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Effect Modification and Mediation

6 October 2017
Stian Lydersen

Updated 8 September 2020

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Background:

What are confounders, colliders, mediators, and modifiers?

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Definition of a confounder

(Rothman: ”Epidemiology: An Introduction”. 2nd ed. Oxford University Press, 2012, page 108.)

Confounding can be thought of as a mixing of effects. A confounding factor, therefore, must have an effect and must be imbalanced between the exposure groups to be compared.

- A confounder must be associated with the disease (either as a cause or a proxy for a cause but not as an effect of the disease).
- A confounder must be associated with the exposure.
- A confounder must not be an effect of the exposure.

Comment: Data can only show us an association. The plausible direction of a causual effect must stem from other substantive knowledge about the phenomenon.

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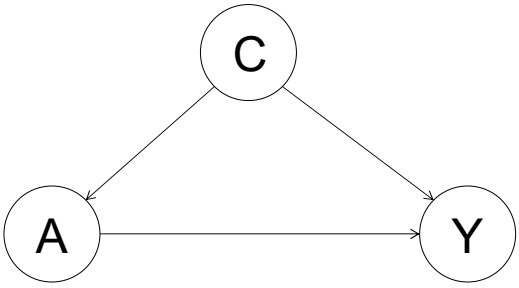
C is a confounder:
Adjust for C in the analysis. Else it would introduce bias.



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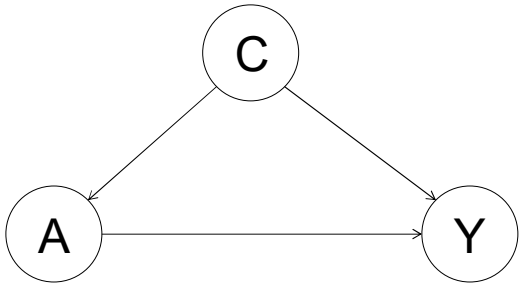
Example:

Age
Sex
SES?



Psychiatric disorder

Substance use
(smoking, alcohol, illicit drugs)

Mangerud, W.L., Bjerkeset, O., Holmen, T.L., Lydersen, S., & Indredavik, M.S. 2014. Smoking, alcohol consumption, and drug use among adolescents with psychiatric disorders compared with a population based sample. *Journal of Adolescence*, 37, (7) 1189-1199

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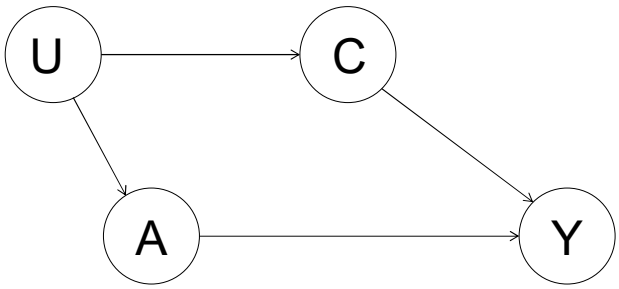
U is an umeasured confounder.
Adjusting for C removes the bias caused by U.



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How to adjust for confounders

- Confounders as covariates in regression analysis
- Stratified analysis
- Separate analyses

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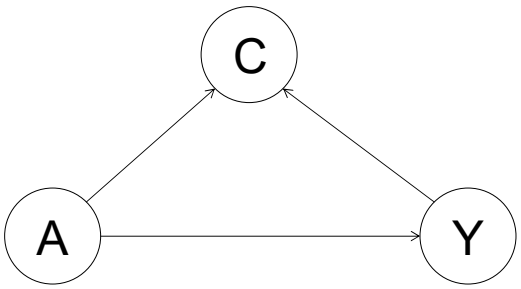
C is a collider:
Do not adjust for C in the analysis
– that would introduce bias.



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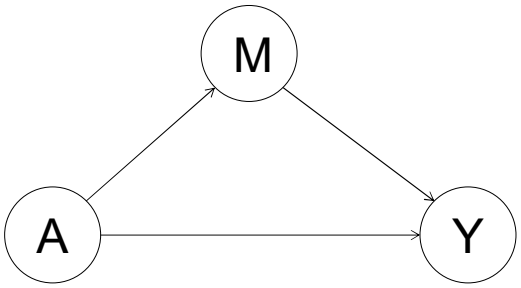
M is a mediator:
Adjust for M? Depends on the research question.
If you adjust for M, the estimated effect of E on D would be only the direct effect not mediated through M.



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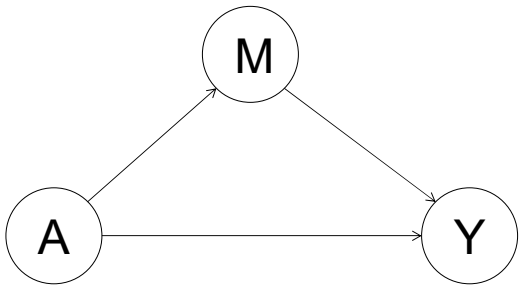
Example:

High blood pressure (hypertension)



Tobacco Smoking

Cardiovasculsar disease (CVD)

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Interaction (effect-measure modification)

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We have illustrated confounders, mediators and colliders in DAG's (Directed Acyclic Graphs).

How about interactions?

"From a practical point-of-view some might miss a DAG representation of interactions. This is perhaps obvious, as an interaction is a scale-dependent concept, and the DAGs do not specify a scale, …"

(Gran, M. G., Stigum. H., Håberg, S. E. and Aalen O. O: Chapter 15: "Causal inference" in Veierød, M., Lydersen, S. and Laake: "Medical statistics in clinical and epidemiological research." Gyldendal Akademisk 2012.)

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Interactions
(also called modifiers, effect modifiers, or moderators)

Linear model:

$$E(Y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \underbrace{\beta_3 x_1 x_2}_{\text{Interaction term}} + \ldots$$

If there is an interaction $(\beta_3 \neq 0)$,
the effect of x_1 depends on the value of x_2.

F.ex. when $x_2 = 0$, the effect of x_1 is β_1,
and when $x_2 = 1$, the effect of x_1 is $\beta_1 + \beta_3$.

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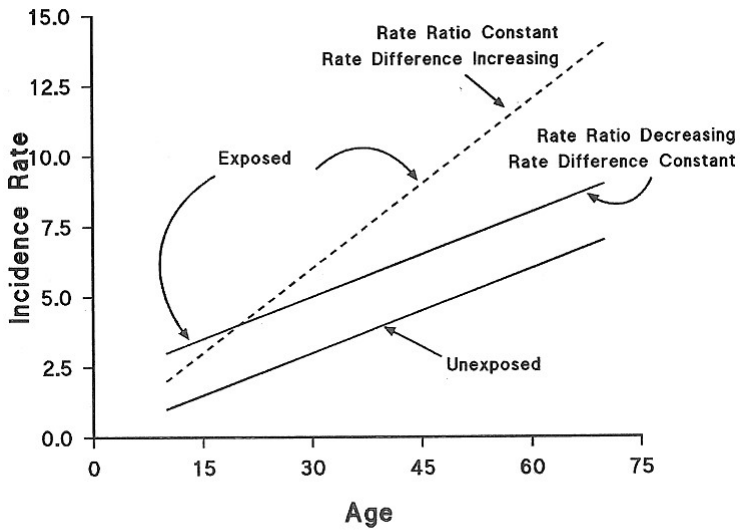

Figure 11–1 Age-incidence curves showing disease incidence increasing linearly with age for unexposed people and two possible linear relations with age for exposed people.

(Rothman: "Epidemiology: An Introduction". 2nd ed. Oxford University Press, 2012, page 199.)

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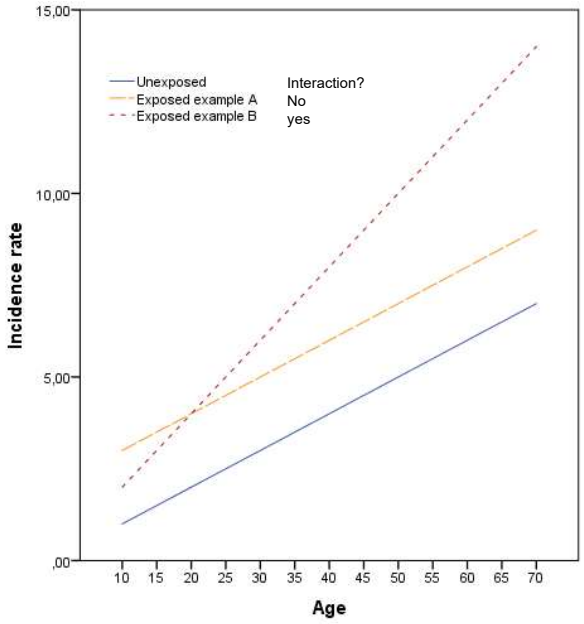

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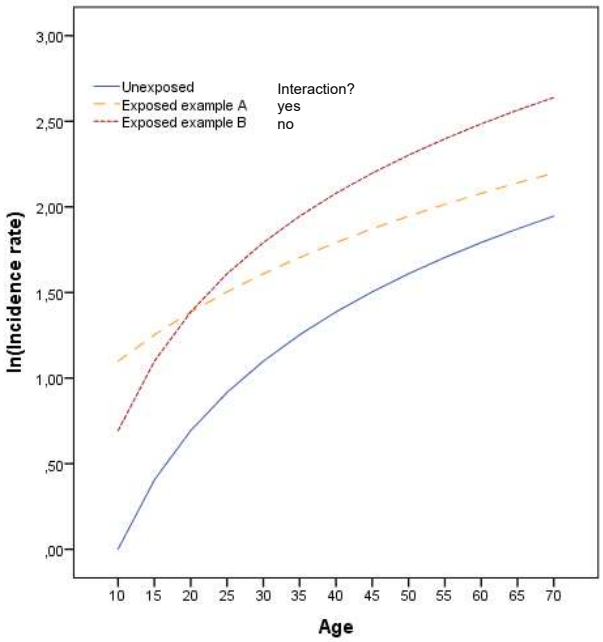

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Example A:
Interaction on a linear scale (additive initeraction) but not on a logartithmic scale (no multiplicative initeraction)

Example B:Vice versa.

The interaction depends on which scale is used!

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EFFECT-MEASURE MODIFICATION

In statistics, the term *interaction* is used to refer to a departure from additivity on the scale used in a statistical model. Because various statistical models use different scales, interaction does not have a consistent, universal meaning; statistical interaction in one model may be different from the interaction in another model based on a transformed scale, even with the same data. The arbitrariness of this concept of interaction has a counterpart in epidemiology in the term *effect-measure modification,* which refers to the common situation in which a measure of effect changes over values of some other variable.

(Rothman: "Epidemiology: An Introduction". 2nd ed. Oxford University Press, 2012, page 199.)

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Rothman (2012, Chapter 11: ”measuring interactions”) :

Biological interaction is interaction on an additive scale.

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Table 11–1 Hypothetical 1-Year Risk of Lung Cancer According to Exposure to Cigarette Smoke and Exposure to Asbestos (Cases per 100,000)

Smoke Exposure	Asbestos Exposure	
	No	Yes
Nonsmokers	1	5
Smokers	10	50

Interaction Risk

$= R_{AB} - R_A - R_B + R_U$

$= 50 - 10 - 5 + 1 = 36$

$36 / 50 = 72\%$

Table 11–2 Risk Ratio of Stroke by Exposure to Oral Contraceptives and Presence or Absence of Hypertension

Oral Contraceptive Use	Hypertension	
	No	Yes
Nonusers	1.0	6.9
Users	3.1	13.6

Data from Collaborative Group for the Study of Stroke in Young Women.[3]

Interaction Risk

$= R_{AB} - R_A - R_B + R_U$

$= 13.6 - 3.1 - 6.9 + 1 = 4.6$

$4.6 / 13.6 = 34\%$

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Psychological Methods
2012, Vol. 17, No. 4, 615–622

1082-989X/12/$12.00 DOI: 10.1037/a0030003

Distinguishing Ordinal and Disordinal Interactions

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University of California, Davis, King Abdulaziz University, and Birkbeck University of London

Re-parameterized regression models may enable tests of crucial theoretical predictions involving interactive effects of predictors that cannot be tested directly using standard approaches. First, we present a re-parameterized regression model for the Linear × Linear interaction of 2 quantitative predictors that yields point and interval estimates of 1 key parameter—the crossover point of predicted values—and leaves certain other parameters unchanged. We explain how resulting parameter estimates provide direct evidence for distinguishing ordinal from disordinal interactions. We generalize the re-parameterized model to Linear × Qualitative interactions, where the qualitative variable may have 2 or 3 categories, and then describe how to modify the re-parameterized model to test moderating effects. To illustrate our new approach, we fit alternate models to social skills data on 438 participants in the National Institute of Child Health and Human Development Study of Early Child Care. The re-parameterized regression model had point and interval estimates of the crossover point that fell near the mean on the continuous environment measure. The disordinal form of the interaction supported 1 theoretical model—differential-susceptibility—over a competing model that predicted an ordinal interaction.

Keywords: multiple regression, interactions, GXE interaction, differential-susceptibility, diathesis-stress

Supplemental materials: http://dx.doi.org/10.1037/a0030003.supp

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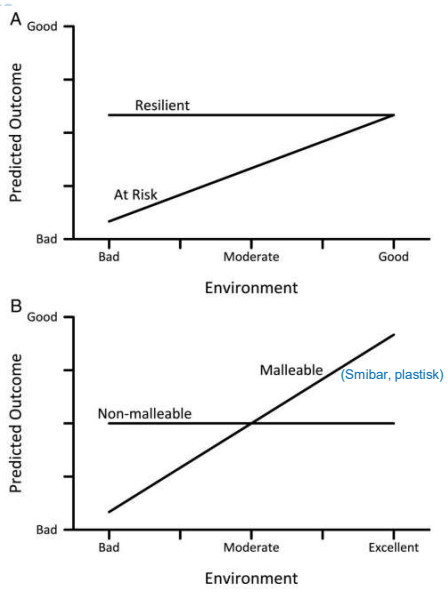

Figure 1. Predicted outcomes of Gene × Environment interaction under diathesis-stress (A) and differential-susceptibility (B).

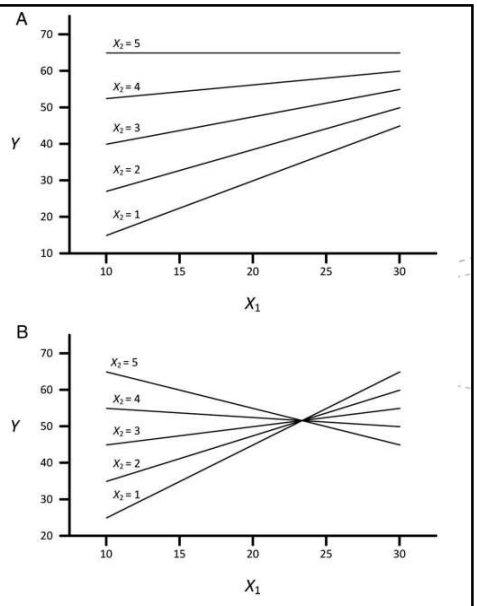

Figure 2. Plots of Linear × Linear interaction of two quantitative predictors X_1 and X_2: ordinal interaction (A) and disordinal interaction (B).

The distinction between ordinal and disordinal interaction is scale-independent!

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Linear model with interaction:

$$E(Y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

Reparametrization (Widaman et al. 2012):

$$E(Y) = \alpha_0 + \beta_1 (x_1 - c) + \beta_3 [(x_1 - c) x_2]$$

Which is not linear in the parameters $\alpha_0, \beta_1, \beta_3, c$
and must be solved using nonlinear regression. OK even in SPSS
(In the reparametrization, $c = -\beta_2 / \beta_3$)

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Developmental Psychology
2015, Vol. 51, No. 8, 1068–1104

0012-1649/15/$12.00 http://dx.doi.org/10.1037/dev0000020

BRIEF REPORT

Child Exposure to Serious Life Events, COMT, and Aggression: Testing Differential Susceptibility Theory

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Both genetic and environmental factors contribute to individual differences in aggression. Catechol-*O*-methyltransferase Val158Met (COMT), a common, functional polymorphism, has been implicated in aggression and aggression traits, as have childhood experiences of adversity. It is unknown whether these effects are additive or interactional and, in the case of interaction, whether they conform to a diathesis-stress or differential susceptibility model. We examined Gene × Environment interactions between COMT and serious life events on measures of childhood aggression and contrasted these 2 models. The sample was composed of community children (N = 704); 355 were boys, and the mean age was 54.8 months (SD = 3.0). The children were genotyped for COMT rs4680 and assessed for serious life events and by teacher-rated aggression. Regression analysis showed no main effects of COMT and serious life events on aggression. However, a significant interactive effect of childhood serious life events and COMT genotype was observed: Children who had faced many serious life events and were Val homozygotes exhibited more aggression (p = .02) than did their Met-carrying counterparts. Notably, in the absence of serious life events, Val homozygotes displayed significantly lower aggression scores than did Met carriers (p = .03). When tested, this constellation of findings conformed to the differential susceptibility hypothesis: In this case, Val homozygotes are more malleable to the effect of serious life events on aggression and not simply more vulnerable to the negative effect of having experienced many serious life events.

Keywords: aggression, serious life events, COMT, gene–environment interaction, differential susceptibility

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Table 1
Sample Characteristics (N = 704)

Variable	*M*	*SD*	Minimum	Maximum	*n*
Demographics					
Child age (months)	54.79	2.97	48.17	67.81	656
Male children (%)	50.4%				355
Age of parent at clinic (in years)	35.03	4.72	21.00	57.00	666
Relation to the child					
Biological parents (%)	98.2%				654
Adoptive parents (%)	1.2%				8
Stepparents (%)	0.2%				1
Foster parents	0.5%				3
Ethnicity					
Ethnicity male parent (%) Norwegian	94.8%				633
Ethnicity female parent (%) Norwegian	96.4%				644
Descriptive statistics for variables in the analyses					
Teacher-rated aggression	4.21	6.44	.00	38.00	626
Serious life events	.74	.92	.00	5.00	668
Children with 0 SLEs					344
Children with 1 SLE					197
Children with 2 SLEs					95
Children with 3 SLEs					26
Children with 4 SLEs					4
Children with 5 SLEs					2
Genotype					704
Genotype Val/Val (%)	21.4%				151
Genotype Val/Met (%)	50.4%				355
Genotype Met/Met (%)	28.1%				198

Note. SLE = serious life events.

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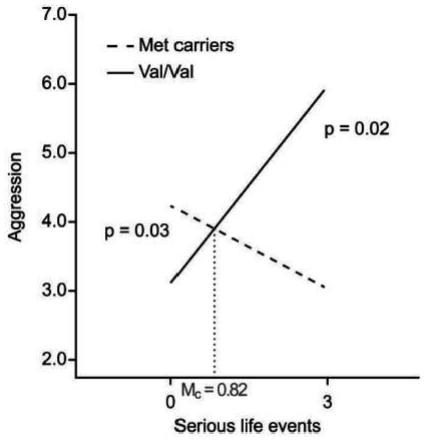

Figure 1. Estimated mean aggression score as function of number of serious life events for the two genotype groups. *p* values for differences in aggression at 0 and 3 serious life events are included.

Interaction p = 0.004

Estimate and CI for the crossing point are computed using a reparametrized regression equation (Widaman et al, 2012). Computed in Mplus for weighted sample:

M = 0.82, 95% CI (0.06 to 1.58), p=0.03

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Mediation

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Journal of Personality and Social Psychology
1986, Vol. 51, No. 6, 1173-1182

0022-3514/86/$00.75

The Moderator–Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations

Reuben M. Baron and David A. Kenny
University of Connecticut

In this article, we attempt to distinguish between the properties of moderator and mediator variables at a number of levels. First, we seek to make theorists and researchers aware of the importance of not using the terms *moderator* and *mediator* interchangeably by carefully elaborating, both conceptually and strategically, the many ways in which moderators and mediators differ. We then go beyond this largely pedagogical function and delineate the conceptual and strategic implications of making use of such distinctions with regard to a wide range of phenomena, including control and stress, attitudes, and personality traits. We also provide a specific compendium of analytic procedures appropriate for making the most effective use of the moderator and mediator distinction, both separately and in terms of a broader causal system that includes both moderators and mediators.

Times Cited: 31,753
(from Web of Science Core Collection)

(Per 18 Sept 2017)

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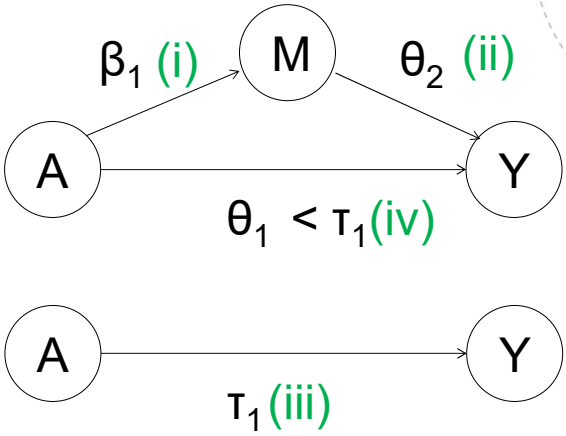
Baron and Kenny (1986) criteria for mediation:



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Baron and Kenny (1986) criteria for mediation: All must be fulfilled.

i. The exposure is (significantly) associated with the mediator ($\beta_1 \neq 0$)
ii. In a model with exposure and mediator, the mediator is (significantly) associated with the outcome ($\theta_2 \neq 0$)
iii. In a model without the mediator, the exposure is (significantly) associated with the outcome. ($\tau \neq 0$)
iv. In a model with exposure and mediator, the exposure is no longer (significantly) associated with the outcome. (The hypothesis $\theta_1 = 0$ is accepted)

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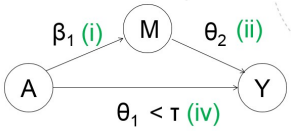
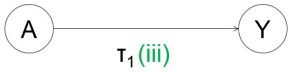


The upper DAG is quite widely accepted as a building block for mediation analysis



An approach limited to sequential significance testing is criticized as summarized by (Hayes 2013):

1) Does not estimate, or make inference about, the direct and indirect effects
2) The combined sequential testing procedure is an underpowered test procedure as a whole
3) There can be a mediated effect even if the total effect is small or insignificant
4) It does not distinguish between partial and complete mediation

(VanderWeele 2015) page 31 and (MacKinnon 2008):
Requirements (i) and (ii) are generally accepted. Requirement (iii) is criticized by many scholars (point 3 above). And requirement (iv) does not distinguish between partial and complete mediation.
(Hayes and Rockwood 2017) page 43: Focus on the indirect effect through M. «By contemorary thinking, tests of significance for the individual paths (i) and (ii) are not required to determine whether M mediates the effect …»

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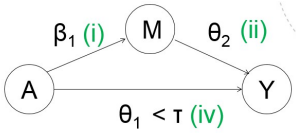

$E(M \mid a) = \beta_0 + \beta_1 a$

$E(Y \mid a,m) = \theta_0 + \theta_1 a + \theta_2 m$

$E(Y \mid a) = \tau_0 + \tau_1 a$

Direct effect: θ_1

Indirect effect:
Product method: $\beta_1 \theta_2$
Difference method: $\tau_1 - \theta_1$

The difference method is more common in epidemiology, while the product method is more common in social sciences. For a continuous outcome on the difference scale, the two methods will coincide (VanderWeele 2015, page 31)

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Sobels's (1982) test and confidence interval for the indirect effect $\beta_1\theta_2$

An (approximate) standard error (based on the delta method) is

$$SE\left(\hat{\beta}_1\hat{\theta}_2\right) = \sqrt{\hat{\beta}_1^2\sigma_{\hat{\theta}_2}^2 + \hat{\theta}_2^2\sigma_{\hat{\beta}_1}^2}$$

If $\hat{\beta}_1\hat{\theta}_2$ is normally distributed, then

$\hat{\beta}_1\hat{\theta}_2 \Big/ SE\left(\hat{\beta}_1\hat{\theta}_2\right)$ is appr. standard normal distributed and a test and CI is easily derived.

But even if $\hat{\beta}_1$ and $\hat{\theta}_2$ are normally distributed, their product is not.

Remedy to Sobel's method: Bootstrap test and CI for the indirect effect.

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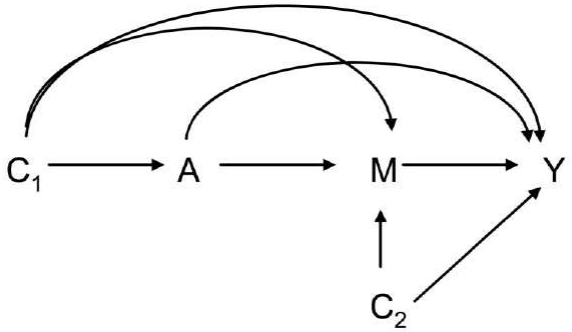

Figure 2. Causal diagram for mediation and confounding. A = exposure; M = mediator; Y = outcome; C_1 and C_2 = covariates.

(Valeri and VanderWeele 2013)

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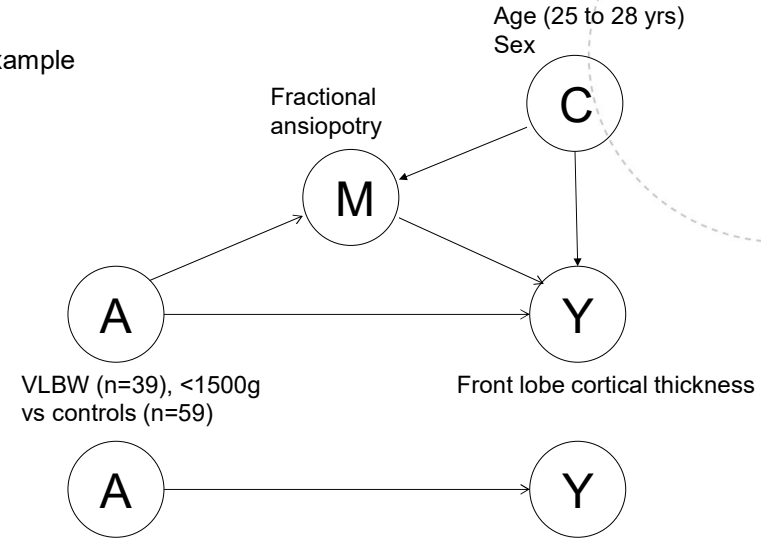
Example



Rimol, L, Botelero, V, … , Lydersen, S, …, Indredavik, M. …: Reduced fractional anisotropy mediates frontal lobe cortical thickening in 26 year-olds with very low birthweight. To be submitted 2017.

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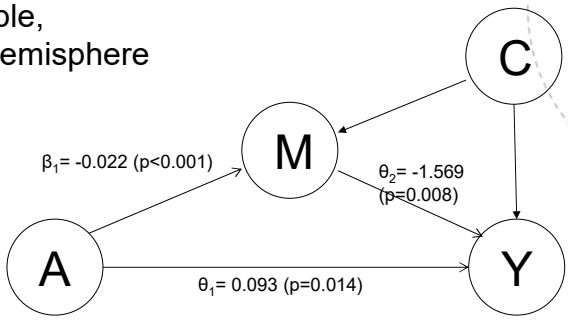
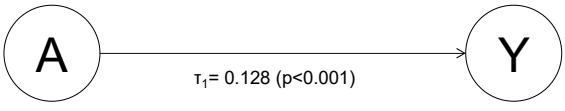
Example,
right hemisphere



Mediated effect (indirect effect) = $\beta_1\theta_2$= 0.035 (p=0.024)
(From Bootstapping, Mplus)



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In 1986, Baron and Kenny also proposed a parametric approach to estimate and test for mediation. The approach is often simply referred to as the "Baron and Kenny approach"; however, others had proposed it previously (Alwin & Hausen, 1975; Hyman, 1955; Judd & Kenny, 1981; Sobel, 1982), and it is also more generally referred to as the "product method." Let A be the treatment, Y the outcome, M the mediator and C additional covariates. For the case of continuous mediator and outcome, consider the following regression models:

$$E[M|a,c] = \beta_0 + \beta_1 a + \beta'_2 c \quad (1)$$

$$E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta'_4 c \quad (2)$$

Suppose we have a continuous outcome and mediator and the mediator regression remains as in Model 1 while the outcome regression is reformulated as

$$E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta'_4 c. \quad (3)$$

(Valeri and VanderWeele 2013)

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Exposure – mediator interaction:
Effect of changing the exposure from level a^* to level a:

Controlled direct effect (if the mediator is controlled at level m):
$CDE = E\left[Y(a,m) - Y(a^*,m) \mid C = c\right]$

(Pure) Natural direct effect:
$NDE = E\left[Y(a,M(a^*)) - Y(a^*,M(a^*)) \mid C = c\right]$

(Total) Natural indirect effect (if exposure is kept at level a):
$NIE = E\left[Y(a,M(a)) - Y(a,M(a^*)) \mid C = c\right]$

From VanderWeele & Vansteelandt (2009)

The total effect is the sum of these two:
$TE = NDE + NIE$

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Similary from VanderWeele & Vansteelandt (2009) page 461: (less relevant?)

Total Natural direct effect:

$$E\left[Y(a, M(a)) - Y(a^*, M(a)) \mid C = c\right]$$

Pure Natural indirect effect (if exposure is kept at level a^*):

$$E\left[Y(a^*, M(a)) - Y(a^*, M(a^*)) \mid C = c\right]$$

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Assuming correctly specified regression models and no unmeasured confounders, in can be shown (Appendix in VanderWeele & Vansteelandt 2009):

$$CDE = (\theta_1 + \theta_3 m)(a - a^*)$$
$$NDE = \{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta' 2c)\}(a - a^*)$$
$$NIE = (\theta_2\beta_1 + \theta_3\beta_1 a)(a - a^*).$$

These expressions generalize those of Baron and Kenny (1986) to allow for interactions between the exposure and the mediator. We describe these effects below. Note that if interaction is not present, so that $\theta_3 = 0$, the controlled direct effect and the natural direct effect are equal to the direct effect obtained using Baron and Kenny approach θ_1 times $(a - a^*)$ and the natural indirect effect is equal to the indirect effect of the Baron and Kenny approach $\theta_2\beta_1$ times $(a - a^*)$.

(Valeri and VanderWeele 2013)

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Example, right hemisphere:

Total effect: 0.128

Mediation without interaction:
Direct effect: 0.093
Indirect effect: 0.035

Mediation with interaction:
CDE* = 0.1040
NDE=0.1214
NIE=0.0070

*Evaluated at average value of mediator in the sample.

For average mediator value in each group:
VLBW: CDE=0.0768
Controls: CDE=0.1220

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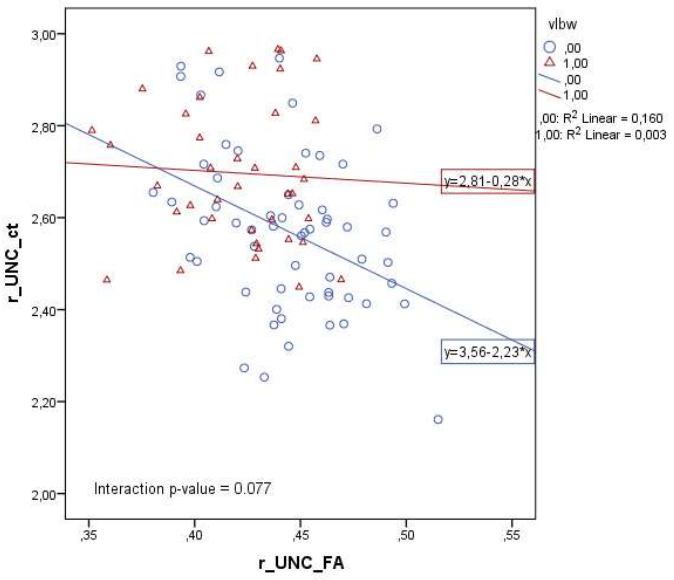

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BMJ 2013;347:f4089 doi: 10.1136/bmj.f4089 (Published 9 July 2013) Page 1 of 10

RESEARCH

Mediators of the association between pre-eclampsia and cerebral palsy: population based cohort study

OPEN ACCESS

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Data:
Singleton births from Medical Birth Registry of Norway and the Cerebral Palsy Registry of Norway 1996 to 2006.

Preeklampsi * Cerebral parese Crosstabulation

			Cerebral parese		
			nei	ja	Total
Preeklampsi	nei	Count	593777	774	594551
		% within Preeklampsi	99,9%	,13	100,0%
	ja	Count	22881	75	22956
		% within Preeklampsi	99,7%	,33	100,0%
Total		Count	616658	849	617507
		% within Preeklampsi	99,9%	,14	100,0%

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Tables

Table 1| **Maternal and pregnancy related characteristics reported as number (percentage) in children with or without exposure to pre-eclampsia and with or without cerebral palsy born in Norway 1996-2006**

	No pre-eclampsia		Pre-eclampsia	
Characteristics	**No cerebral palsy (n=593 777)**	**Cerebral palsy (n=774)**	**No cerebral palsy (n=22 881)**	**Cerebral palsy (n=75)**
Maternal characteristics				
Para 0	235 858 (39.7)	343 (44.3)	13 768 (60.2)	52 (69.3)
Smoker in pregnancy	76 095 (22.6)	106 (23.9)	2642 (19.2)	12 (25.0)
Assisted fertilisation	7024 (1.2)	12 (1.6)	380 (1.7)	5 (6.7)
Child characteristics				
Male	304 574 (51.3)	448 (57.9)	11 865 (51.9)	50 (66.7)
Small for gestational age	43 399 (7.5)	111 (15.1)	4 523 (20.3)	31 (44.3)
Term birth (≥37 weeks)	549 172 (95.4)	504 (67.5)	17 002 (76.3)	21 (29.2)
SGA infants born at term	40 854 (7.4)	76 (15.4)	2676 (15.8)	7 (33.3)
Moderate preterm birth (32-36 weeks)	23 185 (4.0)	106 (14.2)	4092 (18.4)	21 (29.2)
SGA infants born moderately preterm	2206 (9.5)	19 (17.9)	1363 (33.3)	9 (42.9)
Very preterm birth (<32 weeks)	3216 (0.6)	137 (18.3)	1180 (5.3)	30 (41.7)
SGA infants born very preterm	339 (10.6)	16 (11.9)	484 (41.2)	15 (53.6)

SGA=small for gestational age.
18 841 children had missing data on gestational age, 19 460 children had missing data on small for gestational age status.

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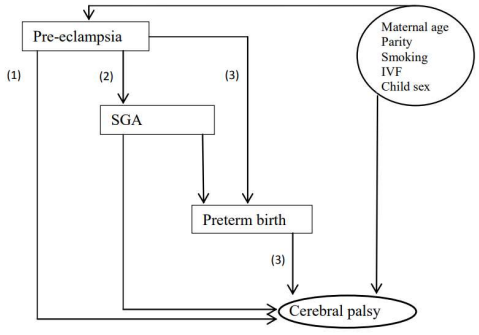
Supplementary figure 2. Proposed conseptual hierarchical framework for the relationship between pre-eclampsia and cerebral palsy (CP). Hypothesized causal pathways added in models 1-3, as well as potential confounders, are shown in the figure. Covariates in the models were:

Model 1: Pre-eclampsia
Model 2: Pre-eclampsia + small for gestational age (SGA)
Model 3: Pre-eclampsia + SGA + gestational age (GA)
Model 4: Pre-eclampsia + SGA + GA + Pre-eclampsia*GA



Adapted from Victoria et al (1997)

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Table 2| **Unadjusted (model 1) and adjusted odds ratios for cerebral palsy after exposure to pre-eclampsia**

Potential mediators	Odds ratios (95% CI)		
	Model 1*	Model 2†	Model 3‡
Pre-eclampsia	2.52 (1.98 to 3.19)	2.14 (1.67 to 2.74)	0.73 (0.56 to 0.96)
Small for gestational age	—	2.30 (1.91 to 2.76)	1.90 (1.58 to 2.30)
Duration of pregnancy:			
37-40 weeks	—	—	1.00 (reference)
32-36 weeks	—	—	5.10 (4.18 to 6.20)
<32 weeks	—	—	40.71 (33.70 to 49.17)

*Unadjusted odds ratio for association between pre-eclampsia and cerebral palsy.
†Adjusted for small for gestational age.
‡Adjusted for small for gestational age and duration of pregnancy.

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Table 3| **Prevalence and odds of cerebral palsy according to exposure to pre-eclampsia and small for gestational age, ~~stratified~~ by duration of pregnancy**

separate analyses

Duration of pregnancy and exposure	Total No at risk	Cerebral palsy	No cerebral palsy	No of cases of cerebral palsy/1000	Odds ratio (95% CI)
≥37 weeks					
Non-small for gestational age:					
No pre-eclampsia	508 228	418	507 810	0.8	1.0 (reference)
Pre-eclampsia	14 323	14	14309	1.0	1.19 (0.70 to 2.03)
Small for gestational age:					
No pre-eclampsia	40 930	76	40 854	1.9	2.26 (1.77 to 2.89)
Pre-eclampsia	2683	7	2676	2.6	3.18 (1.50 to 6.71)
32-36 weeks					
Non-small for gestational age:					
No pre-eclampsia	21 027	87	20 940	4.1	1.0 (reference)
Pre-eclampsia	2736	12	2724	4.4	1.06 (0.58 to 1.94)
Small for gestational age:					
No pre-eclampsia	2225	19	2206	8.5	2.07 (1.26 to 3.41)
Pre-eclampsia	1372	9	1363	6.6	1.59 (0.80 to 3.16)
<32 weeks					
Non-small for gestational age:					
No pre-eclampsia	2964	119	2845	40.1	1.0 (reference)
Pre-eclampsia	705	13	692	18.4	0.45 (0.25 to 0.80)
Small for gestational age:					
No pre-eclampsia	355	16	339	45.1	1.13 (0.66 to 1.93)
Pre-eclampsia	499	15	484	30.1	0.74 (0.43 to 1.28)
Missing data on gestational age:					
No pre-eclampsia	18 231	27	18 204	1.5	1.0 (reference)
Pre-eclampsia	610	3	607	4.9	3.33 (1.01 to 11.01)

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Table 4| **Odds for cerebral palsy according to exposure to pre-eclampsia and duration of pregnancy, compared with reference group of children unexposed to pre-eclampsia and born at term (model 4, adjusted for small for gestational age)**

Pre-eclampsia	Duration of pregnancy	Adjusted odds ratio (95% CI)
Absent	Term	1.00 (reference)
Present	Term	1.28 (0.83 to 1.98)
Absent	Moderately preterm	4.99 (4.05 to 6.16)
Present	Moderately preterm	4.64 (2.98 to 7.23)
Absent	Very preterm	45.90 (37.81 to 55.72)
Present	Very preterm	20.37 (13.74 to 30.22)
Small for gestational age	—	1.95 (1.61 to 2.36)

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Interactions:

Preeclampsia (PE) and small for gestational age (SGA): p= 0.17
(p=0.352 if GA continuous, p=0.331 if GA in 3 categories)

PE and gestational age (GA) : p=0.002
(PE and GA in 3 categories: p<0.001)

Table 3:
Two remarks:
To be precise, these are *separate* analyses for each GA group (epidemiologists often use the term ”stratified” meaning ”separate”, but that is not exactly the same)
The analysis in Table 3 actually allows for both the interactions PE*GA and PE*SGA.

Table 4:
A model including PE*GA, but not including PE*SGA

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Conclusions:
"Exposure to pre-eclampsia was associated with an increased risk of cerebral palsy, and this association was mediated through the children being born preterm or small for gestational age, or both. Among children born at term, pre-eclampsia was a risk factor for cerebral palsy only when the children were small for gestational age."

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BMJ article published 9 July 2013

Chiolero, A. and Kaufman, J.: "Adjustment for a mediator can induce bias." Rapid response, BMJ, 25 July 2013.

"Indeed, if there was an unmeasured common cause of both the mediator gestational age and the outcome cerebral palsy (i.e., a confounder of the association between gestational age and cerebral palsy), adjustment for gestational age could create a spurious association between preeclampsia and cerebral palsy. Intrauterine infection could be such a common cause [3]."

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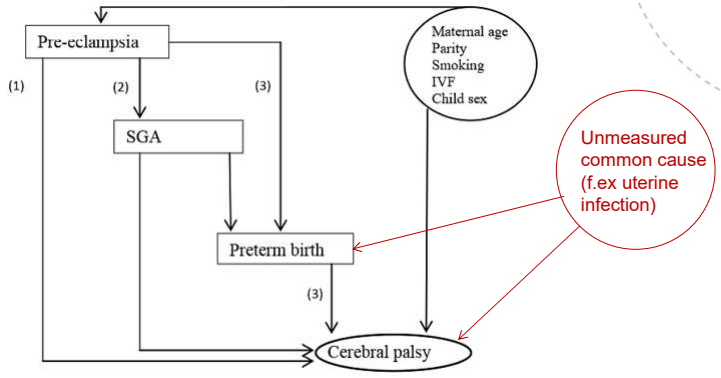

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Article published 9 July 2013
Rapid response, BMJ, 25 July 2013.

Vik, T., and Strand, K.: "Does preeclampsia protect preterm babies from cerebral palsy? " Rapid response, BMJ, 7 August 2013.

" … the lower odds for cerebral palsy probably means that very preterm births "caused by" preeclampsia (mainly iatrogenic, through caesarean section) may have less detrimental effects on the foetal brain than the causes of spontaneous preterm birth. We underscore this interpretation by stating that "In our study, among children with cerebral palsy born very preterm and unexposed to preeclampsia, 65.9% of mothers went into labour spontaneously. The corresponding proportion in children with cerebral palsy exposed to preeclampsia was 13.3%."
We appreciate this opportunity to re-emphasize that our study should not be interpreted as evidence that preeclampsia protects against cerebral palsy. "

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