

**Mini Review**

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# New Direction: Mediation Analysis in Perinatal Epidemiological Studies

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In traditional epidemiology, a multivariable regression model is often applied to evaluate the relationship between an exposure and an outcome while adjusting for confounders and taking into account of interactions. In 1992, Robins and Greenland introduced the mediator counterfactual framework concept, which has helped researchers disentangle the complex causal pathway between exposure and outcome. In the past one decade, mediation analysis has been used in various epidemiological studies, including reproductive and perinatal research. This analysis method has been incorporated into various statistical software packages, including the CAUSALMED procedure in SAS, among various others. Mediation analysis is not only used to explain causal relationships between exposure, mediator, interaction and outcome but also provide solid evidence for decision makers to implement policy.

**Keywords:** Mediator; Mediation analysis; Exposure; Outcome; Confounder; Interaction**Abbreviations:** CHD: Congenital Heart Disease; ART: Assisted Reproductive Technology; CDE: Controlled Direct Effect; MI: Mediated Interaction; RI: Reference Interaction; PIE: Pure Indirect Effect**Introduction**

In traditional epidemiological studies, exposure, outcome, confounders and interactions are variables used to examine an association between a risk factor and outcomes in a multivariable regression model [1]. An exposure variable refers to a factor that we want to examine if this factor has an association with an outcome variable. A confounder is a variable that is associated with both an exposure and an outcome but is not in the direct exposure and outcome causal pathway. If the association between an exposure and an outcome differs by levels of a third variable, this third variable is called interaction [1]. Traditional analysis methods usually only involve one statistical analysis model to examine the relationship between exposure and outcome while adjusting for confounders and taking account of potential interactions [1].

In 1992, Robins and Greenland published a paper to introduce a new concept, called mediator counterfactual framework [2]. They brought the concept of mediators in the causal relationship

between exposure and outcome [2]. Unlike confounders, mediators are in the middle of causal relationship pathway between exposure and outcome Figure 1 [2]. The effect of an exposure on an outcome is mediated by another variable (or mediator) [2]. The total effect of exposure includes two parts: direct and indirect effects [3]. Later on, VanderWeele developed a four-way decomposition concept and method to further interpret the effects of interaction and mediator in the causal pathway [4]. The 4-way decomposition concept is composed of: controlled direct effect (CDE): the effect of an exposure when the mediator does not exist; a reference interaction (RI) means the interaction that plays a role if the mediator is present but exposure does not exist; a mediated interaction (MI) which means that the interaction that exists if the exposure causes the change of the mediator; a pure indirect effect (PIE) means that the effect of the mediator when an exposure does not exist times the effect of the exposure on the mediator [4]. This concept allows researchers to further differentiate the effects of exposures, interactions, and mediators while adjusting for confounders [4] [Figure 1].

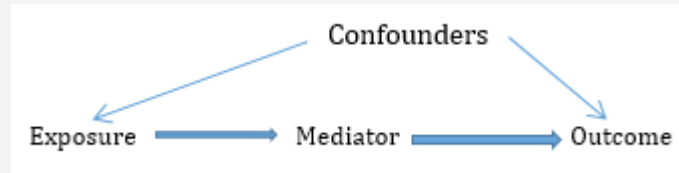


Figure 1: Causal pathway in mediation analysis.

## Discussion

### Mediation analysis in prenatal epidemiological studies

Mediators and mediation analysis have been used in psychology and social science studies for long time [2,5]. Mediator causal pathway and mediation analysis were introduced to epidemiological studies this decade [3]. In reproductive and perinatal research, an increasing number of researchers have adopted this concept and analysis method. Using key words of “mediation”, “mediator”, “ART (Assisted reproductive technology)” and “pregnancy outcome” “birth outcome”, over 20 papers in perinatal epidemiological studies in the past five years can be found. Among them, at least four published studies have found that twinning is a mediator in the relationship between ART and pregnancy complications or adverse birth outcomes [6-9]. Twin birth has contributed to from 17% to 91% of associations in the studies conducted in USA and Sweden [7,9]. In one recent study using population data from Ontario, Canada, the researchers found twinning contributed to 87% of association between ART and congenital heart disease among infants [10]. All these results support the fact that singleton pregnancy may

be preferable for the ART derived pregnancy. Mediation analysis in perinatal studies has provided decision makers solid evidence which could show a direction for policy implement.

### Statistical methods and software

Mediation analysis can be performed using several software tools including SAS, R, STATA and SPSS etc. [11] In the most recent SAS 9.4 version, the CAUSALMED procedure is available for mediational analysis. Three parts of SAS output generated from this analysis, 1) modeling information, 2) summary of estimation of causal mediation effects including total effect, controlled direct effect, natural direct effect, natural indirect effect, percentage mediated, percentage due to interaction and percentage eliminated and 3) various decompositions of total effect including Four-Way decomposition [12]. There are limitations of the CAUSALMED procedure. Only one mediator in one model can be analyzed. The exposure and mediators have to be either continuous or binary variables [12]. The outcome variable has to be binary, continuous or count [12]. For multiple mediators, we have to use other methods and software packages [Table].

Table 1: Summary of recent published studies to examine relationship between ART and CHD.

Authors	Year of publication	Exposure	Outcome	Models	Finding of mediator effect or percentage of effect mediated by twinning	Study population's country
Benedum et al. [6]	2015	ART	Neural Tube Defects	Logistic regression	Yes	USA
Liberman et al. [7]	2017	ART	Birth defects	Log-binomial, regression models	36%	USA
Oberg et al. [9]	2018	ART	Multiple adverse maternal and prenatal outcomes	Logistic regression	17% to 91%	Sweden
Tan et al. [8]	2019	ART	severe maternal morbidities	Logistic regression	Not reported	China
Wen et al. [10]	2020	ART	Congenital heart diseases	Logistic regression	87%	Canada

## Conclusion

Mediation analysis is a useful and promise method, which could help us to further understand complex path causal way between exposure and outcome. More researchers have started to apply mediation analysis in reproductive and perinatal epidemiological studies. Mediation analysis is not only used to explain causal relationships between exposure, mediator, interaction and outcome but also to help us to implement policy.

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## Conflict of Interest

The authors declare no conflict of interest exists.

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