Generalised method of moments estimation of structural mean models

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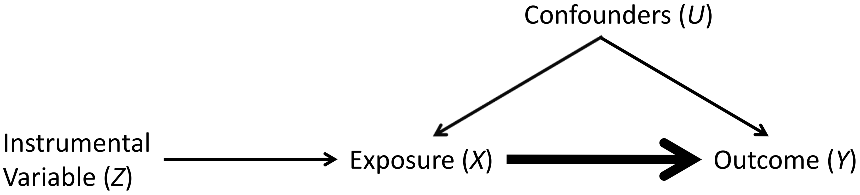
Outline

Generalised method of moments estimation of structural mean models . . . using instrumental variables

- Introduction to Mendelian randomization example
- Multiplicative structural mean model (MSMM)
  - G-estimation, identification, `gmm` syntax, example
- (double) Logistic SMM
  - `gmm` multiple equation syntax, example
- Summary
- MSMM: local risk ratios

Introduction to Mendelian randomization example

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



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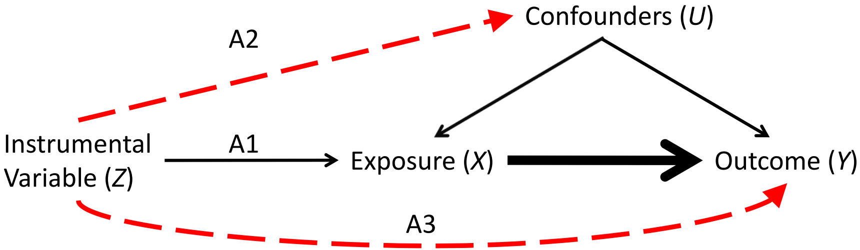

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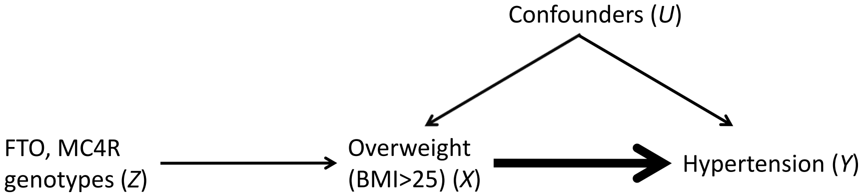

Copenhagen General Population study (N=55,523)

Multiplicative SMM

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

Robins, 1989, 1994; Robins, Rotnitzky, & Scharfstein, 1999; Hernán & Robins, 2006

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

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

ψ : log causal risk ratio

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

MSMM G-estimation

Under the instrumental variable assumptions (Robins, 1989):

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

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

MSMM `gmm` syntax

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

MSMM gmm output

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

Final GMM criterion Q(b) =  .0000425

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 |   .3104495   .1192332     2.60   0.009     .0767568    .5441423
        /ey0 |   .5758842   .0388716    14.82   0.000     .4996973    .6520711
------------------------------------------------------------------------------
Instruments for equation 1: z1 z2 z3 _cons
```

MSMM gmm output

Causal risk ratio $\exp(\psi)$ & Hansen over-id test

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

 ( 1)  [psi]_cons = 0

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

. estat overid

  Test of overidentifying restriction:

  Hansen's J chi2(2) = 2.36125 (p = 0.3071)
```

MSMM gmm syntax including analytic first derivatives

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

Reduces runtime from 4.5 secs to 2.5 secs on 55000 obs

MSMM alternative parameterisation

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

- Same moment condition in `ivpois` (Mullahy, 1997; Nichols, 2007)
- Drukker, 2010: first syntax more numerically stable
- Also see Windmeijer & Santos Silva, 1997; Windmeijer, 2002, 2006; Clarke & Windmeijer, 2010
- Use X as instrument for itself $\equiv$ Gamma regression (log link)
- Slightly different to Poisson regression moment condition:

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

MSMM 2^{nd} syntax & ivpois output

```
. gmm (y*exp(-x*{psi} - {logey0}) - 1), instruments(z1 z2 z3) onestep nolog

------------------------------------------------------------------------------
             |               Robust
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        /psi |    .290323   .1184236     2.45   0.014      .058217    .5224291
     /logey0 |  -.5404186   .0676225    -7.99   0.000    -.6729562   -.4078811
------------------------------------------------------------------------------


. ivpois y, endog(x) exog(z1 z2 z3)
------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y            |
           x |   .2903902   .1184242     2.45   0.014      .058283    .5224973
       _cons |   -.540463   .0676208    -7.99   0.000    -.6729974   -.4079286
------------------------------------------------------------------------------
```

MSMM 'endogenous' & Gamma (log link) output

```
. gmm (y*exp(-1*x*{psi} - {logey0}) - 1), instruments(x) onestep nolog

------------------------------------------------------------------------------
             |               Robust
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        /psi |   .2974176   .0062505    47.58   0.000     .2851668    .3096684
     /logey0 |  -.5444755   .0054942   -99.10   0.000    -.5552439   -.5337072
------------------------------------------------------------------------------

. glm y x, family(gamma) link(log) robust nolog

------------------------------------------------------------------------------
             |               Robust
           y |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           x |   .2974176   .0062506    47.58   0.000     .2851667    .3096685
       _cons |  -.5444755   .0054942   -99.10   0.000     -.555244   -.5337071
------------------------------------------------------------------------------
```

(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

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

(double) Logistic SMM

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

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

- LSMM can't be estimated in a single step (Robins et al., 1999)
- LSMM estimator with first stage association model (Vansteelandt & Goetghebeur, 2003; Bowden & Vansteelandt, 2010):
  - logistic regression of Y on X & Z (& interactions: saturated)
  - predict Y
  - estimate LSMM using predicted Y

(double) LSMM gmm syntax

$$\mathrm{invlogit}(x) = \mathrm{expit}(x) = e^x/(1+e^x)$$

Association model gmm syntax - logistic regression using GMM

```
gmm (y - invlogit({b0} + {xb:x z1 z2 z3 xz1 xz2 xz3})), ///
    instruments(x z1 z2 z3 xz1 xz2 xz3)
predict prres
gen xblog = logit(y - prres)
```

(double) LSMM gmm syntax

$$\text{invlogit}(x) = \text{expit}(x) = e^x/(1+e^x)$$

Association model gmm syntax - logistic regression using GMM

```
gmm (y - invlogit({b0} + {xb:x z1 z2 z3 xz1 xz2 xz3})), ///
    instruments(x z1 z2 z3 xz1 xz2 xz3)
predict prres
gen xblog = logit(y - prres)
```

Causal model gmm syntax

```
gmm (invlogit(xblog - x*{psi}) - {ey0}), instruments(z1 z2 z3)
```

Problem: causal model SEs incorrect - need to incorporate uncertainty from association model

Association model output: gmm & logit

```
. gmm (y - invlogit({xb:x z1 z2 z3 xz1 xz2 xz3} + {b0})), instruments(x z1 z2 z3 xz1 xz2 xz3)
------------------------------------------------------------------------------
             |               Robust
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       /xb_x |   .9034697   .0419769    21.52   0.000     .8211965    .9857428
      /xb_z1 |   .0023852   .0346439     0.07   0.945    -.0655155     .070286
      /xb_z2 |  -.031613    .0375747    -0.84   0.400     -.105258     .042032
      /xb_z3 |   .0285799   .0598671     0.48   0.633    -.0887574    .1459173
     /xb_xz1 |   .0500118   .0509504     0.98   0.326    -.0498492    .1498728
     /xb_xz2 |     .06952   .0543206     1.28   0.201    -.0369464    .1759864
     /xb_xz3 |   .0412161   .0837708     0.49   0.623    -.1229716    .2054038
         /b0 |   .3295621   .0285043    11.56   0.000     .2736947    .3854295
------------------------------------------------------------------------------

. logit y x z1 z2 z3 xz1 xz2 xz3, nolog
------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           x |   .9034696   .0419769    21.52   0.000     .8211964    .9857428
          z1 |   .0023852   .0346439     0.07   0.945    -.0655155     .070286
          z2 |  -.031613    .0375747    -0.84   0.400     -.105258     .042032
          z3 |   .0285799   .0598671     0.48   0.633    -.0887574    .1459173
         xz1 |   .0500117   .0509504     0.98   0.326    -.0498493    .1498727
         xz2 |     .06952   .0543206     1.28   0.201    -.0369465    .1759864
         xz3 |    .041216   .0837708     0.49   0.623    -.1229717    .2054037
       _cons |   .3295621   .0285043    11.56   0.000     .2736947    .3854295
------------------------------------------------------------------------------
. matrix from = e(b)
. predict xblog, xb
```

Causal model output

```
. gmm (invlogit(xblog - x*{psi}) - {ey0}), instruments(z1 z2 z3) nolog

------------------------------------------------------------------------------
             |               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: z1 z2 z3 _cons
. matrix from = (from,e(b))
```

Problem: causal model SEs incorrect - need to incorporate uncertainty from association model

LSMM joint estimation

Joint estimation of association and causal models = correct SEs

(Gourieroux, Monfort, & Renault, 1996)

LSMM gmm multiple equation syntax

```
gmm (y - invlogit({xb:x z1 z2 z3 xz1 xz2 xz3} + {b0})) ///
    (invlogit({xb:} + {b0} - x*{psi}) - {ey0}), ///
    instruments(1:x z1 z2 z3 xz1 xz2 xz3) ///
    instruments(2:z1 z2 z3) ///
    winitial(unadjusted, independent) ///
    from(from)
```

LSMM gmm multiple equation output

```
Number of parameters =   10
Number of moments    =   12
Initial weight matrix: Unadjusted                 Number of obs   =    55523
GMM weight matrix:     Robust
------------------------------------------------------------------------------
             |               Robust
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       /xb_x |   .9091545   .0418464    21.73   0.000     .8271371    .9911719
      /xb_z1 |  -.0207159   .0279367    -0.74   0.458    -.0754708     .034039
      /xb_z2 |  -.0339566   .0343049    -0.99   0.322     -.101193    .0332797
      /xb_z3 |  -.0058356   .0550491    -0.11   0.916    -.1137299    .1020586
     /xb_xz1 |    .039923   .0502901     0.79   0.427    -.0586438    .1384898
     /xb_xz2 |   .0687247   .0542023     1.27   0.205    -.0375099    .1749592
     /xb_xz3 |   .0262868   .0826922     0.32   0.751     -.135787    .1883605
         /b0 |   .3425951   .0253272    13.53   0.000     .2929547    .3922354
        /psi |    1.05276   .4217043     2.50   0.013     .2262351    1.879286
        /ey0 |   .5656666   .0592065     9.55   0.000     .4496241    .6817091
------------------------------------------------------------------------------
```

Causal model SEs $\times 10$!

LSMM gmm multiple equation output

Causal odds ratio $\exp(\psi)$ & Hansen over-id test

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

 ( 1)  [psi]_cons = 0

------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |    2.86555   1.208415     2.50   0.013      1.25387    6.548825
------------------------------------------------------------------------------

. estat overid

  Test of overidentifying restriction:

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

LSMM gmm multiple equation syntax with derivatives

```
local p1 "invlogit({xb:} + {b0})"
local d1 "-1*`p1'*(1 - `p1')"
local p2 "invlogit({xb:} + {b0} - x*{psi})"
local d2 "`p2'*(1 - `p2')"
gmm (y - invlogit({xb:x z1 z2 z3 xz1 xz2 xz3} + {b0})) ///
    (invlogit({xb:} + {b0} - x*{psi}) - {ey0}), ///
    instruments(1:x z1 z2 z3 xz1 xz2 xz3) ///
    instruments(2:z1 z2 z3) ///
    winitial(unadjusted, independent) from(from) ///
    deriv(1/xb = `d1') ///
    deriv(1/b0 = `d1') ///
    deriv(2/xb = `d2') ///
    deriv(2/b0 = `d2') ///
    deriv(2/psi = -1*x*`d2') ///
    deriv(2/ey0 = -1)
```

Stata applies last step of chain rule to derivates of $\{\texttt{xb:}\}$ i.e. $\frac{\partial u}{\partial \beta_j} = \frac{\partial u}{\partial (\mathbf{x}'\beta)} \times \frac{\partial (\mathbf{x}'\beta)}{\partial \beta_j}$

See `help gmm` & manual P593–5

Reduces runtime from 155secs to 32secs on 55000 obs

Summary

- Structural Mean Models estimated using IVs by G-estimation

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

- GMM estimation using multiple instruments
- Multiplicative SMM = `ivpois`
- Specifying analytic derivatives in `gmm` = faster!
- (double) logistic SMM estimation using multiple equations
- `estat overid`: Hansen J-test of joint validity of instruments
- SMMs: subtly different to additive residual IV estimators
  - RR: $Y - \exp(\psi X) \perp\!\!\!\perp Z$ (Cameron & Trivedi, 2009; Johnston, Gustafson, Levy, & Grootendorst, 2008)
  - OR: $Y - \text{expit}(\psi X) \perp\!\!\!\perp Z$ (Foster, 1997; Rassen, Schneeweiss, Glynn, Mittleman, & Brookhart, 2009)
- Review of some of the methods (Palmer et al., 2011)

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- MRC Collaborative grant G0601625
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References I

Bowden, J., & Vansteelandt, S. (2010). Mendelian randomisation analysis of case-control data using structural mean models. *Statistics in Medicine*. (in press)

Cameron, A. C., & Trivedi, P. K. (2009). *Microeconometrics using stata*. College Station, Texas: Stata Press.

Clarke, P. S., & Windmeijer, F. (2010). Identification of causal effects on binary outcomes using structural mean models. *Biostatistics*, *11*(4), 756–770.

Davey Smith, G., & Ebrahim, S. (2003). 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease. *International Journal of Epidemiology*, *32*, 1–22.

Drukker, D. (2010). An introduction to GMM estimation using Stata. In *German stata users group meeting.* Berlin.

Foster, E. M. (1997). Instrumental variables for logistic regression: an illustration. *Social Science Research*, *26*, 487–504.

Goetghebeur, E. (2010). Commentary: To cause or not to cause confusion vs transparency with Mendelian Randomization. *International Journal of Epidemiology*, *39*(3), 918–920.

Gourieroux, C., Monfort, A., & Renault, E. (1996). Two-stage generalized moment method with applications to regressions with heteroscedasticity of unknown form. *Journal of Statistical Planning and Inference*, *50*(1), 37–63.

Hernán, M. A., & Robins, J. M. (2006). Instruments for Causal Inference. An Epidemiologist's Dream? *Epidemiology*, *17*, 360–372.

References II

Imbens, G. W., & Angrist, J. D. (1994). Identification and Estimation of Local Average Treatment Effects. *Econometrica*, *62*, 467–467.

Johnston, K. M., Gustafson, P., Levy, A. R., & Grootendorst, P. (2008). Use of instrumental variables in the analysis of generalized linear models in the presence of unmeasured confounding with applications to epidemiological research. *Statistics in Medicine*, *27*, 1539–1556.

Mullahy, J. (1997). Instrumental–variable estimation of count data models: Applications to models of cigarette smoking behaviour. *The Review of Economics and Statistics*, *79*(4), 568–593.

Nichols, A. (2007). *ivpois: Stata module for IV/GMM Poisson regression.* Statistical Software Components, Boston College Department of Economics. (available at http://ideas.repec.org/c/boc/bocode/s456890.html)

Palmer, T. M., Sterne, J. A. C., Harbord, R. M., Lawlor, D. A., Sheehan, N. A., Meng, S., et al. (2011). Instrumental variable estimation of causal risk ratios and causal odds ratios in mendelian randomization analyses. *American Journal of Epidemiology*.

Rassen, J. A., Schneeweiss, S., Glynn, R. J., Mittleman, M. A., & Brookhart, M. A. (2009). Instrumental Variable Analysis for Estimation of Treatment Effects With Dichotomous Outcomes. *American Journal of Epidemiology*, *169*(3), 273–284.

Robins, J. M. (1989). Health services research methodology: A focus on aids. In L. Sechrest, H. Freeman, & A. Mulley (Eds.), (chap. The analysis of randomized and non-randomized AIDS treatment trials using a new approach to causal inference in longitudinal studies). Washington DC, US: US Public Health Service.

Robins, J. M. (1994). Correcting for non-compliance in randomized trials using structural nested mean models. *Communications in Statistics: Theory and Methods*, *23*(8), 2379–2412.

Robins, J. M., Rotnitzky, A., & Scharfstein, D. O. (1999). Statistical models in epidemiology: The environment and clinical trials. In M. E. Halloran & D. Berry (Eds.), (pp. 1–92). New York, US: Springer.

Vansteelandt, S., & Goetghebeur, E. (2003). Causal inference with generalized structural mean models. *Journal of the Royal Statistical Society: Series B*, *65*(4), 817–835.

Windmeijer, F. (2002). *ExpEnd, A Gauss program for non-linear GMM estimation of exponential models with endogenous regressors for cross section and panel data* (Tech. Rep.). Centre for Microdata Methods and Practice.

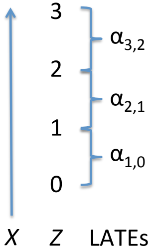
Windmeijer, F. (2006). *GMM for panel count data models* (Bristol Economics Discussion Papers No. 06/591). Department of Economics, University of Bristol, UK. Available from `http://ideas.repec.org/p/bri/uobdis/06-591.html`

References IV

Windmeijer, F., & Santos Silva, J. (1997). Endogeneity in Count Data Models: An Application to Demand for Health Care. *Journal of Applied Econometrics*, *12*(3), 281–294.

Local risk ratios for MSMM

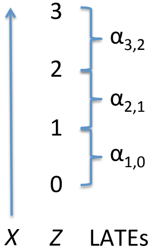
- Identification depends on NEM . . . what if it doesn't hold?
- Alternative assumption of monotonicity: $X(Z_k) \geq X(Z_{k-1})$
- Local Average Treatment Effect (LATE) (Imbens & Angrist, 1994)
  - effect among those whose exposures are changed (upwardly) by changing (counterfactually) the IV from Z_{k-1}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



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

Local risk ratios for MSMM

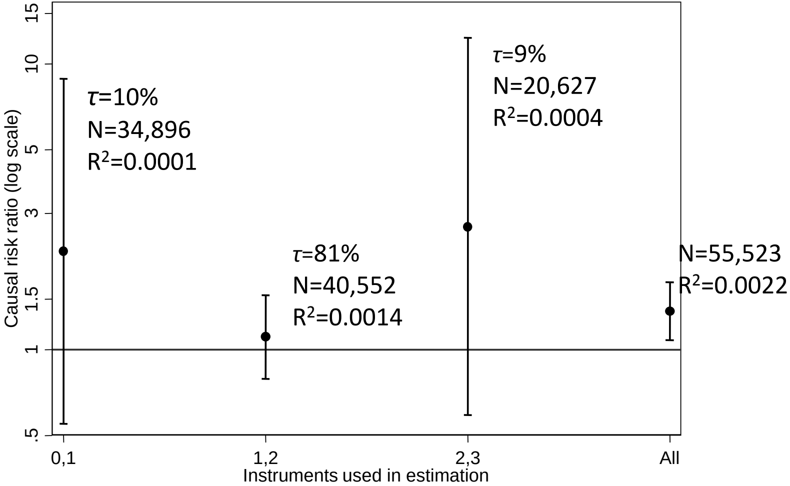
- Identification depends on NEM ... what if it doesn't hold?
- Alternative assumption of monotonicity: $X(Z_k) \geq X(Z_{k-1})$
- Local Average Treatment Effect (LATE) (Imbens & Angrist, 1994)
  - effect among those whose exposures are changed (upwardly) by changing (counterfactually) the IV from Z_{k-1}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



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

Similar result holds for MSMM: $\exp(\psi)_{\text{Overall}} = \sum_{k=1}^{K} \tau_k \exp(\psi)_{k,k-1}$

Local risk ratios in example



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

Compare SMMs with other estimators

	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
(double) LSMM	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)	