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Commentary: Causal Inference for Social Exposures

Jay S. Kaufman

Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec H3A 1A2, Canada; email: jay.kaufman@mcgill.ca

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Abstract

Social epidemiology seeks to describe and quantify the causal effects of social institutions, interactions, and structures on human health. To accomplish this task, we define exposures as treatments and posit populations exposed or unexposed to these well-defined regimens. This inferential structure allows us to unambiguously estimate and interpret quantitative causal parameters and to investigate how these may be affected by biases such as confounding. This paradigm has been challenged recently by some critics who favor broadening the exposures that may be studied beyond treatments to also consider states. Defining the exposure protocol of an observational study is a continuum of specificity, and one may choose to loosen this definition, incurring the cost of causal parameters that become commensurately more vague. The advantages and disadvantages of broader versus narrower definitions of exposure are matters of continuing debate in social epidemiology as in other branches of epidemiology.

When I use a word, it means just what I choose it to mean—neither more nor less.

—Humpty Dumpty, *Through the Looking Glass* by Lewis Carroll

The word "epigraph" sounds like it should be the term for a causal diagram, but rather than being the wisdom of Pearl, it is instead a pearl of wisdom: the short quotation placed at the beginning of an article. A much-used epigraph is the pompous admonition above that Humpty Dumpty delivers to Alice in *Through the Looking Glass*. As epidemiologists, when we refer to something as a "cause," this word should also mean exactly what we intend it to mean, neither more nor less. And likewise, being primarily quantitative scientists, when we report an estimate of causal effect, say a risk ratio (RR) of 1.34, this number too should mean exactly what we intend it to mean, and being neither more nor less implies that we intend to distinguish this reported effect magnitude from both 1.33 and 1.35.

It is easier to first clarify what we do not intend. If we report a causal effect on the RR scale of 1.34, we do not intend to assert that the risk in the exposed is 34% higher than the risk in the unexposed. This quantity would be an observed association, based on comparing exposed and unexposed people, but this is clearly not the same as the causal effect (27). If what we want is the association, and certainly this is a legitimate thing to want in many circumstances, we generally have no need for statistical adjustments (39). Once we start conditioning on covariates, once we start invoking the idea of "confounding," we are clearly after something else. What we are after is something that is not directly observable in the real world, a counterfactual contrast. This contrast is the risk in some target population of people if they were (potentially counter to fact) to be exposed in some specific way, compared with this same target population of people if they were (potentially counter to fact) to be unexposed in the same specific way (62).

To know something about our real world is difficult enough, involving complexities of definition and measurement that can challenge our abilities and require substantial resources. But to aspire to know something about counterfactual worlds is even more audacious. On top of all the challenges of definition and measurement is the additional hurdle of abstraction inherent in conditioning on things that are not true and therefore not directly observable. To say what would have happened under two different scenarios, mutually contradictory, is a courageous ambition, perhaps foolhardy. And to assert that this contrast of unseen worlds would result in exactly RR = 1.34, neither more nor less, is a fantastic conceit. Yet this seemingly impossible task is exactly what we have chosen to do for a living.

To have any credibility in this ambition, one would surely have to be clear about which group of people will be compared as exposed versus unexposed, and over which time period (37). Birth control pills, for instance, have their eponymous therapeutic effect on women more so than on men, and on women aged 30 more so than on woman aged 3 or 93. It also seems self-evident that we need to be precise in our definition of what it means to be exposed, in duration, in intensity, and in any other relevant detail that could modify the effect of interest. Smoking may cause lung cancer in some qualitative sense, for example, but to put a specific number on that relationship, 1.34 and not 1.33 or 1.35, means that one must be commensurately specific about what is being smoked, how much, how long, and in what way. If we aspire only to distinguish an RR of 1 from an RR of 10, then vagueness in the exposure definition may be inconsequential (95). But to get to meaningful decimal places of a causal contrast, a commensurately high degree of precision will be required in the definition and measurement of all aspects of the causal question, including not only the exposure but also the covariates and outcome. Clarity and specificity in this exposure definition are therefore essential for credibility with respect to replication, verification, and sensitivity to error.

REPLICATION AND VERIFICATION

Why should a reader believe an asserted causal estimate of RR = 1.34? It can never be verified directly because the definition of this effect is a contrast of the same people at the same time in mutually contradictory exposure conditions. This issue has been referred to as "the fundamental problem of causal inference" (35, p. 947). Replication and verification are essential to scientific process, and both are facilitated by precise definition and measurement. It would be unthinkable in the physical sciences to describe an experimental treatment in vague terms. Rather, precise laboratory specifications are a universal expectation to facilitate replication of experiments without the unnecessary variability associated with unspecified aspects of the protocol.

Two common forms of verification are applied to observational epidemiology. The first and foremost in perceived credibility is the randomized controlled trial (RCT). Of course, even a perfect RCT does not make the actual causal contrast of the same group of people at the same time under contrasting exposures. Rather than the gold standard, therefore, "the randomized trial is actually one-step removed from the gold standard" (61, p. 682). But it is a small step away because the perfect RCT compares commensurate people under both exposure levels at the same time, even if not the exact same people. Randomization at least provides the assurance of comparability, in expectation, across the treatment groups (17). To verify the estimated causal effect from an observational study in a comparable intervention study, one must know exactly which intervention to perform (85). The observational study therefore requires specification of the "target trial," the protocol of the randomized intervention that is targeted by the analysis of the observational study (32).

The second common form of verification is evaluation of policy changes (19). These are generally not randomized; however, their timing with respect to characteristics of the affected population can be considered essentially randomized, and comparison of the same population at different times can assure comparability in the absence of any important secular trends or concomitant changes. For example, Smithells and colleagues (90) estimated in the 1970s, on the basis of observational associations and background physiological knowledge, that folate supplementation could eliminate up to 80% of neural tube defects. From this evidence, it was recommended that women take folate supplements in pregnancy, but evaluations by population surveillance of the outcomes showed that recommendations alone had little or no impact (4). Direct fortification of wheat flour with folic acid was then implemented in many countries in the late 1990s. Surveillance of cases by Ray et al. (78) in Canada then demonstrated that incidence of open neural tube defects declined by about half after the policy intervention. The short period of observation before and after the policy change minimized the risk of any important time trend in the outcome as an alternative explanation, and alternative designs with control groups are also available to rule out time trends (23).

Replication and verification are abetted by specificity of the exposure regime. In many well-known examples, such as β-carotene and hormone replacement therapy, the trial results contradicted the causal claims from the observational studies. This contradiction may occur because of variation in the specification of the exposure, say between dietary supplements and nutrients in whole foods (9). Or the discrepancy may arise because the statistical analysis does not mimic the trial design, such that the two studies being compared are actually targeting distinct causal quantities (30). Both threats to replication and verification are avoided by establishing a protocol for the observational trial that matches in design and exposure regimen the randomized trial that it is intended to approximate (13). A sufficiently well-defined exposure to establish an intervention protocol is therefore a prerequisite for any convincing quantitative causal claim (56).

SENSITIVITY TO ERROR

To translate epidemiologic findings into practical decisions about policy, one needs more than just a binary classification of effects being present versus absent. One needs a magnitude of effect because true effects, if small, may not warrant policy intervention. But one needs more information still. One also has to know how robust the estimate is to plausible sources of error. If the magnitude of the effect is known only within a wide range of uncertainty, then the benefits of the policy change are also highly uncertain and decisions have to account for this uncertainty (63). Traditional epidemiologic analyses are accompanied only by assessments of random error, such as *p*-values and confidence intervals. At best, these only answer the question of how sensitive the results are to sampling variability associated with studying a random or pseudorandom subset of the population. They do not consider the potential impact of systematic errors, such as confounding, selection bias, measurement error, or model misspecification (57).

Epidemiologists have developed precise definitions for terms such as confounding and selection bias so that these words also mean what we intend them to mean, neither more nor less. These definitions have developed theoretically over many decades toward building a rational strategy for covariate selection and modeling in order to target meaningful causal parameters. For at least the last three decades, confounding has been defined on the basis of hypothetical interventions (21). For example, one can write an average causal effect in the total population for a binary exposure A on binary outcome Y as $\Pr[Y_{a=1} = 1] - \Pr[Y_{a=0} = 1]$, where the subscript in $Y_{a=1}$ is analogous to Pearl's $Y|\text{do}(a = 1)$ or $Y|\text{set}(a = 1)$ (71). This doing or setting is an intervention, an active perturbation of the natural causal system. Likewise, confounding is defined as the distinction between seeing and doing: $\Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0]$ versus $\Pr[Y_{a=1} = 1] - \Pr[Y_{a=0} = 1]$. The first quantity is what you see: the distribution of Y in the factually exposed and the factually unexposed. The second quantity is predicted on the basis of a hypothetical intervention: what you would see if you did one thing to A versus doing another thing to A. If the first and second contrasts are not equal, then there is confounding. If no intervention is contemplated, therefore, no assessment of confounding is possible. Indeed, no definition of confounding is even possible. And if the nature of the intervention is ambiguous, then the magnitude of confounding may be equally ambiguous. Vagueness in the specification of the exposure intervention therefore translates into vagueness about the validity of this estimate, how vulnerable it is to various biases. Similar considerations exist for selection bias (40) and for transporting the estimates of a study in one population to other populations (75).

A RANGE OF DISCIPLINARY CULTURES

Epidemiologists are situated historically and institutionally within the public health movement and therefore have evolved a theory of causal inference that is necessarily focused on application to public policies (11). At the same time, we have also witnessed the development of epidemiologic techniques as the quantitative science of medical evidence, with a more individualized focus (83). Both of these interwoven strands of epidemiologic tradition focus on interventions, whether population-level policies such as mass vaccination, fluoridation of water, and banning of asbestos or individual-level clinical interventions such as diagnostic tests and clinical procedures. Both traditions therefore require well-specified interventions in order to advance causal claims.

This reliance on intervention as a fundamental conceptual anchor is not true of all sciences, however. Astronomers, ecologists, sociologists, anthropologists, geneticists, and many others have a stronger tradition of passive observation, without any overriding motivation to intrude on the natural world. For these scientists, the requirement that causal inference be defined as a hypothetical intervention seems anthropocentric, as if to imply that before humans appeared in

the universe there was no causality (3). Rather, they seek an understanding of causal mechanisms as a rich description of the ordinary dynamic processes that underlie the systems of interest. This passive, descriptive approach to causal reasoning does not preclude statements of causal relation, although it requires a noninterventionist interpretation of such statements. Pearl et al. (73, p. 5) propose that "X is a cause of Y if Y listens to X and decides its value in response to what it hears." This approach avoids the necessity of contemplating any perturbation, although ironically it rescues causality from being anthropocentric by instead anthropomorphizing the variables.

A SPECTRUM OF CONCRETENESS

Even within the culture of biostatistics and epidemiology opinions vary considerably about how concretely to interpret models of causal effect. Just as religious texts can be viewed literally or figuratively, statistical models also invoke a range of interpretations depending on whether the statistical model is taken to be a kind of useful abstraction or a literal map of reality (60). On one end of the spectrum of concreteness, Hernán and his colleagues (33, 34) take the orthodox position that when they assert that a causal effect is RR = 1.34, they mean exactly that, neither more nor less, and this number has a literal interpretation as their prediction of the excess risk that would be observed under a specific intervention, even if this intervention remains necessarily hypothetical. A more centrist position is taken by Schwartz et al. (86), who argue that an important epidemiologic activity is simply the qualitative discovery of causal relations, without viewing a quantitative effect estimate as necessarily having to take its nominal value to be informative or useful. For a pragmatist like Schwartz, when she asserts that RR = 1.34, she means only that it is something relevant for the outcome, and on the positive side of the null, but that imbuing the specific number with any more credence than that is probably being overly credulous of the model and its many unrealistic assumptions. On the opposite end of the spectrum from Hernán are epidemiologists like Krieger, who view statistical models as but one element in an inferential arsenal and who therefore reject all formulaic restrictions on what can or cannot be studied and how. Krieger & Davey Smith (55) propose instead that one seek the "loveliest" and not necessarily the "likeliest" explanation, through some mystical process of triangulation among diverse designs and approaches. For a more radical epidemiologist like Krieger, therefore, when she asserts that RR = 1.34, it really can mean whatever she chooses it to mean, whether more or less.

The lack of consensus about the conditions for causal inference, even within epidemiology and biostatistics, leaves many researchers bewildered, cautious, or cynical. Some shy away from causal claims of any kind, insisting that our analyses of observational data yield only associations, and they carefully scrub their language of any causal vocabulary (76). But this pretense is clearly disingenuous because if we wanted associations instead of causal relations we would not bother to match or adjust. Moreover, we would not make policy recommendations on the basis of our papers if we did not believe that associations reflected some kind of causal process that was amenable to intervention (29). Others have voiced the concern that the wider dissemination and adoption of explicitly causal methods have emboldened epidemiologists to believe too much in literal interpretations, without sufficient skepticism about the identifying structural assumptions and the absence of measurement error (20). Sadly, despite the vigorous debates raging among the epidemiological Pharisees, the vast bulk of biomedical publication continues to be based on mindless null hypothesis significance testing and regression-based adjustments that are not justified according to any coherent philosophy or causal theory (88). In this impoverished environment, even something as simple as adherence to the basic structural logic of the directed acyclic graph (DAG) to avoid adjusting for factors affected by exposure could represent a significant advance for reducing scientific misinformation (84).

SOCIAL EPIDEMIOLOGY

The previous sections reviewed causal inference in epidemiology more generally, but the specific charge for this article was to explore the application of these ideas to social epidemiology in particular. Social epidemiology is the branch of epidemiology that considers how social institutions, interactions, and conventions affect health (69, 70). Human society is characterized by socially defined arrangements that distribute relevant exposures differentially between persons on the basis of relations organized by dimensions or axes of social structure, such as economic class, gender, race/ethnicity, and neighborhood. This subfield therefore includes not only the study of social determinants as exposures themselves, such as inequality, segregation, or social capital, but also the study of the distribution of established behaviors and treatments according to axes of social distinction, such as ethnic differences in alcohol or tobacco use.

Participants in randomized trials receive their treatments according to coin flips, but free-living people embedded in complex societies receive their exposures through all the impossibly messy aspects of human interaction and agency that comprise our cultures and economies. This complex context naturally weds social epidemiology in important methodological and theoretical ways to the social sciences. Many of the past and present leaders of social epidemiology arrived from social science backgrounds, especially sociology, economics, social psychology, anthropology, and geography. And yet, social epidemiology is not a social science, in the sense that social science is aimed at understanding and explaining the social system. To paraphrase a famous quote, social scientists have only interpreted the world in various ways; the point of epidemiology, however, is to change it. As noted previously, epidemiology is not situated historically or administratively within a university's faculty of arts and science. Rather, it generally sits in a school of public health, the *raison d'être* of which is the engineering of a healthier world, not the detached academic study of its normative mechanisms (69). This distinction should also have important implications for our theories of causal inference, as we seek to make our work meaningful as part of the social movement of public health (10).

METHODS FOR SOCIAL EPIDEMIOLOGY

Causal inference is the dominant topic pervading all of modern epidemiologic methodology (81). Aside from purely descriptive surveillance work, epidemiologic methods of study design and analysis are all focused on making contrasts between exposed and unexposed people in such a way as to infer the effects of the exposure and separate these from extraneous differences between the groups. Finding ways to approximate this comparability is obviously the major challenge for the field of social epidemiology, especially for factors such as race, gender, and social class that have such broad and pervasive consequences for individuals that they might seem to generate wholly incommensurate environments and experiences.

Because modern epidemiology built a superstructure of methodology on the counterfactual or potential outcomes model since the 1980s, many authors have argued that we must therefore exclude nonmanipulable factors, such as individual race/ethnicity and gender, from consideration as causes in this sense (44). Instead, Harper & Strumpf (24) proposed that attention be turned to modifiable exposures such as income, education, and occupation, which are potentially impacted by social programs and policies. This narrowed focus has some obvious advantages. It allies social epidemiology with strong analytic traditions in labor economics, development economics, and health economics, all of which also tend to seek causal effects of policy interventions rather than of amorphous states (1). The econometric designs in these disciplines tend to avoid relying on causal identification via the measurement and adjustment for all confounders because for exposures

related to human behavior it is probably too complex to accurately model all the relevant antecedents (47). Focusing on programs, policies, and interventions also adheres to the conservative strand of statistics that associates causal inference with manipulation (35). And it keeps social epidemiology directly tied to the social movement for engineering a healthier society, the mechanism of which generally involves social interventions through incremental policy innovations.

Nevertheless, there have also been critics of this more narrowly focused social epidemiology. Race, gender, and social class clearly do have profound effects on life chances and on all manner of exposures and behaviors, through a myriad of mechanisms that include discrimination, occupational injury, segregation into less healthy residential environments, and differential access to networks of power and privilege (77). Critics object to being confined to a narrow evaluation of programs when broader social forces are much more pervasive and salient as the drivers of health and disease at the population level (51). In Krieger's (52) famous analogy, why study one or another single strand of the web while ignoring the spider? Moreover, critics argue that pinning causal identification to statistical criteria alone is absurd because a rich social theory from decades of sociological and historical research provides a basis for understanding how society works to make people sick, dating from Engels and Virchow, not to mention a rich tradition of activist preventive and social medicine that puts these theories into practice to improve population health (54, 55).

As an example of the more expansive causal definition in social epidemiology, Glymour & Spiegelman (16) defend the study of race and gender as exposures. Like Schwartz et al. (86), Glymour & Spiegelman agree that describing an intervention helps identify ambiguities in the definition of the exposure and clarifies the public health relevance of the question. Describing a conceptual intervention could still be useful, they grant, even if the intervention is not feasible or ethical. But they note that all exposures are necessarily vague to some extent, and so race and gender fall on a continuum; they are not categorically distinct from smoking or income or other factors that appear more assignable in trials. While this continuum of specificity is consistent with the views of more orthodox thinkers, they nonetheless argue for making exposures as precise as possible, recognizing that some ambiguity will always remain but insisting that a better exposure definition yields stronger and more meaningful causal inference (28, 95). Glymour & Spiegelman assert that treating race and gender as causes can be useful because quantifying their overall effects is often a natural starting point for assessing the specific mechanisms mediating those effects. While this approach seems uncontroversial, several recent authors have specifically addressed how this path-specific inference can be conducted without having to assume any intervention on race or gender themselves (36, 67, 97). Glymour & Spiegelman refer to diffuse states such as race and gender as "fat-hand" interventions, like attempting to delicately move one chess piece and knocking down the surrounding pieces. This does not sound like a particularly optimistic perspective on such analyses, but the authors express commitment to the position that the necessary awkwardness of this evaluation should not preclude such work.

Even if one stays closer to the evaluation of concrete policies and interventions, the inferential challenges are by no means simple in social epidemiology. We need causal inference to predict the distribution of disease after some hypothesized policy or intervention to allow for rational public policy to be evidence based (68). But causal inference requires a strong theoretical foundation to justify assumptions of causal order, of no bias due to omitted covariates, and of effect homogeneity (65). For social epidemiology, this background knowledge requires deep appreciation for history and social theory. Some critics have caricatured formal causal inference as being a mechanical algorithm (55, 93); however, this criticism reveals a misunderstanding of causal identification, which rests on the validity of the hypothesized structural relations between variables as well as on theory to justify the variables that are omitted (3, 72). It is a philosophical theorem that empirical data alone cannot discover causal structure because many distinct structures can give rise to

equivalent observed correlations (80). Causal inference procedures exist in statistics, therefore, to provide quantitative inference for the relations depicted in known or hypothesized causal structures, not to discover this structure. This fundamental limitation of statistics is a strong argument for the reliance of social epidemiology on social theory, even when formal causal inference procedures are deployed (54).

The dominant methods in epidemiologic modeling, including causal inference methods such as propensity scores, the parametric g-formula, and marginal structural models, all obtain identification of causal effects via complete measurement of all confounding variables, where the definition of confounding is a structural definition based on an interventionist notion of causality (98). The culture in microeconomics is generally much more suspicious of identification via covariate adjustment because the field evolved with a focus on human behaviors driven by aspects of personality and preference that seemed impossible to model and successfully deconfound (1). Rather, the emphasis has generally been on identification in the analytic design through structural assumptions built around exogenous sources of variation. The classic example of this approach is the instrumental variable method, which promises to identify causal effects even if confounded by unmeasured covariates (18). This identification is leveraged by largely unverifiable assumptions, namely that the proposed instrument predicts the treatment, does not affect the outcome except via the treatment, and does not share any common causes with the outcome (31). Other approaches that promise valid causal estimation under unmeasured confounding via structural assumptions are natural experiments (7) and regression discontinuity (89). These quasi-experimental methods have been deployed extensively in social epidemiology (38).

Another class of models, also borrowed from impact evaluation and popular in social epidemiology, are those that achieve causal identification on the basis of parametric assumptions, even under unmeasured confounding. The most popular of these is the so-called difference-in-differences method, which adds a control group to an interrupted time series model. The causal effect is identified by confirmation that the preintervention trends are parallel between the control group and the group that will receive the intervention. Then, an interaction term between time (pre- versus postintervention) and group is taken as an estimate of the causal effect (99). Because the units that receive or do not receive the intervention are observed at multiple time points, both before and after the intervention, this is a clustered data model and is often estimated with fixed effects at the cluster (22). The fixed effects formulation also removes some unmeasured confounding because inference is cluster specific. So, if US states are compared, some of which transition from not having a policy to later gaining a policy, the causal effect in the fixed effects difference-in-differences model is the effect within a specific state, always self-controlled (25). This approach removes all time-fixed confounding by holding the unit constant in the contrast, an advantage of all self-matched studies in epidemiology such as case-crossover designs (64).

STUDIES OF RACIAL/ETHNIC DISPARITIES

Perhaps the most hotly debated application of causal inference in social epidemiology arises around race and ethnicity as exposures (59). These categories are similar to gender as aspects of identity that are largely (but not entirely) fixed in an individual's lifetime. But they differ in that gender is essentially randomized at birth, and therefore independent of family history, whereas race and ethnicity are not (96). Several designs generate causal estimates for the effects of race and ethnicity, with varying prospects for concreteness and validity (43). One approach is to randomize fictitious subjects to be classified by race and observe differential diagnosis or treatment by a decision maker, as in the case of Loring & Powell (58), who created ambiguous psychiatric profiles with different race and gender labels and sent them to psychiatrists for a diagnosis. The

results from this design are unambiguously interpretable as the effects of race because no background factors among hypothetical patients can be unbalanced. A related design is to also seek the effect of perceived race on the behavior of a decision maker but to do so in actual data collected on real patients. An example is differential pain treatment of patients based on their ethnicity in studies of emergency room patients (92), which can also be a credible estimate of the effect of race on caregiver behavior. This is credible to the extent that the set of covariates that could rationally affect the decision is a tractable set and could be plausibly measured, since unmeasured variables should probably not play any important role in evidenced-based treatment decisions. Heckman (26) contested this interpretation, arguing that decision makers could be aware of unmeasured information about groups that would validly influence their decisions. Balsa & McGuire (2), on the other hand, argued that such stereotyping by doctors tends to disadvantage minority patients, even if the doctors are not overtly biased against them.

Both of the designs described above target the effect of race and ethnicity through the mechanism of discrimination. This type of causal effect is certainly valid and has been cited repeatedly in the literature to defend the idea that fixed states such as race and ethnicity can indeed be legitimate causes (15). Indeed, some epidemiologists argue that it is the only mechanism of racial disparity that is worth studying (53). Consulting the body of published scientific research, however, one finds that this class of effects is a tiny sliver of the enormous volume of etiologic studies about racial and ethnic disparities; the overwhelming majority of studies are focused not on the process in the mind of a decision maker, but rather on some kind of pathological predisposition in the body of the study subject. Obtaining this sort of intrinsic causal effect validly from observed data is, frankly, hopeless because the complete covariate set could never be defined for any disease whose pathophysiology remains largely unknown (45). Race cannot be randomized in this design, even conceptually, nor is any quasi-experimental approach feasible because race is always assigned at birth in a manner that is highly correlated with history and geography. Although genetic variants can differ modestly by geographic ancestry, which is also correlated with race and ethnicity, direct measurement of known risk alleles has thus far shown that these known variations make trivial contributions to observed disparities for almost all common diseases (46, 50). This observation does act to diminish the plausibility that race and ethnicity represent some important degree of unmeasured inherited predisposition to disease, but the hypothesis remains stubbornly popular in the wider biomedical community (91).

One new avenue of progress for causal hypotheses about race and ethnicity operating through multiple pathways is to measure variables on these specific pathways and approach this research program as a mediation problem (41, 42). Several recent papers have begun to explore the assumptions of such models and the specific interpretations of the causal quantities that are generated (36, 67). A crucial development is the formulation of mediated effects that do not require an intervention, real or imaginary, on the race/ethnicity node, but rather posit an intervention only on the intermediates (94). These estimates rely on so-called natural direct and indirect effects, or close analogs to these formulations, which invoke hypothetical interventions to set the mediators to values that they would be expected to manifest for some specified racial/ethnic referent group. Although natural effects are controversial for their more limited application to many public health problems (66), it is notable they may be ideally suited to answer questions about what distribution of mediator values might be expected in a world without racism, which is of course the social justice goal of health disparities research (53). Natural effects imagine disabling the causal arrow that connects race with a mediator such as income and thus allow one to estimate how disparities would change if race exerted no such influence. The identification challenges for such models remain heroic, but they match very closely to the underlying goals of the research, at least conceptually.

STUDIES OF MANIPULABLE SOCIAL VARIABLES

Rehkopf and colleagues (79) review social epidemiology designs for studies of income, education, and neighborhood that seek causal identification. Many of these examples exploit settings with experimental or quasi-experimental variation in the quantities of interest and therefore estimate narrowly defined effects either analogous to trials or embedded within trials (49). For example, Cesarini et al. (5) studied income effects on health by using national registry data in Sweden to track the health outcomes for lottery winners. This design allows for inference on the whole population and for an income exposure that is literally randomized. The authors find no evidence that these kinds of income gains affect mortality or health care utilization for adults, with the one possible exception of mental health. On the one hand, this setting is rather ideal for causal identification, with a well-defined and randomized exposure and the entire target population under surveillance; it doesn't get much better than this. On the other hand, critics can argue that lottery payments are not the mechanism of income acquisition that most interests us because lottery payments are not how the vast majority of the population obtain income, nor do they account for any more than a trivial amount of the variation in income actually earned in society. This critique can be seen as reflecting a consistency assumption violation, in the sense that most people do not share the specific mechanism of exposure that is being studied, and so this largely null finding does not necessarily apply to most people in the population (6).

The lottery study discussed above is a classic example of the tension between causal identification and generality, which inevitably arises when seeking causal estimates in social epidemiology. To take an example from the opposite extreme, Galea (10) exhorts epidemiologists to do consequential work in the sense that it relates to large effects that are common in the population. But his primary example of consequential epidemiology in this landmark essay is the reported finding that 245,000 Americans who died in 2012 would still be alive if they had graduated from high school. This alarming number is calculated by simply comparing the mortality rates in the various education strata and, therefore, is completely associational, making the counterfactual assertion absurd (12). In the sense that this number has no causal validity as a prediction of what would occur under the proposed policy (i.e., somehow forcing all Americans to complete high school), it is ironically the least consequential work one could possibly produce. And herein lies the inevitable tension between a highly credible estimate that applies to almost nobody and a garbage estimate that appropriately conveys the importance of the issue but has no credibility whatsoever as a quantitative prediction. The number 245,000 seems rather precise. Is it? As in the Humpty Dumpty quote, Galea's estimate also means whatever he chooses it to mean, and he chooses to mean that education is an important social determinant of health. Nobody disagrees, but the actual number presented is merely window dressing.

RAMIFICATIONS

There is little possibility for progress in causal inference without carefully formulated questions (48). Perhaps the most consistent message from causal inference scholars over the years is that everything hinges on the care with which we pose a hypothesis and evaluate the evidence in relation to that well-constructed conjecture (82). Nonetheless, we will not likely reach consensus on the best questions to ask because inevitable trade-offs must be negotiated in terms of values and priorities. For example, Schwartz and colleagues (87) raise the very pointed question of whether well-defined exposures, exactly the kind that offer better prospects for causal identification, might not be "conservative" in the sense of functioning implicitly to maintain existing power relations. Several authors have noted that some causal questions, perhaps those with the greatest potential

to "rock the boat," are not readily answerable when stated generally and so need to be reformulated in a more narrow fashion (14, 24). Well-defined exposures tend to be downstream, rather than upstream, and applying the gold standard analogy to the randomized trial tends to lionize this design despite its inherent weaknesses and limitations (8).

While tension between specificity and generality may be inevitable in quantitative estimation of causal effects, causal inference is a broader task than the fitting and interpretation of a statistical model. Many recent critics of formal causal inference have implied that epidemiology has become formulaic and ritualistic, with insufficient attention given to diverse sources of knowledge in the construction and evaluation of theories (20, 55, 93). If this critique is valid, it is in no way dictated by the tenets of causal logic and indeed is antithetical to them (74). Epidemiology as a quantitative science does naturally prioritize this specific kind of knowledge generation. There is no point to estimating and reporting a number such as RR = 1.34 if this number does not mean anything precise and objective, if it does not have an interpretation that we can agree on tentatively or refute with additional evidence. But this computational culture of epidemiology does not negate the kind of qualitative or narrative historical approach to causal reasoning that is equally valid as a human activity. We can also fashion a story of the exposures and outcomes of interest, cast in all the richness and nuance of their specific sociohistorical context, as a historian or novelist might. This scenario can represent the real world, as it actually occurred, rather than the absurdly simplistic representation of the world as a regression model. This way of thinking is how most humans actually do reason, and the two approaches do not need to be set in conflict with one another. Indeed, a truly consequential public health research program requires their synthesis rather than their opposition. And by integrating these ways of thinking, when we refer to something as a "cause," it can mean something that we can agree on and that we can recognize and interpret meaningfully. This mutual understanding can save us from the Humpty Dumpty free-for-all in which causal language can mean anything or nothing.

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LITERATURE CITED

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