Comment of the journal club "Mediation analysis: A practitioner's guide"

September 1, 2023

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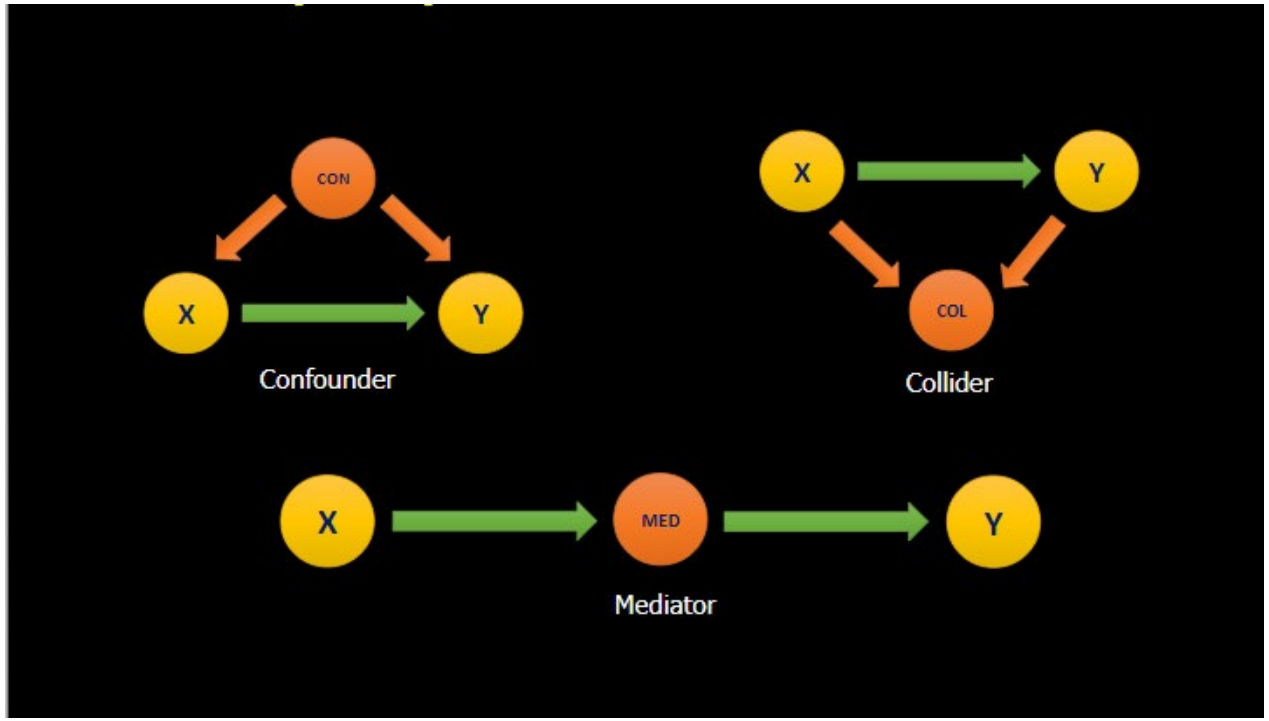

A principled approach to mediation analysis in perinatal epidemiology

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Objectives

1. Review the concepts of confounding and causal inference
2. Introduce the concept of a mediator and illustrate the perils of adjusting for this mediator in an exposure-outcome paradigm
3. Present an overview of causal mediation methods
4. Discuss unmeasured confounding assumptions

Glossary of general epidemiologic terms relevant to causal analysis

Association

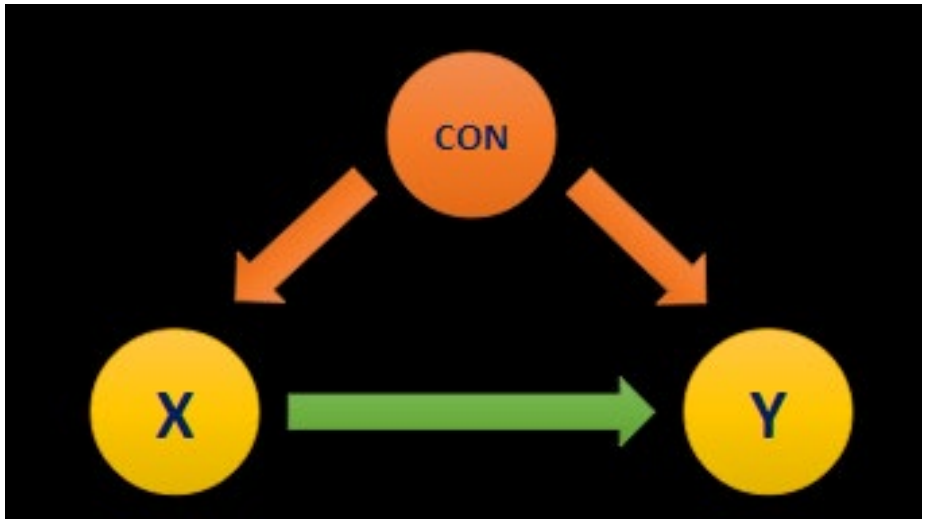
- is a statistical relationship between 2 variables that co-occur
- Non-causal association vs Causal association

Glossary of general epidemiologic terms relevant to causal analysis

Confounder

Definition: A variable that is

- Associate to the exposure
- Associate to the outcome
- Does not feature on the causal pathway
- Need to adjust



Confounding bias occurs when there is a **failure to adjust** for common causes of both the exposure and outcome.

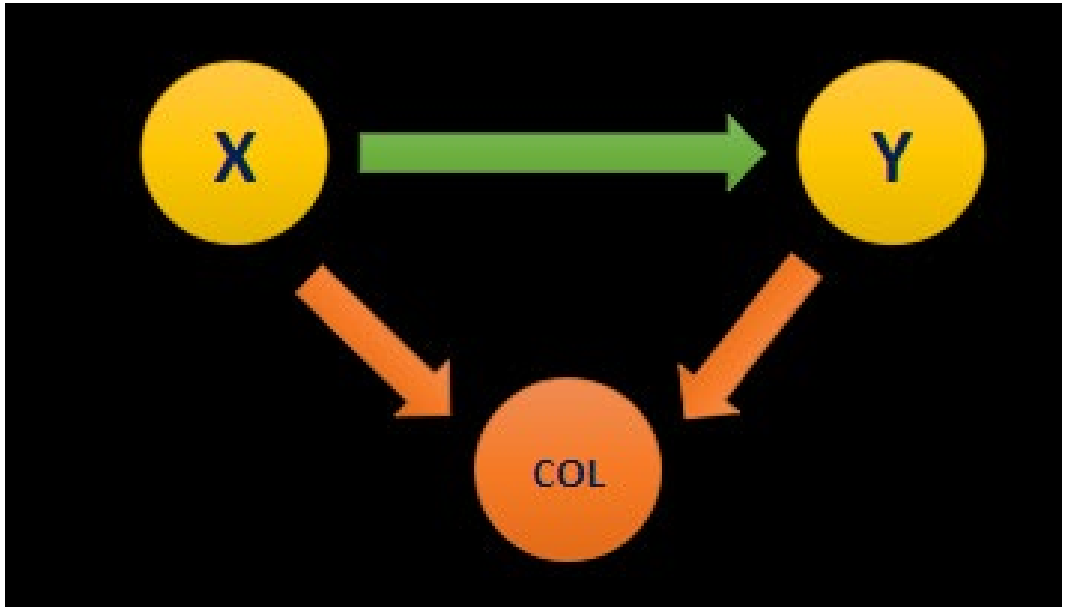
An unmeasured confounder is a “hidden bias”

Glossary of general epidemiologic terms relevant to causal analysis

Collider

- Common effect of both exposure and outcome
- No need for adjustment
- Collider-stratification bias :

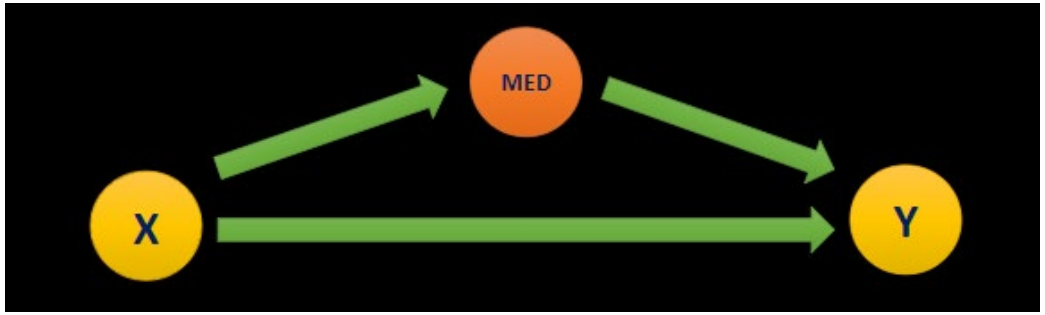
Any adjustment or stratification or matching on a collider induces a collider stratification bias, also referred to as a form of selection bias or bias owing to conditioning on a collider.



Glossary of general epidemiologic terms relevant to causal analysis

Mediator

- is a variable between an exposure and the outcome (intermediate), which is influenced by the exposure on the causal pathway to the outcome.
- A mediation analysis quantifies the extent that an exposure affects the outcome through a specific mediated pathway vs one that is independent of this pathway.



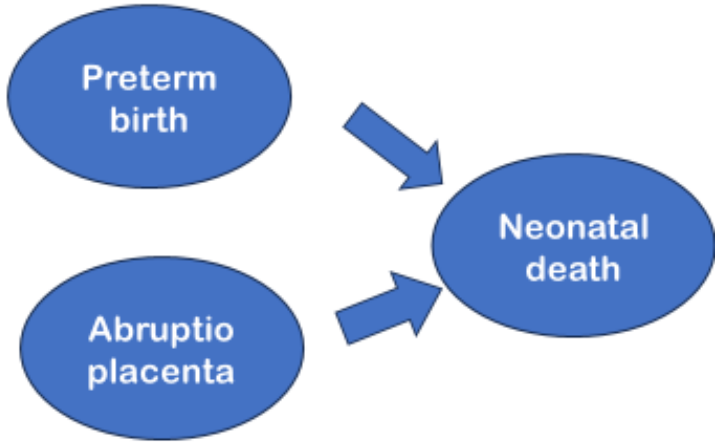
Scenario

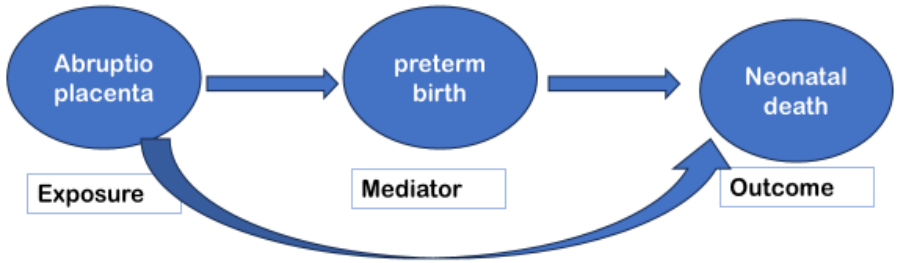
- A pregnant person at 28 weeks' gestation who experiences heavy vaginal bleeding and frequent uterine contractions, requiring urgent evaluation on labor and delivery.
- The patient undergoes an emergent cesarean delivery for suspected placental abruption (exposure), which results in a live-born neonate, who unfortunately dies a week later (outcome).

If this case had been managed differently, deferred delivery may or may not have resulted in stillbirth but may have averted the neonatal death

This reasoning is termed "counterfactual"

Scenario



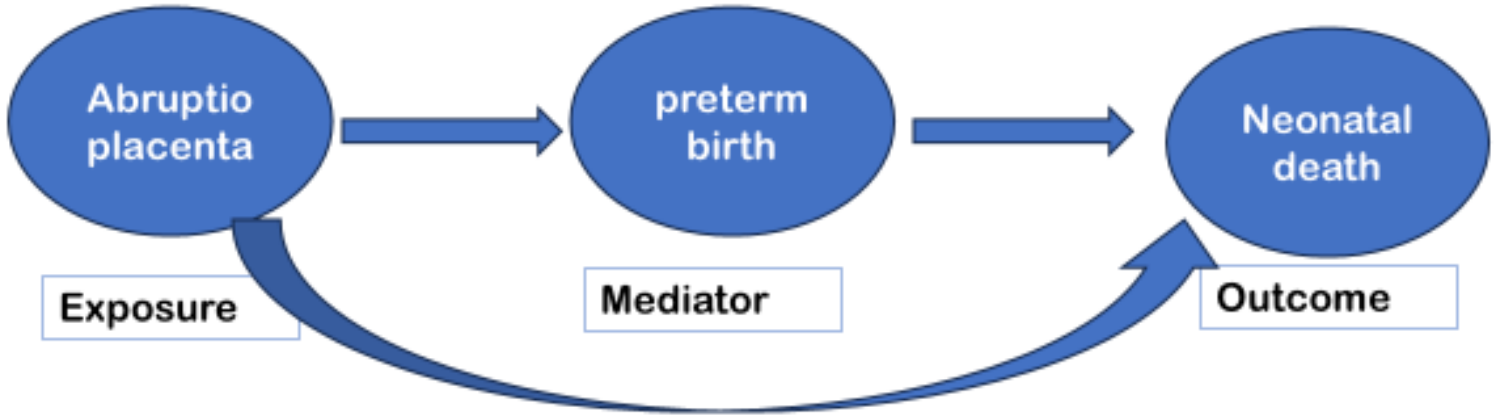


Question

- Did the abruption cause the neonatal death or was early delivery the cause? Or were both factors involved?
- Was the abruption serious enough to warrant an emergent cesarean delivery, which, in turn, led to the neonatal demise?
- How large was the effect of abruption on neonatal death, and how much of the effect on neonatal death was owing to abruption leading to preterm delivery?

Mediation analysis

- Mediation analysis provides a formal analytical framework to understand the causal effect of an exposure (eg, placental abruption) on the outcome (eg, perinatal mortality) and the role of mediators (eg, preterm delivery) that operate within this paradigm



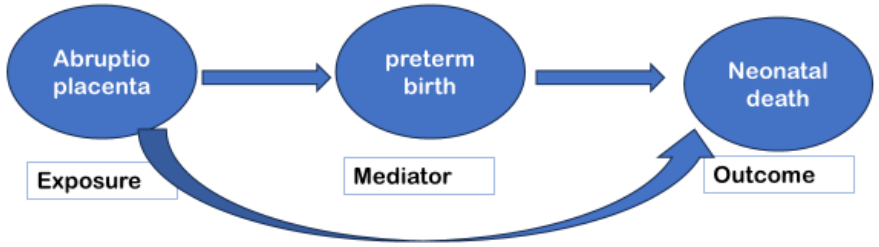
Research causal question

- to estimate the risk of perinatal mortality in a subpopulation experiencing abruption, relative to what would have happened if that subpopulation had not experienced abruption (called the “total effect” [TE]), and determine the extent to which preterm delivery (a proxy for GA) plays a role in this causal effect.

- to examine the causal effect of placental abruption (exposure) on perinatal mortality (outcome; defined as stillbirth plus deaths within the first week of life) from the Collaborative Perinatal Project (1959e1966) data, which includes 50,395 singleton births,.

Directed acyclic graph (DAG)

a visual guide to analyse by conceptualizing the complex relationship among exposure, outcome, and the variables that influence the causal structure.



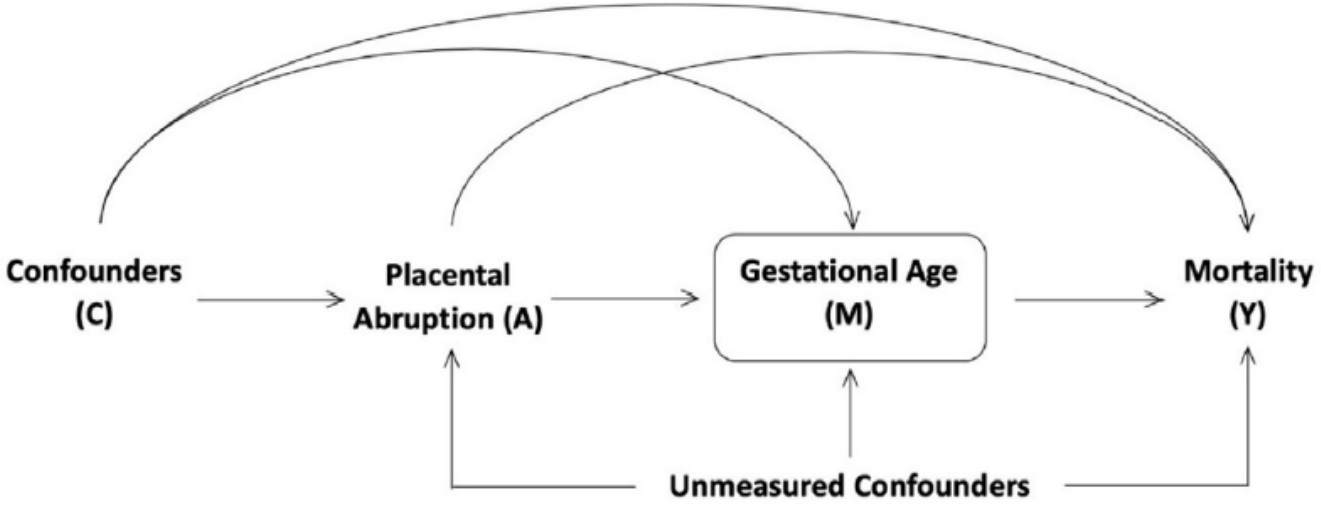


FIGURE 3

Gestational age-specific perinatal mortality rates among women with and without placental abruption: Collaborative Perinatal Project, 1959 to 1966

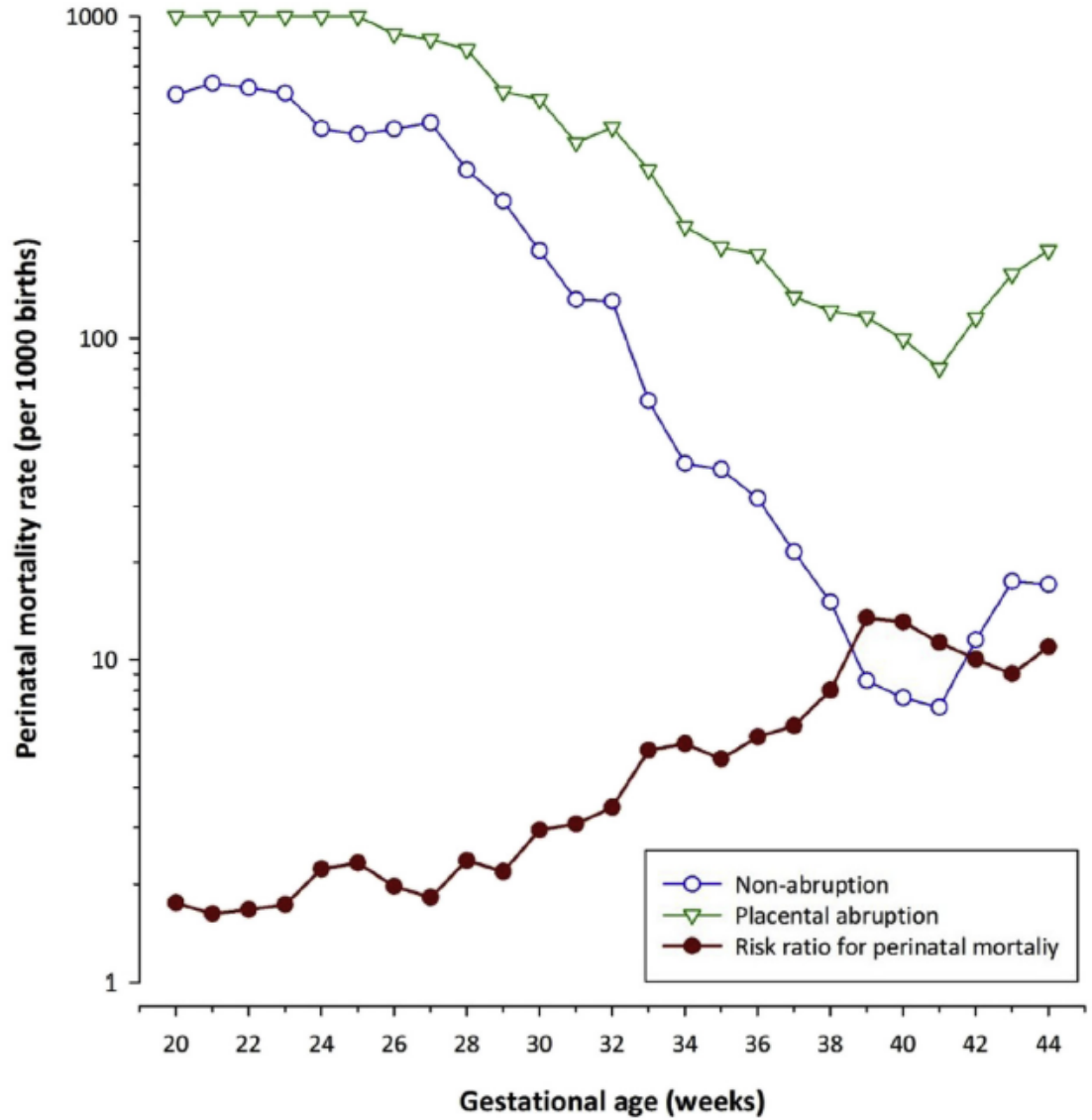


TABLE 2

Perinatal mortality rates among pregnancies with and without placental abruption: Collaborative Perinatal Project, 1959 to 1966

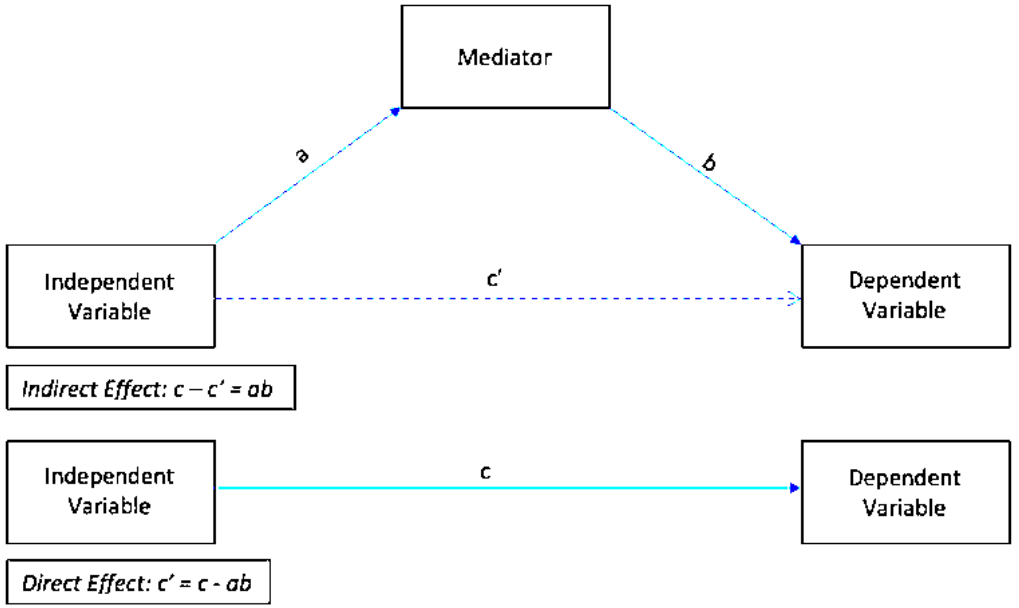
Perinatal mortality	Placental abruption		No placental abruption		
	Total births	Number (rate per 1000)	Total births	Number (rate per 1000)	Risk ratio (95% confidence interval)
Overall	1031	273 (264.8)	49,346	1219 (24.7)	10.72 (9.52–12.70)
Term deliveries[a]	589	57 (96.8)	42,232	463 (11.0)	8.83 (6.78–11.49)
Preterm deliveries[a]	442	216 (488.7)	7114	756 (106.3)	4.60 (4.08–5.19)
Adjusted for preterm delivery[a]	—	—	—	—	5.21 (4.64–5.85)

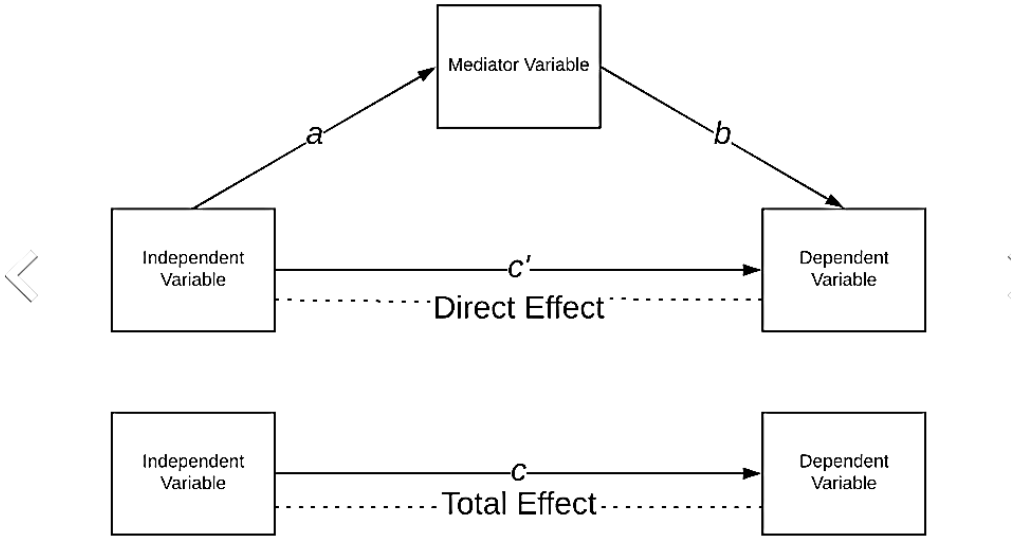
the RR of TE, ignoring mediator effect

When the TE is adjusted for or stratified based on preterm delivery status, an "overadjustment" bias is introduced.
In doing so, they are no longer estimating the TE but instead estimating a direct effect, which can be biased.

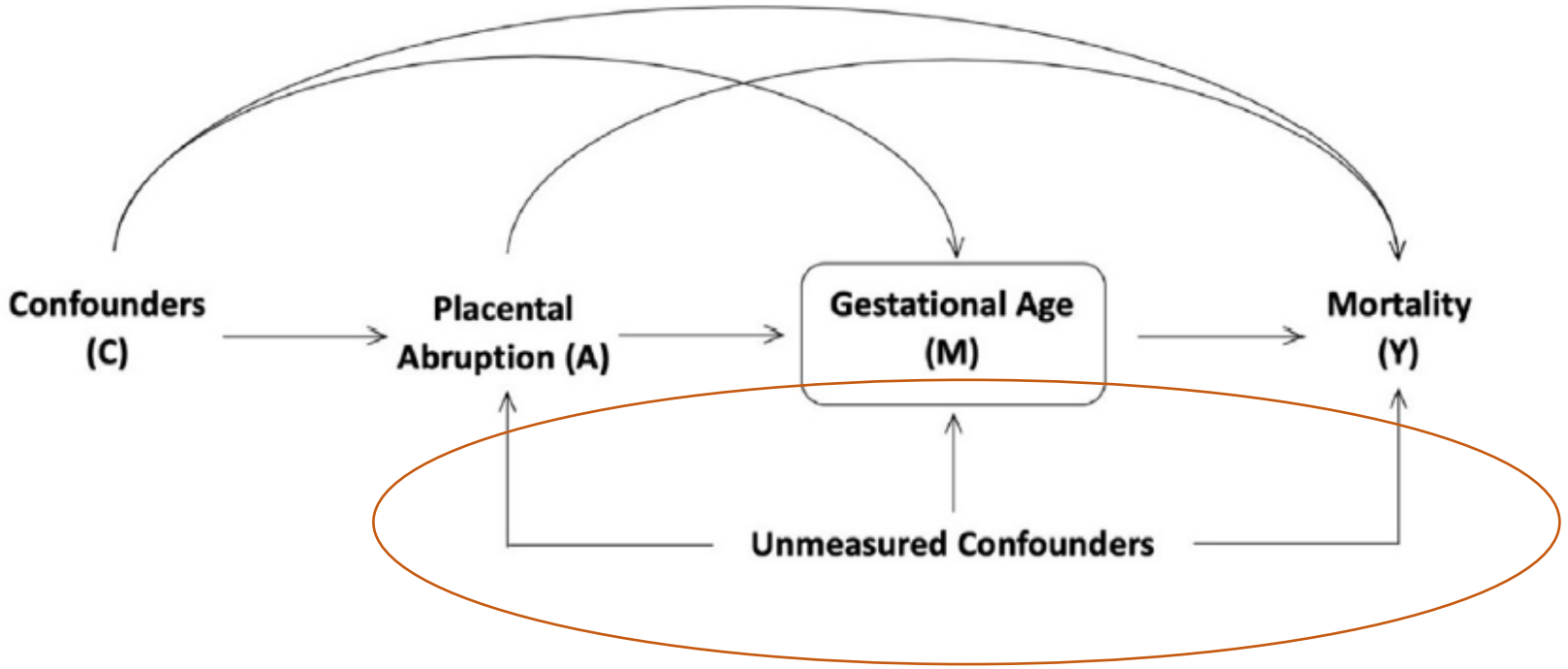
Overadjustment

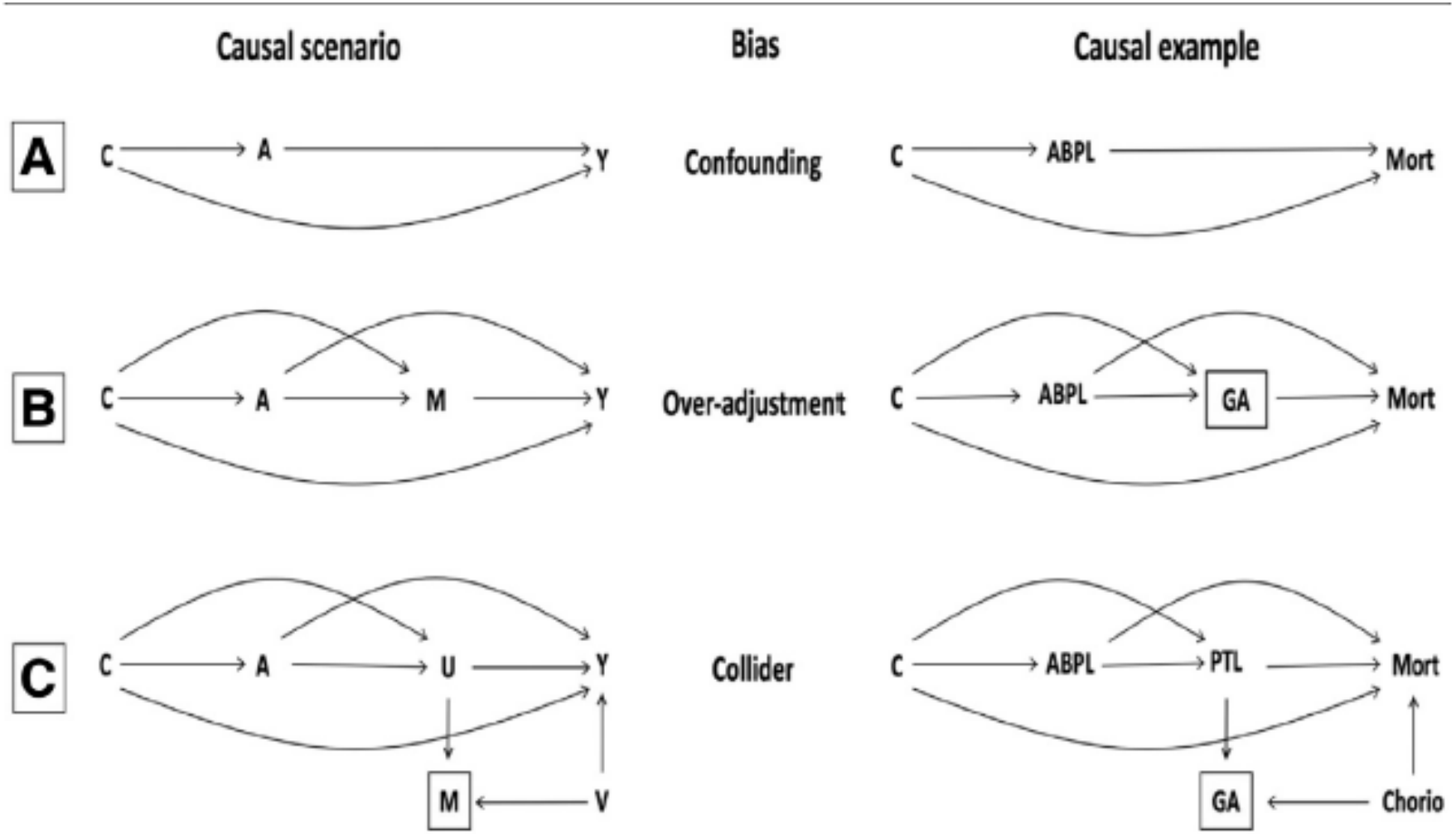
- is a type of bias that is introduced when there is adjustment (or stratification or matching) for a mediator.
- This adjustment no longer results in an estimate of the total effect (but rather a form of a direct effect) and often leads to counterintuitive and/or paradoxical results.





- Stratification, adjustment, or matching on a mediator opens a "backdoor" path through which a portion of the TE goes through unmeasured confounders.
- Failure to account for the backdoor path through correction for unmeasured confounding will render the causal effect biased and invalid.





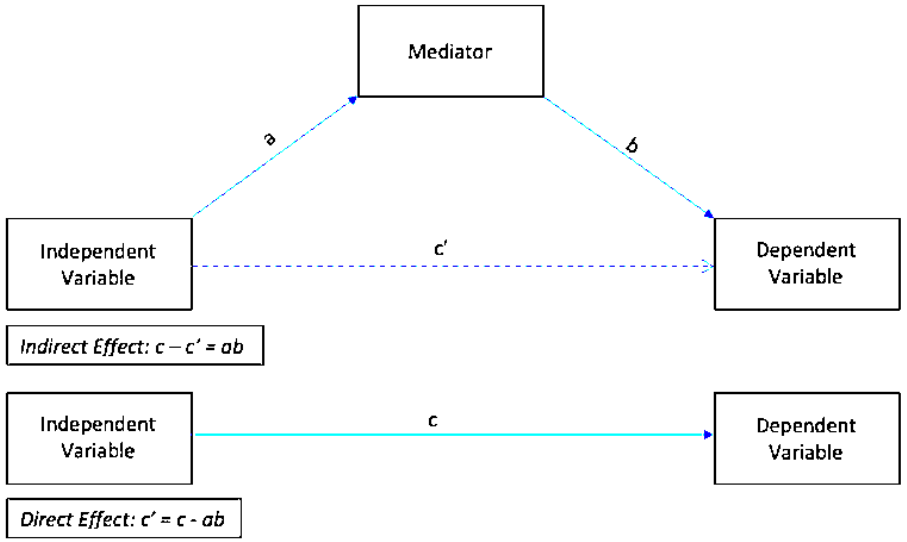
An example for each of the 3 scenarios are shown based on placental abruption (ABPL exposure [A]) and Mort (outcome [Y]) in the presence of confounders (C) and GA (mediator [M]) on the causal pathway and 2 unmeasured confounders, U (PTL) and V (Chorio)

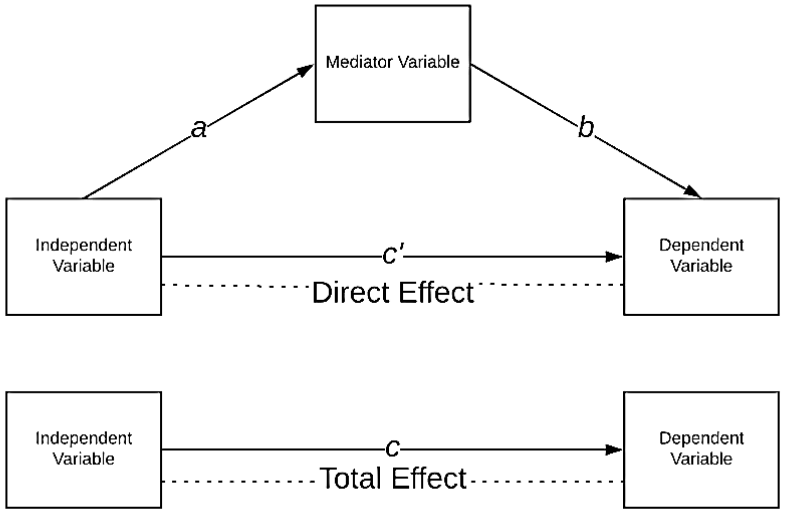
Address the causal question:

- **Does placental abruption increase the risk of perinatal mortality, and how much of the increase in mortality risk is because of preterm delivery (whether via obstetrical intervention or spontaneous preterm delivery)?**

Mediation methods

- account for the impact of mediating variables, such as GA, to estimate the causal effect of an exposure on the outcome.
- Disentangles the TE into 2 components:
  - The indirect effect: an estimate that operates through the mediator
  - The direct effect : an estimate that operate independent of the mediator



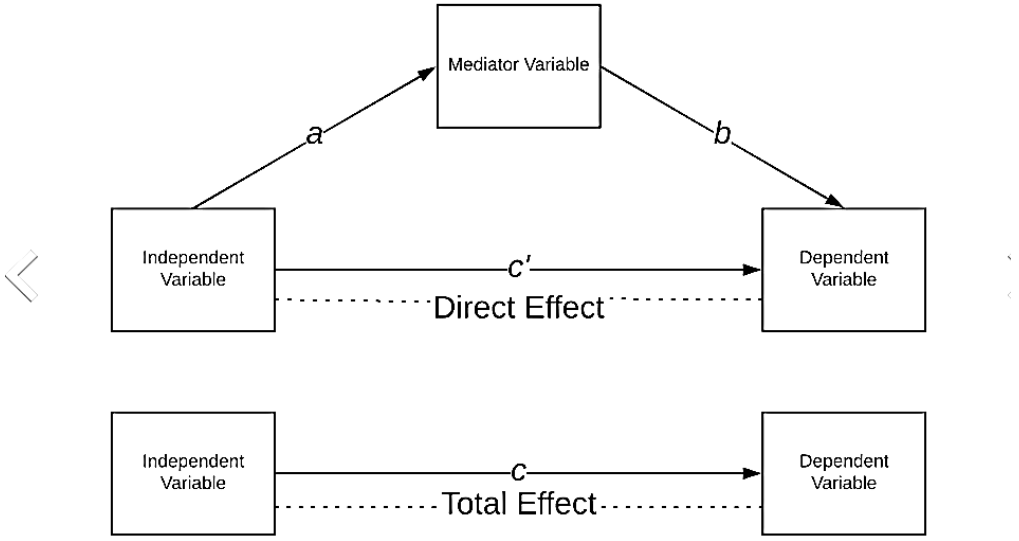


Components of mediation parameters

- **Total Effect (TE) : the overall causal effect of the exposure on the outcome, without accounting for mediating variables.**
- **TE is defined as how much the outcome would change overall for a change in the exposure A from level a=0 to level a=1.**

Risk ratio scale

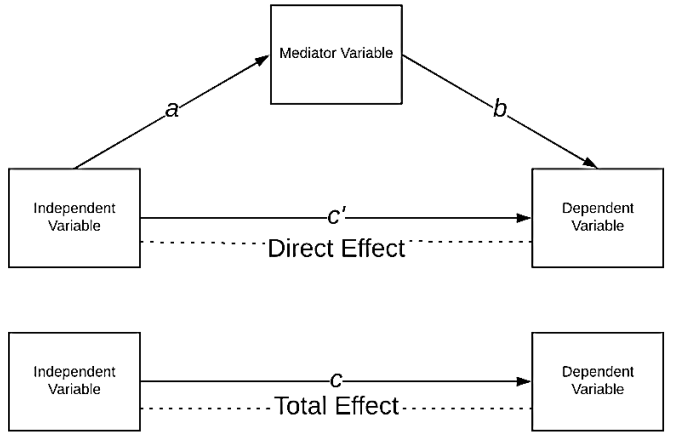
$$RR_{TE} = \frac{Pr(Y_1 = 1)}{Pr(Y_1 = 0)}$$



Components of mediation parameters

- **Controlled direct effect (CDE) : estimate of the expected effect that is directly attributable to the exposure when the mediator is held constant at a fixed value.**
- **CDE provides a contrast of the effect of an individual with an exposure A (a=1) on the outcome with the same individual without the exposure (a=0), a counterfactual, at a fixed level of the mediator at level m.**

$$RR_{CDE} = \frac{Pr(Y_{1M} = 1)}{Pr(Y_{0M} = 0)}$$



Components of mediation parameters

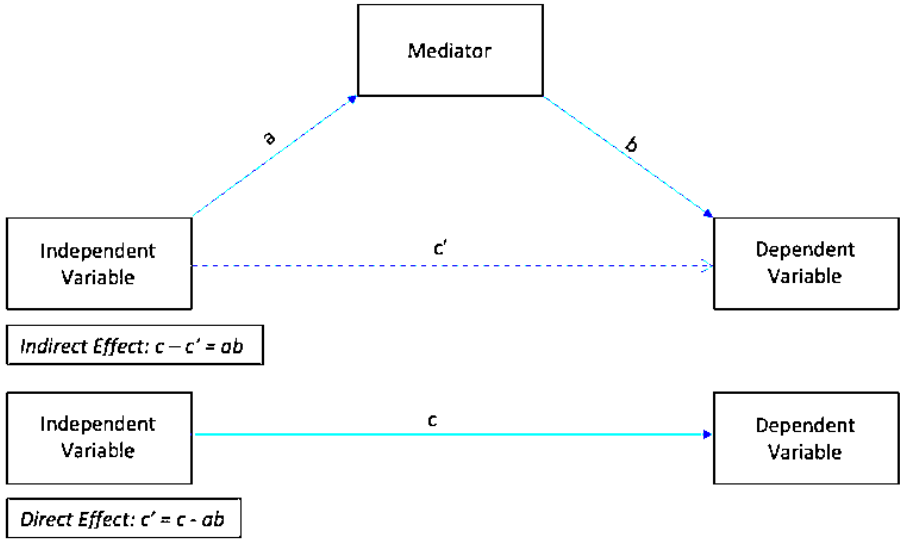
- **Natural direct effect (NDE) : an estimate of the effect of the exposure on the outcome if the mediator were set to what it would have been without the exposure.**
- **NDE expresses how much the outcome would change, on average, if the exposure was set at level a= 1 vs level a= 0, but for each individual, the mediator was kept at the level it would have taken in the absence of the exposure.**

$$RR_{NDE} = \frac{Pr(Y_{1M_0} = 1)}{Pr(Y_{0M_0} = 1)}$$

Components of mediation parameters

- Natural indirect effect (NIE) is the estimate of the effect of the exposure that operates through the mediator. Because the effect operates through the mediator, its effects are termed “indirect.”
- NIE expresses how much the outcome would change, on average, if the exposure A was fixed at level a=1, but the mediator was changed from the level it would take if a=0 to the level it would take if a=1

$$RR_{NIE} = \frac{\Pr(Y_{1M_1} = 1)}{\Pr(Y_{1M_0} = 1)}$$



Components of mediation parameters

- **Proportion mediated (PM) is the proportion of the TE that is explained by the mediator.**
- **It is estimated as the ratio of the natural indirect effect to the TE (PM=NIE/TE).**
- **It is insightful for policy-relevant recommendation.**
- **“how much of the effect of the exposure on the outcome is because of the effect of the exposure on the mediator.”**

$$PM_{\%}^{RR} = \frac{RR_{NIE}}{RR_{TE}}$$

Components of mediation parameters

- **Proportion eliminated (PE)** is the proportion of the TE that could be eliminated by removing the pathway from the exposure to the outcome through the mediator at a fixed (or given) level. The
- PE provides a causal estimate of the proportion of the effect that we could block by intervening on the mediator

$$PE_{\%}^{RR} = \frac{(RR_{TE} - RR_{CDE})}{RR_{TE}}$$

Objectives

1. Review the concepts of confounding and causal inference
2. Introduce the concept of a mediator and illustrate the perils of adjusting for this mediator in an exposure-outcome paradigm
3. Present an overview of causal mediation methods
4. **Discuss unmeasured confounding assumptions**
5. Discussion of the sample size and power analysis for causal mediation analysis
6. Review of available software to accomplish mediation analysis

Unmeasured confounding assumption

- Positivity : every confounder is represented in both exposed and unexposed group
- Exchangeability: no unmeasured confounding and no selection bias
- Consistency
- Lack of measurement error in the variables
- Correct model specification

Interpretation

Scenario

- A pregnant person at 28 weeks' gestation who experiences heavy vaginal bleeding and frequent uterine contractions, requiring urgent evaluation on labor and delivery.
- The patient undergoes an emergent cesarean delivery for suspected placental abruption (exposure), which results in a live-born neonate, who unfortunately dies a week later (outcome).

If this case had been managed differently, deferred delivery may or may not have resulted in stillbirth but may have averted the neonatal death

This reasoning is termed "counterfactual"

TABLE 4

Association between placental abruption and risk of perinatal mortality: mediation effects by preterm delivery (<37 weeks' gestation; binary mediator) and gestational age (continuous mediator): Collaborative Perinatal Project, 1959 to 1966

	Risk ratio (95% CI)				Percentage (95% CI)	
Causal mediators	Total effect	Controlled direct effect among term births	Natural direct effect	Natural indirect effect	Proportion mediated	Proportion eliminated
Preterm delivery						
Unadjusted	10.72 (9.58–12.07)	8.83 (6.70–11.32)	6.21 (5.34–7.20)	1.73 (1.57–1.92)	47 (40–53)	64 (56–73)
Adjusted	11.30 (9.84–12.73)	8.58 (6.47–11.30)	6.07 (5.15–7.22)	1.86 (1.67–2.09)	51 (44–57)	66 (57–75)
Gestational age						
Unadjusted	10.39 (9.00–11.97)	8.16 (6.76–9.81)	6.69 (5.66–7.89)	1.56 (1.47–1.65)	39 (35–44)	43 (38–48)
Adjusted	10.41 (8.90–12.08)	7.97 (6.55–9.83)	6.59 (5.53–7.94)	1.58 (1.49–1.69)	41 (36–45)	44 (39–49)

Causal effects were adjusted for confounding effects of maternal age, primiparity, maternal race, education, single marital status, smoking before and during pregnancy, prepregnancy body mass index, chronic hypertension, clinic vs private patient, and socioeconomic status. The 95% CIs were estimated based on the bias-corrected bootstrap resampling method (with 2000 replications). We used the CAUSALMED procedure in SAS (version 9.4; SAS Institute, Cary, NC) to estimate the causal estimates reported in the table.

CI, confidence interval.

Ananth. Mediation analysis in perinatal epidemiology. Am J Obstet Gynecol 2022.

TABLE 4

Associatio… …ediation ef… …y
(<37 weel… …mediator): …
Project, 1959 to 1966

The causal association between placental abruption and perinatal mortality after adjustment for confounders

Among abruption births, the mortality risk if we were able vs unable to delay delivery to what it would have been without abruption

Causal mediators	Risk ratio (95% CI) Total effect	Controlled direct effect among term births	Natural direct effect	Natural indirect effect	… mediated	… eliminated
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The perinatal mortality risk between those with and without abruption if, in both cases, delivery was delayed to the preterm delivery status that would have occurred without abruption

Causal effects were adjusted for confounding effects of maternal age, primiparity, maternal race, education, single marital status, smoking before and during pregnancy, prepregnancy body mass index, chronic hypertension, clinic vs private patient, and socioeconomic status. The 95% CIs were estimated based on the bias-corrected bootstrap resampling method (with 2000 replications). We used the CAUSALMED procedure in SAS (version 9.4; SAS Institute, Cary, NC) to estimate the causal estimates reported in the table.

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Gestational age						
Unadjusted	10.39 (9.00–11					)
Adjusted	10.41 (8.90–12					)

The risk of perinatal mortality was substantially higher among patients with abruption than patients with non-abruption pregnancies, with slightly more than half of the TE being an indirect effect mediated through preterm delivery (PM of 51%).

Causal effects were adjusted for confounding e s
index, chronic hypertension, clinic vs private pa e
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The proportion of the effect of abruption on perinatal mortality if we were to fix delivery at term gestations.
Another way to interpret PE is the proportion of the abruption-perinatal mortality association that can be eliminated by delivery every birth at term gestation

Methods to assess the unmeasured confounding assumptions

2 approaches

1. Evaluation of role of unmeasured confounding to estimate a bias factor, which indicates how different the true (unobserved) RRs for the TE, NIE, and NDE will be and in the presence of unmeasured confounding.
2. Estimation of an *E* value, which indicates the extent to which the confounder-adjusted RRs for the TE may also be biased because of unmeasured confounders.

The E value

- is defined as the minimum strength of association (on the RR scale) that an unmeasured confounder would need to have with both the exposure and outcome to fully explain the exposure-outcome association, after adjusting for measured confounders
- a large E value (relative to the observed confounder-adjusted RR) will indicate that it is unlikely for unmeasured confounding to wipe out the observed association.
- In contrast, a small E value will indicate that even a small unmeasured confounding is sufficient to account for the observed associations.

- The E values for the estimate of RR and the lower 95% CI of the RR in the abruption-perinatal mortality example for the TE were 22.09 and 19.17, respectively.
- These estimates allow a qualitative assessment of how large an effect of the unmeasured confounders must be, over and above the observed confounders, to reduce the observed RR toward the null.
- Furthermore, the E value provides a lower limit of 95% CI estimate to cross the null of the observed RR. In this case, the results of the sensitivity analysis illustrate that unmeasured confounding is highly unlikely to contribute to the adjusted RRs, strengthening the validity of the observed observations.

In conclusion

This review provides the analytical framework to help researchers determine whether the TE of the exposure on the outcome is influenced by mediators and, if so, methods to quantify the effect of mediators.