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Evidence, illness, and causation: An epidemiological perspective on the Russo–Williamson Thesis

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ABSTRACT

According to the Russo–Williamson Thesis, causal claims in the health sciences need to be supported by both difference-making and mechanistic evidence. In this article, we attempt to determine whether Evidence-based Medicine (EBM) can be improved through the consideration of mechanistic evidence. We discuss the practical composition and function of each RWT evidence type and propose that exposure–outcome evidence (previously known as difference-making evidence) provides associations that can *be explained* through a hypothesis of causation, while mechanistic evidence provides finer-grained associations and knowledge of entities that ultimately *explains* a causal hypothesis. We suggest that mechanistic evidence holds untapped potential to add value to the assessment of evidence quality in EBM and propose initial recommendations for the integration of mechanistic and exposure–outcome evidence to improve EBM by robustly leveraging available evidence in support of good medical decisions.

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1. Introduction

Evidence-based medicine (EBM) has become the predominant paradigm of medical decision-making. It is described by its founders as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients," (Sackett, 1995). This definition inevitably raises the question: what constitutes the current best evidence? Surely many approaches to medical decision-making aspire to use the best evidence; EBM differentiates itself by weighing evidence in a particular way. Specifically, EBM is founded on the belief that information derived from clinical experience or from knowledge of basic biological mechanisms can often be misleading or incorrect if not supplemented by systematic observations from clinical research (Evidence-Based Medicine Working, 1992). EBM's proponents therefore generally count randomized trials and systematic reviews of randomized trials as the most trustworthy sources of evidence, with non-randomized cohort studies, case-control studies, and case series occupying the middle ground, and mechanistic reasoning, clinical experience, and expert opinion forming the least trustworthy sources of evidence (if they are included at all) (Force, 2008; Group, 2011).

EBM's rise in popularity has been accompanied by significant criticism, not least from philosophers of science, for whom the theory of EBM touches upon many familiar topics, including the logic of evidence, causal inference, mechanism, and explanation. Some philosophers have questioned whether EBM's preferred prioritization of evidence sources is justified (Clarke, Gillies, Illari, Russo, & Williamson, 2013), others have asked whether evidence even *can* be prioritized by source (Worrall, 2010), and still others have largely defended EBM's general principles while offering resolutions to specific issues and paradoxes (Howick, 2011). One particular criticism, which we will explore here, suggests that EBM undervalues "non-statistical evidence of mechanisms" (Clarke et al., 2013). The philosophical underpinning for this criticism comes from the Russo–Williamson Thesis (RWT).

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The RWT, first published in 2007, proposes that in order to establish a causal claim in the health sciences, one needs two types of evidence: *difference-making evidence* that the putative cause and effect are correlated and *mechanistic evidence* that there exists some mechanism explaining the difference-making relationship (Clarke et al., 2013; Russo & Williamson, 2007). Although this is certainly a helpful guideline for thinking about causal inference, we hold that if the RWT is to be of use to medical decision-making, it requires clarification beyond previous disambiguations (Illari, 2011) and criticisms (Claveau, 2012). Moreover, we do not subscribe to the view that knowledge of both difference-making and mechanistic evidence is necessary for the establishment of causal claims in the health sciences, although it may very well be (and often is) sufficient for it (Broadbent, 2011).

Here, we approach the RWT from the epidemiologist's point of view. Modern epidemiology is the design, implementation, and analysis of studies in humans that help identify (a) risk factors for certain diseases (so-called observational studies) and (b) interventions that reduce disease burden or prevent illness altogether (mainly, but not exclusively, randomized controlled trials). Therefore, all of the health sciences draw upon information generated by epidemiological research. We believe that the epidemiological perspective we provide in this paper is therefore useful for examining the relationship between the concepts of the RWT and the day-to-day work of evidence gathering and utilization across the health sciences.

Our goal is to determine whether EBM can be improved through the consideration of mechanistic evidence. In order to answer this question, we first attempt to clarify the practical composition and function of each RWT evidence type. We find that exposure–outcome evidence (previously known as difference-making evidence) provides associations that can *be explained* through a hypothesis of causation, while mechanistic evidence provides finer-grained associations and knowledge of entities that ultimately *explains* a causal hypothesis. In light of these clarifications, we find that mechanistic evidence holds untapped potential to add value to the assessment of evidence quality in EBM. Finally, we suggest a path forward, providing initial recommendations for the integration of mechanistic and exposure–outcome evidence to generate an EBM that more robustly leverages the available evidence to make good medical decisions.

2. Illness causation viewed from the epidemiological angle

One might be tempted to think that in order to discuss causal inference in epidemiology, one should be clear about how epidemiologists define causation. Another possible position is that we do not need to know about the nature of a cause in order to find one. In Broadbent's words, "we can know that something exists without knowing what it is" (Broadbent, 2011:59).

However, if asked which ontological position they take when thinking about causation, mechanistic or difference-making, most epidemiologists will probably agree that their notions of illness causation processes seem to fit current philosophical definitions of mechanism quite well (Bechtel & Abrahamsen, 2005; Glennan, 1996; Illari & Williamson, 2012; Machamer, Darden, & Craver, 2000). One particular attractive conception of mechanism is Garson's "functional sense of mechanism" (Garson, 2013). According to this view, mechanisms serve functions and illness causation can be conceptualized as the aberrant function that is due to disrupted mechanisms. Using biomedical terminology, this is the process of moving from the physiological to the pathophysiological state by means of pathomechanisms. The fact that "pathomechanism" is frequently used in biomedicine suggests that Garson's view that "there are no mechanisms for pathology; pathologies result from disrupting mechanisms for functions" (Garson, 2013:317) might not be shared by at least some biomedical scientists.

Unfortunately, pathomechanisms cannot be directly observed by epidemiologists. Indeed, the intra-individual component of the illness causation process (pathogenesis) requires biological studies in model organisms. Epidemiologists can examine how certain antecedent variables act and interact in predicting health outcomes in populations (etiology). The etiology of illness, therefore, can be viewed as the natural history of disease from exposure to risk factors until the illness becomes clinically detectable. As such, disease etiology includes the pathogenesis as the disease mechanism that occupies the black box between exposures and outcomes, though epidemiologists can discuss pathogenesis itself only in rather limited ways. Nevertheless, specialized forms of epidemiologic inquiry such as molecular and genetic epidemiology can make quite interesting contributions to the interdisciplinary discussion of pathomechanisms.

Still, even without exact pathogenetic (mechanistic) knowledge, information about difference-making evidence (we prefer "exposure–outcome evidence", v.i.) can be very useful. This approach has been called the "black box stance", which holds that "epidemiologists need not concern themselves with the discovery of mechanisms, but can directly attack causal questions without worrying about the mechanisms underlying the hypotheses they generate" (Broadbent, 2011:60). Historical case studies of successful prevention of childbed fever by hand disinfection and of lung disease by smoking cessation support the notion that "laboring to uncover mechanisms may well prove to be a waste of time and money, from a public health point of view" (Broadbent, 2011:60).

Most activities in the health sciences are targeted at prevention and health promotion in public health and about treatment of illness by intervention in medicine. Our view of etiology and pathogenesis outlined above suggests that although epidemiologists might be interested in pathomechanisms, they can live without them while still making a contribution to public health by generating etiologic knowledge. Biological bench scientists are better equipped to focus on pathomechanisms that can be targeted with pharmacological interventions.

3. Redefining difference-making evidence for the health sciences

Difference-making evidence in support of a given causal claim in the health sciences has been defined as evidence that a cause "makes a difference to" an effect (Russo & Williamson, 2007) and "evidence that the effect does indeed vary with the postulated cause" (Illari, 2011). The trouble with the term "difference-making" is that it closely resembles the notion of causation, simply because of the similarity between the verbs "making" and "causing". If the statement "A makes a difference to B" is taken as equivalent to the statement "A causes B," then evidence of difference-making is indistinguishable from evidence of causation generally. Obviously, this is not the meaning that Russo and Williamson intended, because it would contradict their notion that evidence of difference-making does not suffice to support causal claims.

For epidemiologists, evidence of difference-making is the result of a two-step discovery process in which evidence of (statistical) association between exposure and outcome is gathered first in order to establish that it is possible that the exposure causes the outcome. This evidence is then supplemented with evidence for possible mechanisms by which the exposure can cause the outcome. Together, both kinds of evidence are sufficient to support a causal claim. Thus, from the epidemiological perspective, evidence for difference-making comprises two kinds of evidence that are very close to the two kinds of evidence