MEDIATION ANALYSIS: A PRACTITIONER'S GUIDE

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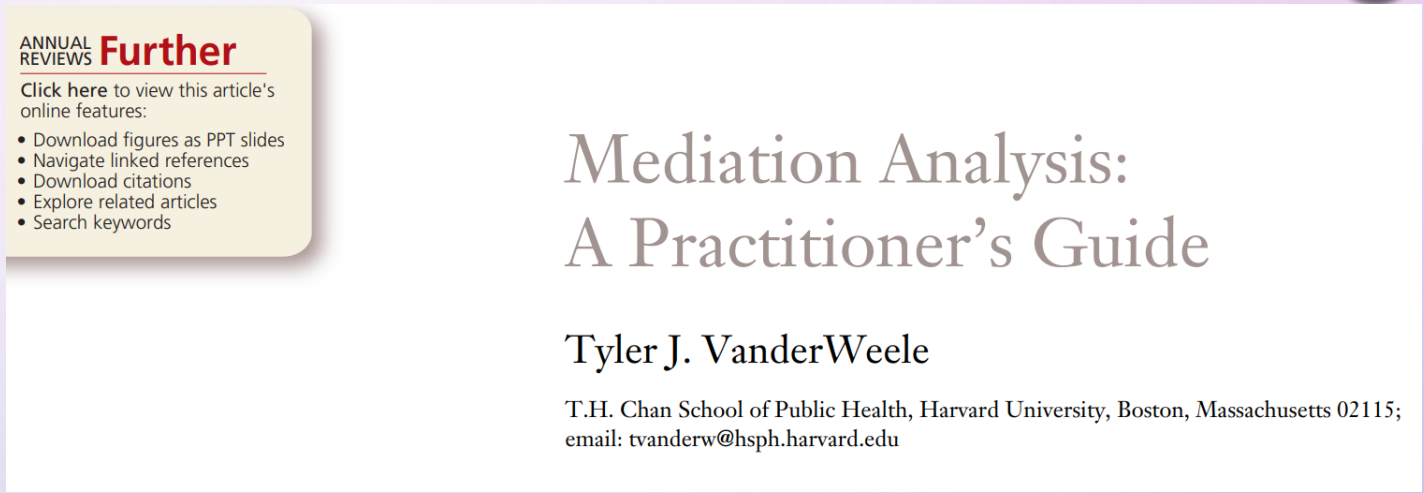

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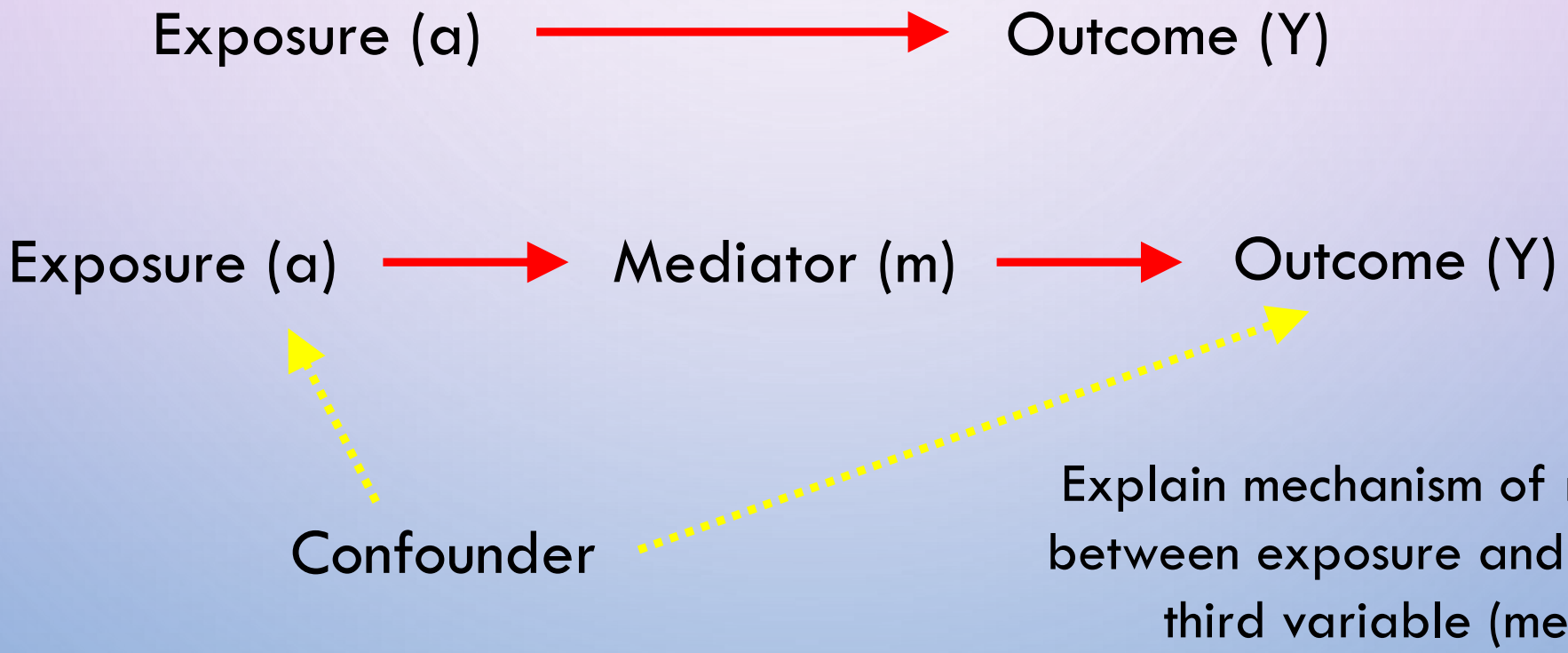
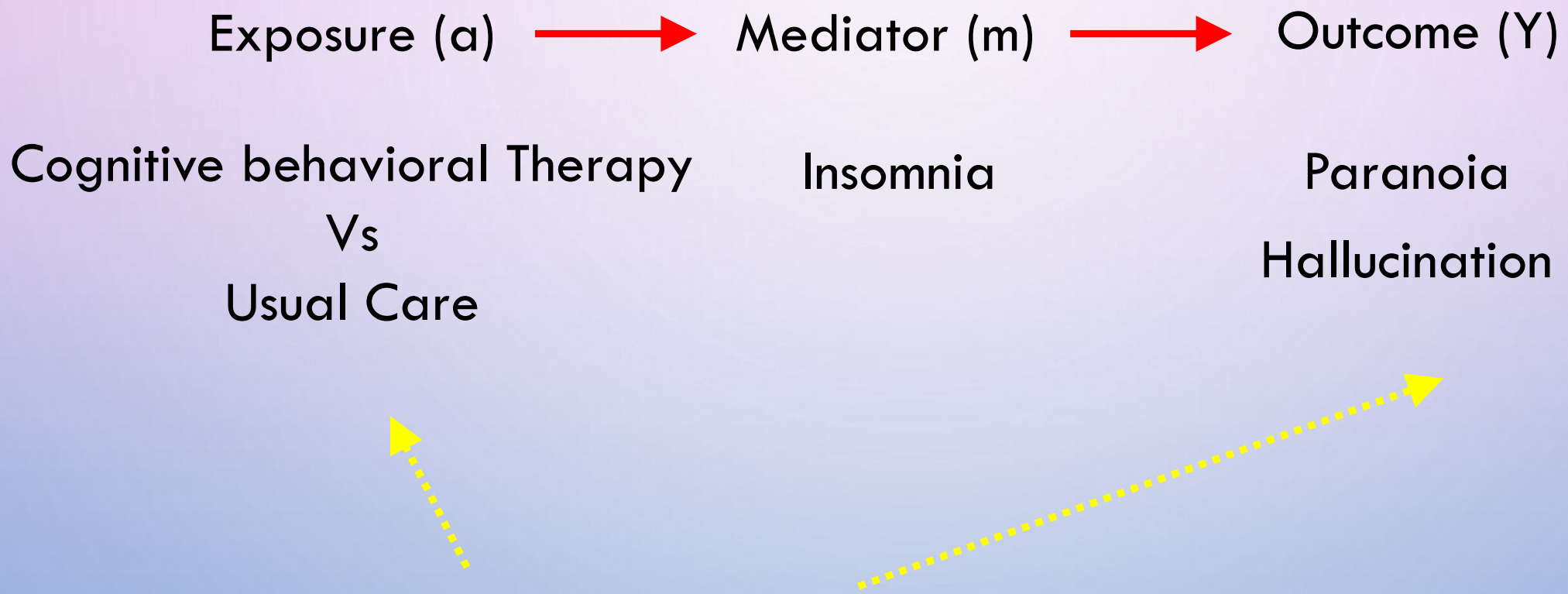
WHAT IS MEDIATION ANALYSIS?




Exposure (a)
Mediator (m)
Outcome (Y)
Cognitive behavioral Therapy
Vs
Usual Care
Insomnia
Paranoia
Hallucination
Confounder
Psychiatric disorder
Substance abuse

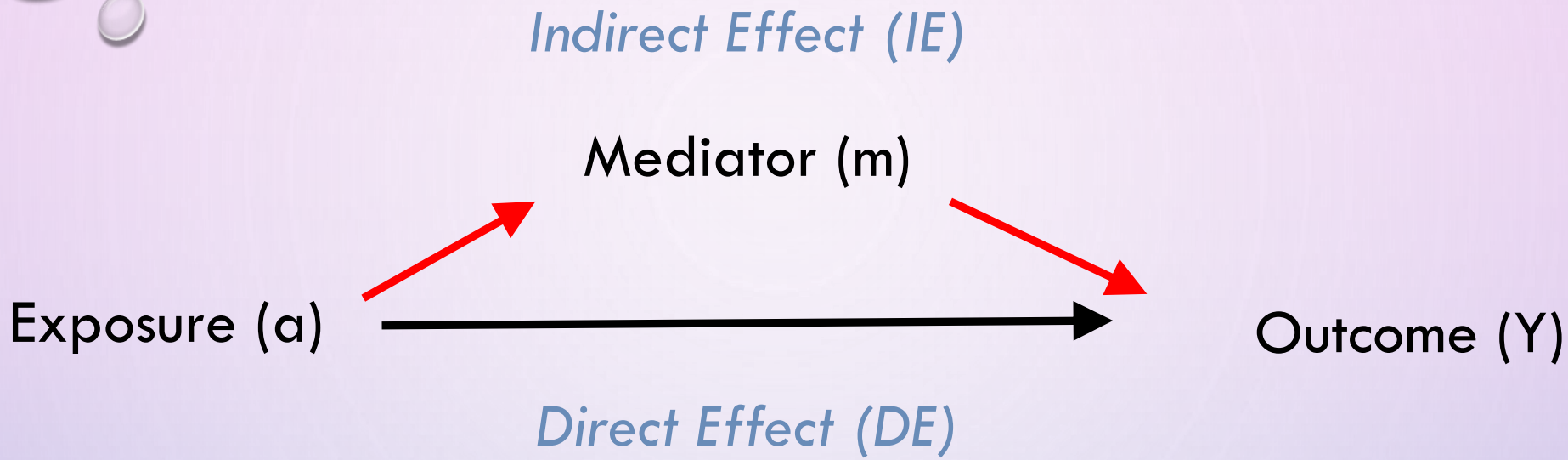
Exposure (a) → Mediator (m) → Outcome (Y)

Cognitive behavioral Therapy
Vs
Usual Care

Insomnia

Paranoia

Hallucination



Difference Method

(biomedical science)

$E[Y \mid a, c] = \phi_0 + \phi_1 a + \phi_4 c.$

$E[Y \mid a, m, c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c.$

$DE = \theta_1.$

$IE = \phi_1 - \theta_1.$

Product Method

(social science)

$E[Y \mid a, m, c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c.$

$E[M \mid a, c] = \beta_0 + \beta_1 a + \beta_2 c.$

$DE = \theta_1.$

$IE = \beta_1 \theta_2.$

Indirect Effect (IE)

Outcome (Y)

Mediator (m)

Exposure (a)

Covariate (c): Gender, educational level

	Insomnia (SCI-8)				Paranoia (GPTS)				Hallucinations (SPEQ)			
	Unadjusted mean		Adjusted difference* (95% CI), d†	p value*	Unadjusted mean		Adjusted difference* (95% CI), d†	p value*	Unadjusted mean		Adjusted difference* (95% CI), d†	p value*
	Control	Treatment			Control	Treatment			Control	Treatment		
Week 3	12·34 (5·85)	14·96 (5·80)	2·62 (2·19 to 3·06), 0·61	<0·0001	24·63 (11·82)	22·61 (9·89)	−1·81 (−2·49 to −1·13), 0·15	<0·0001	5·06 (6·89)	4·06 (5·84)	−0·79 (−1·15 to −0·42), 0·12	<0·0001
Week 10	13·31 (6·45)	18·08 (6·66)	4·78 (4·29 to 5·26), 1·11	<0·0001	23·84 (12·16)	21·06 (9·08)	−2·22 (−2·98 to −1·45), 0·19	<0·0001	4·89 (7·24)	3·12 (5·12)	−1·58 (−1·98 to −1·18), 0·24	<0·0001
Week 22	14·43 (6·71)	19·27 (7·13)	4·81 (4·29 to 5·33), 1·12	<0·0001	23·84 (12·68)	20·75 (9·19)	−2·78 (−3·60 to −1·96), 0·24	<0·0001	4·71 (7·43)	2·87 (5·45)	−1·56 (−1·99 to −1·14), 0·23	<0·0001

Data are mean (SD). At week 3, 1398 participants were in the control group and 1044 participants were in the treatment group. At week 10, 1142 participants were in the control group and 733 participants were in the treatment group. At week 22, 971 participants were in the control group and 603 participants were in the treatment group. SCI-8=Sleep Condition Indicator 8-item version. GPTS=Green et al Paranoid Thought Scales. SPEQ=Specific Psychotic Experiences Questionnaire. *Linear mixed effects model adjusted for gender, student status, week, and interaction of week with randomisation, and including a random effect for student within university. Covariance matrix of within subject measurements was unstructured. †d is standardised effect size (Cohen's d).

Table 2: **Primary outcome results**

	Total effect		Direct effect		Indirect effect		Percentage mediated
	Effect size (95% CI)	p value	Effect size (95% CI)	p value	Effect size (95% CI)	p value	
Paranoia (GPTS) outcome at week 10							
Insomnia at week 3 (SCI-8)	−2·27 (−3·03 to −1·51)	<0·0001	−1·85 (−2·66 to 1·04)	<0·0001	−0·67 (−0·86 to −0·48)	<0·0001	29·5%
Insomnia at week 10 (SCI-8)	−2·27 (−3·03 to −1·51)	<0·0001	−0·97 (−1·80 to −0·14)	<0·0001	−1·31 (−1·60 to −1·02)	<0·0001	57·8%
Hallucinations (SPEQ) outcome at week 10							
Insomnia at week 3 (SCI-8)	−1·60 (−2·00 to −1·20)	<0·0001	−1·36 (−1·79 to −0·94)	<0·0001	−0·33 (−0·43 to −0·23)	<0·0001	20·7%
Insomnia at week 10 (SCI-8)	−1·60 (−2·00 to −1·20)	<0·0001	−0·90 (−1·34 to −0·46)	<0·0001	−0·62 (−0·78 to −0·46)	<0·0001	38·6%

Total n=1718. GPTS=Green et al Paranoid Thought Scales. SCI-8=Sleep Condition Indicator 8-item version. SPEQ=Specific Psychotic Experiences Questionnaire.
*Outcome and mediators modelled by means of linear mixed effects models and the total, direct, and indirect effects determined using the Baron and Kenny[31] approach. The effect size is the adjusted treatment difference (ie, non-standardised treatment difference).

Table 3: **Mediation analysis* results**

CONFOUNDING ASSUMPTION

Assumption 1: Control Exposure -> Outcome
Assumption 2: Control Mediator -> Outcome
Assumption 3: Control Exposure -> Mediator
Assumption 4: No Exposure->Mediator-> Outcome

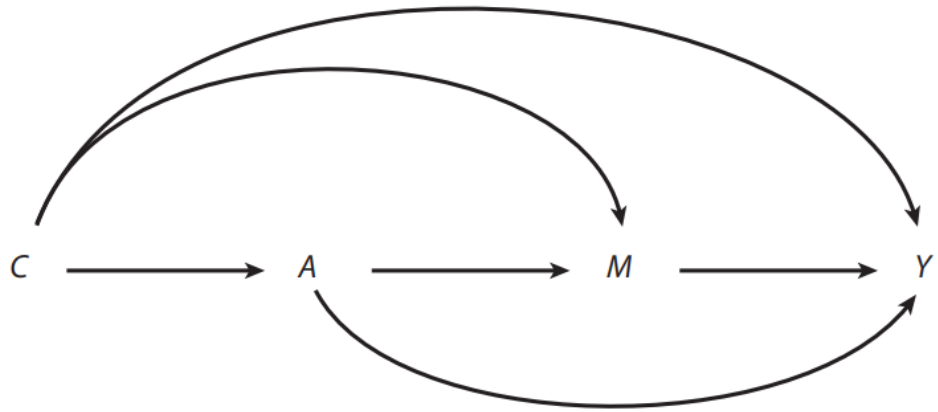


Figure 1

Relations between exposure *A*, mediator *M*, and outcome *Y*, and confounders.

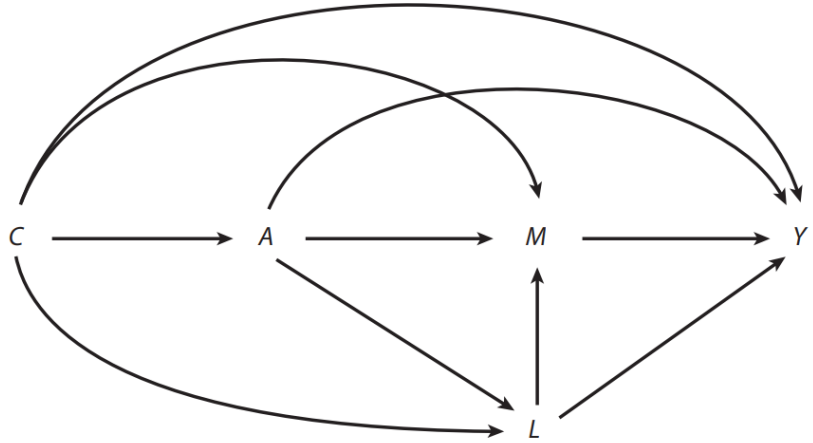


Figure 2

A mediator-outcome confounder *L* that is itself affected by the exposure *A*.

EXPOSURE-MEDIATOR INTERACTION

Exposure (a) → Mediator (m) → Outcome (Y)

Exposure (a=CBT)

Exposure (a*=usual care)

EXPOSURE-MEDIATOR INTERACTION

Exposure (a) → Mediator (m) → Outcome (Y)

Time 3 weeks = a

Time 10 weeks = a*

EXPOSURE-MEDIATOR INTERACTION

Exposure (a) → Mediator (m) → Outcome (Y)

$$E[Y \mid a, m, c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c$$

$$E[M \mid a, c] = \beta_0 + \beta_1 a + \beta_2 c.$$

$$DE = \{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2 c)\}(a - a^*)$$

$$IE = (\beta_1\theta_2 + \beta_1\theta_3 a)(a - a^*)$$

Time 3 weeks = a

Time 10 weeks = a*

	Insomnia (SCI-8)				Paranoia (GPTS)				Hallucinations (SPEQ)			
	Unadjusted mean		Adjusted difference* (95% CI), d†	p value*	Unadjusted mean		Adjusted difference* (95% CI), d†	p value*	Unadjusted mean		Adjusted difference* (95% CI), d†	p value*
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Table 2: **Primary outcome results**

BINARY OUTCOMES AND MEDIATORS

$\text{logit}\{P(Y = 1 \mid a, m, c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c$

$E[M \mid a, c] = \beta_0 + \beta_1 a + \beta_2 c$

$\log\{OR^{DE}\} \sim= \{\theta_1 + \theta_3(\beta_0 + \beta_1 a + \beta_2 c + \theta_2 \sigma^2)\}(a - a*) + 0.5\theta^2_3 \sigma^2(a^2 - a*^2)$

$\log\{OR^{IE}\} \sim= (\theta_2\beta_1 + \theta_3\beta_1 a)(a - a*)$

$$DE = \theta_1(a - a^*) + \theta_3(a - a^*)\frac{\exp(\beta_0 + \beta_1 a^* + \beta_2' c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2' c)}$$

$$IE = (\theta_2 + \theta_3 a)\left\{\frac{\exp(\beta_0 + \beta_1 a + \beta_2' c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2' c)} - \frac{\exp(\beta_0 + \beta_1 a^* + \beta_2' c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2' c)}\right\}.$$

CONCLUSION

Mediation Analysis can be used to assess the relative magnitude of pathway and mechanisms by which exposure may affect the outcome