Life time vascular and metabolic traits and mortality risk

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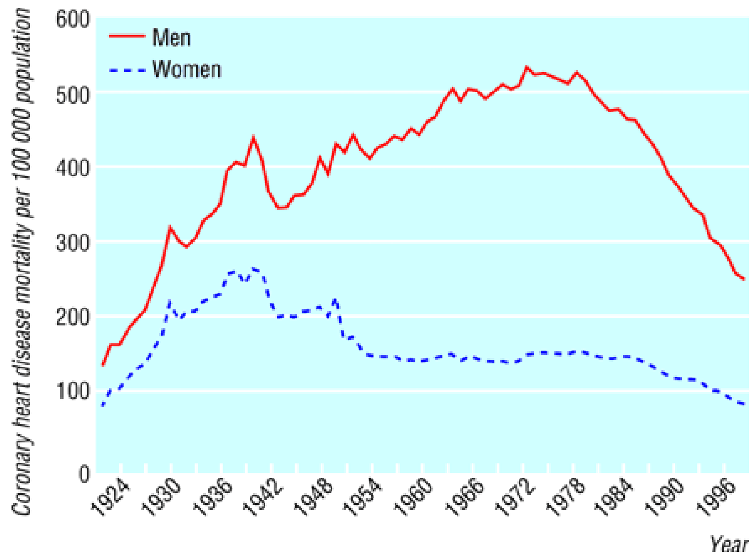
Outline

- Changes in vascular and metabolic traits over the life course
- Associations of vascular and metabolic traits at different ages with mortality risk
- Use of genetic variants as instrumental variables for examining cumulative lifetime exposure to adverse vascular/metabolic traits



Lawlor DA, et al. BMJ 2001

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23rd Infantry US Army Korea October 1951

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Coronary artery disease in young US war fatalities

Korean war - early 1950s (Enos et al, JAMA 1953)

- 200 autopsied combatants, mean age = 22 years
- 77% evidence of atherosclerosis
- 15% clinically significant narrowing of vessel(s)

Vietnam war - late 1960s (McNamara et al, JAMA 1971)

- 105 autopsied combatants, mean age = 22 years
- 45% evidence of atherosclerosis
- 5% clinically significant narrowing of vessel(s)

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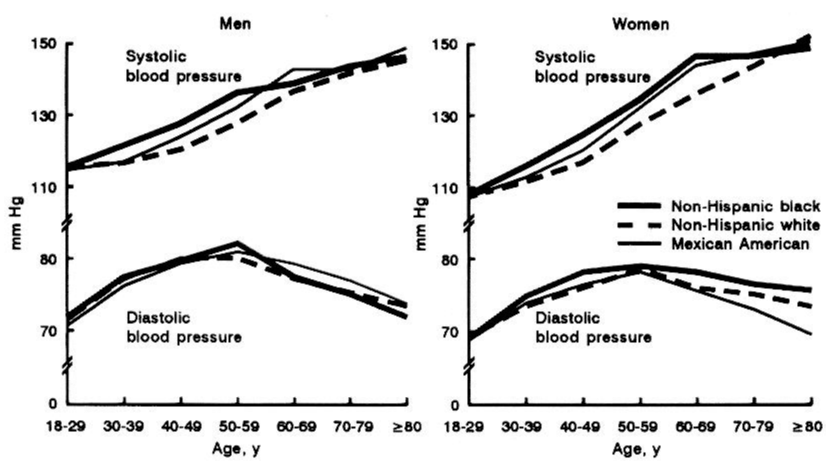
Mean SBP and DBP by age from 18 years USA



Burt VL et al. Hypertension 1995

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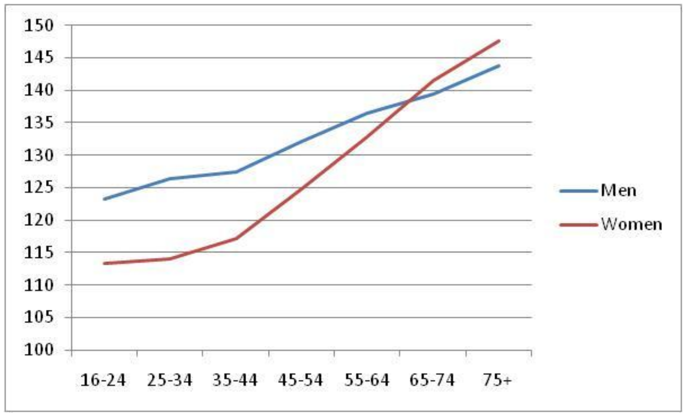
Mean SBP by age from 16 in England



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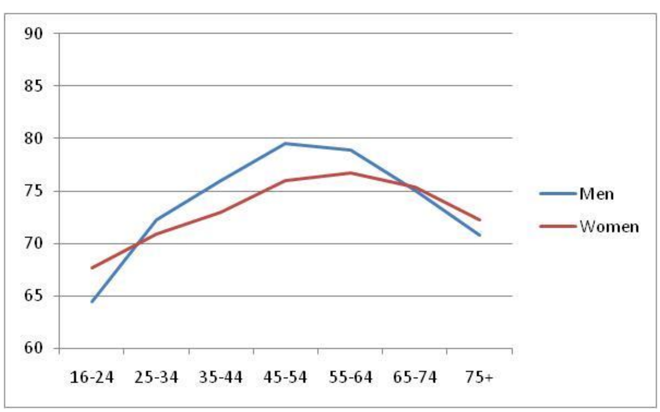
Mean DBP by age from 16 in England



HSE 2003

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Mean SBP and DBP in isolated populations

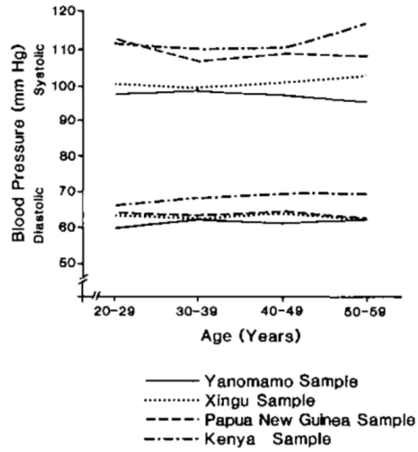

FIGURE 2. *Line graphs of systolic and diastolic pressures by 10-year age groups in the four populations.*

Carvalho et al. Hypertension 1989

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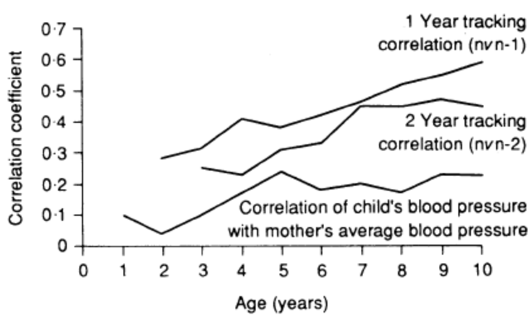
Tracking correlations of average BP



Correlation coefficients for tracking and mothers' average blood pressure with increasing age

From ~ age 15 years onwards 1 year tracking correlations ~0.7 and remain at this through adulthood

de Swiet et al. BMJ 1992

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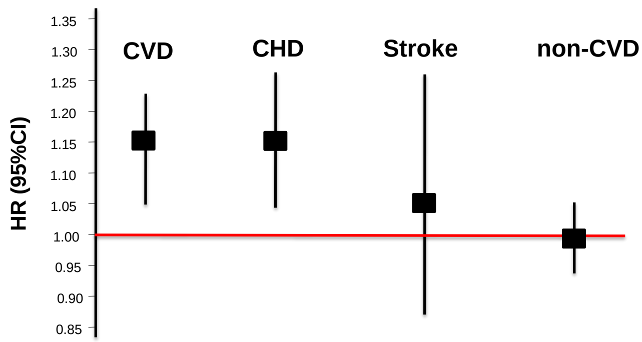
Hazard ratio of mortality per 10mmHg SBP mean age 18



McCarron P, et al. Lancet 2000; 335:1430-1431

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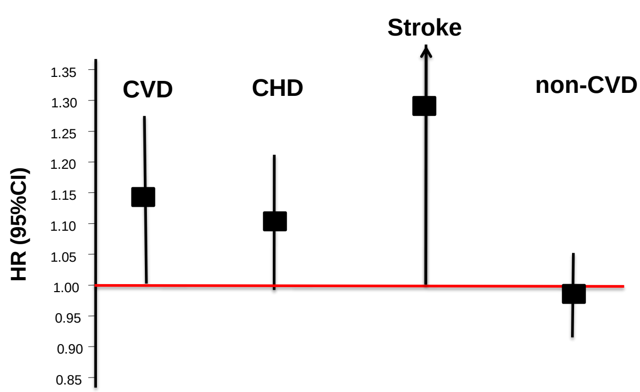
Hazard ratio of mortality per 10mmHg DBP mean age 18



McCarron P, et al. Lancet 2000; 335:1430-1431

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Conclusions – BP across the life course

- In most populations SBP increases from early adulthood to old age; DBP increases to mid-50s and then declines
- In isolated populations both SBP and DBP considerably lower than other populations and there is no age related change
- BP tracks from childhood to adulthood with tracking correlations increasing with age to a maximum in adolescence
- Variation in SBP and DBP in adolescence/early adulthood are positively associated with future CVD mortality

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Tracking correlations of lipids from childhood to adulthood

	Girls	Boys
Total Cholesterol		
2-8 years	0.48	0.53
9-14 years	0.42	0.45
LDLc		
2-8 years	0.48	0.51
9-14 years	0.44	0.50
HDLc		
2-8 years	0.23	0.04
9-14 years	0.34	0.43
Triglycerides		
2-8 years	0.32	0.18
9-14 years	0.25	0.42

Webber LS, et al. AJE 1991;13:884-99

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Association of childhood (age 12-18) risk factors with CIMT measured 21 years later

Table 4. Multivariable Model of the Relationships Between Risk Variables Measured at Ages 12-18 Years and Common Carotid Artery Intima-Media Thickness Measured 21 Years Later (n = 1170)*

Risk Variable	Regression Coefficient†	SE	*P* Value
Male sex	0.023	0.006	<.001
Age	0.002	0.001	.24
LDL-C	0.010	0.003	.001
Body mass index	0.009	0.003	.007
Systolic blood pressure	0.013	0.003	<.001
Smoking (no/yes)	0.016	0.007	.02

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
*Mean age at time of first measurement, 14.9 (SD, 2.4) years.
†Expressed in millimeters for a 1-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

Raitakari OT, et al. JAMA 2003

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Association of adult (age 33-39) risk factors with CIMT measured at same time

Table 3. Multivariable Model of the Relationships Between Current Risk Variables and Common Carotid Artery Intima-Media Thickness in Adults Aged 29 Through 39 Years (N = 2229)*

Risk Variable	Regression Coefficient†	SE	*P* Value
Male, sex	0.009	0.004	.02
Age	0.026	0.002	<.001
LDL-C	0.004	0.002	.06
Body mass index	0.011	0.002	<.001
Systolic blood pressure	0.010	0.002	<.001
Smoking (no/yes)	0.011	0.004	.004

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
*Diastolic blood pressure was also a significant correlate of intima-media thickness ($P<.001$) when entered into the model instead of systolic blood pressure.
†Expressed in millimeters for a 5-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

Magnitudes of childhood and adult associations very similar with exception of LDL-c – stronger in childhood

Raitakari OT, et al. JAMA 2003

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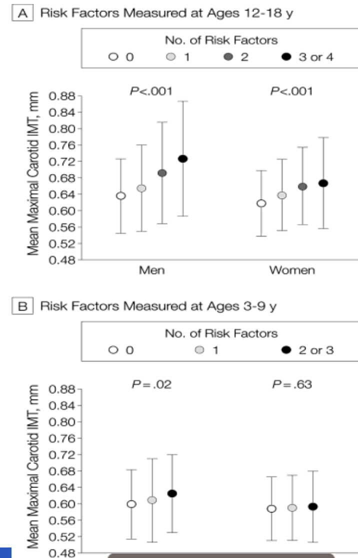
Relationships Between Numbers of Childhood Risk Factors and Common Carotid Artery Intima-Media Thickness (IMT) in Adulthood



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JAMA

Summary for lipids

- Much less extensively studied than BP
- Evidence for tracking from childhood to adulthood
- No studies of variation in early life lipids or other risk factors with CVD mortality
- From one study (Young Finns):
  - Variation in SBP, LDLc, BMI and smoking at age 12-18 (but not 3-9) years positively associated with CIMT in later adulthood
  - Additive effect of childhood risk factors on CIMT
  - HDLc, triglycerides, DBP were not associated with CIMT

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- Using genetic variants to examine causal associations of variation in risk factors across the life course
  ‘Mendelian randomization’

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- Mendel’s second law

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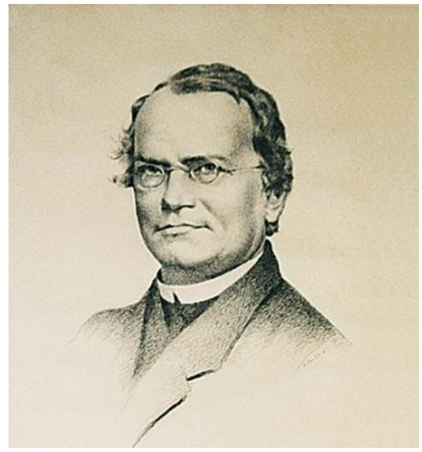
"the behaviour of each pair of differentiating characteristics in hybrid union is independent of the other differences between the two original plants"

(Sometimes called Mendel's second law – the law of independent assortment)

Gregor Mendel, 1865.



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What this means

Comparison of groups of individuals defined by genotype should only differ with respect to the locus under study (and closely related loci in linkage disequilibrium with the locus under study).

Little residual bias, or confounding by any behavioural, socioeconomic or physiological factors

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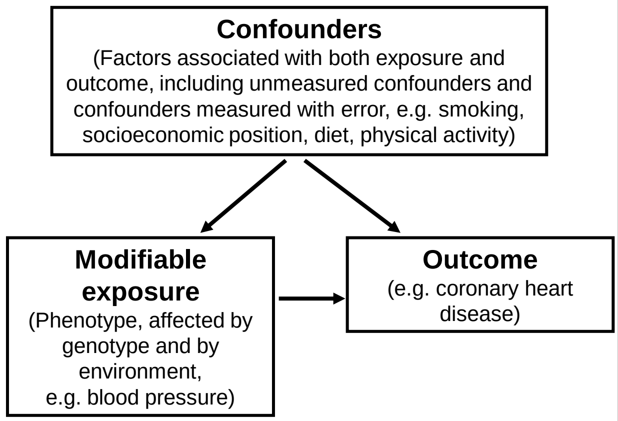
Conventional observational epidemiology



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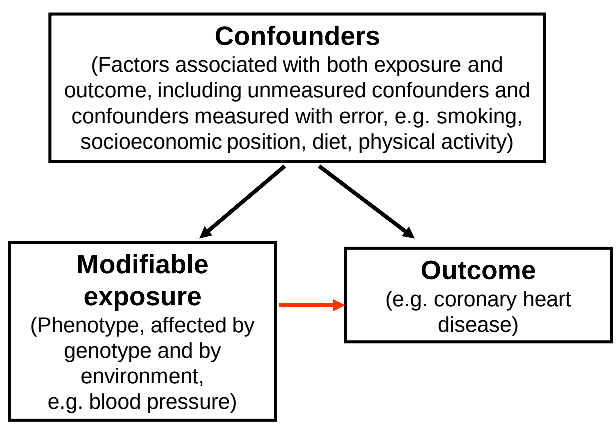
Conventional observational epidemiology



It is often impossible to exclude unmeasured or residual confounding or reverse causality as an explanation for observed exposure/outcome associations

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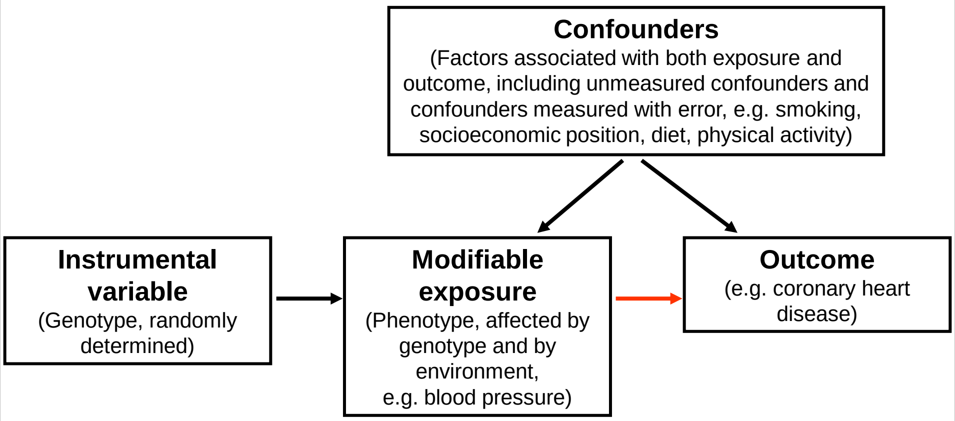
IV Mendelian randomisation approach



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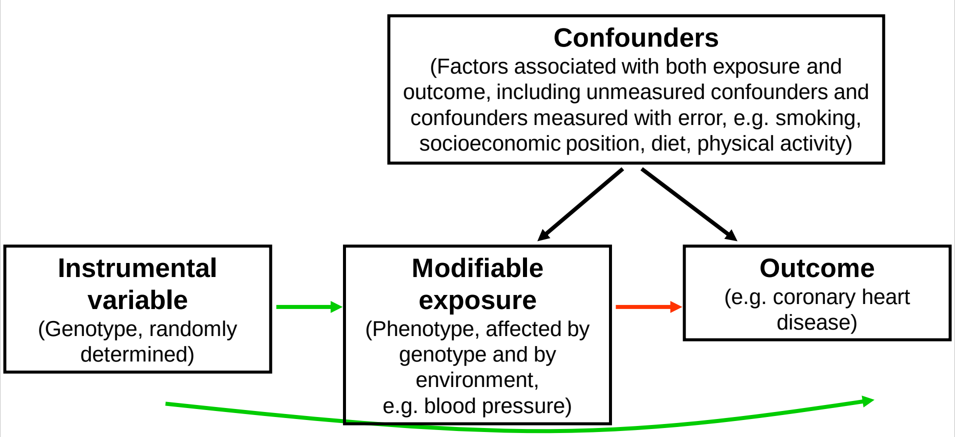
IV Mendelian randomisation approach



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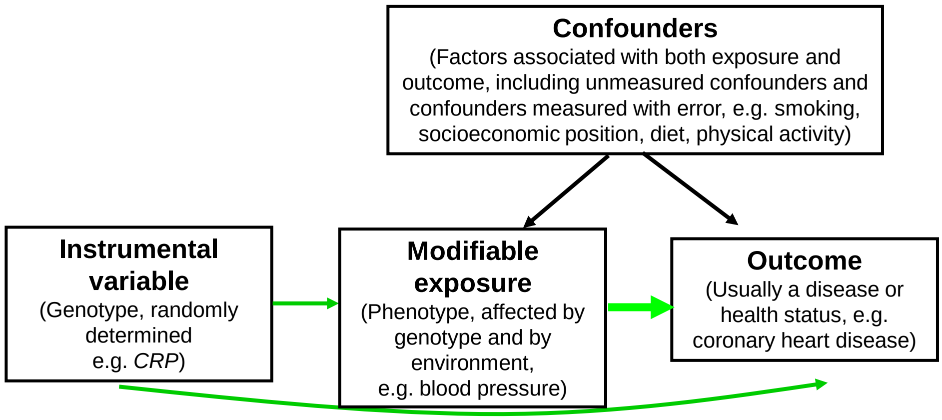
IV Mendelian randomisation approach

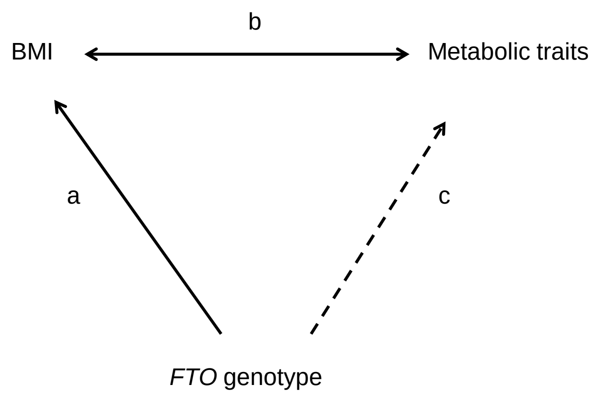


We use associations that are not affected by confounding and cannot be explained by reverse causality to estimate the causal exposure-outcome association

Example: Is greater BMI causally associated with adverse metabolic & vascular traits?

- BMI associated with a wide range of health outcomes, including associations with greater glucose, insulin and adverse lipid profile
- Is the association exaggerated due to confounding by e.g. SEP, physical activity?
- Is the association an underestimate because of masking (confounding) by smoking and reverse causality?

Triangulation of associations



Freathy R, Timpson NJ, Lawlor DA, et al. *Diabetes* 2008

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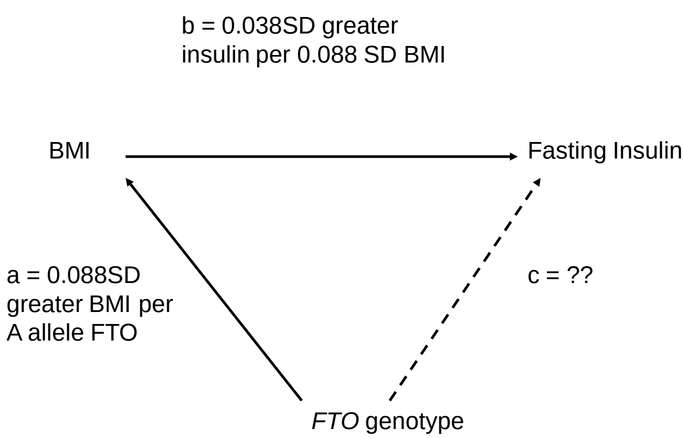
Triangulation: Insulin



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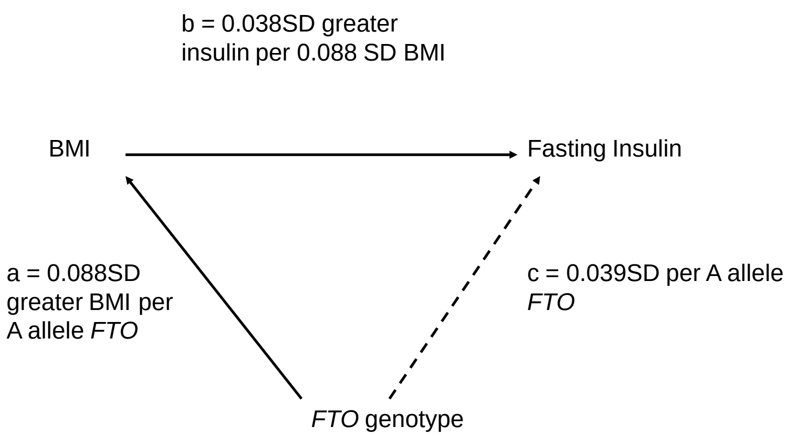
Triangulation: Insulin



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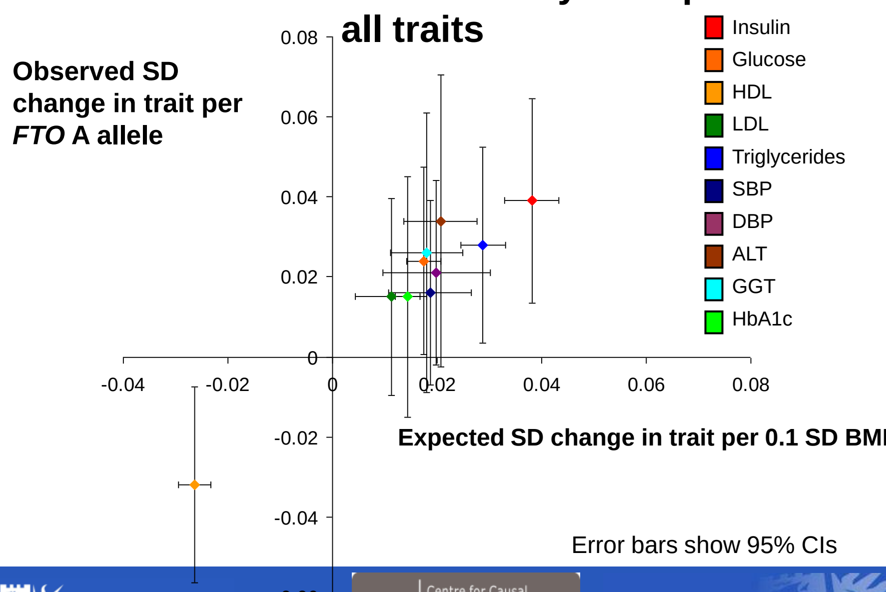
Observed effect sizes were exactly as expected for all traits



Error bars show 95% CIs

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Assessing effect of life time exposure

- In general genetic variants are associated with phenotypes through out life. Therefore:
  - MR may have limited applicability for examining critical / sensitive periods
  - MR often giving estimate of causal effect of lifetime (cumulative) differences
  - E.g. genetic variants associated with LDLc suggest a stronger association of this with CVD than anticipated from statin RCTs

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Conclusions 1

- CHD and stroke mortality declining over last 3-4 decades through changes in adult behaviours and treatment of adult risk factors (antihypertensives and lipids)
- Atherosclerosis pathophysiology begins around adolescence/early adulthood
- Variation in BP in adolescence/early adulthood associated with future CVD mortality

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Conclusions 2

- To date less evidence for effect of early life lipids
- Variation in LDLc in late childhood / early adulthood (age 12-18) may be important
- Causal effect of T2DM / glycaemia in childhood (and adulthood) less clear
- Genetic variants can be used to examine causal associations of lifetime exposures to risk factors but very large studies required.

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