Causal Inference in Environmental Epidemiology: Old and new approaches

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It has been argued that epidemiology is currently going through a methodological revolution involving the 'causal inference' movement [1 2]. This proposes that observational studies should mimic key aspects of randomized trials, since this allows them to be rooted in counterfactual reasoning, which is said to formalize the natural way that humans think about causality [3-5]. These new methods have many merits, particularly for conducting studies of interventions; they have also led to technical analytic innovations [6-9].

However, we and others have argued that causal inference needs integration of a wider range of methods to answer the complex questions needed to improve population health[6-12]. Causal inference almost never hinges on a single method or a single study, but rather involves considering a wide variety of evidence[13]. Thus, we consider it unfortunate that the term 'causal inference' is being used to denote a specific set of newly developed methods rather than taking a pluralistic approach which encompasses both the older traditional methods that we continue to use as well as the newer ones that have become available [9] (we use quotations marks to denote this RCT mimicking set of 'causal inference' methods, in contrast to the broader field of causal inference of which it is a part).

Environmental epidemiologists have always attempted to make inferences about causality from imperfect data and have discovered many major environmental causes of disease (e.g., contaminated water and cholera [14], air pollution and respiratory disease[15], Balkan nephropathy [16], and many more[17]), using 'traditional' methods, i.e., those existing before the new 'counterfactual based' methods. These traditional methods reflect the nature of population level exposures that are fundamental to environmental epidemiology. The purpose of this commentary is to describe the challenges of making causal inferences in environmental epidemiology and to describe complementary causal inference methods (both old and new). In particular, we describe how several methods can be integrated in a triangulation framework to improve causal inference in this field.

Challenges to causal inference in environmental epidemiology

The term 'environmental exposure' is sometimes used loosely to mean any exposure that is not genetic. However, the field of environmental epidemiology is typically restricted to 'physical, chemical and (noninfectious) biological factors in our everyday environment'[18], although some approaches may also include the global eco-environment[19] and the local social environment; many environmental exposures (e.g. pesticides) can also occur in the occupational environment, so the two fields overlap considerably. On the other hand, it does

not usually consider individual behavioural factors. For example, environmental tobacco smoke exposure would be considered as an environmental epidemiology problem, whereas individual smoking behavior typically would not.

Environmental epidemiology has some relatively unique characteristics that have often made causal inference difficult, since it is inherently focused on exposures which occur in dynamic and evolving populations, with their particular societal characteristics. This is typified by issues such as climate change, urban design, public transportation, air pollution, and water and soil contamination, all of which usually affect individuals across entire communities. The implication of this is that it is often difficult to mimic an RCT, with specific well-defined interventions, and (conditional) exchangeability of exposure groups. An extreme but increasingly urgent example, is to determine the effects of climate change on health: mimicking an RCT would require the existence and availability of similar societies that could be (cluster) randomized; this would require at least two planets for a study to be conducted successfully [20 21].

A related issue is that confounders will also often affect entire communities. For example, the association of population-level exposure to contaminated water with health outcomes, is likely to be confounded by other population-level factors such as the level of economic development, poor housing and indoor air pollution. Some sources of confounding so closely co-occur with the specific toxicants or pollutants that are the exposures of interest, such that methods dealing with collinearity and identifiability need to be considered[22]. This has been a particular issue in air pollution studies where it has been difficult to validly estimate the effects of individual components of $PM_{2.5}$ pollution [23].

These methodological difficulties mean that some environmental epidemiology questions cannot be answered simply by doing 'better' studies that more closely mimic RCTs. A pluralistic approach is required, with the integration of evidence provided by a variety of study designs and approaches. Therefore, we briefly describe different approaches to causal inference that we feel have value in environmental epidemiology, and discuss the possibility of integrating findings in a triangulation framework. We group these methods into three general categories: (i) 'traditional' methods; (ii) extensions of these traditional approaches; and (iii) triangulation of evidence.

Table 1 summarizes methods that we consider have specific value for causal inference in environmental epidemiology.

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'Traditional' methods

As noted above, environmental epidemiology is often concerned with population level exposures. Thus, time trends and geographical differences, often disparaged as implying a lower level of causal evidence ('old-fashioned' descriptive epidemiology), may be particularly useful, both in generating new ideas and as a check on existing explanations[24]. For example, global asthma prevalence comparisons have provided strong evidence that 'established' asthma risk factors such as allergen exposure, air pollution, and environmental tobacco smoke do not explain the population patterns, and are likely to be secondary rather than primary causes of asthma itself[25]. Ecologic studies have played a key role in identifying that arsenic in drinking water is a cause of cancer[26]. Similarly, international comparisons of the prevalence of chronic kidney disease of unknown cause (CKDu) are playing a crucial role in the search for the causes of this major public health problem[27].

Furthermore, findings from environmental epidemiology can be more convincing if they are replicated in different populations with different underlying patterns of confounding (an approach known as cross-context comparisons) [12]. For example, exposure to air pollution from truck traffic primarily occurs in poor people in high income countries (HICs) whereas it is often more common in rich urban-dwellers in low-and-middle income countries (LMICs); thus it is reassuring that findings for air pollution from truck traffic and asthma symptoms are similar in HICs and LMICs.[28] The effects of environmental exposures can also be investigated in specific occupational populations where exposures are often higher, and confounding is often minimal, because there are usually few socio-economic and behavioural differences between different groups of workers [29]. Thus, risks from low-level environmental exposures are rarely studied directly; rather, the effects of occupational exposures (which are higher and less subject to confounding) are studied, and the risks to exposed communities are estimated by extrapolation.

Extensions of traditional approaches

In this section we consider several extensions of traditional approaches, many of which have been used for decades in econometrics, but only applied to epidemiology more recently.

Instrumental variable (IV) analyses utilize variables that robustly relate to the exposure of interest in a way that they can be seen as 'as good as randomizing the exposure'. Such variables, like any technique used for proper randomization, should not be related directly to

the outcome, nor to potential confounders (i.e. other risk factors for the outcome). If such a variable is found, it has the potential to improve causal inference[30]. For example, one study, using wind speed and height of the planetary boundary layer as IVs that determine air pollution (and are not direct causes of mortality, nor likely to be associated with other risk factors for mortality), found evidence for an effect of local air pollution (at levels below the US standards) on daily death rates.[31] In another study, differences in the order that piped water was supplied to houses and the water company providing water, in Yemen, were used as IVs to test the effect of piped water supply on childhood diarrhea.[32 33] The results suggested that piped water increased childhood diarrheal diseases due to water rationing or broken pipes resulting in its contamination.

Mendelian randomization (MR), the use of genetic variants as IVs is increasingly used to explore causal effects in epidemiology.[34 35] Whilst genetic IVs may be less prone than non-genetic IVs to violations of the assumptions of IV analyses,[35] they do not reflect the population level exposures that are the focus of this commentary. However, an extension of MR that uses gene-environmental interactions to explore causality could have value in establishing underlying mechanisms in environmental epidemiology. The assumption is that genetic variants that are known to influence the metabolism of, for example, pollutants would only be associated with the relevant health outcomes in populations exposed to that pollutant. For example, trichloroethylene has been found to be associated with renal cancer risk in workers with at least one intact GSTT1 allele (OR=1.88), but not among workers with two deleted alleles (OR=0.93)[36]. Similarly, active GSTT1 genotype was associated with renal cancer risk in those exposed to TCE, but not in those unexposed to TCE. Such analyses are also particularly relevant to studies which explore mechanisms through which population level exposures might act [37].

There are two types of ‘negative control’ studies: outcome and exposure negative controls. Negative control *outcome* studies use associations between the exposure of interest and a condition thought to be unaffected by the exposure to highlight potential residual or uncontrolled confounding.[12] Negative outcome control studies are widely used in pharmacoepidemiology, where the control outcomes are known as ‘prespecified falsification outcomes’[38] We have found few examples of this approach in environmental studies of physical or chemical exposures, but we found one example used in social environmental epidemiology. Numerous studies have shown associations between social networks (i.e. where persons with social ties are more likely to have a similar outcome than two random

people from the same population) and the spread of complex health related outcomes (e.g. smoking, obesity, and depression). The assumed causal mechanism here is that social networks influence behavior, such that (for example) people of a healthy weight who change their social networks towards groups who are overweight or obese, may increase their own risk of becoming overweight or obese (because of moderating their ideas of what constitutes a healthy weight, and changing behaviours to those of the new social network which are more obesogenic). However, a prespecified falsification/negative outcome control study suggested that such hypothesized mechanisms were unlikely, since they found similar associations with outcomes that the authors *a priori* assumed could not be explained by these mechanisms (acne, height, and headaches).[39] On the other hand, negative control *exposure* studies have been widely used in studies of the developmental origins of disease, typically by using the association between paternal exposures (negative control) and outcomes to highlight potential uncontrolled confounding (see eg [40]). Population level exposures in environmental epidemiology make negative control exposure studies less plausible in environmental epidemiology, but we would encourage the greater use of negative control outcome studies. For example, exposure to pesticides from aerial spraying often affects whole districts, and a number of different health outcomes may be affected by these pesticides, but showing associations with one or more outcomes where a confounded association is likely but a causal effect not plausible (e.g. deaths from violence) would raise questions as to whether the observed associations for other outcomes might be also due to confounding.

Regression discontinuity designs[41-43] can be applied when exposure is assigned at a threshold, as is often the case in medicine, particularly if the threshold is a continuously measured variable. The assumption is that people just above or just below the threshold will be assigned different exposures, but that these people are in fact very much alike – given the likely random errors in measuring the variable used for the assignment. An example is the assignment of antiretroviral therapy according to CD4 count, where the idea is that the persons just below or above the threshold may differ little; another is the study of the effect of mailing of a warning letter by a health authority to general practitioners who prescribed an inordinate amount of a particular drug (say, a painkiller or sleeping drug) where the idea is that the general practitioners just above and just below the threshold for mailing the letter might be similar. The design has been applied in a variety of other contexts, including a study of ozone, smog warnings, and asthma hospitalizations [44].

Difference in differences analyses require that the outcome is measured repeatedly over time. They compare the mean change in outcome over time between exposed and unexposed groups (or between different levels of exposure). In all categories of exposure there must be at least one measure of the outcome before, and at least one measure after, exposure occurred. The assumption is that baseline differences in outcome (i.e. prior to exposure) reflect differences in confounders and that rates of change in outcome are similar until the exposure occurs (parallel slope assumption). Under this assumption, the differences in outcome between those exposed and those unexposed, 'before' versus 'after', reflects the causal effect of exposure. In one example, this method was used to explore the impact of greening vacant urban spaces (in comparison with urban spaces which were not greened), finding some evidence of benefits on criminal behavior, but limited effects on health outcomes[45].

Triangulation of evidence

The idea of 'triangulating' evidence from different methods and data sources has been proposed and used implicitly for decades, often without explicitly describing it as triangulation.[10 12 46] In fact, the term 'triangulation' has been used in at least two different ways in health research: (i) to refer to multiple lines of evidence from different research approaches, including integrating epidemiological findings with other forms of evidence; (ii) to refer within the field of epidemiology to different analytical approaches/populations which have been chosen because they have differing key sources of bias (ideally in different directions)[12].

The first type of triangulation is routinely used in environmental, e.g. by the International Agency for Research on Cancer (IARC) Monographs Programme which integrates epidemiological, animal and mechanistic evidence to infer causality for various potential carcinogens, including environmental carcinogens. One application was the assessment of the health effects of environmental tetrachlorodibenzo-*p*-dioxin (TCDD; dioxin) exposure. The main health effects are likely to occur due to exposure to low-levels which are near-ubiquitous across populations, but these were difficult, if not impossible, to elucidate. However, by integrating evidence from different study designs and methods (occupational studies in a number of different countries, animal studies, and mechanistic studies showing that TCDD increases the risk of cancer through its action at the Aryl hydrocarbon (Ah) receptor), IARC has concluded that there is sufficient evidence in human (i.e. epidemiological) studies that dioxin is a cause of cancer[47]. A similar example is that of Balkan Endemic Nephropathy (BEN)[16], for which a wide variety of evidence

(epidemiological, genetic, toxicological) was required before it was established that the likely cause was chronic dietary exposure to aristolochic acid (AA), a contaminant of wheat in the endemic regions. These can be regarded as examples of triangulation in that different methods were brought to bear on the issue, with studies being conducted in a number of different populations; however, the term 'triangulation' was not used in either.

As noted above, the second type of 'triangulation' refers to triangulation of different types of evidence within epidemiology, which might be called 'epidemiologic triangulation'. We have had difficulty in finding examples of the latter approach within environmental epidemiology, and we propose that this approach be used more systematically in this field to improve causal inference and understanding in human populations. Criteria for its use in causal inference in epidemiology have been proposed recently, and these specify that results from at least two (but ideally more) methods that have differing key sources of unrelated bias be compared[12]. If evidence from such different epidemiological approaches all point to the same conclusion, this strengthens confidence that that is the correct causal conclusion, particularly when the key sources of bias of some of the approaches would predict that the findings would point in opposite directions.

The difference between 'epidemiologic triangulation' and the systematic review approach of trials or epidemiological studies is that a systematic review seeks similar studies, which are expected to yield similar findings, and hence can be grouped in a meta-analysis to obtain a more precise estimate of an exposure. Epidemiological triangulation, in contrast, looks for different types of studies, which might be expected to yield different findings, because they involve different potential biases, or biases in different directions; this allows one to assess the likely existence or absence of the biases that one might be concerned about in one particular type of study.

Conclusions

Where does this leave us? It is opportune to write this commentary in *Epidemiology* which has published many of the successes of the 'causal inference' movement, and which is also the official journal for the International Society of Environmental Epidemiology (ISEE). We are not arguing that 'causal inference' methods that mimic randomized controlled trials are not useful; for example, they can improve individual studies with individual-level exposures that can be seen as interventions. Rather, we are arguing that they form only part of the larger set of causal inference methodologies. There have been older methods, as well as other

developments in methodology, which are complementary to, and in some instances superior to ‘causal inference methods’, at least for some risk factors or in some contexts. All methods have assumptions that are often not possible to (fully) test. We believe that all valid methods should be part of the (environmental) epidemiology toolkit and that integrating the resulting evidence in a framework that acknowledges the key sources of bias of each will provide for better causal inference.

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Table 1: Summary of selected epidemiological approaches that could be triangulated to improve causal inference in environmental epidemiology (Note: This is illustrative rather than exhaustive)

Approach	Assumptions	Examples
'Traditional' methods		
Cross population comparisons[12 48]	Populations being compared have different confounding structures; Beyond confounding, the effect of the exposure is the same in populations being compared	Findings for truck traffic air pollution and asthma are similar in high-income countries and low-and-middle income countries[28]
Occupational (homogeneous) cohorts[29]	Different jobs result in different environmental exposures Distributions of confounders are similar in groups doing different jobs	There is little or no confounding by smoking in studies of occupational causes of lung cancer[29], many of which may also be considered as environmental exposures
Extensions of traditional approaches		
Instrumental variable (IV) analyses	IV robustly relates to exposure of interest IV is not related to confounders of exposure outcome association IV is not related to other (independent of the exposure of interest) risk factors of the outcome	Use of wind speed and height of the planetary boundary layer as IVs to test the effects of local air pollution on death.[31]
Gene*environment interactions (as an extension of Mendelian randomization)	Genetic variants would only be associated with the outcome in those who have the environmental exposure Groups can be accurately stratified into those exposed and unexposed	Active GSTT1 genotype is associated with renal cancer risk in those exposed to TCE, but not in those not exposed to TCE [36]
Negative control outcome (also known as pre-specified falsification)	There is no plausible causal effect of the real exposure on the negative control outcome Confounding structures are similar for the real and negative control outcome	Similar patterns of associations of social networks with acne, height and headaches (negative control outcomes) to those seen for, e.g., obesity and smoking, suggest that the assumed mechanisms of developing 'new norms' for obesity and smoking , and behaviours related to these, are not causal mechanisms. [39]

Regression discontinuity	Exposure is assigned on the basis of a threshold of a continuous variable Exposure assignment is judged to be essentially random close to the threshold	Smog alerts cause individuals to take substantial action to reduce exposure, thus reducing the risk of asthma hospitalizations[44]
Difference in differences	Baseline differences in outcome reflect confounding Rates of change in outcome are similar before exposure occurs Differences in differences are due to the exposure and no new confounding was introduced at the time of exposure	Greening vacant urban spaces (in comparison with urban spaces that have not been greened) reduces criminal behavior but has limited effects on health outcomes[45]
Triangulation of epidemiological evidence		
Comparison and integration of evidence from different epidemiological methods which have differing key sources of bias	Bias is in different directions in the populations and/or methods that are being compared Thus, if the findings are similar in different populations, or using different methods, this indicates that bias is not a major problem	Researchers have used this spontaneously in some epidemiological fields for some decades, though we could not find examples in environmental epidemiology. We recommend that it should be used and formalized more in environmental epidemiology.

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