Example R and Stata code for a Mendelian randomization analysis

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# Example R and Stata code to perform a multivariable Mendelian randomization (MVMR) analysis

## R code

* Read in the data

suppressPackageStartupMessages({  
 library(tidyverse)  
 library(haven)  
 library(remotes)  
})  
dat <- read\_dta("https://raw.github.com/remlapmot/mrrobust/master/dodata.dta")  
dat <- dat %>% filter(ldlcp2 < 1e-8)

### Example code using the MendelianRandomization package

* Install the package and load it into memory

library(MendelianRandomization)

* Convert our data frame to the required class

datfmt <- mr\_mvinput(  
 bx = as.matrix(cbind(dat$ldlcbeta, dat$hdlcbeta, dat$tgbeta)),  
 bxse = as.matrix(cbind(dat$ldlcse, dat$hdlcse, dat$tgse)),  
 by = dat$chdbeta,  
 byse = dat$chdse,  
 exposure = "exposure",  
 outcome = "outcome",  
 snps = "snp",  
 effect\_allele = dat$a1,  
 other\_allele = dat$a2,  
 eaf = NA  
)

* Fit an MVMR/MVIVW model

mvivwfit <- mr\_mvivw(datfmt)  
mvivwfit

##   
## Multivariable inverse-variance weighted method  
## (variants uncorrelated, random-effect model)  
##   
## Number of Variants : 73   
##   
## ------------------------------------------------------------------  
## Exposure Estimate Std Error 95% CI p-value  
## exposure\_1 0.429 0.061 0.309, 0.548 0.000  
## exposure\_2 -0.194 0.131 -0.451, 0.062 0.138  
## exposure\_3 0.226 0.123 -0.016, 0.468 0.067  
## ------------------------------------------------------------------  
## Residual standard error = 1.490   
## Heterogeneity test statistic = 155.3766 on 70 degrees of freedom, (p-value = 0.0000)

* Fit an MVMR-Egger model

mvmreggerfit <- mr\_mvegger(datfmt)  
mvmreggerfit

##   
## Multivariable MR-Egger method  
## (variants uncorrelated, random-effect model)  
##   
## Orientated to exposure : 1   
## Number of Variants : 73   
## ------------------------------------------------------------------  
## Exposure Estimate Std Error 95% CI p-value  
## exposure\_1 0.567 0.100 0.371, 0.764 0.000  
## exposure\_2 -0.136 0.133 -0.398, 0.125 0.306  
## exposure\_3 0.274 0.125 0.030, 0.518 0.028  
## (intercept) -0.009 0.005 -0.020, 0.001 0.084  
## ------------------------------------------------------------------  
## Residual standard error = 1.469   
## Heterogeneity test statistic = 148.9290 on 69 degrees of freedom, (p-value = 0.0000)

### Example code using the MVMR and RMVMR packages

* Install the package and load it into memory

if (!requireNamespace("MVMR", quietly = TRUE)) {  
 remotes::install\_github("WSpiller/MVMR")  
}  
library(MVMR)

* Create a data object of the required structure

r\_input <- format\_mvmr(  
 BXGs = dat[,c("ldlcbeta","hdlcbeta","tgbeta")],  
 BYG = dat$chdbeta,  
 seBXGs = dat[,c("ldlcse","hdlcse","tgse")],  
 seBYG = dat$chdse,  
 RSID = dat$rsid  
)

* Fit an MVMR model

mvmrfit <- ivw\_mvmr(r\_input)

##   
## Multivariable MR  
##   
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02  
##   
## Residual standard error: 1.49 on 70 degrees of freedom

* Conditional F-statistics for instrument strength (Sanderson, Spiller, and Bowden 2021)

strength\_mvmr(r\_input)

## Warning in strength\_mvmr(r\_input): Covariance between effect of genetic variants on each exposure  
## not specified. Fixing covariance at 0.

##   
## Conditional F-statistics for instrument strength  
##   
## exposure1 exposure2 exposure3  
## F-statistic 126.7447 35.29937 39.32731

## exposure1 exposure2 exposure3  
## F-statistic 126.7447 35.29937 39.32731

* Fit a radial MVMR model

if (!requireNamespace("RMVMR", quietly = TRUE)) {  
 remotes::install\_github("WSpiller/RMVMR")  
}  
library(RMVMR)  
  
rmvmr\_input <- mrmvinput\_to\_rmvmr\_format(datfmt)  
  
rmvmr\_fit <- ivw\_rmvmr(rmvmr\_input, summary = TRUE)

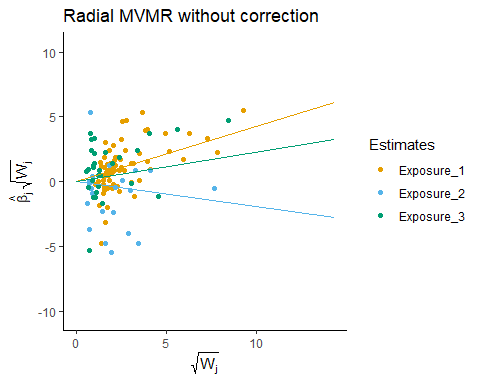
##   
## Radial Multivariable MR  
##   
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02  
##   
## Residual standard error: 1.49 on 70 degrees of freedom

rmvmr\_fit

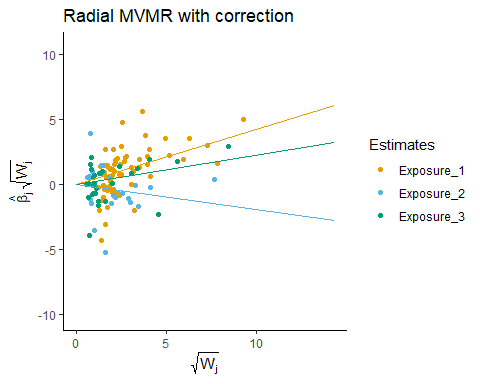
## $coef  
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02  
##   
## $data  
## $data[[1]]  
## Bwj\_1 wj\_1 wj\_2 wj\_3  
## 1 0.87789630 2.414215 0.06584222 0.585264197  
## 2 1.55477359 3.938760 -0.36278051 -0.092249900  
## 3 -1.12639113 3.246657 0.99387453 4.571822818  
## 4 0.70630256 2.001191 0.22954833 0.423781538  
## 5 5.45131044 9.278826 -1.97175058 0.197175058  
## 6 1.47579103 1.317671 -0.23191002 0.084330916  
## 7 0.12566135 1.535861 -0.74465983 0.116353099  
## 8 1.22652812 2.146424 1.83979218 -1.042548902  
## 9 -1.98630020 1.730003 0.64074200 -0.346000681  
## 10 -0.05015358 3.056234 0.72879426 0.321296394  
## 11 2.27343465 7.794633 -1.42901607 1.623881894  
## 12 3.32005412 7.262618 -0.57063430 0.985641066  
## 13 3.71901649 4.938366 -0.18290245 0.792577284  
## 14 1.20035886 2.031377 -0.13388618 0.170820299  
## 15 1.12639113 1.590199 -0.63607970 0.430678961  
## 16 1.25356544 1.919522 -0.33297832 -0.325143536  
## 17 -0.55338472 1.752385 0.50726933 -0.027669236  
## 18 -0.52440051 1.580385 0.79019255 -0.043101412  
## 19 -1.83167403 1.292946 -0.18316740 0.479467614  
## 20 1.25356544 1.880348 0.50839043 0.974995341  
## 21 3.01145376 1.642611 -0.63879322 0.684421309  
## 22 2.32634787 5.146163 0.14099078 0.401823724  
## 23 -0.53883603 2.011655 0.05747584 0.107767206  
## 24 1.43953147 3.153259 0.10282368 1.987924412  
## 25 -0.24042603 2.087910 -0.53779507 0.132867017  
## 26 0.87789630 2.093445 0.24986279 -0.438948148  
## 27 1.89569792 1.579748 0.75827917 2.401217370  
## 28 1.37220381 1.877753 0.54165940 1.011097543  
## 29 1.89569792 2.157173 -0.36606581 0.594856935  
## 30 3.21597976 2.530607 -0.40595154 0.843535675  
## 31 -0.43991317 2.021223 -0.08322682 0.594477251  
## 32 1.20035886 1.418606 0.36374511 -0.982111793  
## 33 0.78919165 1.841447 -0.18414472 0.563708323  
## 34 1.71143956 2.464473 -0.08899486 0.684575823  
## 35 0.84162123 2.685173 3.28633053 -1.122161645  
## 36 0.72247905 1.926611 -0.03010329 0.662272464  
## 37 -0.37185609 2.298747 0.29072385 1.216983565  
## 38 -0.51007346 2.001554 0.83936138 0.594009595  
## 39 2.40891555 1.821375 -2.05639132 3.407734187  
## 40 4.01281081 3.941153 -2.86629344 5.589272201  
## 41 -0.77219321 2.386779 -0.07019938 0.119338951  
## 42 1.34075503 1.723828 0.14556769 -0.264320278  
## 43 0.82389363 1.765486 4.11946815 1.294689991  
## 44 1.88079361 2.298748 0.03482951 -0.508510864  
## 45 5.32672389 3.641740 0.81531488 -0.760960555  
## 46 -0.48172685 1.901553 2.15509380 -1.331087348  
## 47 2.81353534 2.046208 0.27495914 0.703383835  
## 48 0.42614801 1.537647 0.92258847 -0.702924549  
## 49 0.12566135 3.505290 2.57936449 -3.042327345  
## 50 4.75342431 2.778925 -3.47365623 8.409904546  
## 51 2.43237906 2.707743 -0.73430311 0.871984946  
## 52 -4.75342431 1.419854 1.60505236 -0.611154554  
## 53 -3.13818077 1.597619 -0.02282313 -0.205408196  
## 54 4.67081982 2.535588 0.64056958 0.166814994  
## 55 0.00000000 1.222306 -0.71301163 0.361598757  
## 56 -0.91536509 1.525608 -0.18815838 0.284780250  
## 57 0.51007346 1.428206 -7.65110185 1.224176297  
## 58 1.59819314 2.106709 0.50125148 0.646541770  
## 59 2.17009038 3.526397 0.12478020 1.030792929  
## 60 0.69030882 1.656741 -0.20709265 0.593665589  
## 61 0.97411388 1.948228 0.63642107 -0.298728256  
## 62 3.71901649 6.293720 -0.71519548 0.240305681  
## 63 3.97628577 3.834276 -0.78105613 0.291120923  
## 64 3.71901649 4.057109 -0.43952013 4.057108893  
## 65 0.93458929 4.131868 -0.88540038 0.688644741  
## 66 1.69539771 5.933892 -0.64182913 -1.453198037  
## 67 0.06270678 1.818497 -0.20066169 0.877894891  
## 68 0.51007346 1.771088 0.03542177 -0.127518364  
## 69 -0.18911843 1.070482 -0.01427309 -0.235505965  
## 70 1.10306256 2.481891 -0.57910784 0.965179737  
## 71 1.37220381 3.033293 0.17333101 0.440549644  
## 72 -0.69030882 1.587710 2.99133824 0.039117500  
## 73 -0.18911843 1.501249 0.64339258 -0.001949674  
##   
## $data[[2]]  
## Bwj\_2 wj\_1 wj\_2 wj\_3  
## 1 0.87789630 2.414215 0.06584222 0.585264197  
## 2 -1.55477359 -3.938760 0.36278051 0.092249900  
## 3 -1.12639113 3.246657 0.99387453 4.571822818  
## 4 0.70630256 2.001191 0.22954833 0.423781538  
## 5 -5.45131044 -9.278826 1.97175058 -0.197175058  
## 6 -1.47579103 -1.317671 0.23191002 -0.084330916  
## 7 -0.12566135 -1.535861 0.74465983 -0.116353099  
## 8 1.22652812 2.146424 1.83979218 -1.042548902  
## 9 -1.98630020 1.730003 0.64074200 -0.346000681  
## 10 -0.05015358 3.056234 0.72879426 0.321296394  
## 11 -2.27343465 -7.794633 1.42901607 -1.623881894  
## 12 -3.32005412 -7.262618 0.57063430 -0.985641066  
## 13 -3.71901649 -4.938366 0.18290245 -0.792577284  
## 14 -1.20035886 -2.031377 0.13388618 -0.170820299  
## 15 -1.12639113 -1.590199 0.63607970 -0.430678961  
## 16 -1.25356544 -1.919522 0.33297832 0.325143536  
## 17 -0.55338472 1.752385 0.50726933 -0.027669236  
## 18 -0.52440051 1.580385 0.79019255 -0.043101412  
## 19 1.83167403 -1.292946 0.18316740 -0.479467614  
## 20 1.25356544 1.880348 0.50839043 0.974995341  
## 21 -3.01145376 -1.642611 0.63879322 -0.684421309  
## 22 2.32634787 5.146163 0.14099078 0.401823724  
## 23 -0.53883603 2.011655 0.05747584 0.107767206  
## 24 1.43953147 3.153259 0.10282368 1.987924412  
## 25 0.24042603 -2.087910 0.53779507 -0.132867017  
## 26 0.87789630 2.093445 0.24986279 -0.438948148  
## 27 1.89569792 1.579748 0.75827917 2.401217370  
## 28 1.37220381 1.877753 0.54165940 1.011097543  
## 29 -1.89569792 -2.157173 0.36606581 -0.594856935  
## 30 -3.21597976 -2.530607 0.40595154 -0.843535675  
## 31 0.43991317 -2.021223 0.08322682 -0.594477251  
## 32 1.20035886 1.418606 0.36374511 -0.982111793  
## 33 -0.78919165 -1.841447 0.18414472 -0.563708323  
## 34 -1.71143956 -2.464473 0.08899486 -0.684575823  
## 35 0.84162123 2.685173 3.28633053 -1.122161645  
## 36 -0.72247905 -1.926611 0.03010329 -0.662272464  
## 37 -0.37185609 2.298747 0.29072385 1.216983565  
## 38 -0.51007346 2.001554 0.83936138 0.594009595  
## 39 -2.40891555 -1.821375 2.05639132 -3.407734187  
## 40 -4.01281081 -3.941153 2.86629344 -5.589272201  
## 41 0.77219321 -2.386779 0.07019938 -0.119338951  
## 42 1.34075503 1.723828 0.14556769 -0.264320278  
## 43 0.82389363 1.765486 4.11946815 1.294689991  
## 44 1.88079361 2.298748 0.03482951 -0.508510864  
## 45 5.32672389 3.641740 0.81531488 -0.760960555  
## 46 -0.48172685 1.901553 2.15509380 -1.331087348  
## 47 2.81353534 2.046208 0.27495914 0.703383835  
## 48 0.42614801 1.537647 0.92258847 -0.702924549  
## 49 0.12566135 3.505290 2.57936449 -3.042327345  
## 50 -4.75342431 -2.778925 3.47365623 -8.409904546  
## 51 -2.43237906 -2.707743 0.73430311 -0.871984946  
## 52 -4.75342431 1.419854 1.60505236 -0.611154554  
## 53 3.13818077 -1.597619 0.02282313 0.205408196  
## 54 4.67081982 2.535588 0.64056958 0.166814994  
## 55 0.00000000 -1.222306 0.71301163 -0.361598757  
## 56 0.91536509 -1.525608 0.18815838 -0.284780250  
## 57 -0.51007346 -1.428206 7.65110185 -1.224176297  
## 58 1.59819314 2.106709 0.50125148 0.646541770  
## 59 2.17009038 3.526397 0.12478020 1.030792929  
## 60 -0.69030882 -1.656741 0.20709265 -0.593665589  
## 61 0.97411388 1.948228 0.63642107 -0.298728256  
## 62 -3.71901649 -6.293720 0.71519548 -0.240305681  
## 63 -3.97628577 -3.834276 0.78105613 -0.291120923  
## 64 -3.71901649 -4.057109 0.43952013 -4.057108893  
## 65 -0.93458929 -4.131868 0.88540038 -0.688644741  
## 66 -1.69539771 -5.933892 0.64182913 1.453198037  
## 67 -0.06270678 -1.818497 0.20066169 -0.877894891  
## 68 0.51007346 1.771088 0.03542177 -0.127518364  
## 69 0.18911843 -1.070482 0.01427309 0.235505965  
## 70 -1.10306256 -2.481891 0.57910784 -0.965179737  
## 71 1.37220381 3.033293 0.17333101 0.440549644  
## 72 -0.69030882 1.587710 2.99133824 0.039117500  
## 73 -0.18911843 1.501249 0.64339258 -0.001949674  
##   
## $data[[3]]  
## Bwj\_3 wj\_1 wj\_2 wj\_3  
## 1 0.87789630 2.414215 0.06584222 0.585264197  
## 2 -1.55477359 -3.938760 0.36278051 0.092249900  
## 3 -1.12639113 3.246657 0.99387453 4.571822818  
## 4 0.70630256 2.001191 0.22954833 0.423781538  
## 5 5.45131044 9.278826 -1.97175058 0.197175058  
## 6 1.47579103 1.317671 -0.23191002 0.084330916  
## 7 0.12566135 1.535861 -0.74465983 0.116353099  
## 8 -1.22652812 -2.146424 -1.83979218 1.042548902  
## 9 1.98630020 -1.730003 -0.64074200 0.346000681  
## 10 -0.05015358 3.056234 0.72879426 0.321296394  
## 11 2.27343465 7.794633 -1.42901607 1.623881894  
## 12 3.32005412 7.262618 -0.57063430 0.985641066  
## 13 3.71901649 4.938366 -0.18290245 0.792577284  
## 14 1.20035886 2.031377 -0.13388618 0.170820299  
## 15 1.12639113 1.590199 -0.63607970 0.430678961  
## 16 -1.25356544 -1.919522 0.33297832 0.325143536  
## 17 0.55338472 -1.752385 -0.50726933 0.027669236  
## 18 0.52440051 -1.580385 -0.79019255 0.043101412  
## 19 -1.83167403 1.292946 -0.18316740 0.479467614  
## 20 1.25356544 1.880348 0.50839043 0.974995341  
## 21 3.01145376 1.642611 -0.63879322 0.684421309  
## 22 2.32634787 5.146163 0.14099078 0.401823724  
## 23 -0.53883603 2.011655 0.05747584 0.107767206  
## 24 1.43953147 3.153259 0.10282368 1.987924412  
## 25 -0.24042603 2.087910 -0.53779507 0.132867017  
## 26 -0.87789630 -2.093445 -0.24986279 0.438948148  
## 27 1.89569792 1.579748 0.75827917 2.401217370  
## 28 1.37220381 1.877753 0.54165940 1.011097543  
## 29 1.89569792 2.157173 -0.36606581 0.594856935  
## 30 3.21597976 2.530607 -0.40595154 0.843535675  
## 31 -0.43991317 2.021223 -0.08322682 0.594477251  
## 32 -1.20035886 -1.418606 -0.36374511 0.982111793  
## 33 0.78919165 1.841447 -0.18414472 0.563708323  
## 34 1.71143956 2.464473 -0.08899486 0.684575823  
## 35 -0.84162123 -2.685173 -3.28633053 1.122161645  
## 36 0.72247905 1.926611 -0.03010329 0.662272464  
## 37 -0.37185609 2.298747 0.29072385 1.216983565  
## 38 -0.51007346 2.001554 0.83936138 0.594009595  
## 39 2.40891555 1.821375 -2.05639132 3.407734187  
## 40 4.01281081 3.941153 -2.86629344 5.589272201  
## 41 -0.77219321 2.386779 -0.07019938 0.119338951  
## 42 -1.34075503 -1.723828 -0.14556769 0.264320278  
## 43 0.82389363 1.765486 4.11946815 1.294689991  
## 44 -1.88079361 -2.298748 -0.03482951 0.508510864  
## 45 -5.32672389 -3.641740 -0.81531488 0.760960555  
## 46 0.48172685 -1.901553 -2.15509380 1.331087348  
## 47 2.81353534 2.046208 0.27495914 0.703383835  
## 48 -0.42614801 -1.537647 -0.92258847 0.702924549  
## 49 -0.12566135 -3.505290 -2.57936449 3.042327345  
## 50 4.75342431 2.778925 -3.47365623 8.409904546  
## 51 2.43237906 2.707743 -0.73430311 0.871984946  
## 52 4.75342431 -1.419854 -1.60505236 0.611154554  
## 53 3.13818077 -1.597619 0.02282313 0.205408196  
## 54 4.67081982 2.535588 0.64056958 0.166814994  
## 55 0.00000000 1.222306 -0.71301163 0.361598757  
## 56 -0.91536509 1.525608 -0.18815838 0.284780250  
## 57 0.51007346 1.428206 -7.65110185 1.224176297  
## 58 1.59819314 2.106709 0.50125148 0.646541770  
## 59 2.17009038 3.526397 0.12478020 1.030792929  
## 60 0.69030882 1.656741 -0.20709265 0.593665589  
## 61 -0.97411388 -1.948228 -0.63642107 0.298728256  
## 62 3.71901649 6.293720 -0.71519548 0.240305681  
## 63 3.97628577 3.834276 -0.78105613 0.291120923  
## 64 3.71901649 4.057109 -0.43952013 4.057108893  
## 65 0.93458929 4.131868 -0.88540038 0.688644741  
## 66 -1.69539771 -5.933892 0.64182913 1.453198037  
## 67 0.06270678 1.818497 -0.20066169 0.877894891  
## 68 -0.51007346 -1.771088 -0.03542177 0.127518364  
## 69 0.18911843 -1.070482 0.01427309 0.235505965  
## 70 1.10306256 2.481891 -0.57910784 0.965179737  
## 71 1.37220381 3.033293 0.17333101 0.440549644  
## 72 -0.69030882 1.587710 2.99133824 0.039117500  
## 73 0.18911843 -1.501249 -0.64339258 0.001949674  
##   
##   
## attr(,"class")  
## [1] "IVW\_RMVMR"

* Plot the radial MVMR models

plt\_rmvmr <- plot\_rmvmr(rmvmr\_input, rmvmr = rmvmr\_fit)  
plt\_rmvmr$p1



plt\_rmvmr$p2



* Heterogeneity statistics

pleio\_rmvmr <- pleiotropy\_rmvmr(rmvmr\_input, rmvmr = rmvmr\_fit)  
pleio\_rmvmr$gq

## q\_statistic p\_value  
## Exposure\_1 76.37356 2.812609e-01  
## Exposure\_2 59.58894 8.243650e-06  
## Exposure\_3 45.88633 1.308596e-02

head(pleio\_rmvmr$qdat)

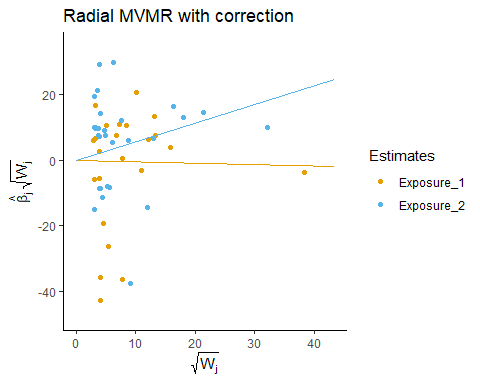
## snp wj corrected\_beta qj qj\_p ref\_exposure  
## 1 snp\_1 2.414215 0.3141338 0.031643343 0.85881269 Exposure\_1  
## 2 snp\_2 3.938760 0.3821443 0.008507667 0.92650973 Exposure\_1  
## 3 snp\_3 3.246657 -0.6057993 3.473998077 0.06234046 Exposure\_1  
## 4 snp\_4 2.001191 0.3273484 0.020524059 0.88608310 Exposure\_1  
## 5 snp\_5 9.278826 0.5414293 0.118081748 0.73112437 Exposure\_1  
## 6 snp\_6 1.317671 1.0713541 0.544339092 0.46064001 Exposure\_1

* Conditional F-statistics for instrument strength (Sanderson, Spiller, and Bowden 2021)

str\_rmvmr <- strength\_rmvmr(rmvmr\_input)

## Warning in MVMR::strength\_mvmr(r\_input, gencov): Covariance between effect of genetic variants on  
## each exposure not specified. Fixing covariance at 0.

str\_rmvmr$plot[[1]]



str\_rmvmr$stat[[2]]

## NULL

## Stata code

* Load the Statamarkdown package to enable Stata code chunks in an R Markdown file

if (!requireNamespace("Statamarkdown", quietly = TRUE)) {  
 remotes::install\_github("Hemken/Statamarkdown")  
}  
library(Statamarkdown)

* Read in the data and create an indicator variable to select observations with *p*-value between the genotype and LDL-C < 10-8

use https://raw.github.com/remlapmot/mrrobust/master/dodata, clear  
gen byte sel1 = (ldlcp2 < 1e-8)

### Example code using the mrrobust package

* Install the mrrobust package using the github package

// Note: output suppressed  
net install mrrobust, from("https://raw.github.com/remlapmot/mrrobust/master/")  
mrdeps

* Fit and MVMR model with phenotypes LDL-c and HDL-c (Burgess, Dudbridge, and Thompson 2015).

mvmr chdbeta ldlcbeta hdlcbeta [aw=1/(chdse^2)] if sel1==1

Number of genotypes = 73  
 Number of phenotypes = 2  
 Standard errors: Random effect  
 Residual standard error = 1.514  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .4670719 .0581901 8.03 0.000 .3530214 .5811224  
 hdlcbeta | -.2930048 .1211822 -2.42 0.016 -.5305175 -.0554921  
------------------------------------------------------------------------------

* Additionally include a third phenotype – triglycerides.

mvmr chdbeta ldlcbeta hdlcbeta tgbeta [aw=1/(chdse^2)] if sel1==1

Number of genotypes = 73  
 Number of phenotypes = 3  
 Standard errors: Random effect  
 Residual standard error = 1.490  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .42862 .0609661 7.03 0.000 .3091286 .5481113  
 hdlcbeta | -.1941989 .1308289 -1.48 0.138 -.4506189 .0622211  
 tgbeta | .2260456 .1232828 1.83 0.067 -.0155842 .4676755  
------------------------------------------------------------------------------

* Report the QA statistic for instrument validity and the conditional F-statistics for instrument strength for each phenotype (Sanderson et al. 2019; Sanderson, Spiller, and Bowden 2021).

mvmr chdbeta ldlcbeta hdlcbeta tgbeta [aw=1/(chdse^2)] if sel1==1, gxse(ldlcse hdlcse tgse)

> e hdlcse tgse)  
  
 Number of genotypes = 73  
 Number of phenotypes = 3  
 Standard errors: Random effect  
 Residual standard error = 1.490  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .42862 .0609661 7.03 0.000 .3091286 .5481113  
 hdlcbeta | -.1941989 .1308289 -1.48 0.138 -.4506189 .0622211  
 tgbeta | .2260456 .1232828 1.83 0.067 -.0155842 .4676755  
------------------------------------------------------------------------------  
 Q\_A statistic for instrument validity; chi2(70) = 152.88 (p = 0.0000)  
 Conditional F-statistics for instrument strength:  
 F\_x1 = 130.31 (ldlcbeta)  
 F\_x2 = 36.29 (hdlcbeta)  
 F\_x3 = 40.44 (tgbeta)

* Fit an MVMR-Egger regression (Rees, Wood, and Burgess 2017), orienting the model with respect to the first phenotype in the main *varlist*.

mrmvegger chdbeta ldlcbeta hdlcbeta tgbeta [aw=1/(chdse^2)] if sel1==1

MVMR-Egger model oriented wrt: ldlcbeta  
 Number of genotypes = 73  
 Number of phenotypes = 3  
 Residual standard error = 1.469  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .5672993 .1002611 5.66 0.000 .370791 .7638075  
 hdlcbeta | -.1364113 .1332727 -1.02 0.306 -.3976209 .1247983  
 tgbeta | .2739803 .1246927 2.20 0.028 .0295871 .5183735  
 \_cons | -.0093655 .0054187 -1.73 0.084 -.019986 .001255  
------------------------------------------------------------------------------

We can also orient the model with respect to HDL-C.

mrmvegger chdbeta ldlcbeta hdlcbeta tgbeta [aw=1/(chdse^2)] if sel1==1, orient(2)

> t(2)  
  
 MVMR-Egger model oriented wrt: hdlcbeta  
 Number of genotypes = 73  
 Number of phenotypes = 3  
 Residual standard error = 1.501  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .4286398 .0614056 6.98 0.000 .308287 .5489926  
 hdlcbeta | -.1989637 .1541909 -1.29 0.197 -.5011723 .1032449  
 tgbeta | .2256794 .1243221 1.82 0.069 -.0179875 .4693463  
 \_cons | .0002155 .0036218 0.06 0.953 -.006883 .0073141  
------------------------------------------------------------------------------

Or we can orient the model with respect to triglycerides.

mrmvegger chdbeta ldlcbeta hdlcbeta tgbeta [aw=1/(chdse^2)] if sel1==1, orient(3)

> t(3)  
  
 MVMR-Egger model oriented wrt: tgbeta  
 Number of genotypes = 73  
 Number of phenotypes = 3  
 Residual standard error = 1.499  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .4203073 .0660026 6.37 0.000 .2909447 .54967  
 hdlcbeta | -.1903089 .1321536 -1.44 0.150 -.4493252 .0687075  
 tgbeta | .2065651 .1365427 1.51 0.130 -.0610537 .474184  
 \_cons | .0013499 .003951 0.34 0.733 -.0063939 .0090936  
------------------------------------------------------------------------------

## R session information for reproducibility

library(sessioninfo)  
session\_info()

- Session info -----------------------------------------------------------------------------------  
 setting value   
 version R version 4.1.1 (2021-08-10)  
 os Windows 10 x64   
 system x86\_64, mingw32   
 ui RTerm   
 language (EN)   
 collate English\_United Kingdom.1252   
 ctype English\_United Kingdom.1252   
 tz Europe/London   
 date 2021-09-22   
  
- Packages ---------------------------------------------------------------------------------------  
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 evaluate 0.14 2019-05-28 [1] CRAN (R 4.1.0)   
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 fastmap 1.1.0 2021-01-25 [1] CRAN (R 4.1.0)   
 forcats \* 0.5.1 2021-01-27 [1] CRAN (R 4.1.0)   
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 fs 1.5.0 2020-07-31 [1] CRAN (R 4.1.0)   
 generics 0.1.0 2020-10-31 [1] CRAN (R 4.1.0)   
 ggplot2 \* 3.3.5 2021-06-25 [1] CRAN (R 4.1.0)   
 glmnet 4.1-2 2021-06-24 [1] CRAN (R 4.1.0)   
 glue 1.4.2 2020-08-27 [1] CRAN (R 4.1.0)   
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 pillar 1.6.2 2021-07-29 [1] CRAN (R 4.1.0)   
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 quantreg 5.86 2021-06-06 [1] CRAN (R 4.1.0)   
 R6 2.5.1 2021-08-19 [1] CRAN (R 4.1.1)   
 RadialMR 1.0 2021-07-12 [1] Github (WSpiller/RadialMR@d63d3fc)   
 Rcpp 1.0.7 2021-07-07 [1] CRAN (R 4.1.0)   
 readr \* 2.0.1 2021-08-10 [1] CRAN (R 4.1.1)   
 readxl 1.3.1 2019-03-13 [1] CRAN (R 4.1.0)   
 remotes \* 2.4.0 2021-06-02 [1] CRAN (R 4.1.0)   
 reprex 2.0.1 2021-08-05 [1] CRAN (R 4.1.0)   
 rjson 0.2.20 2018-06-08 [1] CRAN (R 4.1.0)   
 rlang 0.4.11 2021-04-30 [1] CRAN (R 4.1.0)   
 rmarkdown 2.11 2021-09-14 [1] CRAN (R 4.1.1)   
 RMVMR \* 0.2 2021-06-28 [1] Github (wspiller/rmvmr@5b1198b)   
 robustbase 0.93-8 2021-06-02 [1] CRAN (R 4.1.0)   
 rstudioapi 0.13 2020-11-12 [1] CRAN (R 4.1.0)   
 rvest 1.0.1 2021-07-26 [1] CRAN (R 4.1.0)   
 scales 1.1.1 2020-05-11 [1] CRAN (R 4.1.0)   
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 SparseM 1.81 2021-02-18 [1] CRAN (R 4.1.0)   
 Statamarkdown \* 0.7.0 2021-09-15 [1] Github (Hemken/Statamarkdown@a68a8b9)  
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[1] C:/Users/eptmp/Documents/R/win-library/4.1  
[2] C:/Program Files/R/R-4.1.1/library

## Stata session information for reproducibility

about  
ado describe mrrobust

Stata/MP 16.1 for Windows (64-bit x86-64)  
Revision 08 Jul 2021  
Copyright 1985-2019 StataCorp LLC  
  
Total physical memory: 32.00 GB  
Available physical memory: 20.47 GB  
  
Stata license: Unlimited-user 2-core network, expiring 21 Jan 2022  
Serial number: 501609352178  
 Licensed to: Tom Palmer  
 University of Bristol  
  
  
-------------------------------------------------------------------------------  
[89] package mrrobust from https://raw.github.com/remlapmot/mrrobust/master  
-------------------------------------------------------------------------------  
  
TITLE  
 'mrrobust': Stata package for two-sample Mendelian randomization analyses  
  
DESCRIPTION/AUTHOR(S)  
 Author: Tom Palmer  
 Distribution-Date: 20210917  
  
INSTALLATION FILES  
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 m\mrmedian.sthlp  
 m\mrmedianobs.ado  
 m\mrmedianobs\_work.ado  
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 20 Sep 2021  
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## References

Burgess, S, F Dudbridge, and SG Thompson. 2015. “Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects.” *American Journal of Epidemiology* 181: 251--260. <https://doi.org/10.1093/aje/kwu283>.

Rees, J, A Wood, and S Burgess. 2017. “Extending the MR-Egger method for multivariable Mendelian randomization to correct for both measured and unmeasured pleiotropy.” *Statistics in Medicine* 36: 4705–18. <https://doi.org/10.1002/sim.7492>.

Sanderson, E, G Davey Smith, F Windmeijer, and J Bowden. 2019. “An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings.” *International Journal of Epidemiology* 48: 713–27. <https://doi.org/10.1093/ije/dyy262>.

Sanderson, E, W Spiller, and J Bowden. 2021. “Testing and Correcting for Weak and Pleiotropic Instruments in Two-Sample Multivariable Mendelian Randomization.” *Statistics in Medicine*. <https://doi.org/10.1002/sim.9133>.