Causal inference of mediation mechanism

Part II: 因果中介與實例

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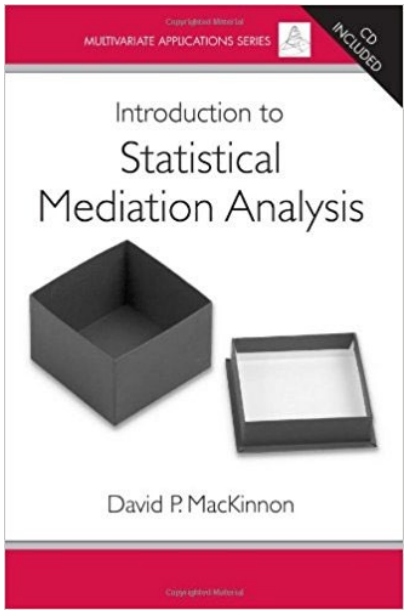
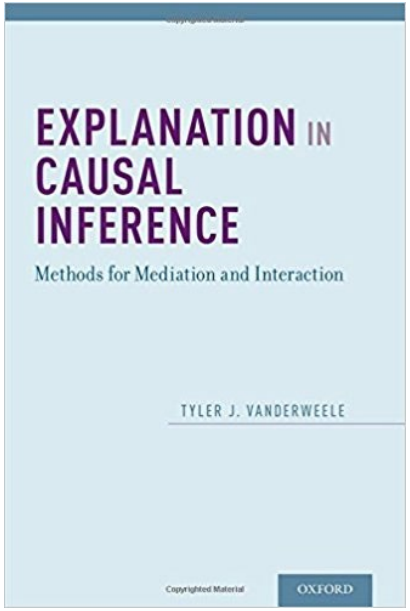
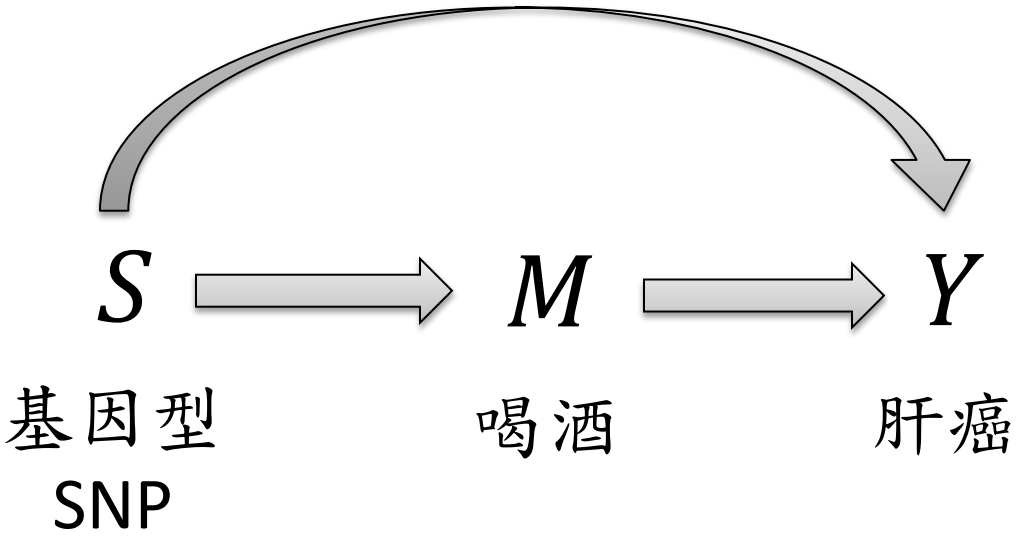




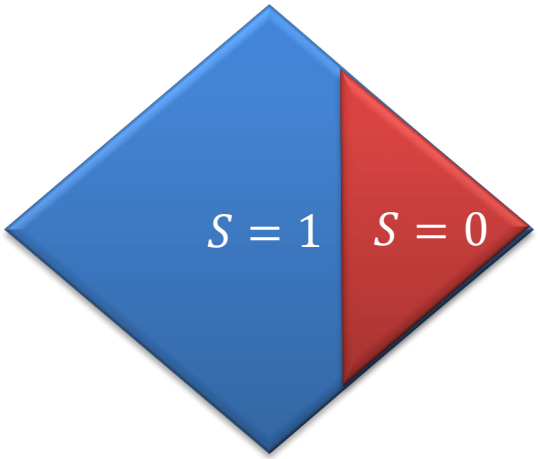
DAG: Directed Acyclic Graph



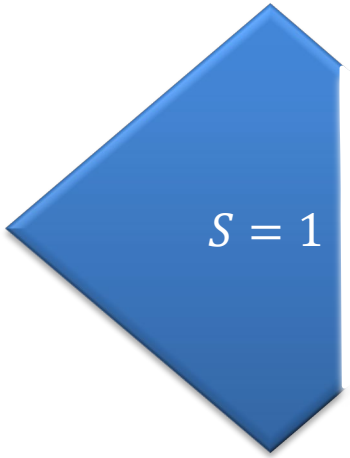
I. Recap

Genetic association studies

Genetic association studies



$$S_1 \Longrightarrow Y$$



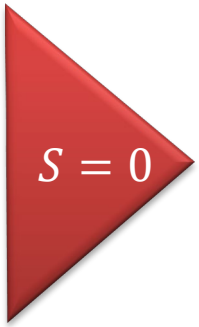
vs.

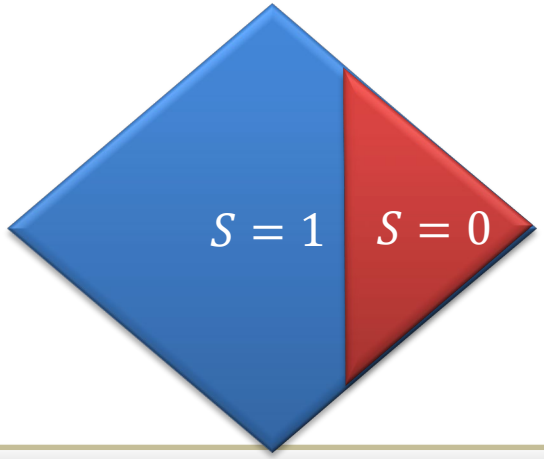
$$S_0 \Longrightarrow Y$$

Association vs. causation

Association

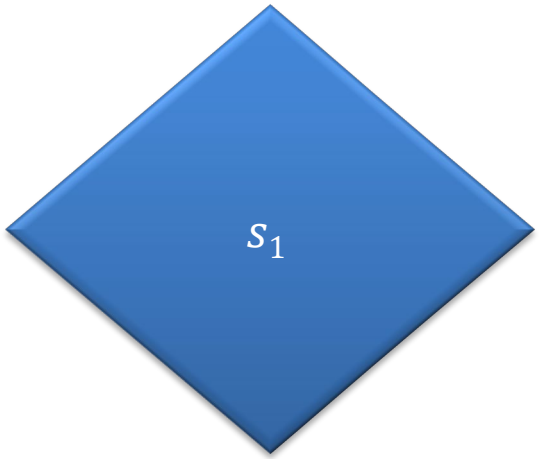
vs.



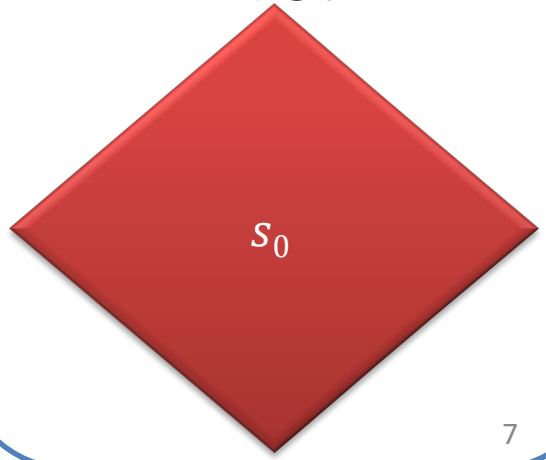


$S \longrightarrow Y$

Causation

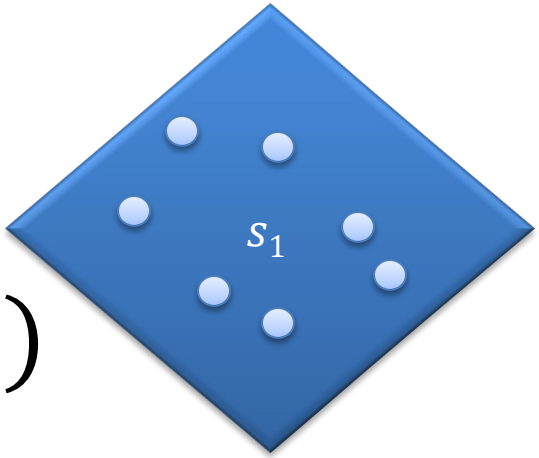


vs.



Potential outcome

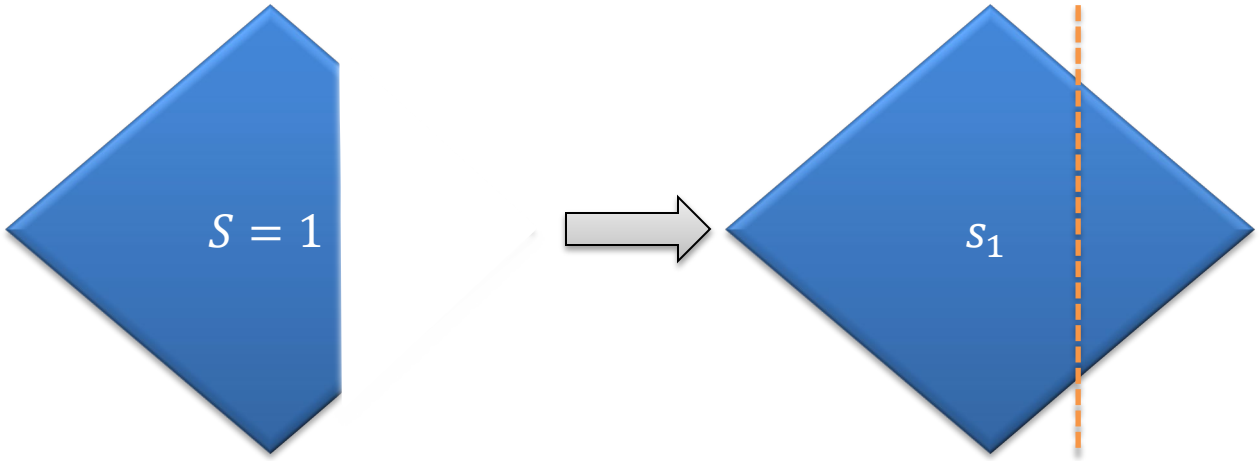
$S_1 \longrightarrow Y(S_1)$



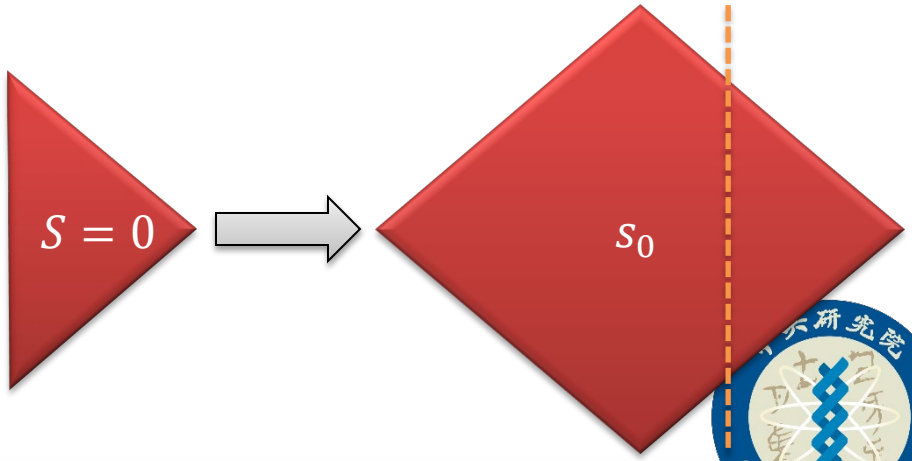
$S_0 \longrightarrow Y(S_0)$

No confounding -> exchangeability

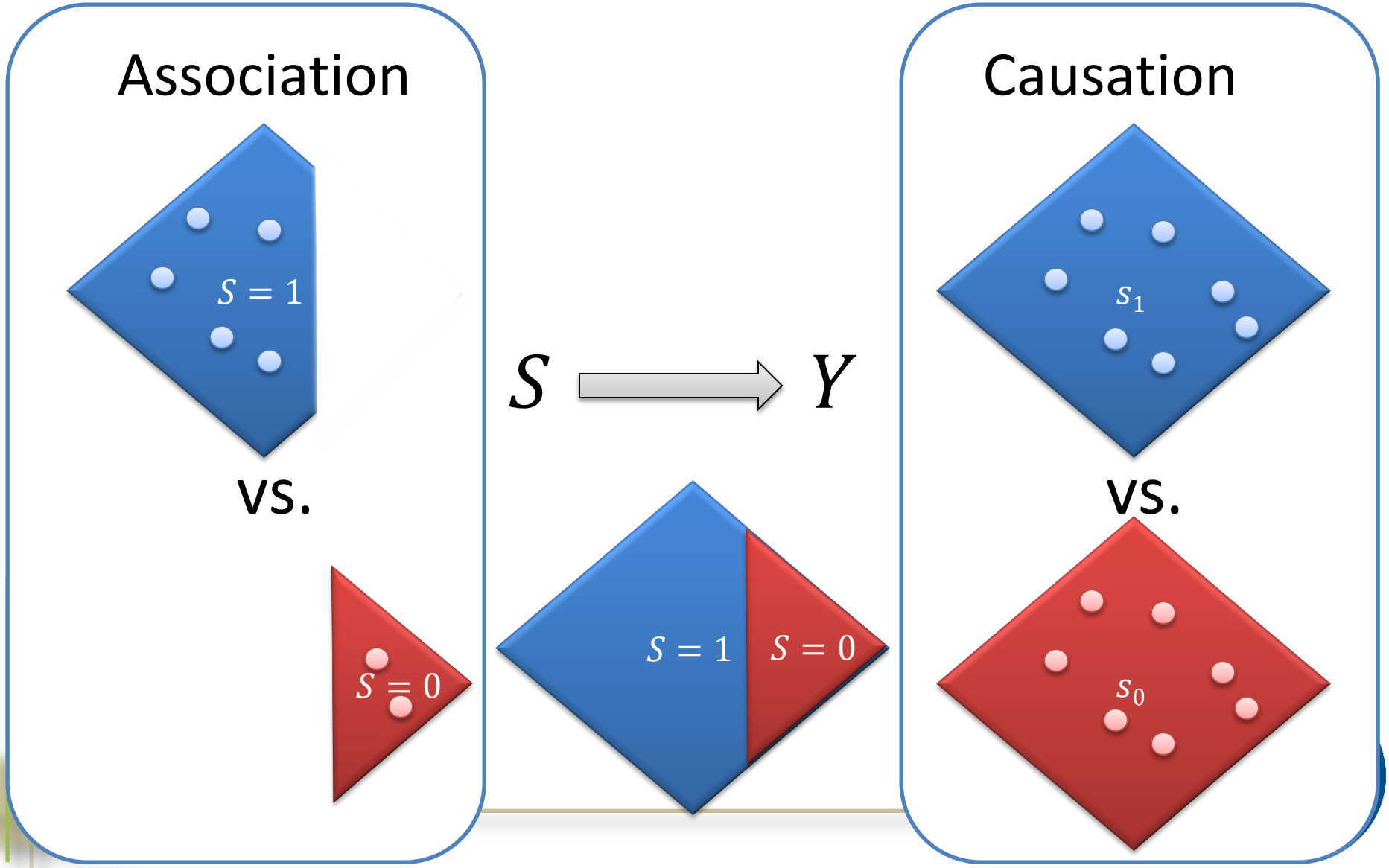
- $Y(s_1) \perp S$



- $Y(s_0) \perp S$



If no confounding, association=causation



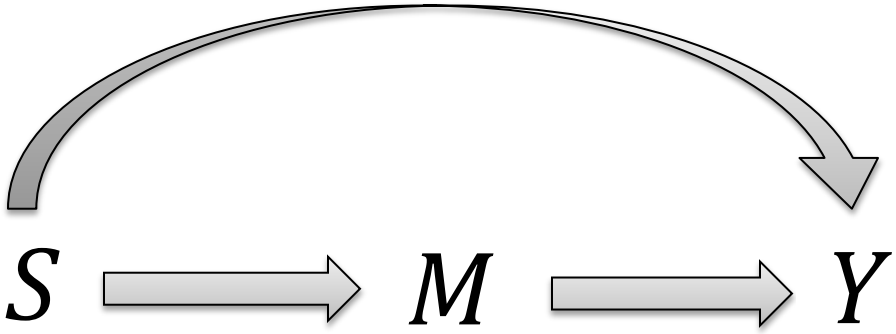
II. Definition

History of Mediation Analysis

- First proposed by Baron and Kenny (1986) in psychology literature; canonical reference in social sciences
- Mediation in causal inference: (Robins and Greenland 1992; Pearl 2001)
  - Counterfactual; assumptions for identifiability
- Recent work on causal mediation model
  - VanderWeele and Vansteelandt (2010) and Imai et al. (2010)

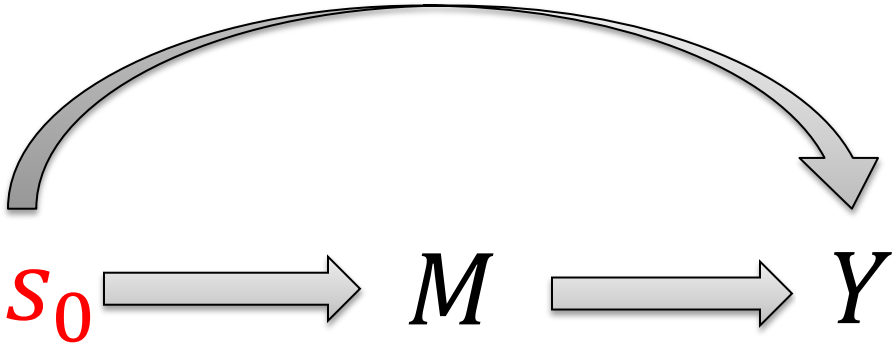
Counterfactual outcome

- Hypothetical intervention steps



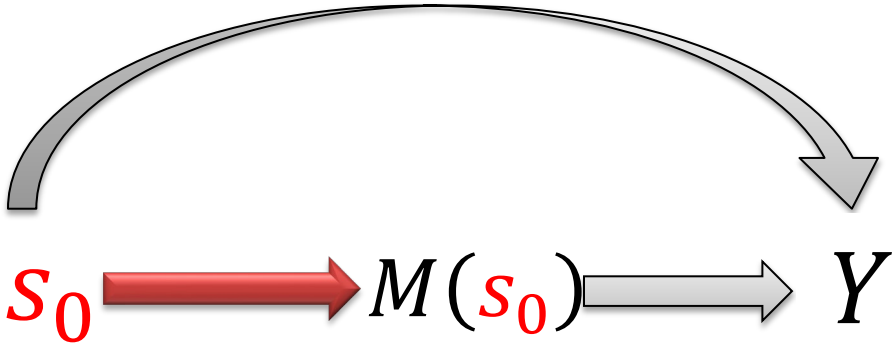
Counterfactual outcome

- Hypothetical intervention steps:
  - Intervene and set SNPs to s_0



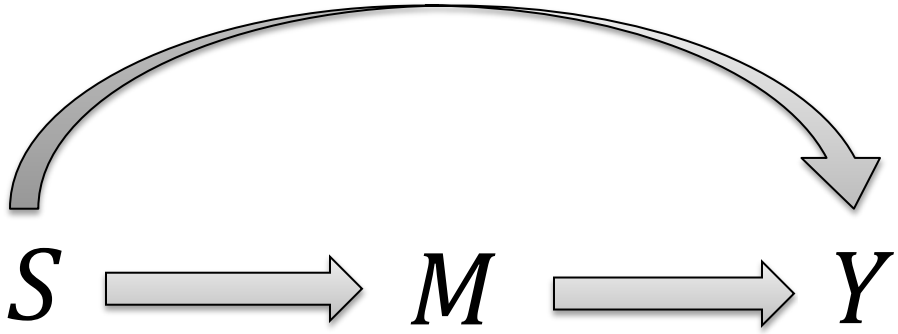
Counterfactual outcome

- Hypothetical intervention steps
  - Observe the counterfactual outcome alcohol consumption behavior, $M(s_0)$



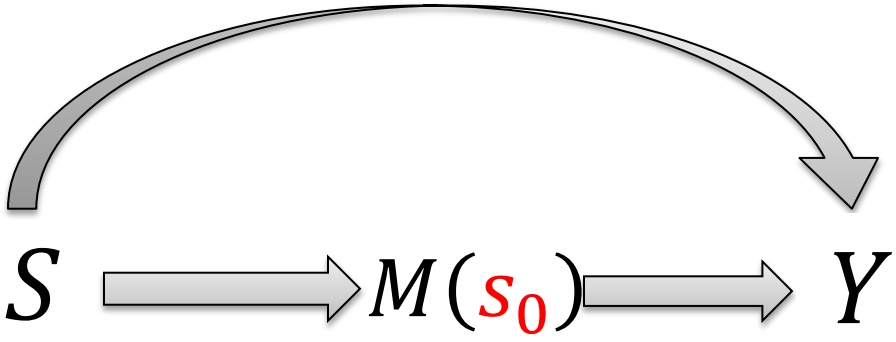
Counterfactual outcome

- Hypothetical intervention steps
  - Return to the pre-intervention state



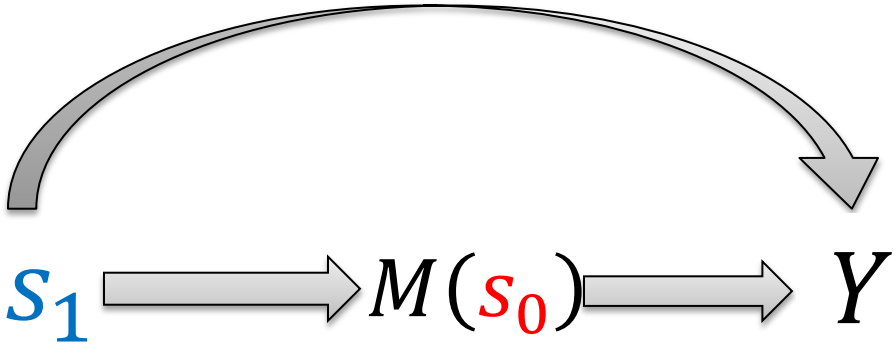
Counterfactual outcome

- Hypothetical intervention steps
  - Intervene to set alcohol consumption behavior to $M(s_0)$…



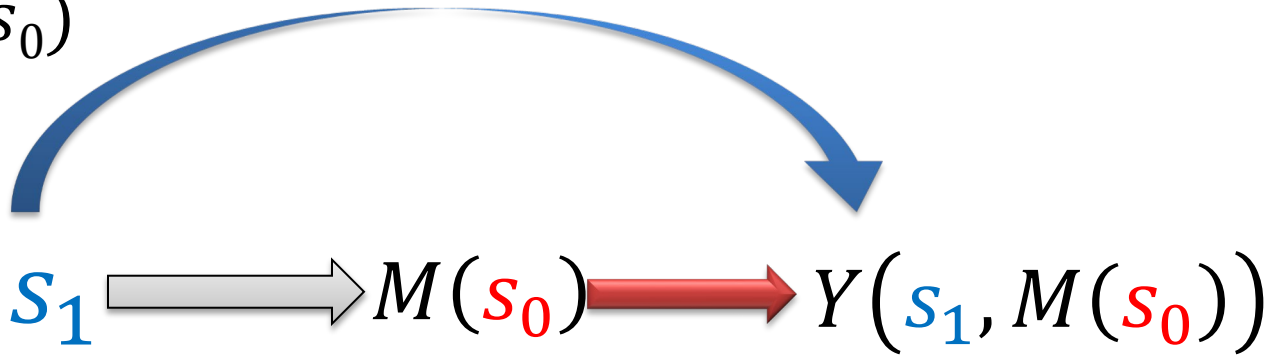
Counterfactual outcome

- Hypothetical intervention steps
  - … and intervene to set SNP to s_1



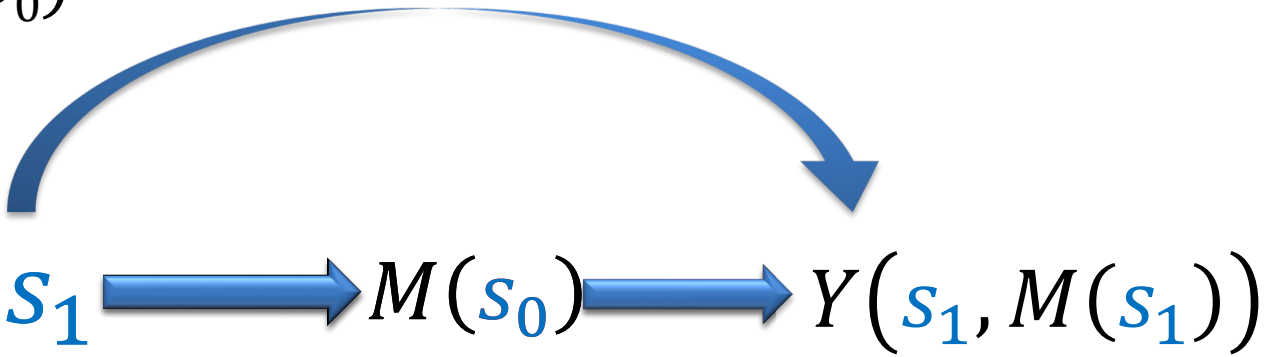
Counterfactual outcome

- Hypothetical intervention steps
  - Observe $Y(s_1, M(s_0))$: the counterfactual outcome, liver cancer risk Y under intervention s_1 and $M(s_0)$



How can this be possible?

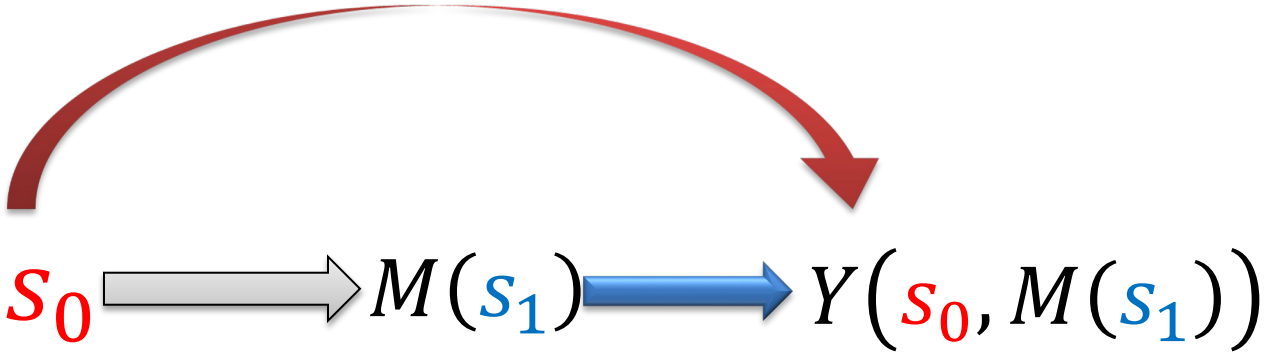
- Hypothetical intervention steps
  - Observe $Y(s_1, M(s_0))$: the counterfactual outcome, liver cancer risk Y under intervention s_1 and $M(s_0)$



  - It takes years for genetics to affect drinking behavior $M(s_0)$, and the time lag makes $Y(s_1, M(s_0))$ identifiable.

Counterfactual outcome

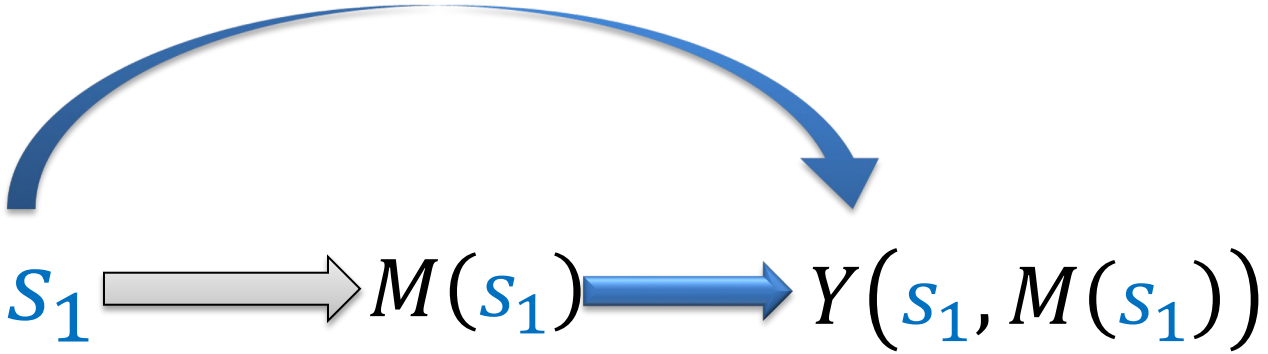
- Hypothetical intervention steps
  - Following similar steps, we can obtain $Y(s_0, M(s_1))$



  - the counterfactual outcome, liver cancer risk Y under intervention for SNP, s_0 and that for alcohol consumption behavior, $M(s_1)$

Counterfactual outcome

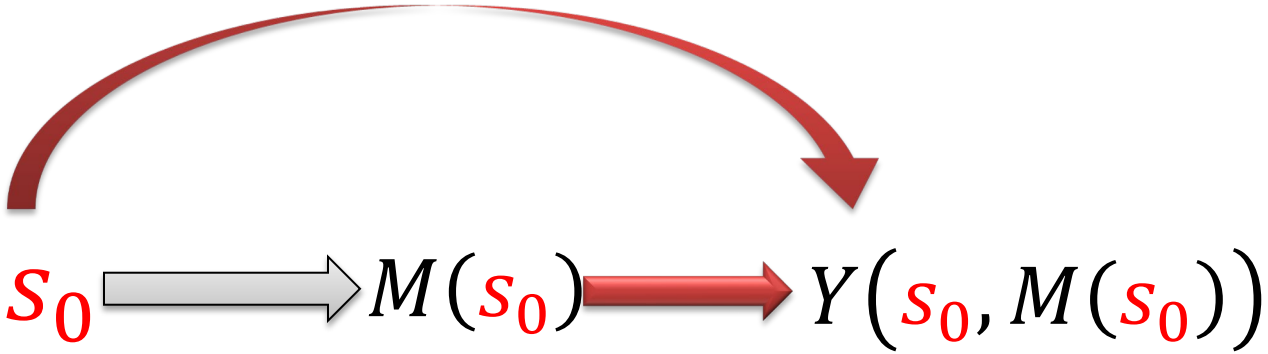
- Hypothetical intervention steps
  - Following similar steps, we can obtain $Y(s_1, M(s_1))$



  - the counterfactual outcome, liver cancer risk Y under intervention for SNP, s_1 and that for alcohol consumption behavior, $M(s_1)$

Counterfactual outcome

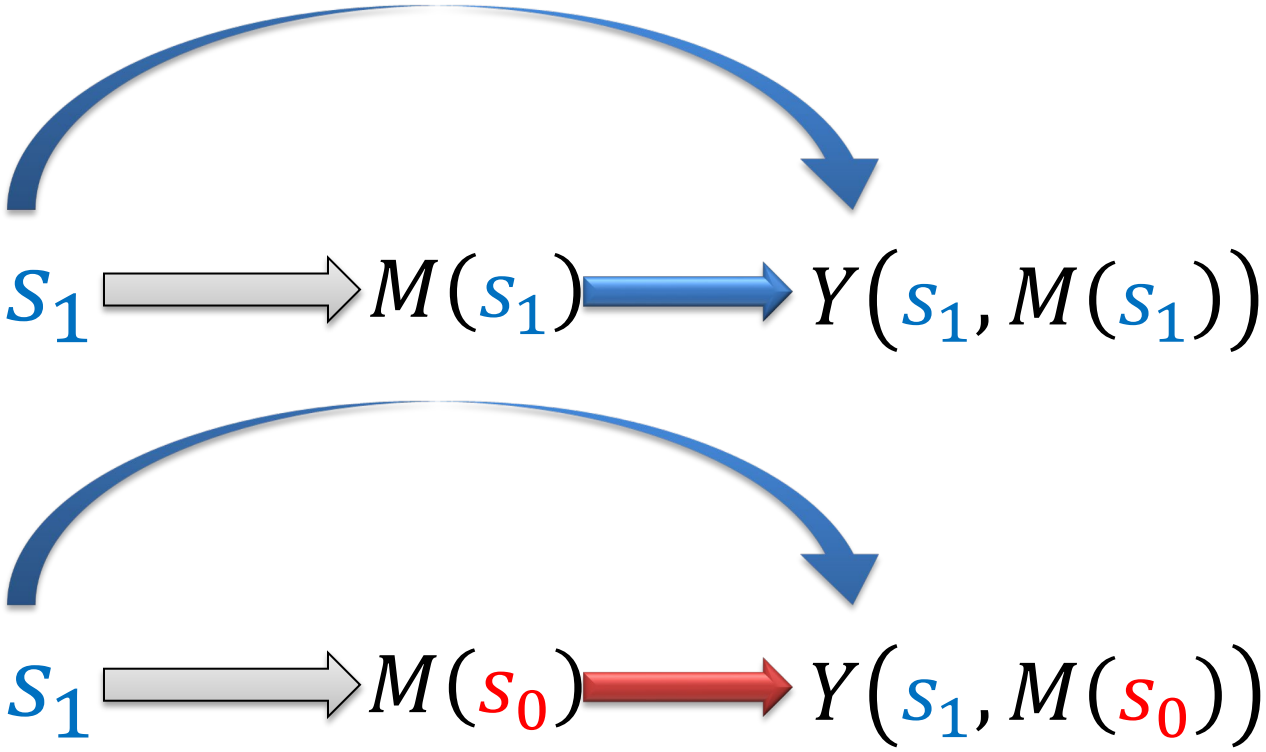
- Hypothetical intervention steps
  - Following similar steps, we can obtain $Y(s_0, M(s_0))$



  - the counterfactual outcome, liver cancer risk Y under intervention for SNP, s_0 and that for alcohol consumption behavior, $M(s_0)$

Natural indirect effect

- $NIE = \mathbb{E}\left[Y\left(s_1, M(s_1)\right)\right] - \mathbb{E}\left[Y\left(s_1, M(s_0)\right)\right]$



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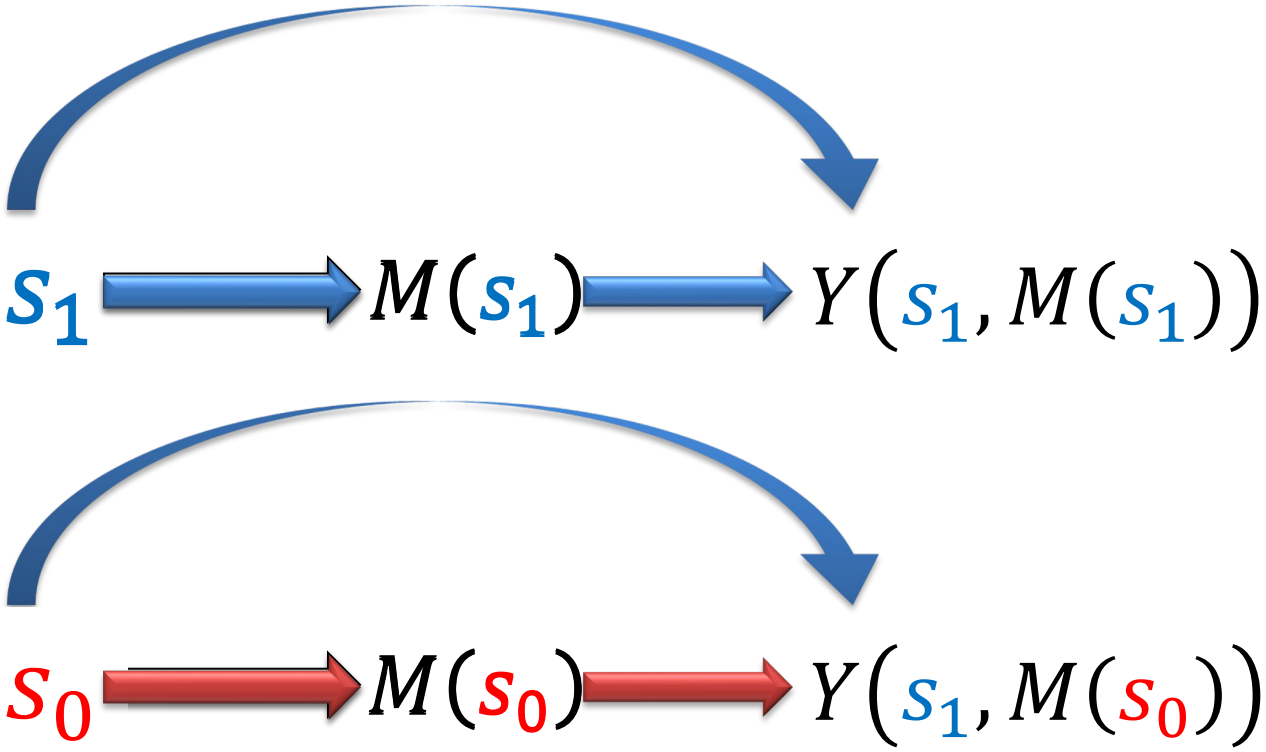
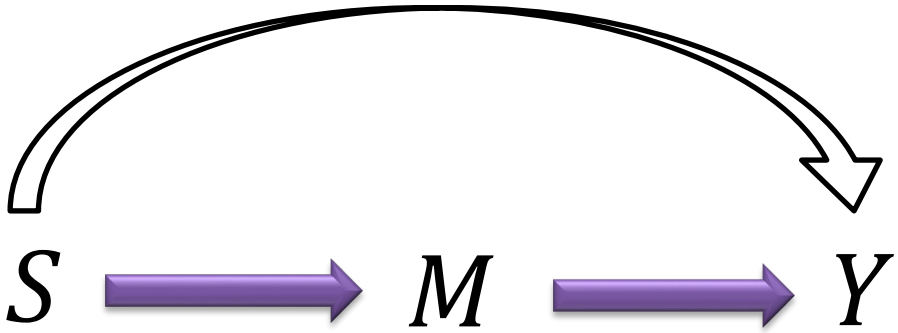


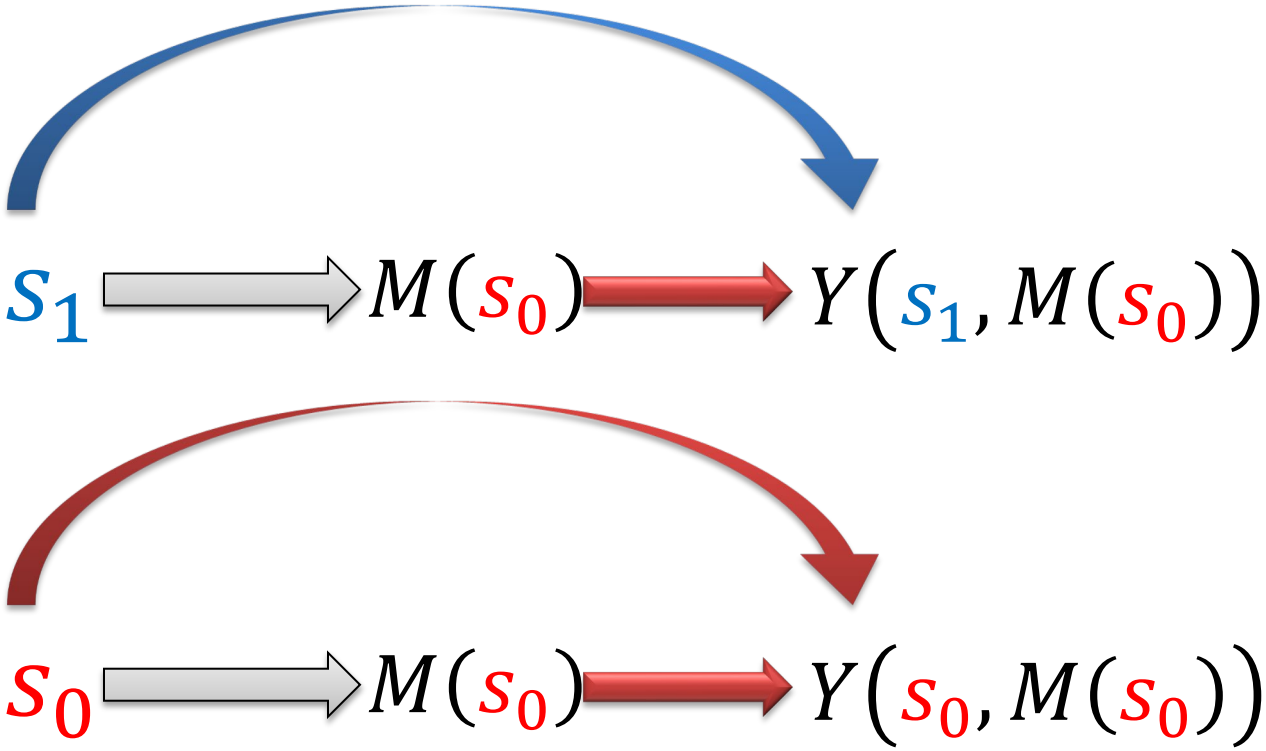
Natural Indirect Effect

- NIE=The effect of SNP (S) on outcome (Y=Liver cancer risk) mediated through mediator (M=alcohol consumption).



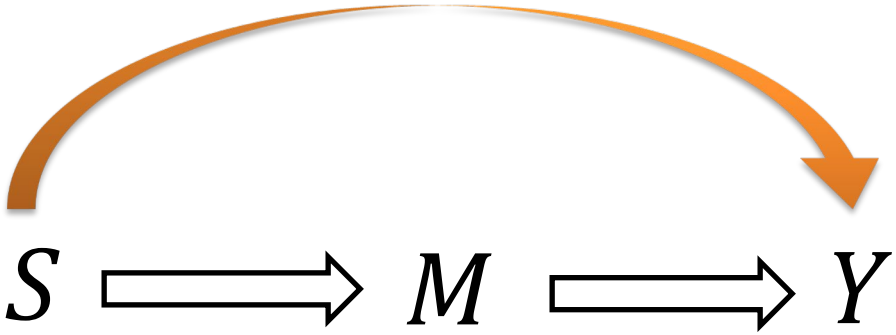
Natural direct effect

- $NDE = \mathbb{E}\left[Y\left(s_1, M(s_0)\right)\right] - \mathbb{E}\left[Y\left(s_0, M(s_0)\right)\right]$



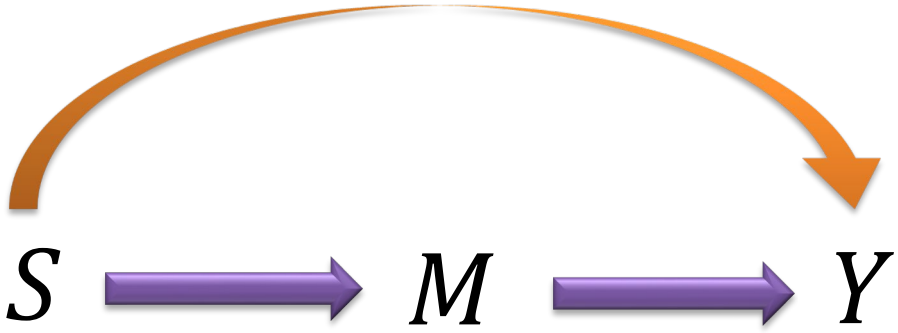
Natural Direct Effect

- NDE=The effect of SNP (S) on outcome (Y=Liver cancer risk) through mechanisms not involving alcohol drinking.



Total Effect

Total Effect=NDE+NIE

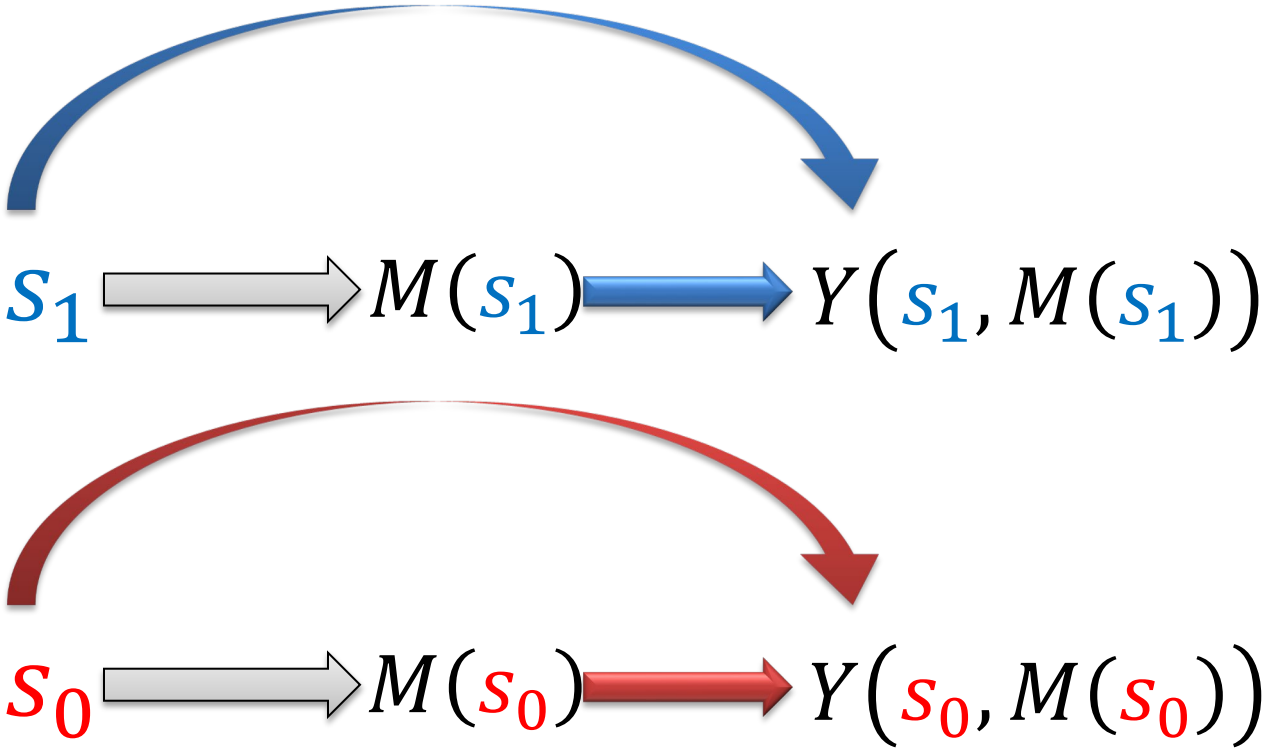


Total effect: effect decomposition

- $TE = NDE + NIE$
- $$TE = \mathbb{E}\left[Y\left(s_1, M(s_0)\right)\right] - \mathbb{E}\left[Y\left(s_0, M(s_0)\right)\right] + \mathbb{E}\left[Y\left(s_1, M(s_1)\right)\right] - \mathbb{E}\left[Y\left(s_1, M(s_0)\right)\right] = \mathbb{E}\left[Y\left(s_1, M(s_1)\right)\right] - \mathbb{E}\left[Y\left(s_0, M(s_0)\right)\right]$$

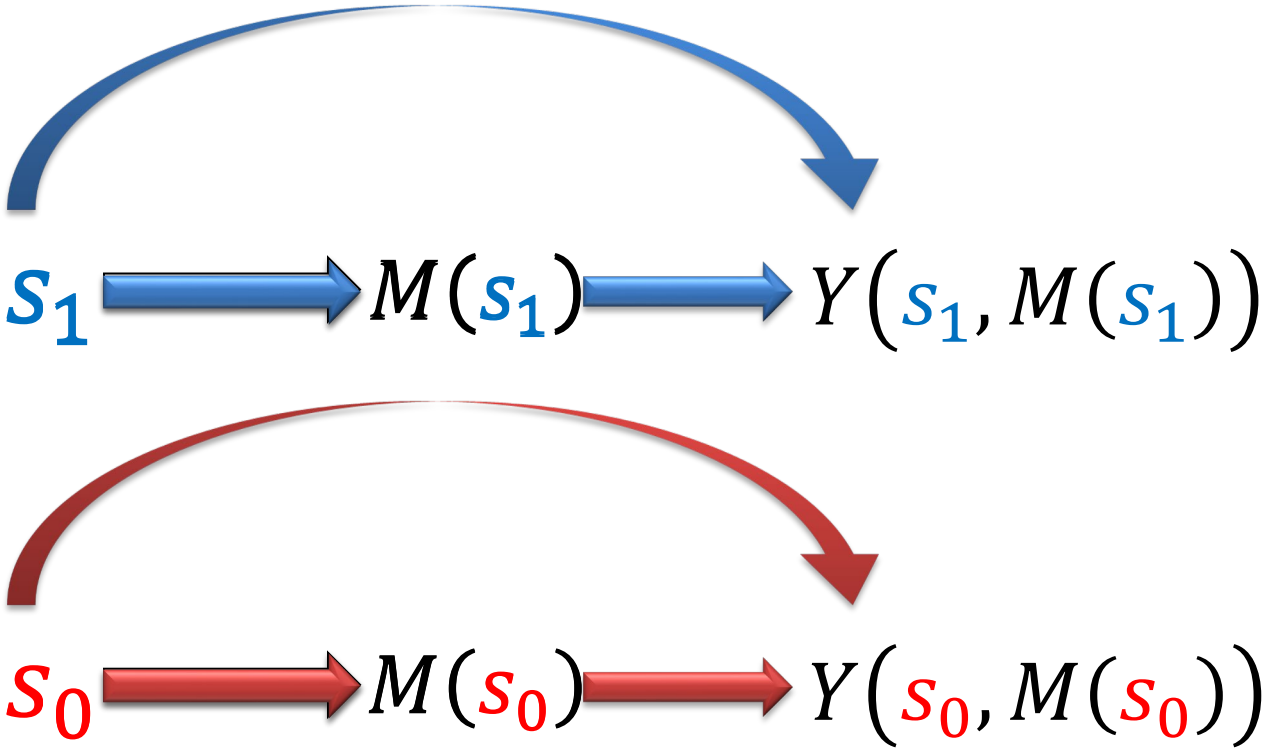
Total effect: effect decomposition

$$TE = \mathbb{E}\left[Y\left(s_1, M(s_1)\right)\right] - \mathbb{E}\left[Y\left(s_0, M(s_0)\right)\right]$$



Total effect: effect decomposition

$$TE = \mathbb{E}\left[Y\left(s_1, M(s_1)\right)\right] - \mathbb{E}\left[Y\left(s_0, M(s_0)\right)\right]$$

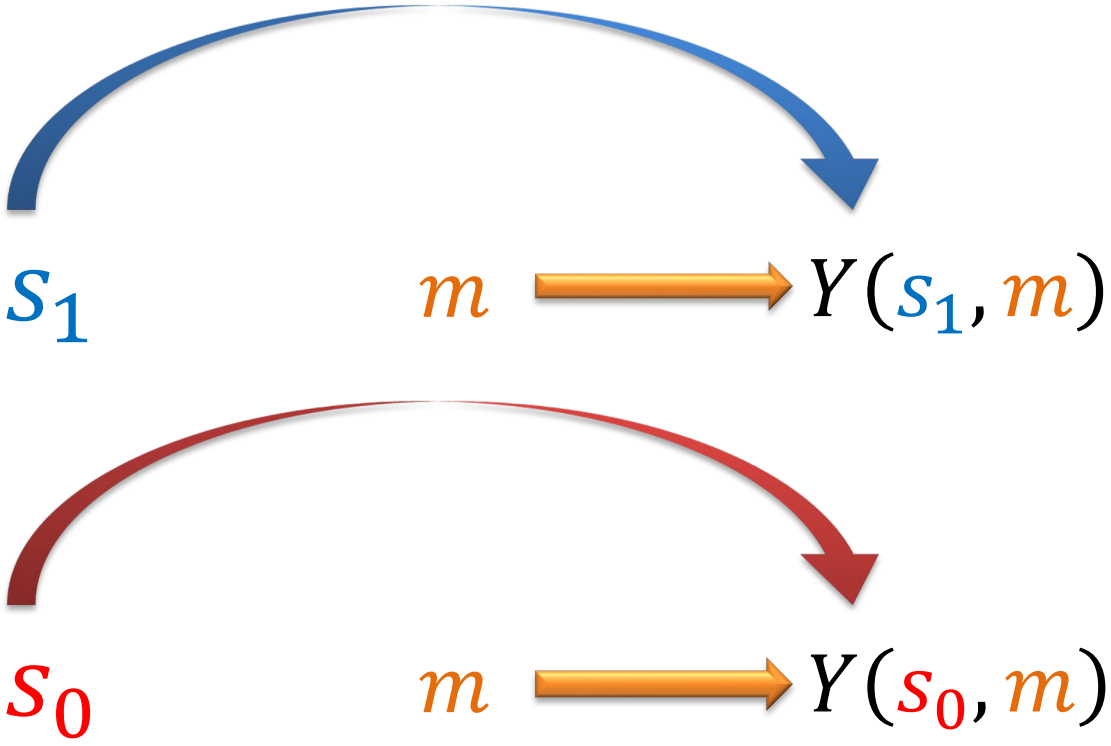


Total effect

$$TE = \mathbb{E}[Y(s_1)] - \mathbb{E}[Y(s_0)]$$

Controlled direct effect

- $CDE = \mathbb{E}[Y(s_1, m)] - \mathbb{E}[Y(s_0, m)]$

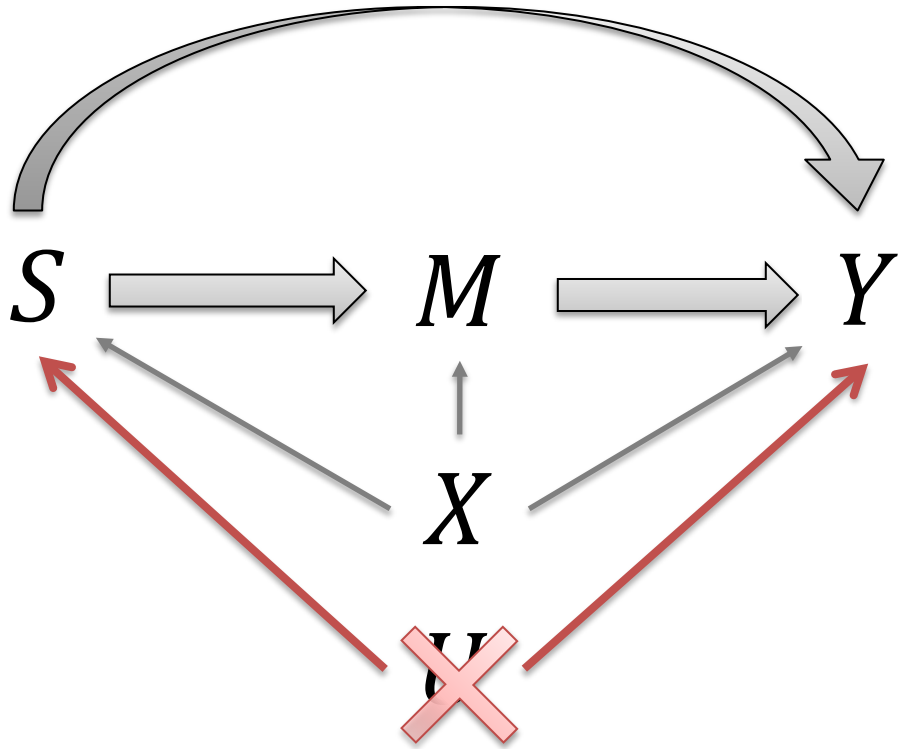


III. Assumptions

Assumption A1

$$Y(s,m) \perp S|X$$

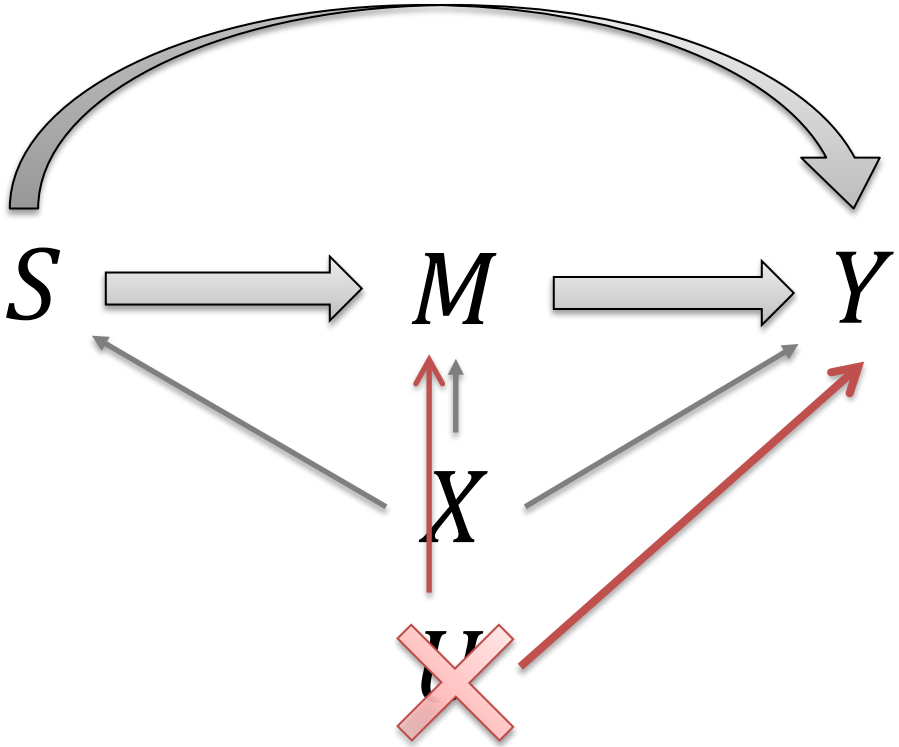
– no unmeasured confounding for the effect of exposure (S) on the outcome (Y);



Assumption A2

$Y(s,m) \perp M|(S,X)$

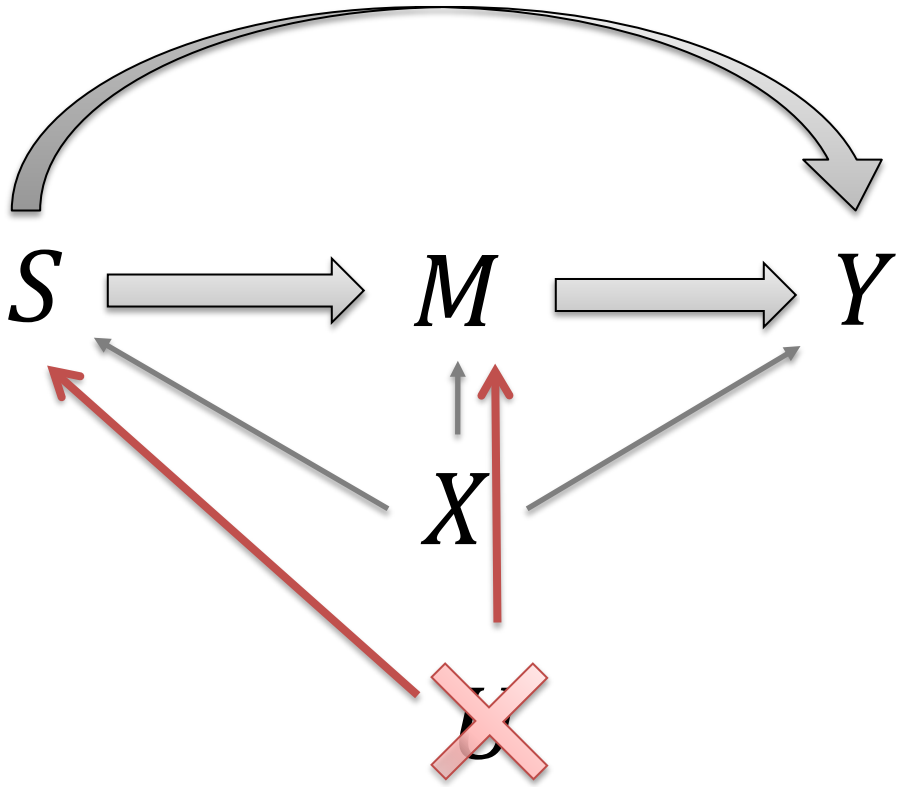
– no unmeasured confounding for the effect of mediator (M) on the outcome (Y) after controlling for exposure (S);



Assumption A3

$$M(s) \perp S|X$$

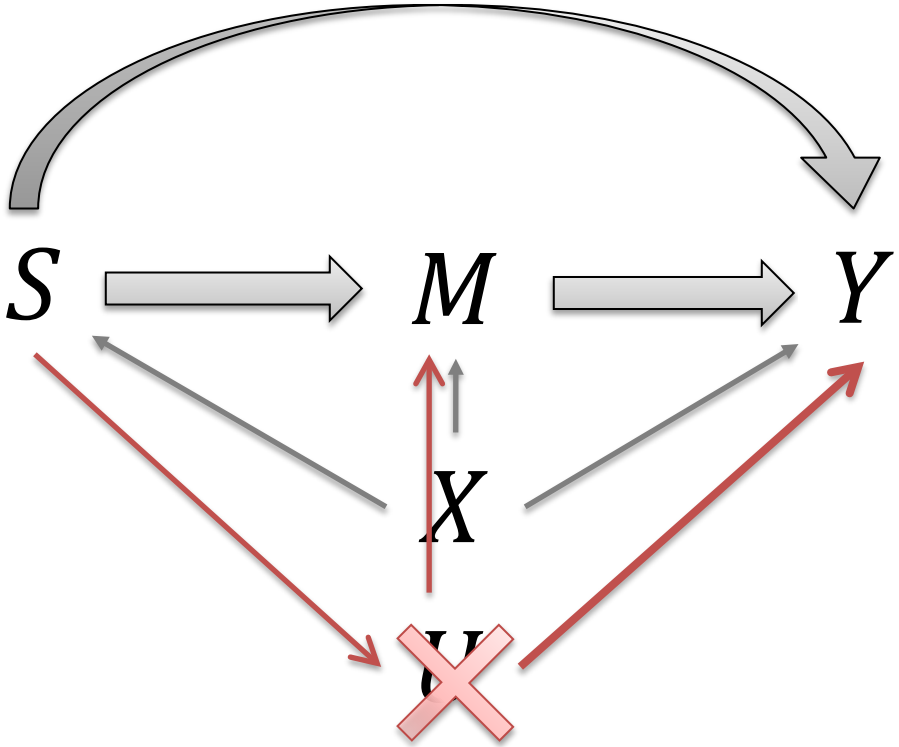
– no unmeasured confounding for the effect of exposure (S) on mediator (M);



Assumption A4

$Y(s,m) \perp M(s^*)|X$

– there is no downstream effect of exposure (S) that can confound mediator-outcome ($M-Y$) relation



IV. Mediation analysis

Two regression models for mediation analysis

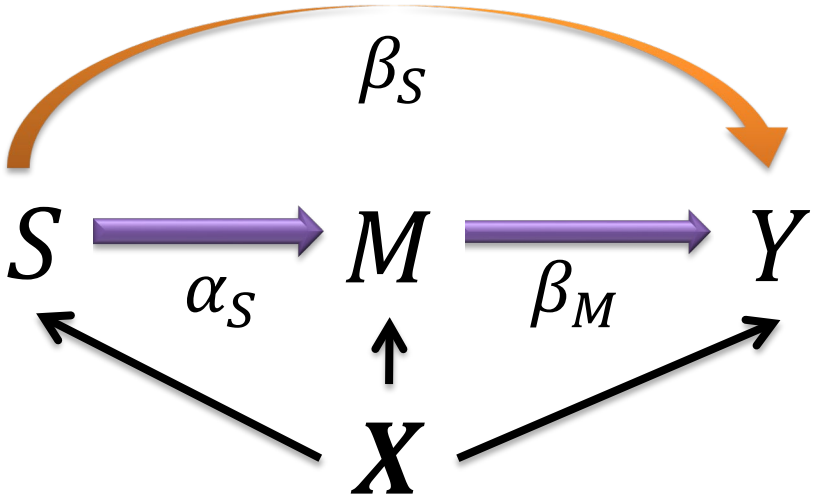
- A model for the mediator, $[M|S, \boldsymbol{X}]$

$$M_i = \boldsymbol{\alpha}_X^T \boldsymbol{X}_i + \alpha_S S_i + \epsilon_{Mi}$$

- Another model for the outcome, $[Y|S, M, \boldsymbol{X}]$

$$Y_i = \boldsymbol{\beta}_X^T \boldsymbol{X}_i + \beta_S S_i + \beta_M M_i + \epsilon_{Yi}$$

- $\epsilon_{Mi} \sim N(0, \sigma_M^2)$ and $\sigma_{Yi}^2 \sim N(0, \sigma_Y^2)$



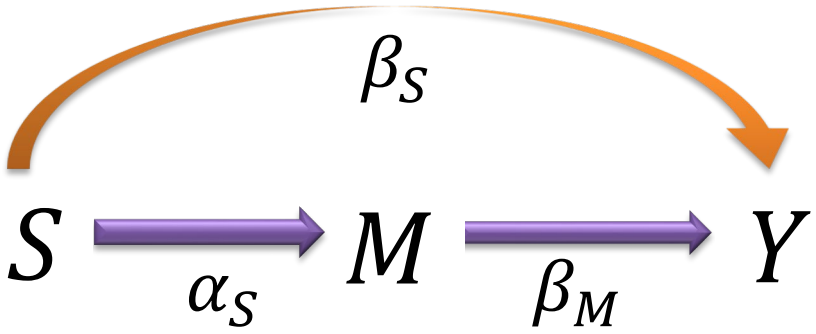
Two regression models for mediation analysis

- A model for the mediator, $[M|S]$

$$M_i = \alpha_0 + \alpha_S S_i + \epsilon_{Mi}$$

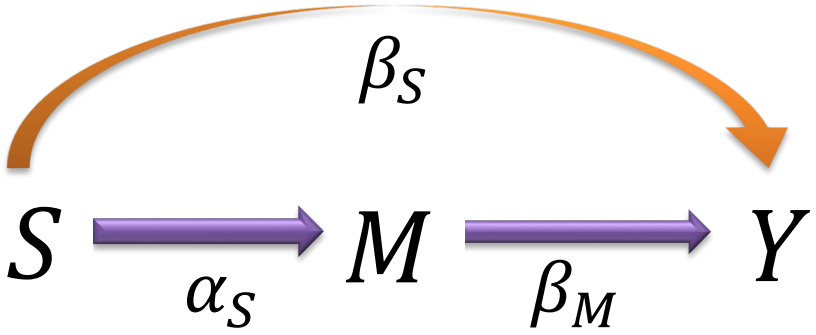
- Another model for the outcome, $[Y|S, M]$

$$Y_i = \beta_0 + \beta_S S_i + \beta_M M_i + \epsilon_{Yi}$$



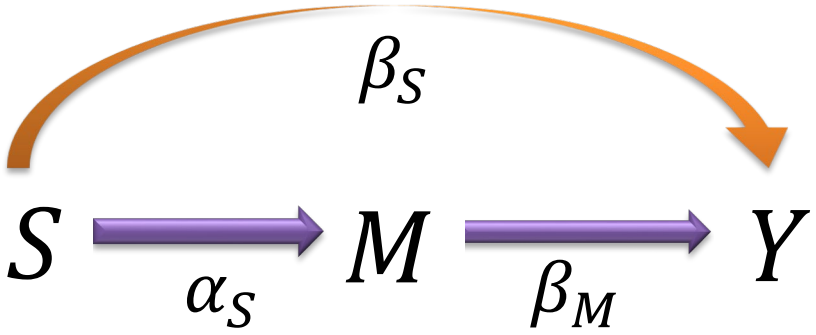
Natural direct effect

- $NDE = \mathbb{E}\left[Y\left(s_1, M(s_0)\right)\right] - \mathbb{E}\left[Y\left(s_0, M(s_0)\right)\right]$
$= \beta_S(s_1 - s_0)$



Natural indirect effect

- $NIE = \mathbb{E}\left[Y\left(s_1, M(s_1)\right)\right] - \mathbb{E}\left[Y\left(s_1, M(s_0)\right)\right]$
$= \alpha_S \beta_M (s_1 - s_0)$



Proof

$$\mathrm{E}\left[Y\left(s_a, M(s_b)\right)\right]$$

$$= \int y\, f_{Y(s_a, M(s_b))}(y)dy$$

$$= \int y \int f_{Y(s_a,m)|M(s_b)}(y|m) f_{M(s_b)}(m)dm\, dy$$

$$= \int y \int f_{Y(s_a,m)}(y) f_{M(s_b)}(m)dm\, dy \qquad \text{by A4}$$

$$= \int y \int f_{Y(s_a,m)|S}(y|s_a) f_{M(s_b)}(m)dm\, dy \qquad \text{by A1}$$

$$= \int y \int f_{Y(s_a,m)|S,M}(y|s_a, m) f_{M(s_b)}(m)dm\, dy \qquad \text{by A2}$$

$$= \int y \int f_{Y|S,M}(y|s_a, m) f_{M(s_b)}(m)dm\, dy \qquad \text{by consistency}$$

$$= \int y \int f_{Y|S,M}(y|s_a, m) f_{M(s_b)|S}(m|s_b)dm\, dy \qquad \text{by A3}$$

$$= \int y \int f_{Y|S,M}(y|s_a, m) f_{M|S}(m|s_b)dm\, dy \qquad \text{by consistency}$$

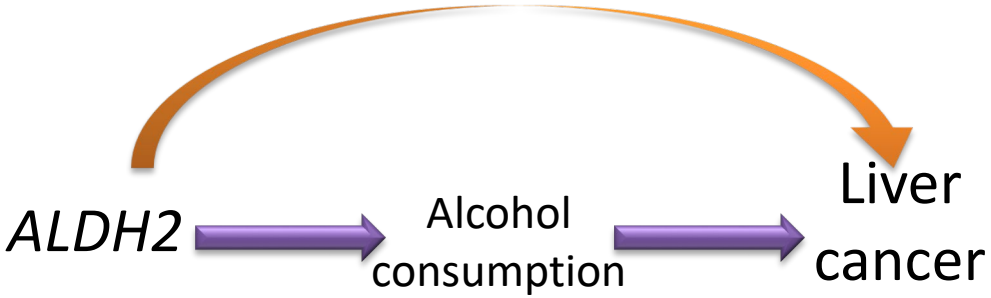
$$= \int \left\{ \int y f_{Y|S,M}(y|s_a, m)dy \right\} f_{M|S}(m|s_b)dm$$

$$= \int \mathrm{E}[Y|S = s_a, M = m] f_{M|S}(m|s_b)dm$$

V. Examples

Gene -> alcohol -> liver cancer

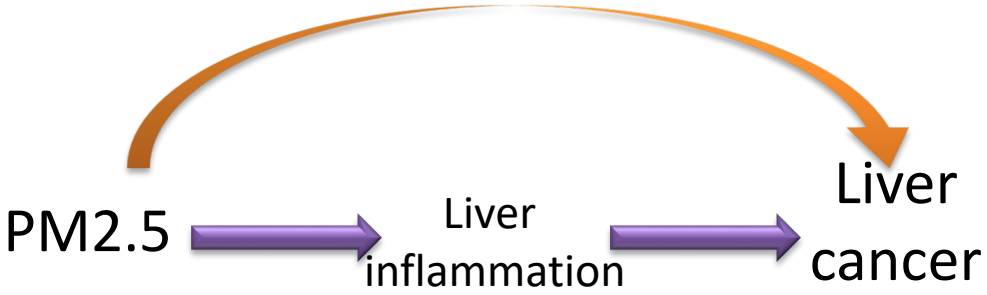
	Relative risk	95% confidence interval	P-value
Direct effect	1.38	(0.98, 1.95)	0.07
Indirect effect	0.70	(0.61, 0.82)	<0.001
Total effect	1.02	(0.84, 1.25)	0.83



Liu J et al. *CEBP* 2016, 25:693-699.

PM2.5 -> liver function -> liver cancer

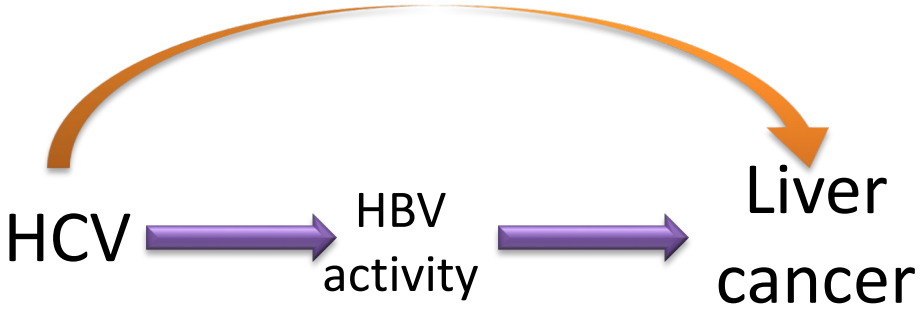
	Relative risk	95% confidence interval	P-value
Direct effect	1.28	(0.88, 1.92)	0.14
Indirect effect	1.21	(1.06, 1.41)	0.005
Total effect	1.23	(1.02, 1.48)	0.03



Pan WC et al. *JNCI* 2016, 108:djv341.

HCV -> HBV -> liver cancer

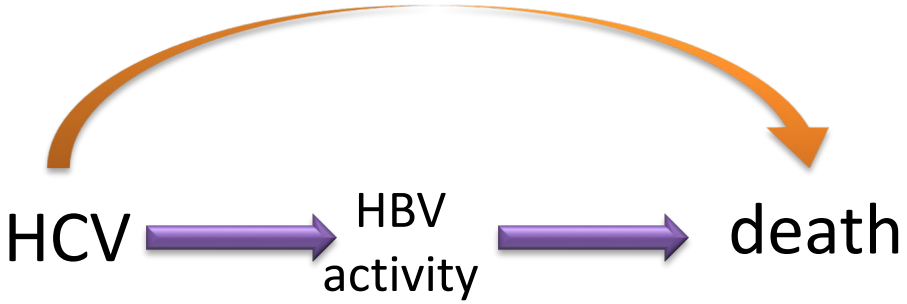
	Relative risk	95% confidence interval	P-value
Direct effect	2.50	(1.70, 3.60)	<0.001
Indirect effect	0.75	(0.67, 0.84)	<0.001
Total effect	1.72	(1.18, 2.50)	0.005



Huang YT et al. *Epidemiology* 2016, 27:14-20.

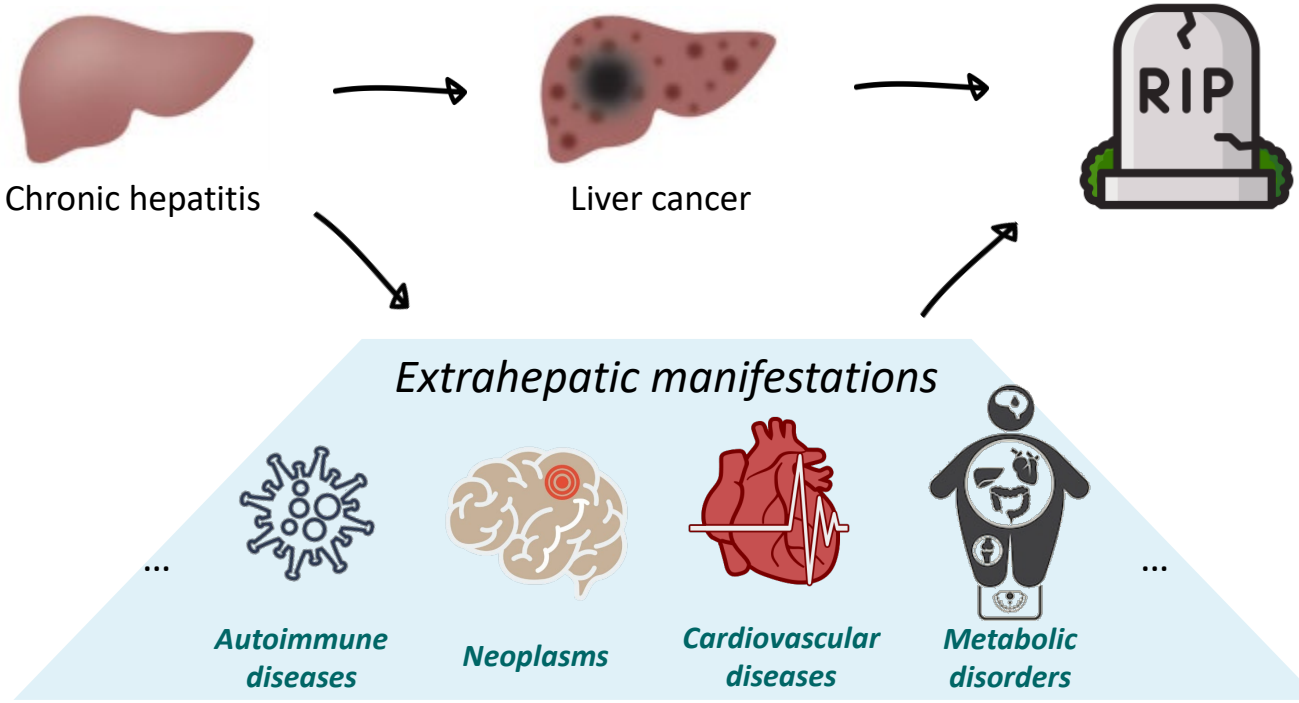
HCV -> HBV -> death

	Relative risk	95% confidence interval	P-value
Direct effect	1.78	(1.06, 3.00)	0.03
Indirect effect	0.78	(0.69, 0.87)	<0.001
Total effect	1.27	(0.59, 2.74)	0.55

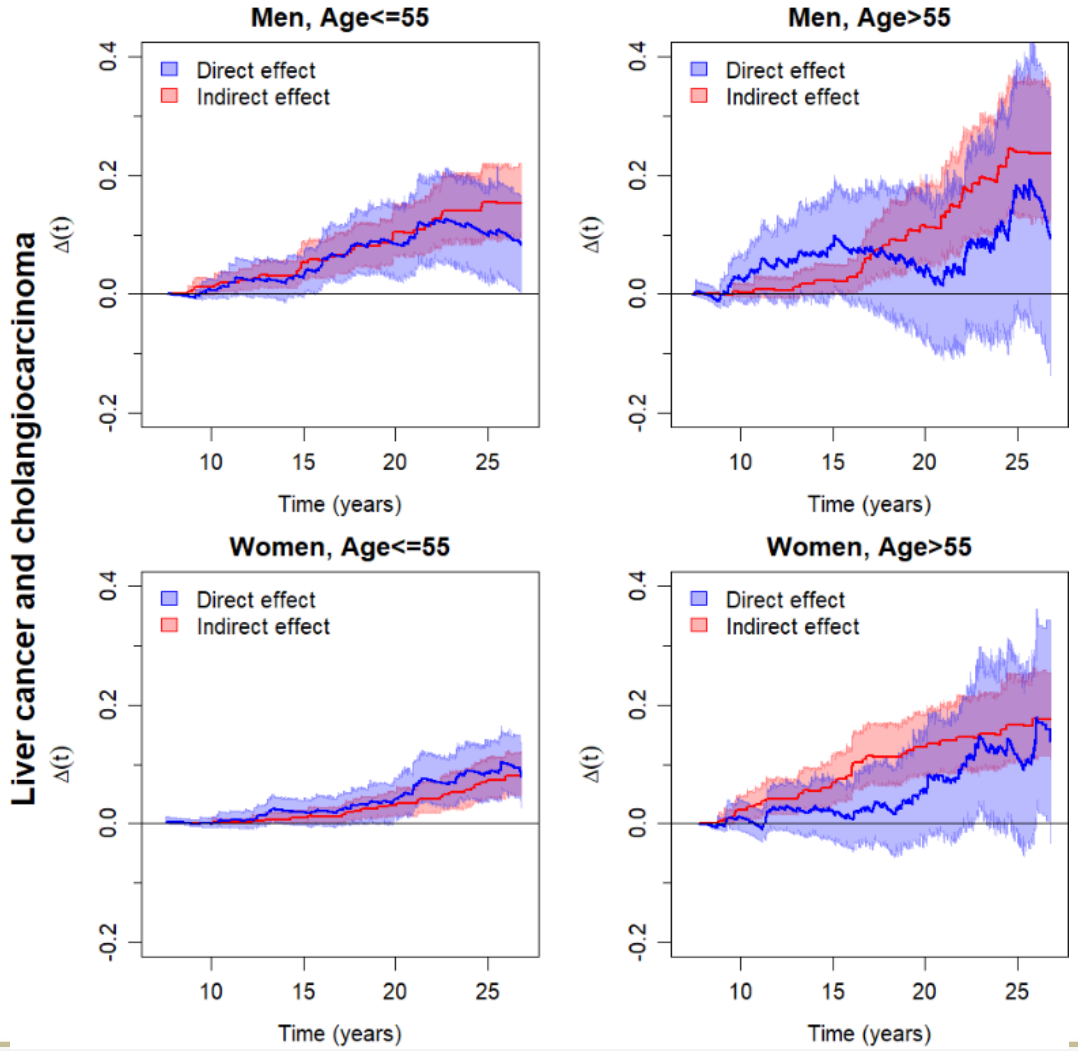


Huang YT et al. *European Journal of Epidemiology* 2016, 31:625-633.

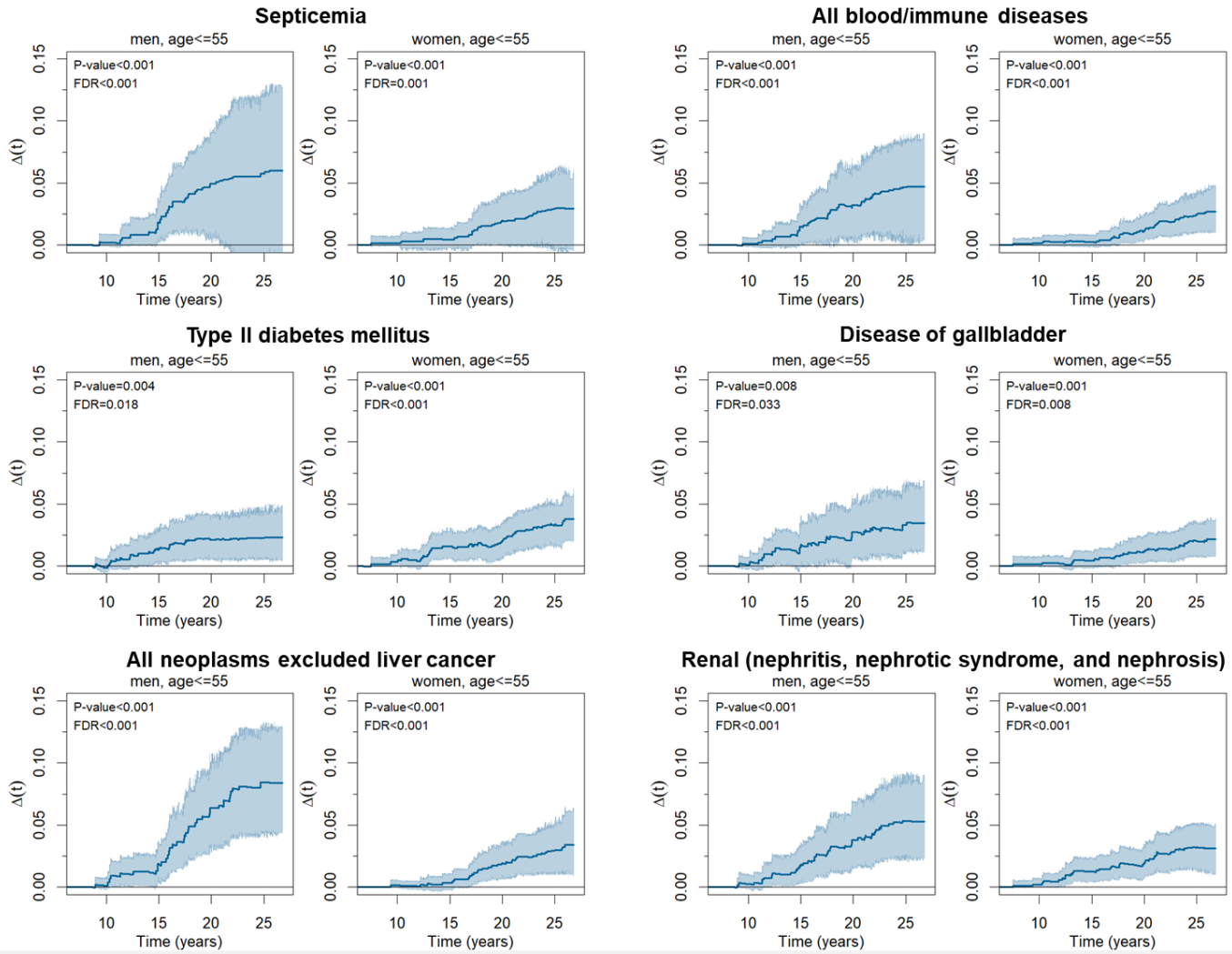
HCV infection is a systematic disease



HCV -> liver cancer -> death



HCV is a systematic disease

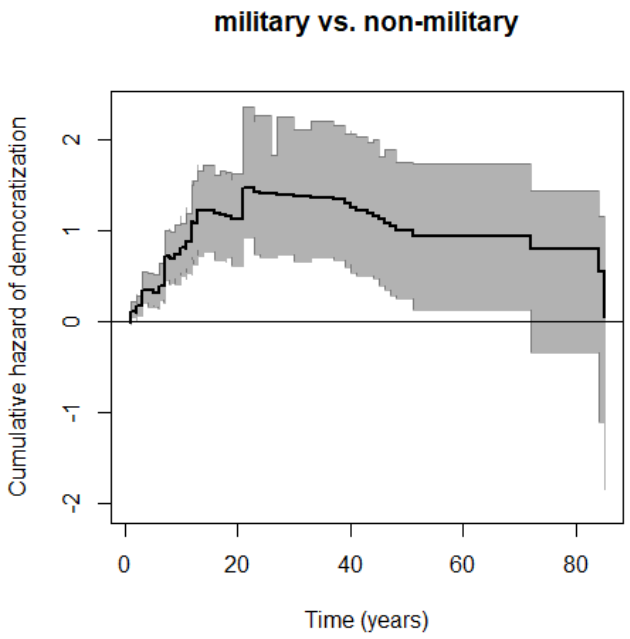


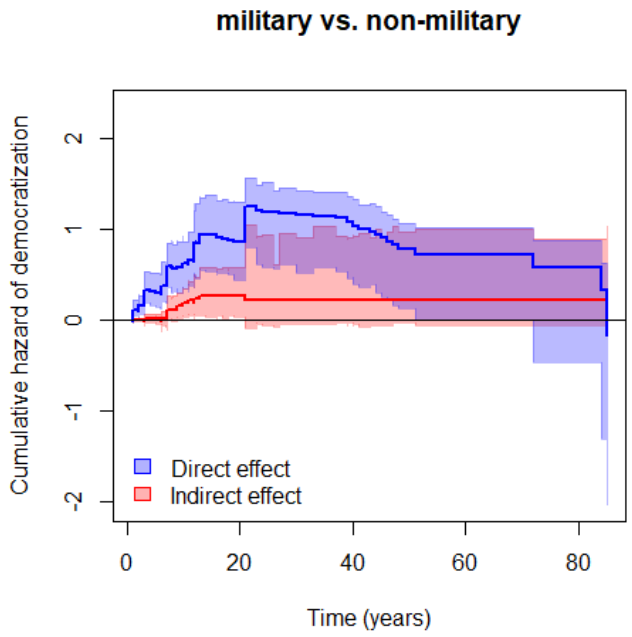
HCV is a systematic disease

Mediating disease	Men, age ≤ 55		Women, age ≤ 55	
	FDR of mediation test	Proportion of mediation (%)	FDR of mediation test	Proportion of mediation (%)
Cirrhosis	**<0.001**	52.8	**<0.001**	40.1
Liver cancer and cholangiocarcinoma	**<0.001**	36.2	**<0.001**	41.1
Other disorders of liver	**0.031**	30.5	**0.005**	29.6
Type II diabetes mellitus	**<0.001**	28	**0.018**	8.5
Renal disease (nephritis, nephrotic syndrome, and nephrosis)	**<0.001**	26.3	**<0.001**	15.1
All neoplasms	**<0.001**	25	**<0.001**	35.8
Septicemia	**0.001**	20.6	**<0.001**	17.7
All neoplasms (excluded liver cancer)	**<0.001**	20.1	**<0.001**	23.4
Intra-abdominal infection	**<0.001**	17.3	0.655	-
All blood/immune diseases	**<0.001**	15.9	**<0.001**	12.9
Diseases of gallbladder	**0.008**	14.2	**0.033**	10.7
Infectious intestinal diseases	**0.026**	14	0.797	0.1
Congestive heart failure	**0.047**	10.3	0.671	1.4
Heart disease	**0.027**	9.2	0.712	0.1
Trachea, bronchial and lung cancers	0.468	-	**0.05**	7.4

軍事政權 -> 政變 -> 民主化

- 非軍事政權：君主專政、政黨專政、個人專政





Joint work with 中研院政治所 吳文欽

Summary

- Causal mediation is defined under the counterfactual framework.
- Total effect can be decomposed into natural direct and indirect effects.
- A set of exchangeability assumptions is required for identifiability of causal mediation.
- Causal mediation analyses can be used for investigating causal mechanism.
- It may also be useful for policy making.

Thank You Very Much.