Variational causal claims in epidemiology

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Abstract. The paper examines definitions of 'cause' in the epidemiological literature. Those definitions all describe causes as factors that make a difference to the distribution of disease or to individual health status. In the philosophical jargon, causes in epidemiology are difference-makers. Two claims are defended. First, it is argued that those definitions underpin an epistemology and a methodology that hinge upon the notion of variation, *contra* the dominant Humean paradigm according to which we infer causality from regularity. Second, despite the fact that causes be defined in terms of 'difference-making', this cannot fixes the causal metaphysics. Causality in epidemiology ought to be interpreted according to the epistemic theory. In this approach relations are *deemed* causal depending on the evidence and on the available methods. Indeed, evidence to establish causal claims requires difference-making considerations; furthermore, those definitions of cause reflect the 'variational' epistemology and methodology of epidemiology.

Keywords. Causality, Causal epistemology, Causal metaphysics, Causal methods, Epidemiology, Regularity, Variation.

1. Definitions of cause in epidemiology

Epidemiology studies the distributions of diseases in and across populations and seeks to identify the factors determining those distributions. This broad characterisation of epidemiological research raises altogether substantial issues of broad philosophical interest. One concerns adopting an explicit causal stance, which is sometimes avoided perhaps as a consequence of humbleness of researchers in claiming to find *causal* relations. Thus, a plain causal terminology is sometimes replaced with a less obvious and more confusing one, using terms such as factors, determinants, but not causes and effects. This is certainly an important issue to debate. Nevertheless, I will take here for granted that an explicit causal stance is justifiable (let alone desirable) and shall tackle another problem arising in causal reasoning in epidemiology.

Various definitions of cause can be found in textbooks and survey papers in epidemiology. Parascandola and Weed (2001) analyse an extensive body of philosophical and scientific literature and come up with five possible definitions of

cause: production, necessary causes, sufficient-component causes, probabilistic causes, and counterfactual causes. Unfortunately, none of these succeeds in attracting a unique consensus nor in accounting for different causal scenarios in epidemiology. To illustrate, consider a 'necessary' definition of cause: this fits the case of AIDS, for HIV infection is a necessary cause of AIDS; however, necessary causes don't seem to suit the case of cancer, for exposure to any carcinogenic substance is neither necessary nor sufficient to develop cancer. Yet, Parascandola and Weed (2001) say that the probabilistic account provides a better picture, as it can encompass other definitions (e.g., sufficient causes raise the probability of its effect occurring to 1, necessary causes raise that probability from 0) and because it accounts for the fact that different factors have a different impact on the disease. According to their definition:

> A probabilistic cause increases the probability of its effect occurring. Such a cause need not to be either necessary or sufficient. (Parascandola and Weed, 2001, p.906)

The literature offers germane definitions of 'cause':

> A determinant [of health] can be any factor, whether event, characteristic, or other definable entity so long as it brings about change for better or worse in a health condition. (Susser, 1973, p. 3)

> […] a factor is a cause of an event if its operation increases the frequency of the event. (Elwood 1988, p.5)

> Being a cause is a special characterisation of some state of affairs characterised by change, i.e. an event, a fact, a state or a deed: in medicine and epidemiology, a cause makes a disease happen or not happen. (Karhausen 2000, p. 59)

> A factor is a cause of a certain disease when alterations in the frequency or intensity of this factor, without concomitant alterations in any other factor, are followed by changes in the frequency of occurrence of the disease, after the passage of a certain time period. (Lagiou et al., 2005, p. 565)

All these definitions have something in common. In slightly different ways they all say what a causal factor does, and what it does is to make changes: changes in

frequencies of disease or changes in the health status of individuals. In the philosophical jargon, according to those definitions, causes are *difference-makers*.

The goal of this paper is to offer a critical evaluation of those definitions, notably to discuss the kind of epistemology, methodology and metaphysics of causation they underpin. In section 2, I shall argue that these definitions support an epistemology and a methodology of causality that hinge upon the notion of variation rather than regularity. However, things get more complicated concerning the underlying metaphysics. In section 3, I shall argue that (i) even though these definitions describe causes as difference-makers, this does not necessarily fix a 'difference-making' causal metaphysics; (ii) instead, causality is better interpreted according to the epistemic theory; and (iii) the fact that these definitions describe causes as difference-makers rather reflects the 'variational' methodology and epistemology of epidemiology.

2. Causal epistemology and methodology

Preliminaries

The definitions mentioned in Sec. 1 describe a cause in terms of what it does, namely producing changes in frequencies of disease or in individual health status. I shall now ask what kind of epistemology and methodology do such definitions underpin; the answer—we shall see—turns out to be that those definitions sustain a fundamental *variational* aspect of the epistemology and methodology of causality. Before getting started, let me make clear from the outset the question I am asking.

The epistemology of causality investigates how we come to know about causal relations. Here, there is a fleeting borderline between epistemology and methodology, but a line between the two can be drawn nonetheless. Whilst methodology is concerned with problems of scientific methods and aims at developing successful methods for the discovery and confirmation of causal relationships, epistemology is rather interested in the conceptual issues behind those methods. Examples of causal methods include Bayesian nets, regression models, structural models, multilevel models, etc. Such methods, although customarily used in the everyday scientific practice, presuppose a number of crucial epistemological questions such as: if correlations do not grant causality what does? Is there epistemic access to causal

relations other than correlations or randomization? Do mechanisms grant better epistemic access to causal relations than correlations or randomization? Can generic causal knowledge inform causal attribution in the single-case?

The philosophical literature produced a whole variety of answers, yet in many ways Hume's heritage is still dominant. In the Humean tradition, also known as "regularism", a token-event *c* caused a token-event *e* if and only if events of type *E* regularly follow events of type *C*. For instance, one infers that smoking causes lung cancer because we observed that cancer-events steadily follow smoking-events; one might then infer that Harry's smoking caused him to develop lung cancer because lung cancer typically follows smoking. Nevertheless, this intuition has some plausibility only because the relation between smoking and lung cancer—indeed, between almost all types of cancer—is well established (Vineis et al. 2004). But consider more controversial (causal) relations. Is it because exposure to electromagnetic fields is regularly followed by cancer that epidemiologists (tentatively) establish a causal relation between the two?

So a central problem in epistemology is what notion or principle *guides* causal reasoning: whatever causality is, what notion *guides* our reasoning in making inferences to establish causal relations? This is a peculiar question about epistemology and it is most relevant to methodology. In Russo (2006 and 2008), *contra* the dominant Humean paradigm, I argue that model building and model testing in the social sciences turn around the notion of *variation*, not of regularity. Simply put, a causal model is built around meaningful co-*variations* between the variables of interest and tests are performed in order to establish which variations are causal. One requirement, among others, is that in large data sets the co-variation between variables also show some regularity. This does not mean that the scientist infers causal relations from regular successions *à la* Hume, but that the scientist requires co-variations to be regular enough in order to rule out accidental or spurious relations (Russo 2008, ch.4). In the following, I shall try to show that epistemology and methodology in epidemiology also crucially turn around the notion of 'variation', *pace* Hume.

Variational epistemology

A case for a 'variational' epistemology can be made by appealing to the goals of epidemiology. Epidemiologists usually claim that their goal is to study the *variability* of disease due to the *variability* of exposure. Isolated and independent voices[1] are brilliantly summarised by Bhopol (1997 and 1999), who carried out a systematic review of epidemiology textbooks and came to the following conclusion (Bhopol 1999, p.1162):

> Certain beliefs—that epidemiology is about the study of health and disease in populations, that there is a *population group variation in disease that is worth of scientific study*, and that such variation is important to public health policy and practice—were common to virtually all textbooks. (My emphasis.)

Bhopol summarises very well the aspect of epidemiology I am concerned with: epidemiologists are interested in how the disease *varies* across individuals, time, space, etc. In other words, epidemiology seeks to establish causal claims by studying *variations* in exposure and in disease. It is worth pointing out that if this were merely a platitude about epidemiology it would not be a noteworthy and widespread belief. Causal epistemology is concerned with how we come to know about causal relations, and the answer here is that we will know about causes of disease by investigating whether some specific *variations* in exposure lead to *variations* in disease.

This is definitively what the definitions of cause we read earlier point to: a *causal* factor is responsible for variations in the distribution of disease or in individual health status. This is can be ascertained by studying the "population group variation in disease". Hence the definitions of cause underpin a *variational* epistemology.

I hurriedly said that causal epistemology in epidemiology is variational, *pace* Hume. Let me develop this point further. The conceptual background pervading philosophy of science and scientific thinking is a paradigm of regularity, a heritage of the Humean conception of causation presented earlier (Hume 1748, sec.VII). However, if the regularity paradigm were the correct one in epidemiology, Bhopol would be misinterpreting the 'common beliefs' of epidemiologists. But perhaps Bhopol is right

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[1] A number of epidemiologists have explicitly supported this idea, for instance, Susser (1973), Timmerick (1994), Lilienfeld and Stolley (1994), Jewell (2004), just to name a few.

and instead Hume is misleadingly called to support causal reasoning in epidemiology. Wittness Karhausen (2000, p.59):

> This paper attempts to charter some of the territory of the concept of causation in epidemiology and its potential interactions with logic and scientific philosophy. David Hume looms large in this matter […]. Being a cause is a special characterisation of some state of affairs characterised by change, i.e. an event, a fact, a state or a deed: in medicine and epidemiology, a cause makes a disease happen or not happen.

Karhausen then points to several misunderstandings of the Humean doctrine both in the philosophical and epidemiological literature. For instance, some authors took Hume as claiming that causal inference is a subjective process, or that causes are not real, or that induction does not exist, etc. (Karhausen 2000, p. 60). Two remarks are in order. The first is that Karhausen, in the quote above, is misunderstanding Hume too, for Hume's influence is in the definition of cause as an object displaying regular behaviour—which Karhausen (2000, p.60) quotes too—not in a definition of cause as given above. The second is that, once again, Karhausen's definition underpins a *variational* epistemology of causality, *contra* Hume, who believed that we infer causation from *regular* successions of events.

The issue is indeed controversial and dissent with the regularist paradigm also comes from the quarters of the health sciences. For instance, Elwood (1988) complains that this paradigm of regularity is not well suited to this domain. He thinks that the regularist account is familiar to the physical sciences, where physical scenarios often exhibit a simplicity lacking in the health and social sciences. The view that a certain event always and invariably follows another event might well fit physics because the causal agent is sufficient, the time lag between the cause and the effect is short, and experimental conditions allow one to replicate causal relations. However, most situations in the health sciences do not fulfil these criteria. Whether or not Elwood is right about the simplicity of situations in physics I shall not investigate. But surely Elwood is right about epidemiology and in fact the definitions of cause we read earlier point to a *variational* epistemology not to a *regularist* one.

Variational methodology

According to the causal epistemology sketched above, epidemiology finds out about causes by examining the variability of disease due to the variability of exposure. Methodology is concerned with *how* this is *practically* done. What I want to show next is that definitions of cause in epidemiology also underpin a *variational methodology*.

Savitz (2003, p.35) notices that epidemiology is primarily interested in establishing statements such as 'the risk of disease is x times greater among exposed persons than unexposed persons'. Such claims contribute to establishing causal relations through *comparative statements*, which are in fact the bulk of a *variational* methodology. This idea can be found already in Susser (1973, p. 3), where he says that epidemiology is all about comparing and interpreting group exposure and response. Notably, comparisons involve establishing whether factors make or do not make a difference, that is whether distributions of disease differ conditional on the exposure, whether relative risks are greater for exposed individuals than for non exposed individuals.

Epidemiology, as it happens, is most often concerned with observational data rather than experimental data. It is apparent that the methodology of experimentation, e.g. in randomised clinical trials, is variational because the idea is just this: to see what changes occur by making certain interventions. In fact, in experimental studies we estimate certain predetermined outcomes of a well defined intervention which is deliberatively administered to certain individuals and we compare results with outcomes in individuals that have not been administered the intervention.[2] Nevertheless, observational studies rely on a variational methodology too. Timmerick (1994, p. 326) expresses this idea very clearly:

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[2] No doubt the most direct tests for causation would be experimentation and intervention; yet, even randomised controlled trials do not 'prove' causation because of practical and methodological pitfalls. A thorough discussion of this issue falls beyond the scope of the paper and I will not reiterate arguments given elsewhere (see e.g., Elwood (1988), Cartwright (2007b), and Glasziou et al. (2007)). Let me just point out that Glasziou et al. (2007) defend the idea that observational evidence can indeed support causal claims, and then provide a significant number of historical examples where convincing causal inferences have been performed without resorting to randomized trials. Timmerick (1994) goes as far as claiming that observational studies provide many more insights into the effects of diseases. The reason is that they deal with population groups, whereas experimental studies deal with individuals or smaller treatments or experimental groups and therefore the inference to relations in large populations is limited. Of course, issues remain concerning the problem of confounding or the

> Observational method of study is based on the concept that changes which are observed in one trait or variable can cause changes in another characteristics or variable, and those changes occur without the event being altered by the epidemiologist or without intervention by a researcher.

That observational methods in epidemiology are variational in character is also clear from the fact that they are all *comparative*. Cohort studies compare individuals exposed to the putative cause with individuals that have not been exposed. Case-control studies compare individuals with the disease with individual that do not have the disease. In cross-sectional studies data is collected at a specific point of time and comparisons are made for that specific moment. It is not my goal here to evaluate strengths, weaknesses, or applicability of those type of studies. Instead, it is my intent to stress their *comparative* aspect: the goal of epidemiological studies is to establish whether and how the distribution or the risk of disease varies according to the exposure and to other medical and social characteristics of individuals.

Interestingly, in Timmerick the hypothesis formulation stage also involves reasoning about variations. Timmerick (1994, ch.10) singles out four different approaches to hypothesis formulation: method of difference, method of agreement, accompanying/co-joint variations, method of analogy.[3] In the method of difference the formulation of the hypothesis is suggested by the fact that the frequency of occurrence is significantly different in different situations and conditions. We use the method of agreement when we hypothesise a same factor as cause of disease in case we identify the same risk factor acting in a variety of different circumstances. In the method of joint variations, the frequency of a risk factor varies with the frequency of the disease. Finally, in the method of analogy, hypotheses are formulated on the basis of similarity of risk factors and pathogen agents of similar diseases. Let me emphasise that hypothesis formulation mirrors a variational rather than a regularist epistemology. Put differently, what guides hypothesis formulation is not the observation of regular successions but of *variations*.

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use of frequentist rather than Bayesian statistics, but those are quite perpendicular to point I am concerned with.

[3] The four methods listed and discussed by Timmerick clearly recall the Millian methods of experimental enquiry (Mill 1843), although he does not explicitly refers to them. For a discussion of the notion of variation in Mill's experimental method, see Russo (2008, ch.4).

It is perhaps obvious, to the eyes of the epidemiologist, that causal methods hinge upon the notion of variation and that the definitions of cause we read at the beginning indeed reflect a variational methodology. Fair enough. But, perhaps, it is less obvious what the metaphysical import of such definitions is. This, I shall discuss in the next section.

3. Causal metaphysics

Preliminaries

So far I argued that definitions of cause mentioned in Sec. 1 grasp the *variational* epistemology and methodology of epidemiological research. Epidemiologists are interested in studying variations of disease due to variations in exposure. This fixes the causal epistemology and methodology—viz. to look for and test *variations* to find out about causal relations. But to what extent this also determines the causal metaphysics to adopt? My argument continues in this section by saying that although the definitions of cause in Sec. 1 all point to difference-making, this does not fix a 'variational' or 'difference-making' metaphysics; rather, this is a reflex of the variational epistemology and methodology of epidemiology. Let me make clear from the outset the question I address in this section.

The metaphysics of causality seeks to know what causality in fact is, what kind of entities causes are, what do we mean when we say that *A causes B*. Those tasks can be achieved in a number of ways. Philosophers of causality provided an analysis of the concept of causality (e.g., Hall 2004), an account of the kind of entities causes are (e.g., Cartwright 1989), or developed a set of conditions under which relations between variables are causal (e.g., Woodward 2003).

The philosophical literature is vast. Broadly speaking, 'traditional' philosophical theories fall into two families: those analysing causality in terms of difference-making and those analysing causality in terms of production and mechanisms. Probabilistic theories and counterfactual theories are examples of the *former sort*: in probabilistic approaches (e.g., Suppes 1970, Eells 1991, Hitchcock 1995) causes, whether positive or negative, are difference-makers as they change, i.e. increase or decrease, the probability of their effects. In Lewis' counterfactual analysis (Lewis 1986) causes are

also difference-makers as 'if the cause had not been, the effect would not have been either'. Examples of the *latter sort* of theories are, for instance, the account developed by Cartwright (1989), where causes are capacities having the ability or disposition to produce or bring about an effect, the process-based approach (Dowe 2000, Salmon 1998) where causes are linked to effects via physical process that intersect and interact, or the mechanist approach (Machamer, Darden and Craver 2000, Glennan 2002, Craver 2007), where *A* causes *B* if and only if there is a suitable mechanism linking the two.

A number of criticism may be raised against these traditional accounts. Usually, counterexamples are construed in order to show that none of them is able to provide the answer to what causality is. In fact counterexamples to each of the above positions can be easily construed—Reiss (2009) offers a detailed overview and discussion of stock examples. Hence, slowly but surely, due to the failures of traditional philosophical theories of causation, *pluralistic* stances have come into range as the most promising solution.[4] Simply put, pluralists say that causality has many aspects, not just one, and causal claims have many meanings, not just one. Thus, for instance, Hall (2004) maintains that causation involves 'dependence' as well as 'production'. Dependence and production are usually cashed out in terms of difference-making and mechanisms, respectively. Thus, a kind of pluralist stance requires that cause make a difference to the effect *and* that the cause be linked to the effect via a mechanism. Alternatively, pluralist may maintain that the right concept in terms of which causality has to be cashed out depends on the context. Thus, Weber (2007) suggests that an analysis in terms of difference-making is suitable for the generic level (e.g., 'smoking causes lung cancer'), whilst an analysis in terms of mechanism is suitable in the single-case (e.g., 'Harry's smoking caused him to develop lung cancer').

But what kind of metaphysics, among the above, should epidemiologists adopt? Is disease causation intrinsically difference-making or mechanist? Or a combination of the two? Answering those questions is the task I undertake next.

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[4] For a discussion see, among others, Campaner and Galavotti (2007), Cartwright (2007b), DeVreese (2006), Godfrey-Smith (forthcoming), Hall (2004), Psillos (2008), Reiss (2009), Russo and Williamson (2007), Weber (2007).

Variational metaphysics?

Definitions of cause in Sec. 1 consistently describe causes as difference-makers. Does it follow that epidemiologists should endorse a difference-making metaphysics? The straight answer is no, because causality in epidemiology is better interpreted according to the epistemic theory.

Whilst traditional accounts cash out causality in terms of 'probability raising', 'physical process', 'mechanism', or 'capacity', the *epistemic theory* (Williamson 2005, 2006) cashes out causality in terms of an individual's beliefs (e.g., a scientist) formed upon available evidence. Under the epistemic theory, causal relations are not real but rather 'representational': causality is not a feature of the physical world, but a feature of an individual's set of beliefs about a phenomenon. Thus the epidemiologist, armed with solid epistemological and methodological tools, will deem some factors causal but not others depending on the evidence and methods at her disposal. IARC procedure to evaluate carcinogenic risks on humans are a good example to illustrate. The evaluation of carcinogenicity of agents is the problem of deciding whether and to what extent an agent causes cancer (in humans or in animals). An agent will be *deemed* carcinogenic depending on what evidence supports such a claim. The IARC monographs (IARC 2006) provide an extensive descriptions of the procedures for the evaluation of carcinogenicity. The point at stake here is that the claim 'the agent x is carcinogenic to humans' *represents* the evidence, methods and evaluation procedures used to come to such a causal conclusion. It is in this sense that causation, under the epistemic theory, is representational.

Pluralist philosophers have argued, in slightly different ways, that causality is a multi-fold concept involving difference-making and mechanisms. However, there is a deep mistake in such analysis: pluralists are confusing the very *concept* of causality and the *evidence* to establish a causal claim. In other words, from the fact that we have multiple sources of evidence, it doesn't follow that should have a multi-fold concept of cause. In the epistemic theory, causality is a feature of the beliefs of scientist—this is what the concept of causality amounts to. A different issue is the evidence needed in order to establish whether a factor or a relation is causal: *evidence* has to involve difference-making *and* mechanistic considerations. Russo and Williamson (2007)

offer various arguments for the claim that difference-making and mechanistic *evidence* is needed in the health sciences: (i) pluralist stances are fallacious exactly because they confuse the concept of causality with the types of evidence to establish causal claims; (ii) history of medicine has paradigmatic cases where causal claims have not been accepted until *both* difference-making and mechanistic evidence has been provided to support a causal claim; (iii) the need for difference-making and mechanistic evidence is current practice in the health sciences, as required, for instance, by IARC procedures to evaluate studies on carcinogenic factors.

Adopting the epistemic theory carries many advantages. One is that the epistemic theory answers the worries of those who argue against an explicit causal terminology on the ground that the notion of cause is metaphysical, i.e. obscure and untestable. Here is an example. Lipton and Odegard (2005, p. 7) say:

> Our point is that although it is important to be able to use epidemiological research to predict and intervene at the public health level, to tell the best story possible about the research findings at hand, one doesn't have to say that *X* causes *Y* to achieve such an outcome. In fact, one cannot definitively claim such a relationship.

Lipton and Odegaard's anti-causal stance is motivated by the belief that metaphysical causal claims are independent of, and even not needed for, the 'use value' of research findings for prediction and intervention. The two sentences 'smoking causes lung cancer' and 'smoking two packs a day increases the risk of lung cancer by ten times', according to Lipton and Odegaard, do not merely differ as to their semantics. The former—they claim—resorts to a "metaphysical and unsupported" notion of cause, whilst the latter already tells a causal story, and in particular it uses a language that allows practical uses such as prediction and interaction. Now, the "metaphysical and unsupported" notion of cause they refer to is Anscombe's (1981) notion, which is cashed out in terms of necessary connection and instantiation of an exceptionless generalisation. I will keep aside historical considerations about the reception of and the critiques to Anscombe's thought in the philosophical literature, and about the advancements in the philosophy of causality after Anscombe.

The point is that Lipton and Odegard's worry is simply dissolved once the epistemic theory is adopted, for epistemic causality is not metaphysically obscure (beliefs can be characterised precisely in probabilistic terms) nor untestable (it is

exactly on the basis of evidence that beliefs are formed and evaluated). The epistemic theory is not far from the position defended by Vineis (2003), where he says that we *believe* that smoking causes lung cancer on the basis of various sources of evidence, e.g., observations in humans, experiments in animals, knowledge about DNA damage in carcinogenesis, etc. This does not force epidemiologists to a 'realist' position according to which "empirical observations do refer to some reality in the external world (independently of theoretical models)" (Vineis 2003, p.85).

Another advantage is that the epistemic theory encompasses different *modus operandi* of the cause. Parascandola and Weed (2001) discuss five possible definitions of cause (production, necessary causes, sufficient-component causes, probabilistic causes, counterfactual causes) and complain that none attract unanimous consensus nor can account for causes in all domains. Consider causes as necessary factors. Agreed, the view that all causes must be necessary for their effects (traditionally associated to the germ theory of disease) has been discarded. Some causes *aren't* necessary for the effect, e.g. carcinogenic substances, but some indeed *are*, for instance tuberculosis is caused by an infectious agent, which is necessary for the development of the disease. Under the epistemic theory, necessary and probabilistic causes can peacefully live together. Since causality is not physical, causes can be variables, particular entities, events, properties or facts, depending on the context. Consider the two causal claims 'exposure to asbestos dust causes lung cancer' and 'the bacteria streptococcus causes irritation and inflammation of the throat'. The first involves variables as causal relata and the cause thereby operating is probabilistic. The second, instead, involves different kinds of relata (bacteria are microorganisms, and irritation and inflammation of the throat is an event describing health status) and the cause is of type sufficient-component.[5] It follows that necessary of probabilistic definitions of cause are not mutually exclusive definitions—that depends on the disease. The point is that we *deem* some relations to be causal and causality lies exactly in this epistemic activity of evaluating the available evidence.

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[5] "A sufficient-component cause is made up of a number of components, no one of which is sufficient for the disease on its own. When all the components of the disease are present, however, a sufficient cause is formed". (Parascandola and Weed 2001, 907)

Furthermore, the epistemic theory is not in contradiction with the definitions of cause given in Sec. 1. The question is, rather, why are causes consistently defined in terms of difference-making? The temptation would be to infer that those definitions underpin a difference-making metaphysic, namely that this is what causality is—to make a difference to the effect. But this is a fallacious way of reasoning for various reasons. One is that some causes are *not* be difference-makers. For instance, causes of states might work differently. The pillar causes the building to stand but is not a difference-maker. The pillar just stands there and makes the building to stand as well.[6] Therefore difference-making is not a universal feature of causes. Another reason, as mentioned above, is that difference-making is *evidence* we need to establish whether a factor is causal, it does not coincide with the very concept of causation.

The reason why definitions of cause prominently display difference-making considerations, instead, is that they reflect the variational epistemology and methodology discussed in Sec. 2. That is to say, difference-making definitions of cause reflect *how* we come to know whether something is a cause—the *how* question is answered by methodology and epistemology. Let me emphasise that whether we deem something a cause is still an *epistemic* activity, so the question is not to reveal once and for all what the 'secret connection' is; there is no secret connection indeed—causality, in epistemic terms, simply results from the epistemology and methodology used by the epidemiologists.

4. Summary and conclusion

Causal issues are extremely important in epidemiology: adopting and justifying an explicit causal stance, disentangling notions such as the 'causal web', let alone providing workable definitions of cause. This paper examined the definitions of the concept of cause found in survey papers or textbooks in epidemiology. Those definitions all share a common feature: they say what the job of a cause is, that is to bring about changes in the distribution of disease or in individual health status. I argued that those definitions underpin a 'variational' epistemology and methodology, but not a 'variational' or 'difference-making' metaphysics.

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[6] For a discussion about causes of states and difference-making, see Russo (2008, ch.3).

By discussing the goals of epidemiological research I showed that the causal epistemology in epidemiology hinges upon the notion of variation rather than regularity. Therefore, the definitions of cause underpin a variational epistemology. Similarly, because causal methods in epidemiology are essentially comparative, methodology in epidemiological research is variational too. I then went on arguing that those definitions do not underpin a variational metaphysics and that causality in epidemiology is better interpreted according to the epistemic theory. According to the epistemic theory, causality is not a physical property of things or of the world, but rather represent particular beliefs of the individual, in our case the epidemiologist. A key feature of epistemic causality is that it clearly distinguishes between the very concept of cause and the evidence needed to establish causal claims. Definitions of cause in epidemiology consistently point to difference-making because this is a crucial evidence for disease causation and in fact it reflects the way epidemiologists come to know about causal relations, namely the variational epistemology and methodology of epidemiological research.

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