**R Scripts for Mendelian Randomization and Mediation Analysis**

library(TwoSampleMR)

library(MRPRESSO)

library(data.table)

#run mr analysis

mr\_fun <- function(id\_exposures, id\_outcomes, p1=5e-8,

 method\_list = c("mr\_ivw","mr\_egger\_regression","mr\_weighted\_median","mr\_weighted\_mode"),

 rm\_snps=NULL){

 #1.read local exposure data

 exposure\_data <- read\_exposure\_data(id\_exposures)

 exposure\_data <- clump\_data(exposure\_data, clump\_p1 = p1, clump\_r2=0.001, clump\_kb=10000)

 #remove some snps

 if(is.null(rm\_snps)){

 exposure\_data <- subset(exposure\_data, !SNP %in% rm\_snps)

 }

 #2.read online ieu outcome data

 outcome\_data <- read\_outcome\_data(id\_outcomes, exposure\_data$SNP)

 #3.harmonise data

 harmonise\_data <- harmonise\_data(exposure\_data, outcome\_data)

 #4.run mr analysis

 mr\_res <- mr(harmonise\_data, method\_list = method\_list)

 #5.sensitivity analysis

 het\_res <- mr\_heterogeneity(harmonise\_data)

 ple\_res <- mr\_pleiotropy\_test(harmonise\_data)

 #6. run presso

 presso\_res <- mr\_presso(harmonise\_data$beta.outcome, harmonise\_data$beta.exposure, harmonise\_data$se.outcome, harmonise\_data$se.exposure)

 return(mr\_res)

}

#read local data and run mr

path\_to\_cfb <- "path\_to\_pqtl"

path\_to\_migraine <- "ukb-saige-189.2.csv"

for(f in list.files(path\_to\_cfb, full.names = T)){

 mr\_fun(f, path\_to\_migraine) #forward

 mr\_fun(path\_to\_migraine, f) #reverse

}

mediation\_fun <- function(id\_exposure, id\_mediation, id\_outcome){

 #1.run exposure to mediator mr

 dat\_exposure\_mediator <- mr\_fun(id\_exposure, id\_mediation, method\_list = "mr\_ivw")

 #2.run exposure to outcome mr

 dat\_exposure\_outcome <- mr\_fun(id\_exposure, id\_outcome, method\_list = "mr\_ivw")

 #3.run mediator to outcome mr

 dat\_mediator\_outcome <- mv\_fun(id\_mediation, id\_outcome, method\_list = "mr\_ivw")

 #4.calculate mediation effect

 a <- as.numeric(dat\_exposure\_mediator$b)

 b <- as.numeric(dat\_mediator\_outcome$b)

 c1 <- as.numeric(dat\_exposure\_outcome$b)

 sa <<- as.numeric(dat\_exposure\_mediator$se)

 sb <<- as.numeric(dat\_mediator\_outcome$se)

 #5.calculat effect

 total\_effect <- c1

 mediator\_effect <- a \* b

 direct\_effect <- c1 - IE

 mediator\_proportion <- IE / TE

}