Instrumental variable estimation of the causal risk ratio in cohorts

Tom Palmer Roger Harbord Vanessa Didelez
Nuala Sheehan Debbie Lawlor Jonathan Sterne

MRC Centre for Causal Analyses in Translational Epidemiology,
School of Social and Community Medicine, University of Bristol

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Outline

- Instrumental variables
- Causal risk ratio
- Outline estimators
  - apply in ALSPAC BMI-asthma Mendelian randomization example
- Discussion

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X exposure/risk factor/phenotype
Y outcome/disease
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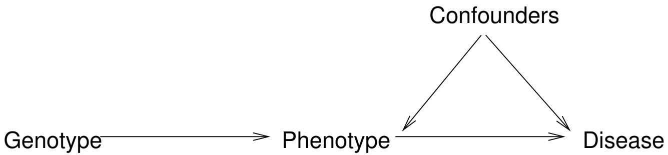

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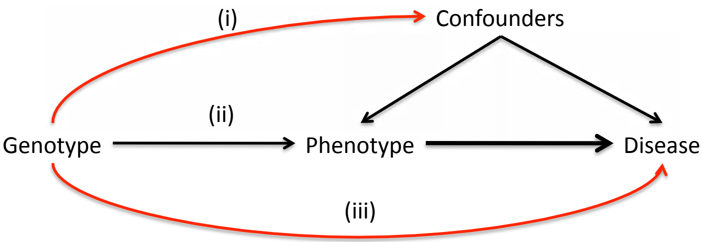

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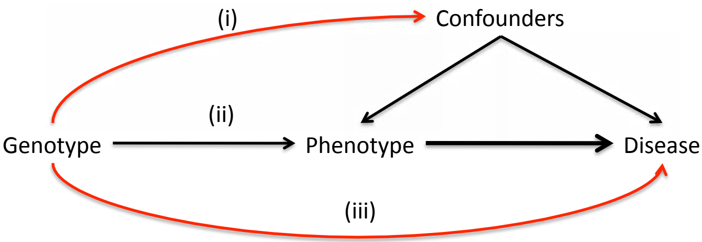

(i) independent of confounders
(ii) associated with phenotype
(iii) independent of outcome given phenotype and confounders

Causal risk ratio

$$\frac{P(Y = 1|X = x + 1)}{P(Y = 1|X = x)}$$

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$$\frac{P(Y=1|do(X=x+1))}{P(Y=1|do(X=x))}$$

Pearl's *do*() operator: set X to x (or potential outcomes)

θ: log CRR

Multiplicative SMM

Multiplicative structural model

Robins, CTSM, 1994; Hernan & Robins, Epi, 2006

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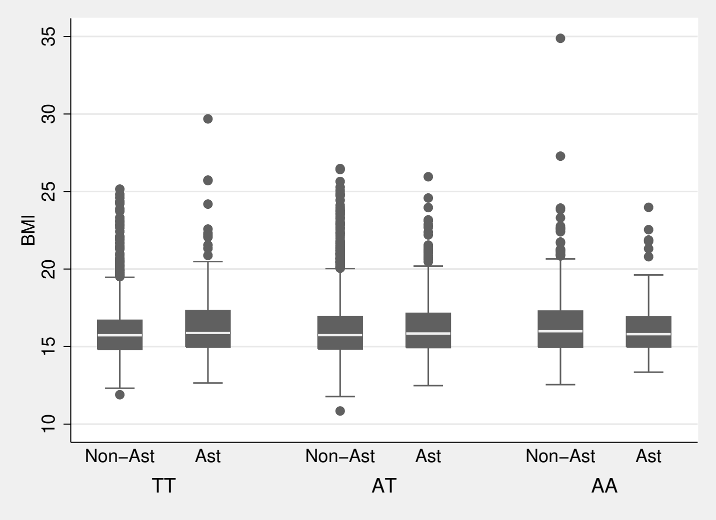
Sample moment condition

$$\sum_i y_i \exp(-\theta x_i)(z_i - \overline{z}) = 0$$

$Y = 1$ provide majority of information

ALSPAC BMI-asthma example

FTO (rs9939609) - BMI - asthma (7yrs)



ALSPAC example estimates

CRR for asthma per unit increase BMI ($N = 4647$)

Estimator	$\widehat{\text{CRR}}$	95% CI
Observational	1.06	1.02, 1.10
Observational*	1.08	1.03, 1.13

* adjusted for sex, birthweight, prenatal maternal smoking, postnatal maternal smoking, maternal education and head of household social class

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Generalised method of moments estimators

GMM - overidentified models (more Zs than Xs)

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linear: $h() = Z(Y - X\theta)$

First guess at a GMM estimator of the CRR

Additive residual Johnston et al. Stats Med 2007

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if $E(U) = 0$, gives moment condition

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Additive GMM does not give same estimate as MSMM

Multiplicative GMM

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Mullahy, RES, 1997; Windmeijer, JAE, 1997; Angrist, JBES, 2001

$$Y = \exp(X\theta + U)$$

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gives moment condition

$$h() = Z(Y \exp(-X\theta) - 1) = Z\left(\frac{Y - \exp(X\theta)}{\exp(X\theta)}\right)$$

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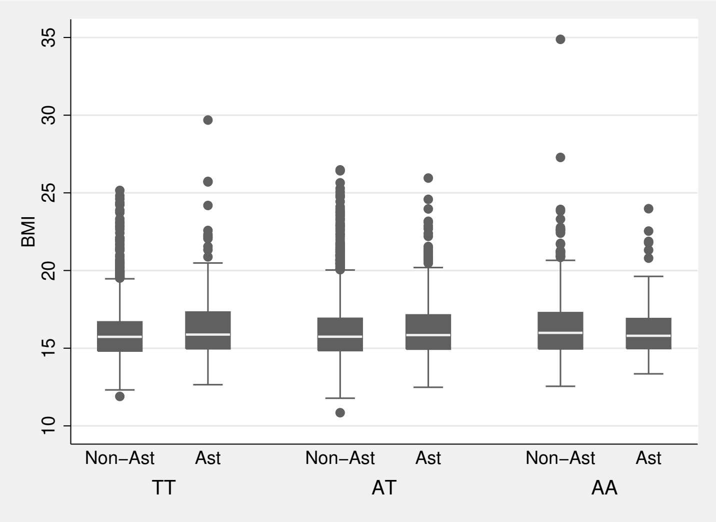
Multiplicative GMM estimate same as MSMM Clarke, Biostats, 2010

User written Stata command `ivpois` Nichols, 2007

MGMM/MSMM other side of null



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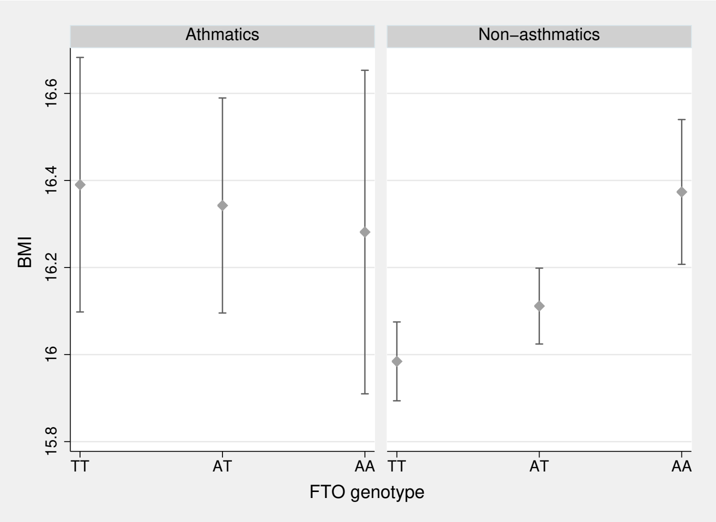

Wald type, two-stage, control function estimators

Wald type estimator: ratio of genotype-disease & genotype-phenotype associations

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Control function estimator Cameron & Trivedi, 2009

Stage 1: additionally save estimated residuals $\widehat{\epsilon}$

Stage 2: Poisson regression of Y on X and $\widehat{\epsilon}$

Rationale: $\widehat{\beta}_{\widehat{\epsilon}} = 0$ endogeneity test

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Single IV: Wald, two-stage, control function estimates the same

Multiple IVs: two-stage, control functions estimates the same

Discussion

Additive GMM estimators of CRR & COR do not give same estimates as SMMs

In our example CIs comparable

MSMM/MGMM estimates can be other side of the null

MSMM and MGMM give same estimate of CRR

More technical comparison of estimators Didelez et al., Stats Sci, 2010

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