R and Stata packages for one-sample Mendelian randomization analyses: OneSampleMR and ivonesamplemr

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Outline

Overview

- Motivation
  - Code from appendix of Clarke et al. (2015) was in R scripts and Stata do-files
  - Over the summer some interesting in using it
- One-sample (a.k.a. individual level) Mendelian randomization (MR) data
  - i.e., not genotype summary level (a.k.a. two-sample) data!
- Aim
  Collection of useful functions and instrumental variable (IV) estimators (that aren't available elsewhere)

What's available elsewhere?

- Stata
  - Official Stata IV commands begin `iv`*something* e.g., `ivregress`, `ivprobit`, `ivpoisson`, `gmm`
  - User-written: `ivreg2`, `ivpois`, and many more ...
- R
  - **sem**
  - **AER**/**ivreg**
  - **ivtools** – excellent but only allows a single instrument (Sjolander et al. 2020)
  - **nlmr** (Staley et al. 2017)
  - and many more ...
- IEU software website https://mrcieu.github.io/
- Chris Moreno-Stokoe webpage https://www.morenostok.io/mrsoftwarelist.html

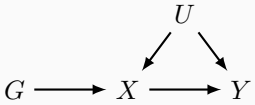
What's missing?

- Some binary outcome IV estimators
  - Structural Mean Models (SMMs); Additive SMM, Multiplicative SMM, Logistic SMM
  - Two-stage predictor substitution (TSPS)
  - Two-stage residual inclusion (TSRI)
  - Some nonlinear estimators, e.g., Burgess, Davies, et al. (2014)

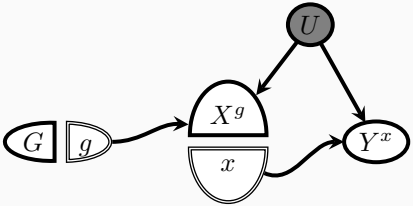
Summary of observational and IV estimators

Outcome	Link fn	Observational estimator	IV estimator
Continuous	Identity	Linear regression	Linear IV: TSLS, ...
Binary	Identity	Binomial regression with identity link	Additive SMM
Binary/Cat.	Log (add.)	Log-binomial/Poisson regresssion	TSPS, TSRI
Binary/Cat.	Log (mult.)	Gamma regression with log link	Multiplicative SMM, TSPS, TSRI
Binary	Logit	Logistic regression	Logistic SMM, TSPS, TSRI

- View potential outcomes on a/*the* IV Directed Acyclic Graph (DAG)



- using a Single World Intervention Graph (SWIG) (Swanson et al. 2018)



Features common to both OneSampleMR and ivonesamplemr packages

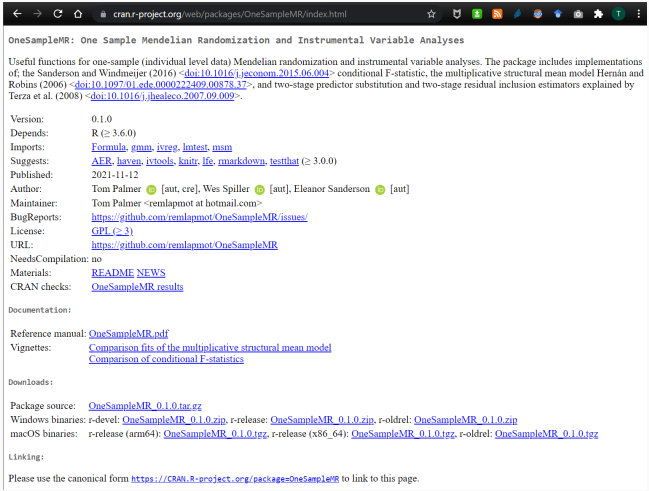
- Multiplicative SMM (Hernán et al. 2006)
- TSPS and TSRI estimators with a choice of second stage link functions (Terza et al. 2008)
- The functions use the generalised method of moments (GMM) estimation approach described in Clarke et al. (2015)

OneSampleMR R package

- Website https://remlapmot.github.io/OneSampleMR/
- Install from CRAN

```
install.packages("OneSampleMR")
```

OneSampleMR R package



OneSampleMR R package

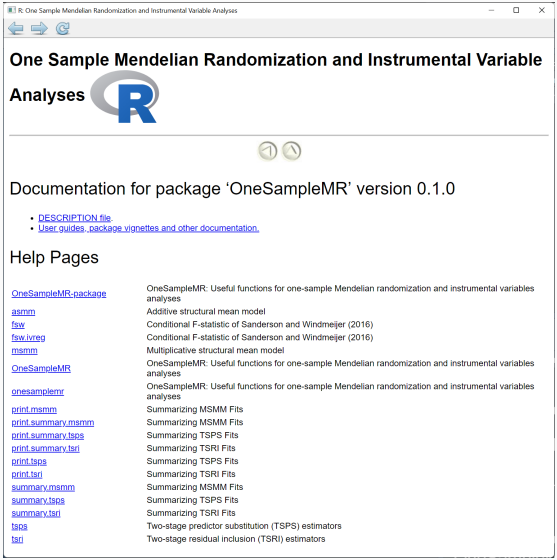
- For IV estimators syntax follows syntax of AER::`ivreg()`/`ivreg::ivreg()`

```
msmm(outcome ~ exposure + confndrs | instruments + confndrs, ...)
```

- Sanderson et al. (2016) conditional F-statistic (already in Stata's user-written `ivreg2` and **lfe** R package); `fsw()`
- Package helpfile

```
help(package = "OneSampleMR")
```

OneSampleMR R package



ivonesamplemr Stata package

- Repository https://github.com/remlapmot/ivonesamplemr
- Install with

```
net install github, from("https://haghish.github.io/github/")
github install remlapmot/ivonesamplemr
```

- Command syntax follows `ivregress` syntax

```
ivmsmm outcome confounders (exposure = instruments), options
```

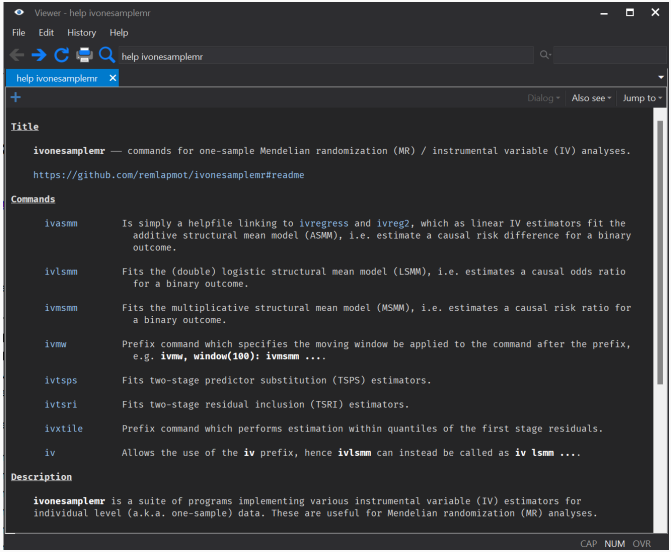
- All commands are named `ivsomething`
- Logistic SMM; `ivlsmm`

ivonesamplemr Stata package

- Moving (sliding/rolling) window of rank ordered first stage residuals (Burgess, Davies, et al. 2014); `ivmw:` prefix command
- Quantiles of first stage residuals (Burgess, Davies, et al. 2014); `ivxtile:` prefix command
- Package helpfile

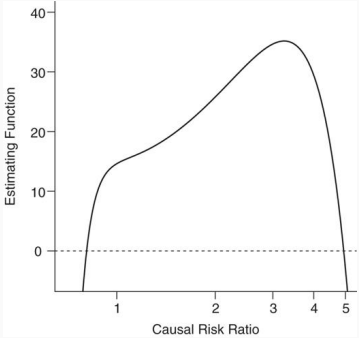
```
help ivonesamplemr
```

ivonesamplemr Stata package



Common pitfalls

- Local minima – even though GMM reports model has converged (Burgess, Granell, et al. 2014)



Common pitfalls

- Extreme estimates, e.g., estimated causal odds ratio of 10
- Very large sample sizes – hanging/non-convergence (write a Julia package??)

Discussion

- R and Stata packages for one-sample (a.k.a. individual level data) MR analyses
- Binary outcome IV estimators (SMMs/TSPS/TSRI)
- Some nonlinear estimators
- Example of use: Madley-Dowd et al. preprint
- Alternative: split sample and use two-sample methods (Burgess et al. 2016)
- **OneSampleMR** was included in the R Views November 2021 “Top 40” New CRAN Packages
- TODO - what would be useful to add?
    - **nlmr** in Stata
    - Option in TSPS/TSRI fns to automate estimation in case-control studies (i.e., first stage fitted only in controls)

References

Burgess, S., N. M. Davies, and S. G. Thompson. 2014. “Instrumental variable analysis with a nonlinear exposure–outcome relationship.” *Epidemiology* 25 (6): 877–885. https://doi.org/10.1097/EDE.0000000000000161.

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Sanderson, E., and F. Windmeijer. 2016. “A weak instrument F-test in linear IV models with multiple endogenous variables.” *Journal of Econometrics* 190 (2): 212–221. https://doi.org/10.1016/j.jeconom.2015.06.004.

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Terza, J. V., A. Basu, and P. J. Rathouz. 2008. “Two-stage residual inclusion estimation: Addressing endogeneity in health econometric modeling.” *Journal of Health Economics* 27 (3): 531–543. https://doi.org/10.1016/j.jhealeco.2007.09.009.