Estimation of structural mean models with multiple instruments

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Aim

Combine two strands of literature:

- Structural mean models [Biostatistics]
- Generalised Method of Moments estimation [Econometrics]

Rationale:

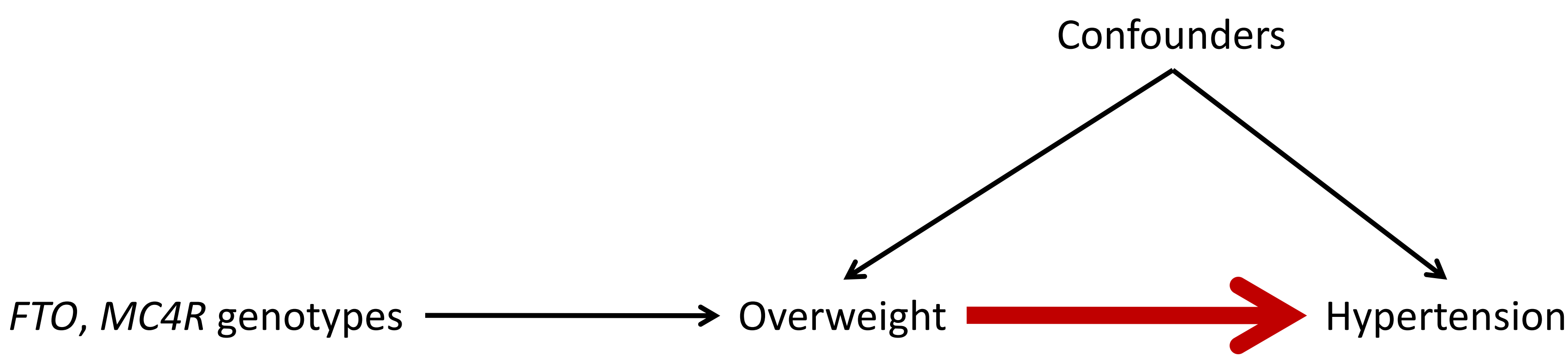
- Concepts such as G-estimation intimidating
- Estimation with multiple instruments
- Straightforward implementation in Stata and R

Outline

- Introduction to example
- Causal parameters & potential outcomes
- Multiplicative SMM
  - What is GMM?
  - Over-identification test
  - Combining multiple instruments
  - Two step GMM
  - Implementation in Stata
  - Local risk ratios
  - MSMM and MGMM
- Logistic SMM
  - Joint estimation
- Summary

Introduction to example

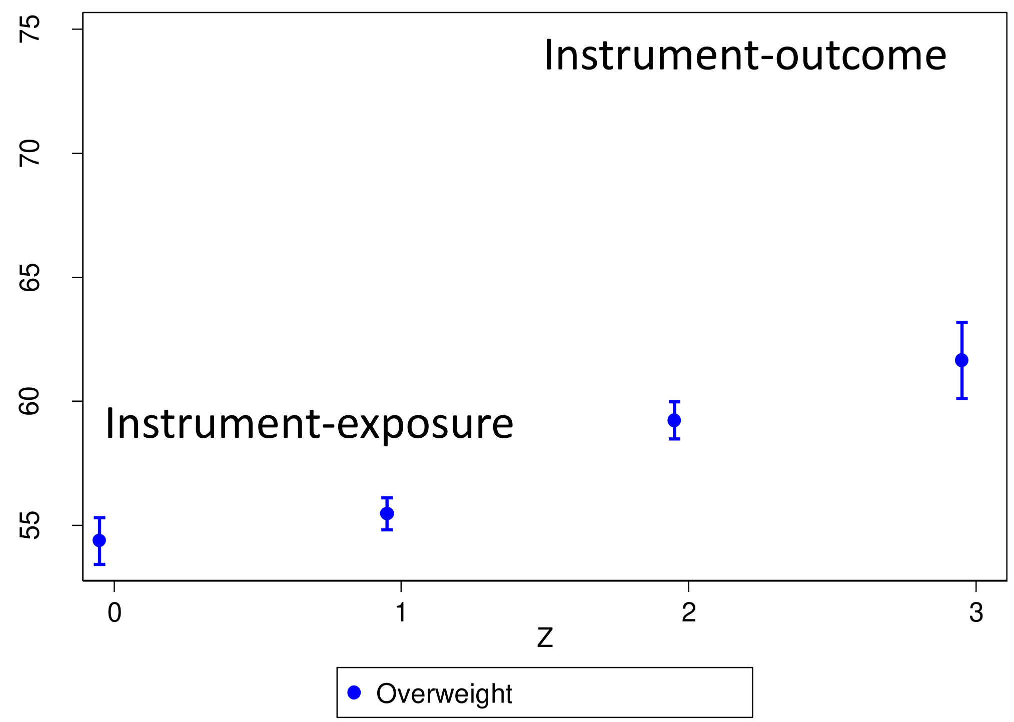
- Copenhagen General Population study
  - N=55,523
- Instruments:
  - *FTO* (rs9939609) chr16, *MC4R* (rs17782313) chr18 genotypes
  - Associated with obesity in GWAS (0.4, 0.2 BMI units). Frayling 2007, Loos 2008
- Exposure:
  - Overweight (body mass index BMI [weight/height^2] >25)
- Outcome:
  - Hypertension (high blood pressure [SBP>140mmHg, or DBP>90mmHg, or taking anti-hypertensives])



	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 χ^2 P<0.001

Risk ratio 1.35 (1.32, 1.37)

FTO	*MC4R*	*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



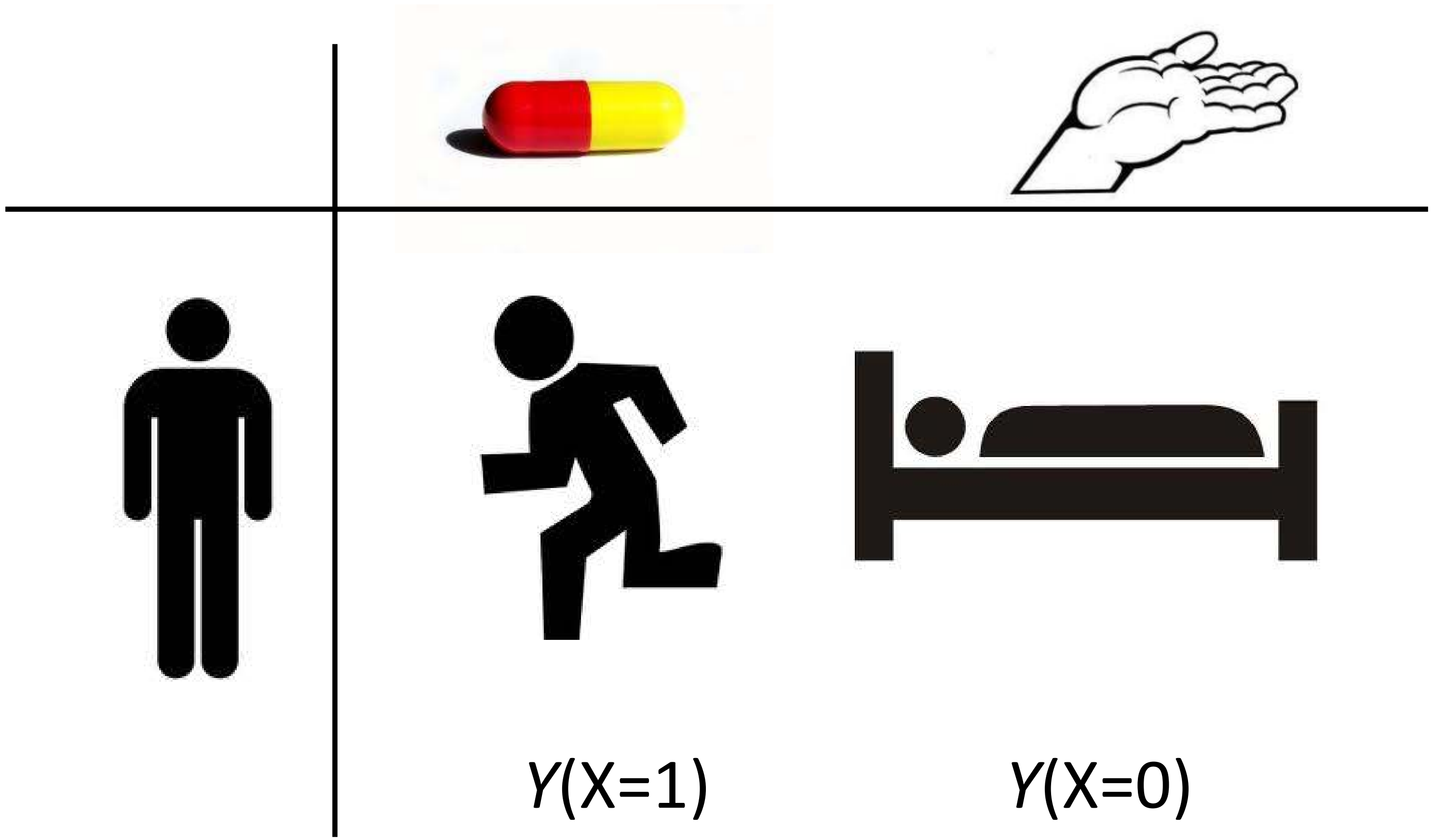
P=0.007

P<0.001
R^2=0.002

Causal parameters and potential outcomes

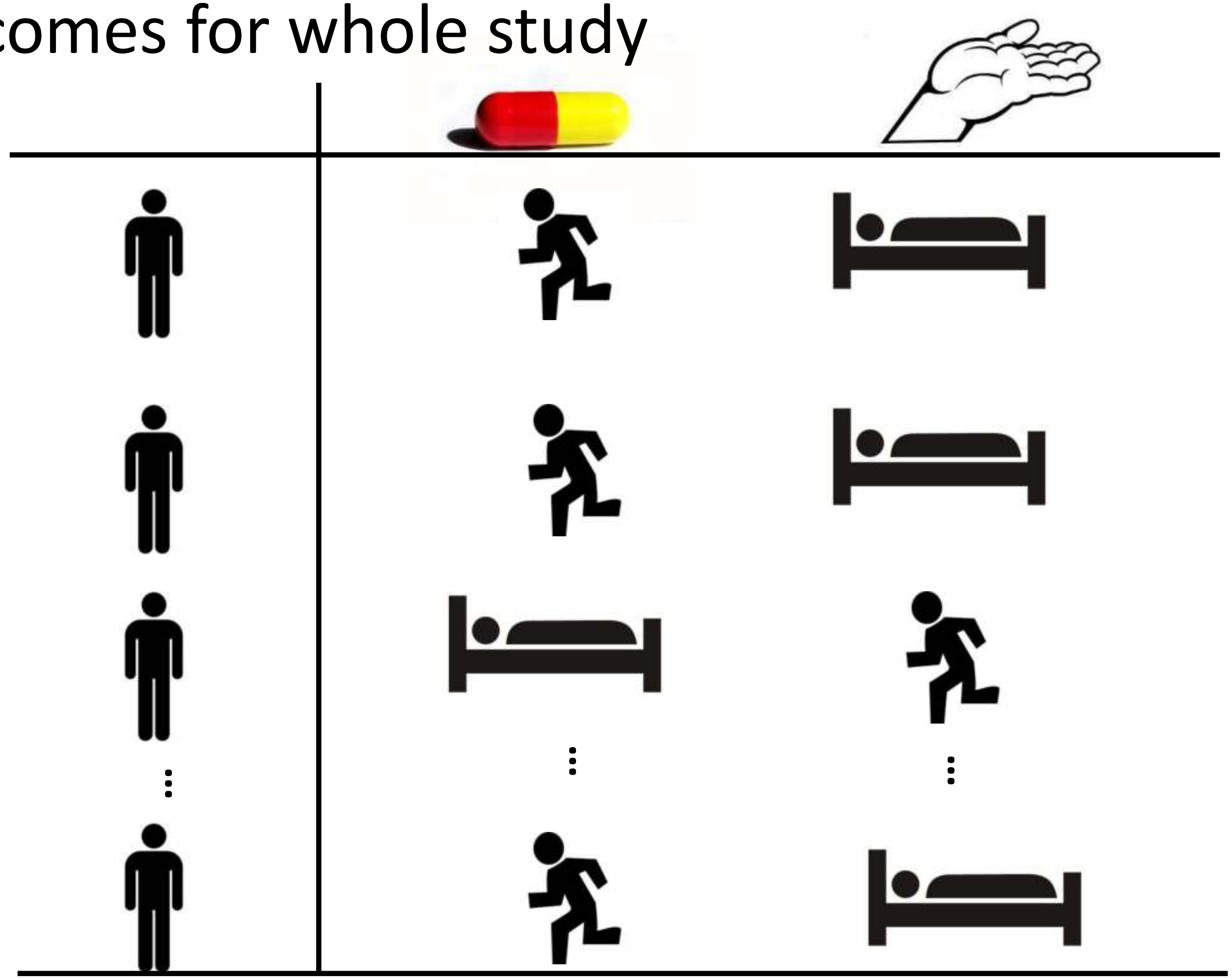
- SMMs defined in terms of potential outcomes Hernan & Robins 2006
- X: exposure/treatment, Y: outcome, Z: IV
- $Y(X=1)$ outcome subject would experience if they were given treatment/exposure under intervention

Potential outcomes for an individual



Potential outcomes for whole study

Recent discussion of G-estimation: Snowden et al., AJE, 2011



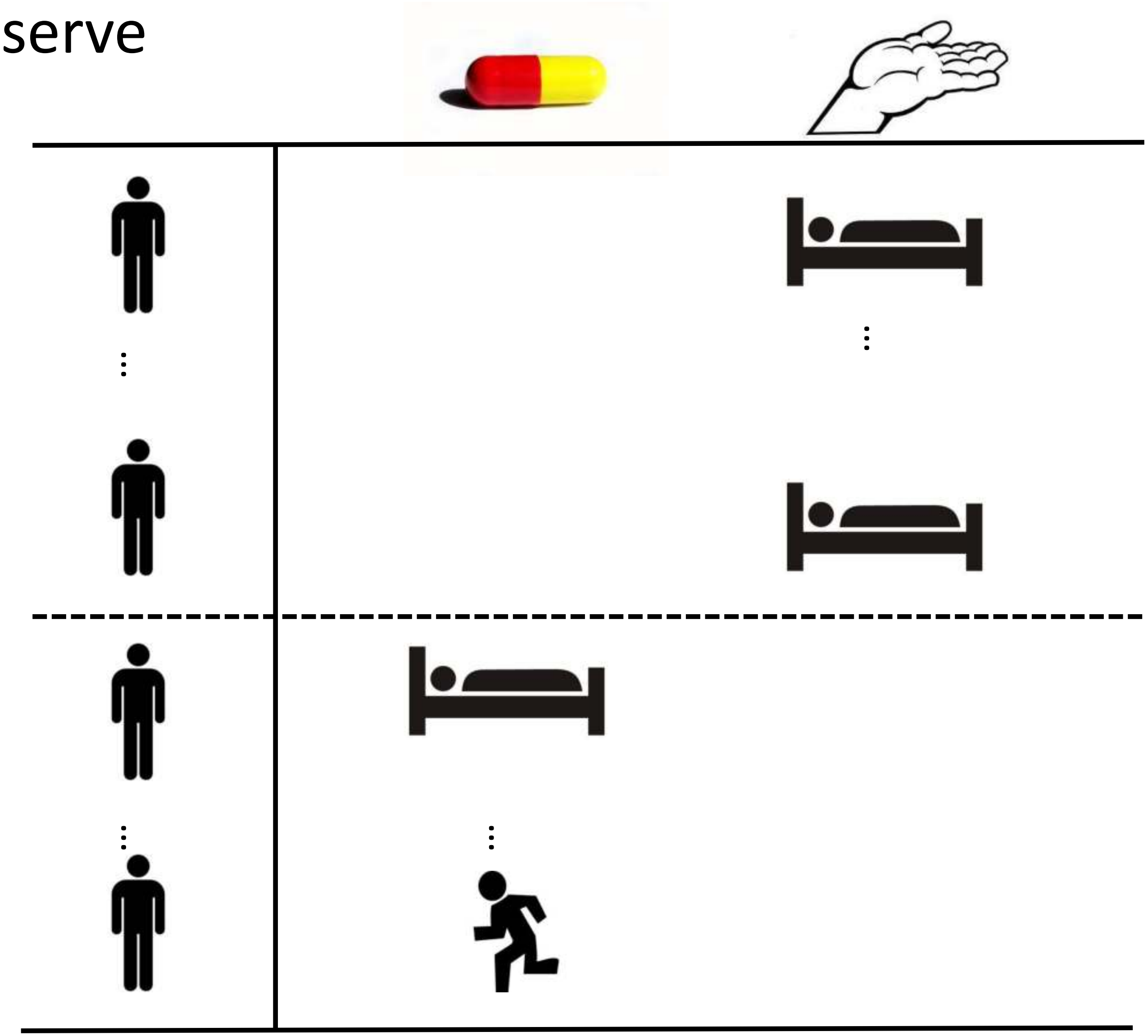
Average treatment effect = $E[Y(X=1)] - E[Y(X=0)]$

binary outcome: causal risk difference

Causal risk ratio = $E[Y(X=1)] \;/\; E[Y(X=0)]$

Causal odds ratio = $\text{odds}[Y(X=1)] \;/\; \text{odds}[Y(X=0)]$

What we observe



$$E[Y(1)|X=1] \quad - \quad E[Y(0)|X=1]$$

SMMs identify effect of treatment of treated

Multiplicative SMM

Z is instrumental variable X is exposure Y is outcome

Y, X and Z are binary

$$\frac{E[Y|X,Z]}{E[Y(0)|X,Z]} = \exp\{(\theta_0 + \theta_1 Z) X\}$$

$Y(0)$ is the exposure- or treatment-free potential outcome

…so far … model non-identified: 2 parameters, 1 equation

No effect modification by Z (NEM): $\theta_1 = 0$

θ_0: log causal risk ratio

Conditional mean independence (CMI) from IV assumptions:

$$E[Y(0)|Z=1] = E[Y(0)|Z=0] = E[Y(0)]$$

Moment conditions

$$\alpha_0 = E\left[Y(0)\right]$$

Multi-valued instrument/multiple instruments

$$\begin{aligned}
E\left[\{Y\exp(-X\theta_0)-\alpha_0\}\,|Z=2\right] &= 0\\
E\left[\{Y\exp(-X\theta_0)-\alpha_0\}\,|Z=1\right] &= 0\\
E\left[\{Y\exp(-X\theta_0)-\alpha_0\}\,|Z=0\right] &= 0
\end{aligned}$$

Over-identified:

3 moment conditions,

2 parameters …

… need GMM

Exactly identified:

2 moment conditions,

2 parameters

E[]=0 since *Z* independent of *Y* given *X*: exclusion restriction

If no E[*Y*(0)] – need to centre the instruments;

Vansteelandt & Goetghebeur, JRSS B, 2003

What is GMM?

Designed to estimate over-identified models

GMM minimises quadratic form wrt parameters to be estimated

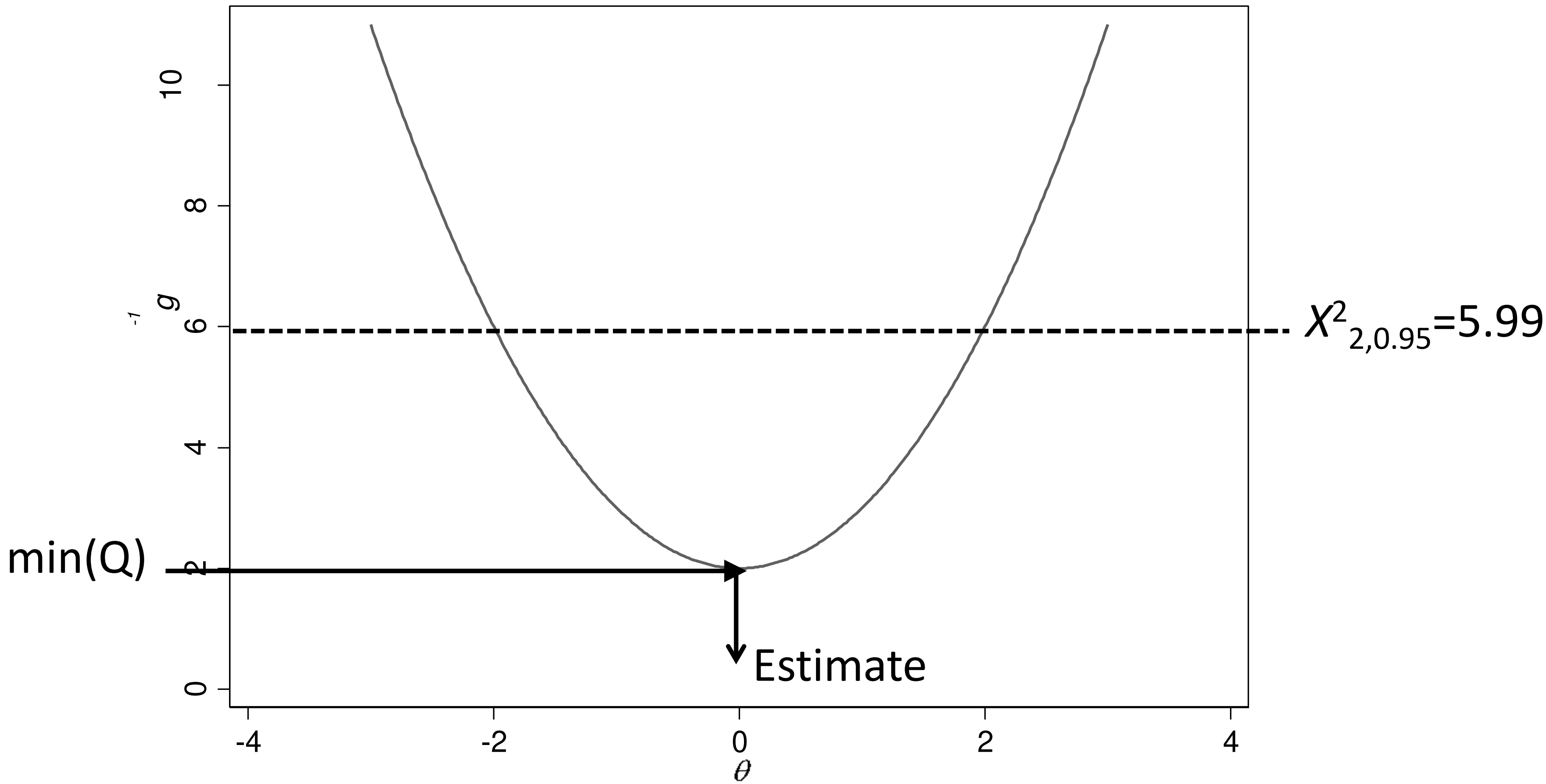
$$\widehat{\delta} = \arg\min_{\delta} \left(\frac{1}{n} \sum_{i=1}^{n} g_i(\delta) \right)' W_n^{-1} \left(\frac{1}{n} \sum_{i=1}^{n} g_i(\delta) \right)$$

$$\begin{pmatrix} \{Y \exp(-X\theta_0) - \alpha_0\}\, Z_0 & \{Y \exp(-X\theta_0) - \alpha_0\}\, Z_1 & \{Y \exp(-X\theta_0) - \alpha_0\}\, Z_2 \end{pmatrix} W_n^{-1} \begin{pmatrix} \{Y \exp(-X\theta_0) - \alpha_0\}\, Z_0 \\ \{Y \exp(-X\theta_0) - \alpha_0\}\, Z_1 \\ \{Y \exp(-X\theta_0) - \alpha_0\}\, Z_2 \end{pmatrix}$$

W^{-1} affects efficiency not consistency: one step/two step GMM

Over-identification test

Profiling over quadratic form (Q) for a single parameter



- Single instrument – exactly identified: min(Q)=0
- Multiple instruments – over identified: min(Q) should be close enough to 0 as given by Hansen over-id test statistic, ***Q ~ X^2_{m-p}*** when moments valid
- Not rejecting the over-id test ***doesn't*** mean the IV assumptions hold

Combining multiple instruments

How does GMM treat multiple instruments?

The instruments get combined into the projection $S\left(S'S\right)^{-1}S'D$, i.e. a constant 1 and the linear projection of $\frac{y_i}{\exp(x_i\theta)}x_i$ on s_i, the projection as proposed by Bowden and Vansteelandt (2010).

GMM satisfies $$D'S\left(S'S\right)^{-1}S'v = 0$$

$$\begin{aligned} D &= \{d_i'\};\ S = \{s_i'\};\ v = \{v_i\} \\ d_i &= \begin{pmatrix} 1 \\ \frac{y_i}{\exp(x_i\theta)}x_i \end{pmatrix};\ v_i = \frac{y_i}{\exp\left(x_i\theta\right)} - \alpha \end{aligned}$$

Two step GMM

Step 1: Estimate parameters and *W*
Step 2: repeat optimization starting from step 1 estimate of *W*

$$\widehat{\delta}_2 = \arg\min_{\delta} \left(\frac{1}{n} \sum_{i=1}^{n} g_i(\delta) \right)' W_n^{-1}\left(\widehat{\delta}_1\right) \left(\frac{1}{n} \sum_{i=1}^{n} g_i(\delta) \right)$$

Two-step GMM is efficient because it's Vcov matrix is the *smallest* (Chamberlain 1987)

One step: $\sqrt{n}\left(\widehat{\delta}_1 - \delta_0\right) \xrightarrow{d} N\left(0, \left(C_0' W C_0\right)^{-1} C_0 W \Omega_0 W C_0 \left(C_0' W C_0\right)^{-1}\right)$

Two step: $\sqrt{n}\left(\widehat{\delta}_2 - \delta_0\right) \xrightarrow{d} N\left(0, \left(C_0' \Omega_0 C_0\right)^{-1}\right)$

MSMM implementation in Stata

`gmm` command (Stata version 11)

Vector of 1's automatically included

Moment condition

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

`lincom [theta]:_cons, eform` Causal risk ratio

`estat overid` Over-identification test

MSMM Stata output 1

```
.
. gmm (hyp*exp(-overw*{theta}) - {ey0}), instruments(Iz1 Iz2 Iz3)

Step 1
Iteration 0:   GMM criterion Q(b) =  .48211942
Iteration 1:   GMM criterion Q(b) =  .00021372
Iteration 2:   GMM criterion Q(b) =  6.662e-06
Iteration 3:   GMM criterion Q(b) =  6.572e-06

Step 2
Iteration 0:   GMM criterion Q(b) =  .00004253
Iteration 1:   GMM criterion Q(b) =  .00004253

GMM estimation

Number of parameters =   2
Number of moments    =   4
Initial weight matrix: Unadjusted                 Number of obs   =    55523
GMM weight matrix:     Robust

------------------------------------------------------------------------------
             |               Robust
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      /theta |   .3104495   .1192332     2.60   0.009     .0767568    .5441423
        /ey0 |   .5758842   .0388716    14.82   0.000     .4996973    .6520711
------------------------------------------------------------------------------
Instruments for equation 1: Iz1 Iz2 Iz3 _cons
```

Two step GMM

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

MSMM Stata output 2

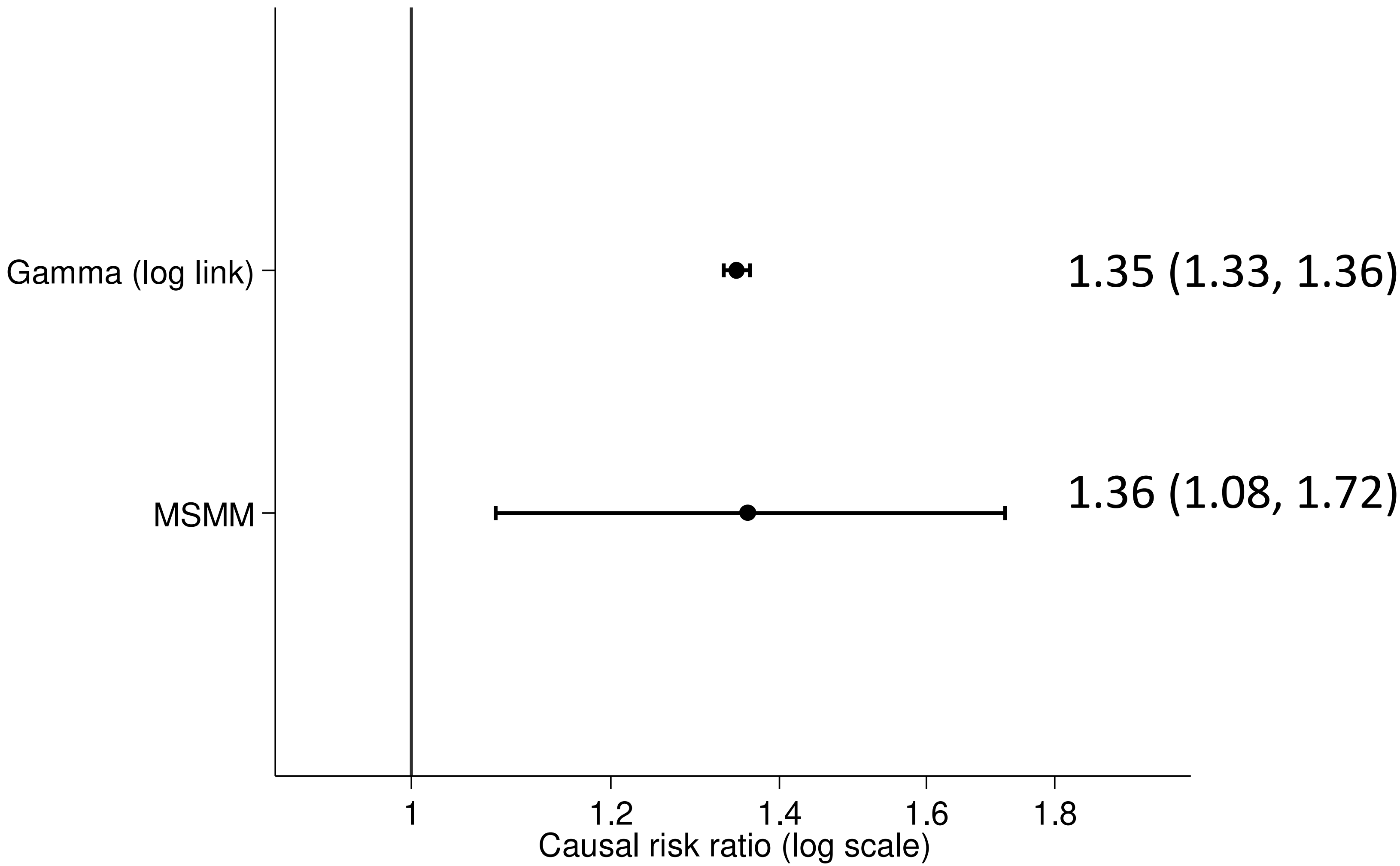
```
. lincom [theta]:_cons, eform

 ( 1)  [theta]_cons = 0
```

Causal risk ratio = 1.36 (1.08, 1.72)

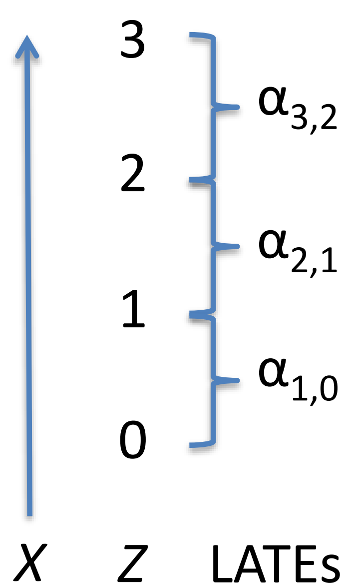
	exp(b)	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	1.364038	.1626386	2.60	0.009	1.079779	1.72313

Observational and IV estimate in example



Local risk ratios

- Identification depends on NEM … what happens if it doesn't hold?
- Alternative assumption of monotonicity: $X(Z_k) \geq X(Z_{k-1})$
- Local Average Treatment Effect (LATE): effect among those whose exposures are changed (upwardly) by changing (counterfactually) the IV from Z_{k-1} to Z_k



Linear IV: Imbens & Angrist 1994

$\alpha_{All} = \lambda_1\alpha_{1,0} + \lambda_2\alpha_{2,1} + \lambda_3\alpha_{3,2}$

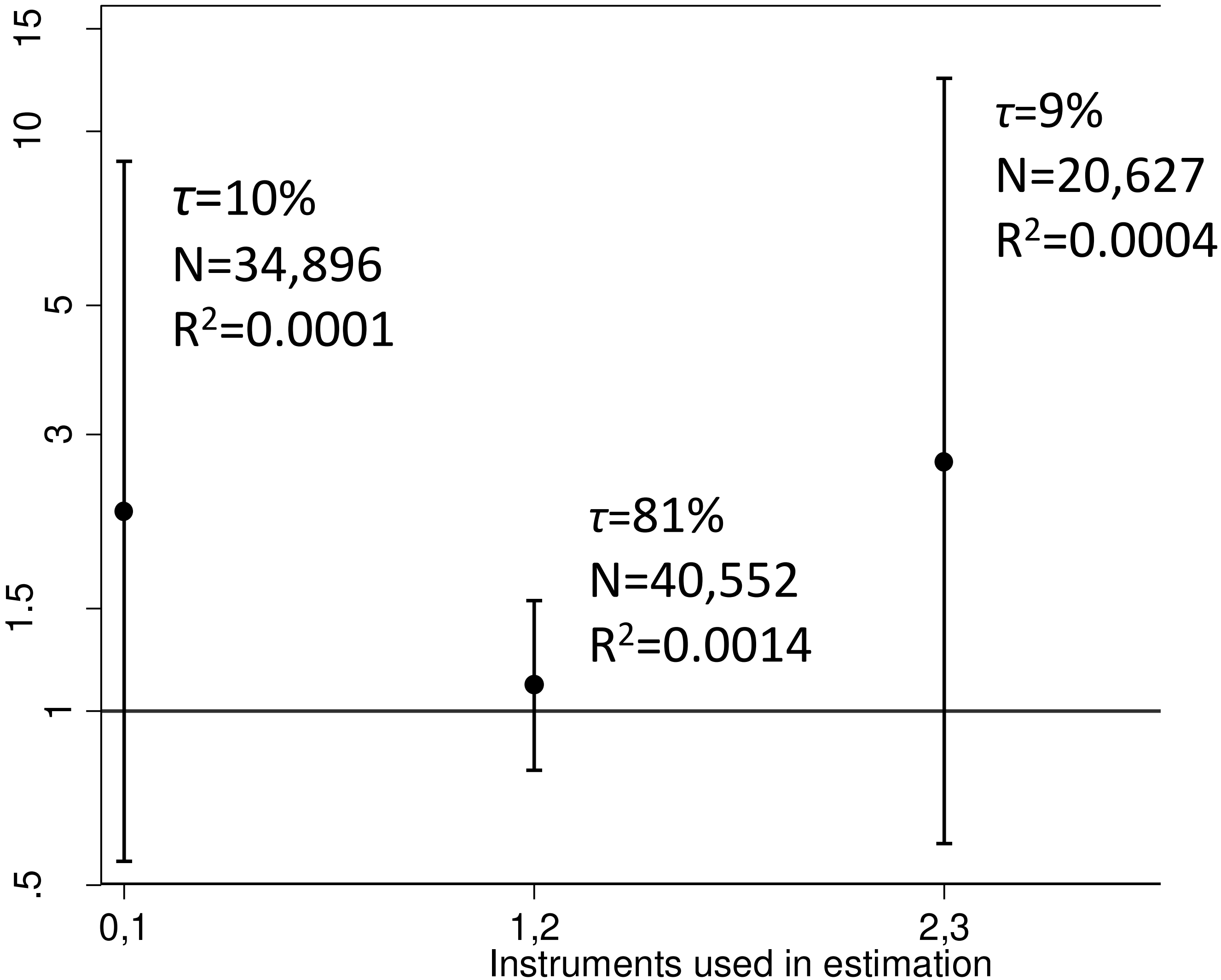
MSMM: We show a similar result holds for MSMM (*X, Y*: binary)

$$e_z^\theta = \sum_{k=1}^{K} \tau_k e_{k,k-1}^\theta$$

…weighted average of risk ratios

… rather than log risk ratios!

Local risk ratios in the example



N=55,523

R^2=0.0022

Check: (0.10 × 2.21) + (0.81 × 1.11) + (0.09 × 2.6

MSMM and MGMM

MGMM: Mullahy 1997 – exponential mean model with multiplicative residual

Additive residual: $Y = \exp(X\theta) + U$

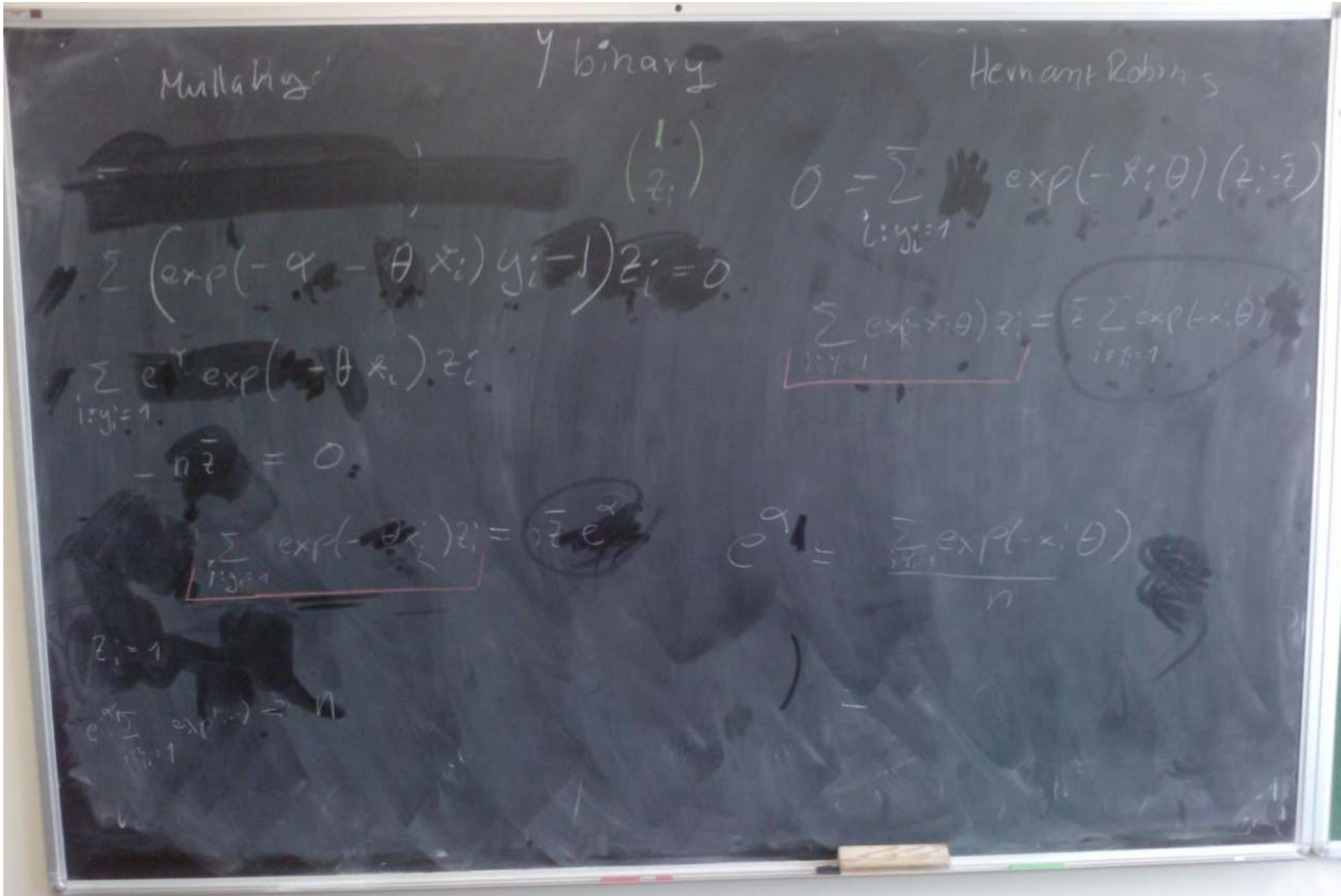
$E[Z\{Y - \exp(X\vartheta)\}] = 0$ Poisson regression

Multiplicative residual: $Y = \exp(X\theta + U)$

$$E\left[\frac{Y - \exp\left(\alpha_0^* + X\theta_0\right)}{\exp\left(\alpha_0^* + X\theta_0\right)} | S\right] = 0 \qquad S = (1, Z_1, Z_2)'$$

Discussed by Windmeijer 1997, 2002, 2006

Proof MSMM = MGMM



Clarke & Windmeijer 2010 ; Didelez, et al. 2010; Palmer et al., AJE, 2011
MGMM (one step GMM): `ivpois` for Stata (Nichols 2007)

Logistic SMM

- Implement joint estimation approach within GMM framework
- Vansteelandt & Goetghebeur (2003), Vansteelandt & Bowden (2010)

Two-stage estimation	Joint estimation
Stage 1 Association model: predict *Y* given *X*, *Z* **Stage 2** Causal model (MSMM/ASMM causal model only)	Estimate association model and causal model together
Need to correct SEs somehow	SEs automatically correct Gourieux 1996, Tan 2010

LSMM implementation in Stata

Two step estimation

```
logit y x z1 z2 xz1 xz2
matrix from = e(b)
predict xblog, xb
```

Association model: predict *Y* given *X*, *Z*

Causal model – incorrect SEs!

```
gmm (invlogit(xblog - x*{psi}) - {ey0}), instruments(z1 z2)
matrix from = (from,e(b))
```

Joint estimation – correct SEs!

```
gmm (y - invlogit({logit:x z1 z2 xz1 xz2} + {logitconst}))
(invlogit({logit:} + {logitconst} - x*{psi}) - {ey0}), ///
instruments(1:x z1 z2 xz1 xz2) instruments(2:z1 z2) ///
winitial(unadjusted, independent) from(from)

lincom [psi]_cons, eform // causal odds ratio
estat overid
```

LSMM Stata output

```
. logit hyp overw Iz1 Iz2 Iz3 Iz1Xoverw Iz2Xoverw Iz3Xoverw

Iteration 0:   log likelihood =  -34179.76
Iteration 1:   log likelihood = -32895.818
Iteration 2:   log likelihood = -32885.846
Iteration 3:   log likelihood = -32885.845

Logistic regression                               Number of obs   =      55523
                                                  LR chi2(7)      =    2587.83
                                                  Prob > chi2     =     0.0000
Log likelihood = -32885.845                       Pseudo R2       =     0.0379
```

Association model

hyp	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
overw	.9034696	.0419769	21.52	0.000	.8211964	.9857428
Iz1	.0023852	.0346439	0.07	0.945	-.0655155	.070286
Iz2	-.031613	.0375747	-0.84	0.400	-.105258	.042032
Iz3	.0285799	.0598671	0.48	0.633	-.0887574	.1459173
Iz1Xoverw	.0500117	.0509504	0.98	0.326	-.0498493	.1498727
Iz2Xoverw	.06952	.0543206	1.28	0.201	-.0369465	.1759864
Iz3Xoverw	.041216	.0837708	0.49	0.623	-.1229717	.2054037
_cons	.3295621	.0285043	11.56	0.000	.2736947	.3854295

```
. matrix from = e(b)

. predict xblog, xb
```

predicted values of outcome (on logit scale here)

```
. gmm (invlogit(xblog - overw*{psi}) - {ey0}), instruments(Iz1 Iz2 Iz3)

Step 1
Iteration 0:   GMM criterion Q(b) =  .48211941
Iteration 1:   GMM criterion Q(b) =  .00078422
Iteration 2:   GMM criterion Q(b) =  .00001363
Iteration 3:   GMM criterion Q(b) =  .00001362

Step 2
Iteration 0:   GMM criterion Q(b) =   .1911576
Iteration 1:   GMM criterion Q(b) =  .16822374
Iteration 2:   GMM criterion Q(b) =  .13183731
Iteration 3:   GMM criterion Q(b) =  .13181315
Iteration 4:   GMM criterion Q(b) =  .13181311

GMM estimation

Number of parameters =   2
Number of moments    =   4
Initial weight matrix: Unadjusted                 Number of obs   =    55523
GMM weight matrix:     Robust

------------------------------------------------------------------------------
             |               Robust
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        /psi |   .6331413   .0362588    17.46   0.000     .5620754    .7042073
        /ey0 |   .6226167    .004652   133.84   0.000      .613499    .6317344
------------------------------------------------------------------------------
Instruments for equation 1: Iz1 Iz2 Iz3 _cons
```

Causal model

Incorrect SEs

```
. gmm (hyp - invlogit({logit:overw Iz1 Iz2 Iz3 Iz1Xoverw Iz2Xoverw Iz3Xoverw}
> + {logitconst})) ///
>         (invlogit({logit:} + {logitconst} - overw*{psi}) - {ey0}), ///
>         instruments(1:overw Iz1 Iz2 Iz3 Iz1Xoverw Iz2Xoverw Iz3Xoverw) ///
>         instruments(2:Iz1 Iz2 Iz3) ///
>         winitial(unadjusted,independent) from(from)
```

Joint estimation

```
Iteration 2:   GMM criterion Q(b) =  .00004429

GMM estimation

Number of parameters =  10
Number of moments    =  12
Initial weight matrix: Unadjusted                 Number of obs   =    55523
GMM weight matrix:     Robust
```

Corrected SEs: causal model SEs ×10

	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
/logit_overw	.9091545	.0418464	21.73	0.000	.8271371	.9911719
/logit_Iz1	-.0207159	.0279367	-0.74	0.458	-.0754708	.034039
/logit_Iz2	-.0339566	.0343049	-0.99	0.322	-.1011929	.0332796
/logit_Iz3	-.0058356	.0550491	-0.11	0.916	-.1137299	.1020586
/logit_Iz1~w	.039923	.0502901	0.79	0.427	-.0586438	.1384898
/logit_Iz2~w	.0687247	.0542023	1.27	0.205	-.0375099	.1749592
/logit_Iz3~w	.0262868	.0826922	0.32	0.751	-.135787	.1883605
/logitconst	.3425951	.0253272	13.53	0.000	.2929548	.3922354
/psi	1.05276	.4217052	2.50	0.013	.2262333	1.879287
/ey0	.5656666	.0592066	9.55	0.000	.4496238	.6817094

```
Instruments for equation 1: overw Iz1 Iz2 Iz3 Iz1Xoverw Iz2Xoverw
    Iz3Xoverw _cons
Instruments for equation 2: Iz1 Iz2 Iz3 _cons
```

```
. lincom [psi]_cons, eform

 ( 1)  [psi]_cons = 0
```

Causal odds ratio = 2.87 (1.25, 6.55)

	exp(b)	Std. Err.	z	P>|z|	[95% Conf.	Interval]
(1)	2.86555	1.208417	2.50	0.013	1.253868	6.548836

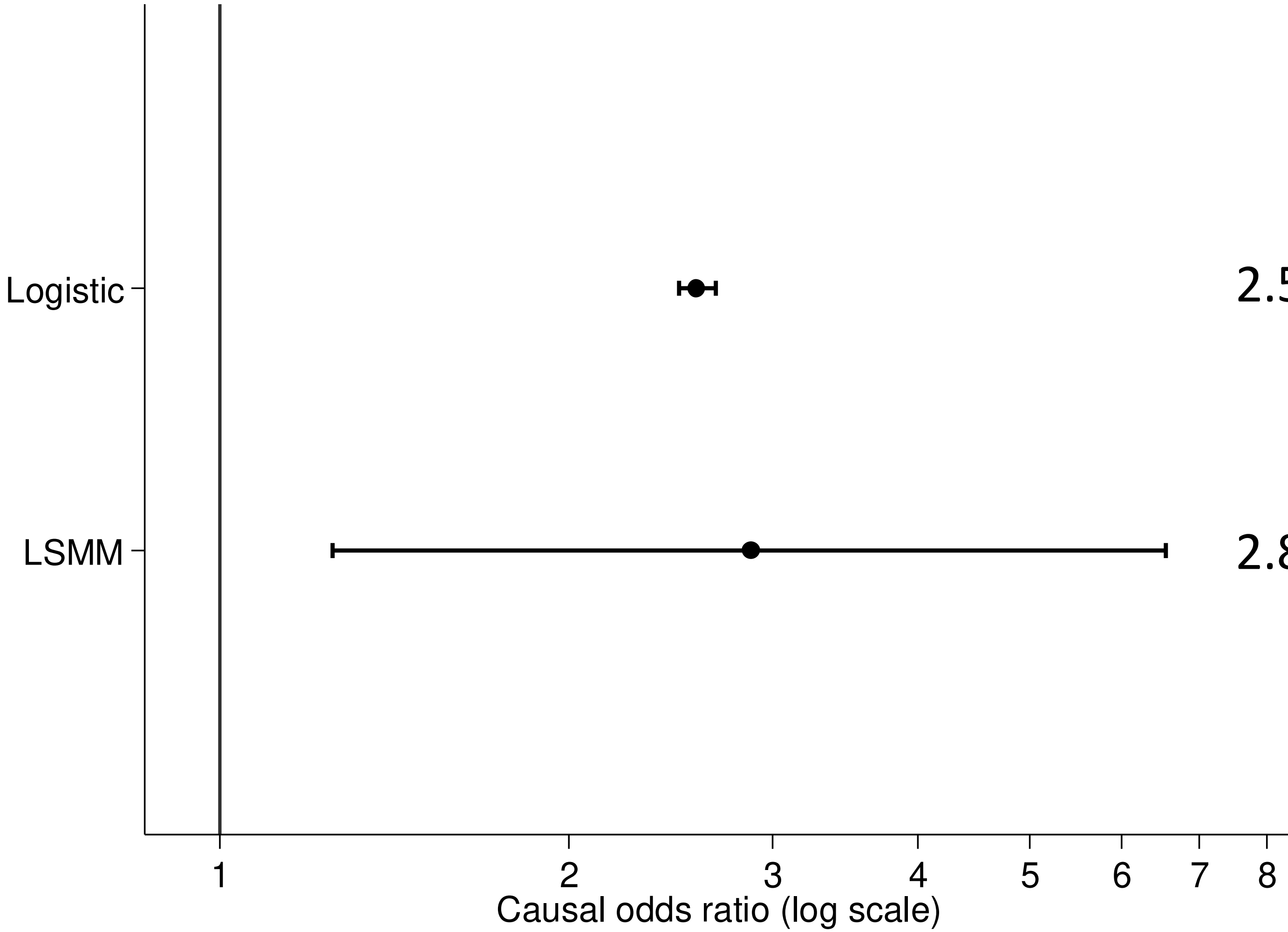
```
. estat overid

  Test of overidentifying restriction:

  Hansen's J chi2(2) =   2.459 (p = 0.2924)
```

Degrees of freedom:
AM: exactly identified
CM: 4 moments – 2 pars

Observational and IV estimate in example



2.58 (2.49, 2.68)

2.87 (1.25, 6.55)

Summary

- Estimate SMMs within GMM framework
- GMM optimal combination of multiple instruments
- Two-step GMM is efficient
- Joint estimation for LSMM
- Hansen over-identification test
  - Joint validity of multiple instruments
  - Can help detect violations in NEM & CMI
- Straightforward implementation in Stata and R

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