The rapid dominance of evidence-based medicine has sparked a philosophical debate concerning the concept of evidence. We urge that evidence-based medicine, if it is to be practised in accordance with its own mandate, should also acknowledge the importance of understanding causal mechanisms.\textsuperscript{1,2} The undersigned include 42 clinicians and philosophers from interdisciplinary research networks working specifically on questions related to causation in medicine worldwide.

Our research has developed out of a conviction that philosophical analysis ought to have a direct impact on the practice of medicine. In particular, if we are to understand what is meant by ‘evidence’, what is the ‘best available evidence’ and how to apply it in the context of medicine, we need to tackle the problem of causation head on.\textsuperscript{1,2,6} In practice, this means understanding the context in which evidence is obtained, as well as how the evidence might be interpreted and applied when making practical clinical decisions.\textsuperscript{7,13} It also means being explicit about what kind of causal knowledge can be gained through various research methods. The possibility that mechanistic and other types of evidence can be used to add value or initiate a causal claim should not be ignored.\textsuperscript{3,2} This appeal for a broader approach to evidence is also important to patients, who need clear information on the benefits and harms of medicines.\textsuperscript{36}

We have arrived at several overlapping conclusions with implications for policy and practice in research and clinical care, which we summarise briefly:

1. ‘Evidence’ is typically evidence of causation. Common terms used in EBM, such as ‘intervention’, ‘outcome’ or ‘increased risk’, are relevant to evidence-based decision-making only insofar as they point to causal matters: causal interventions and their effects. Although there is growing reluctance to make causal claims in areas of uncertainty, the correct response to such uncertainty is not to avoid talking about causation but instead to improve our methods of understanding it.

2. Establishing causation often requires the use of multiple methods since no single method will be universally applicable or perfect for this purpose. This means that statistical approaches, in particular randomised controlled trials and systematic reviews, cannot uncover all causally relevant information, contrary to their widespread assumed status as the universal gold standards of EBM.

3. An understanding of causal mechanisms can help to determine whether an intervention works (ie, its efficacy shown in experiment or effectiveness in clinical practice). In addition, we should strive to understand how an intervention works (ie, its mechanism) and how it can be made to work (ie, the conditions under which it works best). Understanding mechanisms is essential for both of these. For instance, a medical intervention that works experimentally might not do so when combined with a negatively interacting substance.

4. Although animal experiments can shed light on causal mechanisms, other types of evidence can add to our understanding. This is because causal mechanisms are complex, involving multiple causal interactions of various factors. These factors play roles in the effectiveness of the treatment and in interactions between the treatment and the individual patient.

5. Given the multiplicity of methods (cf 2) and a wide interpretation of what counts as a mechanism (cf 3 and 4), causation should be understood in non-reductionist terms. That is, the scope of relevant causal interactions extends beyond the molecular, pharmacological and physiological levels of interaction. Any thorough causal account should also include higher-level factors, such as the behaviour of tissues, whole organs and individuals, including psychological and social factors.

6. ‘Causal evidence’ should be extended to include different types of evidence, including case studies and case reports, which can in some cases provide valuable information for understanding causation and causal mechanisms. This is particularly important when dealing with rare disorders, marginal groups or outliers.

7. Patient narratives and phenomenological approaches are useful tools for looking beyond evidence such as symptoms and outcomes, and to elucidate the core causes or sources for chronic and unexplained conditions.

8. Causation has a non-negligible temporal aspect. Whether of long or short duration, a causal interaction cannot be fully understood from a ‘snapshot’, but requires both backward-looking perspectives (towards the origin) and forward-looking perspectives (towards the outcome).

These conclusions provide a philosophical framework for taking causation seriously in evidence-based approaches to medicine. They also suggest how improvements can be made in the...
methodological basis of medical science and in the application of research results in clinical practice.

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