

Example R and Stata code for a Mendelian randomization analysis

Sanderson et al.

22 September 2021

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.githubusercontent.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 = "snps",  
  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_mvnr(
  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_mvnr(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_mvnr(r_input)

```

```

## Warning in strength_mvnr(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 <- mrmvininput_to_rmvmr_format(datfmt)

rmvmr_fit <- ivw_rmvmr(rmvmr_input, summary = TRUE)

```

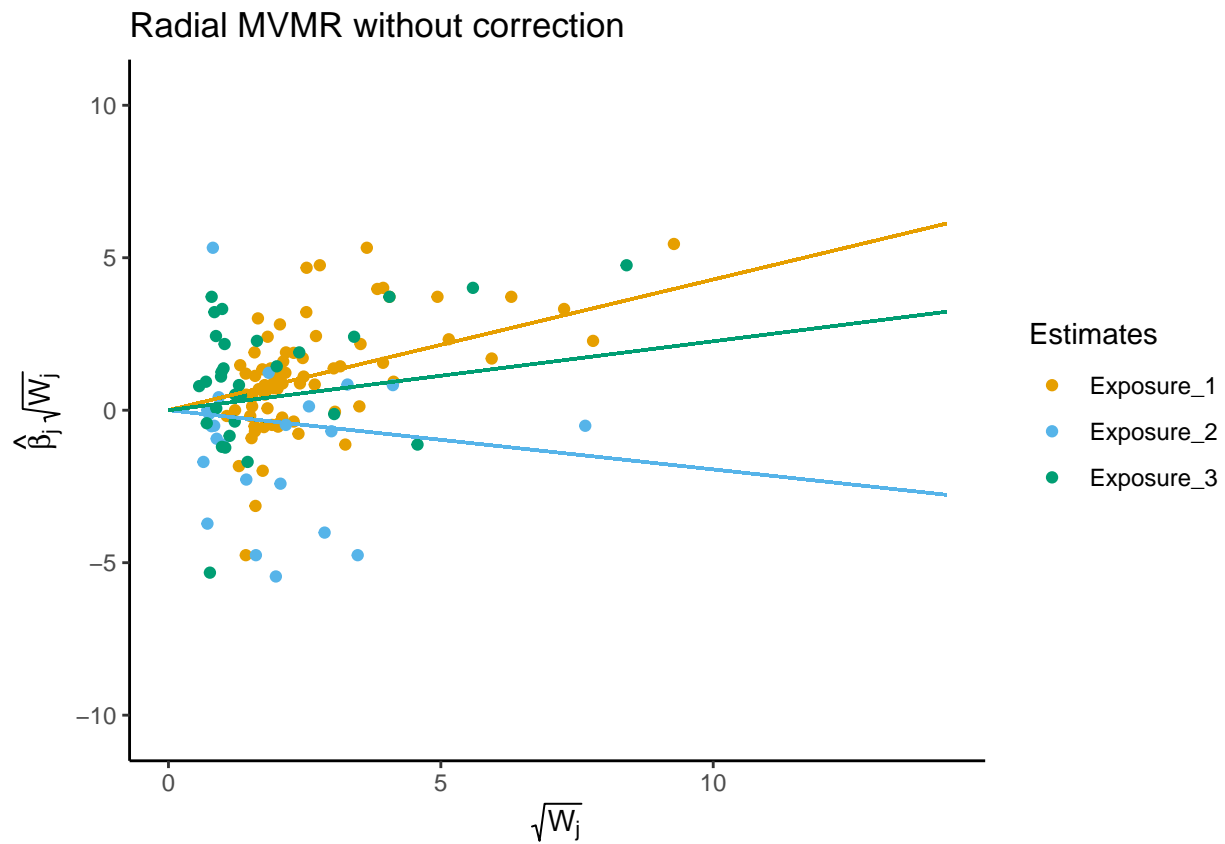
```
##
## Radial Multivariable MR
##
##           Estimate Std. Error   t value    Pr(>|t|)
## exposure1  0.4286200  0.0609661   7.030464 1.099077e-09
## exposure2 -0.1941989  0.1308289  -1.484372 1.421994e-01
## exposure3  0.2260456  0.1232828   1.833554 7.097168e-02
##
## Residual standard error: 1.49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

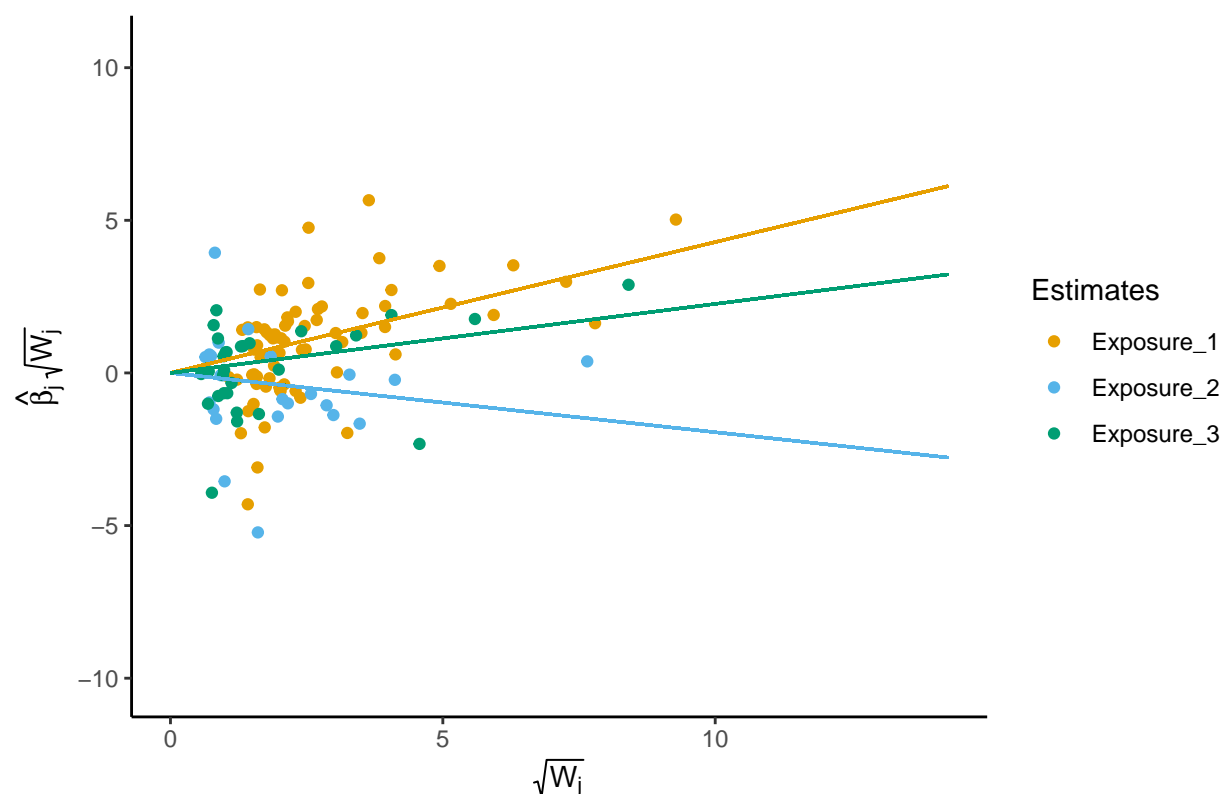
- Plot the radial MVMR models

```
plt_rmvmr <- plot_rmvmr(rmvmr_input, rmvmr = rmvmr_fit)
plt_rmvmr$p1
```



```
plt_rmvmr$p2
```

Radial MVMR with correction



- Heterogeneity statistics

```
pleio_rmvmr <- pleiotropy_rmvmr(rmvmr_input, rmvmr = rmvmr_fit)
pleio_rmvmr$qq
```

```
##          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)
```

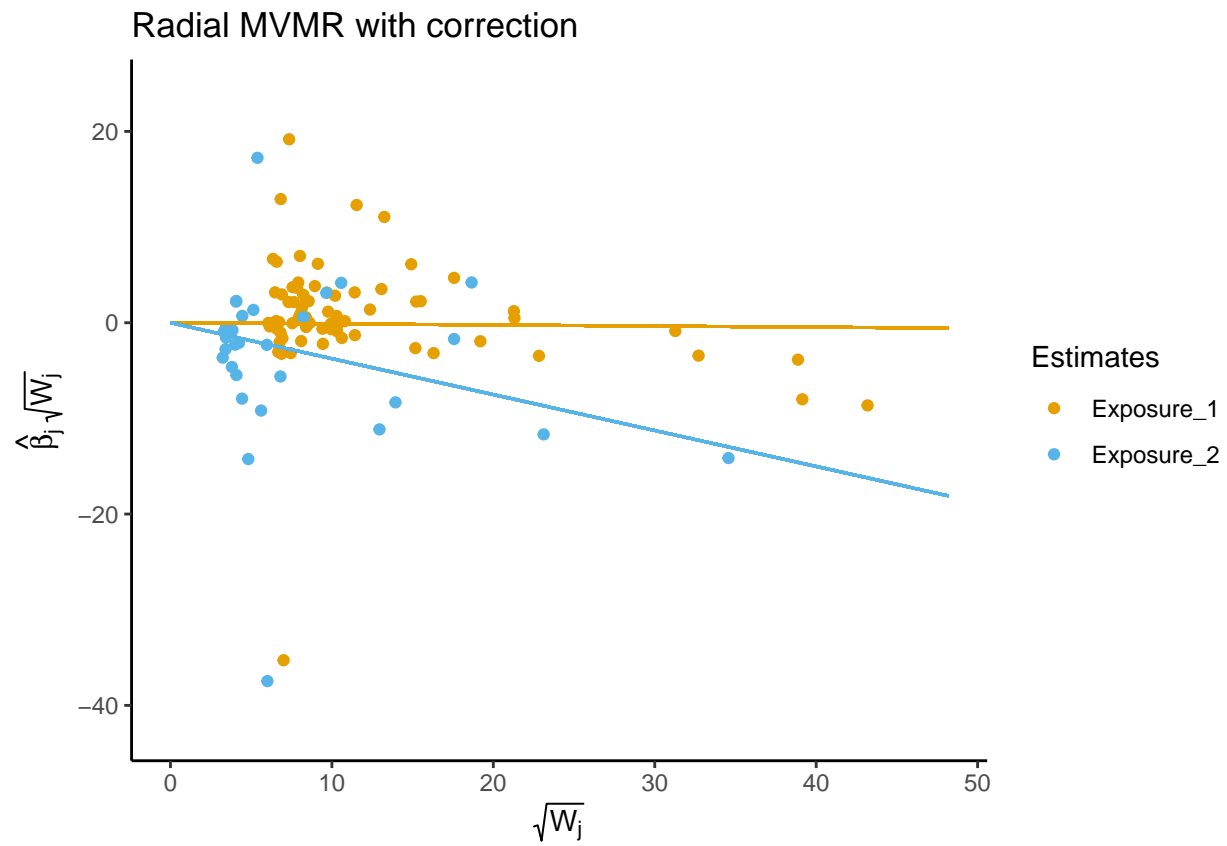
```
##      snp      wj corrected_beta      qj      qj_p ref_exposure
## 1 snp_1 2.414215      0.3141338 0.031643343 0.85881269 Exposure_1
## 2 snp_2 3.938760      0.3821443 0.008507667 0.92650973 Exposure_1
## 3 snp_3 3.246657     -0.6057993 3.473998077 0.06234046 Exposure_1
## 4 snp_4 2.001191      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_mvmm(r_input, gencov): Covariance between effect of genetic variants on
## each exposure not specified. Fixing covariance at 0.
```

```
str_rmvmr$plot[[2]]
```



```
str_rmvmr$qstat[[2]]
```

```
##           q_statistic      p_value
## Exposure_1    335.0602 6.799449e-36
## Exposure_2    371.0830 1.403374e-61
```

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.githubusercontent.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.githubusercontent.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.

```
mrmmvegger 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)
dbplyr	2.1.1	2021-04-06	[1]	CRAN	(R 4.1.0)
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)
MatrixModels	0.5-0	2021-03-02	[1]	CRAN	(R 4.1.0)
matrixStats	0.61.0	2021-09-17	[1]	CRAN	(R 4.1.1)
MendelianRandomization	* 0.5.1	2021-04-16	[1]	CRAN	(R 4.1.0)
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)
tzdb	0.1.2	2021-07-20	[1]	CRAN (R 4.1.0)
utf8	1.2.2	2021-07-24	[1]	CRAN (R 4.1.0)
vctrs	0.3.8	2021-04-29	[1]	CRAN (R 4.1.0)
viridisLite	0.4.0	2021-04-13	[1]	CRAN (R 4.1.0)
withr	2.4.2	2021-04-18	[1]	CRAN (R 4.1.0)
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: 19.80 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.githubusercontent.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

m\mrmedian.ado
m\mrmedian.sthlp
m\mrmedianobs.ado
m\mrmedianobs_work.ado
m\mrmedianobs.sthlp
m\mregger.ado
m\mregger.sthlp
m\mrrobust.sthlp
m\mreggerplot.ado
m\mreggerplot.sthlp
m\mrmodal.ado
m\mrmodal.sthlp
m\mrratio.ado
m\mrratio.sthlp
m\mrivests.ado
m\mrivests.sthlp
m\mrforest.ado
m\mrforest.sthlp
m\mreggersimex.ado
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
m\mvivw.ado
m\mvivw.sthlp
m\mvmr.ado
m\mvmr.sthlp

```
m\mrmvegger.ado
m\mrmvegger.sthlp
m\mrleaveoneout.ado
m\mrleaveoneout.sthlp
m\mrrobust-author.ihlp
```

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>.