

## Appendix 2. Employed R code

The full R code used for estimating the natural effect Cox model is presented below.

```

1 # load data and libraries
2 library (medflex)
3 library (mice)
4 library (survival)
5 workData <- read.csv (" full_data.csv ")
6 maxFollowUpTimeTemp <- 7*365.25
7
8 ##### code to do full mediation analysis
9 ##### Define main function
10 fitNEM <- function (workData, maxFollowUpTimeTemp)
11 {
12   # fit mediation model
13   workData$dhkag3TEMP <- workData$dhkag3
14   fitImp <- survreg (Surv (obs_dod, dod) ~ dhkag3TEMP + asa_
15     treat30 + adp_treat30 + statin_treat30 + beta_treat30
16     + i_alder + factor (sex) + factor (indgrp) +
17     factor (uddankat) + boralone + factor (fi_
18     aar) + mi + card
19     + cochf + puled + shock + cervas + mal +
20     diabet + arf + crf + anemi + pneumoni +
21     sepsis
22     + klap + bleed + Antihyp_12mb + Lipidlow_12
23     mb + ASA_12mb + VitKant_12mb + Diureti_
24     loop_12mb
25     + COPD_12mb + tidl_reva,
26     data=workData)
27
28   # do dataset expansion and imputation
29   tempData1 <- workData
30   tempData1$dhkag3STAR <- tempData1$dhkag3
31   tempData2 <- workData
32   tempData2$dhkag3STAR <- 1-tempData2$dhkag3
33   tempData2$dhkag3TEMP <- tempData2$dhkag3STAR
34   linPredTemp <- predict (fitImp, newdata = tempData2, type="
35     linear")
36   simDodTimesTemp <- rweibull (nrow (tempData2), shape = 1/fitImp$
37     scale, exp (linPredTemp))
38   tempData2$dod <- 1*(simDodTimesTemp<maxFollowUpTimeTemp)
39   tempData2$obs_dod <- simDodTimesTemp*(simDodTimesTemp<
40     maxFollowUpTimeTemp) + maxFollowUpTimeTemp*(simDodTimesTemp

```

```

    >=maxFollowUpTimeTemp)
31
32 expData <- rbind(tempData1, tempData2)
33
34 # fit natural effects model
35 fitNEM <- coxph(Surv(obs_dod, dod) ~ dhrkag3 + dhrkag3STAR
36               + i_alder + sex + factor(indkgrp) + factor(
                 uddankat) + boralene + factor(fi_aar) + mi
                 + card
37               + cochf + puled + shock + cervas + mal +
                 diabet + arf + crf + anemi + pneumoni +
                 sepsis
38               + klap + bleed + Antihyp_12mb + Lipidlow_12mb
                 + ASA_12mb + VitKant_12mb + Diureti_loop_12
                 mb
39               + COPD_12mb + tidl_reva ,
40               data=expData)
41 # summary(fitNEM)
42 # return(fitNEM)
43 return(summary(fitNEM)$coefficients)
44 }
45
46 ##### Get par estimates
47 tempFitNEM <- fitNEM(workData, maxFollowUpTimeTemp=
                 maxFollowUpTimeTemp)
48 tempFitNEM
49
50 Nimp <- 10
51 outTable <- array(NA, dim=c(dim(tempFitNEM),Nimp))
52 for(j in 1:Nimp)
53 {
54   outTable[ , ,j] <- fitNEM(workData, maxFollowUpTimeTemp=
                             maxFollowUpTimeTemp)
55 }
56
57 library(Amelia)
58 temp <- mi.meld(q = outTable[,1,], se = outTable[ , 2, ], byrow
                 = F)
59 tempOut <- tempFitNEM[,1:2]
60 tempOut[,1] <- temp$q.mi
61 tempOut[,2] <- temp$se.mi
62 tempOut
63
64 ### get bootstrap SDs
65 G <- 10^3

```

```

66 outputObj <- array(NA, dim = c(dim(tempFitNEM),G))
67 for(j in 1:G)
68 {
69   tempData <- workData[sample(1:nrow(workData)), ]
70   temp <- try(fitNEM(tempData, maxFollowUpTimeTemp), silent=TRUE
71   )
72   if(class(temp)!="try-error") outputObj[, ,j] <- temp
73   rm(tempData, temp)
74   cat(paste("\n Iteration ", j, " of ", G, " comp. "))
75   save(outputObj, file="outputObj.Rdata")
76 }
77 outTable <- tempFitNEM[,1:2]
78 outTable[,1] <- apply(outputObj[,1,],1, mean, na.rm=T)
79 outTable[,2] <- apply(outputObj[,1,],1, sd, na.rm=T)
80 write.csv(outTable, file="fitNEMbootstrap.csv")
81
82 IE <- outputObj[1,1, ]
83 DE <- outputObj[2,1, ]
84 TE <- IE+ DE
85 Q <- IE/TE
86
87 outTable <- matrix(NA, nrow=4, ncol=3)
88 outTable[1, ] <- c(mean(IE), quantile(IE, c(.025, .975)))
89 outTable[2, ] <- c(mean(DE), quantile(DE, c(.025, .975)))
90 outTable[3, ] <- c(mean(TE), quantile(TE, c(.025, .975)))
91 outTable[4, ] <- c(mean(Q), quantile(Q, c(.025, .975)))
92 rownames(outTable) <- c("IE", "DE", "TE", "Q")
93 outTable

```