Obtaining Actionable Inferences from Epidemiologic Actions

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> *... not only must we observe nature in the raw, but we must also "twist the lion's tail", that is, manipulate our world in order to learn its secrets.*[1] (p 149)

Epidemiology is the science of population health. But what makes any discipline a science? Two key characteristics are often invoked to distinguish science from non-science: observation and experimentation.[2,3] Scientific observation consists of carefully collecting data on features of the world and evaluating their relations. In contrast, experimentation involves active intervention and manipulation of these features to acquire knowledge of the world under well-controlled situations.

At its best, science proceeds when both observation and experimentation are used in tandem. But this is not always possible, a fact which has long led to debate about their relative roles in generating scientific knowledge.[1,2,4] Aspects of this debate have recently appeared in epidemiology, with questions about the causal status of exposures that are not subject to experimentation.[5–10] Examples of "nonmanipulable exposures" include race,[11] education,[12] cholesterol (low- and high-density lipoproteins),[13] and body mass[14] and related measures (e.g., changes in body weight, body mass index, or obesity status).

In this issue, Hutcheon et al[15] re-evaluate the relation between pregnancy weight gain and fetal size. As is common, their fundamental question is whether this relation is "causal." To answer this question, they conduct a matched sibling comparison study, which offers the advantage of being able to control for potential confounders that remain constant between one pregnancy and the next. On the merits of this control, the authors suggest that their results "provide robust evidence that pregnancy weight gain has an effect on fetal growth ... ".[15]

Here, I articulate the challenges involved in determining whether the association between pregnancy weight gain and fetal size is "causal." Several issues can be clarified by framing the analysis as an ideal (hypothetical) randomized trial. Others can be clarified by highlighting practical consequences of our inability to change exposures that cannot be manipulated. I argue that, for an exposure that cannot (even in theory) be experimentally altered, confounding is a comparatively minor threat to the validity of a causal effect estimate. Ultimately, studying practical decisions we can make to optimize weight gain during

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pregnancy will lead to a much clearer picture of how to improve birth outcomes.

HYPOTHETICAL RANDOMIZATION BREEDS CLARITY

One clear advantage of experimental manipulation is that randomization can be used. Formally, randomization provides an ability to identify clearly defined causal effects without resorting to assumptions about whether or how the exposure (or its potential confounders) relate to the outcome. To "identify," in this context, refers to the ability to mathematically equate the data collected in a given study with the primary effect of interest.[16] Indeed, (ideal) randomized trials are held as the gold standard precisely because causal effect identification is (nonparametrically) conferred by exposure randomization.[10]

In the context of the study by Hutcheon et al, the ideal (albeit impossible) randomized trial would involve allocating pregnant women enrolled at conception into weight gain groups (e.g., gain X_1 versus X_2 kg during pregnancy). In such a study, women would be followed until the event of interest (live birth) or a competing risk. The effect of pregnancy weight gain could then be estimated (nonparametrically) by simply contrasting the birthweight of infants in each group.

Practically, such a study is not possible. However, by framing the analysis as a (hypothetical) trial, several challenges in defining and estimating the effect of pregnancy weight gain on fetal size can be clarified. This would allow us to either take steps to mitigate these challenges or clearly articulate the threats to the validity of our results.

Were randomization possible, key challenges in estimating the effect of pregnancy weight gain on fetal size could be handled with relative ease. These include (1) the expected absence of confounding, which would enable effect estimation without resorting to parametric adjustment for a (possibly) high-dimensional confounder space; (2) the ability to properly account for competing risks, including fetal loss and stillbirth; and (3) the ability to define precisely *how* one might "gain X_1 versus X_2 kg" and (relatedly) what is meant by the "effect" of pregnancy weight gain.

Confounding is one of the primary issues that Hutcheon et al seek to address with a sibling-paired design. The approach accounts for confounders that remain constant between pregnancies, but uncontrolled confounders that change between pregnancies are not accounted for. In the study by Hutcheon et al, two of the arguably strongest confounders of the effect of pregnancy weight gain on fetal size could not be adjusted for diet and physical activity. Because of the availability of registry data, studies of the effect of pregnancy weight gain and body mass on birth outcomes are often affected by such unmeasured confounding.

Competing risks are another complication. In an ideal (prospective) trial of the effect of pregnancy weight gain, women recruited at conception would be at risk of miscarriage, stillbirth, and live birth. The occurrence of either miscarriage or stillbirth would preclude the occurrence of live birth and thus the documentation of birth weight at the end of follow-up. As is common, Hutcheon et al constructed their dataset by relying on live birth records, which do not contain any information on pregnancies that ended in stillbirth or miscarriage. Indeed, miscarriage is a particularly difficult outcome to document.[17] While the exact impact of competing risks in Hutcheon et al's study is unclear, a misestimation of the expected fetal size is arguably very likely.[18]

Most importantly, however, is the meaning of "the causal effect of weight gain." This is, in my view, the most considerable challenge of all.[14,19] Indeed, our conceptions of confounding and the consequences of competing risks are only as clear as the definition of the effect we are pursuing. In the absence of a clear causal effect definition, subjecting causal claims to exacting empirical tests is exceedingly difficult. Is the "effect of pregnancy weight gain" the result of fluid retention, changes in adipose tissue content, fat-free mass, or some combination of the three? Is it due to some completely unknown factor (e.g., biomarker) correlated with, but causally unrelated to, weight gain? Or is it because birthweight is somewhat tautologically related to pregnancy weight gain, as the latter is defined as the combination of fetal and maternal weight gain?

Quantifying the causal effects of nonmanipulable exposures presents with such challenges precisely because one cannot physically separate the exposure of interest from other features of the system under study. The experimental method, championed by Francis Bacon (1561–1626) at the turn of the 16th century, met with such great success precisely because it enabled scientists to sever the relations (known or unknown) that can cast so much doubt on claims about the causal status of a particular exposure.[1]

ON ACTIONABLE INFERENCES

The arguments above are not meant to suggest that experimentation (or randomization) is the only means of acquiring reliable knowledge about cause–effect relations. Nor are they meant to suggest that nonmanipulable exposures such as pregnancy weight gain cannot be causes. They are, rather, about the quality and extent of the knowledge we can gain about whether and how nonmanipulable exposures cause health outcomes.

However, there are more practical consequences of our inability to manipulate exposures such as pregnancy weight gain. These consequences are borne out when we attempt to translate the science of epidemiology into the public health forum.

Suppose that Hutcheon et al's study provided irrefutable evidence of the effect of pregnancy weight gain on fetal size. *What can we do to optimize weight gain?* Of course, we can recommend that pregnant women optimize their weight gain and even give them specific numeric target weights or weight trajectories to pursue. We can recommend that women optimize

diet or physical activity. But Hutcheon et al studied the effect of weight gain, not the effect of recommending weight gain changes, or recommending changes in diet or physical activity.

The distinction between the effect of weight gain and the effect of recommending weight gain changes lies at the heart of the problem with nonmanipulable exposures. However, this distinction facilitates recognition of the simple connection between the scientific acts we take as epidemiologists and the actions we wish to take as public health professionals. In effect, *actionable inferences* come best from studies with exposure contrasts that correspond to actions we can take.

There is a large body of evidence on the relation between body mass and weight gain prior to and during gestation and pregnancy outcomes.[20] In light of the uncertainty around the meaning of the "causal effect of pregnancy weight gain," the study by Hutcheon et al is an important addition to this evidence. But clarifying the causal status of pregnancy weight gain will require addressing more than just confounding.

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