

The background features a light purple-to-blue gradient with several realistic water droplets of various sizes scattered across the surface. A faint, large circular graphic is centered behind the title text.

MEDIATION ANALYSIS: A PRACTITIONER'S GUIDE

MASATHA THONGPAN

6537582

CLINICAL EPIDEMIOLOGY PROGRAM

Annual Review Public Health 2016

Lancet Psychiatry 2017

ANNUAL REVIEWS **Further**

Click here to view this article's online features:

- Download figures as PPT slides
- Navigate linked references
- Download citations
- Explore related articles
- Search keywords

Mediation Analysis: A Practitioner's Guide

Tyler J. VanderWeele

T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts 02115;
email: tvanderw@hsph.harvard.edu

The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis

Daniel Freeman, Bryony Sheaves, Guy M Goodwin, Ly-Mee Yu, Alecia Nickless, Paul J Harrison, Richard Emsley, Annemarie I Luik, Russell G Foster, Vanashree Wadekar, Christopher Hinds, Andrew Gumley, Ray Jones, Stafford Lightman, Steve Jones, Richard Bentall, Peter Kinderman, Georgina Rowse, Traolach Brugha, Mark Blagrove, Alice M Gregory, Leanne Fleming, Elaine Walklet, Cris Glazebrook, E Bethan Davies, Chris Hollis, Gillian Haddock, Bev John, Mark Coulson, David Fowler, Katherine Pugh, John Cape, Peter Moseley, Gary Brown, Claire Hughes, Marc Obonsawin, Sian Coker, Edward Watkins, Matthias Schwannauer, Kenneth MacMahon, A Niroshan Siriwardena, Colin A Espie

Summary

Background Sleep difficulties might be a contributory causal factor in the occurrence of mental health problems. If this is true, improving sleep should benefit psychological health. We aimed to determine whether treating insomnia leads to a reduction in paranoia and hallucinations.

WHAT IS MEDIATION ANALYSIS?

Exposure (a)  Outcome (Y)

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



Confounder



Explain mechanism of relationship
between exposure and outcome by
third variable (mediator)

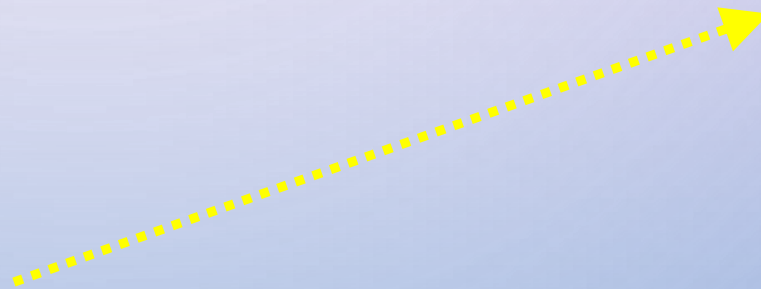
Exposure (a) → Mediator (m) → Outcome (Y)

Cognitive behavioral Therapy
Vs
Usual Care

Insomnia

Paranoia
Hallucination

Confounder
Psychiatric disorder
Substance abuse



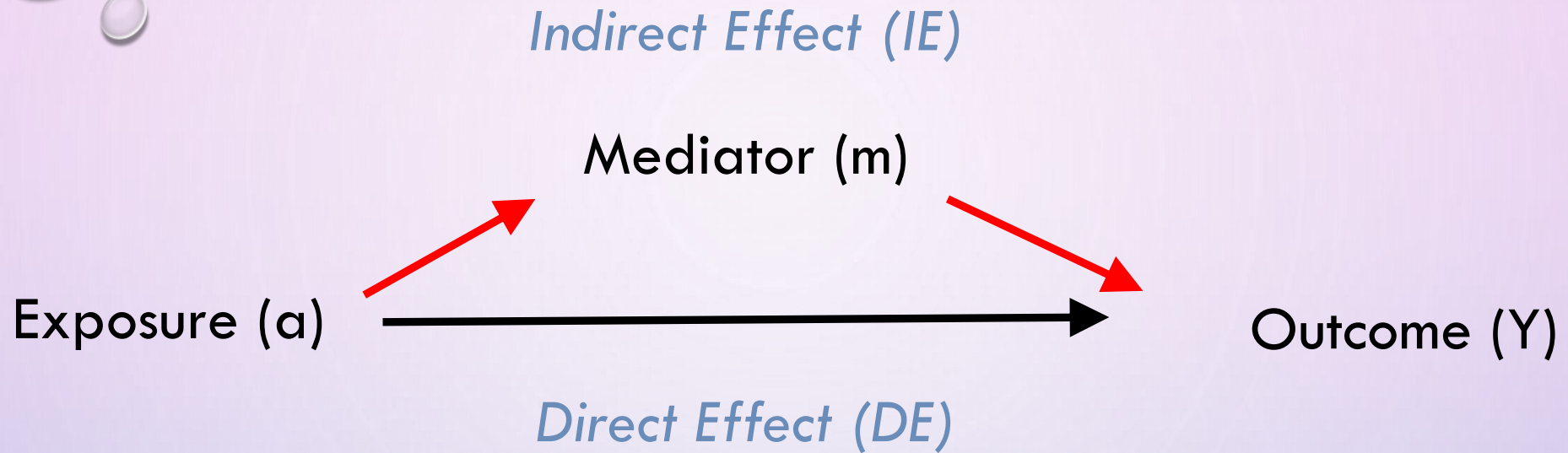
Exposure (a) → Mediator (m) → Outcome (Y)

Cognitive behavioral Therapy
Vs
Usual Care

Insomnia

Paranoia
Hallucination





Difference Method
(biomedical science)

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

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

$$DE = \theta_1.$$

$$IE = \phi_1 - \theta_1.$$

Product Method
(social science)

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

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

$$DE = \theta_1.$$

$$IE = \beta_1 \theta_2.$$

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 Kenny²¹ 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 \rightarrow Outcome

Assumption 2: Control Mediator \rightarrow Outcome

Assumption 3: Control Exposure \rightarrow Mediator

Assumption 4: No Exposure \rightarrow Mediator \rightarrow Outcome

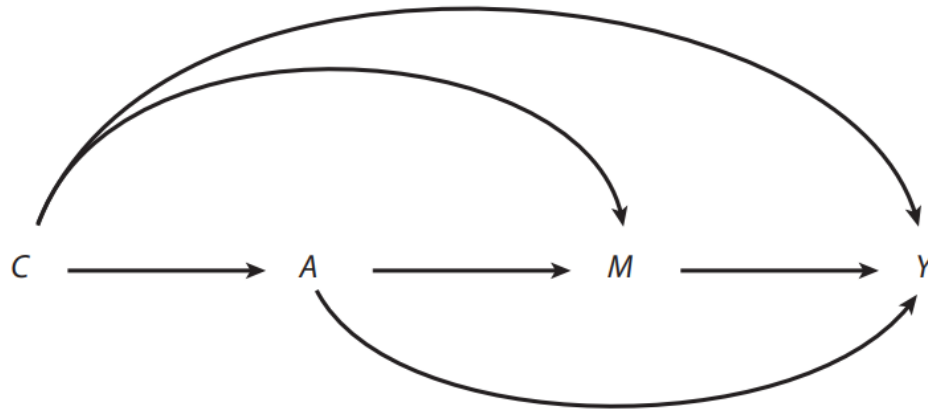


Figure 1

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

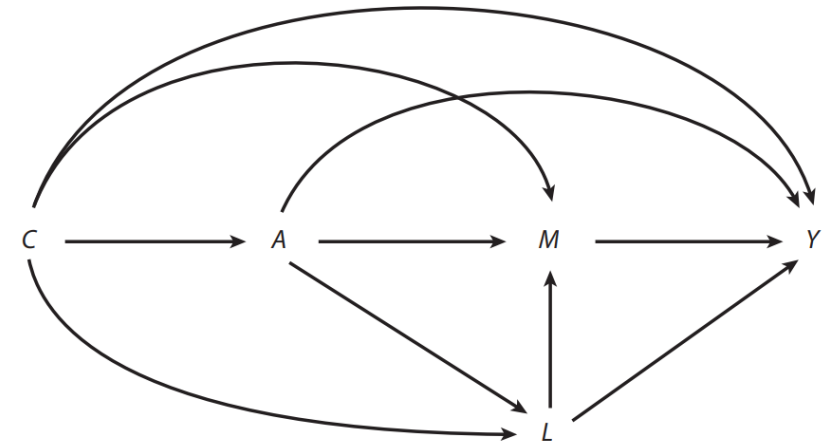


Figure 2

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



Time 3 weeks = a

Time 10 weeks = a*



EXPOSURE-MEDIATOR INTERACTION



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

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

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

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

Time 3 weeks = a

Time 10 weeks = a*

	Insomnia (SCI-8)			Paranoia (GPTS)			Hallucinations (SPEQ)					
	Unadjusted mean		Adjusted difference* (95% CI), d†	Unadjusted mean		Adjusted difference* (95% CI), d†	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

BINARY OUTCOMES AND MEDIATORS

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

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

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

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

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

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

CONCLUSION

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