Birth Weight and Atrial Fibrillation
A Causal Link?

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There is an association between birth weight and cardiovascular mortality later in life. Barker et al demonstrated this link in the United Kingdom and showed that Forsdahl’s findings from Norway on place of birth and risk of dying in middle age were related to birth weight.1,2 Men with a low birth weight had a higher risk of dying later in life, mainly from cardiovascular diseases.2 The birth of the “early origin of adult disease” was then a reality,1,2 and has since been an active area of research.

In this issue of Circulation, Conen and colleagues report on results from the Women’s Health Study and data obtained in the continued observational follow-up after the completion of a randomized treatment period (study participants were given aspirin, vitamin E, both agents, or placebo). The investigators found an increasing risk of self-reported atrial fibrillation in adulthood by increasing level of self-reported birth weight.3 When information on adult height measured at entry to the Women’s Health Study was controlled for, the association between birth weight and atrial fibrillation was substantially attenuated.3

The link between atrial fibrillation and birth weight is novel and is of substantial interest, because it would indicate mechanisms not necessarily related to insulin resistance or obesity. How such a study is best analyzed is an important issue. Many of the previously published studies had only data on birth weight (and perhaps a few other birth characteristics) and morbidity or mortality later in life, without much information between these events. Is birth weight a cause of morbidity later in life, or are causes of birth weight also causing morbidity later in life? If birth weight is a cause is it then a direct cause (which is truly difficult to believe), or does it activate its effect through other intermediate causes? It is, for example, possible that reduced fetal growth also leads to fewer nephrons in the kidney, which may cause hypertension later in life, for example, modified by salt intake. Only when the most proximal cause in the chain of causation is studied will a causal effect be directly causal. More distal causes have, by definition, mediators.

Directed acyclic graphs have been useful tools in making analytic decisions about confounders and mediators and how to best treat them in the statistical analyses.4 In a simple cause-mediator-effect directed acyclic graph, the mediator should not be controlled. For example, in scenario A in the Figure, height should not be controlled for. Unfortunately, height is not only determined by birth weight but also by socioeconomic status, nutrition and other factors. Were these conditions present at birth, they should have been controlled. If we do not have the data, should we then control for height, if height is causally related to atrial fibrillation? Scenario B in the Figure illustrates that we should adjust for socioeconomic status if causes act as in this scenario, but not for height. We need to block the alternative pathway from birth weight to atrial fibrillation, and including socioeconomic status in the statistical model will have this effect. Including height in scenario B will entirely mask the causal effect of birth weight on atrial fibrillation, because the effects run through height. In scenario C, inclusion of height will remove confounding by socioeconomic status and part of the causal effect of birth weight as in scenario B, but the direct association between birth weight and atrial fibrillation remains detectable. Because directed acyclic graphs do not come with quantitative estimates, we therefore need to know more to come up with a well-justified analytic strategy.

If the comparison is fully adjusted at baseline, adjustments during follow-up would normally not be needed. Confounder control during follow-up may both hide causal association by including mediators or by opening up backdoor paths that were closed (controlled) at baseline. The problem with nonrandomized cohorts is, however, that we seldom have...
fully-adjusted cohorts at baseline, and mediators may have other causes than the exposure under study that could cause confounding.

At present, we should accept that studies on early markers of fetal life conditions and adult diseases present interesting and potentially important public health hypotheses. We do not yet have enough information to propose well-justified analytic strategies, and certainly not strategies that in themselves will allow causal interpretations.

**Disclosures**

None.

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**References**


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