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Lude Franke >

Causal inference: mendelian randomization and instrumental variable analysis

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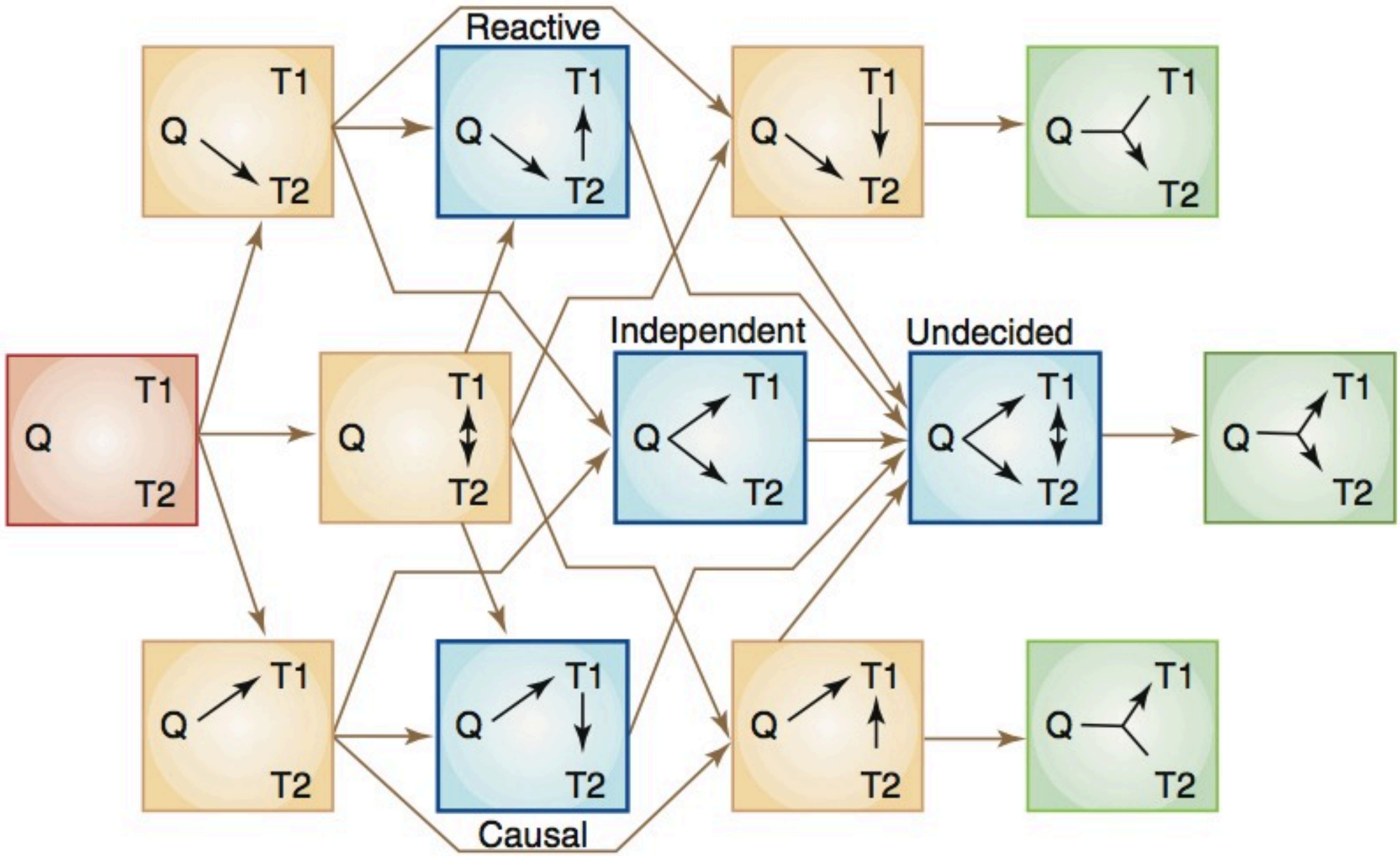
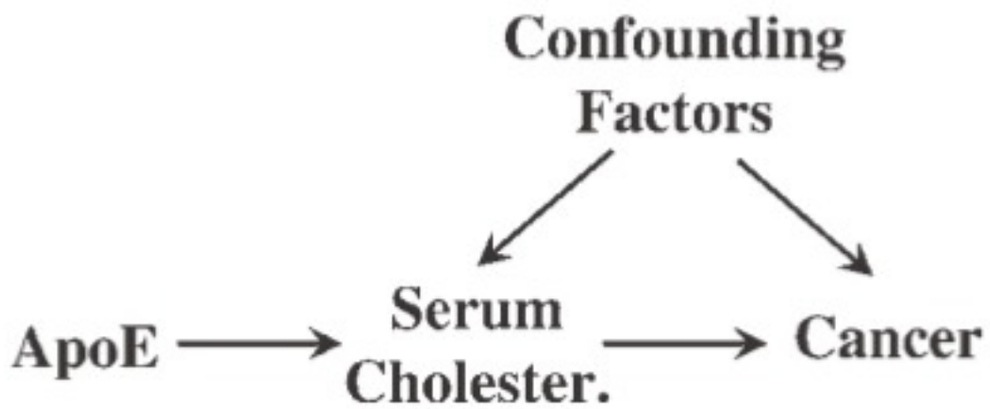
Introduction



Tesson *et al*, Trends in Genetics 2010

Introduction



PLoS Medicine 2008

Examples of mendelian randomisation

Disease or Outcome	Exposure or Phenotype of Interest	Genetic Variant (Instrument)	Findings	Reference(s)
Coronary heart disease	Fibrinogen	Beta-fibrinogen *G-455→A* and *C-148→T* polymorphisms	Evidence from these MR studies would suggest that reported observational plasma fibrinogen–CHD associations are explained by confounding or reverse causation.	[20,21]
Stroke	Homocysteine	*MTHFR C677T* polymorphism	MR evidence is consistent with a causal relation between homocysteine concentration and stroke.	[22]
Carotid intima media thickness	CRP	*CRP* gene (haplotypes derived from 5 SNPs)	MR evidence from this study does not support a causal role for CRP in the development of a thickened intima media (and potentially later CHD).	[23]
Myocardial infarction	CRP	*CRP* gene *+1444 C>T* polymorphism	MR evidence from this study does not support a causal role for CRP in non-fatal myocardial infarction.	[24]
Metabolic phenotypes	CRP	*CRP* gene +1444 C>T polymorphism	CRP has been associated with metabolic phenotypes in observational studies, but MR evidence from this study does not support a causal relationship between CRP levels and any of the metabolic phenotypes studied.	[25]
Blood pressure and hypertension	CRP	*CRP* gene *1059G/C* polymorphism	Evidence from this study does not support a causal relationship between CRP levels and blood pressure or hypertension.	[26]
Blood pressure	Alcohol intake	*ALDH2*2* allele	MR evidence supports the hypothesis that (even modest) alcohol intake increases blood pressure.	[9]
Type 2 diabetes	MIF	*MIF* gene (4 SNPs)	MR evidence supports a causal role for MIF in the development of T2D in women.	[27]
Fat mass	Maternal BMI	*FTO* gene *rs9939609* polymorphism	MR evidence does not support the hypothesis that maternal BMI during pregnancy affects fat mass in children aged 9–11 years.	[34]
Physical function in 65- to 80-year-olds	IL-18	Four *IL-18* gene polymorphisms	MR evidence supports the hypothesis that high IL-18 levels are a cause rather than a consequence of disability in the elderly.	[28]

This table gives a range of examples that illustrate how Mendelian randomisation is used in practice. It is not intended to give a complete and balanced overview of the area, however, as there are many more studies that are not referred to here.
BMI, body mass index; CRP, C-reactive protein; IL, interleukin; MIF, macrophage migration inhibitory factor; MR, Mendelian randomisation; SNP, single nucleotide polymorphisms; T2D, type 2 diabetes.