Supplementary File 1. R code

> if (!require("pacman")) install.packages("pacman")

> pacman::p\_load(readxl, emmeans, lme4, nlme, robustlmm, mice, car, broom, lsmeans, lmerTest, ggplot2, psych, HLMdiag, dplyr, openxlsx)

> setwd("~/Desktop") #Directory where you put the spreadsheet

> REI <- read\_excel("REI\_GDS\_FESI.xlsx")

> #~~~~~~~~~~DATA MANAGEMENT~~~~~~~~~~~~~~~~#

> ##Assign group names##

> REI$group[REI$group==1]<- "REI"

> REI$group[REI$group==2]<- "RE"

> REI$group[REI$group==3]<- "CNT"

> #Assign Values for Sex#

> REI$sex[REI$sex==1]<- "Male"

> REI$sex[REI$sex==0]<- "Female"

> #Education values#

> REI$education[REI$education==1]<- "High"

> REI$education[REI$education==0]<- "Low"

> #MCI#

> REI$mci[REI$mci==1]<- "Yes"

> REI$mci[REI$mci==0]<- "No"

> View(REI)

> REI.v3<-REI[c(1:11)]

> varying <- REI.v3[c(1,3,8,9:length(REI.v3))]

> baseline <- subset(REI.v3[-c(8,9:length(REI.v3))], time==1)

> varying.1 <- subset(varying,time==1)

> varying.2 <- subset(varying,time==2)

> colnames(varying.1) <- paste(colnames(varying.1),"1",sep=".")

> colnames(varying.2) <- paste(colnames(varying.2),"2",sep=".")

> wide.data <- left\_join(baseline,varying.1,by=c("id"="id.1")) %>%

+ left\_join(.,varying.2,by=c("id"="id.2"))

> Timevars <- grep("time",colnames(wide.data),value=TRUE)

> wide.data <- wide.data[,!(colnames(wide.data)%in%Timevars)]

> colnames(wide.data) <- (gsub("\_","",colnames(wide.data)))

> colnames(wide.data) <- (gsub(".1","baseline",colnames(wide.data)))

> set.seed(1234)

> ini <- mice(wide.data,maxit=0, pred=quickpred(wide.data,exclude="id"))

Warning messages:

1: In data.matrix(data) : NAs introduced by coercion

2: In data.matrix(data) : NAs introduced by coercion

3: In data.matrix(data) : NAs introduced by coercion

4: In data.matrix(data) : NAs introduced by coercion

> meth <- ini$meth

> meth

 id group sex age education mci gdsbaseline

 "" "" "" "" "" "" "pmm"

 fesibaseline compositebaseline mocabaseline gds.2 fesi.2 composite.2 moca.2

 "pmm" "pmm" "" "pmm" "pmm" "pmm" "pmm"

> m <- 40

> wide.data.imp <- mice(wide.data,m=m,maxit=40,pred=quickpred(wide.data,exclude="id"),print=FALSE,seed=1234)

Warning messages:

1: In data.matrix(data) : NAs introduced by coercion

2: In data.matrix(data) : NAs introduced by coercion

3: In data.matrix(data) : NAs introduced by coercion

4: In data.matrix(data) : NAs introduced by coercion

> densityplot(wide.data.imp, ~gds.2)

> plot(wide.data.imp)

> wide <- as.list(1:m)

> for (i in 1:m){

+ wide[[i]] <- mice::complete(wide.data.imp,action=i)

+ }

> names <- colnames(wide[[1]])

> names <- gsub("\_","",names)

> names <- gsub(".1","baseline",names)

> wide <- lapply(wide,setNames,names)

> lmm.mi.mdl <- function(y, cov1, cov2, cov3 ,data){

+ fit <- lapply(data, FUN=function(x){

+ lm(as.formula(paste0(y, "~group +", cov1, "+", cov2, "+", cov3)),data=x)

+ })

+ means <- sapply(fit,lsmeans,~group)

+ contrasts <- sapply(means,contrast,"pairwise", adj="none")

+

+ mean\_control <- mean(sapply(means,function(x){summary(x)[1,2]})) #mean of control at Follow-up adjusted for baseline

+ mean\_RE <- mean(sapply(means,function(x){summary(x)[2,2]})) #mean of RE at Follow-up adjusted for baseline

+ mean\_REI <- mean(sapply(means,function(x){summary(x)[3,2]})) #mean of REI at Follow-up adjusted for baseline

+

+ bwvar\_control <- mean(sapply(means,function(x){summary(x)[1,3]^2})) #average variance over imputations for control

+ bwvar\_RE <- mean(sapply(means,function(x){summary(x)[2,3]^2})) #average variance over imputations for RE

+ bwvar\_REI <- mean(sapply(means,function(x){summary(x)[3,3]^2})) #average variance over imputations for control

+

+ withinvar\_control <- sd(sapply(means,function(x){summary(x)[1,2]}))^2 #variance in mean estimates across imputations for control

+ withinvar\_RE <- sd(sapply(means,function(x){summary(x)[2,2]}))^2 #variance in mean estimates across imputations for RE

+ withinvar\_REI <- sd(sapply(means,function(x){summary(x)[3,2]}))^2 #variance in mean estimates across imputations for REI

+

+ dfCorrection <- (m+1)/m

+ totVar\_control <- bwvar\_control+withinvar\_control\*dfCorrection #total variance in control

+ totVar\_RE <- bwvar\_RE+withinvar\_RE\*dfCorrection #total variance in RE

+ totVar\_REI <- bwvar\_REI+withinvar\_REI\*dfCorrection #total variance in RE

+

+ SE\_control <- sqrt(totVar\_control) #square root of variance of control

+ SE\_RE <- sqrt(totVar\_RE) #square root of variance of RE

+ SE\_REI <- sqrt(totVar\_REI) #square root of variance of REI

+

+ mean\_diff\_CNT\_RE <- mean(sapply(contrasts,function(x){summary(x)[1,2]})) #mean difference CNT vs. RE

+ mean\_diff\_CNT\_REI <- mean(sapply(contrasts,function(x){summary(x)[2,2]})) #mean difference CNT vs. REI

+ mean\_diff\_RE\_REI <- mean(sapply(contrasts,function(x){summary(x)[3,2]})) #mean difference RE vs. REI

+

+ t\_ratio\_CNT\_RE <-mean(sapply(contrasts, function (x){summary(x)[1,5]}))

+ t\_ratio\_CNT\_REI <-mean(sapply(contrasts, function (x){summary(x)[2,5]}))

+ t\_ratio\_RE\_REI <-mean(sapply(contrasts, function (x){summary(x)[3,5]}))

+ df\_CNT\_RE <-mean(sapply(contrasts, function (x){summary(x)[1,4]}))

+ df\_CNT\_REI <-mean(sapply(contrasts, function (x){summary(x)[1,4]}))

+ df\_RE\_REI <-mean(sapply(contrasts, function (x){summary(x)[1,4]}))

+

+ bwvar\_diff\_CNT\_RE <- mean(sapply(contrasts,function(x){summary(x)[1,3]^2})) #avarage varaince CNT - RE

+ bwvar\_diff\_CNT\_REI <- mean(sapply(contrasts,function(x){summary(x)[2,3]^2})) #avarage varaince CNT - REI

+ bwvar\_diff\_RE\_REI <- mean(sapply(contrasts,function(x){summary(x)[3,3]^2})) #avarage varaince RE - REI

+

+ withinvar\_diff\_CNT\_RE <- sd(sapply(contrasts,function(x){summary(x)[1,3]}))^2 #variance in mean difference estimates CNT -RE

+ withinvar\_diff\_CNT\_REI <- sd(sapply(contrasts,function(x){summary(x)[2,3]}))^2 #variance in mean difference estimates CNT - REI

+ withinvar\_diff\_RE\_REI <- sd(sapply(contrasts,function(x){summary(x)[3,3]}))^2 #variance in mean difference estimates RE - REI

+

+ totVar\_diff\_CNT\_RE <- bwvar\_diff\_CNT\_RE+withinvar\_diff\_CNT\_RE\*dfCorrection

+ totVar\_diff\_CNT\_REI <- bwvar\_diff\_CNT\_REI+withinvar\_diff\_CNT\_REI\*dfCorrection

+ totVar\_diff\_RE\_REI <- bwvar\_diff\_RE\_REI+withinvar\_diff\_RE\_REI\*dfCorrection

+

+ lambda\_CNT\_RE <- (withinvar\_diff\_CNT\_RE+(withinvar\_diff\_CNT\_RE/m))/totVar\_diff\_CNT\_RE

+ n <- nrow(wide.data.imp$data) #sample size

+ k <- 4 #number of fixed effects estimates in model

+ nu\_old\_CNT\_RE <- (m-1)/lambda\_CNT\_RE^2

+ nu\_com <- n-k #degrees of freedom

+ nu\_obs\_CNT\_RE <- (nu\_com+1)/(nu\_com+3)\*nu\_com\*(1-lambda\_CNT\_RE)

+ nu\_BR\_CNT\_RE <- (nu\_old\_CNT\_RE\*nu\_obs\_CNT\_RE)/(nu\_old\_CNT\_RE+nu\_obs\_CNT\_RE) #barnard-rubin degrees of freedom for T2 contrast

+

+ pvalue\_diff\_CNT\_RE <- pt(q=abs(mean\_diff\_CNT\_RE)/sqrt(totVar\_diff\_CNT\_RE),df=nu\_BR\_CNT\_RE,lower.tail=FALSE)\*2

+ diff\_CNT\_RE\_LL <- mean\_diff\_CNT\_RE-sqrt(totVar\_diff\_CNT\_RE)\*qt(.975,nu\_BR\_CNT\_RE)

+ diff\_CNT\_RE\_UL <- mean\_diff\_CNT\_RE+sqrt(totVar\_diff\_CNT\_RE)\*qt(.975,nu\_BR\_CNT\_RE)

+

+

+ lambda\_CNT\_REI <- (withinvar\_diff\_CNT\_REI+(withinvar\_diff\_CNT\_REI/m))/totVar\_diff\_CNT\_REI

+ nu\_old\_CNT\_REI <- (m-1)/lambda\_CNT\_REI^2

+ nu\_obs\_CNT\_REI <- (nu\_com+1)/(nu\_com+3)\*nu\_com\*(1-lambda\_CNT\_REI)

+ nu\_BR\_CNT\_REI <- (nu\_old\_CNT\_REI\*nu\_obs\_CNT\_REI)/(nu\_old\_CNT\_REI+nu\_obs\_CNT\_REI) #barnard-rubin degrees of freedom for T2 contrast

+

+ pvalue\_diff\_CNT\_REI <- pt(q=abs(mean\_diff\_CNT\_REI)/sqrt(totVar\_diff\_CNT\_REI),df=nu\_BR\_CNT\_REI,lower.tail=FALSE)\*2

+ diff\_CNT\_REI\_LL <- mean\_diff\_CNT\_REI-sqrt(totVar\_diff\_CNT\_REI)\*qt(.975,nu\_BR\_CNT\_REI)

+ diff\_CNT\_REI\_UL <- mean\_diff\_CNT\_REI+sqrt(totVar\_diff\_CNT\_REI)\*qt(.975,nu\_BR\_CNT\_REI)

+

+

+ lambda\_RE\_REI <- (withinvar\_diff\_RE\_REI+(withinvar\_diff\_RE\_REI/m))/totVar\_diff\_RE\_REI

+ nu\_old\_RE\_REI <- (m-1)/lambda\_RE\_REI^2

+ nu\_obs\_RE\_REI <- (nu\_com+1)/(nu\_com+3)\*nu\_com\*(1-lambda\_RE\_REI)

+ nu\_BR\_RE\_REI <- (nu\_old\_RE\_REI\*nu\_obs\_RE\_REI)/(nu\_old\_RE\_REI+nu\_obs\_RE\_REI) #barnard-rubin degrees of freedom for T2 contrast

+

+ pvalue\_diff\_RE\_REI <- pt(q=abs(mean\_diff\_RE\_REI)/sqrt(totVar\_diff\_RE\_REI),df=nu\_BR\_RE\_REI,lower.tail=FALSE)\*2

+ diff\_RE\_REI\_LL <- mean\_diff\_RE\_REI-sqrt(totVar\_diff\_RE\_REI)\*qt(.975,nu\_BR\_RE\_REI)

+ diff\_RE\_REI\_UL <- mean\_diff\_RE\_REI+sqrt(totVar\_diff\_RE\_REI)\*qt(.975,nu\_BR\_RE\_REI)

+

+ return(list(Control\_adjmean=mean\_control,Control\_SE=SE\_control,RE\_adjmean=mean\_RE,

+ RE\_SE=SE\_RE, REI\_adjumean=mean\_REI, REI\_SE=SE\_REI, Diff\_adj\_CNT\_RE=mean\_diff\_CNT\_RE,

+ Diff\_SE\_CNT\_RE=sqrt(totVar\_diff\_CNT\_RE), Diff\_pvalue\_CNT\_RE=pvalue\_diff\_CNT\_RE,

+ LL\_CI\_CNT\_RE=diff\_CNT\_RE\_LL, UL\_CI\_CNT\_RE=diff\_CNT\_RE\_UL, Diff\_adj\_CNT\_REI=mean\_diff\_CNT\_REI,

+ Diff\_SE\_CNT\_REI=sqrt(totVar\_diff\_CNT\_REI), Diff\_pvalue\_CNT\_REI=pvalue\_diff\_CNT\_REI,

+ LL\_CI\_CNT\_REI=diff\_CNT\_REI\_LL, UL\_CI\_CNT\_REI=diff\_CNT\_REI\_UL, Diff\_adj\_RE\_REI=mean\_diff\_RE\_REI,

+ Diff\_SE\_RE\_REI=sqrt(totVar\_diff\_RE\_REI), Diff\_pvalue\_RE\_REI=pvalue\_diff\_RE\_REI,

+ LL\_CI\_RE\_REI=diff\_RE\_REI\_LL, UL\_CI\_RE\_REI=diff\_RE\_REI\_UL))

+ }

> lmm.mi.mdl("gds.2","gdsbaseline", "age", "moca.2", wide) #Returns results for depressive symptoms

$Control\_adjmean

[1] 2.066869

$Control\_SE

[1] 0.3297902

$RE\_adjmean

[1] 2.061742

$RE\_SE

[1] 0.3045786

$REI\_adjumean

[1] 1.773128

$REI\_SE

[1] 0.3114451

$Diff\_adj\_CNT\_RE

[1] 0.005126317

$Diff\_SE\_CNT\_RE

[1] 0.4041072

$Diff\_pvalue\_CNT\_RE

[1] 0.9899201

$LL\_CI\_CNT\_RE

[1] -0.8029655

$UL\_CI\_CNT\_RE

[1] 0.8132181

$Diff\_adj\_CNT\_REI

[1] 0.2937407

$Diff\_SE\_CNT\_REI

[1] 0.4029273

$Diff\_pvalue\_CNT\_REI

[1] 0.4687868

$LL\_CI\_CNT\_REI

[1] -0.5119934

$UL\_CI\_CNT\_REI

[1] 1.099475

$Diff\_adj\_RE\_REI

[1] 0.2886143

$Diff\_SE\_RE\_REI

[1] 0.4045221

$Diff\_pvalue\_RE\_REI

[1] 0.4782815

$LL\_CI\_RE\_REI

[1] -0.5203118

$UL\_CI\_RE\_REI

[1] 1.09754

> lmm.mi.mdl("fesi.2","fesibaseline", "age", "moca.2", wide) #Returns results for depressive symptoms

$Control\_adjmean

[1] 26.80203

$Control\_SE

[1] 1.309545

$RE\_adjmean

[1] 25.90777

$RE\_SE

[1] 1.193595

$REI\_adjumean

[1] 23.61144

$REI\_SE

[1] 1.200539

$Diff\_adj\_CNT\_RE

[1] 0.8942595

$Diff\_SE\_CNT\_RE

[1] 1.550625

$Diff\_pvalue\_CNT\_RE

[1] 0.5662623

$LL\_CI\_CNT\_RE

[1] -2.20653

$UL\_CI\_CNT\_RE

[1] 3.995049

$Diff\_adj\_CNT\_REI

[1] 3.190587

$Diff\_SE\_CNT\_REI

[1] 1.572426

$Diff\_pvalue\_CNT\_REI

[1] 0.0468288

$LL\_CI\_CNT\_REI

[1] 0.04619762

$UL\_CI\_CNT\_REI

[1] 6.334976

$Diff\_adj\_RE\_REI

[1] 2.296327

$Diff\_SE\_RE\_REI

[1] 1.521124

$Diff\_pvalue\_RE\_REI

[1] 0.1363095

$LL\_CI\_RE\_REI

[1] -0.7454409

$UL\_CI\_RE\_REI

[1] 5.338096