

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.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_mvmmr(
  BXGs = dat[,c("ldlcbeta", "hdlcbeta", "tgbeta")],
  BYG = dat$chdbeta,
  seBXGs = dat[,c("ldlcse", "hdlcse", "tgse")],
  seBYG = dat$chdse,
  RSID = dat$rsid
)
```

- Fit an MVMMR model

```
mvmmrfit <- ivw_mvmmr(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_mvmmr(r_input)
```

```
## Warning in strength_mvmmr(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 MVMMR model

```
if (!requireNamespace("RMVMMR", quietly = TRUE)) {
  remotes::install_github("WSpiller/RMVMMR")
}
library(RMVMMR)

rmvmmr_input <- mrmvininput_to_rmvmmr_format(datfmt)

rmvmmr_fit <- ivw_rmvmmr(rmvmmr_input, summary = TRUE)
```

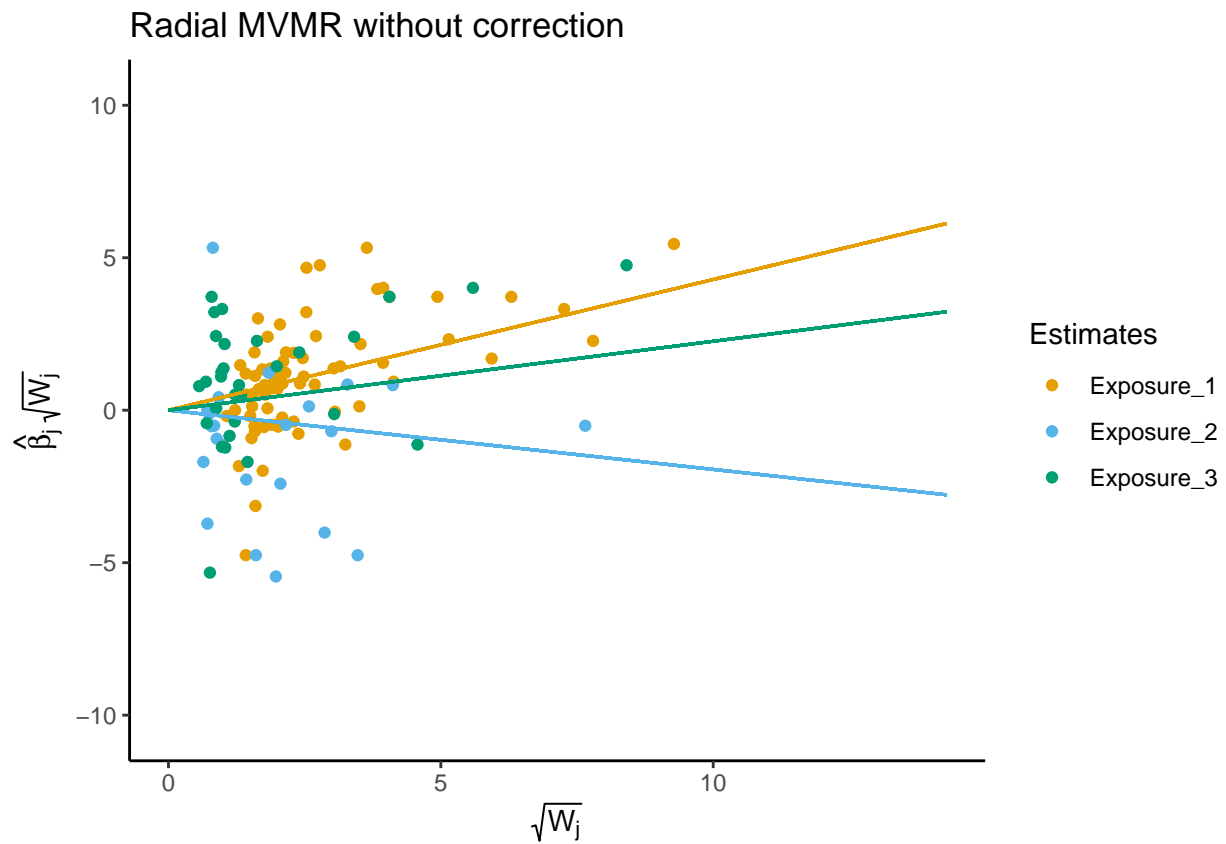
```
##
## Radial Multivariable MR
##
##           Estimate Std. Error  t value    Pr(>|t|)
## exposure1  0.4286200  0.0609661  7.030464 1.099077e-09
## exposure2 -0.1941989  0.1308289 -1.484372 1.421994e-01
## exposure3  0.2260456  0.1232828  1.833554 7.097168e-02
##
## Residual standard error: 1.49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

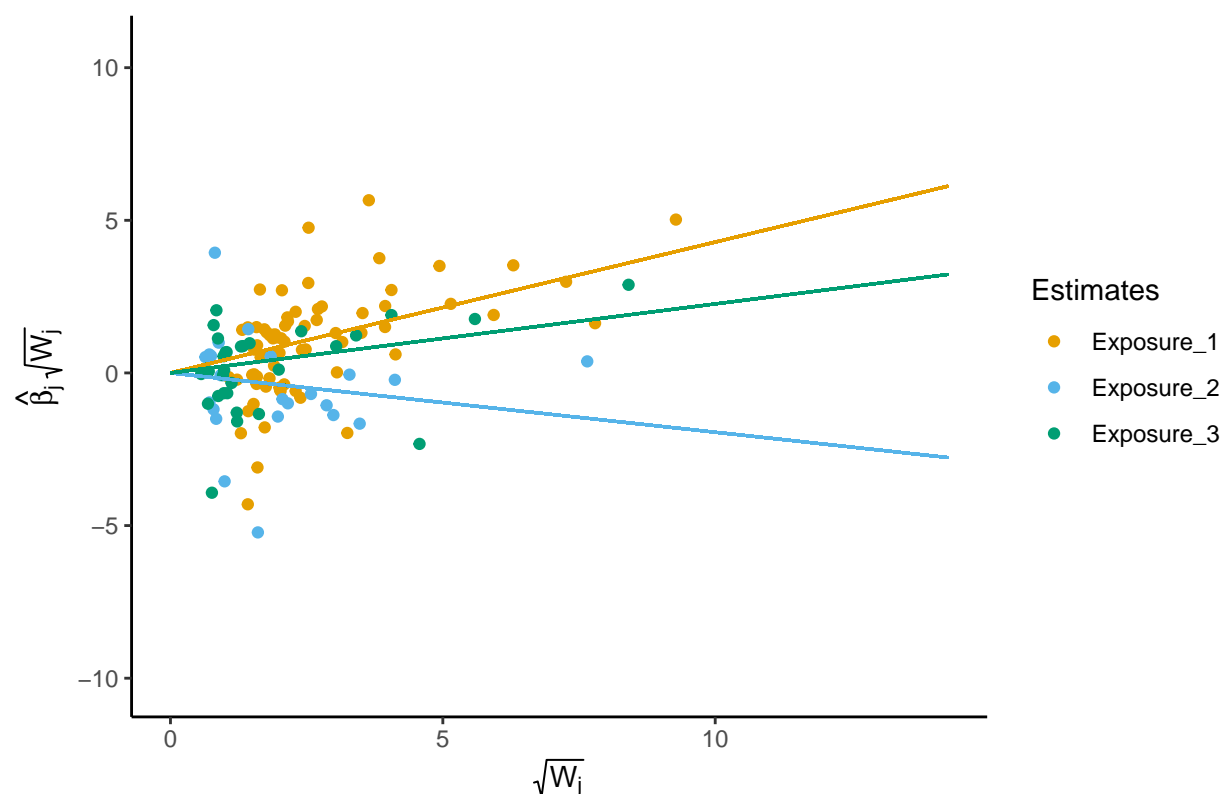
- Plot the radial MVMR models

```
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)
```

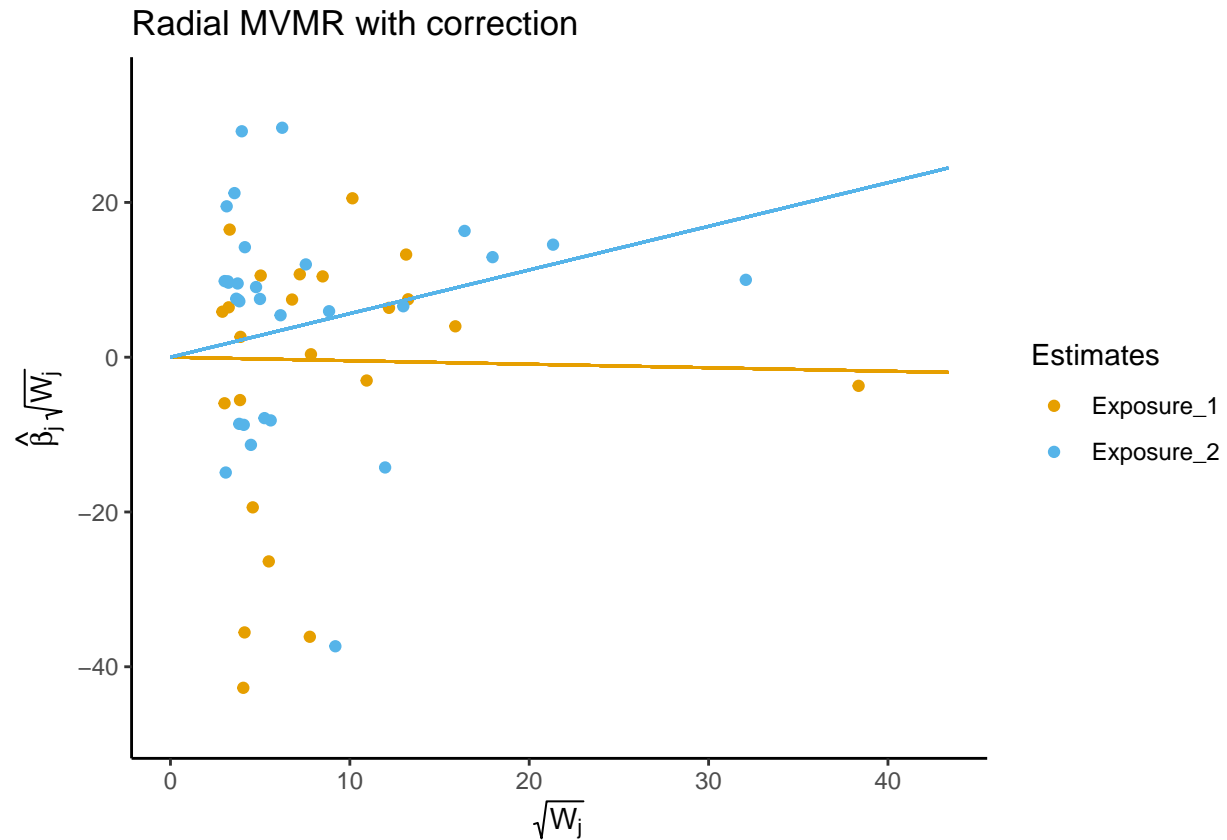
```
##      snp      wj corrected_beta      qj      qj_p ref_exposure
## 1 snp_1 2.414215      0.3141338 0.031643343 0.85881269 Exposure_1
## 2 snp_2 3.938760      0.3821443 0.008507667 0.92650973 Exposure_1
## 3 snp_3 3.246657     -0.6057993 3.473998077 0.06234046 Exposure_1
## 4 snp_4 2.001191      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[[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.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: 20.07 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
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m\mr.sthlp
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m\mvivw.sthlp
m\mvmr.ado
m\mvmr.sthlp

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m\mrleaveoneout.sthlp
m\mrrobust-author.ihlp
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INSTALLED ON
20 Sep 2021

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