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)

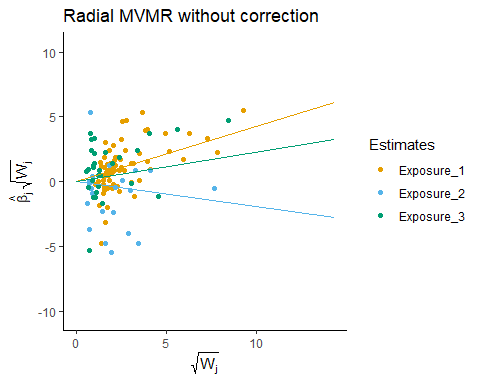
##   
## Radial Multivariable MR  
##   
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02  
##   
## Residual standard error: 1.49 on 70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

rmvmr\_fit$coef

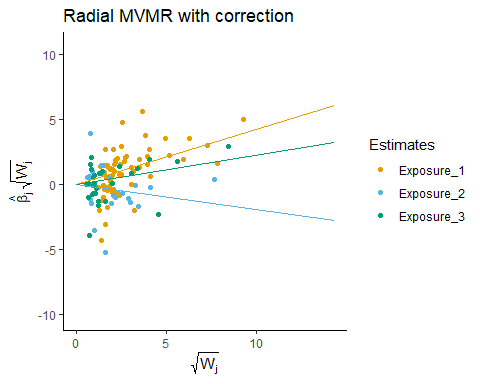
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02

* 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)

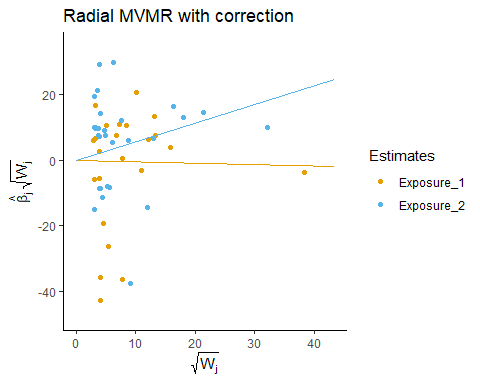
## snp wj corrected\_beta qj qj\_p ref\_exposure  
## 1 snp\_1 2.414215 0.3141338 0.031643343 0.85881269 Exposure\_1  
## 2 snp\_2 3.938760 0.3821443 0.008507667 0.92650973 Exposure\_1  
## 3 snp\_3 3.246657 -0.6057993 3.473998077 0.06234046 Exposure\_1  
## 4 snp\_4 2.001191 0.3273484 0.020524059 0.88608310 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 ---------------------------------------------------------------------------------------  
 package \* version date lib source   
 arrangements 1.1.9 2020-09-13 [1] CRAN (R 4.1.0)   
 assertthat 0.2.1 2019-03-21 [1] CRAN (R 4.1.0)   
 backports 1.2.1 2020-12-09 [1] CRAN (R 4.1.0)   
 broom 0.7.9 2021-07-27 [1] CRAN (R 4.1.0)   
 cellranger 1.1.0 2016-07-27 [1] CRAN (R 4.1.0)   
 cli 3.0.1 2021-07-17 [1] CRAN (R 4.1.0)   
 codetools 0.2-18 2020-11-04 [2] CRAN (R 4.1.1)   
 colorspace 2.0-2 2021-06-24 [1] CRAN (R 4.1.0)   
 conquer 1.0.2 2020-08-27 [1] CRAN (R 4.1.0)   
 crayon 1.4.1 2021-02-08 [1] CRAN (R 4.1.0)   
 curl 4.3.2 2021-06-23 [1] CRAN (R 4.1.0)   
 data.table 1.14.0 2021-02-21 [1] CRAN (R 4.1.0)   
 DBI 1.1.1 2021-01-15 [1] CRAN (R 4.1.0)   
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 DEoptimR 1.0-9 2021-05-24 [1] CRAN (R 4.1.0)   
 digest 0.6.27 2020-10-24 [1] CRAN (R 4.1.0)   
 dplyr \* 1.0.7 2021-06-18 [1] CRAN (R 4.1.0)   
 ellipsis 0.3.2 2021-04-29 [1] CRAN (R 4.1.0)   
 evaluate 0.14 2019-05-28 [1] CRAN (R 4.1.0)   
 fansi 0.5.0 2021-05-25 [1] CRAN (R 4.1.0)   
 farver 2.1.0 2021-02-28 [1] CRAN (R 4.1.0)   
 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)   
 foreach 1.5.1 2020-10-15 [1] CRAN (R 4.1.0)   
 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)   
 gmp 0.6-2 2021-01-07 [1] CRAN (R 4.1.0)   
 gtable 0.3.0 2019-03-25 [1] CRAN (R 4.1.0)   
 haven \* 2.4.3 2021-08-04 [1] CRAN (R 4.1.0)   
 highr 0.9 2021-04-16 [1] CRAN (R 4.1.0)   
 hms 1.1.0 2021-05-17 [1] CRAN (R 4.1.0)   
 htmltools 0.5.2 2021-08-25 [1] CRAN (R 4.1.1)   
 htmlwidgets 1.5.4 2021-09-08 [1] CRAN (R 4.1.1)   
 httr 1.4.2 2020-07-20 [1] CRAN (R 4.1.0)   
 iterators 1.0.13 2020-10-15 [1] CRAN (R 4.1.0)   
 iterpc 0.4.2 2020-01-10 [1] CRAN (R 4.1.0)   
 jsonlite 1.7.2 2020-12-09 [1] CRAN (R 4.1.0)   
 knitr 1.34 2021-09-09 [1] CRAN (R 4.1.1)   
 labeling 0.4.2 2020-10-20 [1] CRAN (R 4.1.0)   
 lattice 0.20-44 2021-05-02 [2] CRAN (R 4.1.1)   
 lazyeval 0.2.2 2019-03-15 [1] CRAN (R 4.1.0)   
 lifecycle 1.0.0 2021-02-15 [1] CRAN (R 4.1.0)   
 lubridate 1.7.10 2021-02-26 [1] CRAN (R 4.1.0)   
 magrittr 2.0.1 2020-11-17 [1] CRAN (R 4.1.0)   
 Matrix 1.3-4 2021-06-01 [2] CRAN (R 4.1.1)   
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 modelr 0.1.8 2020-05-19 [1] CRAN (R 4.1.0)   
 munsell 0.5.0 2018-06-12 [1] CRAN (R 4.1.0)   
 MVMR \* 0.3 2021-08-11 [1] Github (wspiller/mvmr@a6388a8)   
 pillar 1.6.2 2021-07-29 [1] CRAN (R 4.1.0)   
 pkgconfig 2.0.3 2019-09-22 [1] CRAN (R 4.1.0)   
 plotly 4.9.4.1 2021-06-18 [1] CRAN (R 4.1.0)   
 purrr \* 0.3.4 2020-04-17 [1] CRAN (R 4.1.0)   
 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)   
 sessioninfo \* 1.1.1 2018-11-05 [1] CRAN (R 4.1.0)   
 shape 1.4.6 2021-05-19 [1] CRAN (R 4.1.0)   
 SparseM 1.81 2021-02-18 [1] CRAN (R 4.1.0)   
 Statamarkdown \* 0.7.0 2021-09-15 [1] Github (Hemken/Statamarkdown@a68a8b9)  
 stringi 1.7.4 2021-08-25 [1] CRAN (R 4.1.1)   
 stringr \* 1.4.0 2019-02-10 [1] CRAN (R 4.1.0)   
 survival 3.2-13 2021-08-24 [2] CRAN (R 4.1.1)   
 tibble \* 3.1.4 2021-08-25 [1] CRAN (R 4.1.1)   
 tidyr \* 1.1.3 2021-03-03 [1] CRAN (R 4.1.0)   
 tidyselect 1.1.1 2021-04-30 [1] CRAN (R 4.1.0)   
 tidyverse \* 1.3.1 2021-04-15 [1] CRAN (R 4.1.0)   
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 xfun 0.26 2021-09-14 [1] CRAN (R 4.1.1)   
 xml2 1.3.2 2020-04-23 [1] CRAN (R 4.1.0)   
 yaml 2.2.1 2020-02-01 [1] CRAN (R 4.1.0)   
  
[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: 20.12 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  
 m\mrmedianobs.sthlp  
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 m\mregger.sthlp  
 m\mrrobust.sthlp  
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 m\mreggerplot.sthlp  
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 m\mrmodal.sthlp  
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 m\mrratio.sthlp  
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 m\mrforest.ado  
 m\mrforest.sthlp  
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 m\mreggersimex.sthlp  
 m\mreggersimexonce.ado  
 m\mrmodalplot.ado  
 m\mrmodalplot.sthlp  
 m\mrfunnel.ado  
 m\mrfunnel.sthlp  
 m\mrdeps.ado  
 m\mrdeps.sthlp  
 m\mr.ado  
 m\mr.sthlp  
 m\mrmvivw.ado  
 m\mrmvivw.sthlp  
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 m\mvmr.sthlp  
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 m\mrleaveoneout.sthlp  
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INSTALLED ON  
 20 Sep 2021  
-------------------------------------------------------------------------------

## 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>.