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Have Causal Claims About the Gut Microbiome Been Over-Hyped?

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The gut microbiome, which is the ensemble of microbes living in our intestinal tract, has recently been associated with a large number of health conditions, including cancer therapy outcomes.[1] Although microbiome research is booming, claims that the microbiome causes health outcomes are, I will argue, questionable. To do so, I exploit a popular account of causation in philosophy of science, inspired from scientific practice (more particularly controlled experiments), known as the "interventionist account of causation"[2] to show that, following this account, some of the causal claims made in the gut microbiome research do not fully satisfy desirable properties of causal relationships and causal explanations. Some of these ideas are explored from a different angle and in more detail by colleagues.[3,4]

Under the interventionist account, a variable C is considered as a cause of a second variable E, if changing the value of C independently from changing the value of any other variable at a given time (i.e., performing an intervention), produces a change in the value of E at a later point in time. While the interventionist account permits us to assess whether a relationship between two variables is causal, its real interest is that it allows distinguishing (desirable) properties of causal relationships and causal explanations that can serve as a basis to compare them. One such property of causal relationships is the range of influence of its cause(s). Roughly speaking, it measures the number of possible interventions on C leading to a different value of E. For instance, to take an everyday example, tuning the dial of a radio produces a higher number of possible effects (we can hear different channels when the radio is on) than switching it on or off (we hear something or nothing). Thus, the dial has a higher range of influence than the switch. Another property of causal relationships is the degree of insensitivity or robustness when the background conditions of the relationship change, which is called the stability of the relationship. For instance, a drug might be effective in treating a condition only under certain circumstances (say the age of the patient), while another drug might treat the same condition in a larger number of circumstances (at any age). The relationship between the second drug and the outcome would be in this case more stable. The higher the range of influence of its cause and the more stable it is, the more this causal relationship will fit what scientists recognize as a paradigmatic causal relationship.

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Similarly, some causal explanations might be more adequate than others by citing the causal relata at the appropriate grain of description. For instance, suppose you eat a chicken sandwich that contains a heavy load of *Salmonella*, and that as a result you get food poisoning. The causal explanation that the sandwich is the cause of food poisoning, although correct, is somehow inadequate, because one could provide a much more accurate explanation by citing the presence of *Salmonella* on the chicken. In fact, although eating or not eating the sandwich would lead or not lead to food poisoning, the relevant contrast that one is seeking when asking "What caused the food poisoning?" implicitly assumes that the person ate some food. By intervening on the presence/absence of *Salmonella* on the chicken, the food poisoning would or would not have occurred. Thus, citing the sandwich rather than the heavy load of *Salmonella* as the cause for food poisoning gives us an explanation at a grain of description that is too coarse for the explanation sought. It is an example of non-proportional explanation following the terminology used in the interventionist literature. The interventionist account distinguishes other important properties of causal relationships and explanations detailed elsewhere.[2]

Having presented my conceptual apparatus, how can it be deployed to assess causal claims about the causal role of the microbiome? The generic hypothesis that microbiome research aims at testing – as represented in **Figure 1** – is whether the relationship between M and O is causal ($M \rightarrow O$) rather than correlative ($M \leftrightarrow O$). In other words, M is a candidate for C in our generic causal relationship, and O is a candidate for E. Put in interventionist terms, this is equivalent to asking whether intervening on M produces changes in O. Z, the background here – which includes all variables other than M and O, such as for instance the type of host in which M is found, as well as the environment more generally – is also important. In fact, to be generalizable, that is to have a high level of stability, the causal relationship from $M \rightarrow O$ should be insensitive to different hosts, contexts and environments.

How is M operationalized in microbiome research? A survey in the literature demonstrates that M is typically experimentally intervened upon, in at least four different ways, namely by fecal microbiome transplants (FMTs), by probiotics, by prebiotics, and by antibiotics.[5] There is in principle nothing wrong with experimentally intervening in different ways on a variable, quite the opposite. In fact, it permits us to ensure that a relationship is causal rather than spurious, because an *experimental* intervention can only approximate an interventionist account's *ideal* intervention: By experimentally intervening on a variable, the value of other variables might also be changed at the same time. One way to mitigate this problem is thus to experimentally intervene *in different ways* on the variable so that the chances of introducing systematic biases decrease. Yet, these different

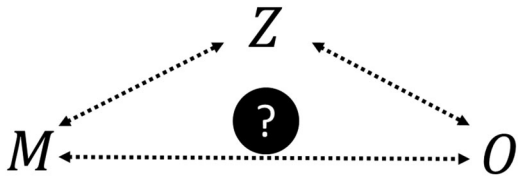

Figure 1. Causal diagram representing the possible associations between *M* (microbiome), *O* (health outcome), and *Z* (factors in the background of *M* and *O*). The generic hypothesis tested by microbiome research is whether the arrow between *M* and *O* is a causal one from *M* to *O* ($M \rightarrow O$).

means to intervene on *M* point toward a fundamental problem: presuming that one can be confident that FMTs contain a representative sample of a human microbiome, probiotics only contain certain taxa which are supplemented to the microbiome of the host, while prebiotics favorize the proliferation of some targeted taxa and antibiotics selectively kill some of them.

Why is that a problem? These differences point to the fact that different health outcomes associated with interventions on the microbiome can be reached while these interventions, by means of probiotics, prebiotics, and antibiotics, concern only a few taxa. From there, the claim that the "microbiome" as a whole is a locus of causation for health outcomes is overblown. In fact, recall the non-proportional explanation of the chicken sandwich causing food poisoning when a better explanation is the presence of *Salmonella* on the chicken. I argue that the same sort of non-proportional explanation occurs when the microbiome is cited as an explanation for health outcomes, while in fact perhaps only a few taxa are causally involved in the relationship, namely the ones added by probiotics, favorized by prebiotics or eliminated by antibiotics. This idea is reinforced from recent evidence that the microbiome can be "edited" with precision — in other words intervened upon — by the oral administration of tungstate in mice with colitis induced in a number of ways, including by FMTs from human patients with inflammatory bowel disease.[6] The authors showed that tungstate can reduce colitis by selectively inhibiting metabolic pathways used by the Enterobacteriaceae family — the family to which *Escherichia coli* belongs — which are functional only during periods of inflammation. Other studies have shown that a handful — or even only a single taxon — might be responsible for treating other infections (one example is found in Ref. [4]).

The same sort of problem can be seen from a different perspective. The microbiome is often characterized as "dysbiotic" (e.g., Ref. [1,6]), that is as being in a state of "imbalance." There are several problems associated with the use of this term.[4] One of them is that it characterizes the microbiome at such a coarse level of description that a proportional explanation stemming from this description can itself only be a very coarse one. Assuming that "dysbiosis" does really cause a disease (such as inflammatory bowel disease), claim that *M* is a cause of disease can at best be regarded as an invitation to look for a finer explanation. By characterizing *M* as "normal" or "dysbiotic" and establishing a causal relationship from *M* to *O* at that level of description, one highlights a causal relationship with a very low range of influence, much less interesting than a causal relationship with a higher range of influence. The analogy with the switch of the radio is useful here. In fact, in the radio example the "causal action" seems to occur more in the tuning of the dial than in switching the radio on or off. Similarly, more seems to be gained from decomposing *M* into sub-variables and intervening on these variables to see whether they bring about the same disease outcome rather than looking at *M* holistically. Here again, were it established that only a single or couple of taxa are involved in the disease outcome, the claim that the "microbiome" is the cause of disease, if not factually wrong, would be misleading because it would elicit the idea of the whole microbiome as the most fine-grained explanation possible for the outcome, when this is in fact an open empirical question.

Finally, given the high variability of the human gut microbiome composition,[7] as well as the high level of interaction between the microbes composing the microbiome, it is reasonable to question whether a strategy of "coarse-graining" — that is providing a description that leaves out a part of the available information because it is irrelevant or redundant — would be successful at characterizing our gut microbiome as a coarse-grained variable (*M*) for the purpose of explaining health outcomes. Coarse-graining methods have recently been proposed to treat the question of biological individuality (see for instance Ref. [8]). It is unclear however whether these methods, if applied to the gut microbiome, would lead to the conclusion that microbiomes can be described equivalently or nearly equivalently at a coarse level (the whole microbiome) rather than by specifying their taxonomic composition.

Do these considerations mean that causal claims about the whole microbiome are inescapably overblown? Not necessarily. Invoking the microbiome as a causal agent could yield proportional and interesting causal explanations if it were established that independent interventions on the different taxa of the microbiome lead to no difference in health outcomes, while interventions on whole microbiomes make lasting differences. This would indicate that a remarkable sort of interactions operates between the different taxa — one that produces synergistic effects that do not occur when a single taxon is manipulated at a time. In the current state of research, whether such microbiome-level synergistic effects exist — beyond the fact that organisms developing without a microbiome do worse than those developing with one — and if they do whether the size of those effect is large, are both questionable. Note furthermore that to be regarded as paradigmatically causal, these relationships would have to produce similar outcomes in different contexts, or in other words — to use the interventionist terminology — to be causally stable. Here again whether this can be established is an open empirical question.

The claim that "the microbiome" is causally responsible for our health is an appealing one because it conveys the idea that a single purposeful agent might be tamed by simple interventions. The reality is much more complex. Rather, "the microbiome" is an umbrella term that regroups different sorts of entities in different contexts, all of which have to do with the microorganisms living in our guts. Although a holistic approach to the relationship between our gut microbes and health should not be rejected as a matter of principle, more should be done to establish whether an appeal to "the whole microbiome" in such contexts is both indispensable and well defined. Causal claims about the microbiome are to be related to those made about the holobiont (a host plus its microbes) as being

the "unit" seen by natural selection (e.g., Ref. [9]), a claim that has attracted similar criticisms and questionings.[4,10,11] Framing causal claims within an interventionist perspective could encourage microbiome researchers to verify whether the microbiome as a locus of intervention/explanation yields outcomes that are not obtained from interventions at the taxa levels, and to give more justifications for considering the gut microbiome as a unitary entity.

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