Example R and Stata code for a Mendelian randomization analysis

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24 September 2021

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## 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)

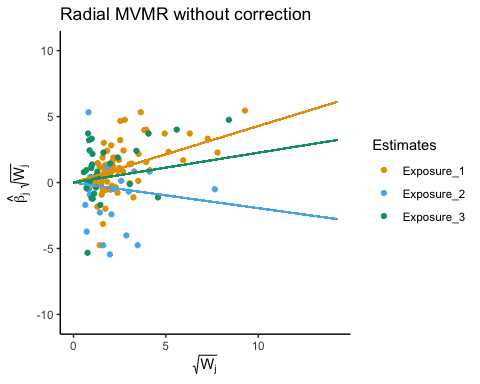
##   
## Radial Multivariable MR  
##   
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02  
##   
## Residual standard error: 1.49 on 70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

rmvmr\_fit$coef

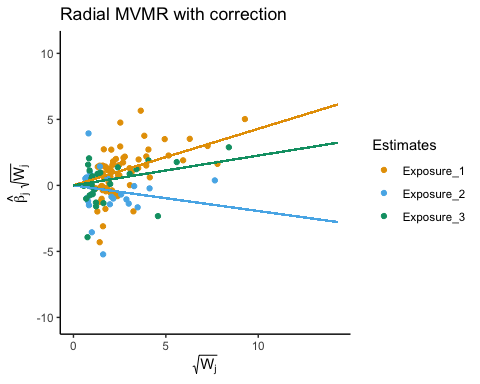
## Estimate Std. Error t value Pr(>|t|)  
## exposure1 0.4286200 0.0609661 7.030464 1.099077e-09  
## exposure2 -0.1941989 0.1308289 -1.484372 1.421994e-01  
## exposure3 0.2260456 0.1232828 1.833554 7.097168e-02

* 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)

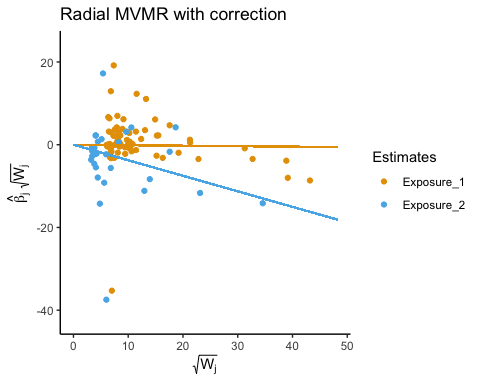
## snp wj corrected\_beta qj qj\_p ref\_exposure  
## 1 snp\_1 2.414215 0.3141338 0.031643343 0.85881269 Exposure\_1  
## 2 snp\_2 3.938760 0.3821443 0.008507667 0.92650973 Exposure\_1  
## 3 snp\_3 3.246657 -0.6057993 3.473998077 0.06234046 Exposure\_1  
## 4 snp\_4 2.001191 0.3273484 0.020524059 0.88608310 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[[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.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 IVW (with fixed effect standard errors)

mregger chdbeta ldlcbeta [aw=1/(chdse^2)] if sel1==1, ivw fe

Number of genotypes = 73  
 Residual standard error constrained at 1  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 ldlcbeta | .4815055 .038221 12.60 0.000 .4065938 .5564173  
------------------------------------------------------------------------------

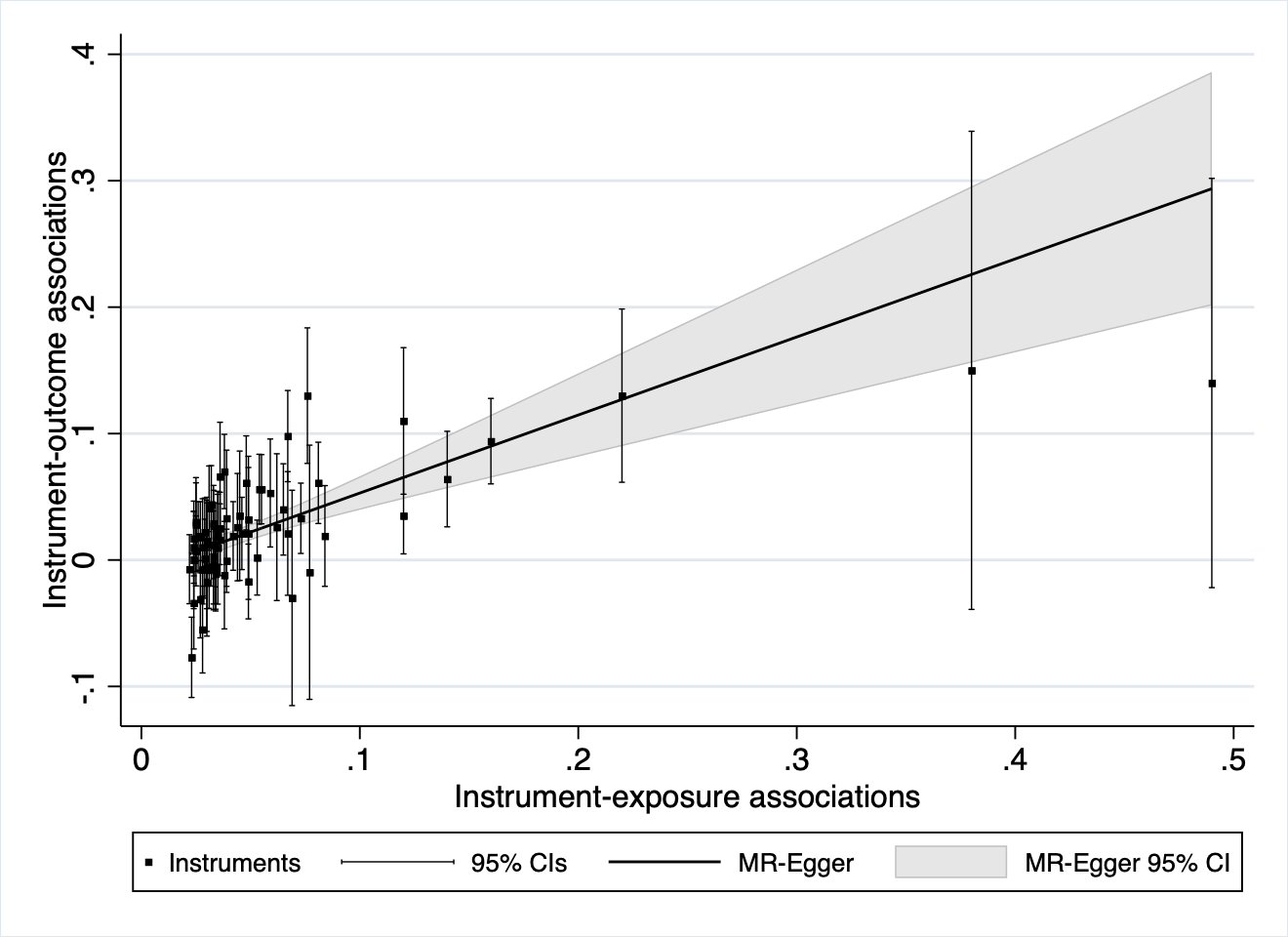
* Fit MR-Egger reporting I2GX statistic and heterogeneity Q-test

mregger chdbeta ldlcbeta [aw=1/(chdse^2)] if sel1==1, gxse(ldlcse) heterogi

Q\_GX statistic (weighted) = 3454.26  
 I^2\_GX statistic (weighted) = 97.92%  
 Number of genotypes = 73  
 Residual standard error = 1.548  
 Ruecker's Q for heterogeneity; chi2(71) = 170.11 (p = 0.0000)  
 I-squared statistic = 58.3% (95% CI 45.8%, 67.8%)  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
chdbeta |  
 slope | .6173131 .1034573 5.97 0.000 .4145405 .8200858  
 \_cons | -.0087706 .0054812 -1.60 0.110 -.0195136 .0019723  
------------------------------------------------------------------------------

* Simple plot of IVW and MR-Egger univariate estimates

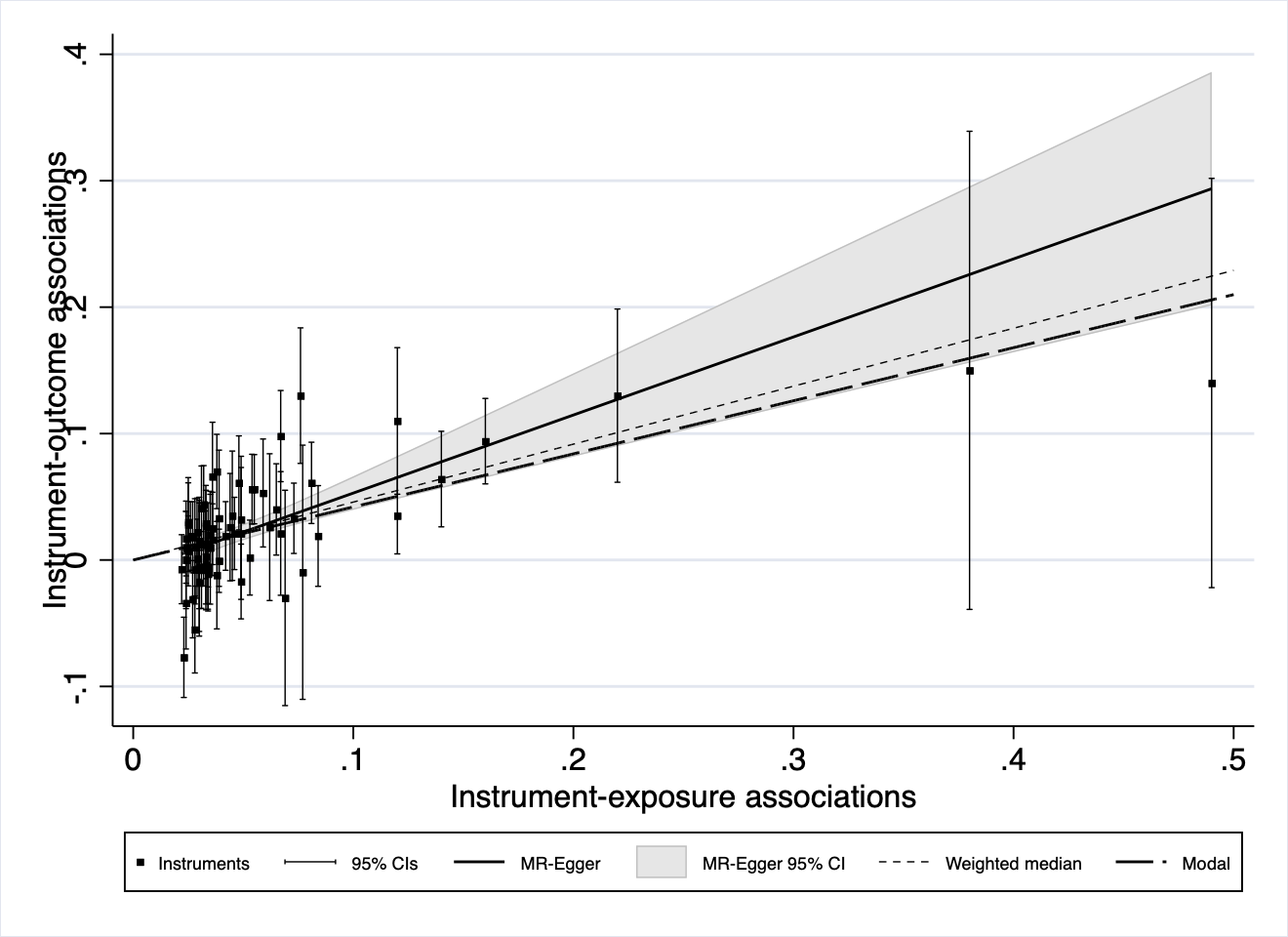
mreggerplot chdbeta chdse ldlcbeta ldlcse if sel1==1  
qui gr export mreggerplot-1.png, replace



* Adding the modal and median estimates onto the plot

mreggerplot chdbeta chdse ldlcbeta ldlcse if sel1==1  
mrmedian chdbeta chdse ldlcbeta ldlcse if sel1==1, weighted  
addplot : function \_b[beta]\*x if sel1==1, ///  
 range(0 0.5) lc(gs0) lp(shortdash) lw(vthin)  
mrmodal chdbeta chdse ldlcbeta ldlcse if sel1==1, phi(.25)  
addplot : function \_b[beta]\*x if sel1==1, ///  
 range(0 0.5) lc(gs0) lp(longdash) ///  
 legend(order(5 "Instruments" ///  
 4 "95% CIs" 3 "MR-Egger" 2 "MR-Egger 95% CI" ///  
 6 "Weighted median" 7 "Modal") ///  
 rows(1) si(vsmall) symx(\*.5))  
qui gr export mreggerplot-2.png, replace

Number of genotypes = 73  
 Replications = 1000  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
 beta | .4582573 .0633137 7.24 0.000 .3341648 .5823499  
------------------------------------------------------------------------------  
  
 Number of genotypes = 73  
 Replications = 1000  
 Phi = .25  
------------------------------------------------------------------------------  
 | Coef. Std. Err. z P>|z| [95% Conf. Interval]  
-------------+----------------------------------------------------------------  
 beta | .4198713 .2260632 1.86 0.063 -.0232045 .8629471  
------------------------------------------------------------------------------



* 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)

> 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)

> (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)

> (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  
------------------------------------------------------------------------------

## Session information for reproducibility

### R session information

library(sessioninfo)  
session\_info()

─ Session info ───────────────────────────────────────────────────────────────────────────────────  
 setting value   
 version R version 4.1.1 (2021-08-10)  
 os macOS Big Sur 11.6   
 system aarch64, darwin20   
 ui X11   
 language (EN)   
 collate en\_GB.UTF-8   
 ctype en\_GB.UTF-8   
 tz Europe/London   
 date 2021-09-24   
  
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 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)   
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 checkmate 2.0.0 2020-02-06 [1] CRAN (R 4.1.1)   
 cli 3.0.1 2021-07-17 [1] CRAN (R 4.1.0)   
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 codetools 0.2-18 2020-11-04 [1] CRAN (R 4.1.1)   
 colorspace 2.0-2 2021-06-24 [1] CRAN (R 4.1.1)   
 conquer 1.0.2 2020-08-27 [1] CRAN (R 4.1.0)   
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 DBI 1.1.1 2021-01-15 [1] CRAN (R 4.1.0)   
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 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 2021-08-26 [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 4.1.1)   
 survival \* 3.2-13 2021-08-24 [1] CRAN (R 4.1.1)   
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 tidyverse \* 1.3.1 2021-04-15 [1] CRAN (R 4.1.0)   
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 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)   
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 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] /Library/Frameworks/R.framework/Versions/4.1-arm64/Resources/library

### Stata session information

about  
ado describe mrrobust

Stata/MP 16.1 for Mac (Apple Silicon)  
Revision 08 Jul 2021  
Copyright 1985-2019 StataCorp LLC  
  
Total physical memory: 8.01 GB  
  
Stata license: Unlimited-user 2-core network, expiring 21 Jan 2022  
Serial number: 501609352178  
 Licensed to: Tom Palmer  
 University of Bristol  
  
  
--------------------------------------------------------------------------------  
[15] 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  
 m/mrmedian.ado  
 m/mrmedian.sthlp  
 m/mrmedianobs.ado  
 m/mrmedianobs\_work.ado  
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 m/mrrobust-author.ihlp  
  
INSTALLED ON  
 24 Sep 2021  
--------------------------------------------------------------------------------

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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>.