Generalised method of moments estimation of mediation models and structural mean models

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Outline

- Introduction to GMM
- I. Mediation models
  - Joint estimation of mediator and outcome models - delta method SE
  - Example
- II. Structural mean models
  - Multiplicative SMM
  - Logistic SMM
- Summary

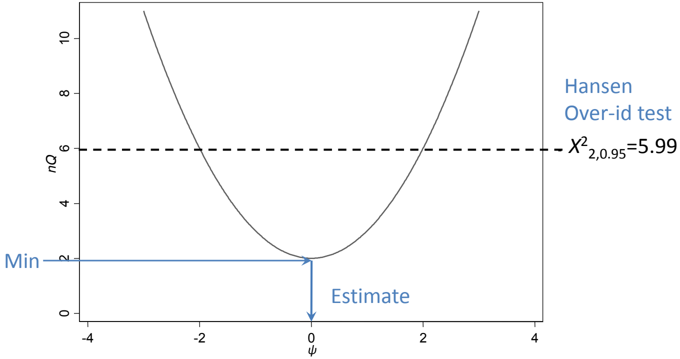
Introduction to Generalised Method of Moments (GMM) I

- Jointly solve system of moment conditions (equations)
- System: exactly identified, # instruments = # parameters
- System: over-identified, # instruments > # parameters
- m vector of moment conditions
- Minimises quadratic form w.r.t parameters (ψ)

$$Q = m'W^{-1}m = \left(\frac{1}{n}\sum_{i=1}^{n} m_i(\psi)\right)' W^{-1} \left(\frac{1}{n}\sum_{i=1}^{n} m_i(\psi)\right)$$

Introduction to Generalised Method of Moments (GMM) II

- Profiling over parameter of interest



- Over-identification test Hansen 1982: $nQ \sim \chi^2_q$
- In quadratic form: W affects efficiency (SEs) rather than consistency

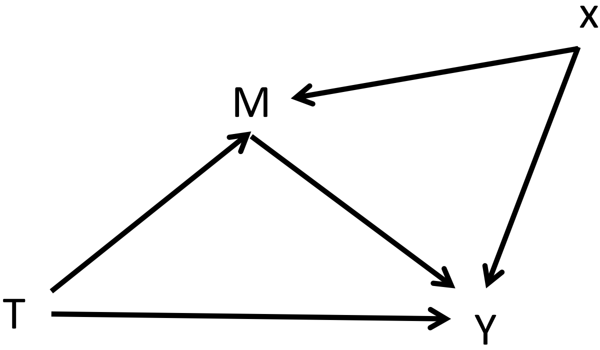
I. Mediation models

Mediation models – common implementation

Baron and Kenny (1986) type models

- Implementations:
  - Stata - `medeff`, `medsens`, `paramed`
  - R - `mediation`
  - bootstrapping for SEs of mediation parameters
- Fit mediator model
- Fit outcome model
- Mediation parameters – function of estimated parameters
- problem: fit models separately – missing covariance between parameters from different models

Mediation model with a single confounder



$$M = \alpha_0 + \alpha_1 T + \alpha_2 x + \epsilon_1$$
$$Y = \beta_0 + \beta_1 T + \beta_2 M + \beta_3 x + \epsilon_2$$

$$
\widehat{\mathbf{V}} = \begin{bmatrix}
\widehat{\sigma}^2_{\alpha 00} & \widehat{\sigma}_{\alpha 01} & \widehat{\sigma}_{\alpha 02} & . & . & . & . \\
\widehat{\sigma}_{\alpha 10} & \widehat{\sigma}^2_{\alpha 11} & \widehat{\sigma}_{\alpha 12} & . & . & . & . \\
\widehat{\sigma}_{\alpha 20} & \widehat{\sigma}_{\alpha 21} & \widehat{\sigma}^2_{\alpha 22} & . & . & . & . \\
. & . & . & \widehat{\sigma}^2_{\beta 00} & \widehat{\sigma}_{\beta 01} & \widehat{\sigma}_{\beta 02} & \widehat{\sigma}_{\beta 03} \\
. & . & . & \widehat{\sigma}_{\beta 10} & \widehat{\sigma}^2_{\beta 11} & \widehat{\sigma}_{\beta 12} & \widehat{\sigma}_{\beta 13} \\
. & . & . & \widehat{\sigma}_{\beta 20} & \widehat{\sigma}_{\beta 21} & \widehat{\sigma}^2_{\beta 22} & \widehat{\sigma}_{\beta 23} \\
. & . & . & \widehat{\sigma}_{\beta 30} & \widehat{\sigma}_{\beta 31} & \widehat{\sigma}_{\beta 32} & \widehat{\sigma}^2_{\beta 33}
\end{bmatrix}
$$

Imai et al. (2010)

$$\text{Natural indirect effect} = \beta_2 \alpha_1$$

$$\text{V(NIE)} = \alpha_1^2 \sigma_{\beta 2}^2 + \beta_2^2 \sigma_{\alpha 1}^2 + 2\beta_2 \alpha_1 \text{cov}(\beta_2, \alpha_1)$$

- bootstrap to estimate SE of mediation parameter
- GMM – *joint estimation of mediation and outcome models*
  - full var-covar matrix then delta-method SE

GMM estimation of GLMs

Estimating equation for GLMs - solve wrt β:

$$\sum_{i=1}^{n} x_i(y_i - g^{-1}(X\beta)) = 0$$

Model	Link fn $g(\mu)$	Inverse link $g^{-1}(X\beta)$
Linear	$I(\mu)$	$I(X\beta)$
Poisson	$\log(\mu)$	$\exp(X\beta)$
Logistic	$\text{logit}(\mu) = \log\left(\frac{\mu}{1-\mu}\right)$	$\text{expit}(X\beta) = \frac{\exp(X\beta)}{1+\exp(X\beta)}$
Probit	$\Phi^{-1}(\mu)$	$\Phi(X\beta)$

In (exactly identified) GMM use covariates as *instruments* for themselves

Moment conditions

$$
\begin{aligned}
E[(M - \alpha_0 - \alpha_1 T - \alpha_2 x)1] &= 0 \\
E[(M - \alpha_0 - \alpha_1 T - \alpha_2 x)T] &= 0 \\
E[(M - \alpha_0 - \alpha_1 T - \alpha_2 x)x] &= 0 \\
E[(M - \beta_0 - \beta_1 T - \beta_2 M - \beta_3 x)1] &= 0 \\
E[(M - \beta_0 - \beta_1 T - \beta_2 M - \beta_3 x)T] &= 0 \\
E[(M - \beta_0 - \beta_1 T - \beta_2 M - \beta_3 x)M] &= 0 \\
E[(M - \beta_0 - \beta_1 T - \beta_2 M - \beta_3 x)x] &= 0
\end{aligned}
$$

Instruments

Implementation

- Stata: `gmm` then `lincom`/`nlcom`
- R: `gmm` package then `deltamethod()` from MSM package

Example from `medsens` helpfile I

$$M = \alpha_0 + \alpha_1 T + \alpha_2 x + \epsilon_1$$
$$Y = \beta_0 + \beta_1 T + \beta_2 M + \beta_3 x + \epsilon_2$$

	Estimate (95% CI)
α_0	0.28 (0.19, 0.36)
α_1	0.17 (0.04, 0.29)
α_2	0.27 (0.21, 0.33)
β_0	0.32 (0.24, 0.41)
β_1	-0.58 (-0.70, -0.46)
β_2	0.71 (0.65, 0.77)
β_3	0.27 (0.21, 0.34)

Estimated variance-covariance matrix:

$$\begin{bmatrix} 0.00178 & & & & & & \\ -0.00178 & 0.00398 & & & & & \\ -0.00001 & 0.00008 & 0.0009 & & & & \\ & & & 0.00193 & & & \\ & & & -0.00181 & 0.0037 & & \\ & & & -0.0003 & -0.00007 & 0.0009 & \\ & & & 0.0002 & -0.00009 & -0.0002 & 0.0010 \end{bmatrix}$$

Estimated variance-covariance matrix:

$$\begin{bmatrix} 0.00178 & & & & & & \\ -0.00178 & 0.00398 & & & & & \\ -0.00001 & 0.00008 & 0.0009 & & & & \\ 0.00009 & -0.00009 & 0.00005 & 0.00193 & & & \\ -0.00007 & -0.00003 & -0.000002 & -0.00181 & 0.0037 & & \\ -0.00005 & 0.00007 & -0.00002 & -0.0003 & -0.00007 & 0.0009 & \\ 0.00006 & -0.00004 & -0.00003 & 0.0002 & -0.00009 & -0.0002 & 0.0010 \end{bmatrix}$$

Example from medsens helpfile II

Estimates of mediation parameters

	Estimate	95% CI	
		Bootstrap	DM (using GMM)
NIE $= \beta_2\alpha_1$	0.12	(0.035, 0.211)	(0.031, 0.209)
CDE $= \beta_1$	-0.58	(-0.697, -0.451)	(-0.697, -0.457)
Total effect	-0.46	(-0.610, -0.304)	(-0.605, -0.309)
% TE mediated	-0.26	(-0.397, -0.198)	(-0.517, -0.008)

DM: delta-method

SEs from joint maximum likelihood estimation

$$\text{logLike} = \text{logLike}_{\text{Mediator}} + \text{logLike}_{\text{Outcome}}$$

	Estimate	95% CI		
		Bootstrap	DM (GMM)	DM (ML)
NIE $= \beta_2\alpha_1$	0.12	(0.035, 0.211)	(0.031, 0.209)	(0.031, 0.208)
CDE $= \beta_1$	-0.58	(-0.697, -0.451)	(-0.697, -0.457)	(-0.697, -0.457)
Total effect	-0.46	(-0.610, -0.304)	(-0.605, -0.309)	(-0.605, -0.308)
% TE mediated	-0.26	(-0.397, -0.198)	(-0.517, -0.008)	(-0.515, -0.009)

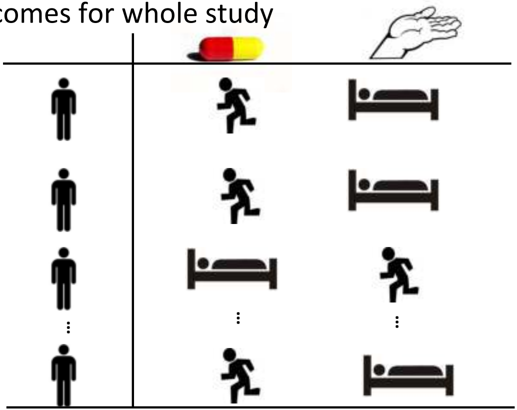
DM: delta-method

GMM SEs here are heteroskedasticity robust SEs

II. Structural mean models

Structural mean models

Potential outcomes for whole study



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

Multiplicative SMM

- X exposure/treatment
- Y outcome
- Z instrument
- $Y(X = 0)$ exposure/treatment free potential outcome

Hernan & Robins 2006

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

ψ : log causal risk ratio

Rearrange for $Y(0)$: $\quad Y(0) = Y \exp(-\psi X)$

Mutliplicative SMM: estimation with multiple instruments

Under the instrumental variable assumptions Robins 1994:

$$Y(0) \perp\!\!\!\perp Z$$
$$Y \exp(-\psi X) \perp\!\!\!\perp Z$$

Mutliplicative SMM: estimation with multiple instruments

Under the instrumental variable assumptions Robins 1994:

$$\begin{aligned} Y(0) &\perp\!\!\!\perp Z \\ Y\exp(-\psi X) &\perp\!\!\!\perp Z \\ \text{trick: } Y\exp(-\psi X) - Y(0) &\perp\!\!\!\perp Z \end{aligned}$$

Mutliplicative SMM: estimation with multiple instruments

Under the instrumental variable assumptions Robins 1994:

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

Moment conditions

Z=0,1

$$E[(Y \exp(-\psi X) - Y(0))1] = 0$$
$$E[(Y \exp(-\psi X) - Y(0))Z_1] = 0$$

Mutliplicative SMM: estimation with multiple instruments

Under the instrumental variable assumptions Robins 1994:

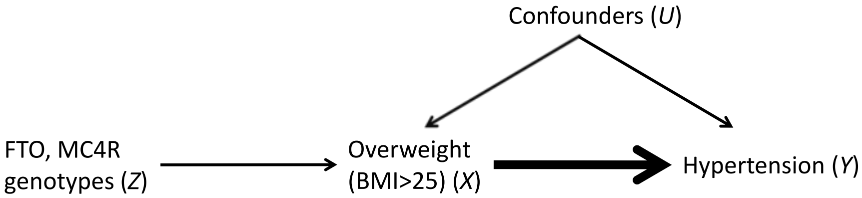
$$
\begin{aligned}
Y(0) &\perp\!\!\!\perp Z \\
Y\exp(-\psi X) &\perp\!\!\!\perp Z \\
\text{trick: } Y\exp(-\psi X) - Y(0) &\perp\!\!\!\perp Z
\end{aligned}
$$

Moment conditions

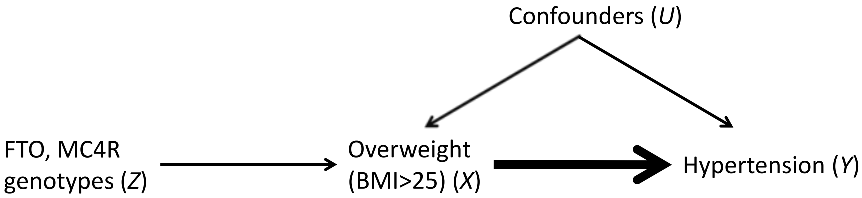
Z=0,1,2,3 Over-identified

$$
\begin{aligned}
E[(Y\exp(-\psi X) - Y(0))1] &= 0 \\
E[(Y\exp(-\psi X) - Y(0))Z_1] &= 0 \\
E[(Y\exp(-\psi X) - Y(0))Z_2] &= 0 \\
E[(Y\exp(-\psi X) - Y(0))Z_3] &= 0
\end{aligned}
$$

Copenhagen example descriptive statistics 1



Copenhagen example descriptive statistics 1



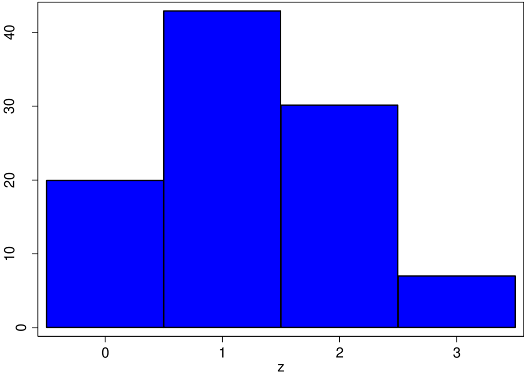
	No Hypertension	Hypertension	Total
Not Overweight	10,066 42%	13,909 58%	23,975
Overweight	6,906 22%	24,642 78%	31,548
Total	16,972 31%	38,551 69%	55,523 χ^2 P<0.001

Risk ratio for hypertension 1.35 (1.32, 1.37)

Copenhagen example descriptive statistics 2

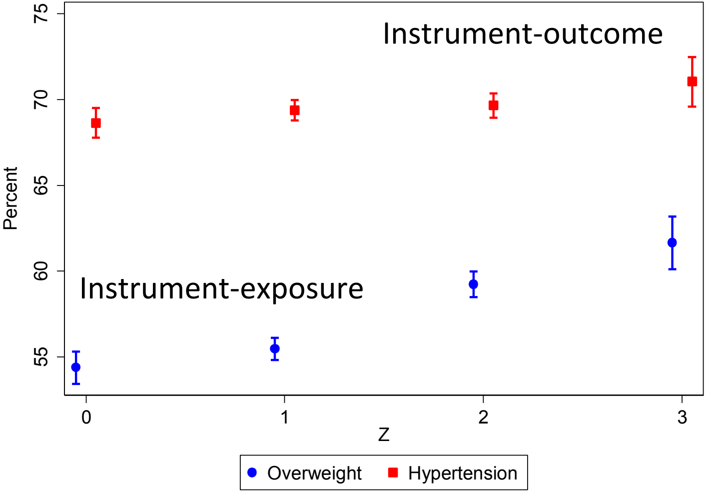
Distribution of instrument (Z)

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



Copenhagen example descriptive statistics 3

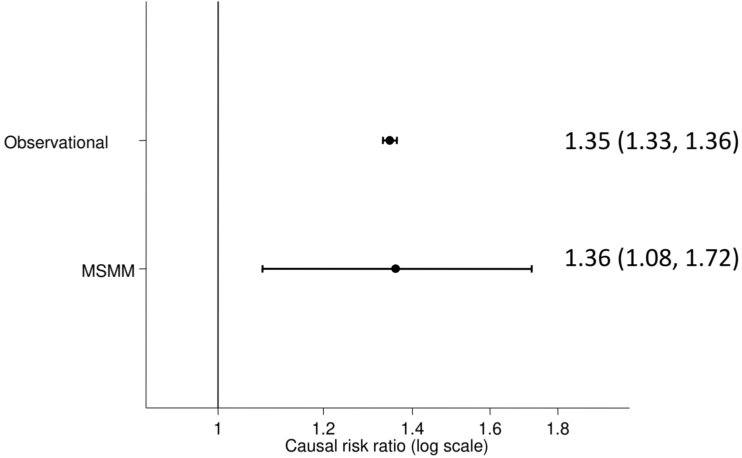
Exposure (over-weight) & outcome (hypertension) by instrument



P=0.007

P<0.001
R^2=0.002

Copenhagen example Multiplicative SMM estimates



MSMM: Hansen over-identification test $P = 0.31$
$E[Y(0)] = 0.58$ (0.50, 0.65)

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

(double) Logistic SMM

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

Goetghebeur, 2010

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

$$\psi: \text{ log causal odds ratio}$$

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

(double) Logistic SMM

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

Goetghebeur, 2010

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

$$\psi: \text{ log causal odds ratio}$$

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

- Can't be estimated in a single step Robins (1999)
- First stage association model Vansteelandt (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

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

Problem: SEs incorrect - need association model uncertainty

LSMM joint estimation

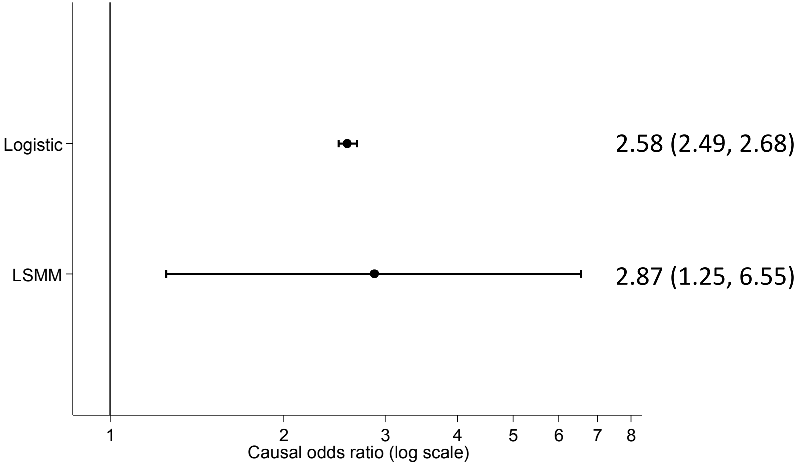
Joint estimation = correct SEs Gourieroux (1996)

Vansteelandt & Goetghebeur (2003)

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

In example causal model SEs increase $\times 10$ from non-joint estimation

Copenhagen example LSMM estimates



LSMM: Hansen over-identification test $P = 0.29$

$\mathrm{E}[Y(0)] = 0.57$ (0.45, 0.68)

Issues estimating SMMs

- Weak identification
  - many values of causal parameter give independence condition close to zero
- GMM convergence at local/global minima
- Hence check estimated $E[Y(0)]$ approx baseline risk
- Sensitive to initial values: in another dataset
  - initial $CRR = 1$ gave $CRR > 1$
  - initial $CRR < 1$ gave $CRR < 1$
- Fit with centred Z (with/without constant E[Y(0)])
- Estimation MSMM/LSMM models with continuous X more problematic than binary X – centring X important for sensible estimates of E[Y(0)]

Summary

- Mediation models
  - GMM exact identification
  - Delta-method SEs alternative to bootstrapping
- Structural mean models
  - fit over-identified models with multiple instruments
  - check if estimated $E[Y(0)]$ is sensible – approx baseline risk
- Straightforward to implement in Stata & R

References

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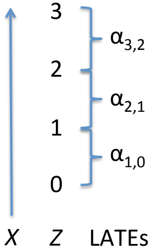
- Robins JM (1994) Correcting for non-compliance in randomized trials using structural nested mean models. CSTM. 23(8) 2379–2412

Local risk ratios for Multiplicative SMM

- Identification: NEM by Z ... what if it doesn't hold?
- Alternative assumption of monotonicity: $X(Z_k) \geq X(Z_{k-1})$
- Local Average Treatment Effect (LATE) Imbens 1994
  - effect among those whose exposures are changed (upwardly) by changing (counterfactually) the IV from Z_{k-1} to Z_k



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

Local risk ratios for Multiplicative SMM

- Identification: NEM by Z ... what if it doesn't hold?
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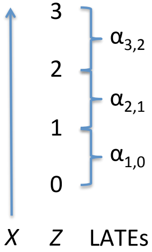
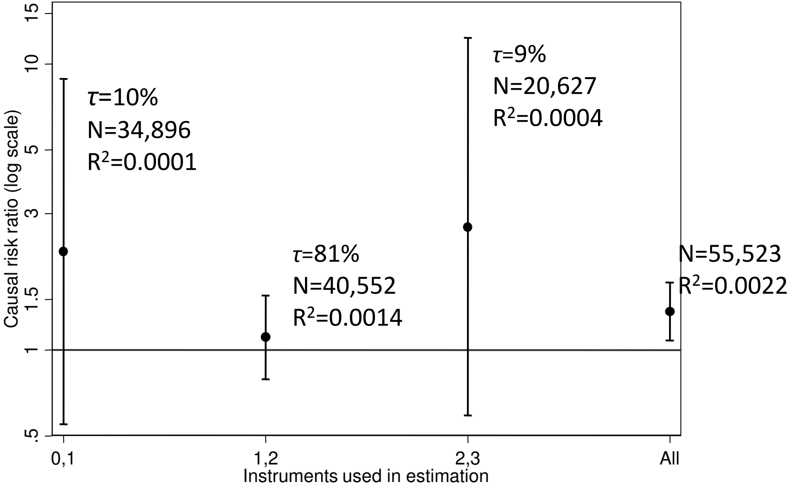


$$\alpha_{All} = \lambda_1\alpha_{1,0} + \lambda_2\alpha_{2,1} + \lambda_3\alpha_{3,2}$$

Similar result holds for MSMM: $e^{\psi}_{\text{All}} = \sum_{k=1}^{K} \tau_k e^{\psi}_{k,k-1}$

Copenhagen example local risk ratios



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