

Estimation using structural mean models with multiple instruments

Tom Palmer¹ Paul Clarke² Frank Windmeijer^{2,3,4}

1. MRC CAiTE Centre, School of Social and Community Medicine, University of Bristol, UK

2. CMPO, University of Bristol, UK

3. Department of Economics, University of Bristol, UK

4. CEMMAP/IFS, London, UK

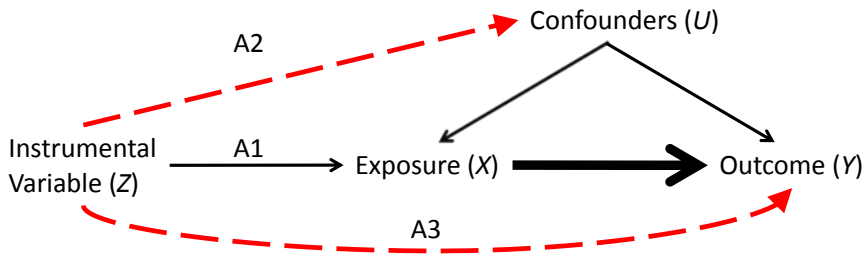
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Outline

- ▶ Introduction to Mendelian randomization example
- ▶ Potential outcomes and causal parameters
- ▶ Multiplicative structural mean model
 - ▶ Identification, G-estimation
 - ▶ GMM & Hansen over-id test
 - ▶ Implementation in Stata & R
 - ▶ Example estimates
 - ▶ Alternative parameterisation
 - ▶ Multiple instruments
 - ▶ Local risk ratios
- ▶ (double) Logistic SMM
 - ▶ Joint estimation of association & causal models
- ▶ Including covariates
- ▶ Summary

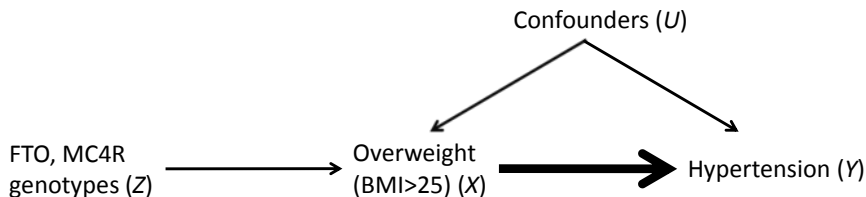
Introduction to Mendelian randomization example

- Mendelian randomization:
use of genotypes **robustly** associated with exposures (from replicated genome-wide association studies, $P < 5 \times 10^{-8}$) as instrumental variables (Davey Smith & Ebrahim, 2003)



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Copenhagen General Population study ($N=55,523$)

Example descriptive statistics 1

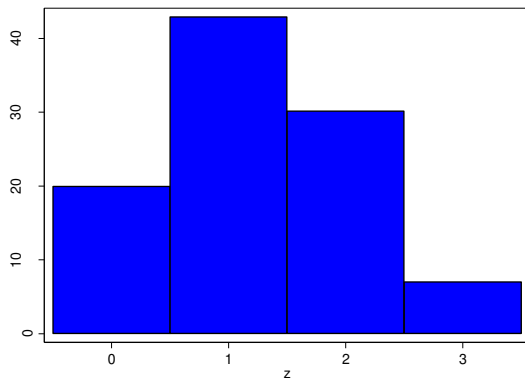
	No Hypertension	Hypertension	Total
Not Overweight	10,066 42%	13,909 58%	23,975
Overweight	6,906 22%	24,642 78%	31,548
Total	16,972 31%	38,551 69%	55,523 $\chi^2 P < 0.001$

Risk ratio for hypertension 1.35 (1.32, 1.37)

Example descriptive statistics 2

Distribution of instrument (Z)

<i>FTO</i>	<i>MC4R</i>	Z	Freq
0	0	0	0.20
0	1	1	0.15
1	0	1	0.27
1	1	2	0.21
2	0	2	0.09
2	1	3	0.07



Multiplicative SMM

- Notation: X exposure/treatment, Y outcome, Z instrument, $Y\{X = 0\}$ exposure/treatment free potential outcome

Robins, Rotnitzky, & Scharfstein, 1999; Hernán & Robins, 2006

$$\log(E[Y|X, Z]) - \log(E[Y\{0\}|X, Z]) = (\psi + \psi_1 Z)X$$

Identification NEM by Z : $\psi_1 = 0$

$$= \psi X$$

$$\frac{E[Y|X, Z]}{E[Y\{0\}|X, Z]} = \exp(\psi X)$$

ψ : log causal risk ratio

Rearrange: $Y\{0\} = Y \exp(-\psi X)$

Under the instrumental variable assumptions (Robins, 1989):

$$Y_{\{0\}} \perp\!\!\!\perp Z$$

$$Y_{\exp(-\psi X)} \perp\!\!\!\perp Z$$

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trick: $Y \exp(-\psi X) - Y\{0\} \perp\!\!\!\perp Z$

MSMM G-estimation

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$$Y\{0\} \perp\!\!\!\perp Z$$

$$Y \exp(-\psi X) \perp\!\!\!\perp Z$$

trick: $Y \exp(-\psi X) - Y\{0\} \perp\!\!\!\perp Z$

Moment conditions

$$Z=0,1$$

$$E[(Y \exp(-\psi X) - Y\{0\})1] = 0$$

$$E[(Y \exp(-\psi X) - Y\{0\})Z_1] = 0$$

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trick: $Y \exp(-\psi X) - Y\{0\} \perp\!\!\!\perp Z$

Moment conditions

$Z=0,1,2,3$

Over-identified

$$E[(Y \exp(-\psi X) - Y\{0\})1] = 0$$

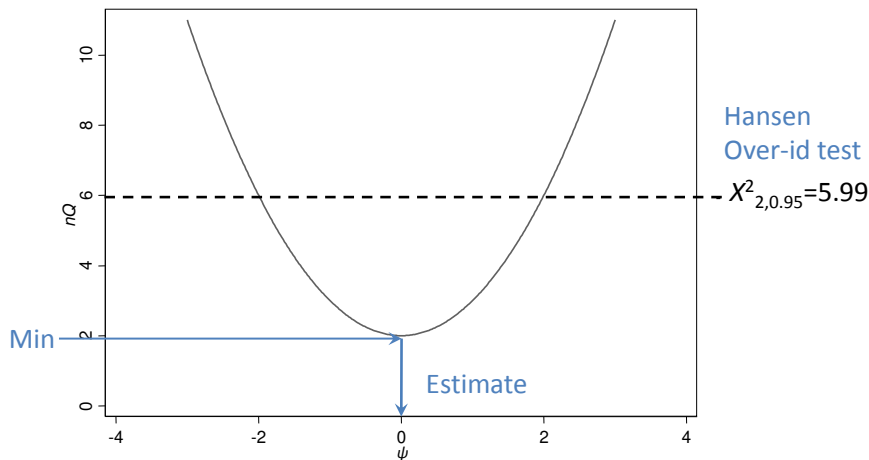
$$E[(Y \exp(-\psi X) - Y\{0\})Z_1] = 0$$

$$E[(Y \exp(-\psi X) - Y\{0\})Z_2] = 0$$

$$E[(Y \exp(-\psi X) - Y\{0\})Z_3] = 0$$

What is GMM?

Minimises quadratic form: $Q = m'W^{-1}m$



Two-step GMM

1. Minimize quadratic form: $m'W^{-1}m$
2. Estimate \widehat{W}_1 , minimize quadratic form starting from \widehat{W}_1
 - ▶ Two-step GMM gives efficient SEs (Chamberlain, 1987)
 - ▶ Stata Hansen test command (`estat overid`) requires this

Implementation in Stata & R

Stata: `gmm` command

```
gmm (y*exp(-1*x*{psi}) - {ey0}), instruments(z1 z2 z3)
```

Implementation in Stata & R

Stata: gmm command

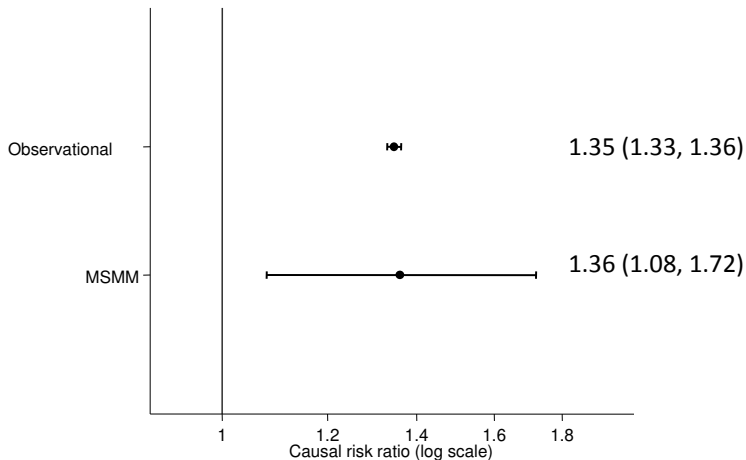
```
gmm (y*exp(-1*x*{psi}) - {ey0}), instruments(z1 z2 z3)
```

R: gmm package (Chaussé, 2010)

```
library(gmm)
msmmMoments <- function(theta,x){
  # extract variables from x
  Y <- x[,1]; X <- x[,2]; Z1 <- x[,3]; Z2 <- x[,4]; Z3 <- x[,5]
  # moments
  m1 <- (Y*exp(- X*theta[2]) - theta[1])
  m2 <- (Y*exp(- X*theta[2]) - theta[1])*Z1
  m3 <- (Y*exp(- X*theta[2]) - theta[1])*Z2
  m4 <- (Y*exp(- X*theta[2]) - theta[1])*Z3
  return(cbind(m1,m2,m3,m4))
}
fit <- gmm(msmmMoments, data, t0=c(0,0))
```

Specifying analytic first derivatives improves runtimes

MSMM example estimates



MSMM: Hansen over-identification test $P = 0.31$

$E[Y\{0\}] = 0.58 (0.50, 0.65)$

MSMM alternative parameterisation

$$Y \exp(-X\psi - \log(Y\{0\})) - 1 = 0$$

- ▶ Same as moments used by Mullahy, 1997; Nichols, 2007
- ▶ First parameterisation more numerically stable (Drukker, 2010)
- ▶ Also see Windmeijer & Santos Silva, 1997; Windmeijer, 2002, 2006; Clarke & Windmeijer, 2010
- ▶ Use X as instrument for itself = Gamma regression (log link)

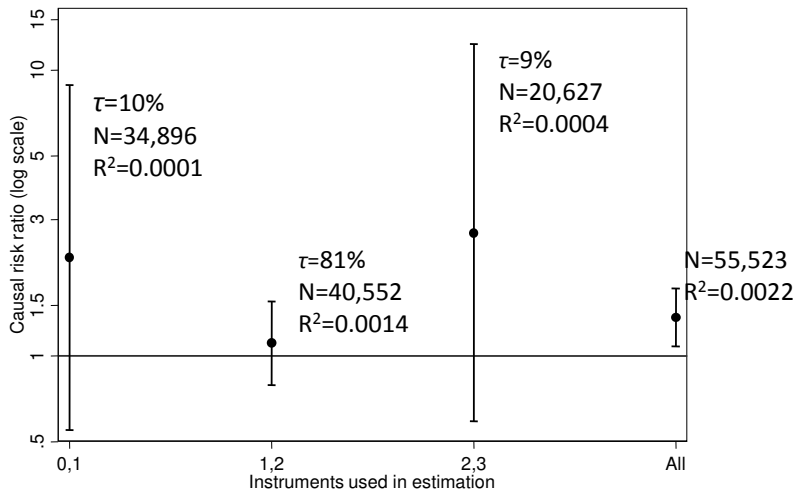
How does GMM deal with multiple instruments?

GMM estimator solution to:

$$\frac{\partial m'(\psi)}{\partial \psi} W^{-1} m(\psi) = 0$$

- ▶ MSMM: instruments combined into linear projection of $YX \exp(-X\psi)$ on $Z = (1, Z_1, Z_2)'$ (Bowden & Vansteelandt, 2010)
- ▶ LSMM: GMM also equivalent to their optimal instruments approach

Local risk ratios in example



$$\text{Check: } (0.10 \times 2.21) + (0.81 \times 1.11) + (0.09 \times 2.69) = 1.36$$

(double) Logistic SMM

$$\text{logit}(p) = \log(p/(1 - p)), \text{expit}(x) = e^x/(1 + e^x)$$

Goetghebeur, 2010

$$\text{logit}(E[Y|X, Z]) - \text{logit}(E[Y\{0\}|X, Z]) = \psi X$$

ψ : log causal odds ratio

$$\text{Rearrange for } Y\{0\} = \text{expit}(\text{logit}(Y) - \psi X)$$

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- ▶ Can't be estimated in a single step (Robins et al., 1999)
- ▶ First stage association model (Vansteelandt & Goetghebeur, 2003):
 - (i) logistic regression of Y on X & Z & interactions
 - (ii) predict Y , estimate LSMM using predicted Y

(double) Logistic SMM moment conditions

Association model moment conditions

Logistic regression using GMM

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))1] = 0$$

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))X] = 0$$

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))Z] = 0$$

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))XZ] = 0$$

(double) Logistic SMM moment conditions

Association model moment conditions

Logistic regression using GMM

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))1] = 0$$

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$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))XZ] = 0$$

Causal model moment conditions

$$E[(\text{expit}(\text{logit}(\hat{p}) - \psi X) - Y\{0\})1] = 0$$

$$E[(\text{expit}(\text{logit}(\hat{p}) - \psi X) - Y\{0\})Z] = 0$$

Problem: SEs incorrect - need association model uncertainty

LSMM joint estimation

Joint estimation = correct SEs (Gourieroux, Monfort, & Renault, 1996)

Vansteelandt & Goetghebeur, 2003; Bowden & Vansteelandt, 2010

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))1] = 0$$

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))X] = 0$$

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))Z] = 0$$

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))XZ] = 0$$

$$E[(\text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ) - \psi X) - Y\{0\})1] = 0$$

$$E[(\text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ) - \psi X) - Y\{0\})Z] = 0$$

Stata `gmm` command - allows multiple equations - still 1 line of code

Example: causal model SEs $\times 10$

Including covariates

TSLS: include covariates in both stages

GMM: use covariates as instruments for themselves

Including (pre-exposure) covariates in MSMM

$$Y\{0\} \perp\!\!\!\perp Z|C$$

$$\log(E[Y|X, Z, C]) - \log(E[Y\{0\}|X, Z, C]) = \psi X + \psi_c C$$

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TSLS: include covariates in both stages

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Including (pre-exposure) covariates in MSMM

$$Y\{0\} \perp\!\!\!\perp Z|C$$

$$\log(E[Y|X, Z, C]) - \log(E[Y\{0\}|X, Z, C]) = \psi X + \psi_c C$$

Example estimates

Covariates	RR (95%CI)	Over-id P
	1.36 (1.08, 1.72)	0.31
sex	1.36 (1.07, 1.72)	0.39
sex, age	1.35 (1.07, 1.71)	0.58
sex, age, chol	1.33 (1.05, 1.68)	0.49

Summary

- ▶ Structural Mean Models estimated using IVs by G-estimation

$$Y\{0\} \perp\!\!\!\perp Z$$

- ▶ GMM estimation approach:

- ▶ Estimate $Y\{0\}$
- ▶ Hansen over-id test of joint validity of instruments
- ▶ Optimal combination of multiple instruments
- ▶ LSMM: joint estimation
- ▶ Implementation in Stata and R (inc. covariates)

- ▶ www.bris.ac.uk/cmpo/publications/papers/2011/wp266.pdf

- ▶ SMMs subtly different to additive residual IV GMM

- ▶ RR: $Y - \exp(\psi X) \perp\!\!\!\perp Z$
- ▶ OR: $Y - \text{expit}(\psi X) \perp\!\!\!\perp Z$

(Cameron & Trivedi, 2009; Johnston, Gustafson, Levy, & Grootendorst, 2008; Foster, 1997; Rassen, Schneeweiss, Glynn, Mittleman, & Brookhart, 2009)

- ▶ Review of some of the methods (Palmer et al., 2011)

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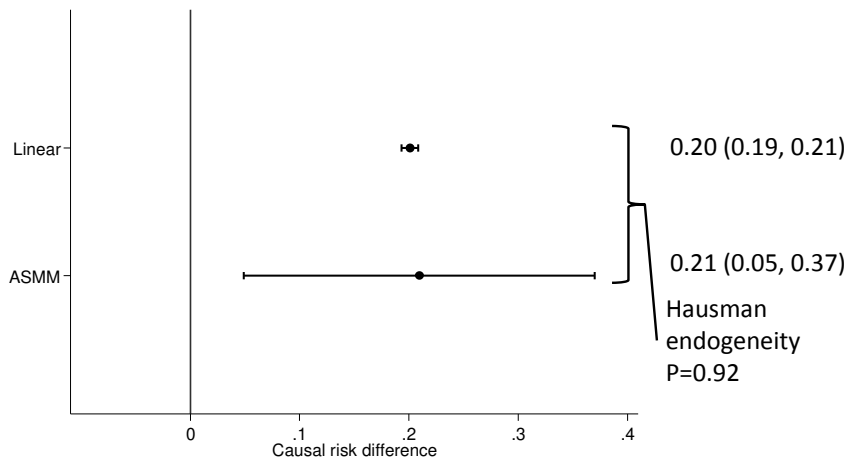
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Comparison example estimates

	RR (95% CI)	P over-id
MSMM	1.36 (1.08, 1.72)	0.31
$Y - \exp(\psi X) \perp\!\!\!\perp Z$	1.36 (1.07, 1.75)	0.30
Control function	1.36 (1.08, 1.71)	
	OR (95% CI)	P over-id
LSMM two-stage	1.88 (1.75, 2.02)	
LSMM joint	2.87 (1.25, 6.55)	0.29
$Y - \text{expit}(\psi X) \perp\!\!\!\perp Z$	2.69 (1.23, 5.90)	0.30
Control function	2.69 (1.21, 5.97)	

ASMM example estimates



MSMM: Hansen over-identification test $P = 0.30$

$E[Y\{0\}] = 0.58 (0.48, 0.67)$