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Commentary Article

Fetal Programming and Conditioning on Birth in Follow-Up Studies

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Fetal programming addresses the health impact of exposures in fetal life on diseases that occur later, often much later, in life. Often we delay our observation time until these adult diseases start producing symptoms. Even when studying childhood diseases like Autism Spectrum Disorder (ASD), we cannot start calculating incidence rates before the children reach a certain age, e.g., 5 years. If ASD cannot be diagnosed before the age of 5, children do not enter the 'population at risk' until the age of 5. If the exposure we study not only causes ASD, but also fetal death, collider stratification bias may affect the results [1,2].

What has been less debated is seeing conditioning on birth also as a selection problem when starting calculating observation time after the onset of exposure. There are several examples of the bias that late entry into a study can entail.

If you, for example, compare exposed workers with unexposed workers at a time when the workers had selected their job and survived in that job for a while, then they are selected in a way that is not seen for the population in general. This is well-known in occupational medicine as 'healthy worker selection' or 'healthy worker effect' or - to illustrate the design flaw - 'the sick population effect'. Or imagine you follow people till they are over 80 years of age. You may then find smokers live as long as non-smokers from 80 years and onwards. This is no proof of smoking being harmless after the age of 80, but could reflect that the 80-year-olds are less susceptible to the smoking hazards (the susceptible have often died at a younger age). These surviving smokers are therefore genetically selected to have a low risk of dying from a smoking related disease. When you start your observation after the onset of exposure, you do not capture forces of selection leading up to your starting time.

Or think about the well-known difference between estimates of effects of Hormone Replacement Therapy (HRT) on cardiovascular diseases [3,4]. Observational studies had shown preventive effects of HRT, but a large Randomized Controlled Trial (RCT) could not corroborate this finding. The reason could be that a RCT starts when the exposure to HRT starts. An observational study would often follow HRT exposure based on a cross-sectional survey of people with different exposure histories. Table 1 shows that in an observational study based on late recruitment from this population, data can show a misleading, preventive effect of HRT exposure on cardiovascular diseases if the exposure moves the onset of disease forward in time, even without changing the cumulative incidence for the time period of study. Even in a population where the cumulative incidence at the end of follow-up (6 years) is the same for exposed and unexposed (RR=1) for the entire follow-up period, the RR will differ with the onset of follow-up when HRT moves the onset of myocardial infarction forward in time, or delays the onset.

In some situations, conditioning on birth induces an unavoidable type of selection bias, similar to what we know from other areas of observational epidemiology when we start counting observation time after the onset of exposure. This may change with fetal medicine, which will give us the opportunity to start observation time at (or before) the time of exposure onset and will improve our options in making proper conclusions when studying fetal programming of chronic diseases [5].

Table 1: Risk of Myocardial Infarction (MI) over a 6-year time period in 100,000 people exposed to hormonal replacement therapy and 100,000 not exposed.

Exposed	MI_1	MI_2	MI_3	MI_4	MI_5	MI_6	All
MI	10	8	6	4	2	0	30
Risk	0.10	0.08	0.06	0.04	0.02	0.00	0.30
Not exposed	MI_1	MI_2	MI_3	MI_4	MI_5	MI_6	All
MI	0	2	4	6	8	10	30
Risk	0.0	0.02	0.04	0.06	0.08	0.10	0.30
RR	∞	4	1.5	0.67	0.25	0	1.0

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