# A principled approach to mediation analysis in perinatal epidemiology



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For many research questions in perinatal epidemiology, gestational age is a mediator that features the causal pathway between exposure and outcome. A mediator is an intermediate variable between an exposure and outcome, which is influenced by the exposure on the causal pathway to the outcome. Therefore, conventional analyses that adjust, stratify, or match for gestational age or its proxy (eg, preterm vs term deliveries) are problematic. This practice, which is entrenched in perinatal research, induces an overadjustment bias. Depending on the causal question, it may be inappropriate to adjust (or condition) for a mediator, such as gestational age, by either design or statistical analysis, but its effect can be quantified through causal mediation analysis. In an exposition of such methods, we demonstrated the relationship between the exposure and outcome and provided a formal analytical framework to quantify the extent to which a causal effect is influenced by a mediator. We reviewed concepts of confounding and causal inference, introduced the concept of a mediator and illustrated the perils of adjusting for a mediator in an exposure-outcome paradigm for a given causal question, adopted causal methods that call for an evaluation of a mediator in a causal exposure effect on the outcome, and discussed unmeasured confounding assumptions in mediation analysis. Furthermore, we reviewed other developments in the causal mediation analysis literature, including decomposition of a total effect when the mediator interacts with the exposure (4-way decomposition), methods for multiple mediators, mediation methods for case-control studies, mediation methods for time-to-event outcomes, sample size and power analysis for mediation analysis, and available software to apply these methods. To illustrate these methods, we provided a clinical example to estimate the risk of perinatal mortality (outcome) concerning placental abruption (exposure) and to determine the extent to which preterm delivery (mediator; a proxy for gestational age) plays a role in this causal effect. We hoped that the adoption of mediation methods described in this review will move research in perinatal epidemiology away from biased adjustments of mediators toward a more nuanced quantification of effects that pose unique challenges and provide unique insights in our field.

**Key words:** causal analysis, collider bias, epidemiology, mediation analysis, perinatal research, unmeasured confounding

## Introduction

This review provides an exposition of methods for causal mediation analysis and illustrated the influence of mediating variables with real-life applications in perinatal epidemiology.

Furthermore, we introduced the concept of causal mediation through the following scenario, drawing on the concepts espoused by Hernán.[1] Consider 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 (all else being equal). This reasoning is termed "counterfactual" (or contrary to the fact).

The example illustrates several salient issues. First, abruption determines gestational age (GA) at delivery,[2–4] and GA, in turn, is a powerful predictor of mortality.[5–7] Therefore, it is likely that the abruption-preterm delivery-perinatal mortality association is causal. Second, in searching for clues into the cause of neonatal death, both abruption and preterm delivery (independently or abruption resulting in preterm delivery) are plausible candidates. Did the abruption cause the neonatal death or was early delivery the cause? Or were both factors involved? In other words, was the abruption serious enough to warrant an emergent cesarean delivery (leading to preterm delivery at 28 weeks' gestation), which, in turn, led to the neonatal demise? If so, 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

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delivery? An analysis that seeks to answer these questions and estimate causal effects are approached through 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.[8,9] Table 1 presents a glossary of common epidemiologic terms relevant to causal analysis.

This review is devoted to an exposition of mediation analysis in perinatal epidemiology for clinician-researchers. The objectives were to (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, and (4) discuss unmeasured confounding assumptions in a mediation analysis and methods to address unmeasured confounding. We further discussed recent developments in the mediation analysis literature, including decomposition of the total effect (TE) in the presence of a mediator when the mediator also interacts with the exposure (called the 4-way decomposition), methods for multiple mediators, mediation methods for case-control studies, and mediation analysis for time-to-event outcomes. In addition, we provided a brief discussion of the sample size and power analysis for causal mediation analysis and review of available software to accomplish mediation analysis. Furthermore, we used this single example to illustrate several causal mediation methods. Currently, it will suffice to declare that the illustration of mediation analysis is built on the premise that preterm delivery is the single mediator of the abruption-perinatal mortality association. Methods to address multiple mediators are presented later.

## Causal Directed Acyclic Graphs

Evaluation of causal effects rests on certain assumptions regarding unmeasured confounding, among others. Directed acyclic graph (DAG) is a causal graph that characterizes assumptions about how exposures, outcomes, confounders, mediators, and unmeasured confounders are interrelated and help identify potential biases (Shrier and Platt[10] provides an overview). We distinguished 3 forms of biases: confounding bias, bias owing to an adjustment for a causal intermediate, and collider stratification bias (Figure 1).

Confounding bias is said to occur when there is a failure to adjust for common causes of the exposure and outcome. A simple definition of the confounder is a variable that is causally associated with the exposure and outcome and does not feature on the causal pathway between the exposure and outcome. In contrast, a mediator (also referred to as an "intermediate") is a variable that does feature on the causal pathway between the exposure and outcome. Another serious bias is a collider stratification bias, a form of selection bias. This is introduced when an adjustment is made for a variable that is affected by the exposure and shares common causes with the outcome.[13−15]

DAGs provide a visual guide to analyses—they facilitate an intuitive and easy-to-understand graphical approach—by conceptualizing the complex relationship among exposure, outcome, and the myriad variables that influence the causal structure.

## Motivating Example

We began with a motivation of the 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. Returning to the abruption example, we used data from the Collaborative Perinatal Project (1959−1966), which includes 50,395 singleton births, to examine the causal effect of placental abruption (exposure) on perinatal mortality (outcome; defined as stillbirth plus deaths within the first week of life). The causal question, which is illustrated in a simplified DAG that depicts this relationship, is described in Figure 2 and will be used throughout this review.

Perinatal mortality rates among patients with abruption and patients with nonabruption pregnancies were 264.8 and 24.7 per 1000 births, respectively (risk ratio [RR], 10.72; 95% confidence interval [CI], 9.52−12.70) (Table 2). This is defined as the RR of TE and refers to the effect of ignoring potential mediators. Patients with abruption were delivered earlier than patients with nonabruption pregnancies to avoid maternal and fetal compromises.[12,16,17] Clinical experience suggests that abruption and preterm delivery exert effects on perinatal mortality. Preterm delivery—regardless of abruption—confers an increased risk of perinatal mortality.[18,19] Simultaneously, abruption shortens GA at delivery (and increases the likelihood of preterm delivery)[17,20−22] as abruption may trigger the onset of spontaneous labor or may lead to a clinician-initiated intervention.[3,23]

It is tempting to examine the effect between abruption and perinatal mortality within the strata of GA groups (eg, preterm gestation vs term gestation) or adjust the effect for GA. There seems to be an entrenched bias that favors the adjustment of GA as a confounder. However, when the TE is adjusted for or stratified based on preterm delivery status, an "over-adjustment" bias is introduced.[11,14,24] Investigators sometimes estimate an effect by adjusting away for a mediator. In doing so, they are no longer estimating the TE but instead estimating a direct effect, which can be biased.[25]

Although perinatal mortality rates sharply decline with increasing GA among both the abruption and nonabruption groups, the decline is less among patients with abruption pregnancies (Figure 3). Furthermore, abruption confers increased perinatal mortality risk at every gestational week, with progressively increasing RR with advancing gestation. When adjustments are made for preterm delivery, the effect is stronger at term (≥37 weeks' gestation) than at preterm gestations (Table 2). When adjusted for preterm delivery, the strength of the causal effect

**TABLE 1**
**Glossary of general epidemiologic terms relevant to causal analysis**

| Terms | Definition |
|---|---|
| Association | An association is a statistical relationship between 2 variables that co-occur. Associations can occur between variables in the presence or absence of a causal relationship. |
| Confounder | A confounder is a variable that is a common "cause" of both the exposure and outcome and is not on the causal pathway between exposure and outcome. The influence of confounders requires adjustment to quantify an association between exposure and outcome to address confounding bias. Confounding bias occurs when there is a failure to adjust for common causes of both the exposure and outcome. |
| Intermediate | An intermediate is a variable that exerts influence on the causal pathway between the exposure and outcome. Directed acyclic graphs illustrate the influence of intermediates in the causal pathway. |
| Unmeasured confounder | An unmeasured confounder is a "hidden bias" that may account for an observed association owing to variables for which data were not ascertained or yet unrealized variables. |
| Mediator | A mediator is an intermediate variable between an exposure and the outcome, 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. |
| Overadjustment | An 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. |
| Collider | A collider is a variable on the causal pathway that is a common "effect" of both the exposure and outcome. 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. An adjustment for a collider can result in distorted causal effects between the exposure and outcome. |

All definitions were adapted from VanderWeele.[8]

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drops by half compared with the estimate of RR not adjusted for preterm delivery. This counterintuitive result does not estimate the TE, but rather reflects the unintended introduction of an overadjustment bias that occurs when an adjustment is made for a mediator.

This example sets the stage for a closer look at GA (or preterm delivery) as a potential mediator in a causal framework. An adjustment for preterm delivery in this example is referred to as an overadjustment problem in perinatal epidemiology.[26,27] Stratification, adjustment, or matching on a mediator opens a "backdoor" path through which a portion of the TE goes through unmeasured confounders.[11,14] Furthermore, failure to account for the backdoor path through correction for unmeasured confounding will render the causal effect biased and invalid. In effect, such an adjustment will result in a biased causal effect, as doing so will result in a common "effect" on both abruption and perinatal mortality that remains unaccounted for in the analysis.

With this backdrop, we delved to reevaluate our causal question. The objective was to 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)? The implicit issue in this causal question was to describe whether (and to what extent) the mortality risk is because of early delivery or to other mechanisms that are independent of GA.

Mediation methods provide the analytical framework to account for the impact of mediating variables, such as GA, to estimate the causal effect of an exposure on the outcome. Mediation disentangles the TE into 2 components: an estimate that operates through the mediator, also called the mediated or the indirect effect, and an estimate that operates independent of the mediator, also called the direct effect.

The remainder of this review was devoted to a nontechnical exposition of mediation methods. To the statistically brilliant reader, we provided the algebraic backdrop and formulas for mediation analysis in the Appendix. We focused on mediation methods devoted to a binary exposure and binary outcome, as is common in most of the research in perinatal epidemiology. For other types of exposures and outcomes, the interested reader is referred to the collection of works by VanderWeele[8] and Hernán and Robins.[9]

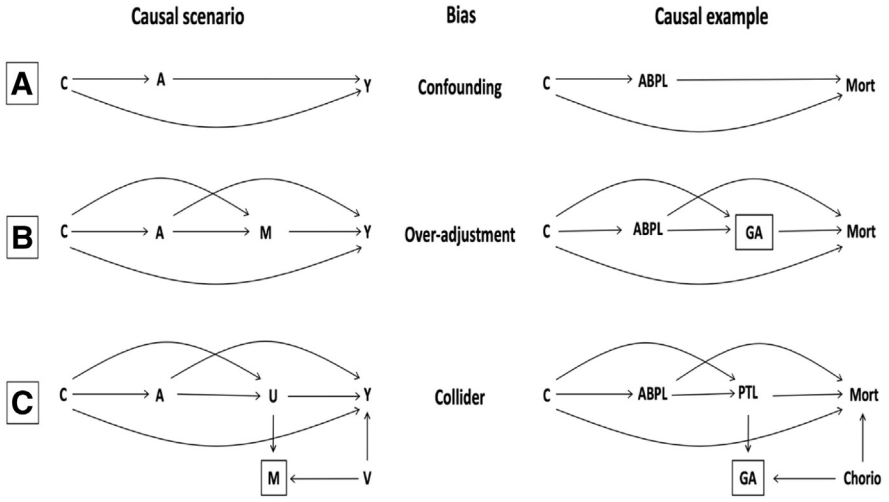
## Components of Mediation Parameters

Six causal parameters were potentially identifiable in the mediation analysis (Table 3).

### Total effect

The TE is the overall causal effect of the exposure on the outcome, without accounting for mediating variables. In other words, TE is a contrast of the outcome risk between those exposed and those unexposed, regardless of downstream mediating variables.

**FIGURE 1**
**Simple directed acyclic graphs depicting the relationship between an exposure and outcome in the presence of confounding, overadjustment, and collider**




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). Panel **A** refers to a causal scenario with confounding; panel **B** refers to a causal scenario with overadjustment; and panel **C** refers to a causal scenario with a collider. Note that there are other scenarios under which a collider bias may be induced. Adapted from Cole et al[11] and Ananth and Schisterman.[12]

*ABPL*, placental abruption; *Chorio*, chorioamnionitis; *GA*, gestational age; *Mort*, perinatal mortality; *PTL*, preterm labor.

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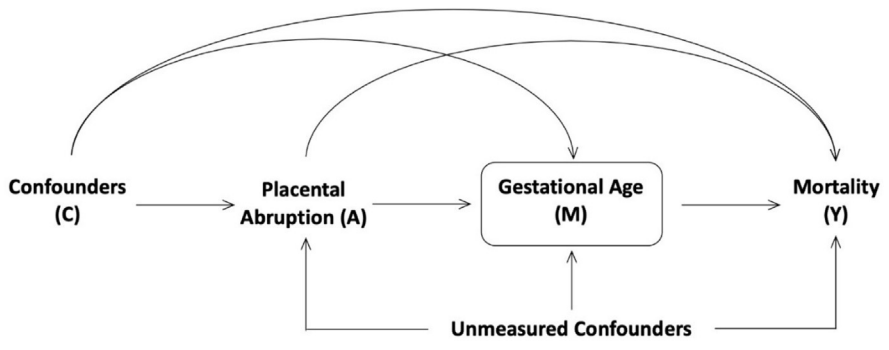
### Controlled direct effect

The controlled direct effect (CDE) is the estimate of the expected effect that is directly attributable to the exposure when the mediator is held constant at a fixed value. This proportion of the effect does not operate through the mediator. Intuitively, the CDE is useful for examining whether there are any pathways for the exposure independent of, or other than, the mediator.

**FIGURE 2**
**Simplified directed acyclic graph depicting the relation between placental abruption (A) and perinatal mortality (Y) with gestational age as the mediator (M) and unmeasured confounders (U)**

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### Natural direct effect

The natural direct effect (NDE) provides 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. The NDE is an estimate of the direct effect of the exposure on the outcome that is independent of the mediator.

### Natural indirect effect

The 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."

### Proportion mediated

Proportion mediated (PM) is the proportion of the TE that is explained or accounted by the mediator. It is estimated as the ratio of the natural indirect effect to the TE (PM=NIE/TE). The PM measures what would happen to the effect of the exposure on the outcome if we were to somehow disable the pathway from the exposure to the causal intermediate.[28] The PM is particularly insightful for policy-relevant recommendations.[28] An important caveat with PM is if the TE and NIE are in the opposite directions of the null (eg, 1.0 for the relative risk or 0.0 for the risk difference), then the PM will be negative. Interpretation of the mediated proportion in such circumstances gets complicated and problematic.

### Proportion eliminated

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.[28]

Further broader discussions of mediation methods and theoretical details are presented in the Appendix.

## Unmeasured Confounding Assumptions for Mediation Analysis

Drawing valid causal inferences from observational data rests on several unverifiable (and some verifiable)

**TABLE 2**
**Perinatal mortality rates among pregnancies with and without placental abruption: Collaborative Perinatal Project, 1959 to 1966**

| | Placental abruption | | No placental abruption | | |
|---|---|---|---|---|---|
| Perinatal mortality | 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) |

[a] Caveat emptor: We recognized the potential for bias in this analysis owing to the stratification and adjustment for a causal intermediate (preterm delivery), potentially leading to a collider bias. The intent was purely for an illustration of the concept.

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assumptions, including positivity[29,30] (ie, every combination observed confounders are represented in both the exposed and unexposed groups), exchangeability[31] (ie, no unmeasured confounding and no selection bias; discussed below), consistency (ie, well-defined exposure and mediator), lack of measurement error in the variables, and correct model specification. Another important assumption pertains to the "cross-world" assumption, which implies that there is independence between the (counterfactual) outcome and mediator values.[32] This assumption is challenging to verify in empirical data and has not been considered further.

For the CDE, NDE, and NIE to be valid and unbiased, several assumptions regarding unmeasured confounding are necessary.[25,33] Even if the TE is unconfounded, the partitioning of the TE through mediation effects can result in the direct and indirect effects being biased because of unmeasured confounding.[34] The identification of CDE, NDE, and NIE requires at least 4 "no unmeasured confounding" assumptions.[35–37]

Two unmeasured confounding assumptions are required to estimate the CDE. These include (1) that there is no unmeasured confounding of the exposure (conditional on observed confounders) on the response and (2) that there is no unmeasured confounding of the mediator (conditional on the exposure and observed confounders) on the response. Failure to adjust the analyses for confounders of the mediator-response relationship (in addition to adjustment for confounders of the exposure-response relationship) can lead to biased estimation of CDE.[38] These 2 assumptions are essential to estimate CDE of the exposure on the response, but 2 additional assumptions are necessary to estimate NDE and NIE. These include (1) no unmeasured confounding of the exposure (conditional on observed confounders)-mediator scenario and (2) no unmeasured confounding of the mediator-response scenario (conditional on observed confounders).[35–37]

## Interpretation of Causal Parameters

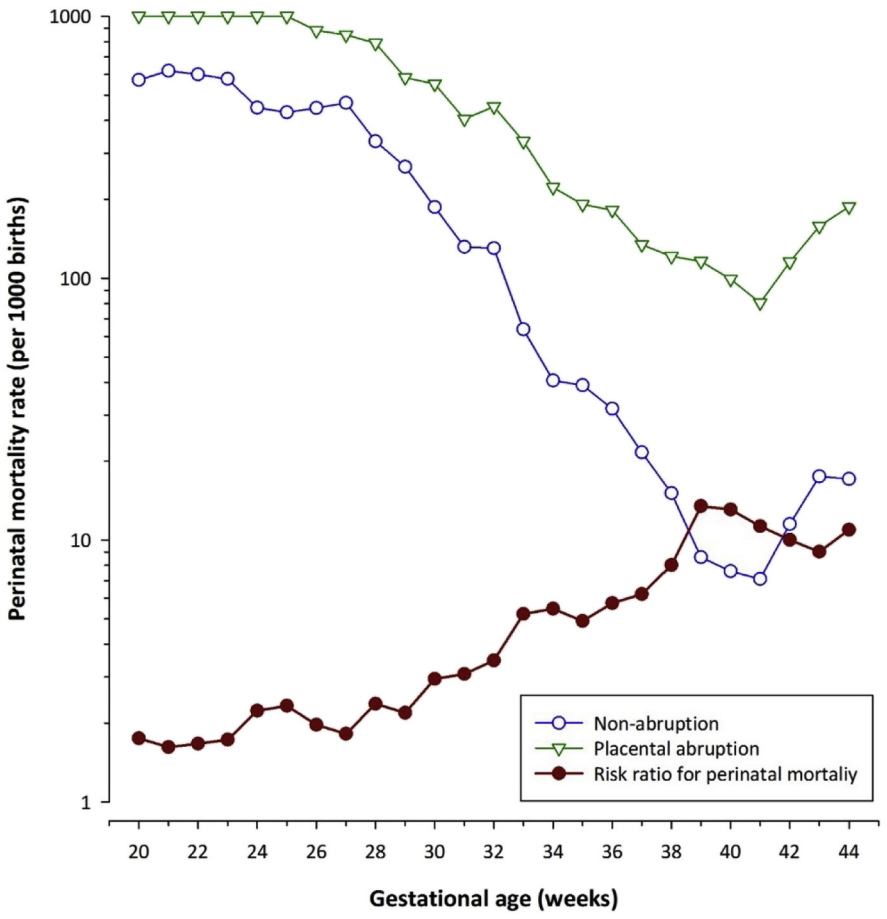
To illustrate these causal parameters, we returned to the example of placental abruption-perinatal mortality with preterm delivery as a binary mediator. The interpretation of the mediation parameters holds insofar as the identifiability assumptions are satisfied. The RRs of TE, NDE, and NIE were 11.30 (95% CI, 9.84–12.73), 6.07 (95% CI, 5.15–7.22), and 1.86 (95% CI, 1.67–2.09), respectively, for the causal effect of abruption on perinatal mortality, adjusted for several confounders (Table 4). The risk of perinatal mortality was substantially higher among patients with abruption than patients with nonabruption pregnancies, with slightly more than half of the TE being an indirect effect mediated through preterm delivery (PM of 51%). In other words, about half of the effects of the increased risk of perinatal deaths owing to abruption were because of preterm delivery, and about half of the TEs were explained through other, yet undiscovered, pathways (other than preterm delivery).

In addition, we illustrated the interpretation of causal parameters when the mediator was continuous (GA). The analysis indicates that the RRs for the NDE and NIE were 6.59 (95% CI, 5.53–7.94) and 1.58 (95% CI, 1.49–1.69), respectively (Table 4). This suggested that 41% of the TEs of abruption on perinatal mortality was mediated through GA. Is the mediated effect similar across the GA range, or might GA show stronger mediation effects, for instance, at earlier GAs compared with later GAs? Allowing more flexible modeling options for the continuous mediator (in the mediator model) may offer different insights.[39]

## Methods to Assess the Unmeasured Confounding Assumptions

There are several sensitivity analysis methods to test these "no unmeasured confounding" assumptions,[34,40,41] but we described 2 simple approaches. The first approach to evaluate the role of unmeasured confounding is to estimate a bias factor,[34] which indicates how different the true (unobserved) RRs for the TE, NIE, and NDE will be and in the presence of unmeasured confounding.[42] The bias-corrected estimates of RRs are then obtained by dividing the observed RR, and the CI limits by the bias factor, and multiplying the indirect effect estimate and CI limits by the bias factor. The bias is the largest

**FIGURE 3**
**Gestational age-specific perinatal mortality rates among women with and without placental abruption: Collaborative Perinatal Project, 1959 to 1966**




Caveat emptor: We recognized the potential for bias in this analysis owing to the stratification and adjustment for a causal intermediate (preterm delivery), potentially leading to a collider bias. The intent was purely for an illustration of the concept.

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factor (beyond adjustments for measured confounders) by which the unmeasured confounder could reduce an observed RR estimate. This method, accomplished through a formal sensitivity analysis, is fairly straightforward to implement.

The second method is the estimation of an *E* value,[43] 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.[43] A second assessment is to evaluate how large an *E* value should be (on the RR scale) to move the lower 95% CI estimate if the RR is >1 or to move the upper 95% CI estimate if the RR <1 to cross the null. Intuitively, 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. Computation of the *E* value can be accomplished using an online program freely available at https://www.evalue-calculator.com.[43,44]

To illustrate the potential impact of unmeasured confounding, 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.

An important caveat that undermines the relevance of unmeasured confounding is the lack of insights as to what these unmeasured confounders are. These unmeasured confounders may be variables that we fail to collect data on or unknown variables as we lack a theoretical hypothesis to justify their importance. We recognized this limitation and emphasized that the "no unmeasured confounding" assumption is relevant to mediation methods but suggested that there is a wider need for the application of these sensitivity analyses to other observational studies in perinatal epidemiology.[45]

## Other Developments in the Mediation Literature

There have been several other important developments in the mediation literature. These include decomposition of a causal effect in the presence of a mediator when the mediator interacts with the exposure (4-way decomposition), methods for multiple mediators, mediation methods for case-control studies, mediation methods for time-to-event outcomes, and sample size and power analysis for mediation analysis. These methods are described in the Appendix, including an exposition of available software applications.

**TABLE 3**
**Definitions of causal mediation parameters based on the counterfactual framework**

| Causal parameter | Definition | Interpretation based on the placental abruption-perinatal mortality example |
|---|---|---|
| TE | TE refers to the average exposure (treatment) effect if everyone were to have been exposed (treated) compared with if everyone were unexposed (untreated). | The causal association between placental abruption and perinatal mortality after adjustment for confounders |
| CDE | CDE provides a contrast of the effect of an exposure on the outcome, at a fixed level of the mediator. Note that for a binary mediator, there will be 2 CDE estimates: one where the mediator is fixed to present, and the other where the mediator is fixed to absent. | The effect of the abruption on perinatal mortality if the preterm delivery were set to what it would have been among nonabruption births |
| NDE | NDE expresses how much the outcome would change, on average, if the exposure were set at level "exposed" vs "unexposed," but the mediator was kept at the level it would have taken in the absence of the exposure. | 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 |
| NIE | NIE expresses the change in the outcome under those exposed, on average, if the mediator was changed to what it would be in the absence of the exposure. | Among abruption births, the mortality risk if we were able vs unable to delay delivery to what it would have been without abruption |
| PM | PM provides an estimate of the proportion of the TE that is explained (or accounted) by the mediator. Another way of expressing PM is "how much of the effect of the exposure on the outcome is because of the effect of the exposure on the mediator." PM is estimated as NIE/TE. | The proportion of the increased abruption-perinatal mortality association that is explained (or mediated) through preterm delivery |
| PE | One definition for PE is the proportion of the effect of the exposure on the outcome that could be eliminated by intervening to set the mediator to being present or absent. In other words, PE is the proportion of the TE that might be blocked by intervening on the mediator. PE is estimated as $(TE-CDE_m)/TE$. | 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 |

Table 4 provides further details about the interpretation based on the placental abruption-perinatal mortality example.

*CDE*, controlled direct effect; *NDE*, natural direct effect; *NIE*, natural indirect effect; *PE*, proportion eliminated; *PM*, proportion mediated; *TE*, total effect.

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## Discussion

In this review, we described mediation methods that call for an evaluation of the contribution of mediating variables in the causal effect of an exposure on the outcome. We provided statistical descriptions of several mediation methods and reviewed statistical software in the Appendix. In addition, we provided guidelines for clinicians by "translating" key technical issues into a relatable real-world example, using the placental abruption-perinatal mortality causal estimate to examine the mediation effects of GA.

GA exists on the causal pathway for many, if not most, outcomes of interest in perinatal research, yet there is an entrenched bias that favors adjustment as a confounder. In this review, we illustrated some of the perils that arise when adjustments are made for GA in the abruption-perinatal mortality paradigm. The practice introduces an over-adjustment bias that obscures the true causal effect. When such research questions are considered through a mediation lens, a more robust analysis can quantify the direct effect of the exposure (abruption) and characterize the indirect effect of the mediator (GA) to provide causal insights into the outcomes of interest. Furthermore, the analysis can estimate the PM and PE, providing insight into the magnitude of the effect attributed to the mediator. These estimates offer a deeper introspection of what pathways (other than the mediator in question) through which the exposure may affect the outcome.[46] Consequently, the results of mediation analysis can generate new research ideas that may provide novel insights and innovative therapeutic targets for common obstetrical and perinatal complications.

There are many applications of mediation analysis in perinatal epidemiology, and the choice of causal parameters rests on the scientific goals of the analysis. If the intent is to understand the causal structure and mechanisms by which an exposure operates on the causal pathway to an outcome, then mediation analysis to estimate the direct and indirect (mediated) effects may be useful. In contrast, if the goal is to understand policy implications, then the mediation analysis to estimate CDE is particularly relevant.[47] For instance, Mendola et al[48] demonstrated the usefulness of CDE to examine the causal effect of preeclampsia on neonatal outcomes and the role of preterm delivery as

**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.

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a mediator. Although there is some ambiguity in the broader applied literature of mediation methods regarding the choice of the causal parameter (Naimi et al[49] examined this topic), the results of mediation analysis can provide insights into diverse research questions across perinatal research.

This review provides the analytical framework to help perinatal 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. We encourage discussions among stakeholders regarding mediators, mediation analysis, and, importantly, approach to the correct interpretation of these results. We hope that these discussions, which fall under the broad framework of causal analysis, will move research in perinatal epidemiology away from the historic disregard (intentional or unintentional) of mediating effects. ■


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## Appendix

### A methodological segue to mediation methods

To the statistically interested reader, we provided the algebraic backdrop and formulas for mediation analysis. We provided detailed descriptions of causal mediation analysis for a binary exposure and binary outcome, as is common in most research studies in perinatal epidemiology. For other types of exposures and outcomes, the interested reader is referred to the collection of works by VanderWeele[1] and Hernán and Robins.[2]

The mediation methods essentially involve 2 approaches. The first approach, which is employed most commonly in social sciences, involves the estimation of mediated effects from a regression-based approach. This is accomplished by comparing the change in regression coefficient associated with the primary exposure variable in the presence and absence of the mediator.[3] In a mediation analysis that involves effect decomposition, this method has come under criticism because of ignoring a potential exposure-mediator interaction. The second approach, which is based on the theory of counterfactuals, involves decomposing the total effect (TE) of the exposure-outcome relationship into a direct effect and an indirect or mediated effect.[4,5]

### Counterfactuals

We presented an introduction to mediation analysis based on the theory of counterfactuals.[4–6] Let A and Y denote the exposure and the outcomes of interest; M denotes a mediator; and C denotes a set of observed confounders that may be associated with A, M, and Y. A simple description of the pathways between A and Y, with M and C, is depicted in a directed acyclic graph (DAG) (Supplemental Figure 1). Let $Y_a$ denote the potential counterfactual outcome if exposure A was set to $a$, possibly contrary to the fact; $M_a$ denotes a subject's counterfactual value of the mediator if exposure A was set to $a$; and $Y_{am}$ denotes a subject's counterfactual outcome if $A = a$ and $M = m$. We defined several parameters that were estimable in a mediation analysis based on the risk ratio (RR) and risk difference (RD) scales (Supplemental Table 1).

### Total effect

TE is the overall causal effect of the exposure on the outcome, without accounting for mediating variables. In other words, TE is a contrast of the outcome risk between those exposed and those unexposed, regardless of downstream variables. On the RD and RR scales, this will translate to $Y_1 - Y_0$ and $Y_1/Y_0$, respectively.

### Controlled direct effect

The controlled direct effect (CDE) provides an estimate of the effect of the exposure on the outcome that is not mediated through $M$, that is, the effect of the exposure on the outcome after intervening to fix the mediator to a value $M = m$. On the RD and RR scales, the CDEs are $Y_{1M} - Y_{0M}$ and $Y_{1M}/Y_{0M}$, respectively. Note that when the mediator is binary (eg, preterm delivery), there will be 2 CDE estimates, one in the presence of the mediator and the other in the absence of the mediator. Intuitively, the CDE is useful for examining whether there are any pathways for the exposure independent of, or other than, the mediator.

### Natural direct effect

The natural direct effect (NDE) provides 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. It is defined as $Y_{1M_0} - Y_{0M_0}$ and $Y_{1M_0}/Y_{0M_0}$ on the RD and RR scales, respectively. The NDE is an estimate of the direct effect of the exposure on the outcome that is independent of the mediator.

### Natural indirect effect

The natural indirect effect (NIE) provides an estimate of the effect on the outcome when the exposure is present after setting the mediator value to what it would have been with vs without the exposure. NIE is defined as $Y_{1M_1} - Y_{1M_0}$ and $Y_{1M_1}/Y_{1M_0}$ on the RD and RR scales, respectively. The NIE provides an estimate of the indirect effect of the exposure on the outcome that operates through the mediator.

### Mediation methods when the outcome and mediator are both binaries

For binary outcomes, we preferred the log-linear models for studies that involve cohort or cross-sectional designs (irrespective of whether the outcome was rare or not) and logistic regression models for case-control study designs. The analytical strategy to estimate CDE, NDE, and NIE involved fitting 2 regression models and integrating their parameters to estimate these effects on the RD and RR scales. The first was a model to establish a model for the outcome that included the exposure (A), mediator (M), their interaction (A × M), and a set of baseline confounders (C) as covariates. The second was a model for the mediator that included, as covariates, the exposure and confounders. When the outcome and mediator were both binary, log-linear regression models fit the form:

$$\log[\Pr(Y = 1|A, M, C)] = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 (A \times M) + \theta_4' C, \text{ and}$$

$$\log[\Pr(M = 1|EA, C)] = \beta_0 + \beta_1 A + \beta_2' C$$

From these log-linear models, we estimated the RRs for the CDE, NDE, and NIE as follows:[7]

$$\mathrm{RR}_{\mathrm{CDE}} = \exp(\theta_1 + \theta_3 M)$$

$$\mathrm{RR}_{\mathrm{NDE}} = \frac{\exp(\theta_1)\left[1 + \exp\left(\theta_2 + \theta_3 + \beta_0 + \beta_2' C\right)\right]}{1 + \exp\left(\theta_2 + \theta_3 + \beta_2' C\right)}$$

$$RR_{NIE} = \frac{\left[1+\exp\left(\beta_0+\beta_2'C\right)\right]\left[1+\exp\left(\theta_2+\theta_3+\beta_0+\beta_1+\beta_2'C\right)\right]}{\left[1+\exp\left(\beta_0+\beta_1+\beta_2'C\right)\right]\left[1+\exp\left(\theta_2+\theta_3+\beta_0+\beta_2'C\right)\right]}$$

The standard errors and confidence intervals (CIs) for these RRs can be derived using the delta method or based on the bootstrapping resampling technique.[7,8] Note that the TE of the A and Y associations can be estimated by fitting a log-linear model for the outcome without the mediator. This association was delineated as follows:

$$\log[\Pr(Y=1|A,C)] = \theta_0+\theta_1A+\theta_2'C$$

Furthermore, the TE can be decomposed into NDE and NIE on the RD and RR scales, respectively, as follows:

$$RD_{TE} = (Y_{1M_0}-Y_{0M_0})+(Y_{1M_1}-Y_{1M_0}) = RD_{NDE} + RD_{NIE}, \text{ and}$$

$$RR_{TE} = (Y_{1M_0}-Y_{0M_0})\times(Y_{1M_1}-Y_{1M_0}) = RR_{NDE}\times RR_{NIE}$$

These analyses allowed the estimation of an additional important parameter. If the TE of the exposure on the outcome is mediated by M, the next logical question would be "by how much?" The mediated proportion provided an answer to this question and was derived accordingly:

$$PM_{\%}^{RD} = 100\times\left[\frac{RR_{NDE}(RR_{NIE}-1)}{RR_{NDE}\times RR_{NIE}-1}\right]$$

There is an important caveat with the formulation for the mediated proportion. If the TE and NIE are in the opposite directions of the null (0.0 in the case of RD or 1.0 in the case of RR), then the mediated proportion will result in a negative proportion. Interpretation of the mediated proportion in such circumstances becomes complicated and, potentially, problematic.

## Mediation methods when the outcome is binary and the mediator is continuous

We discussed briefly the approach to mediation analysis for a binary exposure-outcome association and a continuous mediator (eg, gestational age [GA]). The mediation methods for a continuous mediator essentially followed the same principles as for a binary mediator, but with the mediator modeled based on an ordinary least squares linear regression (if the model applies), as follows:

$$E(M=1|A,C) = \beta_0+\beta_1A+\beta_2'C$$

However, the interpretation of the mediation parameter, NIE, in the setting of a continuous mediator was different compared with when the mediator is binary. As one would expect, the mediated effect, on an RR scale, and PM parameter for the exposure-mediator-outcome relationship provided important clues to understand the causal question. In this situation, the mediated effect and proportion mediated [PM] estimate (for a continuous mediator) presented a unique challenge regarding clinical interpretation.

## Other developments in causal mediation analysis

*Mediation analysis for case-control designs.*

Epidemiologists and clinicians often design and implement case-control studies to test associations. The methods for mediation discussed thus far apply to cohort and cross-sectional study designs. When the outcome is rare, the model for the outcome for cohort studies applies to case-control studies. However, the model for the mediator needs to be adjusted to accommodate the case-control sampling structure.[7,9] Two methods to fit the model for the mediator are available. The first approach, a straightforward method, fit the model for mediator restricted to controls and estimated the CDE, NDE, and NIE in terms of odds ratios from fitting logistic regression models for the outcome and mediator (when both are binary). The second approach was based on a weighting approach[7,9]; readers interested in this method can refer to the textbook by VanderWeele.[1]

*Mediation analysis for time-to-event responses.*

Many of the outcomes examined in perinatal epidemiology involved a time-to-event response. Estimating causal parameters in a mediation framework for time-to-event responses worked along with the same general framework for binary responses in a regression modeling setting.[10] A Cox model was fit for the outcome, and a logistic model was fit for a binary mediator. The regression coefficients from these 2 models were combined to estimate the TE, NDE, NIE, and PM effects. The Cox proportional-hazards regression model in this setting requires the assumption of "rare outcome" at the end of the follow-up period, usually <10%.[6,10] When this assumption was not met, the Cox model was replaced with an accelerated failure time model (Wei[11] provides a nice discussion of this model).

*Four-way decomposition of mediation and interaction.*

In the causal mediation framework, what if the mediator also interacts with the exposure? VanderWeele[12] described a 4-way decomposition mediation analysis to characterize the relationship among exposure, outcome, and intermediates. This decomposition provided more granularity to explain and quantify these complex relationships. The effects were decomposed to correspond to the portion of the exposure-outcome association that was neither because of mediation or interaction with a mediator [CDE]), just to interaction but not

mediation (reference interaction [$INT_{REF}$]), to both mediation and interaction (mediation-interaction [$INT_{MED}$]), and to just mediation but not interaction (pure indirect effect [PIE]). The sum of these 4 decomposed effects amounted to 100% on the RD scale.

The concept of the 4-way decomposition was illustrated in the following example. Let us consider the proportion of the TE mediated by preterm delivery in the smoking (exposure)-perinatal mortality (outcome) paradigm. We hoped to determine if increased perinatal mortality risk concerning maternal smoking was mediated through preterm delivery or if the increased risk was the result of an interaction between smoking and preterm delivery or both. From a clinical interpretation viewpoint, the 4-way decomposition allowed us to determine how much of the TE was the direct result of exposure to smoking (CDE) and how much of the TE was attributed to (mediation with) GA (PIE). However, the decomposition went further because GA also interacted with the exposure (eg, gestational age-smoking interaction on preterm birth). The proportion of the TE that was owing to interaction, could be calculated as the $INT_{REF}$, and the proportion that was owing to mediation and interaction could be calculated as the $INT_{REF}$. This decomposition provides insight into how GA drives the risk of perinatal mortality.

We illustrated the causal mediation framework based on the 4-way decomposition method using data on singleton births in the Collaborative Perinatal Project. Among the 1031 and 49,346 pregnancies with and without placental abruption, respectively, perinatal mortality rates were 264.8 and 24.7 per 1000 births (adjusted RR, 12.34; 95% CI, 11.51−14.58). This yielded an adjusted excess RR of 12.34−1.00=11.34 (95% CI, 10.51−13.58) (Supplemental Table 2). The excess risk was decomposed into 4 components of mediation and interaction: 4.90 (95% CI, 3.63−6.23) attributable to CDE (where abruption was set to nonabruption [a counterfactual] among term deliveries), 1.08 (95% CI, 1.02−1.15) attributable to reference interaction, 4.37 (95% CI, 4.17−5.28) attributable to mediated interaction, and 0.99 (95% CI, 0.86−1.17) attributable to a pure indirect effect. A sum of the 4 effects (4.90+1.08+4.37+0.99=11.34) added up to the total excess risk. The last column in Supplemental Table 2 presents the relative contribution of each of the 4 effects to the TE. As previously discussed, the *E* value or the bias formula may be applied to assess the impact of unmeasured confounding. The bias factor was estimated as $RR_{EU} \times RR_{UD}/(RR_{EU} \times RR_{UD} - 1)$, where $RR_{EU}$ *and* $RR_{UD}$ denote the RRs for the exposure-unmeasured confounder and unmeasured confounder-outcome scenarios, respectively.

This analysis showed that the TE of the placental abruption-perinatal mortality that was attributable to mediation by preterm delivery was 48%, which was the sum of the mediated interaction and the PIE proportions (Supplemental Figure 2). Similarly, the overall proportion that was attributable to interaction was 48%, which was the sum of the reference interaction and mediated interaction proportions. This suggested that the TE of the abruption on perinatal mortality has an equal mediated component through preterm delivery and interaction with preterm delivery. Similar to conventional mediation methods, this observation would be obscured by conventional methods that inappropriately control for GA at delivery.

An advantage of the 4-way decomposition existed in the separation of pure mediation effects vs an interaction effect that may not be realized by conventional mediation methods. The distinction between the NIE and mediated interaction effect remained in its subtility. In a traditional mediation analysis, the NIE "picks up" a component of the indirect effect that arises from an interaction between the exposure and mediator. In a 4-way decomposition method, this NIE was decomposed further to a "pure indirect effect" (ie, one that does not involve the interaction) and a "mediated interaction effect" (ie, an effect that is attributable to the exposure-mediator interaction).[13]

**Multiple mediators**

A recent development in the mediation literature was the establishment of methods to tackle multiple mediators simultaneously in a causal framework.[14] One approach to handling multiple mediators was to examine the effects of each individually and to sum up their effects thereafter. This method often failed for 2 reasons. First, if the mediators affected one another, this approach would not provide informative results, particularly the PM effect. Second, even if the mediators were not associated with each other, this approach would fail if there were interactions between the mediators on the outcome. Importantly, under both scenarios, the estimates of the PM by multiple mediators may be overestimated, or sometimes even exceed 100%, a situation that remained unrealistic. Simply put, the sum of the mediated effects, considered one at a time, may not equal the joint mediated effect.[14]

There are different methods to estimate mediation effects in the setting of multiple mediators. The first is the usual regression-based approach (described earlier). Another method is based on a weighting approach, which offers flexibility particularly when adjustments are needed for multiple confounders. VanderWeele and Vansteelandt[14] provided a detailed exposition of both methods (along with SAS programming codes [SAS Institute, Cary, NC]).

To illustrate the concept of multiple mediators, we used the data on births in the United States. VanderWeele and Vansteelandt[14] examined the association between adequate prenatal care (PNC) and preterm birth (<37 weeks), with inadequate care as the reference, in a study of 2,629,247 US births. They considered 2 potential mediators of this PNC-preterm birth association: (1) maternal smoking and/or drinking and (2) preeclampsia. The authors adjusted their analyses for maternal age, ethnicity, education, and marital status as baseline confounders. Notice that the 2 mediators in this example were considered sequential in the causal structure: smoking or alcohol use ($M_1$) and preeclampsia ($M_2$). The pathways were

depicted in a causal DAG (Supplemental Figure 2).

With associations evaluated based on logistic regression models, the authors initially considered maternal smoking or drinking as the first mediator. Their analysis showed that the direct and indirect effects of adequate PNC through maternal smoking or drinking resulted in reductions in the risks of preterm birth of 5.6% (95% CI, 5.5−5.7) and 0.09% (95% CI, 0.08−0.10), respectively. Furthermore, they evaluated preeclampsia as the second mediator after the first analysis. This analysis showed virtually identical results compared with the first: the direct and indirect effects of preeclampsia on the PNC-preterm birth associations resulted in reductions in the risks of preterm birth of 5.6% (95% CI, 5.5−5.7) and 0.09% (95% CI, 0.08−0.10), respectively. The authors concluded that the effect of adequate PNC on preterm birth operating through preeclampsia was very minimal, but maternal smoking or drinking seemed to invoke relatively larger contributions to understand the PNC-preterm birth association.

### Sample size estimation for mediation analysis

The methods to estimate the sample size required for a mediation analysis have largely focused on the minimum study size required to detect the mediated (or indirect) effect in a given causal structure for a prespecified power (often 0.8). Furthermore, sample size programs allowed flexibility in estimating power (to detect a mediated effect) for a fixed sample size. The first program was medssp[15, 16] in R,[17] which can be used for continuous and binary exposures and mediators and continuous, binary, count, and survival outcomes, based on linear, logistic, Poisson, and Cox regression models. Importantly, the program offers flexibility in accounting for confounding of the exposure-mediator and mediator-outcome relationships during the sample size estimation.

The second program, also in R,[17] was powerMediation.[18] This program offers flexibility for estimating the required sample size for mediation analysis when the outcome is continuous (linear regression model), binary (logistic regression model), event rates (Poisson regression model), and time-to-event (Cox proportional-hazards regression model).

### Software for mediation analysis

Several standard software programs offer capabilities for undertaking mediation analysis with varying capabilities, including SAS (SAS Institute, Cary NC), STATA (StataCorp LLC, College Station, TX), R,[17] SPSS (IBM Corp, Armonk, NY), and Mplus.[19] Valeri and VanderWeele[8] provided finer technical details for mediation analysis and related applications in SAS and SPSS; Valente et al[20] provided a comprehensive review of available software for carrying out mediation analysis. A comprehensive software includes the recent release of a suite of R programs for DAG visualization, statistical modeling, and sensitivity analysis for causal mediation analysis.[21] Further discussion about this is outside the scope of this review.

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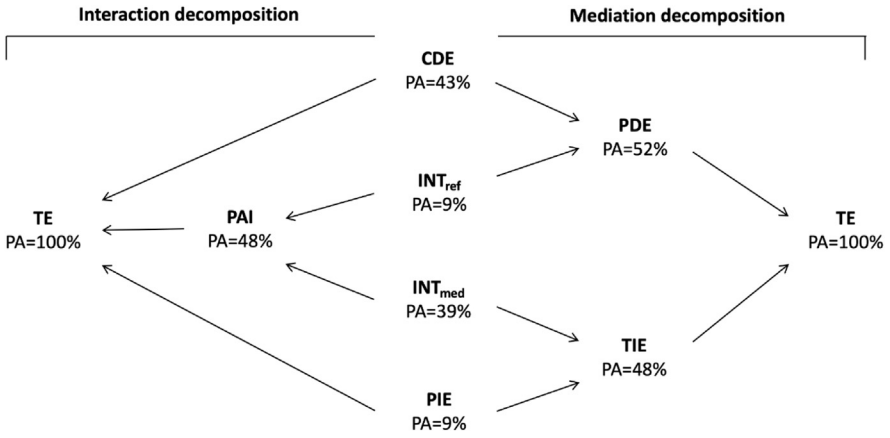
**SUPPLEMENTAL FIGURE 1**

**Four-way decomposition of the TE of placental abruption on perinatal mortality that can be attributed to interaction and mediation through preterm delivery**




The figure shows how the TE of the placental abruption-perinatal mortality association can be decomposed into the CDE, $INT_{ref}$, $MED_{int}$, and PIE. PA denotes the proportion attributable to each of the 4 decomposed effects, expressed as a percentage of the TE. The depiction demonstrates how the causal parameters can be combined to yield components of interaction and mediation in a 4-way causal decomposition analysis

*CDE*, controlled direct effect; *$INT_{ref}$*, reference interaction; *$MED_{int}$*, mediated interaction; *PAI*, portion attributable to interaction; *PDE*, pure direct effect; *TE*, total effect.

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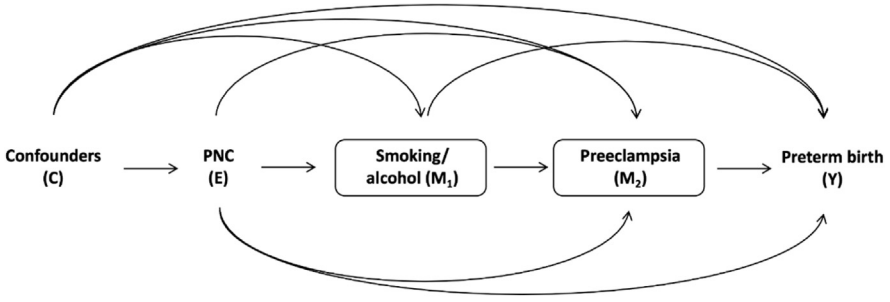
**SUPPLEMENTAL FIGURE 2**

**Simplified directed acyclic graph depicting the effect of prenatal care on preterm birth, with two sequential mediators**




The directed acyclic graph shows the relationship between adequate PNC (E, exposure) on preterm birth (Y, outcome), with 2 sequential mediators: maternal smoking or alcohol use during pregnancy ($M_1$) and preeclampsia ($M_2$). C denotes confounders measured at baseline.

*PNC*, prenatal care.

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**SUPPLEMENTAL TABLE 1**

## Definitions of mediation parameters based on the counterfactual framework

| Causal parameter | Definition | Counterfactual formulation | |
|---|---|---|---|
| | | Risk difference scale | Risk ratio scale |
| TE | 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. | $RD_{TE} = E(Y_1 - Y_0)$ | $RR_{TE} = \frac{Pr(Y_1 = 1)}{Pr(Y_1 = 0)}$ |
| CDE | 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. | $RD_{CDE} = E(Y_{1M} - Y_{0M})$ | $RR_{CDE} = \frac{Pr(Y_{1M} = 1)}{Pr(Y_{0M} = 0)}$ |
| NDE | 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. | $RD_{NDE} = E(Y_{1M_0} - Y_{0M_0})$ | $RR_{NDE} = \frac{Pr(Y_{1M_0} = 1)}{Pr(Y_{0M_0} = 1)}$ |
| NIE | 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 | $RD_{NIE} = E(Y_{1M_1} - Y_{1M_0})$ | $RR_{NIE} = \frac{Pr(Y_{1M_1} = 1)}{Pr(Y_{1M_0} = 1)}$ |
| PM | PM provides an estimate of the proportion of the TE that is explained (or accounted) by the mediator. Another way of expressing PM is "how much of the effect of the exposure on the outcome is because of the effect of the exposure on the mediator." | $PM^{RD}_{\%} = \frac{RR_{NDE}(RR_{NIE} - 1)}{RR_{NDE} \times RR_{NIE} - 1}$ | $PM^{RR}_{\%} = \frac{RR_{NIE}}{RR_{TE}}$ |
| PE | PE is defined as the proportion of the effect of the exposure on the outcome that could be eliminated by intervening to set the mediator to being present or absent. In other words, PE is the proportion of the TE that might be blocked by intervening on the mediator. | | $PE^{RR}_{\%} = \frac{(RR_{TE} - RR_{CDE})}{RR_{TE}}$ |

All definitions were adapted from VanderWeele.[1]

*CDE*, controlled direct effect; *NDE*, natural direct effect; *NIE*, natural indirect effect; *PE*, proportion eliminated; *PM*, proportion mediated; *TE*, total effect.

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**SUPPLEMENTAL TABLE 2**

## Four-way decomposition of the placental abruption-preterm delivery-perinatal mortality association: Collaborative Perinatal Project, 1959 to 1966

| Mediation-interaction decomposition | Adjusted RR (95% CI) | Adjusted excess RR (95% CI) | Proportion attributable (% [95% CI]) |
|---|---|---|---|
| Total effect | 12.34 (11.51–14.58) | 11.34 (10.51–13.58) | 100 |
| Controlled direct effect | 5.90 (4.63–7.23) | 4.90 (3.63–6.23) | 43 (34–47) |
| Reference interaction | 2.08 (2.02–2.15) | 1.08 (1.02–1.15) | 9 (8–12) |
| Mediated interaction | 5.37 (5.17–6.28) | 4.37 (4.17–5.28) | 39 (36–44) |
| Pure indirect effect | 1.99 (1.86–2.17) | 0.99 (0.86–1.17) | 9 (7–10) |

Analyses were adjusted for 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 (2000 replications).

*CI*, confidence interval; *RR*, risk ratio.

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