Instrumental variable estimation of the causal risk ratio in cohorts

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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
Z instrument/genotype

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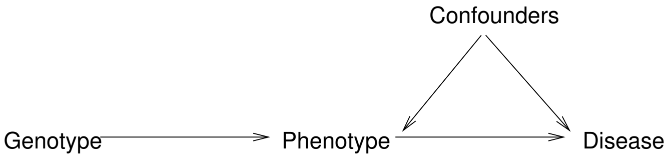

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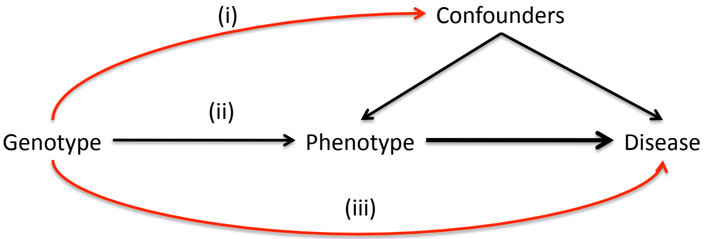

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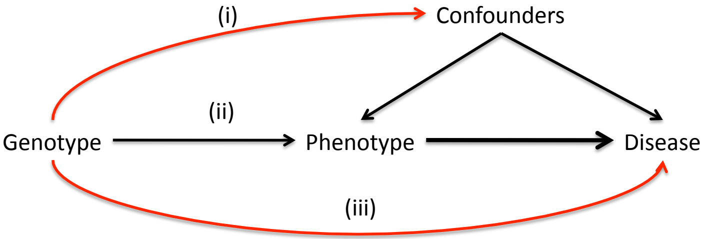

(i) independent of confounders
(ii) associated with phenotype
(iii) independent of outcome given phenotype and confounders

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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$$\frac{E(Y = 1|X, Z)}{E(Y|X, Z, do(X = 0))} = \exp(\theta X)$$

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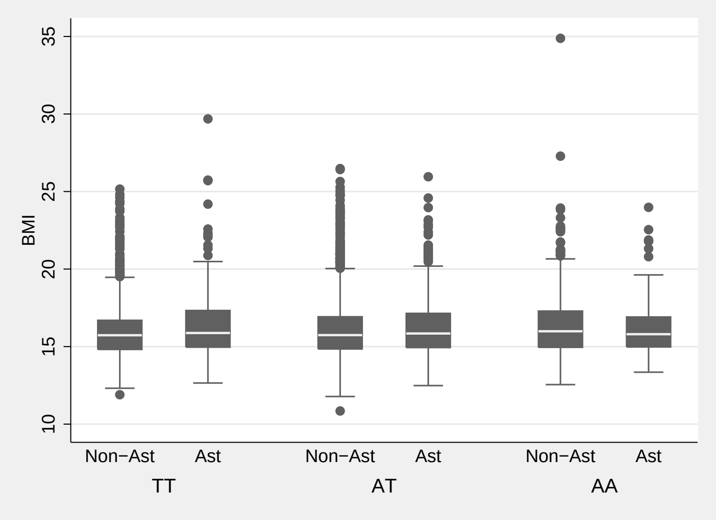
Sample moment condition

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

$Y = 1$ 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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$$Y = \exp(X\theta + U)$$

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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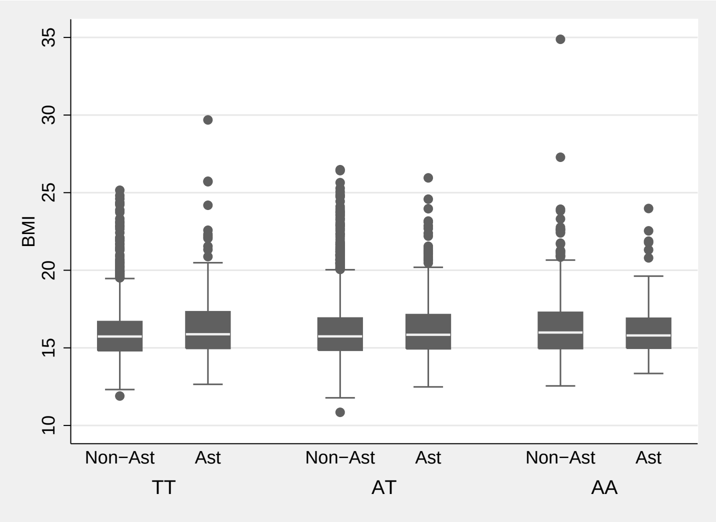
Multiplicative GMM estimate same as MSMM Clarke, Biostats, 2010

User written Stata command `ivpois` Nichols, 2007

MGMM/MSMM other side of null



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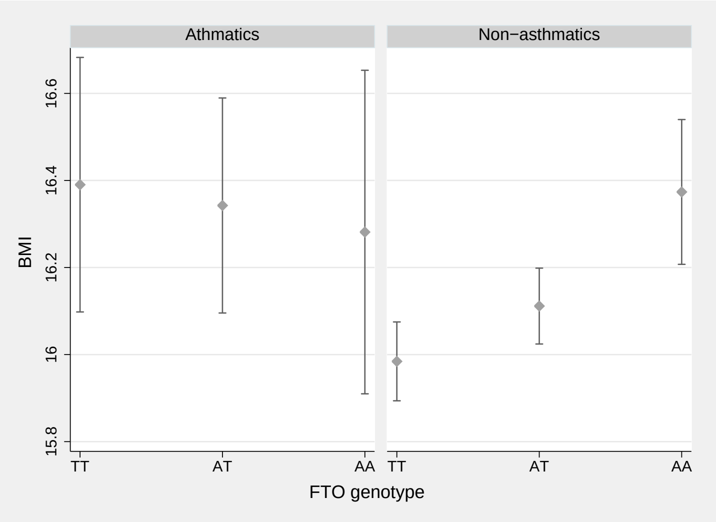

Wald type, two-stage, control function estimators

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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