistics for the ancillary parameters, which in this case is the overall individual-specific value for each person (a_i). The baseline measurement y_{i1} is not the sufficient statistics for this, but it is close and easier to handle.

The model (2.1) induces a 2-dimensional normal distribution of the measurements y_1 and y_7:

$$\begin{pmatrix} y_1 \\ y_7 \end{pmatrix} \sim \mathcal{N}\left[\begin{pmatrix} \mu_1 \\ \mu_7 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_7 \\ \rho\sigma_1\sigma_7 & \sigma_7^2 \end{pmatrix}\right]$$

From standard statistical theory we know that under this model, the conditional distribution of y_7 given y_1 is:

$$y_7|y_1 \sim \mathcal{N}\left(\mu_7 + \frac{\rho\sigma_7}{\sigma_1}(y_1 - \mu_1), \sigma_7^2(1-\rho^2)\right)$$

Now in the model (2.1) we have the following values for the parameters μ_1, μ_7, σ_1^2, σ_7^2 and ρ in the 2-dimensional normal model outlined above. For convenience we set $\eta = \alpha_1 \texttt{o.65} + \alpha_2 \texttt{per.ins} + \alpha_1 \texttt{SDC}$, and so we have:

$$\begin{aligned} \mu_1 &= \mu + \delta_m + \eta \\ \mu_7 &= \mu + \delta_m + \beta_7 + \gamma_{m7} + \eta \\ \sigma_1^2 &= \tau^2 + \sigma^2 \\ \sigma_7^2 &= \tau^2 + \sigma^2 \\ \rho &= \frac{\tau^2}{\sigma^2 + \tau^2} \end{aligned}$$

Note that we have a term in the model, δ_m, allowing the two randomization groups to have different means at baseline, accounting for any baseline imbalance that might have arisen despite the randomization.

Using this in the formulae for the conditional distribution, gives the conditional distribution of y_7 given y_1 in terms of the model parameters from (2.1) (well, we maintain ρ):

$$\begin{aligned} y_7|y_1 &\sim \mathcal{N}\left(\mu + \delta_m + \beta_7 + \gamma_{m7} + \eta + \rho\big(y_1 - (\mu + \delta_m + \eta)\big), (\sigma^2 + \tau^2)(1-\rho^2)\right) \\ &= \mathcal{N}\left(\big((1-\rho)\mu + \beta_7\big) + \big((1-\rho)\delta_m + \gamma_{m7}\big) + \rho y_1 + (1-\rho)\eta, (\sigma^2 + \tau^2)(1-\rho^2)\right) \end{aligned}$$

Hence, when fitting the conditional model, the term $(1-\rho)\mu + \beta_7$ should show up as the intercept, the term $(1-\rho)\delta_m + \gamma_{m7}$ as the coefficient to the treatment indicator, ρ as the coefficient to the baseline measurement y_1, and the coefficients to the stratum-variables (generally speaking any other covariates) should appear scaled by $1-\rho$. Finally the residual standerd deviation should be $\sqrt{\sigma^2 + \tau^2)(1-\rho^2}$.

2.4.1 Fitting the two models on complete data

For illustration we now fit the random effects model to the complete (y_1, y_7) data (with and without compensation for baseline imbalance) and fit the conditional model to y_7 using y_1 as covariate. These do not necessarily give the same results, but here is an empirical comparison. Note that as opposed to the analysis above, we only use persons with complete information:

```
> compl <- mimt$subjid[mimt$visit=="7a"]
> cmimt <- subset( mimt, subjid %in% compl )
> table( cmimt$visit )


 1a  7a
371 371


> str( cmimt )


'data.frame':        742 obs. of  47 variables:
 $ subjid            : Factor w/ 412 levels "10001","10002",..: 1 1 2 2 3 3 4 4 5 5 ...
 $ visit             : Factor w/ 2 levels "1a","7a": 1 2 1 2 1 2 1 2 1 2 ...
 $ fimtavg           : num  0.825 0.86 0.925 0.76 0.94 0.95 1.02 1.01 0.71 0.695 ...
 $ fimtmin           : num  0.595 0.67 0.795 0.58 0.725 0.78 0.75 0.75 0.52 0.525 ...
 $ fimtmax           : num  0.98 1.03 1.07 0.93 1.1 ...
 $ minvesseldia      : num  10.86 10.76 NaN NaN 8.61 ...
 $ maxvesseldia      : num  11.46 11.52 NaN NaN 8.96 ...
 $ vesselareal       : num  103.1 104.2 NaN NaN 63.2 ...
 $ lumenareal        : num  74.8 76 NaN NaN 39.4 ...
 $ imtareal          : num  28.3 28.2 NaN NaN 23.8 ...
 $ systolicpressure  : num  142 124 115 140 153 154 116 122 132 133 ...
 $ diastolicpressure : num  86 73 69 72 95 85 81 80 77 76 ...
 $ ddpct             : num  5.51 7.05 NaN NaN 4.09 ...
 $ csdpct            : num  11.33 14.6 NaN NaN 8.36 ...
 $ dc                : num  0.0107 0.0149 NaN NaN 0.00606 ...
 $ csc1              : num  0.19 0.26 NaN NaN 0.0837 ...
 $ csc2              : num  0.00202 0.00286 NaN NaN 0.00144 0.00163 NaN NaN 0.0021 0.0019 ...
 $ iem               : num  2680 1914 NaN NaN 3520 ...
 $ MetforminCode     : num  1 1 0 0 0 0 0 0 0 0 ...
 $ InsulinTypeCode   : num  3 3 3 3 1 1 3 3 3 3 ...
 $ left_fimtavg      : num  0.85 0.84 1.01 NA 0.84 0.88 1.02 1.01 0.64 0.59 ...
 $ left_fimtmin      : num  0.65 0.63 0.91 NA 0.58 0.7 0.75 0.75 0.45 0.44 ...
 $ left_fimtmax      : num  0.96 1.03 1.14 NA 1 1.03 1.26 1.21 0.81 0.74 ...
 $ left_minvesseldia : num  10.86 10.76 NA NA 8.15 ...
 $ left_maxvesseldia : num  11.5 11.5 NA NA 8.5 ...
 $ left_vesselareal  : num  103.1 104.2 NA NA 56.7 ...
 $ left_lumenareal   : num  74.8 76 NA NA 36.5 ...
 $ left_imtareal     : num  28.3 28.2 NA NA 20.2 ...
 $ left_csc1         : num  0.19 0.26 NA NA 0.079 0.0829 NA NA 0.0892 NA ...
 $ left_csc2         : num  0.00202 0.00286 NA NA 0.00151 0.0016 NA NA 0.002 NA ...
 $ left_iem          : num  2680 1914 NA NA 3262 ...
 $ right_fimtavg     : num  0.8 0.88 0.84 0.76 1.04 1.02 NA NA 0.78 0.8 ...
 $ right_fimtmin     : num  0.54 0.71 0.68 0.58 0.87 0.86 NA NA 0.59 0.61 ...
 $ right_fimtmax     : num  1 1.03 1 0.93 1.21 1.2 NA NA 0.91 1 ...
 $ right_minvesseldia: num  NA NA NA NA 9.07 8.58 NA NA 8.5 8.58 ...
 $ right_maxvesseldia: num  NA NA NA NA 9.42 9.06 NA NA 9 9.04 ...
 $ right_vesselareal : num  NA NA NA NA 69.7 ...
 $ right_lumenareal  : num  NA NA NA NA 42.3 ...
 $ right_imtareal    : num  NA NA NA NA 27.4 ...
 $ right_csc1        : num  NA NA NA NA 0.0883 0.0961 NA NA 0.12 0.11 ...
 $ right_csc2        : num  NA NA NA NA 0.00137 0.00166 NA NA 0.0022 0.0019 ...
 $ right_iem         : num  NA NA NA NA 3778 ...
 $ o.65              : int  1 1 1 1 0 0 0 0 0 0 ...
```

```
 $ pre.ins           : int  0 0 0 0 1 1 0 0 1 1 ...
 $ SDC               : int  0 0 0 0 0 0 0 0 0 0 ...
 $ met               : Factor w/ 2 levels "Plc","Met": 2 2 1 1 1 1 1 1 1 1 ...
 $ ins               : Factor w/ 3 levels "NR+Lv","Lv","NM30": 3 3 3 3 1 1 3 3 3 3 ...
```

We want to extract the quantities to compare with the results from the conditional analysis, so we set up an array to hold the results for comparison:

```
> param <- NArray( list( Parameter=c("sig2",
+                                    "tau2",
+                                    "rho",
+                                    "int",
+                                    "beta",
+                                    "delta",
+                                    "gamma",
+                                    "o.65",
+                                    "pre.ins",
+                                    "SDC"),
+                        Model=c("Ran-eff, dif-B",
+                                "Ran-eff, eq-B") ) )
```

2.4.1.1 Random-effects with baseline difference

First we fit the random effects model with a parameter allowing for baseline imbalance:

```
> mc <- lmer( fimtavg ~ visit*met + o.65 + pre.ins + SDC +(1|subjid),
+             data = cmimt )
> summary( mc )
```

```
Linear mixed model fit by REML
Formula: fimtavg ~ visit * met + o.65 + pre.ins + SDC + (1 | subjid)
   Data: cmimt
   AIC   BIC logLik deviance REMLdev
 -1313 -1271  665.5    -1383   -1331
Random effects:
 Groups   Name        Variance Std.Dev.
 subjid   (Intercept) 0.014578 0.120739
 Residual             0.002640 0.051381
Number of obs: 742, groups: subjid, 371

Fixed effects:
               Estimate Std. Error t value
(Intercept)     0.787233   0.014677   53.64
visit7a        -0.013544   0.005386   -2.51
metMet         -0.014940   0.013638   -1.10
o.65            0.088787   0.014619    6.07
pre.ins        -0.006101   0.014574   -0.42
SDC            -0.017517   0.013436   -1.30
visit7a:metMet  0.013200   0.007546    1.75

Correlation of Fixed Effects:
            (Intr) visit7 metMet o.65   pre.ns SDC
visit7a     -0.183
metMet      -0.452  0.197
o.65        -0.192  0.000 -0.027
pre.ins     -0.548  0.000 -0.028 -0.086
SDC         -0.306  0.000  0.010 -0.041 -0.217
visit7:mtMt  0.131 -0.714 -0.277  0.000  0.000  0.000
```

Then we can extract the relevant parameters from this model and stick in the array:

```
> param["sig2" ,1] <- attr(VarCorr(mc),"sc")^2
> param["tau2" ,1] <- as.numeric(VarCorr(mc)$subjid)
> param["rho"  ,1] <- param["tau2",1]/(param["sig2",1]+param["tau2",1])
> param["int"  ,1] <- fixef( mc )["(Intercept)"]
> param["beta" ,1] <- fixef( mc )["visit7a"]
> param["delta",1] <- fixef( mc )["metMet"]
> param["gamma",1] <- fixef( mc )["visit7a:metMet"]
> param[c("o.65","pre.ins","SDC"),1] <- fixef( mc )[c("o.65","pre.ins","SDC")]
```

2.4.1.2 Using the randomization assumption

If we rely on the assumption that there is no difference between the groups at baseline, that is that $\delta_m = 0$ we fit the model:

```
> mr <- lmer( fimtavg ~ visit + I((visit=="7a")*(met=="Met")) + o.65 + pre.ins + SDC +(1|subjid),
+             data = cmimt )
> summary( mr )
```

```
Linear mixed model fit by REML
Formula: fimtavg ~ visit + I((visit == "7a") * (met == "Met")) + o.65 +      pre.ins + SDC + (1 | su
   Data: cmimt
   AIC   BIC logLik deviance REMLdev
 -1320 -1284  668.2    -1382   -1336
Random effects:
 Groups   Name        Variance  Std.Dev.
 subjid   (Intercept) 0.0145858 0.120771
 Residual             0.0026401 0.051382
Number of obs: 742, groups: subjid, 371

Fixed effects:
                                    Estimate Std. Error t value
(Intercept)                         0.779973   0.013099   59.55
visit7a                            -0.012379   0.005280   -2.34
I((visit == "7a") * (met == "Met"))  0.010914   0.007252    1.50
o.65                                0.088362   0.014618    6.04
pre.ins                            -0.006546   0.014572   -0.45
SDC                                -0.017363   0.013439   -1.29

Correlation of Fixed Effects:
            (Intr) visit7 I="*(=" o.65   pre.ns
visit7a     -0.108
I((=="7*(="  0.007 -0.700
o.65        -0.229  0.005 -0.008
pre.ins     -0.628  0.006 -0.008  -0.086
SDC         -0.338 -0.002  0.003  -0.040 -0.217
```

and the resulting derived parameters from `mr` are then:

```
> param["sig2" ,2] <- attr(VarCorr(mr),"sc")^2
> param["tau2" ,2] <- as.numeric(VarCorr(mr)$subjid)
> param["rho"  ,2] <- param["tau2",2]/(param["sig2",2]+param["tau2",2])
> param["int"  ,2] <- fixef( mr )["(Intercept)"]
> param["beta" ,2] <- fixef( mr )["visit7a"]
> param["delta",2] <- 0
> param["gamma",2] <- fixef( mr )[3]
> param[c("o.65","pre.ins","SDC"),2] <- fixef( mr )[c("o.65","pre.ins","SDC")]
```

2.4.1.3 Conditional analysis

The corresponding analysis on the complete cases from the `wimt` dataset (after making sure that it is the same persons):

```
> summary( wimt )
```

```
     subjid     met           o.65          pre.ins           SDC
 10001  :  1   Plc:206   Min.   :0.000   Min.   :0.0000   Min.   :0.0000
 10002  :  1   Met:206   1st Qu.:0.000   1st Qu.:0.0000   1st Qu.:0.0000
 10003  :  1             Median :0.000   Median :1.0000   Median :0.0000
 10004  :  1             Mean   :0.284   Mean   :0.6917   Mean   :0.4927
 10005  :  1             3rd Qu.:1.000   3rd Qu.:1.0000   3rd Qu.:1.0000
 10006  :  1             Max.   :1.000   Max.   :1.0000   Max.   :1.0000
 (Other):406
   fimtavg.1a       fimtavg.7a
 Min.   :0.4850   Min.   :0.5200
 1st Qu.:0.6950   1st Qu.:0.6850
 Median :0.7850   Median :0.7700
 Mean   :0.7936   Mean   :0.7849
 3rd Qu.:0.8712   3rd Qu.:0.8700
 Max.   :1.2800   Max.   :1.1850
                  NA's   :41
```

```
> cwimt <- wimt[complete.cases(wimt),]
> dim( cwimt )
```

```
[1] 371   7
```

```
> length( intersect( compl, cwimt$subjid ) )
```

```
[1] 371
```

```
> cc <- lm( fimtavg.7a ~ fimtavg.1a + met + o.65 + pre.ins + SDC,
+           data=cwimt )
> summary( cc )
```

```
Call:
lm(formula = fimtavg.7a ~ fimtavg.1a + met + o.65 + pre.ins +
    SDC, data = cwimt)

Residuals:
      Min        1Q    Median        3Q       Max
-0.246178 -0.039118  0.000996  0.042370  0.218314

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.111079   0.023192   4.790 2.43e-06
fimtavg.1a   0.839373   0.027631  30.378  < 2e-16
metMet       0.010418   0.007252   1.437   0.1517
o.65         0.020962   0.008412   2.492   0.0132
pre.ins      0.005352   0.008056   0.664   0.5069
SDC         -0.011232   0.007432  -1.511   0.1316

Residual standard error: 0.06966 on 365 degrees of freedom
Multiple R-squared:  0.7439,        Adjusted R-squared:  0.7404
F-statistic:   212 on 5 and 365 DF,  p-value: < 2.2e-16
```

We can now use the collected parameters from the two random-effects models to reproduce the effects from the conditional model:

```
> round( param, 4 )
```

```
         Model
Parameter Ran-eff, dif-B Ran-eff, eq-B
  sig2            0.0026        0.0026
  tau2            0.0146        0.0146
  rho             0.8467        0.8467
  int             0.7872        0.7800
  beta           -0.0135       -0.0124
  delta          -0.0149        0.0000
  gamma           0.0132        0.0109
  o.65            0.0888        0.0884
  pre.ins        -0.0061       -0.0065
  SDC            -0.0175       -0.0174
```

```
> round(
+ rbind( rho = c( coef(cc)["fimtavg.1a"], param["rho",] ),
+    met.eff = c( coef(cc)["metMet"], (1-param["rho",])*param["delta",]+param["gamma",] ),
+      sigma = c( summary(cc)$sigma^2, (param["sig2",]+param["tau2",])*(1-param["rho",]^2) ),
+  Intercept = c( coef(cc)["(Intercept)"], (1-param["rho",])*param["int",] + param["beta",] ),
+       o.65 = c( coef( cc )["o.65"], (1-param["rho",])*param["o.65",] ),
+    pre.ins = c( coef( cc )["pre.ins"], (1-param["rho",])*param["pre.ins",] ),
+        SDC = c( coef( cc )["SDC"], (1-param["rho",])*param["SDC",] ) ), 5 )
```

```
          fimtavg.1a Ran-eff, dif-B Ran-eff, eq-B
rho          0.83937       0.84667       0.84674
met.eff      0.01042       0.01091       0.01091
sigma        0.00485       0.00488       0.00488
Intercept    0.11108       0.10716       0.10716
o.65         0.02096       0.01361       0.01354
pre.ins      0.00535      -0.00094      -0.00100
SDC         -0.01123      -0.00269      -0.00266
```

We see that the coefficient of the baseline measurement is pretty close to the derived ρ, and the other parameters are pretty close too.

However, it is only in the latter case, assuming no mean difference between the baseline measurements in the two randomization groups that we have the conditional model estimating the same quantity (γ_{7m}) as in the random effects model:

```
> round( param["gamma",], 5 )
```

```
Ran-eff, dif-B  Ran-eff, eq-B
       0.01320        0.01091
```

```
> round( rbind(
+        ci.lin( mc, subset=":" ),
+        ci.lin( mr, subset="Met" ),
+        ci.lin( cc, subset="met" ) ), 4 )
```

```
                                  Estimate StdErr      z      P    2.5%  97.5%
visit7a:metMet                      0.0132 0.0075 1.7492 0.0803 -0.0016 0.0280
I((visit == "7a") * (met == "Met"))   0.0109 0.0073 1.5050 0.1323 -0.0033 0.0251
metMet                              0.0104 0.0073 1.4366 0.1508 -0.0038 0.0246
```

We see that the standard deviation of the treatment effect estimate is the same same in all three models, so the differences in p-values are merely attributable to the differences in effect-size under the different models.

Thus if we want to allow for baseline differences between the randomization groups in the comparison, the only way is to fit the random effects model. In this case there was a (non-significant) difference between the randomization groups:

```
> round( ci.lin( mc, subset="Met" ), 4 )
```

```
                Estimate StdErr       z      P    2.5%  97.5%
metMet           -0.0149 0.0136 -1.0954 0.2733 -0.0417 0.0118
visit7a:metMet    0.0132 0.0075  1.7492 0.0803 -0.0016 0.0280
```

— the metformin group had baseline measurements on average 0.015 mm smaller than the placebo group. This is the explanation that the model assuming equal mean baseline levels produces a smaller effect estimate (0.0109 / 0.0104) than the model correcting for the baseline difference (0.0132).

2.4.2 Mean change in each group

If we want to report the individual changes in each group, that is β_7 in the placebo group and $\beta_7 + \gamma_{m7}$ in the metformin group, these quantities are not available in the conditional model. This is because the intercept in the conditional model is $(1 - \rho)\mu + \beta_7$, with three parameters of which only ρ is known as the regression coefficient to y_1. The two others we have no handle on. Hence if we want to report the individual changes in each group, we *must* use a model that explicitly addresses these parameters. The conditional model deems these group changes irrelevant *a priori*.

Moreover, if we are going to report these alongside estimates from the conditional model, we should derive them from a model *not* correcting for baseline imbalance, otherwise we are reporting quantities from different models. But if we fit the random effects model without baseline correction we might as well report *all* parameters from that model — the core effect measure is not likely to be much different from that of the conditional model anyway.

2.5 Using multiply imputed data for random effects models

If we were to use the multiply imputed data for analysis by a proper random effects model we would simply construct a function that did this analysis based on the wide datsset, and use this on each of the imputed datasets, and then summarize the results.

Chapter 3

Glucose-related variables

Here is the documentation of the reading of the data:

```
1                                  "Program: gethbmv.sas"      13:54 Monday, September 16, 2013

NOTE: Copyright (c) 2002-2008 by SAS Institute Inc., Cary, NC, USA.
NOTE: SAS (r) Proprietary Software 9.2 (TS2M3)
      Licensed to NOVO NORDISK - BASIC PACKAGE, Site 50800704.
NOTE: This session is executing on the W32_VSPRO  platform.



NOTE: SAS initialization used:
      real time           4.39 seconds
      cpu time            0.42 seconds


NOTE: AUTOEXEC processing beginning; file is c:\stat\sas\autoexec.sas.

---------------------------------------------------------------
C:\Bendix\Steno\LLCh\CIMT\sas\gethbmv.sas
---------------------------------------------------------------
NOTE: Libref HER was successfully assigned as follows:
      Engine:        V9
      Physical Name: C:\Bendix\Steno\LLCh\CIMT\sas
NOTE: Libref DATA was successfully assigned as follows:
      Engine:        V9
      Physical Name: C:\Bendix\Steno\LLCh\CIMT\data

NOTE: AUTOEXEC processing completed.

1          option validvarname = v6;
2
3          libname    hba xport '../data/hba.xpt' ;
NOTE: Libref HBA was successfully assigned as follows:
      Engine:        XPORT
      Physical Name: C:\Bendix\Steno\LLCh\CIMT\data\hba.xpt
4          libname    hyp xport '../data/hyp.xpt' ;
NOTE: Libref HYP was successfully assigned as follows:
      Engine:        XPORT
      Physical Name: C:\Bendix\Steno\LLCh\CIMT\data\hyp.xpt
5          libname    sae xport '../data/sae.xpt' ;
NOTE: Libref SAE was successfully assigned as follows:
      Engine:        XPORT
      Physical Name: C:\Bendix\Steno\LLCh\CIMT\data\sae.xpt
6          libname src2rd       '../data' ;
NOTE: Libname SRC2RD refers to the same physical library as DATA.
NOTE: Libref SRC2RD was successfully assigned as follows:
      Engine:        V9
      Physical Name: C:\Bendix\Steno\LLCh\CIMT\data
7
8          proc copy  in = src2rd   out = hba ;
9            select hba ;
10         run ;

NOTE: Copying SRC2RD.HBA to HBA.HBA (memtype=DATA).
NOTE: Data file SRC2RD.HBA.DATA is in a format that is native to another host, or the file encoding does not match the
      session encoding. Cross Environment Data Access will be used, which might require additional CPU resources and
      might reduce performance.
NOTE: The variable name insdose_doegn_kg has been truncated to insdose_.
NOTE: The variable insdose_ now has a label set to insdose_doegn_kg.
NOTE: The variable name insdose_doegn has been truncated to insdose_.
NOTE: The variable insdose_ now has a label set to insdose_doegn.
NOTE: Variable INSDOSE_ already exists on file HBA.HBA, using INSDOSE2 instead.
NOTE: The variable name above_sixtyfive has been truncated to above_si.
NOTE: The variable above_si now has a label set to above_sixtyfive.
```

```
NOTE: The variable name prior_ins has been truncated to prior_in.
NOTE: The variable prior_in now has a label set to prior_ins.
NOTE: The variable name MetforminCode has been truncated to Metformi.
NOTE: The variable Metformi now has a label set to MetforminCode.
NOTE: The variable name InsulinTypeCode has been truncated to InsulinT.
NOTE: The variable InsulinT now has a label set to InsulinTypeCode.
NOTE: There were 2581 observations read from the data set SRC2RD.HBA.
NOTE: The data set HBA.HBA has 2581 observations and 12 variables.
NOTE: PROCEDURE COPY used (Total process time):
      real time           0.84 seconds
      cpu time            0.01 seconds


11
12         proc copy  in = src2rd   out = hyp ;
13           select hypo ;
14         run ;

NOTE: Copying SRC2RD.HYPO to HYP.HYPO (memtype=DATA).
NOTE: Data file SRC2RD.HYPO.DATA is in a format that is native to another host, or the file encoding does not match the
      session encoding. Cross Environment Data Access will be used, which might require additional CPU resources and
      might reduce performance.
NOTE: The variable name sum_episodes_ikke_klaret_selv has been truncated to sum_epis.
NOTE: The variable sum_epis now has a label set to sum_episodes_ikke_klaret_selv.
NOTE: The variable name sum_episodes_ikke_klaret_selv_v has been truncated to sum_epis.
NOTE: The variable sum_epis now has a label set to sum_episodes_ikke_klaret_selv_v.
NOTE: Variable SUM_EPIS already exists on file HYP.HYPO, using SUM_EPI2 instead.
NOTE: The variable name severe_hypo_sum has been truncated to severe_h.
NOTE: The variable severe_h now has a label set to severe_hypo_sum.
NOTE: The variable name MetforminCode has been truncated to Metformi.
NOTE: The variable Metformi now has a label set to MetforminCode.
NOTE: The variable name InsulinTypeCode has been truncated to InsulinT.
NOTE: The variable InsulinT now has a label set to InsulinTypeCode.
NOTE: The variable name above_sixtyfive has been truncated to above_si.
NOTE: The variable above_si now has a label set to above_sixtyfive.
NOTE: The variable name prior_ins has been truncated to prior_in.
NOTE: The variable prior_in now has a label set to prior_ins.
NOTE: The variable name any_severe_hypo has been truncated to any_seve.
NOTE: The variable any_seve now has a label set to any_severe_hypo.
2 "Program: gethbmv.sas"                                                                    13:54 Monday, September 16, 2013

WARNING: Engine XPORT does not support SORTEDBY operations.  SORTEDBY information cannot be copied.
NOTE: There were 415 observations read from the data set SRC2RD.HYPO.
NOTE: The data set HYP.HYPO has 415 observations and 11 variables.
NOTE: PROCEDURE COPY used (Total process time):
      real time           0.14 seconds
      cpu time            0.03 seconds


15
16         proc contents data = src2rd.sae ;
NOTE: Data file SRC2RD.SAE.DATA is in a format that is native to another host, or the file encoding does not match the
      session encoding. Cross Environment Data Access will be used, which might require additional CPU resources and
      might reduce performance.
17         run ;

NOTE: PROCEDURE CONTENTS used (Total process time):
      real time           0.54 seconds
      cpu time            0.06 seconds

NOTE: The PROCEDURE CONTENTS printed page 1.

18
19         data sae ;
20           set src2rd.sae ( drop=desc ) ;
NOTE: Data file SRC2RD.SAE.DATA is in a format that is native to another host, or the file encoding does not match the
      session encoding. Cross Environment Data Access will be used, which might require additional CPU resources and
      might reduce performance.
21         run ;

NOTE: There were 155 observations read from the data set SRC2RD.SAE.
NOTE: The data set WORK.SAE has 155 observations and 5 variables.
NOTE: DATA statement used (Total process time):
      real time           0.11 seconds
      cpu time            0.01 seconds


22
23         proc copy  in = work   out = sae ;
24           select sae ;
25         run ;

NOTE: Copying WORK.SAE to SAE.SAE (memtype=DATA).
NOTE: There were 155 observations read from the data set WORK.SAE.
NOTE: The data set SAE.SAE has 155 observations and 5 variables.
NOTE: PROCEDURE COPY used (Total process time):
      real time           0.07 seconds
      cpu time            0.00 seconds
```

```
NOTE: SAS Institute Inc., SAS Campus Drive, Cary, NC USA 27513-2414
NOTE: The SAS System used:
      real time           6.88 seconds
      cpu time            0.63 seconds

The SAS System                                                          13:54 Monday, September 16, 2013   1

The CONTENTS Procedure

Data Set Name        SRC2RD.SAE                             Observations          155
Member Type          DATA                                   Variables             6
Engine               V9                                     Indexes               0
Created              12. september 2013 torsdag 15:29:36    Observation Length    672
Last Modified        12. september 2013 torsdag 15:29:36    Deleted Observations  0
Protection                                                  Compressed            NO
Data Set Type                                               Sorted                NO
Label
Data Representation  WINDOWS_64
Encoding             wlatin1  Western (Windows)


                  Engine/Host Dependent Information

Data Set Page Size          16384
Number of Data Set Pages    7
First Data Page             1
Max Obs per Page            24
Obs in First Data Page      21
Number of Data Set Repairs  0
Filename                    C:\Bendix\Steno\LLCh\CIMT\data\sae.sas7bdat
Release Created             9.0301M2
Host Created                X64_7PRO


      Alphabetic List of Variables and Attributes

#    Variable    Type    Len    Format       Informat

2    DATE        Num       8    DDMMYY10.    DDMMYY10.
3    DESC        Char    547    $547.        $547.
5    LLT1        Char     37    $37.         $37.
6    SOC1        Char     67    $67.         $67.
1    SUBJID      Num       8    BEST12.      BEST32.
4    TYPE        Char      3    $3.          $3.
```

3.1 Hb_{A1c}

```
> options( width=110 )
> library( Epi )
> library( foreign )
> library( lme4 )
> hba <- read.xport( "./data/hba.xpt" )
> names( hba ) <- tolower( names( hba ) )
> names( hba ) <- gsub( "_", ".", names( hba ) )
> hba$grp <- factor( hba$metformi, labels=c("plc","met") )
> names( hba )[2] <- "inspw"
> str( hba )


'data.frame':        2581 obs. of  13 variables:
 $ subjid  : num  10001 10001 10001 10001 10001 ...
 $ inspw   : num  0.115 0.442 0.53 0.515 0.51 ...
 $ visit   : num  1 2 3 4 5 6 7 1 2 3 ...
 $ insdose2: num  14 54 64 64 64 70 70 14 38 40 ...
 $ weight  : num  122 122 121 124 125 ...
 $ hba1c   : num  7.9 7.1 6.3 5.9 6.1 6.8 6.3 7.6 7.5 6.9 ...
 $ randdate: Factor w/ 412 levels "01-03-2010 08:40:50 CET",..: 372 372 372 372 372 372 372 386 386
 $ above.si: num  1 1 1 1 1 1 1 1 1 1 ...
 $ prior.in: num  0 0 0 0 0 0 0 0 0 0 ...
 $ sdc     : num  0 0 0 0 0 0 0 0 0 0 ...
 $ metformi: num  1 1 1 1 1 1 1 0 0 0 ...
 $ insulint: num  3 3 3 3 3 3 3 3 3 3 ...
 $ grp     : Factor w/ 2 levels "plc","met": 2 2 2 2 2 2 2 1 1 1 ...
```

```
> summary( hba )
```

```
     subjid          inspw            visit          insdose2         weight           hba1c
 Min.   :10001   Min.   :0.04561   Min.   :1.000   Min.   :  4.00   Min.   : 63.30   Min.   : 4.600
 1st Qu.:60015   1st Qu.:0.52658   1st Qu.:2.000   1st Qu.: 48.00   1st Qu.: 87.70   1st Qu.: 7.200
 Median :90019   Median :0.82549   Median :4.000   Median : 81.50   Median : 97.60   Median : 7.900
 Mean   :70510   Mean   :0.97791   Mean   :3.917   Mean   : 98.85   Mean   : 98.78   Mean   : 8.092
 3rd Qu.:91109   3rd Qu.:1.24402   3rd Qu.:6.000   3rd Qu.:130.00   3rd Qu.:108.30   3rd Qu.: 8.800
 Max.   :91231   Max.   :4.62863   Max.   :7.000   Max.   :518.00   Max.   :152.00   Max.   :13.400
                 NA's   :3                         NA's   :3
                     randdate       above.si         prior.in          sdc            metformi
 01-03-2010 10:01:33 CET :   7   Min.   :0.0000   Min.   :0.0000   Min.   :0.0000   Min.   :0.0000
 01-04-2009 08:19:12 CEDT:   7   1st Qu.:0.0000   1st Qu.:0.0000   1st Qu.:0.0000   1st Qu.:0.0000
 01-04-2009 09:53:02 CEDT:   7   Median :0.0000   Median :1.0000   Median :1.0000   Median :1.0000
 01-07-2009 14:40:11 CEDT:   7   Mean   :0.2883   Mean   :0.6916   Mean   :0.5021   Mean   :0.5138
 01-11-2010 08:34:19 CET :   7   3rd Qu.:1.0000   3rd Qu.:1.0000   3rd Qu.:1.0000   3rd Qu.:1.0000
 01-11-2010 08:36:48 CET :   7   Max.   :1.0000   Max.   :1.0000   Max.   :1.0000   Max.   :1.0000
 (Other)                 :2539
    insulint      grp
 Min.   :1.000   plc:1255
 1st Qu.:1.000   met:1326
 Median :2.000
 Mean   :2.014
 3rd Qu.:3.000
 Max.   :3.000
```

How many persons with how many measurements

```
> ( tt <- with( hba, table(table(subjid)) ) )
```

```
  1   2   3   4   5   6   7
 21  16   6   7  16  20 326
```

```
> round( 100*tt/sum(tt), 1 )
```

```
   1    2    3    4    5    6    7
 5.1  3.9  1.5  1.7  3.9  4.9 79.1
```

3.1.1 The complete cases

We select for a start those with complete follow-up

```
> vv <- with( hba, table(subjid) )
> cplv <- names( vv[vv==7] )
> hbc <- subset( hba, subjid %in% cplv )
> with( hba, table(table(subjid)) )
```

```
  1   2   3   4   5   6   7
 21  16   6   7  16  20 326
```

```
> with( hbc, table(table(subjid)) )
```

```
  7
326
```

```
> names( hbc )
```

```
 [1] "subjid"   "inspw"    "visit"    "insdose2" "weight"   "hba1c"    "randdate" "above.si" "prior.
[10] "sdc"      "metformi" "insulint" "grp"
```

We set up a random effects model using `lmer`

```
> mc <- lmer( hba1c ~ grp + grp:factor(visit) - 1 +
+                     factor(sdc) + factor(above.si) + factor(prior.in) +
+                     (1|subjid), data=hbc )
> ma <- update( mc, data=hba )
> ( eM <- cbind(1,rbind(0,diag(6))) )
```

```
     [,1] [,2] [,3] [,4] [,5] [,6] [,7]
[1,]    1    0    0    0    0    0    0
[2,]    1    1    0    0    0    0    0
[3,]    1    0    1    0    0    0    0
[4,]    1    0    0    1    0    0    0
[5,]    1    0    0    0    1    0    0
[6,]    1    0    0    0    0    1    0
[7,]    1    0    0    0    0    0    1
```

```
> ci.lin( mc )
```

```
                         Estimate     StdErr          z             P       2.5%       97.5%
grpplc                  8.3903161 0.11383428  73.706408 0.000000e+00  8.1672050  8.61342720
grpmet                  8.5229882 0.11244061  75.799912 0.000000e+00  8.3026087  8.74336776
factor(sdc)1           -0.1994041 0.09313140  -2.141105 3.226558e-02 -0.3819383 -0.01686991
factor(above.si)1      -0.3266977 0.10084108  -3.239728 1.196437e-03 -0.5243426 -0.12905280
factor(prior.in)1       0.3626956 0.10078985   3.598533 3.200169e-04  0.1651512  0.56024010
grpplc:factor(visit)2   0.1405229 0.07728432   1.818259 6.902461e-02 -0.0109516  0.29199735
grpmet:factor(visit)2  -0.6271676 0.07267985  -8.629182 6.179254e-18 -0.7696175 -0.48471774
grpplc:factor(visit)3  -0.3388018 0.07757285  -4.367531 1.256589e-05 -0.4908418 -0.18676183
grpmet:factor(visit)3  -0.9229740 0.07279907 -12.678377 7.792891e-37 -1.0656576 -0.78029046
grpplc:factor(visit)4  -0.3342506 0.07742776  -4.316935 1.582110e-05 -0.4860062 -0.18249496
grpmet:factor(visit)4  -0.9335260 0.07267985 -12.844358 9.251648e-38 -1.0759759 -0.79107612
grpplc:factor(visit)5  -0.3633987 0.07728432  -4.702101 2.574975e-06 -0.5148732 -0.21192422
grpmet:factor(visit)5  -0.9121387 0.07267985 -12.550091 3.970546e-36 -1.0545886 -0.76968884
grpplc:factor(visit)6  -0.4505794 0.07757292  -5.808463 6.304912e-09 -0.6026195 -0.29853926
grpmet:factor(visit)6  -0.9028879 0.07279906 -12.402466 2.534041e-35 -1.0455714 -0.76020435
grpplc:factor(visit)7  -0.4860592 0.07674559  -6.333383 2.398436e-10 -0.6364778 -0.33564059
grpmet:factor(visit)7  -0.8551529 0.07249825 -11.795497 4.117645e-32 -0.9972468 -0.71305892
```

```
> c.plc <- ci.lin( mc, ctr.mat=eM, subset="plc" )[,-(2:4)]
> c.met <- ci.lin( mc, ctr.mat=eM, subset="met" )[,-(2:4)]
> c.dif <- ci.lin( mc, subset=c("met","plc"), ctr.mat=cbind(-eM,eM) )
> round( c.dif, 3 )
```

```
     Estimate StdErr      z     P   2.5% 97.5%
[1,]   -0.133  0.115 -1.155 0.248 -0.358 0.093
[2,]    0.635  0.115  5.527 0.000  0.410 0.860
[3,]    0.452  0.115  3.920 0.000  0.226 0.677
[4,]    0.467  0.115  4.057 0.000  0.241 0.692
[5,]    0.416  0.115  3.621 0.000  0.191 0.641
[6,]    0.320  0.115  2.775 0.006  0.094 0.545
[7,]    0.236  0.114  2.066 0.039  0.012 0.461
```

```
> ci.lin( ma )
```

```
                        Estimate     StdErr          z            P        2.5%       97.5%
grpplc                 8.4112931 0.10883155  77.287269 0.000000e+00  8.19798721  8.62459904
grpmet                 8.5305443 0.10925211  78.081279 0.000000e+00  8.31641409  8.74467448
factor(sdc)1          -0.1170267 0.09170689  -1.276095 2.019220e-01 -0.29676887  0.06271551
factor(above.si)1     -0.3400086 0.09972468  -3.409473 6.508862e-04 -0.53546536 -0.14455178
factor(prior.in)1      0.3372593 0.09955364   3.387715 7.047750e-04  0.14213779  0.53238088
grpplc:factor(visit)2  0.2398171 0.07149836   3.354162 7.960566e-04  0.09968289  0.37995130
grpmet:factor(visit)2 -0.5847396 0.07062367  -8.279656 1.235319e-16 -0.72315949 -0.44631980
grpplc:factor(visit)3 -0.2518710 0.07293298  -3.453458 5.534487e-04 -0.39481696 -0.10892495
grpmet:factor(visit)3 -0.8864332 0.07111621 -12.464573 1.164940e-35 -1.02581843 -0.74704800
grpplc:factor(visit)4 -0.2652236 0.07347752  -3.609589 3.066826e-04 -0.40923694 -0.12121035
grpmet:factor(visit)4 -0.8761372 0.07159759 -12.236966 1.972695e-34 -1.01646594 -0.73580856
grpplc:factor(visit)5 -0.2633456 0.07429404  -3.544640 3.931500e-04 -0.40895926 -0.11773197
grpmet:factor(visit)5 -0.8411384 0.07198693 -11.684598 1.528004e-31 -0.98223019 -0.70004660
grpplc:factor(visit)6 -0.3677517 0.07619067  -4.826729 1.387938e-06 -0.51708271 -0.21842076
grpmet:factor(visit)6 -0.8558165 0.07292811 -11.735071 8.425572e-32 -0.99875297 -0.71288004
grpplc:factor(visit)7 -0.3478157 0.07150816  -4.864000 1.150370e-06 -0.48796913 -0.20766228
grpmet:factor(visit)7 -0.7666058 0.07088658 -10.814540 2.937636e-27 -0.90554090 -0.62767061
```

```
> a.plc <- ci.lin( ma, ctr.mat=cbind(1,rbind(0,diag(6))), subset="plc" )[,-(2:4)]
> a.met <- ci.lin( ma, ctr.mat=cbind(1,rbind(0,diag(6))), subset="met" )[,-(2:4)]
> a.dif <- ci.lin( ma, subset=c("met","plc"), ctr.mat=cbind(-eM,eM) )
> round( a.dif, 3 )
```

```
     Estimate StdErr      z     P   2.5% 97.5%
[1,]   -0.119  0.109 -1.093 0.274 -0.333 0.095
[2,]    0.705  0.112  6.316 0.000  0.486 0.924
[3,]    0.515  0.113  4.564 0.000  0.294 0.737
[4,]    0.492  0.114  4.330 0.000  0.269 0.714
[5,]    0.459  0.114  4.011 0.000  0.234 0.683
[6,]    0.369  0.116  3.175 0.001  0.141 0.596
[7,]    0.300  0.112  2.678 0.007  0.080 0.519
```

```
> P.all <- Wald( ma, H0=rep(0,7), subset=c("met","plc"), ctr.mat=cbind(eM,-eM) )
> P.last<- Wald( ma, H0=0, subset=c("met","plc"), ctr.mat=cbind(eM,-eM)[7,,drop=F] )
> win.metafile( "hba1c.emf", width=10, height=6, pointsize=20 )
> eclr <- c("yellow","green","orange")
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1,
+      bg=#"black",
+         "transparent",
+      col.axis=eclr[4], col.lab=eclr[4], bty="n" )
> matplot( 0:6*3, cbind( a.plc, a.met ),
+          xlab="Months since trial entry", xaxt="n", xlim=c(0,19.5),
+          ylim=c(7,9.5),  yaxs="i", yaxt="n",
+          ylab=expression( "Hb"*A[1][c]*" (%)  [Mean (95% CI)]" ),
+          type="n", lwd=c(4,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> # abline( h=seq(7,9.5,0.5), col=gray(0.5) )
> matlines( 0:6*3, cbind( a.plc, a.met ),
+          type="l", lwd=c(5,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> axis( side=1, at=0:6*3, col=eclr[4] )
> axis( side=2, at=7:9, col=eclr[4] )
> text( c(20,20), c(9.1,9.3), c("Placebo","Metformin"), col=eclr[1:2],
+      font=2, adj=1, cex=1 )
> text( 20, 8.8, substitute( "Equal Hb"*A[1][c]*" 0-18 mth: P ="*pval,
+                            list(pval = formatC( P.all[3], format="f", digits=3 )) ),
+       col=eclr[4], adj=1 )
> text( 20, 8.6,substitute( "Equal Hb"*A[1][c]*" at end: P ="*pval,
+                            list(pval = formatC( P.last[3], format="f", digits=3 )) ),
+       col=eclr[4], adj=1 )
```

```
> # text( 19.2, 8.55, "HbA1c change\n from baseline", col=eclr[4], adj=c(1,1) )
> text( c(20,20), c(a.plc[7,1],a.met[7,1]),
+       paste( formatC( c(a.plc[7,1],a.met[7,1])-c(a.plc[1,1],a.met[1,1]),
+                       format="f", digits=1 ), "%", sep="" ),
+       col=eclr[1:2], adj=1 )
> dev.off()


null device
          1
```

3.2 Insulin dose

3.2.1 The complete cases

We select for a start those with complete follow-up

```
> vv <- with( hba, table(subjid) )
> cplv <- names( vv[vv==7] )
> hbc <- subset( hba, subjid %in% cplv )
> with( hba, table(table(subjid)) )


  1   2   3   4   5   6   7
 21  16   6   7  16  20 326


> with( hbc, table(table(subjid)) )


  7
326


> names( hbc )


 [1] "subjid"   "inspw"    "visit"    "insdose2" "weight"   "hba1c"    "randdate" "above.si" "prior.
[10] "sdc"      "metformi" "insulint" "grp"


> with( hba, tapply( inspw, visit, function(x) sum( !is.na(x) ) ) )


  1   2   3   4   5   6   7
410 381 367 359 350 329 382


> with( hba, tapply( inspw, visit, function(x) sum(  is.na(x) ) ) )


1 2 3 4 5 6 7
2 1 0 0 0 0 0
```

We set up a random effects model using `lmer`

```
> mc <- lmer( inspw ~ grp + grp:factor(visit) - 1 +
+                     factor(sdc) + factor(above.si) + factor(prior.in) +
+                     (1|subjid),
+            data = subset( hba, visit!=7) )
> round( ci.lin( mc ), 3 )
```

```
                     Estimate StdErr      z     P   2.5%  97.5%
grpplc                  0.316  0.059  5.382 0.000  0.201  0.431
grpmet                  0.335  0.059  5.702 0.000  0.220  0.451
factor(sdc)1            0.101  0.051  1.976 0.048  0.001  0.202
factor(above.si)1      -0.175  0.056 -3.134 0.002 -0.284 -0.065
factor(prior.in)1       0.235  0.056  4.219 0.000  0.126  0.345
grpplc:factor(visit)2   0.557  0.030 18.824 0.000  0.499  0.616
grpmet:factor(visit)2   0.324  0.029 11.133 0.000  0.267  0.382
grpplc:factor(visit)3   0.714  0.030 23.656 0.000  0.655  0.773
grpmet:factor(visit)3   0.413  0.029 14.069 0.000  0.355  0.470
grpplc:factor(visit)4   0.775  0.030 25.467 0.000  0.715  0.834
grpmet:factor(visit)4   0.451  0.030 15.270 0.000  0.393  0.509
grpplc:factor(visit)5   0.815  0.031 26.473 0.000  0.754  0.875
grpmet:factor(visit)5   0.474  0.030 15.953 0.000  0.416  0.532
grpplc:factor(visit)6   0.835  0.032 26.464 0.000  0.774  0.897
grpmet:factor(visit)6   0.495  0.030 16.433 0.000  0.436  0.554
```

```
> ( eM <- cbind(1,rbind(0,diag(5))) )
```

```
     [,1] [,2] [,3] [,4] [,5] [,6]
[1,]    1    0    0    0    0    0
[2,]    1    1    0    0    0    0
[3,]    1    0    1    0    0    0
[4,]    1    0    0    1    0    0
[5,]    1    0    0    0    1    0
[6,]    1    0    0    0    0    1
```

```
> c.plc <- ci.lin( mc, ctr.mat=eM, subset="plc" )[,-(2:4)]
> c.met <- ci.lin( mc, ctr.mat=eM, subset="met" )[,-(2:4)]
> c.dif <- ci.lin( mc, subset=c("met","plc"), ctr.mat=cbind(eM,-eM) )
> round( c.dif, 3 )
```

```
     Estimate StdErr      z     P   2.5%  97.5%
[1,]    0.019  0.056  0.344 0.731 -0.091  0.129
[2,]   -0.214  0.057 -3.746 0.000 -0.326 -0.102
[3,]   -0.282  0.057 -4.903 0.000 -0.394 -0.169
[4,]   -0.304  0.058 -5.270 0.000 -0.417 -0.191
[5,]   -0.321  0.058 -5.538 0.000 -0.435 -0.207
[6,]   -0.321  0.059 -5.480 0.000 -0.436 -0.206
```

```
> P.all <- Wald( mc, H0=rep(0,6), subset=c("met","plc"), ctr.mat=cbind(eM,-eM) )
> P.last<- Wald( mc, H0=0, subset=c("met","plc"), ctr.mat=cbind(eM,-eM)[6,,drop=F] )
```

For annotation we compute the empirical mean insulin doses in each of the randomization groups, at visit 6:

```
> ( IL <- with( hba, tapply( insdose2, list( metformi, visit), mean ) )[,6] )
```

```
       0        1
130.03896  99.76571
```

```
> eclr <- c("yellow","green","orange")
> win.metafile( "inspw.emf", width=10, height=6, pointsize=20 )
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1,
+      bg=#"black",
+         "transparent",
+      col.axis=eclr[4], col.lab=eclr[4], bty="n" )
> matplot( 0:5*3, cbind( c.plc, c.met ),
+          xlab="Months since trial entry", xaxt="n", xlim=c(0,18),
+          ylim=c(0,1.3),  yaxs="i", yaxt="n",
+          ylab=expression( "Insulin (IU/kg/day) [Mean (95% CI)]" ),
+          type="n", lwd=c(4,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> abline( h=seq(7,9.5,0.5), col=gray(0.5) )
> matlines( 0:5*3, cbind( c.plc, c.met ),
+           type="l", lwd=c(5,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> axis( side=1, at=0:6*3, col=eclr[4] )
> axis( side=2, at=seq(0,1.2,0.2), col=eclr[4] )
> text( c(18,18), c(0.35,0.45), c("Placebo","Metformin"), col=eclr[1:2],
+      font=2, adj=1, cex=1 )
> text( 18, 0.2, paste( "Equal insulin dose 0-15 mth: P =",
+                       formatC( P.all[3], format="f", digits=3 ) ),
+       col=eclr[4], adj=1 )
> text( 18, 0.1, paste( "Equal insulin dose at end: P =",
+                       formatC( P.last[3], format="f", digits=3 ) ),
+       col=eclr[4], adj=1 )
> text( c(18,18), c(c.plc[6,1],c.met[6,1]),
+       paste( round(IL), "IU/day"), col=eclr[1:2], adj=1 )
> dev.off()


null device
          1
```

3.3 Weight

We use the same dataset as before:

```
> names( hba )


 [1] "subjid"   "inspw"    "visit"    "insdose2" "weight"   "hba1c"    "randdate" "above.si" "prior.
[10] "sdc"      "metformi" "insulint" "grp"


> with( hba, tapply( weight, visit, function(x) sum( !is.na(x) ) ) )


  1   2   3   4   5   6   7
412 382 367 359 350 329 382


> with( hba, tapply( weight, visit, function(x) sum(  is.na(x) ) ) )


1 2 3 4 5 6 7
0 0 0 0 0 0 0
```

3.3.1 Absolute weight

We set up a random effects model using `lmer`

```
> mc <- lmer( weight ~ grp + grp:factor(visit) - 1 +
+                      factor(sdc) + factor(above.si) + factor(prior.in) +
+                      (1|subjid),
+             data = hba )
> round( ci.lin( mc ), 3 )
```

```
                     Estimate StdErr      z     P    2.5%   97.5%
grpplc                100.792  1.668 60.421 0.000  97.522 104.062
grpmet                100.941  1.676 60.234 0.000  97.656 104.225
factor(sdc)1           -1.856  1.528 -1.215 0.225  -4.851   1.139
factor(above.si)1      -8.282  1.664 -4.978 0.000 -11.542  -5.021
factor(prior.in)1      -0.628  1.658 -0.379 0.705  -3.878   2.622
grpplc:factor(visit)2   1.295  0.267  4.852 0.000   0.772   1.818
grpmet:factor(visit)2   0.374  0.263  1.421 0.155  -0.142   0.889
grpplc:factor(visit)3   2.516  0.272  9.234 0.000   1.982   3.050
grpmet:factor(visit)3   0.928  0.265  3.502 0.000   0.409   1.447
grpplc:factor(visit)4   3.388  0.275 12.339 0.000   2.850   3.926
grpmet:factor(visit)4   1.462  0.267  5.478 0.000   0.939   1.985
grpplc:factor(visit)5   3.805  0.278 13.706 0.000   3.261   4.349
grpmet:factor(visit)5   1.278  0.268  4.763 0.000   0.752   1.804
grpplc:factor(visit)6   4.285  0.285 15.050 0.000   3.727   4.843
grpmet:factor(visit)6   1.591  0.272  5.854 0.000   1.059   2.124
grpplc:factor(visit)7   4.152  0.267 15.547 0.000   3.629   4.676
grpmet:factor(visit)7   1.522  0.264  5.764 0.000   1.004   2.039
```

```
> ( eM <- cbind(1,rbind(0,diag(6))) )
```

```
     [,1] [,2] [,3] [,4] [,5] [,6] [,7]
[1,]    1    0    0    0    0    0    0
[2,]    1    1    0    0    0    0    0
[3,]    1    0    1    0    0    0    0
[4,]    1    0    0    1    0    0    0
[5,]    1    0    0    0    1    0    0
[6,]    1    0    0    0    0    1    0
[7,]    1    0    0    0    0    0    1
```

```
> c.plc <- ci.lin( mc, ctr.mat=eM, subset="plc" )[,-(2:4)]
> c.met <- ci.lin( mc, ctr.mat=eM, subset="met" )[,-(2:4)]
> c.dif <- ci.lin( mc, subset=c("met","plc"), ctr.mat=cbind(eM,-eM) )
> round( c.dif, 3 )
```

```
     Estimate StdErr      z     P   2.5% 97.5%
[1,]    0.149  1.512  0.098 0.922 -2.815 3.112
[2,]   -0.773  1.515 -0.510 0.610 -3.742 2.197
[3,]   -1.439  1.516 -0.949 0.342 -4.412 1.533
[4,]   -1.778  1.517 -1.172 0.241 -4.751 1.196
[5,]   -2.379  1.518 -1.567 0.117 -5.354 0.596
[6,]   -2.545  1.520 -1.675 0.094 -5.524 0.434
[7,]   -2.482  1.515 -1.638 0.101 -5.451 0.488
```

```
> P.all <- Wald( mc, H0=rep(0,7), subset=c("met","plc"), ctr.mat=cbind(eM,-eM) )
> P.last<- Wald( mc, H0=0, subset=c("met","plc"), ctr.mat=cbind(eM,-eM)[7,,drop=F] )
```

```
> win.metafile( "weight.emf", width=10, height=6, pointsize=24 )
> eclr <- c("yellow","green","orange")
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1,
+      bg=#"black",
+         "transparent",
+      col.axis=eclr[4], col.lab=eclr[4], bty="n" )
> matplot( 0:6*3, cbind( c.plc, c.met ),
+          xlab="Months since trial entry", xaxt="n", xlim=c(0,18),
+          ylim=c(90,110),
+          yaxs="i", yaxt="n",
+          ylab=expression( "Weight (kg) [Mean (95% CI)]" ),
+          type="n", lwd=c(4,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> # abline( h=seq(7,9.5,0.5), col=gray(0.5) )
> matlines( 0:6*3, cbind( c.plc, c.met ),
+           type="l", lwd=c(5,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> axis( side=1, at=0:6*3, col=eclr[4] )
> axis( side=2, at=seq(90,110,5), col=eclr[4] )
> text( c(17,17), c(0.25,0.35), c("Placebo","Metformin"), col=eclr[1:2],
+      font=2, adj=1, cex=1 )
> text( 17, 0.15, paste( "Equal insulin dose 0-15 mth: P =",
+                        formatC( P.all[3], format="f", digits=3 ) ),
+       col=eclr[4], adj=1 )
> text( 17, 0.1, paste( "Equal insulin dose at end: P =",
+                        formatC( P.last[3], format="f", digits=3 ) ),
+       col=eclr[4], adj=1 )
> dev.off()


null device
          1
```

3.3.2 Weight change

The fitted model also contains the estimates of the weight change, it is merely a question of changing the contrast matrix, by replacing the 1-row that fishes out the baseline at time 0 by a row of 0s that fixes the effect at time 0 to 0, and hence the estimates to changes:

```
> round( ci.lin( mc ), 3 )
```

	Estimate	StdErr	z	P	2.5%	97.5%
grpplc	100.792	1.668	60.421	0.000	97.522	104.062
grpmet	100.941	1.676	60.234	0.000	97.656	104.225
factor(sdc)1	-1.856	1.528	-1.215	0.225	-4.851	1.139
factor(above.si)1	-8.282	1.664	-4.978	0.000	-11.542	-5.021
factor(prior.in)1	-0.628	1.658	-0.379	0.705	-3.878	2.622
grpplc:factor(visit)2	1.295	0.267	4.852	0.000	0.772	1.818
grpmet:factor(visit)2	0.374	0.263	1.421	0.155	-0.142	0.889
grpplc:factor(visit)3	2.516	0.272	9.234	0.000	1.982	3.050
grpmet:factor(visit)3	0.928	0.265	3.502	0.000	0.409	1.447
grpplc:factor(visit)4	3.388	0.275	12.339	0.000	2.850	3.926
grpmet:factor(visit)4	1.462	0.267	5.478	0.000	0.939	1.985
grpplc:factor(visit)5	3.805	0.278	13.706	0.000	3.261	4.349
grpmet:factor(visit)5	1.278	0.268	4.763	0.000	0.752	1.804
grpplc:factor(visit)6	4.285	0.285	15.050	0.000	3.727	4.843
grpmet:factor(visit)6	1.591	0.272	5.854	0.000	1.059	2.124
grpplc:factor(visit)7	4.152	0.267	15.547	0.000	3.629	4.676
grpmet:factor(visit)7	1.522	0.264	5.764	0.000	1.004	2.039

```
> ( eM <- cbind(0,rbind(0,diag(6))) )
```

```
     [,1] [,2] [,3] [,4] [,5] [,6] [,7]
[1,]    0    0    0    0    0    0    0
[2,]    0    1    0    0    0    0    0
[3,]    0    0    1    0    0    0    0
[4,]    0    0    0    1    0    0    0
[5,]    0    0    0    0    1    0    0
[6,]    0    0    0    0    0    1    0
[7,]    0    0    0    0    0    0    1
```

```
> c.plc <- ci.lin( mc, ctr.mat=eM, subset="plc" )[,-(2:4)]
> c.met <- ci.lin( mc, ctr.mat=eM, subset="met" )[,-(2:4)]
> c.dif <- ci.lin( mc, subset=c("met","plc"), ctr.mat=cbind(eM,-eM) )
> round( c.dif, 3 )
```

```
     Estimate StdErr      z     P   2.5%  97.5%
[1,]    0.000  0.000    NaN   NaN  0.000  0.000
[2,]   -0.921  0.375 -2.458 0.014 -1.656 -0.187
[3,]   -1.588  0.380 -4.178 0.000 -2.333 -0.843
[4,]   -1.926  0.383 -5.031 0.000 -2.677 -1.176
[5,]   -2.527  0.386 -6.546 0.000 -3.284 -1.771
[6,]   -2.694  0.394 -6.843 0.000 -3.465 -1.922
[7,]   -2.630  0.376 -7.004 0.000 -3.366 -1.894
```

```
> P.all <- Wald( mc, H0=rep(0,6), subset=c("met","plc"), ctr.mat=cbind(eM,-eM)[-1,] )
> P.last<- Wald( mc, H0=0, subset=c("met","plc"), ctr.mat=cbind(eM,-eM)[7,,drop=F] )
```

```
> win.metafile( "wchg.emf", width=10, height=6, pointsize=20 )
> eclr <- c("yellow","green","orange")
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1,
+      bg=#"black",
+         "transparent",
+      col.axis=eclr[4], col.lab=eclr[4], bty="n" )
> matplot( 0:6*3, cbind( c.plc, c.met ),
+          xlab="Months since trial entry", xaxt="n", xlim=c(0,18),
+          ylim=c(0,6.2), yaxt="n",
+          ylab=expression( "Weight change (kg) [Mean (95% CI)]" ),
+          type="n", lwd=c(4,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> # abline( h=seq(7,9.5,0.5), col=gray(0.5) )
> matlines( 0:6*3, cbind( c.plc, c.met ),
+           type="l", lwd=c(5,1,1), lty=1, col=rep(eclr[1:2],each=3) )
> axis( side=1, at=0:6*3, col=eclr[4] )
> axis( side=2, at=0:6, col=eclr[4] )
> text( c(0.5,0.5), c(5.7,6.2), c("Placebo","Metformin"), col=eclr[1:2],
+      font=2, adj=0, cex=1 )
> text( 0.5, 5.2, paste( "Equal weight change 0-18 mth: P =",
+                        formatC( P.all[3], format="f", digits=3 ) ),
+       col=eclr[4], adj=0 )
> text( 0.5, 4.7, paste( "Equal weight change end: P =",
+                        formatC( P.last[3], format="f", digits=3 ) ),
+       col=eclr[4], adj=0 )
> dev.off()
```

```
null device
          1
```