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Best practice guidelines

Privation, stress, and human sex ratio at birth

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ABSTRACT

This article reviews the growing interdisciplinary literature on the effect of privation and stress on human sex ratio at birth. Borrowing strength from the *potential outcomes causal analysis framework*, the discussion focuses on the issues of study design and identification strategy and how they have influenced the current state of the field. The review suggests that much of the inconsistency in the literature regarding the effect of privation and stress on human sex ratio at birth is due to the weak designs and over-simplistic identification strategies used in previous studies. Studies based on natural experimental designs and well-thought-out identification strategies, on the other hand, have produced rather compelling and consistent evidence suggesting that maternal privation and stress during pregnancy reduce male births.

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1. Introduction

Evolutionary theories suggest that natural selection favors the development of parental ability to adjust offspring sex composition adaptively to achieve optimal survival and reproductive results [1]. Although a consensus has yet to be reached regarding the underlying mechanisms, most evolutionary biologists would agree that parents under privation and stress are less likely to have male births [2,3], which was well supported by animal-based evidence from experimental studies [4,5].

Human-based evidence regarding such a relationship is much less compelling. Because of the additional legal and ethical restrictions on the use of human subjects in scientific research, human-based experimental evidence is virtually non-existent. Non-experimental studies, which employed a wide range of statistical techniques to analyze heterogeneous data that come from different sources, in different formats, with drastically different sizes, have not revealed a clear and consistent pattern.

Unfortunately, the reliance on non-experimental data in human-based sex ratio studies is unlikely to change in the near future. What we can do, however, is to find better ways to use these data to answer our research questions. The potential outcome causal framework, first proposed by Rubin [6] and subsequently elaborated by many others, provides a rigorous approach to assess the causal validity and strength of empirical evidence based on non-experimental data. Unlike many other causal frameworks, which intentionally avoided a formal definition of "causal effect" [7], the potential outcomes framework begins by offering an intuitive and non-controversial definition of causal effect, at both the individual- and group-levels, and then builds the main

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ideas of causal inference on the basis of such a definition in a tightly integrated and deductive way.

For the sake of simplicity, assume that we are interested in estimating the causal effect of a binary treatment, d, on outcome y. For any given individual i, it can be defined as the simple difference between the two potential outcomes under the treatment and control conditions:

$$\delta_i = y_i^1 - y_i^0. \tag{1}$$

Here y_i^1 denotes the potential outcome under the treatment condition ($d = 1$) whereas y_i^0 denotes the potential outcome under the control condition ($d = 0$). Unfortunately, for any given individual, only one of the two potential outcomes can be observed because one cannot be both in the treatment and control groups at the same time. This is known as the *fundamental problem of causal inference* [8]. Alternatively, one can focus on the average causal effect at the group-level [9]:

$$\begin{aligned} E[\delta] = &\left\{\pi E\left[Y^1\middle|D=1\right] + (1-\pi)E\left[Y^1\middle|D=0\right]\right\} \\ &-\left\{\pi E\left[Y^0\middle|D=1\right] + (1-\pi)E\left[Y^0\middle|D=0\right]\right\} \end{aligned} \tag{2}$$

in which π denotes the proportion of the population that is assigned to the treatment group, $E[Y^1|D = 1]$ and $E[Y^0|D = 0]$ denote the observed outcomes for the treatment/control groups under the actual conditions they were assigned to whereas $E[Y^1|D = 0]$ and $E[Y^0|D = 1]$ denote the unobserved outcomes for the treatment/control groups under the counterfactual conditions they were not assigned to. Randomized experiment fills the gap because, by forcing the treatment assignment to be completely independent of the potential outcomes, it replaces the unobserved counterfactual quantities in Eq. (2) with the observed ones:

$$E\left[Y^0\middle|D=0\right] = E\left[Y^0\middle|D=1\right], \tag{3}$$

$$E\left[Y^1\middle|D=1\right] = E\left[Y^1\middle|D=0\right]. \tag{4}$$

In other words, with randomization, the treatment and control groups are expected to have the same potential outcomes, had they been subject to the same treatment or control conditions. Eq. (2) can then be simplified to:

$$E[\delta] = E\left[Y^1\middle|D=1\right] - E\left[Y^0\middle|D=0\right]. \tag{5}$$

It only involves observed quantities and thus can be readily calculated from empirical data.

Without randomization, Eqs. (3) and (4) no longer hold. As a result, Eq. (5) no longer yield unbiased estimate of the causal effect of interest. A critical step in causal analysis, as defined in Eq. (2), is to find suitable substitutes for $E[Y^0|D = 1]$ and $E[Y^1|D = 0]$, the two unobserved counterfactual quantities. There are different ways to impute such quantities and the choice can have important influence on the validity and strength of the causal conclusions in non-experimental studies.

In this review, I compare four different types of non-experimental on the relationship between privation and stress and human sex ratio at birth, including (1) purely observation studies, (2) natural experimental studies with simple cohort comparison, (3) natural experimental studies with difference-in-differences analysis, and (4) natural experimental studies with interrupted time series analysis. For each type of study, I focus on (1) treatment assignment, (2) definition of the treatment and control groups, and (3) the imputation of the unobserved counterfactual quantities.

2. A selective review of the literature

All non-experimental studies share one thing in common: no researcher-designed randomization procedures are used in treatment assignment. Within that broad category, there are two different subcategories and they differ significantly from each other. On one hand, there is the purely observational study that completely ignores the issue of treatment assignment. On the other hand, there is the natural experimental study with "as-if" random treatment assignment via "natural" forces. Within the category of natural experimental studies, depending on how the counterfactuals are constructed, there is the distinction between simple cohort comparison, difference-in-differences (DID), and interrupted time series analysis, among many others.

2.1. Purely observational studies

In purely observational studies, the issue of treatment assignment is completely ignored. For example, in the study of the relationship between maternal malnutrition and offspring sex ratio, a number of studies focus on the association between measures of mothers' nutritional condition during pregnancy and the sex of their babies [10–13]. The effect of maternal malnutrition is taken as the difference in the probabilities of male birth associated with different maternal nutritional status. This amounts to using Eq. (5) for causal inference without the support of Eqs. (3) and (4).

What can go wrong? In human societies, under normal conditions, malnourished women are different from other women in many different ways (e.g., family background, socioeconomic status, place of residence, race and ethnicity, health status, cognitive and non-cognitive abilities, etc.). The common approach of "controlling for" these potential confounding factors in a multivariate regression is not sufficient because many of these variables are difficult or even impossible to measure accurately [14]. This leads to the notorious omitted variable bias [15], which makes it virtually impossible to draw meaningful causal conclusions from the estimated regression coefficients.

As a revealing example, among the four purely observational studies mentioned above, two of them indicate that maternal malnutrition during pregnancy reduces male births [10,13] whereas the other two show no such effects [11,12]. Given the limitations of the purely observational design, such inconsistency is not unexpected. Furthermore, even if all four sets of results agreed with each other, it does not necessarily justify any causal conclusions simply because there are too many competing explanations (i.e., the influence of unobserved confounders) to rule out.

2.2. Natural experimental studies

Another type of non-experimental study, known as the *natural experimental study*, has a much better handle on treatment assignment. A natural experiment refers to a sudden and unexpected event that mimics important aspects of a randomized experiment such that the mechanisms that determine whether a particular individual receives the treatment condition or not depend on exogenous forces that are unrelated to individual-level characters or processes [16,17]. In natural experimental settings, because people have no control over their own treatment status, it is unavoidable that some individuals end up in the group in which they would otherwise never be under normal conditions. For example, in virtually all human societies, people of low socioeconomic status face much higher stress in life than people of high socioeconomic status under normal conditions. If we conduct regression analysis between offspring sex and maternal stress, the estimated maternal stress coefficient is confounded by, among other things, the effect of socioeconomic status. Controlling for socioeconomic status does not help much because it will simply extrapolate information that does not exist in the data (i.e., low-status people with low stress and high-status people with high stress) based on some parametric distributional assumptions. Earthquake provides an opportunity to tackle this problem [18,19]. When earthquake happens, all affected individuals, regardless of their socioeconomic status or any other characteristics, experience a sudden increase in stress. For this particular "treatment"