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Commentary: Mediation and moderation analyses: a novel approach to exploring the complex pathways between maternal medical conditions, preterm birth and associated newborn morbidity risk

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Whereas infants born at earlier gestational ages suffer the greatest morbidity and mortality, adverse health consequences of late preterm and early term births are also well documented.[1] The aetiology of preterm birth is multifactorial and the pathways leading to it probably vary with gestational age.[2] They include infection or inflammation, uteroplacental ischaemia or haemorrhage, uterine overdistension, stress and other immunologically mediated processes.[2] Each of these pathways probably has its own initiating factors and mediators. How pre-existing or pregnancy-related medical conditions and complications interact with or result in preterm birth to increase risk of neonatal morbidity is not well understood. Regrettably, most studies were not designed to explore these complex and poorly understood pathways.

In this issue of the *International Journal of Epidemiology*, Brown and colleagues[3] make an important contribution to knowledge of how biological determinants of preterm birth may act through and with gestational age to increase the risk of adverse neonatal outcomes. Using a retrospective cohort study design and linking administrative databases, the authors use mediation and moderation analyses to explore associations, comparing infants born late preterm and early term with their term counterparts. Mediation analysis answered the question, ‘Does gestational age act as a partial mediator between biological determinants of preterm birth and poor neonatal outcomes? Moderation analysis answered the question, ‘Do biological determinants of preterm birth modify the effect of gestational age on poor neonatal outcomes?’

For the mediation analysis, the authors[3] used general estimating equations to test the significance of differences in coefficients between full (with gestational age) and reduced (without gestational age) models.[4] To infer an indirect effect of the biological determinants, they depended on differences in coefficients. For the moderation analyses, the authors determined the presence of additive interaction by calculating the relative excess risk due to interaction.[5] They showed that the effect of gestational age on newborn morbidity is

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partially explained by biological components, and specifically that placental ischaemia and other hypoxia conditions exacerbate the effect of gestational age on adverse neonatal outcomes among infants born late preterm and early term. To my knowledge, this is the first study to use both mediation and moderation analyses to explore these complex relationships. The study is timely because rates of deliveries before 39 weeks of gestation remain a concern, as evidenced by new recommendations and campaigns focused on reducing non-medically indicated deliveries before 39 weeks of gestation.

The study is clinically meaningful for several reasons. First, most studies comparing late preterm and/or early term with term births have explored the relationship between biological determinants of preterm birth and gestational age by simply separating spontaneous from medically indicated deliveries. This method may be inadequate because some maternal medical conditions occur in both spontaneous and medically indicated deliveries.[6] Few studies have applied a more sophisticated analysis to examine the relationship between gestational age and specific maternal medical conditions and the risk of newborn morbidity. For example, authors[7] have studied both the independent and joint effects of gestational age and preexisting maternal medical conditions and complications of pregnancy on the risk of newborn morbidity by estimating measures of interaction on an additive scale (calculating the relative excess risk due to interaction).

Although the methods used by Brown and colleagues[3] importantly try to tease out interactions and explain the causal pathway comprehensively, some notable limitations remain. First, the measurements of biological determinants of preterm birth were abstracted from administrative data sources. Like other retrospectively collected data, these administrative variables may not adequately and accurately characterize the severity and management of these underlying conditions. Moreover, they cannot provide insight into the decision-making practices related to obstetric interventions.[8] Similarly, the outcomes used to quantify neonatal morbidity, namely neonatal intensive care unit triage/admission and neonatal respiratory morbidity, are crude measures of morbidity that cannot completely capture the extent and severity of newborn complications and morbidity. Lastly, because gestational age was a proxy for fetal maturity, the true functional maturity of the fetus and subsequent newborn cannot be known.[8]

There are some other shortcomings. First, although the relationship under study is clearly complex, a simple conceptual model relating the biological determinants of preterm birth to the outcomes is presented. Use of Directed Acyclic Graphs (DAGs) might have been an alternative approach to explaining the complex temporal events or pathways leading to preterm birth and the neonatal outcomes.[9] DAGs demonstrate the authors' a priori assumptions about the underlying biological mechanisms linking the variables being studied. Moreover, DAGs can help investigators to identify confounders and determine a minimal set of covariates needed to remove confounding. For the current analysis, the authors relied on automatic variable selection procedures and significance-level testing to identify confounders, but alternative approaches (e.g. DAGs) may have resulted in more robust and parsimonious models. Finally, as the authors correctly point out, mediation and moderation analyses have been the subject of recent criticism.[10] Future research should consider newer

causal inference approaches. Again, DAGs may be useful in explaining assumptions related to using these mediation and moderation methods.

Despite these limitations, applying knowledge about the causal structure and use of novel analytic methods to disentangle complex relationships is key to closing knowledge gaps about factors leading to preterm birth and resulting adverse effects. We need mediation and moderation methods to improve our knowledge and understanding of how underlying mechanisms and pathways contribute to preterm birth, and to elucidate how factors act directly and indirectly with gestational age (or fetal maturity) to increase newborn morbidity risk. Some maternal medical conditions are potentially preventable or may be amenable to treatment. Understanding complex causal pathways may lead to improved screening and earlier detection of complications, thereby increasing the likelihood of developing or implementing targeted and effective interventions, which may ultimately decrease the rates of newborn morbidity and mortality related to preterm birth.

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