Invited Commentary

Invited Commentary: Identifying the Improbable, the Value of Incremental Insights

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There has been a long-standing debate about whether birth weight directly affects adult blood pressure, or whether the association is entirely mediated through current weight. In this issue of the *Journal*, Chiolero et al. (*Am J Epidemiol.* 2014;179(1):4–11) quantitatively evaluate whether bias from an unmeasured confounder of the relationship between current weight and current blood pressure could artificially create the appearance of a direct effect of birth weight on current blood pressure. Their results suggest that the conditions required to induce such a bias are improbable, given their assumptions. This insight moves the debate forward, and the next step is to evaluate their assumptions with similar quantitative rigor. It is also useful at this stage to reflect on the origins of the research question and the substantive implications of the debate. In particular, is birth weight actually a causal actor or a proxy for some other factor, such as fetal environment? In other words, would an intervention that changed birth weight affect current blood pressure? Speculation can produce many plausible scenarios, but our intuitions are often misleading. It is quantitative evaluation of these scenarios that provides incremental insights. Chiolero et al. illustrate an elegant application of theoretical methods to a substantive question.

bias; birth weight; blood pressure; causality

Abbreviation: DAG, directed acyclic graph.

In *The Sign of the Four*, Sherlock Holmes says, “...when you have eliminated the impossible, whatever remains, however improbable, must be the truth” (1, p. 111). In the realm of fiction, this maxim seems eloquently persuasive, but the real world is rarely so simple. Instead of separating the impossible from the improbable, we are forced to weigh the probability of numerous possible explanations against one another. Furthermore, our ability to distinguish between improbable and probable inferences is often flawed because our intuitions lead us astray (2). We can temper the unrecognized limitations of our qualitative reasoning to some degree through quantitative bias analyses. In the current issue of the *Journal*, Chiolero et al. (3) elegantly illustrate the value of such quantitative analyses by applying them to a research question that has been the subject of a long-standing debate.

Ever since Barker began promoting the idea that adult disease could have fetal origins (4), researchers have tried to assess whether birth weight has an effect on blood pressure later in life (4–7). One area of uncertainty has been the role that current weight might play in the observed association between birth weight and current blood pressure (4–10). Chiolero et al. (3) use directed acyclic graph (DAG) theory and bias analysis to evaluate whether birth weight could have an effect on current blood pressure that is not mediated through current weight in sixth-grade children. They focus on whether such an effect could be due to an unmeasured confounder of the relationship between current weight and current blood pressure.

The application of DAG theory to the interplay between birth weight, current weight, and current blood pressure has highlighted the possibility that current weight is an intermediate between birth weight and current blood pressure (10, 11). This hypothesis introduces at least 2 possible research questions. One is whether there is any effect of birth weight on current blood pressure, and the other is whether such an effect is entirely mediated through current weight. If current weight is an intermediate (e.g., as illustrated in Figures 1, 2, and 3A in Chiolero et al. (3)) and the question is whether birth weight has an effect on current blood pressure, then an effect
estimate that is not adjusted for current weight—but is adjusted for any confounders of the relationship between birth weight and current blood pressure (as represented by $C1$ in Chiolero et al. (3)”—would estimate the total effect of birth weight on current blood pressure.

If, as in Chiolero et al. (3), the question is whether birth weight has any effect on current blood pressure that is not mediated through current weight, then it is necessary to adjust for current weight, as well as any confounders of the relationship between birth weight and current blood pressure (i.e., $C1$) and any confounders of the relationship between current weight and current blood pressure (i.e., $C2$ and $U$ in Chiolero et al. (3)) (12). The resulting estimate is often referred to as the “direct effect” of birth weight on current blood pressure. However, it is likely that there are unidentified mediators between birth weight and current blood pressure, so a more accurate label would be “the effect of birth weight on current blood pressure that is not mediated through current weight.”

The specific problem that Chiolero et al. address is the possibility that the estimated “direct” effect of birth weight on current blood pressure is due to an unmeasured confounder (i.e., $U$) of the relationship between current weight and current blood pressure (3, 12). They evaluate under what conditions bias from such an unmeasured confounder could create the appearance of a “direct” effect, when in fact there was no such effect. Given their assumptions, it appears that a spurious association would be observed only under fairly extreme conditions. Specifically, the prevalence of $U$ would need to differ by 20% or more between low–birth weight and normal–birth weight individuals for a given current weight, and $U$ would need to be strongly associated with current blood pressure (regression coefficient of $\geq 2.5$ or $\leq -2.5$) (3). Although these conditions are not impossible, less extreme conditions are more probable.

The authors’ findings, the next step might be to evaluate their key assumptions with similar rigor. Assumptions are necessary in the exploration of any research question, and those made by Chiolero et al. (3) are clearly specified and reasonable as a first step. However, relaxing these assumptions raises other possible noncausal reasons that birth weight could appear to have a “direct” effect on current blood pressure. Chiolero et al. mention some of these alternative explanations in their thoughtful discussion.

First, their analysis is based on a DAG in which birth weight causes current weight and current blood pressure, but it is possible, as Weinberg posited (9), that birth weight does not have an effect on either. Chiolero et al. (3) illustrate 1 version of this possibility in their Figure 3B. In this DAG, the association between birth weight and both current weight and current blood pressure is entirely due to confounding, including confounding by an unidentified factor $Z$. This DAG cannot be dismissed easily, and it (or a variant) is consistent with the original hypothesis put forth by Barker (4). Barker posited that adult disease was affected by an adverse fetal environment during critical windows of development but indicated that the specific mechanism was still in the realm of speculation. Although Chiolero et al. (3) intend $Z$ in their Figure 3A to represent an intervention that affects birth weight, Figure 3A can be repurposed to illustrate a scenario in which $Z$ represents an adverse fetal environment that affects birth weight, which in turn affects both current weight and current blood pressure. In this scenario, the adverse fetal environment would affect current blood pressure through birth weight. In contrast, their Figure 3B could illustrate an alternative scenario in which birth weight is only a proxy for the fetal environment ($Z$) and does not have “direct” effects of its own.

Assuming that the objective of this line of research is to identify factors on which we can intervene to reduce hypertension, the distinction between these 2 DAGs is important. If Figure 3A is correct, then an intervention to increase birth weight would reduce blood pressure later in life. However, even in this situation, different interventions to change birth weight could have different effects (3, 13). If, however, Figure 3B is correct, then an intervention on birth weight would be beneficial only if it also altered the adverse fetal environment (i.e., $Z$) during the critical window. It seems possible that even a well-defined intervention on birth weight could affect birth weight without affecting $Z$. For example, a maternal smoking cessation intervention during the second trimester of pregnancy might decrease the risk of having a low–birth weight baby (14, 15) but would occur too late to prevent any effects of maternal smoking on fetal cardiovascular development during the first trimester.

Second, even if birth weight directly affects blood pressure, the bias analysis method implemented by Chiolero et al. required additional assumptions (3, 16). Two assumptions in particular were illustrated in their DAG. The first assumption was that $U$ is not associated with birth weight conditional on $C1$. The authors point out that this assumption could be violated if $U$ had an effect on birth weight or birth weight had an effect on $U$ (3). This assumption could also be violated if there was a common cause of birth weight and $U$. A second assumption was that $U$ and $C1$ are independent conditional on birth weight and current weight. As with the first assumption, there are several possible theoretical scenarios that would lead to a violation of this assumption (e.g., a common cause of $C1$ and $U$). Although it is easy to propose scenarios that might lead to a violation of either of these assumptions, the identification of such possibilities is of limited value without a sense of their probability and, more specifically, their likely effect on the estimated “direct” effect of birth weight on current blood pressure. Given the limitations of our intuitions (2), potential bias from these alternative scenarios ideally would be evaluated quantitatively. Methods exist that allow the above assumptions to be relaxed (16), but these methods are more complex to implement than the method illustrated by Chiolero et al. (3).

Sherlock Holmes’ eloquent reasoning, quoted at the beginning of this commentary, ignores the fact that in the real world, even after the elimination of the impossible, there remain numerous explanations that are plausible to varying degrees. Chiolero et al. (3) provide a model of how theoretical epidemiologic methods can be applied to a long-debated research question and can incrementally move the debate toward a resolution. They provide quantitative results that demote 1 hypothesis from probable to plausible but improbable. This insight does not resolve all questions regarding the “direct” effect of birth weight on current blood pressure, but it moves our knowledge forward and points us toward the next level of complexity that should be addressed.
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