Neuropathy outcomes in CIMT

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Contents

Chapter 1

Data

1.1 Data from original CIMT project

The original data from the CIMT project are in the files `base.Rda` and `AD.Rda`:

```
> library( Epi )
> library( dplyr )
> library( foreign )
> options( width = 85 )
> clear()
> load( "~/sdc/proj/CIMT/data/base.Rda" )
> load( "~/sdc/proj/CIMT/data/AD.Rda" )
> lls()
  name mode      class      dim            size(Kb)
1 AD   list      data.frame 2587 187        3,587.6
2 base list      data.frame 412 111           351.4
3 clr  character character  4                   0.3
4 gN   character character  2                   0.2
5 iclr character character  4                   0.3
6 iN   character character  3                   0.3
```

Here is a brief overview of the variables available in the baseline dataset for the CIMT-study:

```
> names( base )
  [1] "subjid"   "grp"      "igr"      "over.65"  "pre.ins"  "sdc"      "birthdat"
  [8] "visitdat" "sex"      "diabetes" "peri.neu" "auto.neu" "laserbeh" "sys1.b0"
 [15] "dia1.b0"  "sys2.b0"  "dia2.b0"  "pulse.b0" "microalb" "macroalb" "e.gfr"
 [22] "b1bdato"  "smoking." "alcohol." "hba1c.b1" "hba1c.b7" "gluc.b1a" "gluc.b7a"
 [29] "cpep.b1a" "cpep.b7a" "ins.b1a"  "ins.b7a"  "chol.b1a" "chol.b7a" "trig.b1a"
 [36] "trig.b7a" "ldl.b1a"  "ldl.b7a"  "vldl.b1a" "vldl.b7a" "hdlc.b1a" "hdlc.b7a"
 [43] "gad65.b1" "weight.b" "weight.2" "height.b" "height.2" "talje.b1" "talje.b7"
 [50] "hofte.b1" "hofte.b7" "avgnatua" "avgnatu2" "metformi" "su"       "statin"
 [57] "fibrat"   "lipids"   "asa"      "thyre"    "apurin"   "nsaid"    "painkill"
 [64] "antidep"  "gaba"     "impo"     "ntg"      "gastro"   "contrace" "antibiot"
 [71] "dvit"     "calc"     "alendr"   "bvit"     "lung"     "other"    "plataggr"
 [78] "iron"     "fishoil"  "othernat" "loop.ccb" "dvit.cal" "bvit.iro" "dob"
 [85] "dov"      "dodm"     "dor"      "caucas"   "gad.0"    "gad.pos"  "retin"
 [92] "cvd"      "ras"      "oah"      "oad"      "aav"      "dmdurav"  "xdate"
 [99] "xtype"    "total.sa" "any.sae." "allhypos" "sum.klar" "sevhypos" "any.hypo"
[106] "any.seve" "nonsevhy" "sae.sevh" "any.sae2" "any.nons" "pp"
```

First a brief overview of the number of time points (really records) for each patient in the CIMT study:

```
> with( base,            table(table(subjid))  )
  1
412
> with(   AD, addmargins(table(table(subjid))) )
  1   2   3   4   5   6   7 Sum
 21  16   6   7  16  14 332 412
```

— and the same subdivided by randomization group, which requires a bit of tweaking to get a nicely formatted table:

```
> Table <-
+ function(x)
+ {
+ tt <- rep(0,7)
+ names(tt) <- 1:7
+ TT <- table(x)[names(table(x))!="0"]
+ tt[as.numeric(names(TT))] <- TT
+ tt
+ }
> tt <- as.table( with( AD,
+                      apply( table(grp,
+                                   igr,
+                                   subjid),
+                             1:2,
+                             Table ) ) )
> names(dimnames(tt))[1] <- "No. records:"
> ftable( addmargins(tt), col.vars=1 )
         No. records:   1   2   3   4   5   6   7 Sum
grp igr
Plc Biph                3   2   1   0   2   1  58  67
    AspD                3   2   3   3   2   3  57  73
    Detm                7   5   1   1   6   4  42  66
    Sum                13   9   5   4  10   8 157 206
Met Biph                2   1   0   0   2   0  65  70
    AspD                2   3   1   1   3   4  51  65
    Detm                4   3   0   2   1   2  59  71
    Sum                 8   7   1   3   6   6 175 206
Sum Biph                5   3   1   0   4   1 123 137
    AspD                5   5   4   4   5   7 108 138
    Detm               11   8   1   3   7   6 101 137
    Sum                21  16   6   7  16  14 332 412
```

We also show how many persons met for each visit; first we verify that at most one record exist for each combination of visit and subject:

```
> with( AD, addmargins( table( table( visit, subjid ) ) ) )
   0    1  Sum
 297 2587 2884
> with( AD, ftable( addmargins( table( grp, igr, visit ) ) ) )
         visit   v1   v2   v3   v4   v5   v6   v7  Sum
grp igr
Plc Biph         67   63   61   61   60   58   62  432
    AspD         73   69   66   62   61   57   67  455
    Detm         66   57   53   52   46   43   55  372
    Sum         206  189  180  175  167  158  184 1259
```

```
Met Biph          70   68   67   67   67   65   65  469
    AspD          65   61   60   58   55   52   60  411
    Detm          71   65   64   62   61   60   65  448
    Sum          206  194  191  187  183  177  190 1328
Sum Biph         137  131  128  128  127  123  127  901
    AspD         138  130  126  120  116  109  127  866
    Detm         137  122  117  114  107  103  120  820
    Sum          412  383  371  362  350  335  374 2587
```

1.2 Merging with neuropathy and B12 data

We now read the data on the neuropathic outcomes (also including B12 measurements):

```
> neu <- read.xport( "./data/neuvar210217.xpt")
> names( neu ) <- tolower( names(neu) )
> sort( names( neu ) )
 [1] "b2b"     "bestvib" "cpul05"  "cpul15"  "cpul3"   "cpul5"   "cpul7"   "d3"
 [9] "d30"     "d5"      "d7"      "d90"     "dia_lig" "ecsort3" "ecsort5" "ecsort7"
[17] "esc37"   "mins37"  "minsys3" "minsys5" "osv37"   "osvim3"  "osvim5"  "osvim7"
[25] "pul05"   "pul1_5"  "pul3"    "pul5"    "pul7"    "resthr"  "s3"      "s30"
[33] "s5"      "s7"      "s90"     "subjid"  "sys_lig" "vibage"  "vibhcon" "vibvcon"
[41] "visit"

> levels( neu$visit )

[1] "1a" "7a"

> levels( neu$visit ) <- c("v1","v7")
> str( neu )

'data.frame':        807 obs. of  41 variables:
 $ subjid : num  10001 10001 10002 10002 10003 ...
 $ visit  : Factor w/ 2 levels "v1","v7": 1 2 1 2 1 2 1 2 1 2 ...
 $ vibhcon: num  50.1 50.1 13 19 15 14 37 32 36 35 ...
 $ vibvcon: num  50.1 50.1 14 28 15 14 50.1 42 42 40 ...
 $ b2b    : num  8 6 27 23 19 10 9 5 8 5 ...
 $ s30    : num  145 144 118 124 134 150 109 106 113 136 ...
 $ d30    : num  89 81 73 68 86 86 76 72 74 67 ...
 $ pul05  : num  98 86 82 74 96 82 71 72 103 87 ...
 $ s90    : num  152 146 137 153 133 151 108 116 134 139 ...
 $ d90    : num  90 76 80 69 88 84 80 76 85 70 ...
 $ pul1_5 : num  94 80 81 68 92 79 76 71 104 86 ...
 $ s3     : num  150 143 133 154 149 143 114 114 134 150 ...
 $ d3     : num  90 81 80 69 90 82 86 75 78 72 ...
 $ pul3   : num  93 80 79 66 92 78 74 71 102 89 ...
 $ s5     : num  155 134 135 154 149 162 114 113 134 149 ...
 $ d5     : num  92 81 78 71 89 94 89 78 89 78 ...
 $ pul5   : num  94 80 80 66 101 82 76 72 108 89 ...
 $ s7     : num  152 137 125 161 129 161 108 110 134 141 ...
 $ d7     : num  90 80 81 68 91 94 86 76 83 75 ...
 $ pul7   : num  94 82 80 67 98 82 79 73 102 86 ...
 $ resthr : num  83.5 76.5 72 61 78 73 67.5 65.5 87 72.5 ...
 $ dia_lig: num  89.5 78 74.5 62 87.5 85.5 90.5 78.5 73 64 ...
 $ sys_lig: num  146 138 120 124 150 ...
 $ minsys3: num  145 143 118 124 133 143 108 106 113 136 ...
 $ minsys5: num  145 134 118 124 133 143 108 106 113 136 ...
 $ mins37 : num  152 134 125 154 129 161 108 110 134 141 ...
```

```
 $ ecsort3: num  0 0 0 0 0 0 1 1 0 0 ...
 $ osvim3 : num  NA NA NA NA NA NA 1 1 NA NA ...
 $ ecsort5: num  0 0 0 0 0 0 1 1 0 0 ...
 $ osvim5 : num  NA NA NA NA NA NA 1 1 NA NA ...
 $ ecsort7: num  0 0 0 0 1 0 1 1 0 0 ...
 $ osvim7 : num  NA NA NA NA 1 NA 1 1 NA NA ...
 $ esc37  : num  NA NA NA NA 1 NA NA NA NA NA ...
 $ osv37  : num  NA NA NA NA NA NA NA NA NA NA ...
 $ cpul05 : num  14.5 9.5 10 13 18 9 3.5 6.5 16 14.5 ...
 $ cpul15 : num  10.5 3.5 9 7 14 6 8.5 5.5 17 13.5 ...
 $ cpul3  : num  9.5 3.5 7 5 14 5 6.5 5.5 15 16.5 ...
 $ cpul5  : num  10.5 3.5 8 5 23 9 8.5 6.5 21 16.5 ...
 $ cpul7  : num  10.5 5.5 8 6 20 9 11.5 7.5 15 13.5 ...
 $ vibage : num  1 1 0 0 0 0 1 0 1 0 ...
 $ bestvib: num  50.1 50.1 13 19 15 14 37 32 36 35 ...
```

Then read the vitamin B data:

```
> b12 <- read.xport( "./data/b12mma180917.xpt" )
> names( b12 ) <- tolower(names( b12 ))
> levels( b12$visit )
[1] "1a" "7a"
> levels( b12$visit ) <- c("v1","v7")
> # Doctoring of large value
> b12$b12 <- as.numeric( ifelse( b12$b12==">1476", "1500", b12$b12 ) )
> str( b12 )
'data.frame':        809 obs. of  4 variables:
 $ visit : Factor w/ 2 levels "v1","v7": 1 2 1 2 1 2 1 2 1 2 ...
 $ mma   : num  0.27 0.36 0.23 0.16 0.24 0.17 0.31 0.25 0.21 0.22 ...
 $ subjid: num  10001 10001 10002 10002 10003 ...
 $ b12   : num  47 50 255 210 51 43 193 289 214 134 ...
```

Then we merge the b12 data with the neuropathy data:

```
> intersect( names(neu), names(b12) )
[1] "subjid" "visit"
> dim( neu )
[1] 807  41
> neu <- merge( b12, neu )
> dim( neu )
[1] 807  43
```

Only include those with both baseline and follow-up records

```
> tt <- with( neu, addmargins(table(subjid,visit),2) )
> length( incl <- rownames(tt)[tt[,"Sum"]==2] )
[1] 373
```

Only include those with both baseline and follow-up records (and show how many)

```
> tt <- with( neu, addmargins(table(subjid,visit),2) )
> # How many with both BL & FU
> length( incl <- rownames(tt)[tt[,"Sum"]==2] )
[1] 373
> neu <- subset( neu, subjid %in% incl )
```

Once we have the neuropathy measurements for those who completed both neuropathy sessions, we can merge with the randomization data and select information from visits 1 and 7. Note that we do not specify `all` as argument to `merge`, meaning that we only get rows with id and visit from both `neu` and `AD`:

```
> str( AD[,1:7] )
'data.frame':        2587 obs. of  7 variables:
 $ subjid : int  10001 10001 10001 10001 10001 10001 10001 10002 10002 10002 ...
 $ grp    : Factor w/ 2 levels "Plc","Met": 2 2 2 2 2 2 2 1 1 1 ...
 $ igr    : Factor w/ 3 levels "Biph","AspD",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ over.65: Factor w/ 2 levels "<65",">65": 2 2 2 2 2 2 2 2 2 2 ...
 $ pre.ins: Factor w/ 2 levels "preIns","noIns": 2 2 2 2 2 2 2 2 2 2 ...
 $ sdc    : Factor w/ 2 levels "SDC","notSDC": 2 2 2 2 2 2 2 2 2 2 ...
 $ visit  : Factor w/ 7 levels "v1","v2","v3",..: 1 2 3 4 5 6 7 1 2 3 ...
> dim( AD )
[1] 2587  187
> dim( neu )
[1] 746  43
> wh <- c(1:26,39,51,84,118,121:127)
> names( AD )[wh]
 [1] "subjid"   "grp"      "igr"      "over.65"  "pre.ins"  "sdc"      "visit"
 [8] "weight"   "bmi"      "whr"      "hba1c"    "gluc"     "ins"      "idos"
[15] "ipkg"     "cpep"     "chol"     "ldl"      "hdl"      "vldl"     "trig"
[22] "sys"      "dia"      "pulse"    "vdate"    "dov"      "sex"      "e.gfr"
[29] "metformi" "caucas"   "retin"    "cvd"      "ras"      "oah"      "oad"
[36] "aav"      "dmdurav"
> ana <- merge( neu, AD[,wh], by=c("subjid","visit") )
> dim( ana )
[1] 744  78
> ana <- transform( ana, oah = factor( oah, labels=c("N","Y") ),
+                   metformi = factor( metformi, labels=c("N","Y") ),
+                        sex = factor( sex, labels=c("F","M") ),
+                     vibmax = pmin( vibhcon, vibvcon, na.rm=TRUE ) )
> str( ana )
'data.frame':        744 obs. of  79 variables:
 $ subjid  : num  10001 10001 10002 10002 10003 ...
 $ visit   : Factor w/ 2 levels "v1","v7": 1 2 1 2 1 2 1 2 1 2 ...
 $ mma     : num  0.27 0.36 0.23 0.16 0.24 0.17 0.31 0.25 0.21 0.22 ...
 $ b12     : num  47 50 255 210 51 43 193 289 214 134 ...
 $ vibhcon : num  50.1 50.1 13 19 15 14 37 32 36 35 ...
 $ vibvcon : num  50.1 50.1 14 28 15 14 50.1 42 42 40 ...
 $ b2b     : num  8 6 27 23 19 10 9 5 8 5 ...
 $ s30     : num  145 144 118 124 134 150 109 106 113 136 ...
 $ d30     : num  89 81 73 68 86 86 76 72 74 67 ...
 $ pul05   : num  98 86 82 74 96 82 71 72 103 87 ...
 $ s90     : num  152 146 137 153 133 151 108 116 134 139 ...
 $ d90     : num  90 76 80 69 88 84 80 76 85 70 ...
 $ pul1_5  : num  94 80 81 68 92 79 76 71 104 86 ...
 $ s3      : num  150 143 133 154 149 143 114 114 134 150 ...
 $ d3      : num  90 81 80 69 90 82 86 75 78 72 ...
 $ pul3    : num  93 80 79 66 92 78 74 71 102 89 ...
 $ s5      : num  155 134 135 154 149 162 114 113 134 149 ...
 $ d5      : num  92 81 78 71 89 94 89 78 89 78 ...
```

```
$ pul5    : num  94 80 80 66 101 82 76 72 108 89 ...
$ s7      : num  152 137 125 161 129 161 108 110 134 141 ...
$ d7      : num  90 80 81 68 91 94 86 76 83 75 ...
$ pul7    : num  94 82 80 67 98 82 79 73 102 86 ...
$ resthr  : num  83.5 76.5 72 61 78 73 67.5 65.5 87 72.5 ...
$ dia_lig : num  89.5 78 74.5 62 87.5 85.5 90.5 78.5 73 64 ...
$ sys_lig : num  146 138 120 124 150 ...
$ minsys3 : num  145 143 118 124 133 143 108 106 113 136 ...
$ minsys5 : num  145 134 118 124 133 143 108 106 113 136 ...
$ mins37  : num  152 134 125 154 129 161 108 110 134 141 ...
$ ecsort3 : num  0 0 0 0 0 0 1 1 0 0 ...
$ osvim3  : num  NA NA NA NA NA NA 1 1 NA NA ...
$ ecsort5 : num  0 0 0 0 0 0 1 1 0 0 ...
$ osvim5  : num  NA NA NA NA NA NA 1 1 NA NA ...
$ ecsort7 : num  0 0 0 0 1 0 1 1 0 0 ...
$ osvim7  : num  NA NA NA NA 1 NA 1 1 NA NA ...
$ esc37   : num  NA NA NA NA 1 NA NA NA NA NA ...
$ osv37   : num  NA NA NA NA NA NA NA NA NA NA ...
$ cpul05  : num  14.5 9.5 10 13 18 9 3.5 6.5 16 14.5 ...
$ cpul15  : num  10.5 3.5 9 7 14 6 8.5 5.5 17 13.5 ...
$ cpul3   : num  9.5 3.5 7 5 14 5 6.5 5.5 15 16.5 ...
$ cpul5   : num  10.5 3.5 8 5 23 9 8.5 6.5 21 16.5 ...
$ cpul7   : num  10.5 5.5 8 6 20 9 11.5 7.5 15 13.5 ...
$ vibage  : num  1 1 0 0 0 0 1 0 1 0 ...
$ bestvib : num  50.1 50.1 13 19 15 14 37 32 36 35 ...
$ grp     : Factor w/ 2 levels "Plc","Met": 2 2 1 1 1 1 1 1 1 1 ...
$ igr     : Factor w/ 3 levels "Biph","AspD",..: 1 1 1 1 2 2 1 1 1 1 ...
$ over.65 : Factor w/ 2 levels "<65",">65": 2 2 2 2 1 1 1 1 1 1 ...
$ pre.ins : Factor w/ 2 levels "preIns","noIns": 2 2 2 2 1 1 2 2 1 1 ...
$ sdc     : Factor w/ 2 levels "SDC","notSDC": 2 2 2 2 2 2 2 2 2 2 ...
$ weight  : num  121.7 124.2 66.8 71 98.8 ...
$ bmi     : num  33 33.7 25.1 26.7 34.2 ...
$ whr     : num  1.103 1.058 0.968 0.968 1.042 ...
$ hba1c   : num  7.9 6.3 7.6 6.1 9.3 7.9 8.9 7.4 8.7 7.2 ...
$ gluc    : num  12.6 8.9 10.4 8.3 9.2 4.3 10.6 9.9 10.6 9.5 ...
$ ins     : num  60 132 56 32 134 18 66 78 249 219 ...
$ idos    : num  14 NA 14 NA 40 NA 14 NA 70 NA ...
$ ipkg    : num  0.115 NA 0.21 NA 0.405 ...
$ cpep    : num  1192 1017 829 473 932 ...
$ chol    : num  4.4 4 3.8 4.2 3.6 5 2.6 3.9 4.6 4.9 ...
$ ldl     : num  2.3 2.3 1.7 1.6 1.9 3.3 0.6 2.2 2.8 2.7 ...
$ hdl     : num  1.3 1.22 1.66 2.08 1.01 1.17 0.5 0.75 0.81 0.83 ...
$ vldl    : num  0.8 0.5 0.5 0.5 0.7 0.6 1.5 1 1 1.4 ...
$ trig    : num  1.82 1.03 1.03 1.05 1.61 1.27 3.31 2.1 2.28 3.09 ...
$ sys     : num  149 148 128 107 156 ...
$ dia     : num  86 77.5 75.5 66.5 93 NA 83.5 81 60 72.5 ...
$ pulse   : num  89 87 77 73 80 NA 85 69 77 78 ...
$ vdate   : Date, format: "2008-09-22" "2010-03-22" ...
$ dov     : num  2009 2010 2009 2010 2009 ...
$ sex     : Factor w/ 2 levels "F","M": 2 2 1 1 1 1 1 1 2 2 ...
$ e.gfr   : num  151 151 81 81 135 135 60 60 145 145 ...
$ metformi: Factor w/ 2 levels "N","Y": 2 2 2 2 2 2 2 2 2 2 ...
$ caucas  : num  1 1 1 1 1 1 1 1 1 1 ...
$ retin   : Factor w/ 3 levels "None","Simplex",..: 3 3 1 1 1 1 1 1 2 2 ...
$ cvd     : logi  FALSE FALSE FALSE FALSE FALSE FALSE ...
$ ras     : logi  TRUE TRUE TRUE TRUE FALSE FALSE ...
$ oah     : Factor w/ 2 levels "N","Y": 2 2 2 2 1 1 2 2 1 1 ...
```

```
 $ oad     : logi  FALSE FALSE FALSE FALSE FALSE FALSE ...
 $ aav     : num  66.2 66.2 70.6 70.6 61.3 ...
 $ dmdurav : num  12.63 12.63 8.64 8.64 5.65 ...
 $ vibmax  : num  50.1 50.1 13 19 15 14 37 32 36 35 ...
```

```
> head( ana )
```

```
  subjid visit  mma b12 vibhcon vibvcon b2b s30 d30 pul05 s90 d90 pul1_5  s3 d3 pul3
1  10001    v1 0.27  47    50.1    50.1   8 145  89    98 152  90     94 150 90   93
2  10001    v7 0.36  50    50.1    50.1   6 144  81    86 146  76     80 143 81   80
3  10002    v1 0.23 255    13.0    14.0  27 118  73    82 137  80     81 133 80   79
4  10002    v7 0.16 210    19.0    28.0  23 124  68    74 153  69     68 154 69   66
5  10003    v1 0.24  51    15.0    15.0  19 134  86    96 133  88     92 149 90   92
6  10003    v7 0.17  43    14.0    14.0  10 150  86    82 151  84     79 143 82   78
   s5 d5 pul5  s7 d7 pul7 resthr dia_lig sys_lig minsys3 minsys5 mins37 ecsort3
1 155 92   94 152 90   94   83.5    89.5   146.0     145     145    152       0
2 134 81   80 137 80   82   76.5    78.0   138.5     143     134    134       0
3 135 78   80 125 81   80   72.0    74.5   120.0     118     118    125       0
4 154 71   66 161 68   67   61.0    62.0   124.0     124     124    154       0
5 149 89  101 129 91   98   78.0    87.5   149.5     133     133    129       0
6 162 94   82 161 94   82   73.0    85.5   156.0     143     143    161       0
  osvim3 ecsort5 osvim5 ecsort7 osvim7 esc37 osv37 cpul05 cpul15 cpul3 cpul5 cpul7
1     NA       0     NA       0     NA    NA    NA   14.5   10.5   9.5  10.5  10.5
2     NA       0     NA       0     NA    NA    NA    9.5    3.5   3.5   3.5   5.5
3     NA       0     NA       0     NA    NA    NA   10.0    9.0   7.0   8.0   8.0
4     NA       0     NA       0     NA    NA    NA   13.0    7.0   5.0   5.0   6.0
5     NA       0     NA       1      1     1    NA   18.0   14.0  14.0  23.0  20.0
6     NA       0     NA       0     NA    NA    NA    9.0    6.0   5.0   9.0   9.0
  vibage bestvib grp  igr over.65 pre.ins    sdc weight      bmi       whr hba1c
1      1    50.1 Met Biph     >65   noIns notSDC  121.7 33.01324 1.1034483   7.9
2      1    50.1 Met Biph     >65   noIns notSDC  124.2 33.69141 1.0578512   6.3
3      0    13.0 Plc Biph     >65   noIns notSDC   66.8 25.14208 0.9677419   7.6
4      0    19.0 Plc Biph     >65   noIns notSDC   71.0 26.72287 0.9677419   6.1
5      0    15.0 Plc AspD     <65  preIns notSDC   98.8 34.18685 1.0423729   9.3
6      0    14.0 Plc AspD     <65  preIns notSDC   97.8 33.84083 1.0254237   7.9
  gluc ins idos      ipkg cpep chol ldl  hdl vldl trig sys  dia pulse      vdate
1 12.6  60   14 0.1150370 1192  4.4 2.3 1.30  0.8 1.82 149 86.0    89 2008-09-22
2  8.9 132   NA        NA 1017  4.0 2.3 1.22  0.5 1.03 148 77.5    87 2010-03-22
3 10.4  56   14 0.2095808  829  3.8 1.7 1.66  0.5 1.03 128 75.5    77 2008-09-23
4  8.3  32   NA        NA  473  4.2 1.6 2.08  0.5 1.05 107 66.5    73 2010-03-26
5  9.2 134   40 0.4048583  932  3.6 1.9 1.01  0.7 1.61 156 93.0    80 2008-10-01
6  4.3  18   NA        NA  328  5.0 3.3 1.17  0.6 1.27  NA   NA    NA 2009-06-03
       dov sex e.gfr metformi caucas  retin   cvd   ras oah   oad      aav   dmdurav
1 2008.724   M   151        Y      1 Prolif FALSE  TRUE   Y FALSE 66.21492 12.632444
2 2010.219   M   151        Y      1 Prolif FALSE  TRUE   Y FALSE 66.21492 12.632444
3 2008.727   F    81        Y      1   None FALSE  TRUE   Y FALSE 70.55441  8.635181
4 2010.230   F    81        Y      1   None FALSE  TRUE   Y FALSE 70.55441  8.635181
5 2008.749   F   135        Y      1   None FALSE FALSE   N FALSE 61.28679  5.653662
6 2009.420   F   135        Y      1   None FALSE FALSE   N FALSE 61.28679  5.653662
  vibmax
1   50.1
2   50.1
3   13.0
4   19.0
5   15.0
6   14.0
```

```
> tail( ana )
```

```
    subjid visit  mma b12 vibhcon vibvcon b2b s30 d30 pul05 s90 d90 pul1_5  s3  d3
739  91229    v1 0.17 317    38.0      28  19 135  81    77 125  85     82 125  85
740  91229    v7 0.18 248    50.1      21  24 111  82    89 108  85     86 114  83
741  91230    v1 0.18  67    10.0      10  16 156 101    95 155 107    100 157 114
742  91230    v7 0.16  95    12.0      14   8 156 116   104 163 118    104 157 124
743  91231    v1 0.25 212    24.0      22   3 121  81   109 139  87    106 123  86
744  91231    v7 0.21 207    25.0      20   3 103  63   101 128  82    102 133  77
    pul3  s5  d5 pul5  s7  d7 pul7 resthr dia_lig sys_lig minsys3 minsys5 mins37
739   83 124  86   85 132  86   85   68.5    74.0   119.5     125      124     124
740   91 114  80   87 113  86   91   71.0    75.0   121.0     108      108     113
741  110 161 103  113 158 104  112   81.5    90.0   142.5     155      155     158
742  109 155 118  109 155 114  111   86.5   107.5   164.0     156      155     155
743  109 138  86  101 124  87  106   94.5    88.0   143.0     121      121     124
744  103 146  74  102 126  71   99   95.0    70.5   151.5     103      103     126
    ecsort3 osvim3 ecsort5 osvim5 ecsort7 osvim7 esc37 osv37 cpul05 cpul15 cpul3
739       0     NA       0     NA       0     NA    NA    NA    8.5   13.5  14.5
740       0     NA       0     NA       0     NA    NA    NA   18.0   15.0  20.0
741       0     NA       0     NA       0     NA    NA    NA   13.5   18.5  28.5
742       0     NA       0     NA       0     NA    NA    NA   17.5   17.5  22.5
743       1      1       1      1       1      1    NA    NA   14.5   11.5  14.5
744       1      1       1      1       1      1    NA    NA    6.0    7.0   8.0
    cpul5 cpul7 vibage bestvib grp  igr over.65 pre.ins sdc weight      bmi
739  16.5  16.5      0      28 Plc AspD     <65  preIns SDC  118.3 34.56538
740  16.0  20.0      0      21 Plc AspD     <65  preIns SDC  121.3 35.44193
741  31.5  30.5      0      10 Met Detm     <65  preIns SDC   87.2 29.13562
742  22.5  24.5      0      12 Met Detm     <65  preIns SDC   85.9 28.70126
743   6.5  11.5      0      22 Met Biph     <65  preIns SDC  103.0 36.93212
744   7.0   4.0      0      20 Met Biph     <65  preIns SDC  113.3 40.62534
         whr hba1c gluc ins idos      ipkg cpep chol ldl  hdl vldl trig   sys   dia
739 1.0087719  10.9 15.0 124   70 0.5917160 1370  4.1 2.5 0.87  0.8 1.68 121.0  70.5
740 1.0825688  10.1  6.9  19   NA        NA  249  3.9 2.5 0.80  0.6 1.25 122.5  84.0
741 0.9357798   8.3  7.6  46   34 0.3899083  676  6.8 3.9 1.68  1.2 2.69 161.0 106.5
742 1.0185185   8.2 13.3  83   NA        NA 1446  7.4  NA 1.66   NA 6.34 136.0  93.0
743 1.1363636   7.8 10.9  51   56 0.5436893  883  3.6  NA 0.76   NA 5.92 127.0  84.5
744 0.8550725   7.5  8.9  NA   NA        NA   NA  4.1  NA 0.93   NA 7.15 149.5  87.0
    pulse      vdate      dov sex e.gfr metformi caucas   retin   cvd  ras oah   oad
739    85 2011-04-06 2011.259   M   184        Y      1    None FALSE TRUE   N FALSE
740    72 2012-07-04 2012.505   M   184        Y      1    None FALSE TRUE   N FALSE
741    92 2011-04-15 2011.284   F   133        Y      1 Simplex FALSE TRUE   N FALSE
742    91 2012-09-17 2012.710   F   133        Y      1 Simplex FALSE TRUE   N FALSE
743    85 2011-04-06 2011.259   M    97        Y      1  Prolif  TRUE TRUE   Y FALSE
744    90 2012-09-03 2012.672   M    97        Y      1  Prolif  TRUE TRUE   Y FALSE
        aav   dmdurav vibmax
739 46.85832  7.211499     28
740 46.85832  7.211499     21
741 52.35318  5.212868     10
742 52.35318  5.212868     12
743 62.68309 10.212183     22
744 62.68309 10.212183     20
```

1.3 Analysis variables

We shall analyze the following variables and assess to what extent they are influenced by the treatment (that is how much the change from visit 1 to visit 7 in these variables differ between the treatment groups).

1.3.1 Pulse variables

We have the pulse variable (`rethr`) and the pulse after getting up, so we construct the *changes*:

```
> ana <- mutate( ana, chp30  = resthr - pul05,
+                     chp90  = resthr - pul1_5,
+                     chp180 = resthr - pul3 )
```

1.3.2 Blood pressure variables

We have the blood pressure(s) in the lying position and after standing up at 0.5, 1.5, 3, 5 and 7 minutes, the latter 5 used to compute the drop in blood pressure since standing up:

```
> ana <- mutate( ana, dc30 = dia_lig - d30,
+                     dc90 = dia_lig - d90,
+                     dc3  = dia_lig - d3 ,
+                     dc5  = dia_lig - d5 ,
+                     dc7  = dia_lig - d7 ,
+                     sc30 = sys_lig - s30,
+                     sc90 = sys_lig - s90,
+                     sc3  = sys_lig - s3 ,
+                     sc5  = sys_lig - s5 ,
+                     sc7  = sys_lig - s7 )
```

It is thought that early blood pressure drop is sign of autonomous neuropathy. Measurements beyond 3 minutes are not of any particular interest, so we shall not include these in analyses.

1.3.3 Target variables

The variables of interest are shown in table 1.1. In this vein we define the variables of interest from the data frame in two sets, one set of analysis variables and one set for baseline variables (allocation, confounders and potential predictors):

```
> wh <- c("vibhcon","vibvcon","b2b",
+         "resthr","chp30","chp90","chp180",
+         "dia_lig","dc30","dc90","dc3",
+         "sys_lig","sc30","sc90","sc3",
+         "ecsort3","vibage","b12","mma","metformi","hba1c")
> bv <- c("grp","igr","oah","sex")
> match( wh, names(ana) )
 [1]  5  6  7 23 80 81 82 24 83 84 85 25 88 89 90 29 42  4  3 70 52
> match( bv, names(ana) )
[1] 44 45 75 68
> save( ana, file="./data/ana.Rda" )
```

1.3.4 Relationship between variables

We can briefly show how the relevant variables relate to each other:

```
> pairs( ana[,wh[-length(wh)]], gap=0,
+        lower.panel=function(x,y) points(x[ana$visit=="v1"],
+                                         y[ana$visit=="v1"],
+                                         pch=16, cex=0.2),
+        upper.panel=function(x,y) points(x[ana$visit=="v7"],
+                                         y[ana$visit=="v7"],
+                                         pch=16, cex=0.2) )
```

1.3.5 Baseline and follow-up

In the analysis of these variables we need both the baseline values (`visit == v1`) and the follow-up values (`visit == v7`) in the same record. Hence we merge the records from visit 1 with those from visit 7 on the subject id (`subjid`). Note that we use the `select=` so that all other variables than the target variables refer to baseline values:

```
> ana1 <- merge( subset( ana, visit=="v1", select=c("subjid",bv,wh) ),
+                subset( ana, visit=="v7", select=c("subjid"   ,wh) ),
+                by="subjid" )
> dim( ana )
[1] 744  92
> dim( ana1 )
[1] 372  47
> head( ana1 )
  subjid grp  igr oah sex vibhcon.x vibvcon.x b2b.x resthr.x chp30.x chp90.x
1  10001 Met Biph   Y   M      50.1      50.1     8     83.5   -14.5   -10.5
```

Table 1.1: *Table of target (outcome) variables for the analyses of CIMT interventions on neuropathy.*

Name — Meaning	units
`vibhcon` — vibration sense, right — right-censored at 50	volt
`vibvcon` — vibration sense, left — right-censored at 50	volt
`b2b` — beat-to-beat	ratio
`resthr` — resting heart rate	bpm
`chp30` — pulse change after 30 sec	bpm
`chp90` — pulse change after 90 sec	bpm
`chp180` — pulse change after 180 sec	bpm
`dia_lig` — diastolic blood pressure in lying position	mmHg
`dc30` — diastolic blood pressure change 30 sec after standing	mmHg
`dc90` — diastolic blood pressure change 90 sec after standing	mmHg
`dc3` — diastolic blood pressure change 3 min after standing	mmHg
`sys_lig` — systolic blood pressure in lying position	mmHg
`sc30` — systolic blood pressure change 30 sec after standing	mmHg
`sc90` — systolic blood pressure change 90 sec after standing	mmHg
`sc3` — systolic blood pressure change 3 min after standing	mmHg
`ecsort3` — ECS criteria for orthostatic hypertension met	Y/N
`vibage` — age-corrected vibration sensation threshold	Y/N

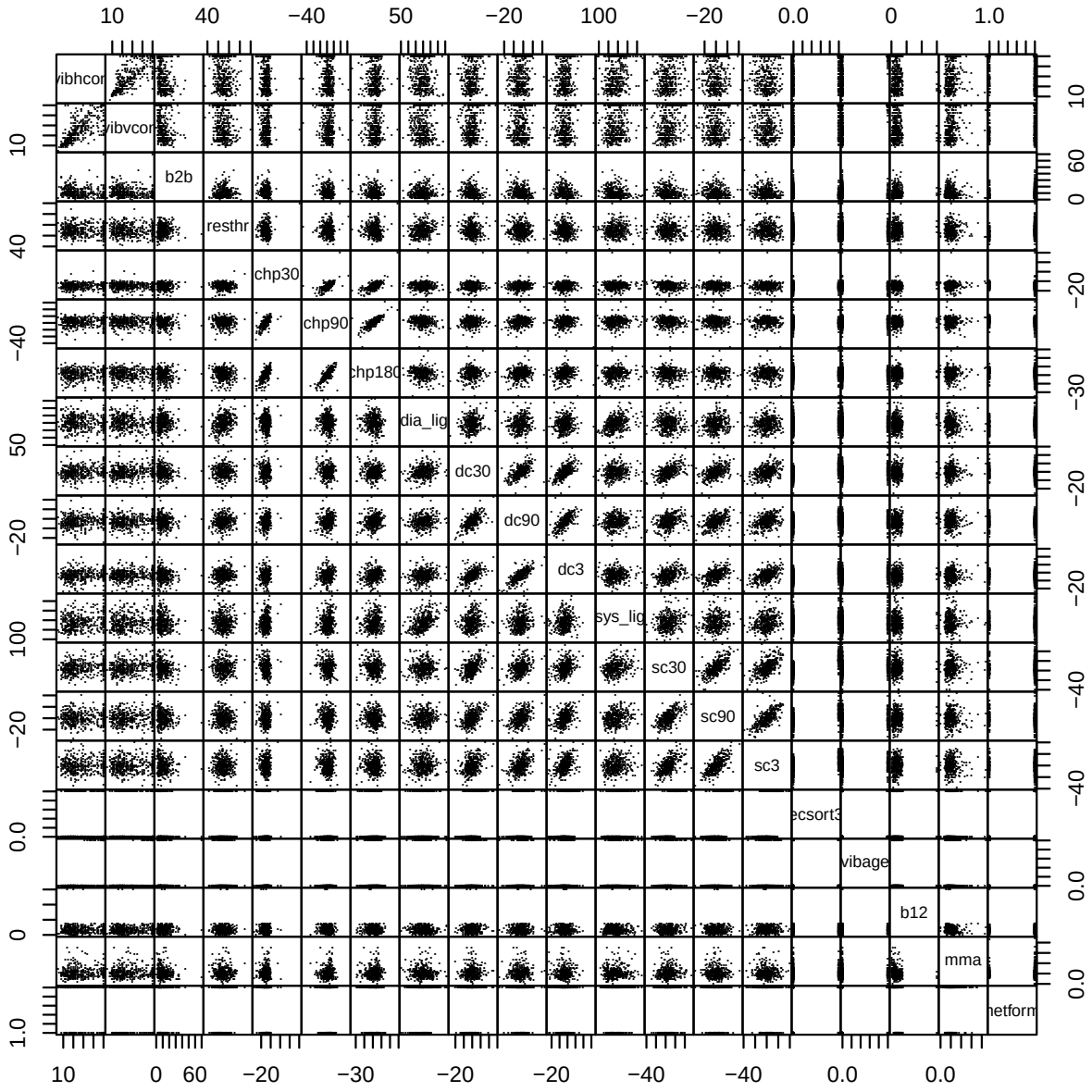

Figure 1.1: *Pairwise scatter-plots of the variables in* `ana`*. Panels below the diagonal are for values from visit 1; panels above diagonal for values from visit 7. It is seen that strong correlations mainly exist between blood pressure variables.* `./graph/neu-pairs`

```
2  10002 Plc Biph   Y   F      13.0      14.0    27     72.0   -10.0    -9.0
3  10003 Plc AspD   N   F      15.0      15.0    19     78.0   -18.0   -14.0
4  10004 Plc Biph   Y   F      37.0      50.1     9     67.5    -3.5    -8.5
5  10005 Plc Biph   N   M      36.0      42.0     8     87.0   -16.0   -17.0
6  10006 Plc Biph   Y   M      22.0      32.0    11     58.5   -14.5   -13.5
  chp180.x dia_lig.x dc30.x dc90.x dc3.x sys_lig.x sc30.x sc90.x sc3.x ecsort3.x
1     -9.5      89.5    0.5   -0.5  -0.5     146.0    1.0   -6.0  -4.0         0
2     -7.0      74.5    1.5   -5.5  -5.5     120.0    2.0  -17.0 -13.0         0
3    -14.0      87.5    1.5   -0.5  -2.5     149.5   15.5   16.5   0.5         0
4     -6.5      90.5   14.5   10.5   4.5     126.0   17.0   18.0  12.0         1
```

```
5    -15.0      73.0   -1.0  -12.0  -5.0     127.0   14.0   -7.0  -7.0         0
6    -11.5      86.0    4.0   -5.0   1.0     149.5   15.5   -0.5  -3.5         0
  vibage.x b12.x mma.x metformi.x hba1c.x vibhcon.y vibvcon.y b2b.y resthr.y chp30.y
1        1    47  0.27          Y     7.9      50.1      50.1     6     76.5    -9.5
2        0   255  0.23          Y     7.6      19.0      28.0    23     61.0   -13.0
3        0    51  0.24          Y     9.3      14.0      14.0    10     73.0    -9.0
4        1   193  0.31          Y     8.9      32.0      42.0     5     65.5    -6.5
5        1   214  0.21          Y     8.7      35.0      40.0     5     72.5   -14.5
6        0    41  0.20          Y     8.6      17.0      18.0    10     58.5   -16.5
  chp90.y chp180.y dia_lig.y dc30.y dc90.y dc3.y sys_lig.y sc30.y sc90.y sc3.y
1    -3.5     -3.5      78.0   -3.0    2.0  -3.0     138.5   -5.5   -7.5  -4.5
2    -7.0     -5.0      62.0   -6.0   -7.0  -7.0     124.0    0.0  -29.0 -30.0
3    -6.0     -5.0      85.5   -0.5    1.5   3.5     156.0    6.0    5.0  13.0
4    -5.5     -5.5      78.5    6.5    2.5   3.5     132.5   26.5   16.5  18.5
5   -13.5    -16.5      64.0   -3.0   -6.0  -8.0     125.5  -10.5  -13.5 -24.5
6   -15.5    -14.5      86.0   12.0    9.0   9.0     133.5   31.5   15.5  23.5
  ecsort3.y vibage.y b12.y mma.y metformi.y hba1c.y
1         0        1    50  0.36          Y     6.3
2         0        0   210  0.16          Y     6.1
3         0        0    43  0.17          Y     7.9
4         1        0   289  0.25          Y     7.4
5         0        0   134  0.22          Y     7.2
6         1        0    15  0.21          Y     7.1
```

By the convention of the `merge` function the baseline values of the variables are suffixed by `.x` (because they are from the dataset mentioned first) and the follow-up values by `.y` (because they are from the dataset mentioned last).

Thus we now have a dataset with one record per person, with baseline values ("`.x`") and follow-up values ("`.y`") for the variables of interest, as well as the only confounder we shall use, `oah`, use of oral anti-hypertensive drugs.

Chapter 2

Analysis

The purpose of the analysis is to see to what extent the different treatment regimens in CIMT influence changes in neuropathy between visit 1 and 7. In this context neuropathy is defined as represented by the variables in table 1.1 above.

2.1 Statistical models and interpretation

We consider the value at the follow up for the i^{th} person, y_{fi}, as a function of the treatment regimen $r = (\text{Met}, \text{Plc}) \times (\text{Biph}, \text{AspD}, \text{Detm})$ while controlling for the baseline value, y_{bi}, for the i^{th} person and possibly other confounders:

$$y_{fi} = \mu + \delta_r + \beta y_{bi} + e_i$$

The difference $\delta_r - \delta_s$ represents the difference in the follow-up values between treatment regimens r and s controlled for the baseline value. It is neither the mean difference between the follow-up values under the two regimens, nor the mean difference between the changes. It is the mean difference between follow-up means between regimens *conditional* on having the `same` baseline value — this is essentially what it means to "control" for baseline value.

Note that the model assumes that the *difference* in change between treatments is independent of the baseline value, although the the changes are not. Comparing treatment groups r and s at follow-up conditional on the same baseline value for the two persons, $y_{bi} = y_b$, say, gives:

regimen	follow-up: y_{fi}	change: $y_{fi} - y_{bi}$
r	$\mu + \delta_r + \beta y_b$	$\mu + \delta_r + (\beta - 1) y_b$
s	$\mu + \delta_s + \beta y_b$	$\mu + \delta_s + (\beta - 1) y_b$
treatment difference	$\delta_r - \delta_s$	$\delta_r - \delta_s$

Hence the treatment differences both for follow-up and change are independent of the baseline values, but it is also seen that the changes themselves from baseline to follow-up are not. Thus, the change depend on the baseline value in both treatment groups. But they do so in the same way, so the *difference* in change between treatments is independent of the baseline value.

2.1.1 Model diagnostics

In order to check essential model assumptions we make three diagnostic plots for each outcome variable analyzed:

1. To check if there is a non-linear effect of the predictor we plot the residuals versus the fitted values. This should exhibit a horizontal relationship on average.
2. The assumption of normality of residuals is checked by a QQ-plot of the residuals; this plot will also reveal substantial skewness of residuals that might suggest some sort of transformation.
3. The homogeneity of variance across the range is checked by plotting the standardized residual versus the fitted values. This should also reveal a horizontal relationship.)

Thus for each variable we get three plots illuminating different aspects of the fit.

2.2 Continuous responses

2.2.1 Effects of B12 and methyl malonic acid

We expand analyses by including also `b12` and `mma` as explanatory variables (with linear effect) added to the model with metformin only. The target for inference is the *change* in the variables, this the differnec in these variable from baseline to follow-up is included in the model.

Since we believe that these variable are *mediators* we expect the estimated metform effect to be smaller when these variables are included in the model, we include the variables only in the model where metformin allocation is the only allocation variable incuded.

2.2.2 Beat-to-beat

This is in the variable `b2b`, so we use this as response variable when fitting models with effect of metformin/placebo alone, insulin regimen alone, with both effects and with the interaction between the two — the latter corresponding to 6 treatment groups:

```
> n.b2   <- lm( b2b.y ~ b2b.x, data = ana1 )
> m.b2   <- update( n.b2, . ~ . + grp )
> i.b2   <- update( n.b2, . ~ . + igr )
> im.b2  <- update( m.b2, . ~ . + igr )
> iim.b2 <- update( n.b2, . ~ . + interaction(igr,grp) )
> x12.b2 <- update( m.b2, . ~ . + I((b12.y-b12.x)/100)
+                               + I((mma.y-mma.x)*10)
+                               + metformi.x,
+                   data = subset( ana1, b12.x<700 | b12.y<700 ) )
```

The simple model only has a metformin-effect (`grp`) — the difference in change between the metformin group and the placebo group (implicitly assuming no effect of insulin):

```
> round( ci.lin( n.b2 ), 3 )
            Estimate StdErr      z P  2.5% 97.5%
(Intercept)    4.377  0.555  7.891 0 3.290 5.464
b2b.x          0.569  0.040 14.150 0 0.491 0.648
```

```
> round( ci.lin( n.b2 ), 3 )
            Estimate StdErr      z P  2.5% 97.5%
(Intercept)    4.377  0.555  7.891 0 3.290 5.464
b2b.x          0.569  0.040 14.150 0 0.491 0.648
```

The insulin-only model has two parameters, namely the differences (in change) on two of the regimens relative to the third (reference) group, in this case biphasic insulin:

```
> round( ci.lin( i.b2 ), 3 )
            Estimate StdErr      z     P   2.5% 97.5%
(Intercept)    3.962  0.694  5.708 0.000  2.602 5.323
b2b.x          0.568  0.040 14.058 0.000  0.488 0.647
igrAspD        0.708  0.762  0.929 0.353 -0.785 2.202
igrDetm        0.609  0.781  0.779 0.436 -0.922 2.139
```

The main-effects model assumes that there is effect of both insulin regimens and metformin, but that they are independent of each other:

```
> round( ci.lin( im.b2, subset="gr" ), 3 )
        Estimate StdErr      z     P   2.5% 97.5%
grpMet    -1.135  0.631 -1.799 0.072 -2.372 0.101
igrAspD    0.645  0.760  0.849 0.396 -0.845 2.135
igrDetm    0.650  0.779  0.834 0.404 -0.877 2.176
```

Finally the interaction model shows the combined effects regarding the 6 groups as separate with no prior assumption about relationship between the effects seen in them; here is shown the effects relative to the reference (placebo,biphasic).

```
> ci.lin( iim.b2 )
                                Estimate     StdErr          z            P
(Intercept)                    3.8483800 0.89354314  4.3068765 1.655760e-05
b2b.x                          0.5683269 0.04023698 14.1244897 2.683365e-45
interaction(igr, grp)AspD.Plc  1.2625525 1.04374500  1.2096370 2.264182e-01
interaction(igr, grp)Detm.Plc  2.1712213 1.11636251  1.9449070 5.178617e-02
interaction(igr, grp)Biph.Met  0.2123858 1.07587690  0.1974072 8.435089e-01
interaction(igr, grp)AspD.Met  0.2511377 1.10460831  0.2273545 8.201481e-01
interaction(igr, grp)Detm.Met -0.5611594 1.07820950 -0.5204549 6.027466e-01
                                    2.5%     97.5%
(Intercept)                    2.09706760 5.5996923
b2b.x                          0.48946382 0.6471899
interaction(igr, grp)AspD.Plc -0.78315007 3.3082552
interaction(igr, grp)Detm.Plc -0.01680905 4.3592516
interaction(igr, grp)Biph.Met -1.89629413 2.3210658
interaction(igr, grp)AspD.Met -1.91385478 2.4161302
interaction(igr, grp)Detm.Met -2.67441121 1.5520924
```

Finally it is of course also of interest to formally test whether there actually is effects of Metformin and insulin regimens separately, and also whether there is an interaction:

```
> ( tt <- anova( n.b2, m.b2, im.b2, n.b2, i.b2, im.b2, iim.b2, test="Chisq" ) )
Analysis of Variance Table

Model 1: b2b.y ~ b2b.x
Model 2: b2b.y ~ b2b.x + grp
Model 3: b2b.y ~ b2b.x + grp + igr
Model 4: b2b.y ~ b2b.x
```

```
Model 5: b2b.y ~ b2b.x + igr
Model 6: b2b.y ~ b2b.x + grp + igr
Model 7: b2b.y ~ b2b.x + interaction(igr, grp)
  Res.Df   RSS Df Sum of Sq Pr(>Chi)
1    332 10996
2    331 10887  1   108.667  0.06888
3    329 10856  2    31.398  0.61995
4    332 10996 -3  -140.065  0.23417
5    330 10963  2    33.250  0.60271
6    329 10856  1   106.815  0.07129
7    327 10737  2   118.604  0.16430
```

```
> pval <- tt[c(2,6,5,3,7),5]
> names(pval) <- c("Met","Met|Ins","Ins","Ins|Met","MxI")
> round( pval, 3 )
```

```
    Met Met|Ins     Ins Ins|Met     MxI
  0.069   0.071   0.603   0.620   0.164
```

2.2.2.1 B12 ans MMA effects

We can assess the joint effect of the extra explanatory variables, however not by `anova`, but only by `Wald`

```
> round( ci.lin(   m.b2 ), 3 ) ; round( ci.lin( x12.b2 ), 3 )
```

```
            Estimate StdErr      z     P   2.5% 97.5%
(Intercept)    4.968  0.641  7.746 0.000  3.711 6.225
b2b.x          0.567  0.040 14.123 0.000  0.488 0.645
grpMet        -1.142  0.628 -1.818 0.069 -2.373 0.089
```

```
                        Estimate StdErr      z     P   2.5% 97.5%
(Intercept)                4.638  1.006  4.610 0.000  2.666 6.610
b2b.x                      0.564  0.041 13.866 0.000  0.484 0.644
grpMet                    -1.191  0.654 -1.819 0.069 -2.473 0.092
I((b12.y - b12.x)/100)    -0.216  0.206 -1.050 0.294 -0.619 0.187
I((mma.y - mma.x) * 10)   -0.314  0.384 -0.817 0.414 -1.067 0.439
metformi.xY                0.498  0.895  0.557 0.578 -1.256 2.252
```

```
> round( Wald( x12.b2, subset=c("b12","mma") ), 3 )
```

```
Chisq  d.f.     P
1.618 2.000 0.445
```

2.2.2.2 Diagnostic plots

In order to check if model assumptions are met we make diagnostic plots, which we for sake of simplicity only do for the interaction model. First we define a small function to use when putting text in a corner of a plot, and then we do the diagnostic plot:

```
> cnr <-
+ function(px,py)
+ list( x=par("usr")[1:2] %*% c(100-px,px)/100,
+       y=par("usr")[3:4] %*% c(100-py,py)/100 )
> par( mfrow=c(1,3), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( m.b2, 1:3 )
> text(cnr(98,98),"b2b",adj=c(1,1),cex=1.5,font=2)
```

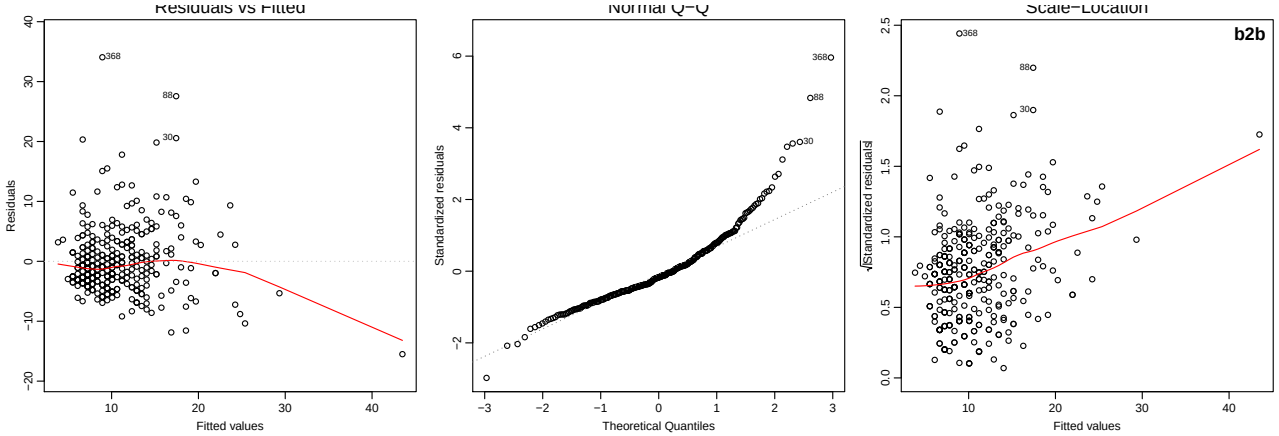

Figure 2.1: *Residual plots for beat-to-beat (*b2b*), for the metformin-only model* ./graph/neu-b2

2.2.2.3 Extracting estimates from models

In order to extract the estimated effects for all 6 groups under the main effects model (im.b2) we construct a suitable contrast matrix to use on this model:

```
> M2I <- cbind( rep(1:0,each=3),
+               rep(c(0,1,0),2),
+               rep(c(1,0,0),2) )
> rownames(M2I) <- paste( c(levels(ana1$grp),"")[c(2,3,3,1,3,3)],
+                         rep(levels(ana1$igr)[3:1],2) )
> M2I
         [,1] [,2] [,3]
Met Detm    1    0    1
 AspD       1    1    0
 Biph       1    0    0
Plc Detm    0    0    1
 AspD       0    1    0
 Biph       0    0    0
```

With this we can now make a complete overview of the estimated effects:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( rbind( ci.exp(  m.b2,subset="gr",Exp=FALSE),
+                 ci.exp(  i.b2,subset="gr",Exp=FALSE),
+                 ci.exp( im.b2,subset="gr",ctr.mat=M2I,Exp=FALSE),
+                 ci.exp(iim.b2,subset="interaction",Exp=FALSE)[5:1,], 0 ),
+          y=c(10,8.5,7.5,6:2+0.15,1,6:2-0.15,1),
+        txt=c(levels(ana1$grp)[2],
+              levels(ana1$igr)[3:2],
+              rownames(M2I), rep("",6)),
+     txtpos=c(10,8.5,7.5,6:1,6:1),
+       vref=0, cex=2, lwd=3, xlab="Beat-to-beat",
+        col=c(rep(c("black","gray"),c(9,5)),"black")
+         )
> abline( h=c(9.25,6.75), col=gray(0.8) )
```

The resulting plot shows estimates from all 4 fitted models in one figure 2.2.

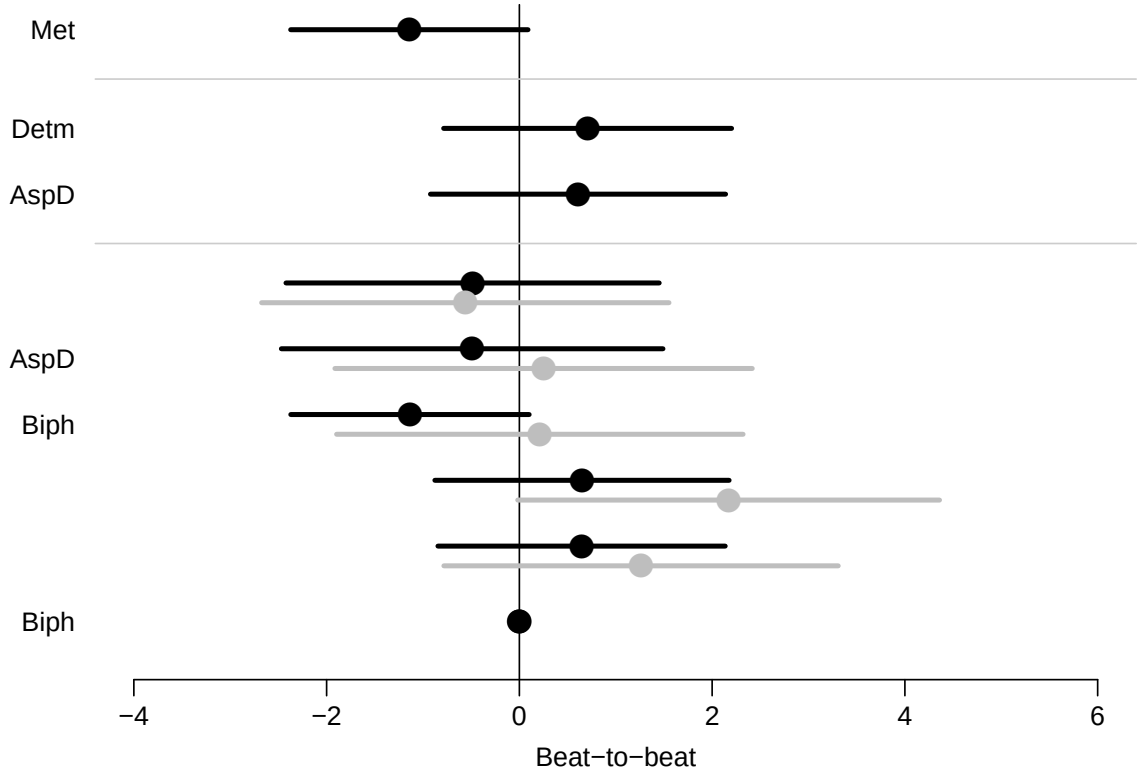

Figure 2.2: *Beat-to-beat: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-b2-est`

2.2.2.4 Further simplification

In order to simplify things further for use on the other outcome variables of interest, we wrap the model fitting, diagnostic plots and parameter extraction in three functions that only require that the variable of interest and a suitable label be specified:

```
> mfit <-
+ function( vnam, tit )
+ {
+ wh <- grep( vnam, names(ana1) )
+ ana1$FU <- ana1[,wh[2]]
+ ana1$BA <- ana1[,wh[1]]
+ cat( "=====================================================\n",
+       tit, ": Follow-up in ", names(ana1)[wh[2]],
+            ", Baseline in ", names(ana1)[wh[1]],
+    "\n-----------------------------------------------------\n", sep="" )
+ n.mod   <- lm( FU ~ BA, data = ana1 )
+ m.mod   <- update( n.mod, . ~ . + grp )
+ i.mod   <- update( n.mod, . ~ . + igr )
+ im.mod  <- update( m.mod, . ~ . + igr )
+ iim.mod <- update( n.mod, . ~ . + interaction(igr,grp) )
+ x12.mod <- update( m.mod, . ~ . + I((b12.y-b12.x)/100)
+                                 + I((mma.y-mma.x)*10)
+                                 + I((hba1c.y-hba1c.x)*10)
+                                 + metformi.x,
```

```
+                   data = subset( ana1, b12.x<700 | b12.y<700 ) )
+
+ print( round( ci.lin( m.mod   ), 4 ) )
+ print( round( ci.lin( i.mod   ), 4 ) )
+ print( round( ci.lin( im.mod  ), 4 ) )
+ print( round( ci.lin( iim.mod ), 4 ) )
+
+ tt <- anova( n.mod, m.mod, im.mod, n.mod, i.mod, im.mod, iim.mod, test="Chisq" )
+ pval <- tt[c(2,6,5,3,7),5]
+ names(pval) <- c("Met","Met|Ins","Ins","Ins|Met","MxI|MI")
+ cat("\nTests of effects (P-values):\n")
+ print( round( pval, 4 ) )
+ cat("\nEstimates with and without b12 and mma:\n")
+ print( round( ci.lin(   m.mod, subset=c("BA","Met") ), 4 ) )
+ print( round( ci.lin( x12.mod ), 4 ) )
+ cat("\nTest for joint effect fo b12 and mma:\n")
+ print( round( Wald( x12.mod, subset=c("b12","mma") ), 4 ) )
+ list( m.mod   = m.mod,
+       i.mod   = i.mod,
+       im.mod  = im.mod,
+       iim.mod = iim.mod,
+       vnam=vnam, tit=tit )
+ }
> res.b2b <- mfit( "b2b", "Beat-to-beat" )

==================================================
Beat-to-beat: Follow-up in b2b.y, Baseline in b2b.x
--------------------------------------------------
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)   4.9679 0.6413  7.7464 0.0000  3.7109 6.2248
BA            0.5667 0.0401 14.1227 0.0000  0.4881 0.6454
grpMet       -1.1417 0.6282 -1.8176 0.0691 -2.3729 0.0894
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)   3.9622 0.6941  5.7082 0.0000  2.6018 5.3227
BA            0.5676 0.0404 14.0578 0.0000  0.4885 0.6468
igrAspD       0.7082 0.7620  0.9293 0.3527 -0.7854 2.2017
igrDetm       0.6086 0.7810  0.7792 0.4359 -0.9222 2.1394
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)   4.5602 0.7675  5.9418 0.0000  3.0560 6.0644
BA            0.5648 0.0403 14.0249 0.0000  0.4859 0.6437
grpMet       -1.1352 0.6309 -1.7992 0.0720 -2.3718 0.1014
igrAspD       0.6454 0.7603  0.8489 0.3959 -0.8447 2.1355
igrDetm       0.6497 0.7787  0.8343 0.4041 -0.8766 2.1760
                            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)                   3.8484 0.8935  4.3069 0.0000  2.0971 5.5997
BA                            0.5683 0.0402 14.1245 0.0000  0.4895 0.6472
interaction(igr, grp)AspD.Plc 1.2626 1.0437  1.2096 0.2264 -0.7832 3.3083
interaction(igr, grp)Detm.Plc 2.1712 1.1164  1.9449 0.0518 -0.0168 4.3593
interaction(igr, grp)Biph.Met 0.2124 1.0759  0.1974 0.8435 -1.8963 2.3211
interaction(igr, grp)AspD.Met 0.2511 1.1046  0.2274 0.8201 -1.9139 2.4161
interaction(igr, grp)Detm.Met -0.5612 1.0782 -0.5205 0.6027 -2.6744 1.5521

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.0689  0.0713  0.6027  0.6200  0.1643

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
```

```
BA       0.5667 0.0401 14.1227 0.0000  0.4881 0.6454
grpMet  -1.1417 0.6282 -1.8176 0.0691 -2.3729 0.0894
                           Estimate StdErr       z      P    2.5%  97.5%
(Intercept)                 4.7206 1.0074  4.6861 0.0000  2.7462 6.6950
BA                          0.5670 0.0407 13.9260 0.0000  0.4872 0.6468
grpMet                     -1.0888 0.6590 -1.6522 0.0985 -2.3804 0.2028
I((b12.y - b12.x)/100)     -0.2492 0.2072 -1.2026 0.2291 -0.6554 0.1569
I((mma.y - mma.x) * 10)    -0.2899 0.3845 -0.7540 0.4509 -1.0434 0.4637
I((hba1c.y - hba1c.x) * 10)  0.0303 0.0244  1.2418 0.2143 -0.0175 0.0781
metformi.xY                  0.5124 0.8942  0.5730 0.5666 -1.2402 2.2650

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
1.8660 2.0000 0.3934
```

The model checking is quite straight-forward as before, but also wrapped in a convenience function:

```
> mod.diag <-
+ function( obj )
+ {
+ par( mfrow=c(1,3), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
+ plot( obj$m.mod, 1:3 )
+ text( cnr(98,98),
+       paste( obj$tit,"\n(",obj$vnam,")",sep=""),
+       adj=c(1,1),cex=1.5,font=2)
+ }
> mod.diag( res.b2b )
```

Finally we wrap the parameter extraction in a function too:

```
> CIMTres <- function( obj )
+ {
+ plotEst( rbind( ci.exp(obj$m.mod  ,subset="gr",Exp=FALSE),
+                 ci.exp(obj$i.mod  ,subset="gr",Exp=FALSE),
+                 ci.exp(obj$im.mod ,subset="gr",ctr.mat=M2I,Exp=FALSE),
+                 ci.exp(obj$iim.mod,subset="interaction",Exp=FALSE)[5:1,], 0 ),
+          y=c(10,8.5,7.5,6:2+0.15,1,6:2-0.15,1),
+        txt=c(levels(ana1$grp)[2],
+              levels(ana1$igr)[3:2],
+              rownames(M2I), rep("",6)),
+     txtpos=c(10,8.5,7.5,6:1,6:1),
+       vref=0, cex=2, lwd=3,
+       xlab=paste( obj$tit, "(",obj$vnam,")" ),
+        col=c(rep(c("black","gray"),c(9,5)),"black")
+         )
+ abline( h=c(9.25,6.75), col=gray(0.8) )
+ }
> CIMTres( res.b2b )
```

So now we have the machinery to mill all remaining (continuous variables through the machinery)

2.2.3 Vibration sense measures

We have separate recordings from left and right foot, so we analyze these separately, but also the maximum sensitivity of the two, which we need to construct as a separate variable, taken as the *smallest* recording of the two, corresponding to the foot with the maximal sensitivity:

```
> ana1 <- transform( ana1, vibmax.y = pmin( vibhcon.y, vibvcon.y, na.rm=TRUE ),
+                          vibmax.x = pmin( vibhcon.x, vibvcon.x, na.rm=TRUE ) )
```

Observations are right-censored at 50:

```
> names(ana1)[wh<-grep( "vib", names(ana1) )]
[1] "vibhcon.x" "vibvcon.x" "vibage.x"  "vibhcon.y" "vibvcon.y" "vibage.y"
[7] "vibmax.y"  "vibmax.x"
> apply( ana1[,wh], 2, function(x) table(x==50,exclude=NULL) )
$vibhcon.x

FALSE  TRUE  <NA>
  365     5     2

$vibvcon.x

FALSE  TRUE  <NA>
  367     4     1

$vibage.x

FALSE  <NA>
  371     1

$vibhcon.y

FALSE  TRUE  <NA>
  366     2     4

$vibvcon.y

FALSE  TRUE  <NA>
  363     4     5

$vibage.y

FALSE  <NA>
  371     1

$vibmax.y

FALSE  TRUE  <NA>
  370     1     1

$vibmax.x

FALSE  TRUE  <NA>
  368     3     1
```

From this we see that very few observations are censored at 50, and only one is censored when we take the best recording. Thus we make life a bit easier for ourselves by excluding all censored observations:

```
> ana1[,wh][ana1[,wh]==50] <- NA
> apply( ana1[,wh], 2, function(x) table(x==50,exclude=NULL) )
      vibhcon.x vibvcon.x vibage.x vibhcon.y vibvcon.y vibage.y vibmax.y vibmax.x
FALSE       365       367      371       366       363      371      370      368
<NA>          7         5        1         6         9        1        2        4
```

With this data grooming we now analyze the vibration sense data:

2.2.3.1 Vibration sense left

We fit the relevant models and make the diagnostic plots:

```
> vibl <- mfit( "vibvcon", "Vibration sense, left")
=====================================================
Vibration sense, left: Follow-up in vibvcon.y, Baseline in vibvcon.x
-----------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   8.2284 1.1672  7.0498 0.0000  5.9407 10.5160
BA            0.7339 0.0371 19.7664 0.0000  0.6611  0.8067
grpMet        1.4672 0.9085  1.6149 0.1063 -0.3135  3.2479
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   8.9599 1.2744  7.0306 0.0000  6.4621 11.4577
BA            0.7327 0.0375 19.5506 0.0000  0.6592  0.8061
igrAspD      -0.0181 1.1109 -0.0163 0.9870 -2.1954  2.1591
igrDetm       0.1463 1.1264  0.1299 0.8966 -2.0614  2.3540
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   8.1854 1.3602  6.0178 0.0000  5.5194 10.8513
BA            0.7340 0.0374 19.6243 0.0000  0.6607  0.8073
grpMet        1.4664 0.9143  1.6038 0.1088 -0.3257  3.2584
igrAspD       0.0566 1.1094  0.0510 0.9593 -2.1178  2.2309
igrDetm       0.0693 1.1249  0.0616 0.9509 -2.1355  2.2742
                            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                   7.9113 1.4707  5.3792 0.0000  5.0287 10.7938
BA                            0.7330 0.0376 19.4989 0.0000  0.6593  0.8066
interaction(igr, grp)AspD.Plc -0.0211 1.5354 -0.0137 0.9891 -3.0304  2.9883
interaction(igr, grp)Detm.Plc  1.2204 1.6476  0.7407 0.4589 -2.0089  4.4496
interaction(igr, grp)Biph.Met  2.0637 1.5735  1.3116 0.1897 -1.0202  5.1477
interaction(igr, grp)AspD.Met  2.2721 1.6077  1.4133 0.1576 -0.8789  5.4231
interaction(igr, grp)Detm.Met  1.1598 1.5525  0.7471 0.4550 -1.8831  4.2027

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.1077  0.1091  0.9873  0.9978  0.5194

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.7339 0.0371 19.7664 0.0000  0.6611 0.8067
grpMet   1.4672 0.9085  1.6149 0.1063 -0.3135 3.2479
                          Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 8.2837 1.6371  5.0599 0.0000  5.0750 11.4924
BA                          0.7425 0.0378 19.6177 0.0000  0.6683  0.8167
grpMet                      1.6438 0.9444  1.7405 0.0818 -0.2073  3.4948
I((b12.y - b12.x)/100)      0.3138 0.3041  1.0321 0.3020 -0.2821  0.9098
I((mma.y - mma.x) * 10)    -0.5770 0.5597 -1.0310 0.3025 -1.6739  0.5199
I((hba1c.y - hba1c.x) * 10) 0.0129 0.0356  0.3622 0.7172 -0.0569  0.0826
metformi.xY                -0.4315 1.2947 -0.3333 0.7389 -2.9690  2.1061
```

```
Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
2.3461 2.0000 0.3094
```

```
> mod.diag( vibl )
```

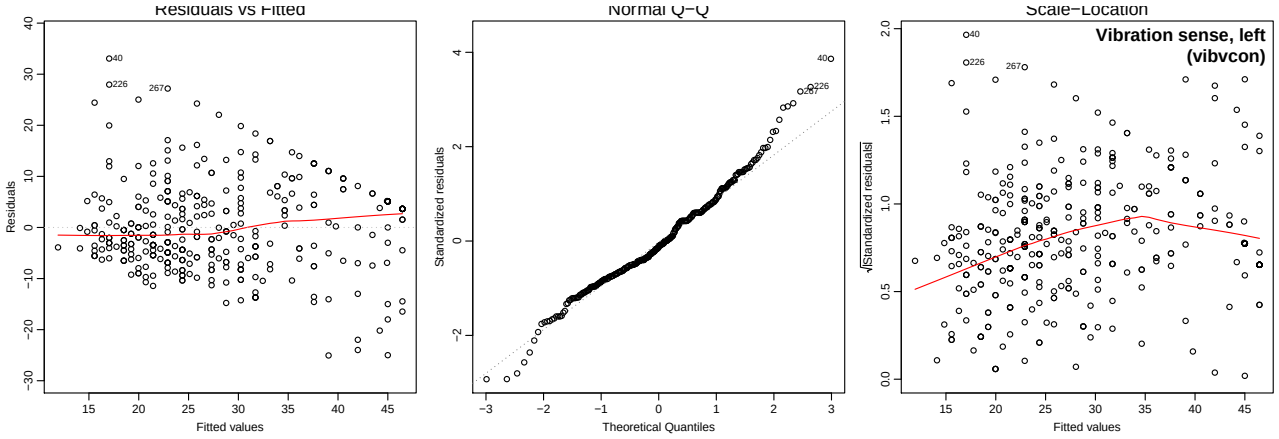

Figure 2.3: *Residual plots for vibration sense left (*`vibvcon`*)* `./graph/neu-vibl-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( vibl )
```

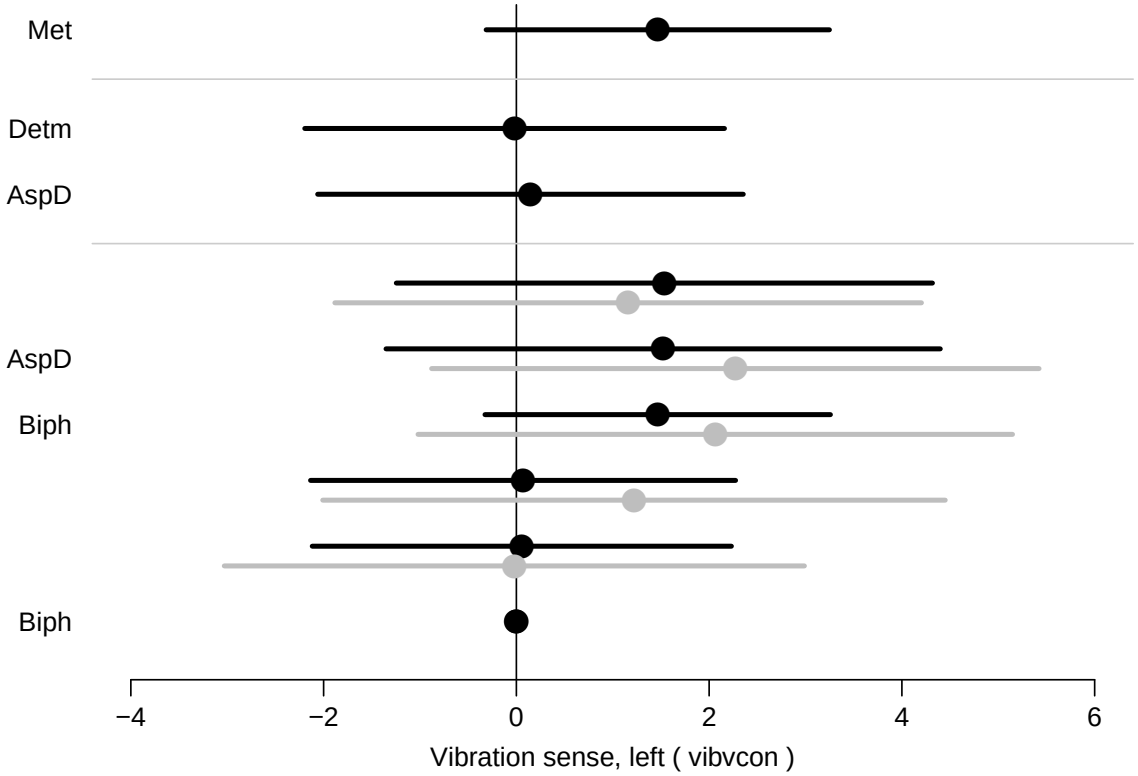

Figure 2.4: *Vibration sense, left: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-vibl-est`

2.2.3.2 Vibration sense, right

We fit the relevant models and make the diagnostic plots:

```
> vibr <- mfit( "vibhcon", "Vibration sense, right")
=================================================
Vibration sense, right: Follow-up in vibhcon.y, Baseline in vibhcon.x
-------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  10.9016 1.2594  8.6562 0.0000  8.4332 13.3700
BA            0.6759 0.0398 16.9662 0.0000  0.5978  0.7539
grpMet        1.3908 1.0100  1.3771 0.1685 -0.5887  3.3704
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  11.5953 1.4116  8.2141 0.0000  8.8286 14.3621
BA            0.6792 0.0401 16.9343 0.0000  0.6006  0.7578
igrAspD       0.2954 1.2324  0.2397 0.8106 -2.1201  2.7110
igrDetm      -0.5485 1.2467 -0.4400 0.6600 -2.9921  1.8950
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  10.9255 1.4857  7.3536 0.0000  8.0135 13.8375
BA            0.6771 0.0401 16.8934 0.0000  0.5985  0.7556
grpMet        1.4473 1.0145  1.4266 0.1537 -0.5410  3.4357
igrAspD       0.3427 1.2311  0.2784 0.7807 -2.0702  2.7556
igrDetm      -0.6270 1.2461 -0.5031 0.6149 -3.0693  1.8154
                            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                  10.5038 1.6153  6.5026 0.0000  7.3378 13.6698
BA                            0.6751 0.0403 16.7703 0.0000  0.5962  0.7540
interaction(igr, grp)AspD.Plc 0.7043 1.7129  0.4112 0.6809 -2.6529  4.0615
interaction(igr, grp)Detm.Plc 0.5501 1.8231  0.3017 0.7629 -3.0232  4.1233
interaction(igr, grp)Biph.Met 2.3907 1.7384  1.3752 0.1691 -1.0165  5.7979
interaction(igr, grp)AspD.Met 2.3838 1.7706  1.3464 0.1782 -1.0864  5.8541
interaction(igr, grp)Detm.Met 0.7328 1.7192  0.4263 0.6699 -2.6367  4.1023

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.1700  0.1544  0.7916  0.7359  0.6691

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.6759 0.0398 16.9662 0.0000  0.5978 0.7539
grpMet   1.3908 1.0100  1.3771 0.1685 -0.5887 3.3704
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 11.0782 1.7429  6.3561 0.0000  7.6621 14.4943
BA                           0.6871 0.0393 17.4897 0.0000  0.6101  0.7640
grpMet                       1.0363 1.0262  1.0099 0.3126 -0.9750  3.0476
I((b12.y - b12.x)/100)       0.2399 0.3294  0.7283 0.4664 -0.4057  0.8854
I((mma.y - mma.x) * 10)      0.4020 0.5943  0.6764 0.4988 -0.7629  1.5669
I((hba1c.y - hba1c.x) * 10) -0.0229 0.0380 -0.6031 0.5465 -0.0975  0.0516
metformi.xY                 -0.5282 1.4025 -0.3766 0.7065 -3.2769  2.2206

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
0.9068 2.0000 0.6355
> mod.diag( vibr )
```

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( vibr )
```

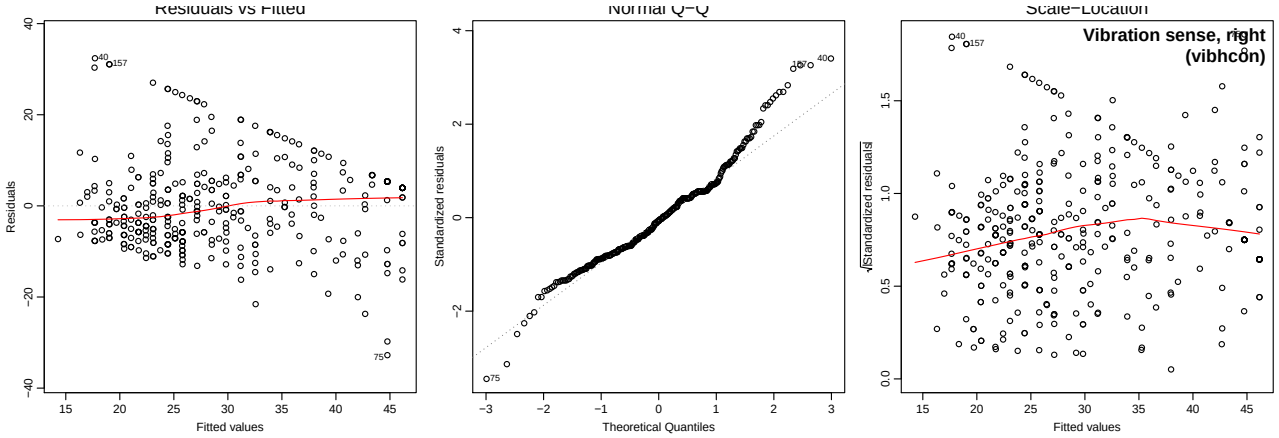

Figure 2.5: *Residual plots for vibration sense right* (`vibvcon`) `./graph/neu-vibr-diag`

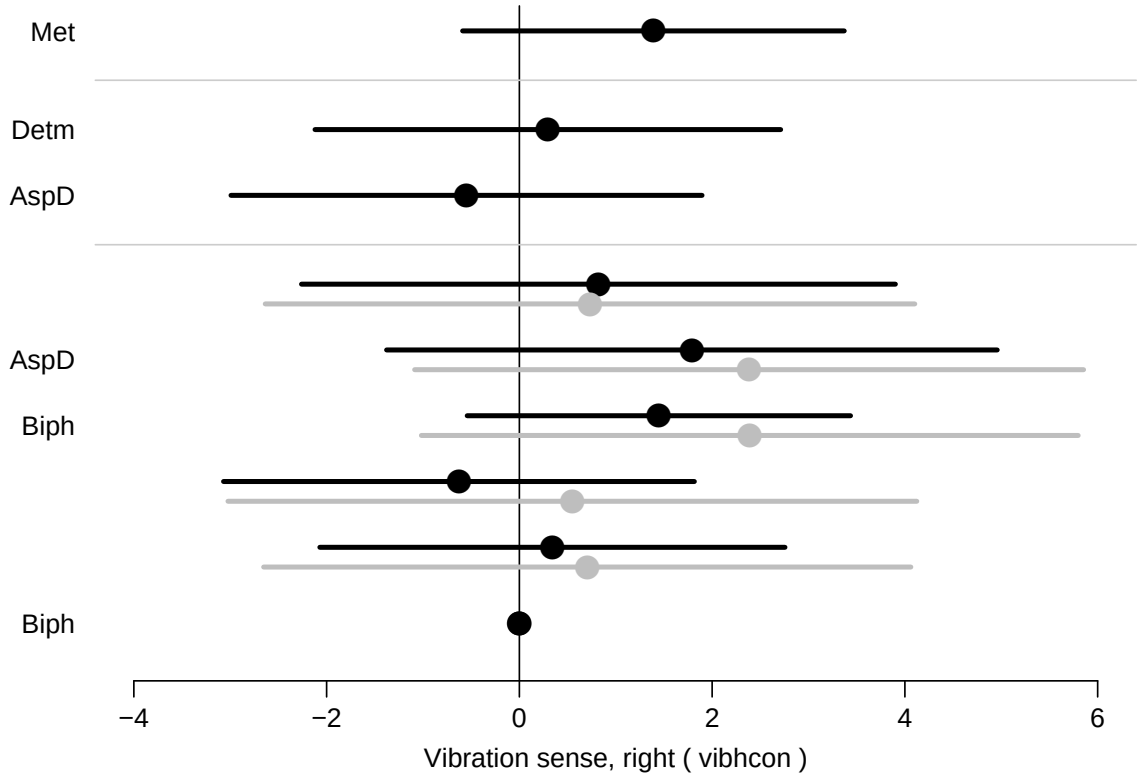

Figure 2.6: *Vibration sense, right: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-vibr-est`

2.2.3.3 Maximal vibration sense

We fit the relevant models and make the diagnostic plots:

```
> vibm <- mfit( "vibmax", "Maximal vibration sense, l/r")
=================================================
Maximal vibration sense, l/r: Follow-up in vibmax.x, Baseline in vibmax.y
-------------------------------------------------
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)   5.2203 1.0782  4.8418 0.0000  3.1071 7.3335
BA            0.7082 0.0348 20.3424 0.0000  0.6399 0.7764
grpMet       -0.3312 0.8475 -0.3908 0.6959 -1.9922 1.3298
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)   5.4803 1.2002  4.5660 0.0000  3.1279 7.8327
BA            0.7041 0.0347 20.2959 0.0000  0.6361 0.7721
igrAspD      -1.4012 1.0258 -1.3659 0.1720 -3.4117 0.6094
igrDetm       0.4796 1.0370  0.4625 0.6437 -1.5529 2.5121
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)   5.6656 1.2554  4.5130 0.0000  3.2051 8.1262
BA            0.7053 0.0348 20.2618 0.0000  0.6371 0.7735
grpMet       -0.4314 0.8474 -0.5092 0.6106 -2.0922 1.2294
igrAspD      -1.4161 1.0273 -1.3785 0.1681 -3.4295 0.5974
igrDetm       0.4994 1.0388  0.4808 0.6307 -1.5366 2.5355
                            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)                   4.9141 1.3660  3.5976 0.0003  2.2369 7.5914
BA                            0.7021 0.0349 20.0934 0.0000  0.6336 0.7706
interaction(igr, grp)AspD.Plc -0.1601 1.4332 -0.1117 0.9111 -2.9690 2.6489
interaction(igr, grp)Detm.Plc  1.7664 1.5158  1.1654 0.2439 -1.2044 4.7373
interaction(igr, grp)Biph.Met  1.2214 1.4557  0.8390 0.4015 -1.6318 4.0745
interaction(igr, grp)AspD.Met -1.4953 1.4799 -1.0104 0.3123 -4.3960 1.4053
interaction(igr, grp)Detm.Met  0.5530 1.4381  0.3845 0.7006 -2.2657 3.3716

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.6953  0.6107  0.1675  0.1589  0.3764

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.7082 0.0348 20.3424 0.0000  0.6399 0.7764
grpMet  -0.3312 0.8475 -0.3908 0.6959 -1.9922 1.3298
                           Estimate StdErr       z      P    2.5%  97.5%
(Intercept)                 5.0730 1.5341  3.3068 0.0009  2.0662 8.0797
BA                          0.7154 0.0354 20.2059 0.0000  0.6460 0.7848
grpMet                     -0.4847 0.8839 -0.5484 0.5834 -2.2171 1.2477
I((b12.y - b12.x)/100)     -0.1093 0.2862 -0.3820 0.7025 -0.6702 0.4516
I((mma.y - mma.x) * 10)     0.7752 0.5119  1.5145 0.1299 -0.2280 1.7784
I((hba1c.y - hba1c.x) * 10) -0.0258 0.0331 -0.7791 0.4359 -0.0906 0.0391
metformi.xY                 -0.0174 1.2092 -0.0144 0.9885 -2.3874 2.3526

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
2.5634 2.0000 0.2776
> mod.diag( vibm )
```

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( vibm )
```

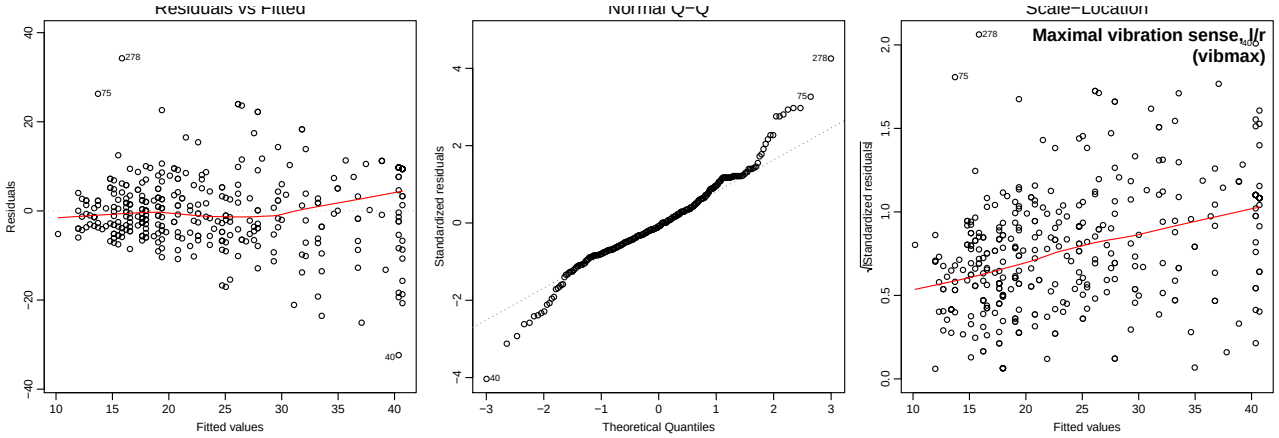

Figure 2.7: *Residual plots for vibration sense right (*`vibvcon`*)* `./graph/neu-vibm-diag`

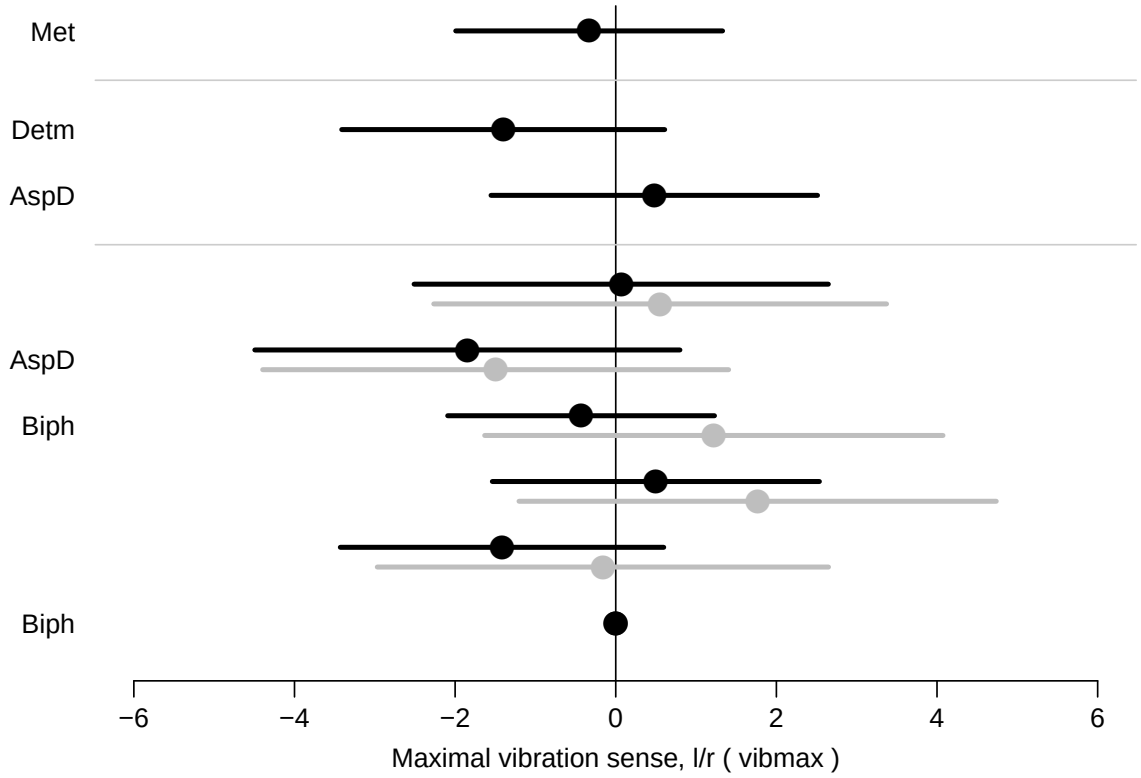

Figure 2.8: *Vibration sense, maximal: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-vibm-est`

2.2.4 Resting heart rate

This is in the variable `resthr`, so we fit the relevant models and make the diagnostic plots:

```
> rhr <- mfit( "resthr", "Resting heart rate")
================================================
Resting heart rate: Follow-up in resthr.y, Baseline in resthr.x
------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  16.1452 2.7644  5.8405 0.0000 10.7271 21.5632
BA            0.7631 0.0391 19.5201 0.0000  0.6865  0.8397
grpMet        1.0300 0.7878  1.3074 0.1911 -0.5141  2.5740
            Estimate StdErr       z     P    2.5%   97.5%
(Intercept)  16.5100 2.8469  5.7992 0.000 10.9301 22.0899
BA            0.7654 0.0393 19.4906 0.000  0.6885  0.8424
igrAspD      -0.2449 0.9616 -0.2547 0.799 -2.1297  1.6398
igrDetm       0.2221 0.9709  0.2288 0.819 -1.6807  2.1249
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  16.1282 2.8602  5.6387 0.0000 10.5222 21.7341
BA            0.7635 0.0393 19.4444 0.0000  0.6865  0.8405
grpMet        1.0088 0.7917  1.2742 0.2026 -0.5429  2.5606
igrAspD      -0.1894 0.9618 -0.1969 0.8439 -2.0745  1.6957
igrDetm       0.1932 0.9703  0.1991 0.8422 -1.7085  2.0949
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 15.7378 2.9122  5.4040 0.0000 10.0299 21.4457
BA                           0.7690 0.0394 19.5379 0.0000  0.6919  0.8461
interaction(igr, grp)AspD.Plc -0.9164 1.3364 -0.6857 0.4929 -3.5358  1.7030
interaction(igr, grp)Detm.Plc  1.1138 1.4070  0.7917 0.4286 -1.6438  3.8714
interaction(igr, grp)Biph.Met  1.0170 1.3520  0.7522 0.4519 -1.6330  3.6669
interaction(igr, grp)AspD.Met  1.7091 1.3981  1.2224 0.2216 -1.0312  4.4493
interaction(igr, grp)Detm.Met  0.4338 1.3513  0.3210 0.7482 -2.2146  3.0822

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.1917  0.2021  0.8907  0.9257  0.2395

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.7631 0.0391 19.5201 0.0000  0.6865 0.8397
grpMet   1.0300 0.7878  1.3074 0.1911 -0.5141 2.5740
                          Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                16.2080 2.8431  5.7008 0.0000 10.6357 21.7804
BA                          0.7323 0.0406 18.0590 0.0000  0.6528  0.8118
grpMet                      1.1689 0.8223  1.4216 0.1552 -0.4427  2.7806
I((b12.y - b12.x)/100)      0.1569 0.2666  0.5886 0.5561 -0.3657  0.6795
I((mma.y - mma.x) * 10)     0.0139 0.4773  0.0291 0.9768 -0.9216  0.9494
I((hba1c.y - hba1c.x) * 10) -0.0071 0.0307 -0.2315 0.8170 -0.0673  0.0531
metformi.xY                 2.3604 1.1369  2.0761 0.0379  0.1321  4.5887

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
0.3469 2.0000 0.8407
> mod.diag( rhr )
```

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( rhr )
```

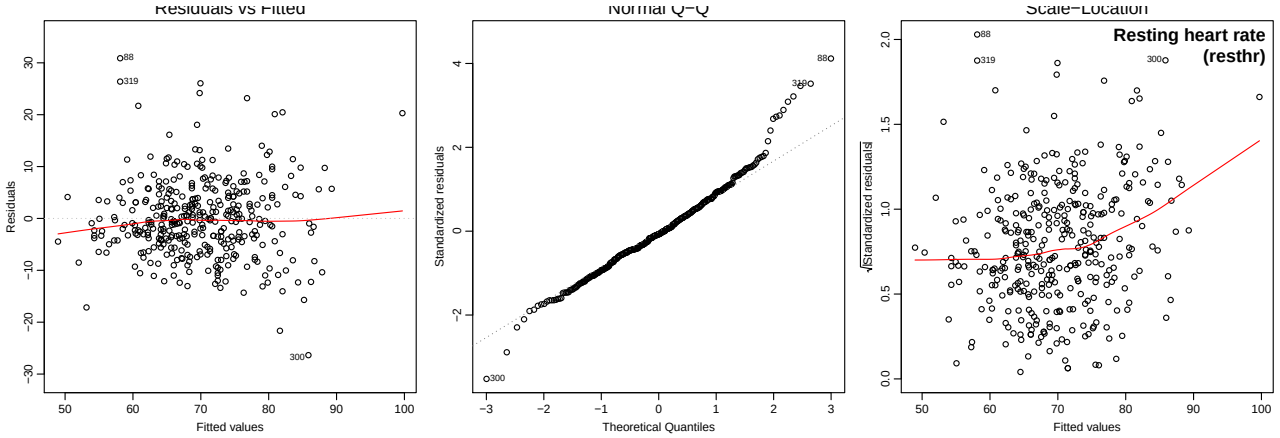

Figure 2.9: *Residual plots for resting heart rate (*`rhr`*)* `./graph/neu-rhr-diag`

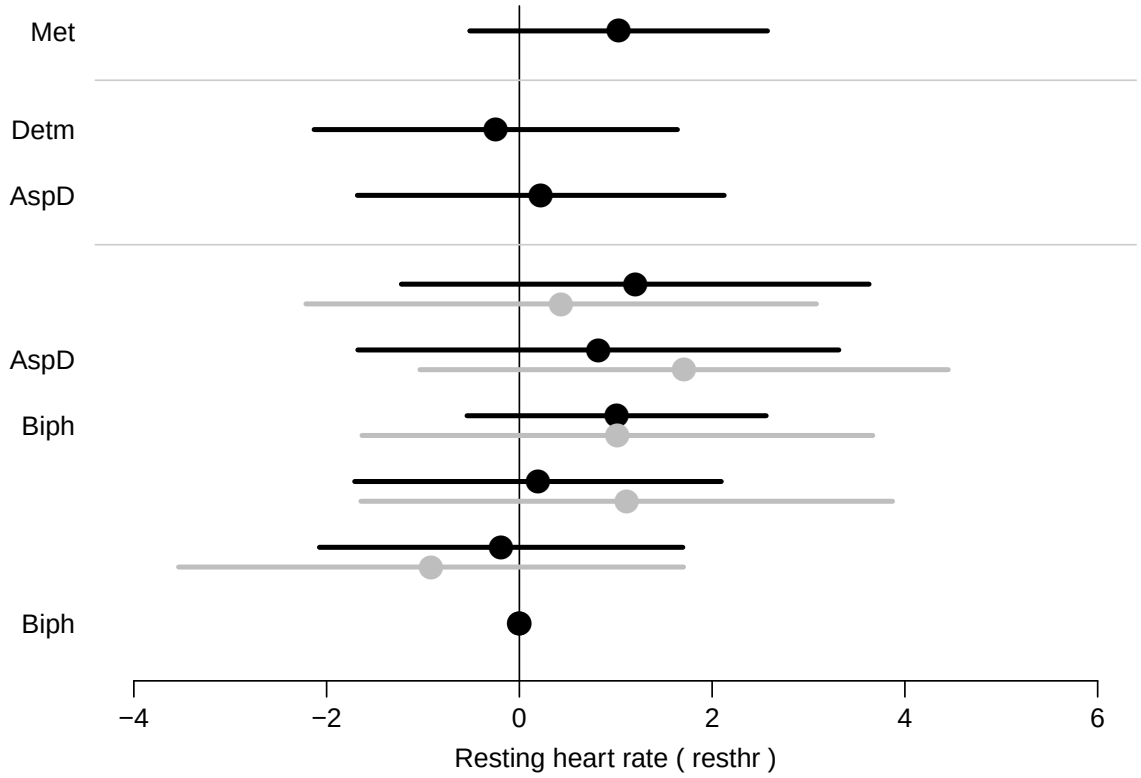

Figure 2.10: *Resting heart rate: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-rhr-est`

2.2.4.1 Change in HR at 30 sec

This is in the variable `chp30`, so we fit the relevant models and make the diagnostic plots:

```
> chp30 <- mfit( "chp30", "Heart rate change at 30 sec")
=================================================
Heart rate change at 30 sec: Follow-up in chp30.y, Baseline in chp30.x
-------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.0130 0.6840 -5.8672 0.0000 -5.3535 -2.6724
BA            0.5693 0.0514 11.0727 0.0000  0.4686  0.6701
grpMet        0.0903 0.6497  0.1391 0.8894 -1.1830  1.3637
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.9342 0.7577 -5.1922 0.0000 -5.4193 -2.4491
BA            0.5703 0.0517 11.0414 0.0000  0.4691  0.6716
igrAspD      -0.1439 0.7883 -0.1825 0.8552 -1.6889  1.4012
igrDetm       0.0791 0.8007  0.0988 0.9213 -1.4902  1.6484
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.9739 0.8251 -4.8164 0.0000 -5.5910 -2.3568
BA            0.5705 0.0517 11.0259 0.0000  0.4691  0.6719
grpMet        0.0799 0.6526  0.1224 0.9026 -1.1991  1.3589
igrAspD      -0.1394 0.7902 -0.1764 0.8600 -1.6883  1.4094
igrDetm       0.0781 0.8018  0.0974 0.9224 -1.4934  1.6496
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 -3.7940 0.9350 -4.0577 0.0000 -5.6266 -1.9614
BA                           0.5673 0.0520 10.9128 0.0000  0.4654  0.6692
interaction(igr, grp)AspD.Plc  -0.7019 1.1058 -0.6347 0.5256 -2.8692  1.4654
interaction(igr, grp)Detm.Plc   0.0622 1.1639  0.0534 0.9574 -2.2191  2.3434
interaction(igr, grp)Biph.Met  -0.3298 1.1157 -0.2956 0.7675 -2.5166  1.8570
interaction(igr, grp)AspD.Met   0.1467 1.1517  0.1274 0.8986 -2.1105  2.4040
interaction(igr, grp)Detm.Met  -0.2311 1.1302 -0.2045 0.8380 -2.4463  1.9841

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.8899  0.9027  0.9614  0.9634  0.7041

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.5693 0.0514 11.0727 0.0000  0.4686 0.6701
grpMet   0.0903 0.6497  0.1391 0.8894 -1.1830 1.3637
                          Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                -3.1096 1.0256 -3.0319 0.0024 -5.1198 -1.0994
BA                          0.5586 0.0526 10.6256 0.0000  0.4556  0.6616
grpMet                      0.0780 0.6843  0.1140 0.9093 -1.2633  1.4192
I((b12.y - b12.x)/100)      0.1230 0.2211  0.5562 0.5781 -0.3104  0.5564
I((mma.y - mma.x) * 10)    -0.5754 0.3959 -1.4535 0.1461 -1.3513  0.2005
I((hba1c.y - hba1c.x) * 10) -0.0289 0.0254 -1.1365 0.2558 -0.0787  0.0209
metformi.xY                -1.4928 0.9286 -1.6076 0.1079 -3.3129  0.3272

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
2.5692 2.0000 0.2768
> mod.diag( chp30 )
```

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( chp30 )
```

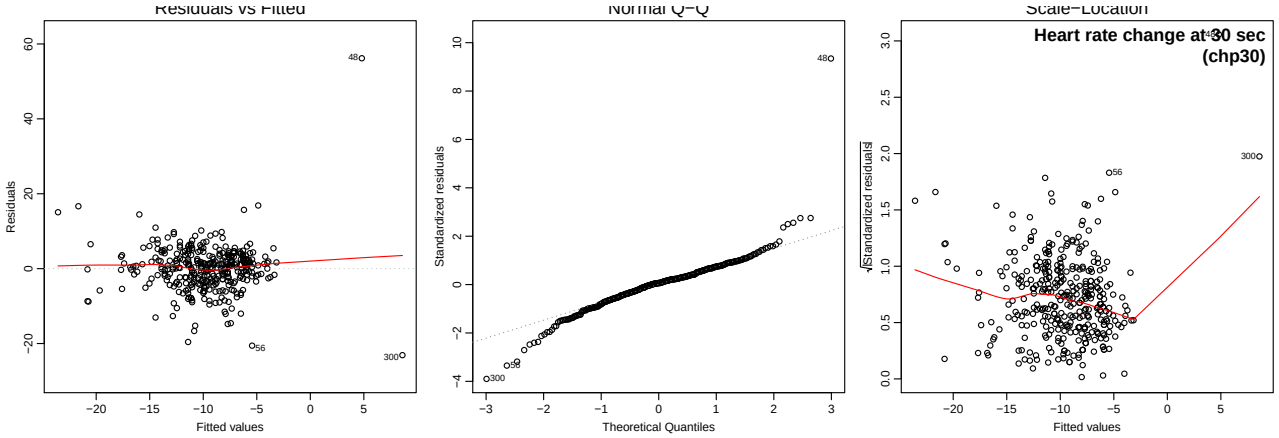

Figure 2.11: *Residual plots for resting heart rate (*`rhr`*)* `./graph/neu-chp30-diag`

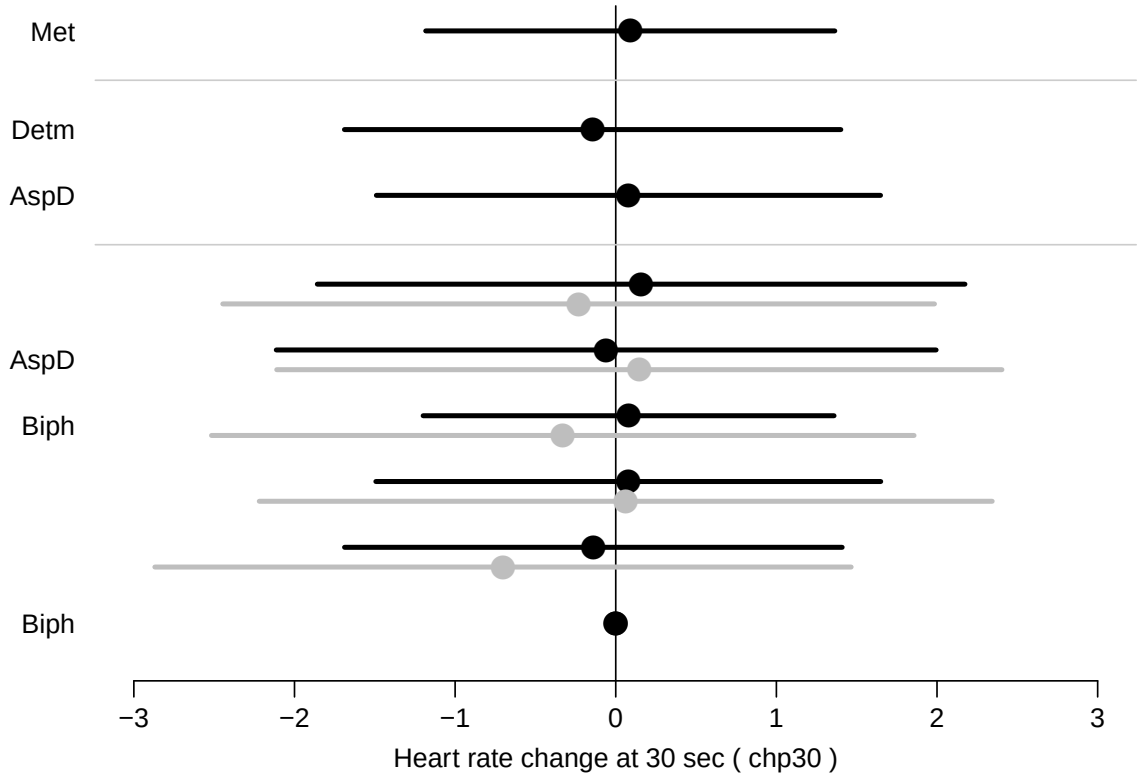

Figure 2.12: *Change in heart rate at 30 sec: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-chp30-est`

2.2.4.2 Change in HR at 90 sec

This is in the variable `chp90`, so we fit the relevant models and make the diagnostic plots:

```
> chp90 <- mfit( "chp90", "Heart rate change at 90 sec")
=================================================
Heart rate change at 90 sec: Follow-up in chp90.y, Baseline in chp90.x
-------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.4440 0.5960 -7.4561 0.0000 -5.6122 -3.2758
BA            0.4376 0.0496  8.8200 0.0000  0.3403  0.5348
grpMet        0.1901 0.5679  0.3348 0.7377 -0.9228  1.3031
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.1046 0.6692 -6.1336 0.0000 -5.4162 -2.7930
BA            0.4366 0.0496  8.7947 0.0000  0.3393  0.5339
igrAspD       0.0037 0.6883  0.0054 0.9957 -1.3453  1.3528
igrDetm      -0.7980 0.6978 -1.1437 0.2528 -2.1657  0.5696
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.2185 0.7271 -5.8017 0.0000 -5.6436 -2.7934
BA            0.4369 0.0497  8.7893 0.0000  0.3395  0.5343
grpMet        0.2296 0.5692  0.4033 0.6867 -0.8861  1.3453
igrAspD       0.0148 0.6896  0.0214 0.9829 -1.3369  1.3665
igrDetm      -0.8052 0.6988 -1.1523 0.2492 -2.1750  0.5645
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 -4.9974 0.8055 -6.2044 0.0000 -6.5761 -3.4188
BA                           0.4411 0.0496  8.8911 0.0000  0.3439  0.5383
interaction(igr, grp)AspD.Plc  0.6782 0.9518  0.7126 0.4761 -1.1872  2.5436
interaction(igr, grp)Detm.Plc  1.1417 1.0059  1.1349 0.2564 -0.8299  3.1133
interaction(igr, grp)Biph.Met  1.8404 0.9652  1.9067 0.0566 -0.0514  3.7321
interaction(igr, grp)AspD.Met  1.2382 0.9918  1.2485 0.2119 -0.7057  3.1822
interaction(igr, grp)Detm.Met -0.7240 0.9664 -0.7492 0.4538 -2.6182  1.1701

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.7360  0.6845  0.4173  0.4067  0.0262

Estimates with and without b12 and mma:
       Estimate StdErr      z      P    2.5%  97.5%
BA       0.4376 0.0496 8.8200 0.0000  0.3403 0.5348
grpMet   0.1901 0.5679 0.3348 0.7377 -0.9228 1.3031
                          Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                -4.4742 0.8994 -4.9746 0.0000 -6.2371 -2.7114
BA                          0.4422 0.0510  8.6758 0.0000  0.3423  0.5420
grpMet                     -0.0345 0.5986 -0.0575 0.9541 -1.2078  1.1389
I((b12.y - b12.x)/100)     -0.2669 0.1934 -1.3797 0.1677 -0.6460  0.1122
I((mma.y - mma.x) * 10)     0.0828 0.3466  0.2389 0.8111 -0.5965  0.7621
I((hba1c.y - hba1c.x) * 10) -0.0205 0.0223 -0.9185 0.3583 -0.0643  0.0232
metformi.xY                 0.1085 0.8115  0.1337 0.8936 -1.4820  1.6990

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
2.0298 2.0000 0.3624
> mod.diag( chp90 )
```

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( chp90 )
```

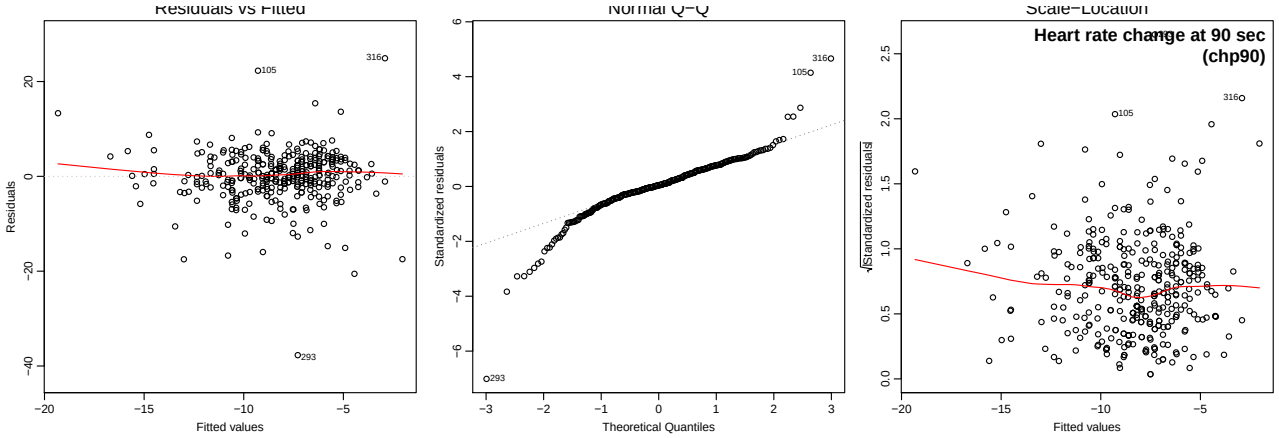

Figure 2.13: *Residual plots for resting heart rate (*`rhr`*)* `./graph/neu-chp90-diag`

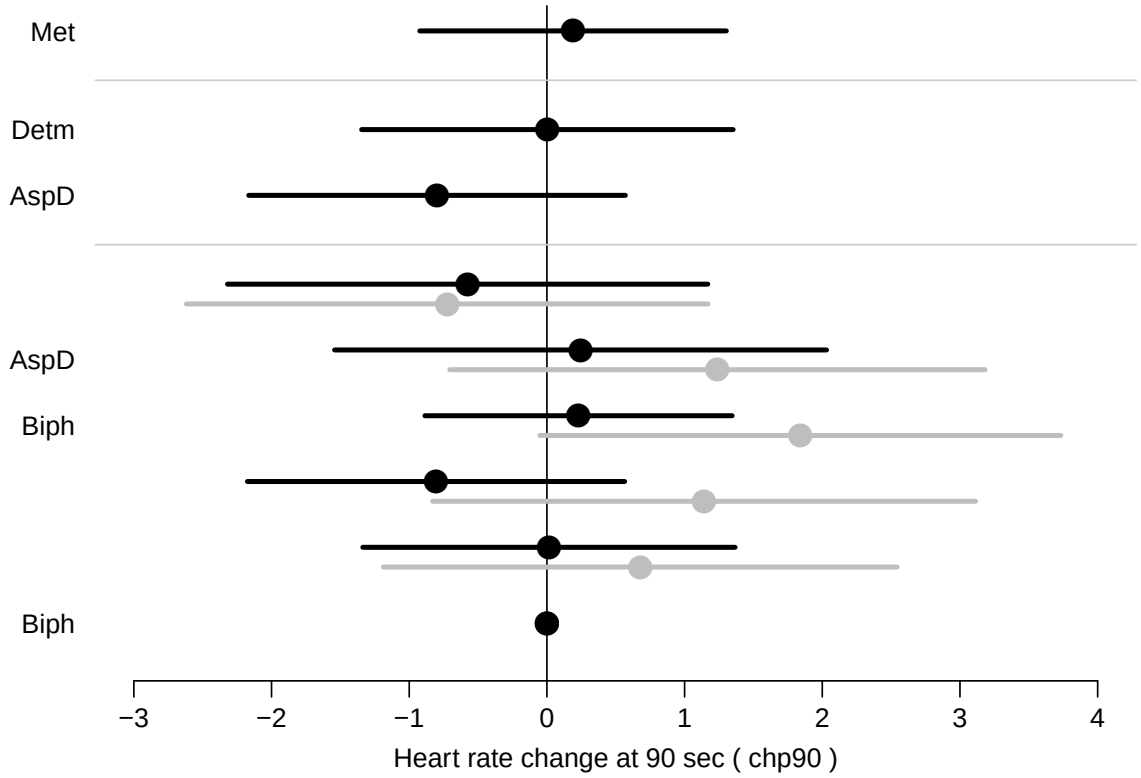

Figure 2.14: *Change in heart rate at 90 sec: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-chp90-est`

2.2.4.3 Change in HR at 180 sec

This is in the variable `chp180`, so we fit the relevant models and make the diagnostic plots:

```
> chp180 <- mfit( "chp180", "Heart rate change at 180 sec")
==================================================
Heart rate change at 180 sec: Follow-up in chp180.y, Baseline in chp180.x
--------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.3714 0.5632 -7.7615 0.0000 -5.4753 -3.2675
BA            0.4534 0.0460  9.8562 0.0000  0.3632  0.5436
grpMet        0.3996 0.5391  0.7413 0.4585 -0.6569  1.4561
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.3499 0.6342 -5.2820 0.0000 -4.5929 -2.1069
BA            0.4579 0.0459  9.9749 0.0000  0.3679  0.5479
igrAspD      -1.2116 0.6534 -1.8542 0.0637 -2.4922  0.0691
igrDetm      -1.1487 0.6608 -1.7384 0.0821 -2.4438  0.1464
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.5433 0.6897 -5.1373 0.0000 -4.8951 -2.1914
BA            0.4582 0.0459  9.9736 0.0000  0.3681  0.5482
grpMet        0.3855 0.5384  0.7160 0.4740 -0.6697  1.4406
igrAspD      -1.1928 0.6544 -1.8229 0.0683 -2.4754  0.0897
igrDetm      -1.1589 0.6614 -1.7522 0.0797 -2.4552  0.1374
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 -4.0617 0.7739 -5.2484 0.0000 -5.5785 -2.5449
BA                           0.4604 0.0462  9.9625 0.0000  0.3698  0.5510
interaction(igr, grp)AspD.Plc  -0.5915 0.9091 -0.6506 0.5153 -2.3734  1.1904
interaction(igr, grp)Detm.Plc  -0.0982 0.9556 -0.1028 0.9181 -1.9712  1.7747
interaction(igr, grp)Biph.Met   1.4475 0.9245  1.5657 0.1174 -0.3645  3.2595
interaction(igr, grp)AspD.Met  -0.3445 0.9481 -0.3633 0.7164 -2.2027  1.5137
interaction(igr, grp)Detm.Met  -0.6889 0.9231 -0.7463 0.4555 -2.4981  1.1203

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
 0.4568  0.4738  0.1147  0.1170  0.3005

Estimates with and without b12 and mma:
       Estimate StdErr      z      P    2.5%  97.5%
BA       0.4534 0.0460 9.8562 0.0000  0.3632 0.5436
grpMet   0.3996 0.5391 0.7413 0.4585 -0.6569 1.4561
                          Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                -3.7684 0.8399 -4.4865 0.0000 -5.4146 -2.1221
BA                          0.4662 0.0465 10.0207 0.0000  0.3750  0.5574
grpMet                      0.0187 0.5576  0.0336 0.9732 -1.0741  1.1116
I((b12.y - b12.x)/100)     -0.3604 0.1799 -2.0035 0.0451 -0.7130 -0.0078
I((mma.y - mma.x) * 10)    -0.8420 0.3225 -2.6112 0.0090 -1.4740 -0.2100
I((hba1c.y - hba1c.x) * 10)  -0.0481 0.0208 -2.3079 0.0210 -0.0889 -0.0073
metformi.xY                -0.7560 0.7546 -1.0019 0.3164 -2.2350  0.7229

Test for joint effect fo b12 and mma:
  Chisq    d.f.       P
10.0202  2.0000  0.0067
> mod.diag( chp180 )
```

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( chp180 )
```

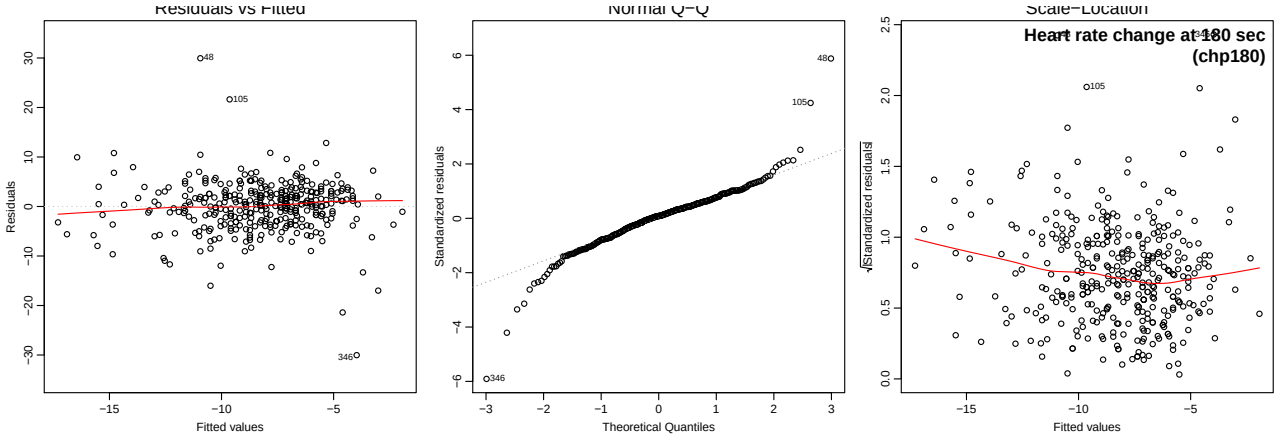

Figure 2.15: *Residual plots for resting heart rate (*`rhr`*)* `./graph/neu-chp180-diag`

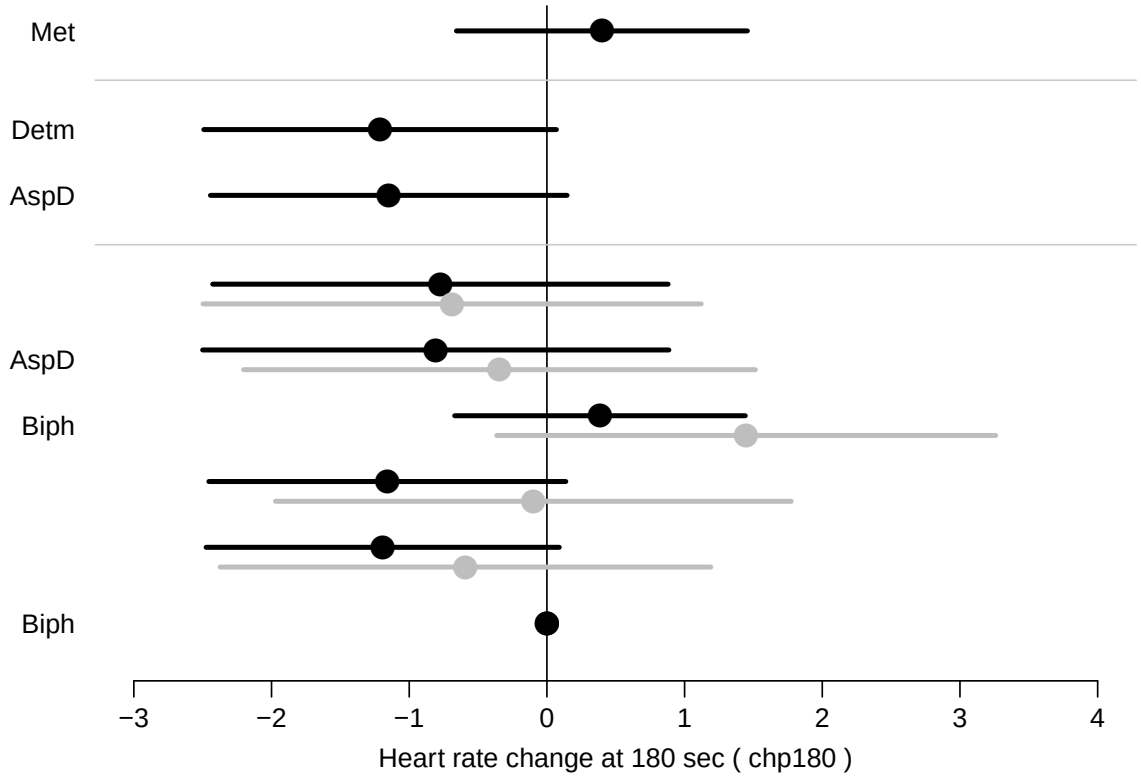

Figure 2.16: *Change in heart rate at 180 sec: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-chp180-est`

2.2.5 Summary of heart rate

We extract the metformin effects from the simple model from the fitted obejcts:

```
> ests <- rbind(
+ ci.exp(    rhr$m.mod, subset="grp", Exp=F ),
+ ci.exp(  chp30$m.mod, subset="grp", Exp=F ),
+ ci.exp(  chp90$m.mod, subset="grp", Exp=F ),
+ ci.exp( chp180$m.mod, subset="grp", Exp=F ) )
> rownames( ests ) <- c("Resting","0-30 sec.","0-90 sec.","0-180 sec.")
> round( ests, 3 )
           Estimate   2.5% 97.5%
Resting        1.03 -0.514 2.574
0-30 sec.      0.09 -1.183 1.364
0-90 sec.      0.19 -0.923 1.303
0-180 sec.     0.40 -0.657 1.456


> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( ests,
+          y=4:1,
+          vref=0, cex=1.5, lwd=3,
+          xlab="Metformin effect (BPM)" )
```

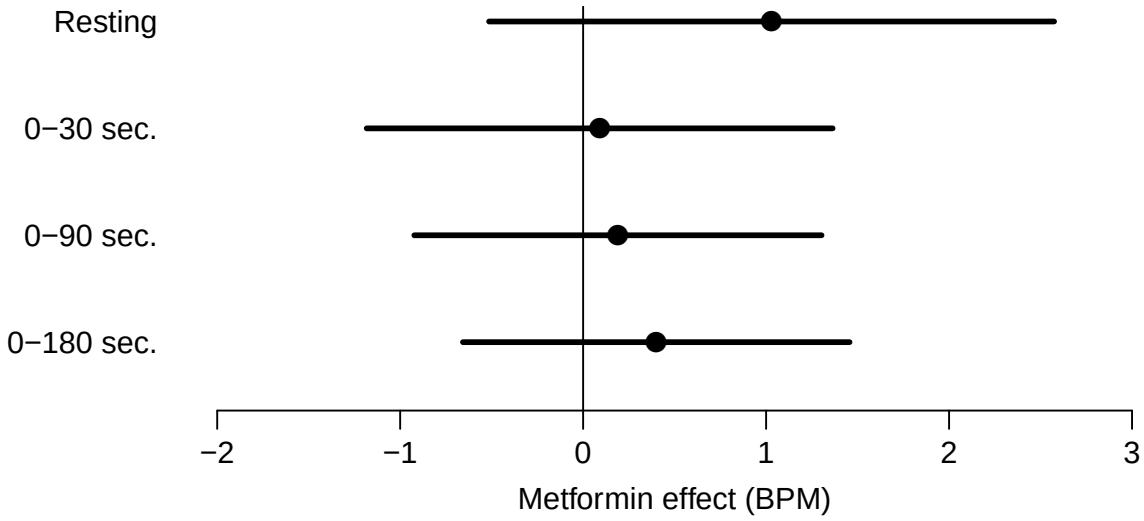

Figure 2.17: *Summary of metformin effect on resting heart rate and change in heart rate from resting (resting−after).* `./graph/neu-HR-est`

2.2.6 Blood pressure

In analyses of blood pressure it is relevant to take use of anti-hypertensive medication (OAH, `oah`) into account but only baseline status is available, so we use this as confounder in the models. This means that we must modify the function that fits the models of interest — the only difference relative to the previous one is the inclusion of the `oah` variable in the model:

```
> mfit <-
+ function( vnam, tit )
+ {
+ wh <- grep( vnam, names(ana1) )
+ ana1$FU <- ana1[,wh[2]]
+ ana1$BA <- ana1[,wh[1]]
+ cat( "====================================================\n",
+       tit, ": Follow-up in ", names(ana1)[wh[2]],
+            ", Baseline in ", names(ana1)[wh[1]],
+    "\n (controlled for hypertensive medication (oah))",
+    "\n----------------------------------------------------\n", sep="" )
+ n.mod   <- lm( FU ~ BA + oah, data = ana1 )
+ m.mod   <- update( n.mod, . ~ . + grp )
+ i.mod   <- update( n.mod, . ~ . + igr )
+ im.mod  <- update( m.mod, . ~ . + igr )
+ iim.mod <- update( n.mod, . ~ . + interaction(igr,grp) )
+ x12.mod <- update( m.mod, . ~ . + I((b12.y-b12.x)/100)
+                                 + I((mma.y-mma.x)*10)
+                                 + metformi.x,
+                   data = subset( ana1, b12.x<700 | b12.y<700 ) )
+
+ print( round( ci.lin( m.mod   ), 4 ) )
+ print( round( ci.lin( i.mod   ), 4 ) )
+ print( round( ci.lin( im.mod  ), 4 ) )
+ print( round( ci.lin( iim.mod ), 4 ) )
+
+ tt <- anova( n.mod, m.mod, im.mod, n.mod, i.mod, im.mod, iim.mod, test="Chisq" )
+ pval <- tt[c(2,6,5,3,7),5]
+ names(pval) <- c("Met","Met|Ins","Ins","Ins|Met","MxI|MI")
+ cat("\nTests of effects (P-values):\n")
+ print( round( pval, 3 ) )
+ cat("\nEstimates with and without b12 and mma:\n")
+ print( round( ci.lin(   m.mod, subset=c("BA","Met") ), 4 ) )
+ print( round( ci.lin( x12.mod ), 4 ) )
+ cat("\nTest for joint effect fo b12 and mma:\n")
+ print( round( Wald( x12.mod, subset=c("b12","mma") ), 4 ) )
+ list( m.mod   = m.mod,
+       i.mod   = i.mod,
+       im.mod  = im.mod,
+       iim.mod = iim.mod,
+       vnam=vnam, tit=tit )
+ }
```

This is the only modification needed in the functions, the rest will work as previously set up for the other variables.

2.2.7 Resting blood pressures

2.2.7.1 Resting diastolic blood pressure

This is in the variable `dia_lig`, so we fit the relevant models and make the diagnostic plots:

```
> rdia <- mfit( "dia_lig", "Resting diastolic bp")
==================================================
Resting diastolic bp: Follow-up in dia_lig.y, Baseline in dia_lig.x
 (controlled for hypertensive medication (oah))
--------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  39.5054 3.3122 11.9274 0.0000 33.0137 45.9972
BA            0.5012 0.0405 12.3605 0.0000  0.4217  0.5807
oahY         -1.5786 0.7646 -2.0646 0.0390 -3.0772 -0.0800
grpMet       -0.3741 0.7594 -0.4926 0.6223 -1.8625  1.1143
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  39.1862 3.3578 11.6703 0.0000 32.6051 45.7673
BA            0.5015 0.0403 12.4416 0.0000  0.4225  0.5805
oahY         -1.6890 0.7597 -2.2232 0.0262 -3.1780 -0.2000
igrAspD      -0.8039 0.9166 -0.8770 0.3805 -2.6004  0.9926
igrDetm       1.3495 0.9247  1.4594 0.1445 -0.4629  3.1618
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  39.3164 3.3668 11.6776 0.0000 32.7176 45.9152
BA            0.5027 0.0404 12.4473 0.0000  0.4235  0.5819
oahY         -1.6539 0.7623 -2.1695 0.0300 -3.1481 -0.1597
grpMet       -0.4795 0.7570 -0.6334 0.5265 -1.9632  1.0043
igrAspD      -0.8254 0.9180 -0.8991 0.3686 -2.6246  0.9738
igrDetm       1.3634 0.9257  1.4728 0.1408 -0.4509  3.1777
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 39.5486 3.4380 11.5035 0.0000 32.8103 46.2869
BA                           0.5022 0.0405 12.3977 0.0000  0.4228  0.5816
oahY                        -1.6688 0.7656 -2.1797 0.0293 -3.1694 -0.1682
interaction(igr, grp)AspD.Plc -0.9151 1.2822 -0.7137 0.4754 -3.4281  1.5979
interaction(igr, grp)Detm.Plc  0.8455 1.3475  0.6274 0.5304 -1.7955  3.4864
interaction(igr, grp)Biph.Met -0.8448 1.2970 -0.6513 0.5148 -3.3870  1.6973
interaction(igr, grp)AspD.Met -1.6096 1.3332 -1.2073 0.2273 -4.2227  1.0035
interaction(igr, grp)Detm.Met  0.9801 1.2972  0.7556 0.4499 -1.5623  3.5225

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.621   0.527   0.065   0.060   0.852

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.5012 0.0405 12.3605 0.0000  0.4217 0.5807
grpMet  -0.3741 0.7594 -0.4926 0.6223 -1.8625 1.1143
                        Estimate StdErr       z      P    2.5%   97.5%
(Intercept)              39.4906 3.3541 11.7737 0.0000 32.9166 46.0646
BA                        0.4905 0.0417 11.7702 0.0000  0.4088  0.5722
oahY                     -1.6819 0.7705 -2.1828 0.0291 -3.1920 -0.1717
grpMet                    0.0056 0.7805  0.0072 0.9943 -1.5242  1.5354
I((b12.y - b12.x)/100)    0.4402 0.2532  1.7390 0.0820 -0.0559  0.9364
I((mma.y - mma.x) * 10)   0.4350 0.4569  0.9520 0.3411 -0.4605  1.3305
metformi.xY               0.9500 1.0866  0.8743 0.3820 -1.1797  3.0797

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
```

```
3.6539 2.0000 0.1609
> mod.diag( rdia )
```

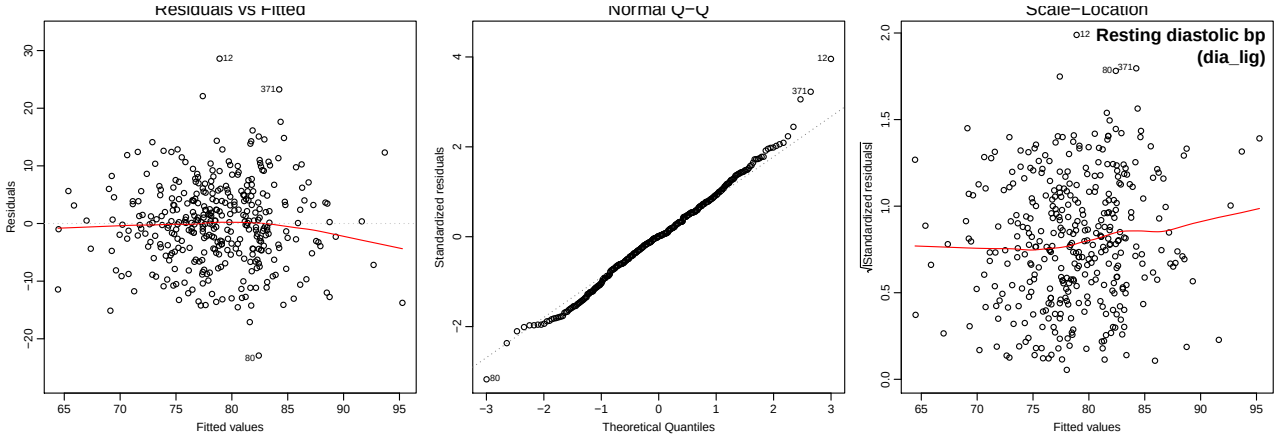

Figure 2.18: *Residual plots for resting diastolic blood pressure (*`dia_lig`*).*`./graph/neu-rdia-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( rdia )
```

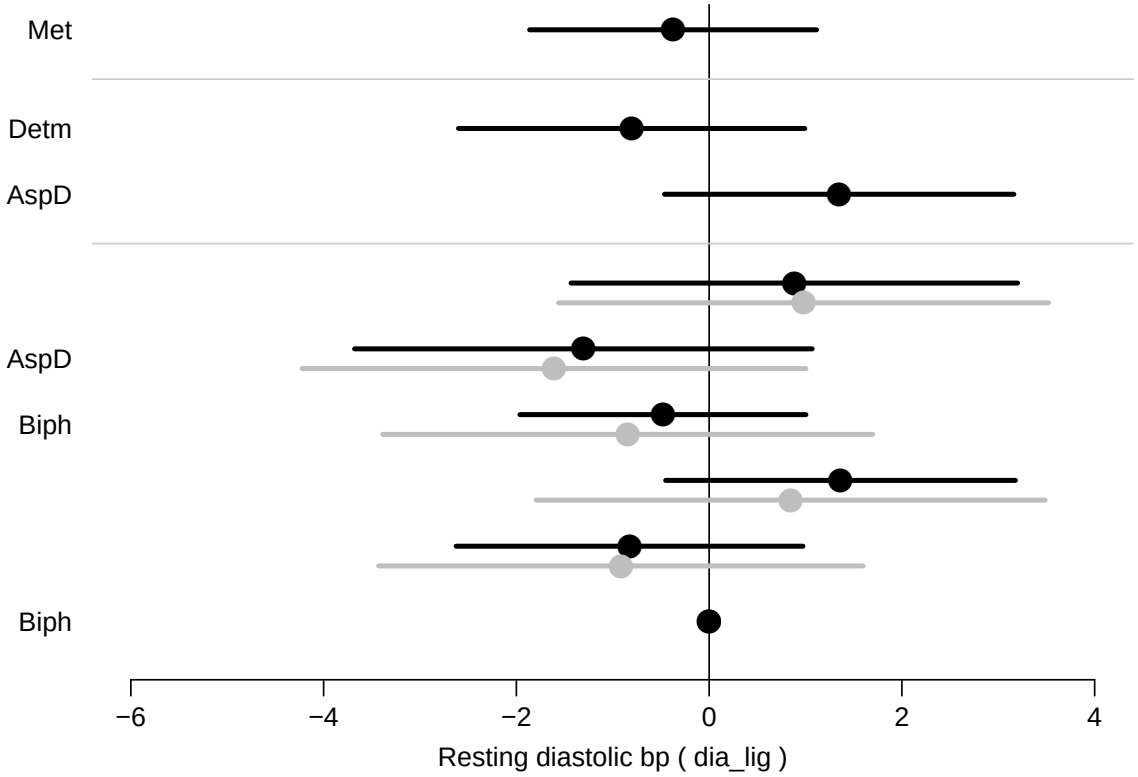

Figure 2.19: *Resting diastolic blood pressure: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-rdia-est`

2.2.7.2 Resting systolic blood-pressure

This is in the variable `sys_lig`, so we fit the relevant models and make the diagnostic plots:

```
> rsys <- mfit( "sys_lig", "Resting systolic bp")
==================================================
Resting systolic bp: Follow-up in sys_lig.y, Baseline in sys_lig.x
 (controlled for hypertensive medication (oah))
--------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  59.2085 5.8168 10.1790 0.0000 47.8079 70.6092
BA            0.5521 0.0437 12.6448 0.0000  0.4665  0.6377
oahY          2.0436 1.3440  1.5206 0.1284 -0.5905  4.6777
grpMet        1.0550 1.2952  0.8146 0.4153 -1.4835  3.5936
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  60.9764 5.8519 10.4199 0.0000 49.5068 72.4459
BA            0.5492 0.0435 12.6147 0.0000  0.4639  0.6346
oahY          1.9643 1.3382  1.4679 0.1421 -0.6585  4.5871
igrAspD      -2.7323 1.5656 -1.7452 0.0810 -5.8009  0.3362
igrDetm       0.3536 1.5807  0.2237 0.8230 -2.7445  3.4518
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  60.7056 5.8689 10.3435 0.0000 49.2027 72.2085
BA            0.5481 0.0436 12.5700 0.0000  0.4626  0.6335
oahY          1.9071 1.3416  1.4215 0.1552 -0.7224  4.5367
grpMet        0.9014 1.2932  0.6970 0.4858 -1.6332  3.4359
igrAspD      -2.6907 1.5679 -1.7161 0.0861 -5.7636  0.3823
igrDetm       0.3316 1.5822  0.2096 0.8340 -2.7694  3.4326
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 60.3639 5.9228 10.1919 0.0000 48.7555 71.9723
BA                           0.5485 0.0435 12.6102 0.0000  0.4632  0.6337
oahY                         1.7457 1.3409  1.3019 0.1930 -0.8824  4.3738
interaction(igr, grp)AspD.Plc -0.7881 2.1779 -0.3619 0.7175 -5.0567  3.4805
interaction(igr, grp)Detm.Plc -0.7474 2.2899 -0.3264 0.7441 -5.2355  3.7406
interaction(igr, grp)Biph.Met  1.6491 2.2063  0.7475 0.4548 -2.6751  5.9733
interaction(igr, grp)AspD.Met -3.2185 2.2676 -1.4194 0.1558 -7.6629  1.2258
interaction(igr, grp)Detm.Met  2.8672 2.2090  1.2980 0.1943 -1.4623  7.1968

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.413   0.485   0.100   0.110   0.150

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.5521 0.0437 12.6448 0.0000  0.4665 0.6377
grpMet   1.0550 1.2952  0.8146 0.4153 -1.4835 3.5936
                        Estimate StdErr       z      P    2.5%   97.5%
(Intercept)              60.0274 6.1068  9.8295 0.0000 48.0582 71.9966
BA                        0.5457 0.0446 12.2385 0.0000  0.4583  0.6331
oahY                      2.0130 1.3819  1.4567 0.1452 -0.6955  4.7214
grpMet                    1.0616 1.3546  0.7837 0.4332 -1.5934  3.7165
I((b12.y - b12.x)/100)   -0.3137 0.4396 -0.7136 0.4755 -1.1753  0.5479
I((mma.y - mma.x) * 10)  -0.5312 0.7919 -0.6709 0.5023 -2.0832  1.0208
metformi.xY               0.0984 1.8562  0.0530 0.9577 -3.5397  3.7364

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
0.8784 2.0000 0.6445
> mod.diag( rsys )
```

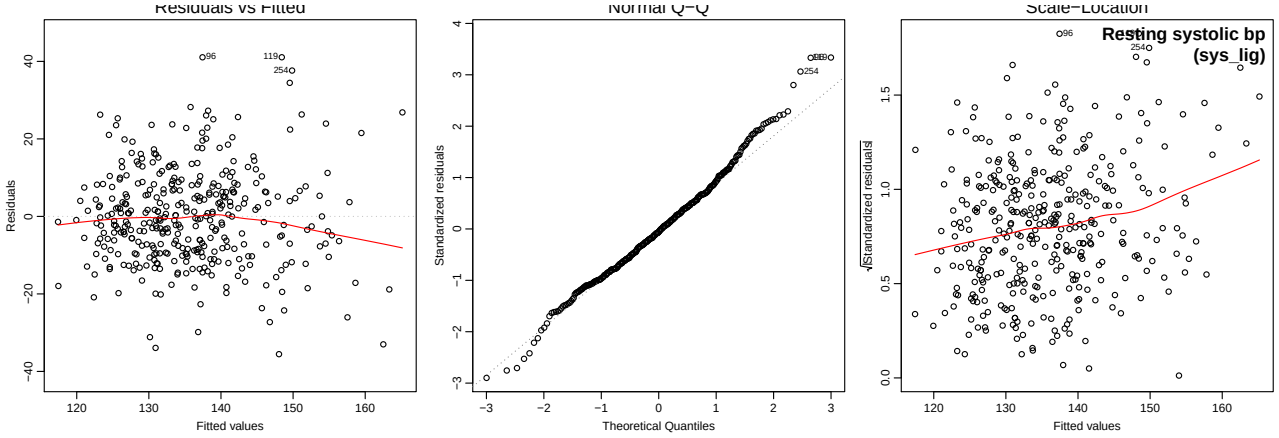

Figure 2.20: *Residual plots for resting systolic blood pressure (*`sys_lig`*)* `./graph/neu-rsys-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( rsys )
```

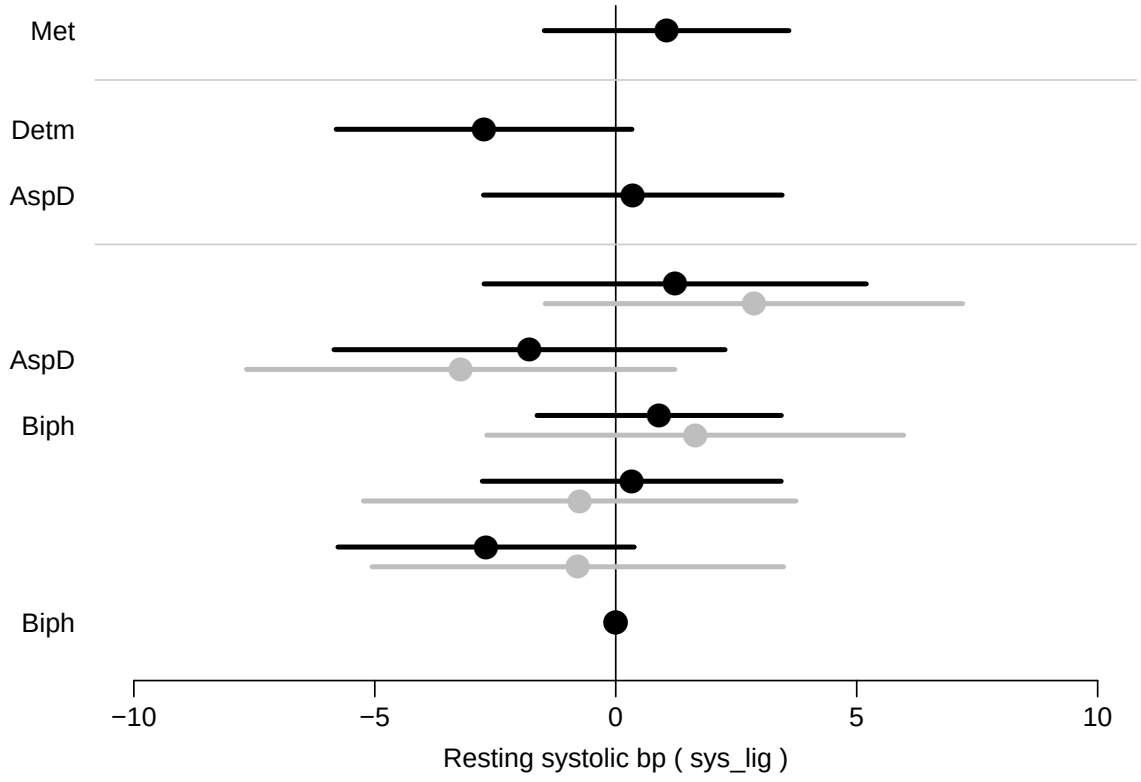

Figure 2.21: *Resting systolic blood pressure: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-rsys-est`

2.2.8 Blood pressure changes

We analyze the blood pressure changes from lying position at 30, 90 seconds and 3 minutes, that is a total of 6 analyses:

2.2.8.1 Diastolic blood pressure change at 30 seconds

This is in the variable `dc30`, so we fit the relevant models and make the diagnostic plots:

```
> dc30 <- mfit( "dc30", "Diastolic bp at 30 sec")
================================================
Diastolic bp at 30 sec: Follow-up in dc30.y, Baseline in dc30.x
 (controlled for hypertensive medication (oah))
------------------------------------------------
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)  -0.8105 0.5537 -1.4639 0.1432 -1.8956 0.2747
BA            0.3545 0.0493  7.1946 0.0000  0.2579 0.4511
oahY          0.0518 0.6326  0.0819 0.9347 -1.1881 1.2918
grpMet        1.1736 0.6215  1.8884 0.0590 -0.0445 2.3917
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   0.5628 0.6455  0.8718 0.3833 -0.7024  1.8280
BA            0.3516 0.0496  7.0880 0.0000  0.2543  0.4488
oahY          0.0825 0.6318  0.1306 0.8961 -1.1557  1.3208
igrAspD      -1.5750 0.7528 -2.0923 0.0364 -3.0503 -0.0996
igrDetm      -0.8379 0.7617 -1.1001 0.2713 -2.3308  0.6550
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   0.0251 0.7074  0.0354 0.9717 -1.3614  1.4115
BA            0.3460 0.0495  6.9864 0.0000  0.2490  0.4431
oahY          0.0022 0.6312  0.0034 0.9973 -1.2351  1.2394
grpMet        1.1344 0.6202  1.8291 0.0674 -0.0812  2.3500
igrAspD      -1.5292 0.7507 -2.0371 0.0416 -3.0006 -0.0579
igrDetm      -0.8517 0.7592 -1.1218 0.2619 -2.3398  0.6364
                            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                   0.2939 0.8358  0.3517 0.7251 -1.3441  1.9320
BA                            0.3469 0.0499  6.9527 0.0000  0.2491  0.4446
oahY                          0.0552 0.6337  0.0871 0.9306 -1.1869  1.2973
interaction(igr, grp)AspD.Plc -2.3074 1.0464 -2.2052 0.0274 -4.3583 -0.2566
interaction(igr, grp)Detm.Plc -0.8870 1.1065 -0.8016 0.4228 -3.0558  1.2817
interaction(igr, grp)Biph.Met  0.5528 1.0635  0.5198 0.6032 -1.5315  2.6372
interaction(igr, grp)AspD.Met -0.1309 1.0850 -0.1207 0.9040 -2.2574  1.9956
interaction(igr, grp)Detm.Met -0.2522 1.0714 -0.2354 0.8139 -2.3520  1.8477

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.058   0.068   0.110   0.124   0.480

Estimates with and without b12 and mma:
       Estimate StdErr      z     P    2.5%  97.5%
BA       0.3545 0.0493 7.1946 0.000  0.2579 0.4511
grpMet   1.1736 0.6215 1.8884 0.059 -0.0445 2.3917
                       Estimate StdErr       z      P    2.5%  97.5%
(Intercept)             -0.2109 0.9320 -0.2263 0.8210 -2.0376 1.6158
BA                       0.3610 0.0496  7.2727 0.0000  0.2637 0.4583
oahY                    -0.1004 0.6414 -0.1565 0.8756 -1.3575 1.1567
grpMet                   1.3772 0.6421  2.1448 0.0320  0.1187 2.6358
I((b12.y - b12.x)/100)   0.4018 0.2067  1.9437 0.0519 -0.0034 0.8069
I((mma.y - mma.x) * 10)  0.2614 0.3730  0.7009 0.4834 -0.4697 0.9926
```

```
metformi.xY              -0.7781 0.8749 -0.8894 0.3738 -2.4928 0.9367

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
4.0540 2.0000 0.1317
```

```
> mod.diag( dc30 )
```

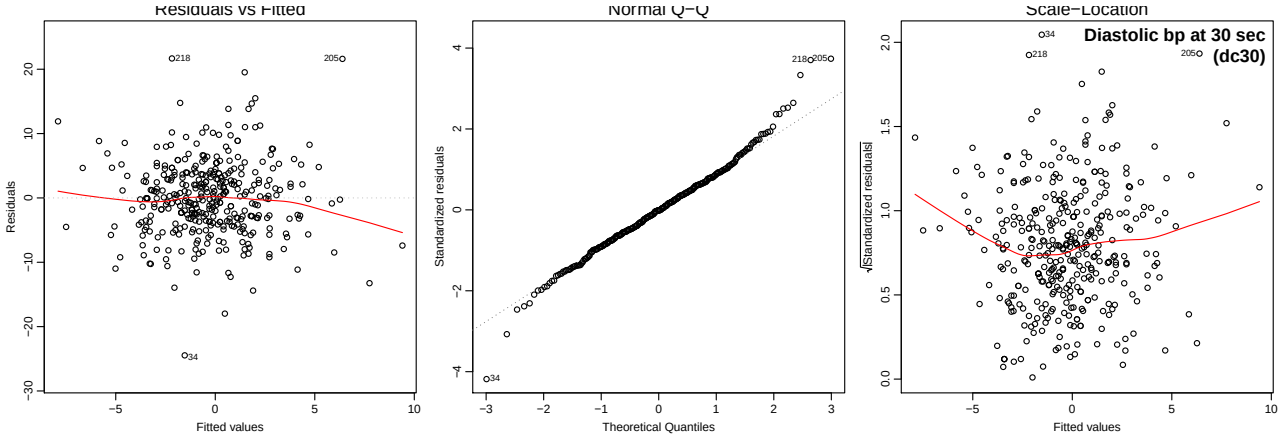

Figure 2.22: *Residual plots for systolic blood pressure at 30 sec (*dc30*)* `./graph/neu-dc30-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( dc30 )
```

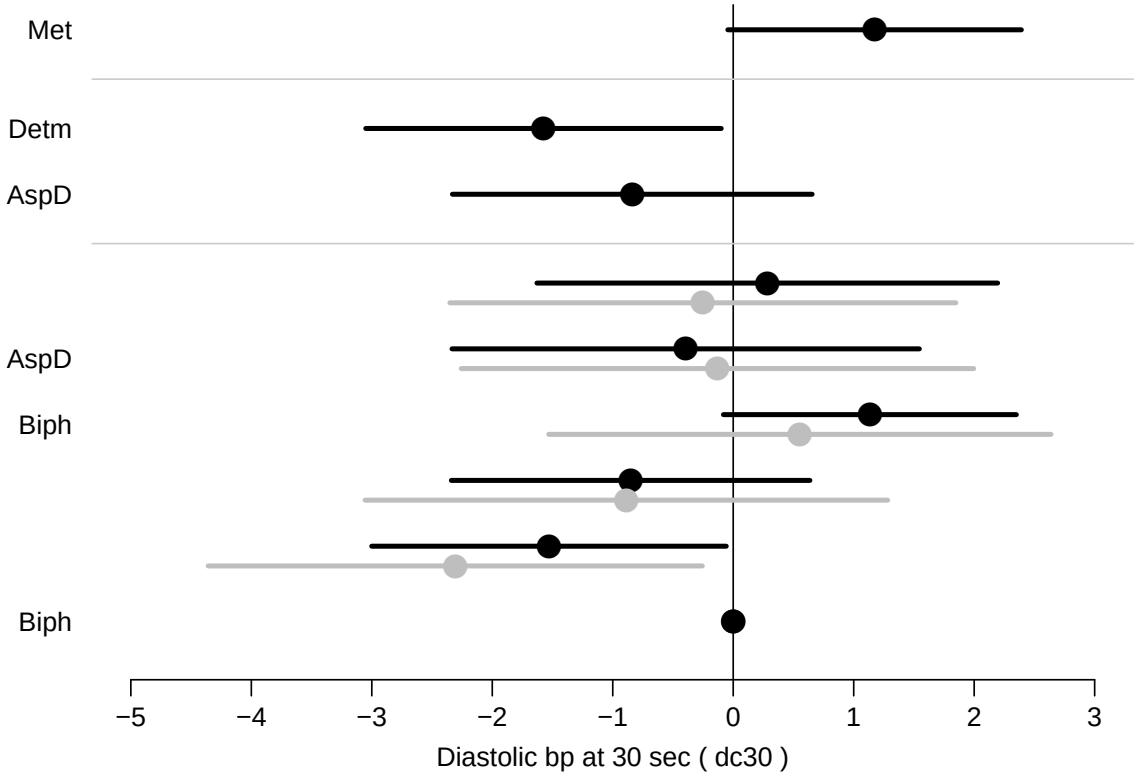

Figure 2.23: *Diastolic blood pressure at 30 sec: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-dc30-est`

2.2.8.2 Systolic blood pressure change at 30 seconds

This is in the variable `sc30`, so we fit the relevant models and make the diagnostic plots:

```
> sc30 <- mfit( "sc30", "Systolic bp at 30 sec")
================================================
Systolic bp at 30 sec: Follow-up in sc30.y, Baseline in sc30.x
 (controlled for hypertensive medication (oah))
------------------------------------------------
            Estimate StdErr      z      P    2.5%  97.5%
(Intercept)   0.2699 1.2052 0.2239 0.8228 -2.0922 2.6320
BA            0.4787 0.0526 9.0954 0.0000  0.3755 0.5818
oahY          2.8840 1.3522 2.1327 0.0329  0.2336 5.5343
grpMet        3.0908 1.3386 2.3090 0.0209  0.4672 5.7145
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   3.3418 1.4145  2.3626 0.0181  0.5695  6.1141
BA            0.4697 0.0532  8.8282 0.0000  0.3655  0.5740
oahY          2.9683 1.3521  2.1953 0.0281  0.3182  5.6184
igrAspD      -3.5608 1.6232 -2.1937 0.0283 -6.7422 -0.3794
igrDetm      -0.9554 1.6505 -0.5788 0.5627 -4.1902  2.2795
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)   1.9584 1.5389  1.2726 0.2032 -1.0579  4.9747
BA            0.4688 0.0529  8.8585 0.0000  0.3651  0.5725
oahY          2.7319 1.3490  2.0252 0.0428  0.0880  5.3759
grpMet        2.9604 1.3353  2.2170 0.0266  0.3432  5.5776
igrAspD      -3.4228 1.6156 -2.1186 0.0341 -6.5892 -0.2563
igrDetm      -0.9969 1.6416 -0.6073 0.5437 -4.2144  2.2205
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                  3.0678 1.7914  1.7126 0.0868 -0.4432  6.5788
BA                           0.4760 0.0534  8.9207 0.0000  0.3714  0.5806
oahY                         2.7467 1.3540  2.0285 0.0425  0.0928  5.4006
interaction(igr, grp)AspD.Plc -5.0469 2.2566 -2.2365 0.0253 -9.4697 -0.6240
interaction(igr, grp)Detm.Plc -2.8698 2.3975 -1.1970 0.2313 -7.5688  1.8291
interaction(igr, grp)Biph.Met  0.7137 2.2876  0.3120 0.7551 -3.7700  5.1974
interaction(igr, grp)AspD.Met -1.0511 2.3401 -0.4492 0.6533 -5.6377  3.5354
interaction(igr, grp)Detm.Met  1.4030 2.3108  0.6072 0.5437 -3.1260  5.9320

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.021   0.027   0.076   0.095   0.479

Estimates with and without b12 and mma:
       Estimate StdErr      z      P   2.5%  97.5%
BA       0.4787 0.0526 9.0954 0.0000 0.3755 0.5818
grpMet   3.0908 1.3386 2.3090 0.0209 0.4672 5.7145
                       Estimate StdErr       z      P    2.5%  97.5%
(Intercept)              1.1001 2.0268  0.5428 0.5873 -2.8724 5.0725
BA                       0.4865 0.0538  9.0508 0.0000  0.3812 0.5919
oahY                     2.7163 1.3912  1.9525 0.0509 -0.0104 5.4430
grpMet                   3.3301 1.4027  2.3740 0.0176  0.5807 6.0794
I((b12.y - b12.x)/100)   0.3439 0.4525  0.7599 0.4473 -0.5430 1.2307
I((mma.y - mma.x) * 10) -0.0709 0.8170 -0.0868 0.9308 -1.6723 1.5304
metformi.xY             -1.0717 1.9118 -0.5606 0.5751 -4.8187 2.6753

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
0.6015 2.0000 0.7403
> mod.diag( sc30 )
```

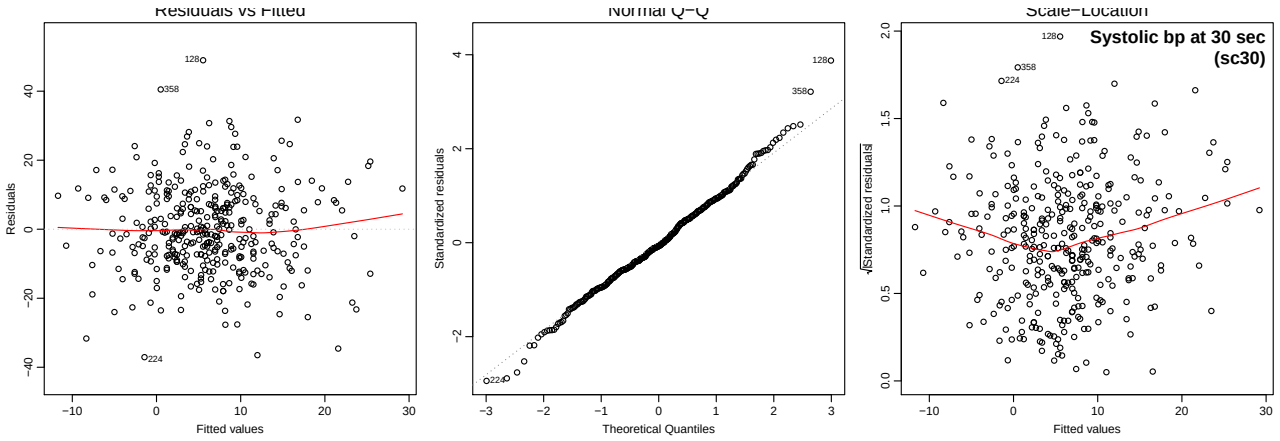

Figure 2.24: *Residual plots for systolic blood pressure at 30 sex (*sc30*)* `./graph/neu-sc30-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( sc30 )
```

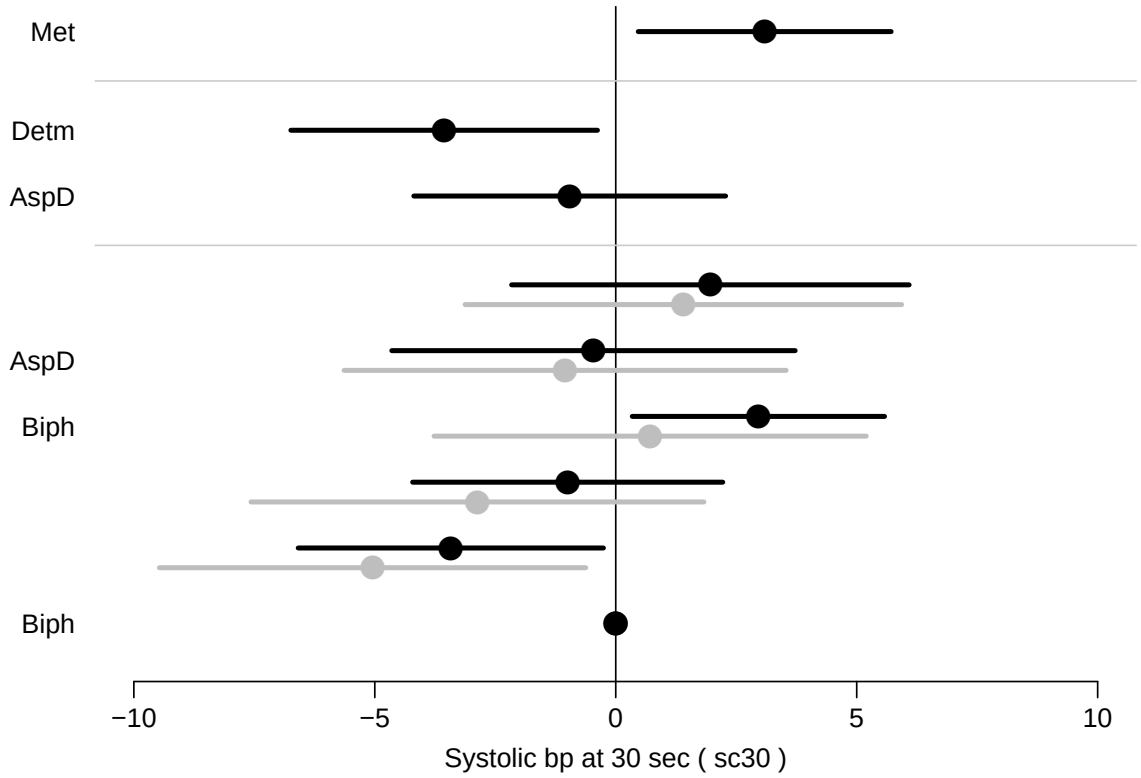

Figure 2.25: *Systolic blood pressure at 30 sec: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-sc30-est`

2.2.8.3 Diastolic blood pressure change at 90 seconds

This is in the variable `dc90`, so we fit the relevant models and make the diagnostic plots:

```
> dc90 <- mfit( "dc90", "Diastolic bp at 90 sec")
==================================================
Diastolic bp at 90 sec: Follow-up in dc90.y, Baseline in dc90.x
 (controlled for hypertensive medication (oah))
--------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -1.7683 0.5660 -3.1242 0.0018 -2.8776 -0.6589
BA            0.3528 0.0518  6.8145 0.0000  0.2513  0.4543
oahY         -0.8065 0.6027 -1.3380 0.1809 -1.9878  0.3749
grpMet        0.4361 0.5944  0.7337 0.4631 -0.7289  1.6012
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -0.8551 0.6429 -1.3302 0.1835 -2.1152  0.4049
BA            0.3573 0.0514  6.9489 0.0000  0.2565  0.4581
oahY         -0.7775 0.6000 -1.2960 0.1950 -1.9535  0.3984
igrAspD      -0.5778 0.7139 -0.8093 0.4183 -1.9769  0.8214
igrDetm      -1.5771 0.7251 -2.1749 0.0296 -2.9984 -0.1559
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -1.0897 0.7059 -1.5438 0.1226 -2.4731  0.2938
BA            0.3544 0.0516  6.8724 0.0000  0.2533  0.4555
oahY         -0.8061 0.6013 -1.3406 0.1800 -1.9847  0.3724
grpMet        0.4783 0.5930  0.8067 0.4199 -0.6839  1.6405
igrAspD      -0.5587 0.7146 -0.7818 0.4343 -1.9593  0.8419
igrDetm      -1.5916 0.7257 -2.1931 0.0283 -3.0140 -0.1692
                           Estimate StdErr       z      P    2.5%  97.5%
(Intercept)                 -0.9828 0.8262 -1.1895 0.2343 -2.6022 0.6366
BA                           0.3506 0.0519  6.7623 0.0000  0.2490 0.4523
oahY                        -0.7346 0.6023 -1.2196 0.2226 -1.9151 0.4459
interaction(igr, grp)AspD.Plc -1.3134 0.9948 -1.3202 0.1868 -3.2632 0.6365
interaction(igr, grp)Detm.Plc -1.1854 1.0557 -1.1229 0.2615 -3.2545 0.8837
interaction(igr, grp)Biph.Met  0.1638 1.0137  0.1615 0.8717 -1.8231 2.1507
interaction(igr, grp)AspD.Met  0.4581 1.0349  0.4427 0.6580 -1.5702 2.4864
interaction(igr, grp)Detm.Met -1.7547 1.0125 -1.7330 0.0831 -3.7392 0.2298

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.461   0.419   0.090   0.085   0.258

Estimates with and without b12 and mma:
       Estimate StdErr      z      P    2.5%  97.5%
BA       0.3528 0.0518 6.8145 0.0000  0.2513 0.4543
grpMet   0.4361 0.5944 0.7337 0.4631 -0.7289 1.6012
                       Estimate StdErr       z      P    2.5%  97.5%
(Intercept)             -1.3017 0.9156 -1.4218 0.1551 -3.0962 0.4928
BA                       0.3465 0.0536  6.4640 0.0000  0.2415 0.4516
oahY                    -0.8459 0.6183 -1.3682 0.1712 -2.0577 0.3658
grpMet                   0.6397 0.6223  1.0279 0.3040 -0.5800 1.8594
I((b12.y - b12.x)/100)   0.1983 0.2002  0.9906 0.3219 -0.1941 0.5907
I((mma.y - mma.x) * 10) -0.2028 0.3619 -0.5603 0.5753 -0.9120 0.5065
metformi.xY             -0.7336 0.8463 -0.8668 0.3861 -2.3924 0.9252

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
1.4079 2.0000 0.4946
> mod.diag( dc90 )
```

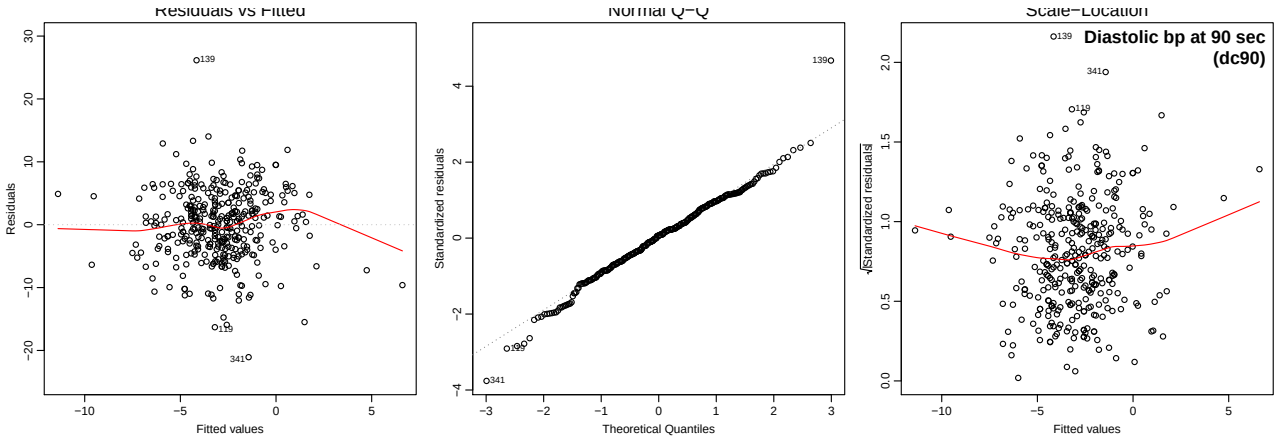

Figure 2.26: *Residual plots for diastolic blood pressure at 90 sec (*dc90*)* `./graph/neu-dc90-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( dc90 )
```

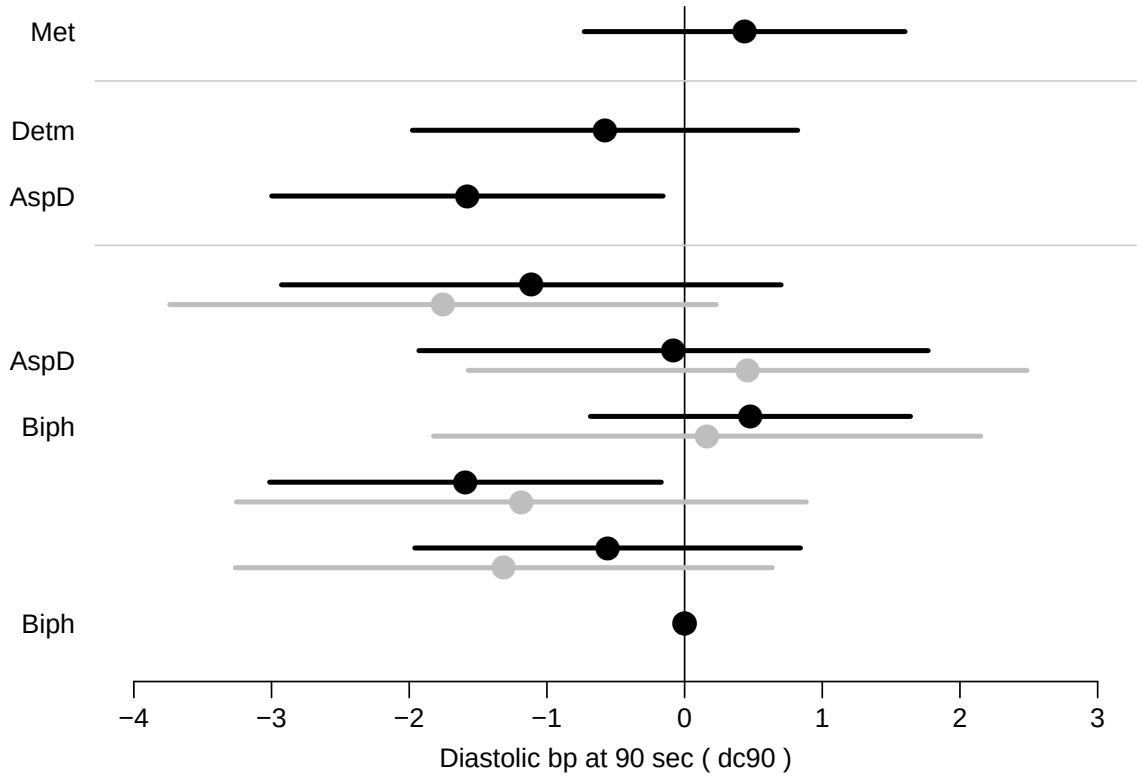

Figure 2.27: *Diastolic blood pressure at 90 sec: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-dc90-est`

2.2.8.4 Systolic blood pressure change at 90 seconds

This is in the variable `sc90`, so we fit the relevant models and make the diagnostic plots:

```
> sc90 <- mfit( "sc90", "Systolic bp at 90 sec")
================================================
Systolic bp at 90 sec: Follow-up in sc90.y, Baseline in sc90.x
 (controlled for hypertensive medication (oah))
------------------------------------------------
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)  -1.4481 1.0242 -1.4139 0.1574 -3.4556 0.5593
BA            0.4330 0.0530  8.1737 0.0000  0.3291 0.5368
oahY          1.4640 1.1666  1.2549 0.2095 -0.8225 3.7505
grpMet       -0.0115 1.1578 -0.0100 0.9920 -2.2807 2.2576
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)  -0.8779 1.2017 -0.7305 0.4651 -3.2333 1.4775
BA            0.4372 0.0533  8.2016 0.0000  0.3327 0.5417
oahY          1.4643 1.1662  1.2556 0.2093 -0.8215 3.7501
igrAspD      -0.5138 1.4005 -0.3669 0.7137 -3.2586 2.2311
igrDetm      -1.2719 1.4268 -0.8914 0.3727 -4.0684 1.5246
            Estimate StdErr       z      P    2.5%  97.5%
(Intercept)  -0.8857 1.3201 -0.6710 0.5022 -3.4730 1.7015
BA            0.4372 0.0534  8.1867 0.0000  0.3325 0.5419
oahY          1.4631 1.1707  1.2498 0.2114 -0.8313 3.7576
grpMet        0.0168 1.1615  0.0145 0.9884 -2.2596 2.2933
igrAspD      -0.5131 1.4032 -0.3657 0.7146 -3.2633 2.2370
igrDetm      -1.2723 1.4292 -0.8902 0.3733 -4.0735 1.5288
                           Estimate StdErr       z      P    2.5%  97.5%
(Intercept)                 -0.5906 1.5484 -0.3814 0.7029 -3.6255 2.4443
BA                           0.4399 0.0538  8.1725 0.0000  0.3344 0.5454
oahY                         1.4395 1.1761  1.2240 0.2210 -0.8656 3.7445
interaction(igr, grp)AspD.Plc -0.6566 1.9598 -0.3351 0.7376 -4.4977 3.1844
interaction(igr, grp)Detm.Plc -2.0555 2.0828 -0.9869 0.3237 -6.1378 2.0268
interaction(igr, grp)Biph.Met -0.5372 1.9844 -0.2707 0.7866 -4.4265 3.3520
interaction(igr, grp)AspD.Met -0.9367 2.0327 -0.4608 0.6449 -4.9207 3.0472
interaction(igr, grp)Detm.Met -1.1196 1.9939 -0.5615 0.5745 -5.0275 2.7883

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.992   0.988   0.672   0.672   0.862

Estimates with and without b12 and mma:
       Estimate StdErr       z     P    2.5%  97.5%
BA       0.4330 0.0530  8.1737 0.000  0.3291 0.5368
grpMet  -0.0115 1.1578 -0.0100 0.992 -2.2807 2.2576
                       Estimate StdErr       z      P    2.5%  97.5%
(Intercept)              0.6018 1.7338  0.3471 0.7285 -2.7964 3.9999
BA                       0.4276 0.0538  7.9475 0.0000  0.3222 0.5331
oahY                     1.2389 1.1908  1.0404 0.2982 -1.0950 3.5728
grpMet                   0.4398 1.2036  0.3654 0.7148 -1.9193 2.7988
I((b12.y - b12.x)/100)   0.4969 0.3885  1.2793 0.2008 -0.2644 1.2583
I((mma.y - mma.x) * 10) -0.3259 0.7021 -0.4641 0.6425 -1.7019 1.0502
metformi.xY             -2.6281 1.6406 -1.6019 0.1092 -5.8436 0.5874

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
1.9805 2.0000 0.3715
> mod.diag( sc90 )
```

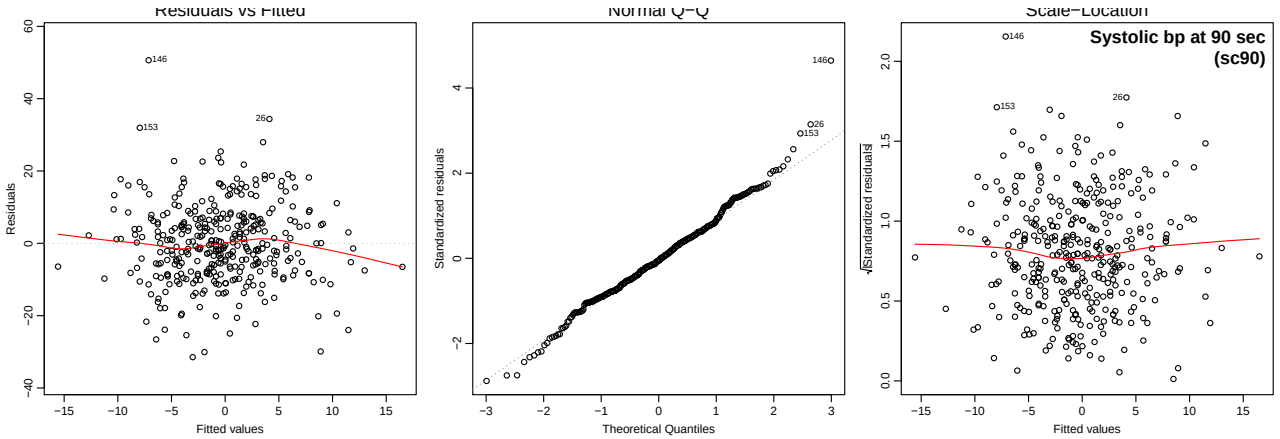

Figure 2.28: *Residual plots for systolic blood pressure at 90 sec (*sc90*)* ./graph/neu-sc90-diag

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( sc90 )
```

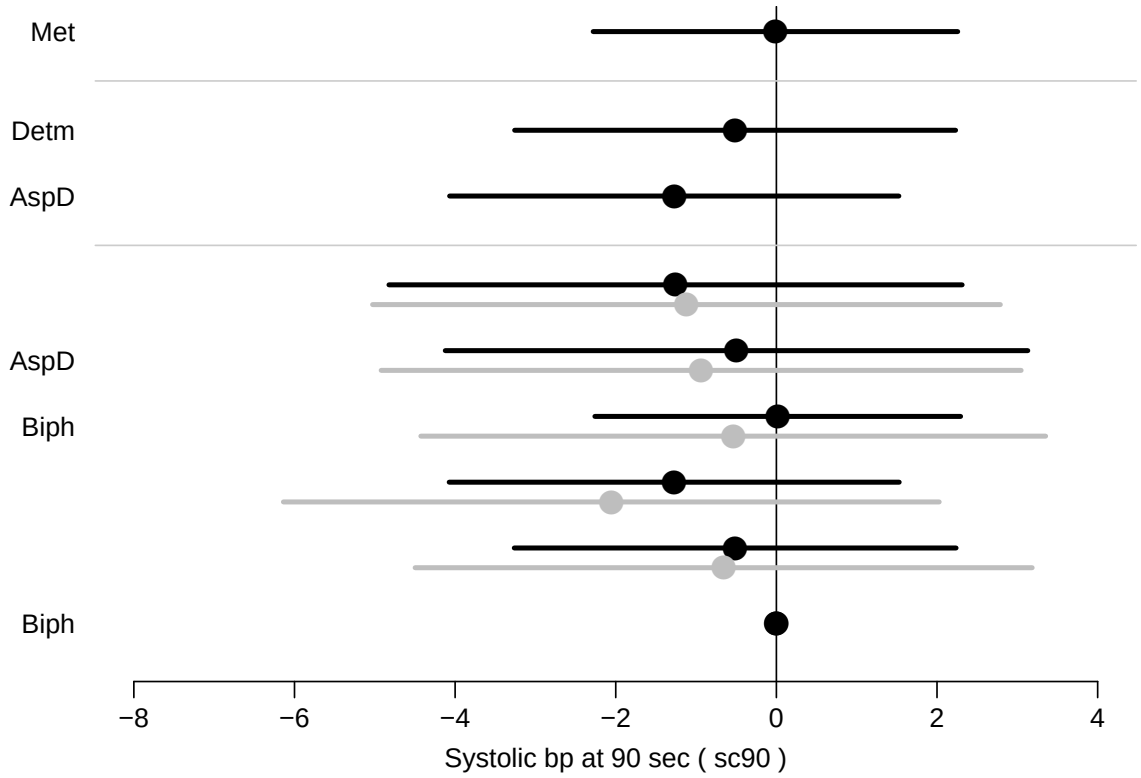

Figure 2.29: *Systolic blood pressure at 90s: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* ./graph/neu-sc90-est

2.2.8.5 Diastolic blood pressure change at 3 minutes

This is in the variable `dc3`, so we fit the relevant models and make the diagnostic plots:

```
> dc3 <- mfit( "dc3", "Diastolic bp at 3 min")
================================================
Diastolic bp at 3 min: Follow-up in dc3.x, Baseline in dc30.x
 (controlled for hypertensive medication (oah))
------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.1231 0.5069 -8.1335 0.0000 -5.1166 -3.1295
BA            0.5268 0.0453 11.6347 0.0000  0.4380  0.6155
oahY          0.8681 0.5787  1.5002 0.1336 -0.2660  2.0023
grpMet        0.4764 0.5690  0.8372 0.4025 -0.6388  1.5916
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.6541 0.5908 -6.1856 0.0000 -4.8120 -2.4963
BA            0.5343 0.0455 11.7336 0.0000  0.4450  0.6235
oahY          0.9089 0.5780  1.5725 0.1158 -0.2240  2.0418
igrAspD      -0.0044 0.6887 -0.0064 0.9949 -1.3543  1.3454
igrDetm      -0.7797 0.6999 -1.1139 0.2653 -2.1516  0.5922
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.8938 0.6509 -5.9823 0.0000 -5.1695 -2.6181
BA            0.5319 0.0456 11.6570 0.0000  0.4425  0.6213
oahY          0.8770 0.5794  1.5137 0.1301 -0.2585  2.0125
grpMet        0.5004 0.5698  0.8783 0.3798 -0.6163  1.6172
igrAspD       0.0140 0.6892  0.0203 0.9838 -1.3369  1.3649
igrDetm      -0.7878 0.7002 -1.1250 0.2606 -2.1602  0.5847
                           Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                 -4.3500 0.7705 -5.6456 0.0000 -5.8602 -2.8398
BA                           0.5250 0.0459 11.4367 0.0000  0.4350  0.6149
oahY                         0.9164 0.5810  1.5772 0.1147 -0.2224  2.0551
interaction(igr, grp)AspD.Plc  0.3496 0.9634  0.3629 0.7167 -1.5385  2.2378
interaction(igr, grp)Detm.Plc  0.2382 1.0216  0.2331 0.8157 -1.7642  2.2406
interaction(igr, grp)Biph.Met  1.3406 0.9805  1.3673 0.1715 -0.5811  3.2623
interaction(igr, grp)AspD.Met  1.0434 0.9935  1.0501 0.2937 -0.9039  2.9907
interaction(igr, grp)Detm.Met -0.3627 0.9847 -0.3684 0.7126 -2.2928  1.5673

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.403   0.380   0.445   0.430   0.377

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.5268 0.0453 11.6347 0.0000  0.4380 0.6155
grpMet   0.4764 0.5690  0.8372 0.4025 -0.6388 1.5916
                       Estimate StdErr       z      P    2.5%   97.5%
(Intercept)             -3.4961 0.8650 -4.0417 0.0001 -5.1915 -1.8007
BA                       0.5264 0.0461 11.4155 0.0000  0.4361  0.6168
oahY                     0.7902 0.5935  1.3314 0.1831 -0.3731  1.9535
grpMet                   0.4509 0.5953  0.7575 0.4488 -0.7158  1.6176
I((b12.y - b12.x)/100)  -0.0287 0.1923 -0.1493 0.8813 -0.4056  0.3482
I((mma.y - mma.x) * 10)  0.3128 0.3467  0.9022 0.3670 -0.3667  0.9923
metformi.xY             -0.6037 0.8086 -0.7466 0.4553 -2.1886  0.9812

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
0.8680 2.0000 0.6479
> mod.diag( dc3 )
```

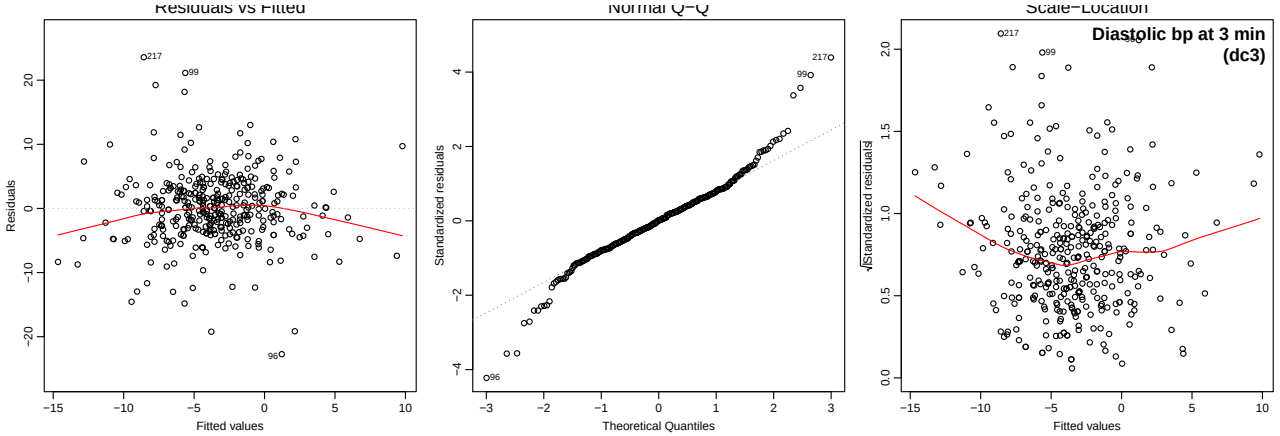

Figure 2.30: *Residual plots for diastolic blood pressure at 3 min (*dc3*)* `./graph/neu-dc3-diag`

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( dc3 )
```

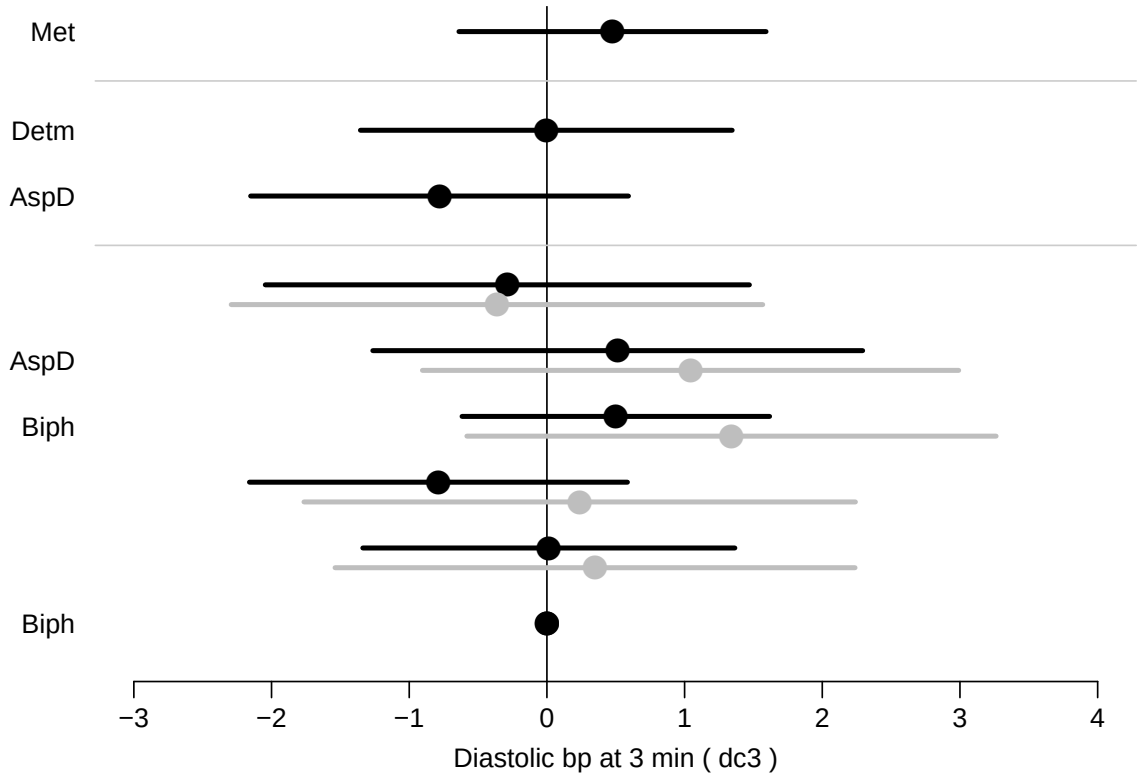

Figure 2.31: *Diastolic blood pressure at 3 min: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* `./graph/neu-dc3-est`

2.2.8.6 Systolic blood pressure at 3 minutes

This is in the variable `sc3`, so we fit the relevant models and make the diagnostic plots:

```
> sc3 <- mfit( "sc3", "Systolic bp at 3 min")
================================================
Systolic bp at 3 min: Follow-up in sc3.x, Baseline in sc30.x
 (controlled for hypertensive medication (oah))
------------------------------------------------
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.7398 0.9164 -4.0808 0.0000 -5.5360 -1.9436
BA            0.5095 0.0401 12.7095 0.0000  0.4309  0.5881
oahY          0.1042 1.0276  0.1014 0.9192 -1.9098  2.1182
grpMet        1.1073 1.0177  1.0880 0.2766 -0.8874  3.1021
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -3.5170 1.0761 -3.2682 0.0011 -5.6261 -1.4078
BA            0.5089 0.0406 12.5432 0.0000  0.4294  0.5885
oahY          0.1932 1.0292  0.1877 0.8511 -1.8241  2.2104
igrAspD       0.3326 1.2353  0.2693 0.7877 -2.0886  2.7538
igrDetm       0.5532 1.2600  0.4391 0.6606 -1.9164  3.0229
            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)  -4.0366 1.1783 -3.4259 0.0006 -6.3460 -1.7273
BA            0.5088 0.0406 12.5439 0.0000  0.4293  0.5883
oahY          0.1152 1.0315  0.1116 0.9111 -1.9066  2.1369
grpMet        1.1050 1.0216  1.0816 0.2794 -0.8973  3.1072
igrAspD       0.3755 1.2357  0.3038 0.7612 -2.0464  2.7973
igrDetm       0.5281 1.2600  0.4191 0.6751 -1.9414  2.9976
                            Estimate StdErr       z      P    2.5%   97.5%
(Intercept)                  -3.8034 1.3750 -2.7662 0.0057 -6.4983 -1.1085
BA                            0.5081 0.0409 12.4223 0.0000  0.4279  0.5883
oahY                          0.1743 1.0358  0.1683 0.8663 -1.8558  2.2044
interaction(igr, grp)AspD.Plc -0.4623 1.7279 -0.2675 0.7891 -3.8489  2.9244
interaction(igr, grp)Detm.Plc  0.6914 1.8407  0.3756 0.7072 -2.9164  4.2992
interaction(igr, grp)Biph.Met  0.5904 1.7543  0.3366 0.7365 -2.8480  4.0289
interaction(igr, grp)AspD.Met  1.8743 1.7830  1.0512 0.2931 -1.6202  5.3689
interaction(igr, grp)Detm.Met  1.0017 1.7661  0.5672 0.5706 -2.4599  4.4633

Tests of effects (P-values):
    Met Met|Ins     Ins Ins|Met  MxI|MI
  0.279   0.280   0.906   0.910   0.679

Estimates with and without b12 and mma:
       Estimate StdErr       z      P    2.5%  97.5%
BA       0.5095 0.0401 12.7095 0.0000  0.4309 0.5881
grpMet   1.1073 1.0177  1.0880 0.2766 -0.8874 3.1021
                        Estimate StdErr       z      P    2.5%   97.5%
(Intercept)              -0.5180 1.5239 -0.3399 0.7339 -3.5048  2.4688
BA                        0.5123 0.0403 12.7179 0.0000  0.4334  0.5913
oahY                     -0.2236 1.0405 -0.2149 0.8299 -2.2629  1.8158
grpMet                    0.9923 1.0504  0.9447 0.3448 -1.0665  3.0512
I((b12.y - b12.x)/100)   -0.2871 0.3406 -0.8427 0.3994 -0.9547  0.3806
I((mma.y - mma.x) * 10)  -0.8200 0.6136 -1.3364 0.1814 -2.0226  0.3826
metformi.xY              -3.6097 1.4299 -2.5244 0.0116 -6.4123 -0.8071

Test for joint effect fo b12 and mma:
 Chisq   d.f.      P
2.3126 2.0000 0.3146
> mod.diag( sc3 )
```

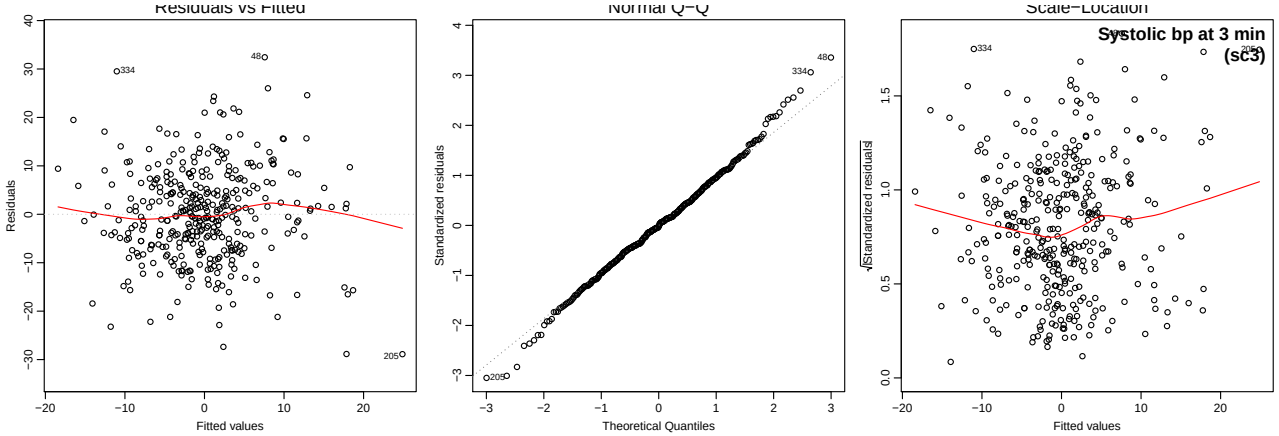

Figure 2.32: *Residual plots for systolic blood pressure at 3 min (*sc3*)* ./graph/neu-sc3-diag

Finally we extract the estimates and plot them:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> CIMTres( sc3 )
```

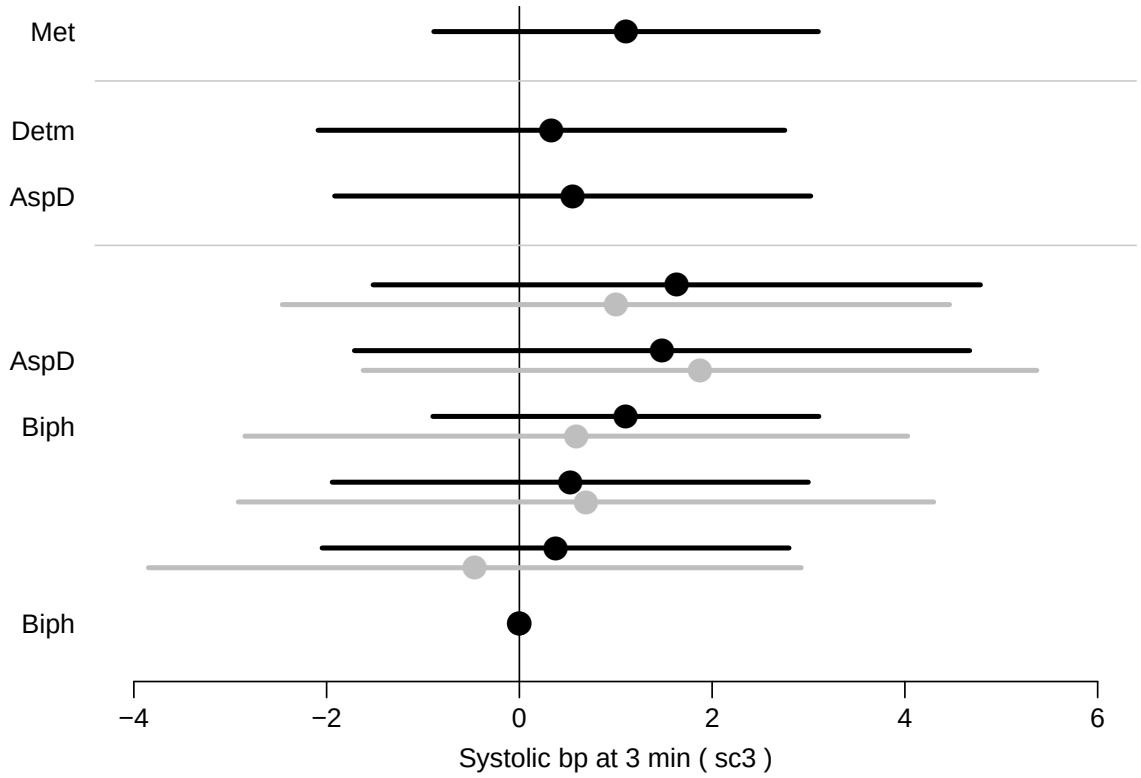

Figure 2.33: *Systolic blood pressure at 3 min: Estimates of the treatment effects from 4 different models: 1(top) model with Metformin/Placebo only, 2(2nd) model with insulin assignment only, 3(bottom, black) main effects model with identical insulin effects in both metformin and placebo and 4(bottom,gray) interaction model. All models use (placebo,biphasic) as reference.* ./graph/neu-sc3-est

2.2.9 Summary of blood pressure

We extract the metformin effects from the simple model from the fitted obejcts:

```
> ests <- rbind(
+ ci.exp( rsys$m.mod, subset="grp", Exp=F ),
+ ci.exp( rdia$m.mod, subset="grp", Exp=F ),
+ ci.exp( sc30$m.mod, subset="grp", Exp=F ),
+ ci.exp( dc30$m.mod, subset="grp", Exp=F ),
+ ci.exp( sc90$m.mod, subset="grp", Exp=F ),
+ ci.exp( dc90$m.mod, subset="grp", Exp=F ),
+ ci.exp(  sc3$m.mod, subset="grp", Exp=F ),
+ ci.exp(  dc3$m.mod, subset="grp", Exp=F ) )
> rownames( ests ) <- paste(
+     c("Resting","","0-30 sec.","","0-90 sec.","","0-180 sec.",""),
+                           rep(c("systolic","diastolic"),2) )
> round( ests, 3 )
                    Estimate   2.5% 97.5%
Resting systolic       1.055 -1.483 3.594
 diastolic            -0.374 -1.862 1.114
0-30 sec. systolic     3.091  0.467 5.714
 diastolic             1.174 -0.044 2.392
0-90 sec. systolic    -0.012 -2.281 2.258
 diastolic             0.436 -0.729 1.601
0-180 sec. systolic    1.107 -0.887 3.102
 diastolic             0.476 -0.639 1.592


> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plotEst( ests,
+          y=8:1+rep(c(0,0.3),4),
+          vref=0, cex=1.5, lwd=3,
+          xlab="Metformin effect (mmHg)" )
```

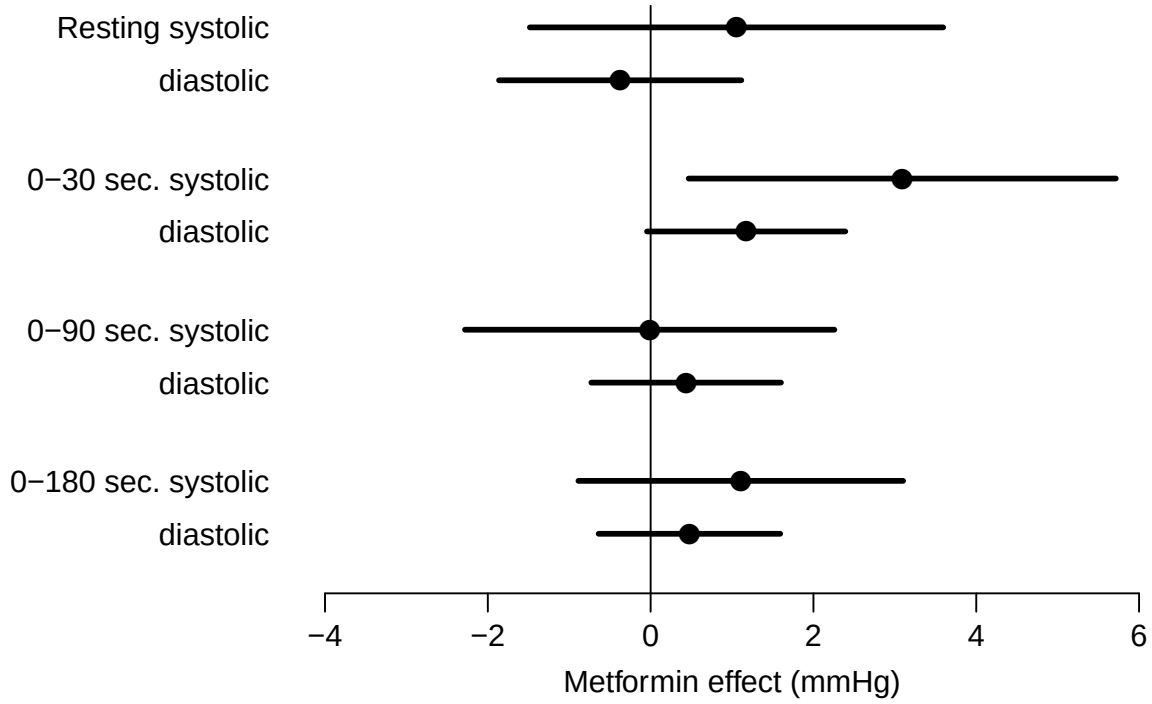

Figure 2.34: *Summary of metformin effect on resting blood pressure and drop in blood pressure from resting (resting−after).* `./graph/neu-BP-est`

2.3 Binary outcomes

We have two binary outcomes `ecsort3` and `vibage`

```
> with( ana1, ftable( grp, vibage.x, vibage.y, useNA="ifany" ) )
             vibage.y   0   1  NA
grp vibage.x
Plc 0                  146  11   0
    1                   10  15   0
    NA                   0   0   0
Met 0                  149  16   0
    1                    6  17   0
    NA                   0   0   0
```

```
> with( ana1, ftable( grp, ecsort3.x, ecsort3.y, useNA="ifany" ) )
              ecsort3.y   0   1  NA
grp ecsort3.x
Plc 0                   129  22   0
    1                    16  14   0
    NA                    0   0   0
Met 0                   119  25   0
    1                    22  18   0
    NA                    0   0   0
```

2.3.1 `ecsort3`

First `ecsort3`, and a logistic regression of follow-up status given baseline status equal to 0 gives:

```
> m0 <- glm( ecsort3.y ~ grp,
+            family= binomial,
+            data = subset(ana1,ecsort3.x==0) )
> round( ci.exp( m0, pval=T ), 3 )
            exp(Est.)  2.5% 97.5%     P
(Intercept)     0.171 0.109 0.268 0.000
grpMet          1.232 0.660 2.301 0.513
```

Nothing much ensues using the insulin or the combination of insulin and metformin:

```
> mm  <- update( m0 , . ~ . + I((b12.y-b12.x)/100)
+                           + I((mma.y-mma.x)*10)
+                           + metformi.x )
> mmi <- update( mm , . ~ . + igr )
> mi  <- update( mmi, . ~ . - grp )
> round( ci.exp( mmi, pval=T ), 3 )
                         exp(Est.)  2.5% 97.5%     P
(Intercept)                  0.288 0.119 0.696 0.006
grpMet                       1.332 0.700 2.534 0.382
I((b12.y - b12.x)/100)       1.160 0.971 1.385 0.102
I((mma.y - mma.x) * 10)      1.285 0.875 1.889 0.201
metformi.xY                  0.620 0.277 1.388 0.245
igrAspD                      0.758 0.357 1.608 0.470
igrDetm                      0.779 0.352 1.721 0.536
```

```
> round( ci.exp( mi , pval=T ), 3 )
```

```
                         exp(Est.)  2.5% 97.5%     P
(Intercept)                  0.338 0.151 0.753 0.008
I((b12.y - b12.x)/100)       1.148 0.963 1.369 0.123
I((mma.y - mma.x) * 10)      1.298 0.880 1.914 0.188
metformi.xY                  0.608 0.272 1.358 0.225
igrAspD                      0.757 0.358 1.604 0.468
igrDetm                      0.790 0.358 1.742 0.559
```

```
> anova( mm, mmi, mi, test="Chisq" )
```

```
Analysis of Deviance Table

Model 1: ecsort3.y ~ grp + I((b12.y - b12.x)/100) + I((mma.y - mma.x) *
    10) + metformi.x
Model 2: ecsort3.y ~ grp + I((b12.y - b12.x)/100) + I((mma.y - mma.x) *
    10) + metformi.x + igr
Model 3: ecsort3.y ~ I((b12.y - b12.x)/100) + I((mma.y - mma.x) * 10) +
    metformi.x + igr
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1       283     250.75
2       281     250.13  2  0.61819   0.7341
3       282     250.89 -1 -0.76705   0.3811
```

Basically, `ecsort3` is not influenced by the treatment modality.

2.3.2 `vibage`

Secondly `vibage`, and a logistic regression of follow-up status given baseline status equal to 0 gives:

```
> m0 <- glm( vibage.y ~ grp,
+            family= binomial,
+            data = subset(ana1,vibage.x==0) )
> round( ci.exp( m0, pval=T ), 3 )
```

```
            exp(Est.)  2.5% 97.5%     P
(Intercept)     0.075 0.041 0.139 0.000
grpMet          1.425 0.640 3.175 0.386
```

Nothing much ensues using the insulin or the combination of insulin and metformin:

```
> mm  <- update( m0 , . ~ . + I((b12.y-b12.x)/100)
+                           + I((mma.y-mma.x)*10)
+                           + metformi.x )
> mmi <- update( mm , . ~ . + igr )
> mi  <- update( mmi, . ~ . - grp )
> round( ci.exp( mmi, pval=T ), 3 )
```

```
                         exp(Est.)  2.5% 97.5%     P
(Intercept)                  0.086 0.025 0.295 0.000
grpMet                       1.327 0.572 3.081 0.510
I((b12.y - b12.x)/100)       0.950 0.744 1.213 0.679
I((mma.y - mma.x) * 10)      1.243 0.780 1.981 0.361
metformi.xY                  1.236 0.392 3.894 0.718
igrAspD                      0.664 0.252 1.746 0.406
igrDetm                      0.629 0.229 1.724 0.367
```

```
> round( ci.exp( mi , pval=T ), 3 )
```

```
                         exp(Est.)  2.5% 97.5%     P
(Intercept)                  0.101 0.033 0.311 0.000
I((b12.y - b12.x)/100)       0.933 0.734 1.186 0.570
I((mma.y - mma.x) * 10)      1.258 0.785 2.017 0.340
metformi.xY                  1.219 0.388 3.829 0.735
igrAspD                      0.659 0.251 1.732 0.398
igrDetm                      0.647 0.237 1.763 0.394
```

```
> anova( mm, mmi, mi, test="Chisq" )
Analysis of Deviance Table

Model 1: vibage.y ~ grp + I((b12.y - b12.x)/100) + I((mma.y - mma.x) *
    10) + metformi.x
Model 2: vibage.y ~ grp + I((b12.y - b12.x)/100) + I((mma.y - mma.x) *
    10) + metformi.x + igr
Model 3: vibage.y ~ I((b12.y - b12.x)/100) + I((mma.y - mma.x) * 10) +
    metformi.x + igr
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1       308     177.47
2       306     176.43  2  1.03821   0.5951
3       307     176.87 -1 -0.43642   0.5089
```

Basically, `vibage` is not influenced by the treatment modality.

Chapter 3

Baseline tables

3.1 Retrieving the analysis data set

We retrieve the long versions of the group names and the color scemes along the base data:

```
> library(Epi)
> clear()
> setwd("/home/bendix/sdc/coll/csvh")
> source("fromC.txt")
> load( file="./data/ana.Rda" )
> ana$men <- ana$sex=="M"
> lls()
  name   mode      class      dim          size(Kb)
1 ana    list      data.frame 744 93          516.7
2 Cat    character character  31               2.0
3 Catfu  character character  2                0.2
4 Cont   character character  25               1.6
5 Contfu character character  18               1.2
```

Here are the varibels CSVH requred in the base (& FU) tables as continuous and categorical:

```
> Cat
 [1] "men"      "smoking." "alcohol." "caucas"   "auto.neu" "peri.neu" "microalb"
 [8] "macroalb" "cvd"      "retin"    "metformi" "pre.ins"  "su"       "oad"
[15] "ras"      "bblock"   "oah"      "statin"   "asa"      "acei"     "acei.thi"
[22] "arb"      "arbcomb"  "arb.ccb"  "loop"     "ccb"      "thiazid"  "spiron"
[29] "aht"      "ecsort3"  "vibage"
> Catfu
[1] "ecsort3" "vibage"
> match(Catfu,Cat)
[1] 30 31
> Cont
 [1] "aav"     "bmi"     "dmdurav" "hba1c"   "hba1c"   "ldl"     "e.gfr"   "b12"
 [9] "mma"     "vibhcon" "vibvcon" "vibmax"  "b2b"     "resthr"  "pul05"   "pul1_5"
[17] "pul3"    "sys_lig" "s30"     "s90"     "s3"      "dia_lig" "d30"     "d90"
[25] "d3"
> Contfu
 [1] "b12"     "mma"     "vibhcon" "vibvcon" "vibmax"  "b2b"     "resthr"  "pul05"
 [9] "pul1_5"  "pul3"    "sys_lig" "s30"     "s90"     "s3"      "dia_lig" "d30"
[17] "d90"     "d3"
```

```
> match(Contfu,Cont)
 [1]  8  9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
```

We check if they are in the analysis data set:

```
> ( whm <- match( Cont, names(ana) ) )
 [1] 77 50 78 52 52 59 69  4  3  5  6 79  7 23 10 13 16 25  8 11 14 24  9 12 15
> ( whm <- match( Cat, names(ana) ) )
 [1] 93 NA NA 71 NA NA NA NA 73 72 70 47 NA 76 74 NA 75 NA NA NA NA NA NA NA NA NA NA NA
[29] NA 29 42
> Cat[is.na(whm)]
 [1] "smoking." "alcohol." "auto.neu" "peri.neu" "microalb" "macroalb" "su"
 [8] "bblock"   "statin"   "asa"      "acei"     "acei.thi" "arb"      "arbcomb"
[15] "arb.ccb"  "loop"     "ccb"      "thiazid"  "spiron"   "aht"
```

So some of the needed variables are not in the analysis data set, so we must include them, so we read the extended baseline file, but only for retrieval of the omitted variables:

```
> library( foreign )
> newbase <- read.xport( "/home/bendix/sdc/proj/CIMT/data/baseline.xpt" )
> ( names( newbase ) <- gsub( "_", ".", tolower( names( newbase ) ) ) )
  [1] "subjid"   "birthdat" "visitdat" "sex"      "etnicity" "diabetes" "peri.neu"
  [8] "retinopa" "auto.neu" "laserbeh" "ami"      "heartsur" "ihd"      "heartins"
 [15] "apopl"    "tci"      "vascsurg" "amp"      "sys1.b0"  "dia1.b0"  "sys2.b0"
 [22] "dia2.b0"  "pulse.b0" "microalb" "macroalb" "e.gfr"    "b1bdato"  "smoking."
 [29] "alcohol." "hba1c.b1" "hba1c.b7" "gluc.b1a" "gluc.b7a" "cpep.b1a" "cpep.b7a"
 [36] "ins.b1a"  "ins.b7a"  "chol.b1a" "chol.b7a" "trig.b1a" "trig.b7a" "ldl.b1a"
 [43] "ldl.b7a"  "vldl.b1a" "vldl.b7a" "hdlc.b1a" "hdlc.b7a" "gad65.b1" "weight.b"
 [50] "weight.2" "height.b" "height.2" "talje.b1" "talje.b7" "hofte.b1" "hofte.b7"
 [57] "avgnatua" "avgnatu2" "metformi" "insulin"  "su"       "rosiglit" "glp1"
 [64] "dpp4"     "repaglin" "glucagon" "acei"     "loop"     "arb"      "arbcomb"
 [71] "ccb"      "bblock"   "thiazid"  "spiron"   "aht"      "statin"   "fibrat"
 [78] "lipids"   "asa"      "thyre"    "apurin"   "nsaid"    "painkill" "antidep"
 [85] "gaba"     "impo"     "ntg"      "gastro"   "contrace" "antibiot" "dvit"
 [92] "calc"     "alendr"   "bvit"     "lung"     "other"    "plataggr" "iron"
 [99] "fishoil"  "othernat" "acei.thi" "loop.ccb" "dvit.cal" "bvit.iro" "arb.ccb"
[106] "metform2" "insulint" "randdate" "above.si" "prior.in" "sdc"
> newbase$visit <- "v1"
> ( wh3 <- match( Cat[is.na(whm)], names(newbase) ) )
 [1]  28  29   9   7  24  25  61  72  76  79  67 101  69  70 105  68  71  73  74  75
> whvar <- c("subjid","visit",Cat[is.na(whm)])
```

We then add the (baseline) variables to the analysis dataset; note that the default behaviour of merge is only to take the intersection of the keys from the two datasets. Moreover we only want information for the 372 persons who are in the neuro-follow-up:

```
> dim( ana )
[1] 744  93
> intersect( names(ana), names(newbase[whvar]) )
[1] "subjid" "visit"
> anax <- merge( ana, newbase[,whvar], all.x=TRUE )
> rbind( ana=dim(ana), anax=dim(anax) )
```

```
     [,1] [,2]
ana   744   93
anax  744  113
> # Check that the added variables actually are all missing for v7:
> chkarr <- NArray( list( whvar[-(1:2)], visit=c("v1","v7") ) )
> for( vv in whvar[-(1:2)] )
+   chkarr[vv,] <- with(anax,tapply(anax[,vv],list(visit),mean,na.rm=TRUE))


> ( whm <- match( Cont, names(anax) ) )
 [1] 77 50 78 52 52 59 69  4  3  5  6 79  7 23 10 13 16 25  8 11 14 24  9 12 15
> ( whm <- match( Cat , names(anax) ) )
 [1]  93  94  95  71  96  97  98  99  73  72  70  47 100  76  74 101  75 102 103 104 105
[22] 106 107 108 109 110 111 112 113  29  42
> dim( anax )
[1] 744 113
> names( anax )
  [1] "subjid"   "visit"    "mma"      "b12"      "vibhcon"  "vibvcon"  "b2b"
  [8] "s30"      "d30"      "pul05"    "s90"      "d90"      "pul1_5"   "s3"
 [15] "d3"       "pul3"     "s5"       "d5"       "pul5"     "s7"       "d7"
 [22] "pul7"     "resthr"   "dia_lig"  "sys_lig"  "minsys3"  "minsys5"  "mins37"
 [29] "ecsort3"  "osvim3"   "ecsort5"  "osvim5"   "ecsort7"  "osvim7"   "esc37"
 [36] "osv37"    "cpul05"   "cpul15"   "cpul3"    "cpul5"    "cpul7"    "vibage"
 [43] "bestvib"  "grp"      "igr"      "over.65"  "pre.ins"  "sdc"      "weight"
 [50] "bmi"      "whr"      "hba1c"    "gluc"     "ins"      "idos"     "ipkg"
 [57] "cpep"     "chol"     "ldl"      "hdl"      "vldl"     "trig"     "sys"
 [64] "dia"      "pulse"    "vdate"    "dov"      "sex"      "e.gfr"    "metformi"
 [71] "caucas"   "retin"    "cvd"      "ras"      "oah"      "oad"      "aav"
 [78] "dmdurav"  "vibmax"   "chp30"    "chp90"    "chp180"   "dc30"     "dc90"
 [85] "dc3"      "dc5"      "dc7"      "sc30"     "sc90"     "sc3"      "sc5"
 [92] "sc7"      "men"      "smoking." "alcohol." "auto.neu" "peri.neu" "microalb"
 [99] "macroalb" "su"       "bblock"   "statin"   "asa"      "acei"     "acei.thi"
[106] "arb"      "arbcomb"  "arb.ccb"  "loop"     "ccb"      "thiazid"  "spiron"
[113] "aht"
> with( anax, table(table(subjid)) )
  2
372
```

3.2 Descriptive table by Met / Plc

This descriptive table is based on the datset `anax`:

This is a table of patient characteristics at entry into the study on variables that are not measured (or of any particular interst) at follow-up. We now set up a table to hold the values in the baseline table, first defining what variables to use:

```
> anax <- transform( anax, s.ret = (retin=="Simplex"),
+                          p.ret = (retin=="Prolif"),
+                       metformi = metformi=="Y",
+                        ini.ins = pre.ins=="preIns",
+                            oah = oah=="Y" )
> ( wr <- match( 'retin', Cat ) )
```

```
[1] 10
> nC <- length(Cat)
> Catg <- c( Cat[1:(wr-1)],"s.ret","p.ret",Cat[(wr+1):nC] )
> Catg[grep("pre.ins",Catg)] <- "ini.ins"
> match( Catg, names( anax ) )
 [1]  93  94  95  71  96  97  98  99  73 114 115  70 116 100  76  74 101  75 102 103 104
[22] 105 106 107 108 109 110 111 112 113  29  42
> match( Catfu, Catg )
[1] 31 32
> match( Cont, names( anax ) )
 [1] 77 50 78 52 52 59 69  4  3  5  6 79  7 23 10 13 16 25  8 11 14 24  9 12 15
> # Baseline variables
> bvars <- c( Catg, Cont )
> bin <- rep(1:0,c(length(Catg),length(Cont)))
> data.frame( bin, bvars )
   bin    bvars
1    1      men
2    1 smoking.
3    1 alcohol.
4    1   caucas
5    1 auto.neu
6    1 peri.neu
7    1 microalb
8    1 macroalb
9    1      cvd
10   1    s.ret
11   1    p.ret
12   1 metformi
13   1  ini.ins
14   1       su
15   1      oad
16   1      ras
17   1   bblock
18   1      oah
19   1   statin
20   1      asa
21   1     acei
22   1 acei.thi
23   1      arb
24   1  arbcomb
25   1  arb.ccb
26   1     loop
27   1      ccb
28   1  thiazid
29   1   spiron
30   1      aht
31   1  ecsort3
32   1   vibage
33   0      aav
34   0      bmi
35   0  dmdurav
36   0    hba1c
37   0    hba1c
38   0      ldl
```

```
39   0    e.gfr
40   0      b12
41   0      mma
42   0  vibhcon
43   0  vibvcon
44   0   vibmax
45   0      b2b
46   0   resthr
47   0    pul05
48   0   pul1_5
49   0     pul3
50   0  sys_lig
51   0      s30
52   0      s90
53   0       s3
54   0  dia_lig
55   0      d30
56   0      d90
57   0       d3
```

```
> # FU variables
> fvars <- c( Catfu, Contfu )
> fbin <- rep(1:0,c(length(Catfu),length(Contfu)))
> data.frame( fbin, fvars )
```

```
   fbin   fvars
1     1 ecsort3
2     1  vibage
3     0     b12
4     0     mma
5     0 vibhcon
6     0 vibvcon
7     0  vibmax
8     0     b2b
9     0  resthr
10    0   pul05
11    0  pul1_5
12    0    pul3
13    0 sys_lig
14    0     s30
15    0     s90
16    0      s3
17    0 dia_lig
18    0     d30
19    0     d90
20    0      d3
```

Once we have defined the variables to be summarized at baseline and at follow-up we can set up the array to hold the relevant numbers; but first we split the dataset in baseline and follow-up:

```
> anab <- subset( anax, visit=="v1" )
> anaf <- subset( anax, visit=="v7" )
> cbind( table(table(anab$subjid)), table(table(anaf$subjid)) )
```

```
  [,1] [,2]
1  372  372
```

3.2.1 Baseline tables

Then we can set up the table of the baseline summary

```
> BB <- NArray( list( bvars,
+                     levels(anab$grp),
+                     c( paste( c(2,1,3)/4), "mean", "sd" ) ) )
> str( BB )
 logi [1:57, 1:2, 1:5] NA NA NA NA NA NA ...
 - attr(*, "dimnames")=List of 3
  ..$ : chr [1:57] "men" "smoking." "alcohol." "caucas" ...
  ..$ : chr [1:2] "Plc" "Met"
  ..$ : chr [1:5] "0.5" "0.25" "0.75" "mean" ...
> for( vv in 1:dim(BB)[1] )
+    {
+  #  cat( vv, ": ", bvars[vv], " ", class(anab[,bvars[vv]]), "\n" )
+ for( gg in dimnames(BB)[[2]] )
+ {
+ if( bin[vv] == 0 )
+ BB[vv,gg,] <- c( quantile( anab[anab$grp==gg,bvars[vv]],
+                            probs=c(2,1,3)/4, na.rm=TRUE ),
+                       mean( anab[anab$grp==gg,bvars[vv]], na.rm=TRUE ),
+                         sd( anab[anab$grp==gg,bvars[vv]], na.rm=TRUE ) )
+ else
+ BB[vv,gg,1:2] <-
+ BB[vv,gg,4:5] <- c( sum( anab[anab$grp==gg,bvars[vv]], na.rm=TRUE ),
+                     mean( anab[anab$grp==gg,bvars[vv]], na.rm=TRUE )*100 )
+ }
+ }
```

Then we print out the median and IQR from this array for the continuous variables and the number and percentage of the categorical ones:

```
> round( tt <- ftable( BB[,,1:3], col.vars=2:3), 1 )
            Plc                Met
            0.5  0.25  0.75    0.5  0.25  0.75
men       127.0  69.4    NA 130.0  68.8    NA
smoking.   25.0  13.7    NA  34.0  18.0    NA
alcohol.  755.5 417.4    NA 840.0 451.6    NA
caucas    178.0  97.3    NA 184.0  97.4    NA
auto.neu   33.0  18.2    NA  28.0  14.9    NA
peri.neu   65.0  35.7    NA  71.0  37.8    NA
microalb   33.0  18.3    NA  44.0  23.9    NA
macroalb    8.0   4.4    NA  12.0   6.5    NA
cvd        41.0  22.4    NA  40.0  21.2    NA
s.ret      53.0  29.6    NA  55.0  30.1    NA
p.ret       9.0   5.0    NA  14.0   7.7    NA
metformi  157.0  85.8    NA 155.0  82.0    NA
ini.ins   124.0  67.8    NA 133.0  70.4    NA
su         51.0  27.9    NA  53.0  28.0    NA
oad        25.0  13.7    NA  29.0  15.3    NA
ras       133.0  72.7    NA 147.0  77.8    NA
bblock     35.0  19.1    NA  37.0  19.6    NA
oah        96.0  52.5    NA 113.0  59.8    NA
statin    165.0  90.2    NA 158.0  83.6    NA
asa       109.0  59.6    NA 103.0  54.5    NA
```

```
acei       74.0  40.4    NA  56.0  29.6    NA
acei.thi   10.0   5.5    NA  21.0  11.1    NA
arb        38.0  20.8    NA  51.0  27.0    NA
arbcomb    17.0   9.3    NA  28.0  14.8    NA
arb.ccb     0.0   0.0    NA   1.0   0.5    NA
loop       23.0  12.6    NA  27.0  14.3    NA
ccb        53.0  29.0    NA  73.0  38.6    NA
thiazid    36.0  19.7    NA  41.0  21.7    NA
spiron      7.0   3.8    NA   6.0   3.2    NA
aht         8.0   4.4    NA   7.0   3.7    NA
ecsort3    30.0  16.4    NA  41.0  21.8    NA
vibage     25.0  13.7    NA  23.0  12.2    NA
aav        62.3  53.5  66.3  62.5  55.3  66.7
bmi        31.7  29.1  34.5  32.0  29.4  34.9
dmdurav    11.1   7.2  15.0  12.4   8.7  17.9
hba1c       8.3   7.7   9.1   8.3   7.8   9.4
hba1c       8.3   7.7   9.1   8.3   7.8   9.4
ldl         2.1   1.6   2.6   2.1   1.5   2.6
e.gfr     118.0  93.5 158.0 121.0 100.0 147.0
b12       148.0  96.0 221.0 162.0  85.0 247.0
mma         0.2   0.2   0.3   0.2   0.2   0.2
vibhcon    22.5  16.0  35.0  24.0  18.0  38.0
vibvcon    22.0  16.5  34.5  23.5  16.0  35.0
vibmax     20.0  15.0  29.0  22.0  16.0  32.0
b2b         9.0   6.0  16.0   9.0   6.0  15.0
resthr     68.0  62.5  76.2  69.5  63.0  76.0
pul05      79.0  72.0  86.0  81.0  72.0  88.8
pul1_5     78.0  71.2  85.0  79.0  70.0  87.0
pul3       78.0  71.0  85.0  79.0  70.0  87.0
sys_lig   134.0 124.0 143.0 135.5 124.0 145.5
s30       129.5 118.0 138.0 129.0 117.0 142.0
s90       134.0 123.5 144.0 134.0 120.2 146.0
s3        134.0 123.0 145.0 136.5 123.0 146.0
dia_lig    80.0  74.5  86.0  80.5  75.0  87.0
d30        81.0  75.0  86.0  80.0  73.0  87.0
d90        83.0  78.0  89.0  83.0  76.2  90.0
d3         84.0  78.0  90.0  84.0  76.0  90.0
> row.names(tt) <- attr(tt,"row.vars")[[1]]
> cat( "; Plc ;     ; Met ;     \n",
+      "; Med ; IQR ; Med ; IQR \n",
+      ";   N ;   % ;   N ;   % \n",
+      file="./csvh-Tabb.csv" )
> for( i in 1:nrow(tt) )
+ write.table( if( bin[i]==1 ) cbind( tt[i,1],
+                                     formatC( tt[i,2], format="f", dig=1 ),
+                                     tt[i,4],
+                                     formatC( tt[i,5], format="f", dig=1 ) )
+              else cbind( formatC( tt[i,1,drop=F], format="f", digits=1 ),
+              paste( "(", formatC( tt[i,2,drop=F], format="f", digits=1 ), ",",
+                          formatC( tt[i,3,drop=F], format="f", digits=1 ), ")" ),
+                          formatC( tt[i,4,drop=F], format="f", digits=1 ),
+              paste( "(", formatC( tt[i,5,drop=F], format="f", digits=1 ), ",",
+                          formatC( tt[i,6,drop=F], format="f", digits=1 ), ")" ) ),
+              file="./csvh-Tabb.csv", append=TRUE, row.names=TRUE, col.names=FALSE,
+              quote=F, sep=";", dec=",")
```

Then we print the table with mean and sd of the continuous baseline-variables:

```
> round( tt <- ftable( BB[,,4:5], col.vars=2:3), 2 )
```

	Plc		Met	
	mean	sd	mean	sd
men	127.00	69.40	130.00	68.78
smoking.	25.00	13.74	34.00	17.99
alcohol.	755.50	417.40	840.00	451.61
caucas	178.00	97.27	184.00	97.35
auto.neu	33.00	18.23	28.00	14.89
peri.neu	65.00	35.71	71.00	37.77
microalb	33.00	18.33	44.00	23.91
macroalb	8.00	4.42	12.00	6.52
cvd	41.00	22.40	40.00	21.16
s.ret	53.00	29.61	55.00	30.05
p.ret	9.00	5.03	14.00	7.65
metformi	157.00	85.79	155.00	82.01
ini.ins	124.00	67.76	133.00	70.37
su	51.00	27.87	53.00	28.04
oad	25.00	13.66	29.00	15.34
ras	133.00	72.68	147.00	77.78
bblock	35.00	19.13	37.00	19.58
oah	96.00	52.46	113.00	59.79
statin	165.00	90.16	158.00	83.60
asa	109.00	59.56	103.00	54.50
acei	74.00	40.44	56.00	29.63
acei.thi	10.00	5.46	21.00	11.11
arb	38.00	20.77	51.00	26.98
arbcomb	17.00	9.29	28.00	14.81
arb.ccb	0.00	0.00	1.00	0.53
loop	23.00	12.57	27.00	14.29
ccb	53.00	28.96	73.00	38.62
thiazid	36.00	19.67	41.00	21.69
spiron	7.00	3.83	6.00	3.17
aht	8.00	4.37	7.00	3.70
ecsort3	30.00	16.39	41.00	21.81
vibage	25.00	13.66	23.00	12.23
aav	60.26	9.14	61.02	8.55
bmi	31.95	4.23	32.25	4.25
dmdurav	11.94	6.24	13.51	6.30
hba1c	8.46	0.99	8.63	1.12
hba1c	8.46	0.99	8.63	1.12
ldl	2.13	0.77	2.17	0.83
e.gfr	126.60	44.93	129.96	44.52
b12	173.15	136.57	182.11	167.46
mma	0.22	0.09	0.22	0.11
vibhcon	26.40	12.93	27.36	12.99
vibvcon	26.39	12.46	26.65	12.77
vibmax	23.64	11.84	24.47	12.12
b2b	11.54	7.42	10.92	8.07
resthr	69.26	10.26	70.09	10.04
pul05	79.19	11.09	80.24	12.25
pul1_5	78.20	11.62	79.21	12.41
pul3	78.36	11.75	79.18	12.62
sys_lig	134.52	14.20	136.46	16.22
s30	128.85	15.84	130.24	18.47
s90	134.63	15.33	135.30	17.88
s3	135.38	16.56	135.70	18.41

```
dia_lig    79.94   8.67  80.77   9.97
d30        80.76   9.12  80.46  10.68
d90        83.34   9.14  83.00  10.90
d3         84.05   9.02  83.72  11.33
> row.names(tt) <- attr(tt,"row.vars")[[1]]
> cat( "; Plc ;     ; Met ;     \n",
+      "; Mean ; SD ; Mean ; SD \n",
+      ";   N ;   % ;   N ;   % \n",
+      file="./csvh-Tabbm.csv" )
> for( i in 1:nrow(tt) )
+ write.table( if( bin[i]==1 ) cbind( tt[i,1],
+                                     formatC( tt[i,2], format="f", dig=1 ),
+                                     tt[i,3],
+                                     formatC( tt[i,4], format="f", dig=1 ) )
+              else formatC( tt[i,,drop=F], format="f", digits=1 ),
+              file="./csvh-Tabbm.csv", append=TRUE, row.names=TRUE, col.names=FALSE,
+              quote=F, sep=";", dec=",")
```

3.2.2 FU tables

Then we can set up the table of the follow-up summary

```
> FF <- NArray( list( fvars,
+                     levels(anaf$grp),
+                     c( paste( c(2,1,3)/4), "mean", "sd" ) ) )
> str( FF )
 logi [1:20, 1:2, 1:5] NA NA NA NA NA NA ...
 - attr(*, "dimnames")=List of 3
  ..$ : chr [1:20] "ecsort3" "vibage" "b12" "mma" ...
  ..$ : chr [1:2] "Plc" "Met"
  ..$ : chr [1:5] "0.5" "0.25" "0.75" "mean" ...
> # Which are the binary among the FU-variables
> fbin <- bin[match(fvars,bvars)]
> names( fbin ) <- fvars
> fbin
ecsort3  vibage     b12     mma vibhcon vibvcon  vibmax     b2b  resthr   pul05  pul1_5
      1       1       0       0       0       0       0       0       0       0       0
   pul3 sys_lig     s30     s90      s3 dia_lig     d30     d90      d3
      0       0       0       0       0       0       0       0       0
> for( vv in 1:dim(FF)[1] )
+    {
+    cat( vv, ": ", fvars[vv], " ", class(anab[,fvars[vv]]), "\n" )
+ for( gg in dimnames(FF)[[2]] )
+ {
+ if( fbin[vv] == 0 )
+ FF[vv,gg,] <- c( quantile( anaf[anaf$grp==gg,fvars[vv]],
+                            probs=c(2,1,3)/4, na.rm=TRUE ),
+                      mean( anaf[anaf$grp==gg,fvars[vv]], na.rm=TRUE ),
+                        sd( anaf[anaf$grp==gg,fvars[vv]], na.rm=TRUE ) )
+ else
+ FF[vv,gg,1:2] <-
+ FF[vv,gg,4:5] <- c( sum( anaf[anaf$grp==gg,fvars[vv]], na.rm=TRUE ),
+                     mean( anaf[anaf$grp==gg,fvars[vv]], na.rm=TRUE )*100 )
+ }
+ }
```

```
1 :  ecsort3   numeric
2 :  vibage   numeric
3 :  b12   numeric
4 :  mma   numeric
5 :  vibhcon   numeric
6 :  vibvcon   numeric
7 :  vibmax   numeric
8 :  b2b   numeric
9 :  resthr   numeric
10 :  pul05   numeric
11 :  pul1_5   numeric
12 :  pul3   numeric
13 :  sys_lig   numeric
14 :  s30   numeric
15 :  s90   numeric
16 :  s3   numeric
17 :  dia_lig   numeric
18 :  d30   numeric
19 :  d90   numeric
20 :  d3   numeric
```

Then we print out the median and IQR from this array for the continuous variables and the number and percentage of the categorical ones:

```
> round( tt <- ftable( FF[,,1:3], col.vars=2:3), 1 )
           Plc               Met
           0.5  0.25  0.75   0.5  0.25  0.75

ecsort3   36.0  19.9    NA  44.0  23.8    NA
vibage    26.0  14.3    NA  34.0  18.0    NA
b12      193.0 136.5 269.5 135.0  82.0 211.0
mma        0.2   0.2   0.2   0.2   0.2   0.2
vibhcon   25.0  18.0  38.0  29.0  19.8  42.5
vibvcon   24.0  18.0  38.0  26.5  18.0  40.0
vibmax    22.0  16.2  32.0  25.0  18.0  37.0
b2b        9.0   6.0  15.0   8.0   6.0  14.0
resthr    69.0  63.0  75.2  69.5  62.0  77.5
pul05     78.5  72.0  86.2  80.0  71.8  88.2
pul1_5    77.0  70.0  85.0  78.0  69.0  87.0
pul3      78.0  70.0  86.0  78.0  69.0  87.0
sys_lig  132.0 125.0 144.2 136.0 125.0 146.5
s30      130.0 118.0 141.2 127.5 115.0 140.0
s90      134.0 122.0 147.0 136.0 125.0 146.0
s3       134.0 122.0 147.2 134.5 124.0 148.0
dia_lig   78.5  73.5  84.5  78.0  73.0  83.5
d30       80.0  73.0  86.0  79.0  70.0  84.2
d90       82.0  76.0  89.0  82.0  74.0  88.0
d3        82.0  76.0  90.0  82.0  74.0  89.0
> row.names(tt) <- attr(tt,"row.vars")[[1]]
> cat( "; Plc ;     ; Met ;     \n",
+      "; Med ; IQR ; Med ; IQR \n",
+      ";   N ;   % ;   N ;   % \n",
+      file="./csvh-Tabf.csv" )
> for( i in 1:nrow(tt) )
+ write.table( if( bin[i]==1 ) cbind( tt[i,1],
+                                     formatC( tt[i,2], format="f", dig=1 ),
+                                     tt[i,4],
```

```
+                                    formatC( tt[i,5], format="f", dig=1 ) )
+              else cbind( formatC( tt[i,1,drop=F], format="f", digits=1 ),
+              paste( "(", formatC( tt[i,2,drop=F], format="f", digits=1 ), ",",
+                          formatC( tt[i,3,drop=F], format="f", digits=1 ), ")" ),
+                          formatC( tt[i,4,drop=F], format="f", digits=1 ),
+              paste( "(", formatC( tt[i,5,drop=F], format="f", digits=1 ), ",",
+                          formatC( tt[i,6,drop=F], format="f", digits=1 ), ")" ) ),
+              file="./csvh-Tabf.csv", append=TRUE, row.names=TRUE, col.names=FALSE,
+              quote=F, sep=";", dec=",")
```

Then we print the table with mean and sd of the continuous baseline-variables:

```
> round( tt <- ftable( FF[,,4:5], col.vars=2:3), 2 )
            Plc           Met
           mean     sd   mean     sd

ecsort3   36.00  19.89  44.00  23.78
vibage    26.00  14.29  34.00  17.99
b12      214.84 161.29 165.84 164.68
mma        0.20   0.08   0.22   0.12
vibhcon   28.73  12.85  30.89  13.02
vibvcon   27.83  12.48  29.14  12.85
vibmax    25.95  12.11  27.67  12.55
b2b       11.51   7.96  10.18   6.43
resthr    69.00  10.54  70.60  10.97
pul05     78.99  11.71  80.26  12.82
pul1_5    77.59  11.53  78.81  12.64
pul3      77.83  11.18  78.61  13.00
sys_lig  134.55  13.94 136.75  16.20
s30      130.01  18.16 128.71  18.62
s90      135.25  17.34 136.80  17.83
s3       135.15  16.91 135.80  17.47
dia_lig   78.74   7.92  78.67   9.33
d30       79.78   9.67  78.14   9.99
d90       82.11   9.51  81.28  10.40
d3        82.34   9.66  81.45  10.77
> row.names(tt) <- attr(tt,"row.vars")[[1]]
> cat( "; Plc ;     ; Met ;     \n",
+      "; Mean ; SD ; Mean ; SD \n",
+      ";   N ;   % ;   N ;   % \n",
+      file="./csvh-Tabfm.csv" )
> for( i in 1:nrow(tt) )
+ write.table( if( bin[i]==1 ) cbind( tt[i,1],
+                                     formatC( tt[i,2], format="f", dig=1 ),
+                                     tt[i,3],
+                                     formatC( tt[i,4], format="f", dig=1 ) )
+              else formatC( tt[i,,drop=F], format="f", digits=1 ),
+              file="./csvh-Tabfm.csv", append=TRUE, row.names=TRUE, col.names=FALSE,
+              quote=F, sep=";", dec=",")
```