

The Problem of Mooted Models for Analyses of Microbiome Causality

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Target article: “How Causal are Microbiomes? A Comparison with the *Helicobacter pylori* Explanation of Ulcers” by Kate E. Lynch, Emily C. Parke, Maureen A. O’Malley

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Lynch, Parke, and O’Malley highlight the need for better evaluative criteria for causal explanations in microbiome research. They propose new interventionist criteria, show that paradigmatic examples of microbiome explanations are flawed using those criteria, and suggest numerous ways microbiome explanations can be improved. While we endorse their primary criticisms and suggestions for improvements in microbiome research, we make several observations regarding the use of mooted causal models in microbiome research that have significant implications for their overall argument. In sum, we contend that their critique is too modest and that even flawed causal inferences like those they criticize can be valuable for generating better causal models and evaluating explanatory outcome in individual cases.

1. Problems with Mooted Models

As an alternative to using Koch’s postulates for identifying microbiome causal factors, Lynch, Park and O’Malley defend Proportionality, Specificity, and Stability interventionist criteria for evaluating the strength of possible causal explanations. They show that widely received explanations of obesity and mental health outcomes do not fulfill these criteria. Moreover, they suggest that such causal inferences could be improved if microbiome researchers: (i) are more specific about how they conceive of target microbiomes, (ii) pay explicit attention to how well their mooted explanatory models meet their criteria for causal explanations, (iii) define outcomes in more nuanced, non-binary, ways, and (iv) focus on specified factors within target microbiome rather than making claims about any microbiome as a whole. We contend that even adopting these suggestions won’t produce causal explanations that fulfill the interventionist criteria they endorse. Examining the cases they use to illustrate the virtues of that interventionist schema helps show why they won’t.

1.1. *H. pylori* and Ulcers

Lynch, Parke, and O’Malley present the *H. pylori* case as a “traditional” microbial causal explanations rather than microbiome causation; since it appeals to one species rather than a

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4 microbiome as a whole. They argue that the claim that '*H. Pylori* causes ulcers' fulfills the
5 Proportionality criterion (or at least does better than the competing hypothesis that ulcers are
6 due to activation of the immune system) even though it fails the Stability or Specificity criteria.
7 The reasons it fails the latter are instructive.
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10 The endorsed interventionist schema requires specifying a mooted model in which values of all
11 variables except the one being tested can remain fixed while the tested one is intervened upon.
12 Importantly, the quality of inferences that can be drawn from experimental interventions
13 depends on the quality of that mooted model. If potentially relevant confounds are left out, the
14 causal inference to *H. pylori* is underdetermined. Lynch, Parke, and O'Malley show that the
15 model according to which '*H. pylori* causes ulcers' does not even "achieve a key explanatory
16 standard in microbiology," since it fails Koch's postulate according to which an acceptable
17 microbial cause must be shown to correspond specifically with the target disease and shown to
18 induce the disease when introduced in healthy animals. They note that the postulate was not
19 even fulfilled in the landmark Marshall *et al* (1985) study in which Marshall drank a culture of *H.*
20 *pylori* to test himself as an animal host—because he was the sole test host and didn't even go on
21 to develop ulcers but just gastritis. Moreover, key evidence supporting the inference to *H. pylori*
22 was derived from an overly simplistic mooted model and accordingly oversimplified
23 experimental designs.
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30 The mooted model was myopically focused on only one type of bacteria, because it was the one
31 that the researchers found and could culture and because four patients with ulcers who had *H.*
32 *pylori* in their guts responded to treatment with multiple antibiotics that eliminated *H. pylori*
33 (Marshall 2005). Only *H. pylori* was cultured from the stomachs of ulcer patients. However,
34 when additional species are present, the success of antibacterial treatments does not warrant
35 the inference to *H. pylori*—because such interventions only show that *something* present in the
36 microbiome was causally relevant to ulcers not that it was *H. pylori*. So, in this case,
37 interventions established the causal claim because they only targeted the mooted cause. Of
38 course, a better experimental design would work with a model that accounts for potential
39 confounds and tests for outcomes whether or not they are present.
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44 Lynch, Parke, and O'Malley's discussion reveals similar problems in the case of *C. diff*. Fecal
45 Microbiome Transplant (FMT) interventions on entire microbiomes are effective in curing *C. diff*.
46 Following principles that allow the inference to the causal role of Helicobacter thus supports
47 inferring a causal explanation from this intervention. This, they explain, is in some tension with a
48 more focused explanation of the treatment of *C. diff* in terms of specific organisms and
49 pathways. The model that refers to the entire microbiome seems to fail the Proportionality
50 criterion even though interventionist principles license it. However, the apparent tension
51 between these explanations is resolved once we recognize that good interventionist inferences
52 require sufficiently detailed mooted models. The success of the intervention tells us something
53 in the microbiome is plausibly playing a role, but a more focused intervention is needed to
54 determine what. And to know how to design a more focused intervention, we need more
55 detailed models that specify the variables to be kept fixed and those to be intervened upon.
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4 These cases seem to show that problems with Proportionality derive from inadequate mooted
5 models. Failures of the Specificity and Stability criteria on the other hand have more to do with
6 the complexity of causal relations in nature. A causal relationship's "stability" is a function of its
7 robustness across a variety of background conditions. The relationship between *H. pylori* and
8 ulcers is not very robust, since background conditions play a large role in determining whether
9 infected people contract ulcers. Similarly, Specificity is not satisfied if there are multiple,
10 independent, pathways to an effect. The works Lynch, Parke, and O'Malley reference mention
11 two (*H. pylori* and non-steroidal anti-inflammatory usage). More recent works identify many
12 more independent causes. One large study found "risk for ulcer related to stress was similar
13 among subjects who were *H pylori* seropositive, those who were *H pylori* seronegative, and
14 those exposed to neither *H pylori* nor nonsteroidal anti-inflammatory drugs" (Levenstein *et al*
15 2015, 498). Multivariable analysis in that study also showed that "stress, socioeconomic status,
16 smoking, *H pylori* infection, and use of nonsteroidal anti-inflammatory drugs were independent
17 predictors of ulcer" (Ibid.).
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23 **1.2 Microbiomes and Obesity**

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26 Let us now consider Lynch, Park, and O'Malley's recommendations (i-iv) for improving causal
27 inferences in microbiology. It seems these recommendations are not sufficient to overcome the
28 above sorts of problems, at least in the near term. Consider, for instance, their critique of the
29 mooted relationship between the Firmicutes/Bacteroidetes ratio and obesity on the grounds of
30 Stability and the existence of potential confounds. Here, developing an apt mooted model is
31 impossible in practice even though a widely-received causal explanation is well specified; since
32 the mooted relationship is not between a microbiome taken as a unitary entity but between
33 obesity-risk and the ratio of two phyla in the guts of mice and humans. Despite this specificity,
34 the causal relationship lacks stability because it is sensitive to background conditions—of which
35 some are known (e.g. fat in the diet) while others are not (since increases and decreases in
36 Firmicutes are both associated with obesity). The mooted model also overlooks potential
37 confounds; including the noted problems with germ-free mice, and, alternatively with mice
38 treated with antibiotics. Since we do not yet have a theoretical handle on these background
39 conditions and potential confounds, we are not yet in a position to construct an apt mooted
40 model to guide experimental manipulations that could found strong causal claims.
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47 Given the complexity of interaction effects, we may never arrive at particularly stable causal
48 claims about microbiome factors and obesity-risk. We may only ever be able to provide much
49 more restricted claims; e.g., that certain components of a microbiome, given certain background
50 conditions, tend to produce some degree of obesity-risk. Lynch, Park, and O'Malley note that
51 similar comments apply to Specificity. If, as seems plausible, there are multiple pathways to
52 similar outcomes, the relevant sorts of causal claims fail the Specificity criterion. We cannot say
53 that obesity is *always* produced by a certain feature of the microbiome, but only that sometimes,
54 in some circumstances, obesity is produced by that feature.
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58 Studies on obesity and specific bacterium even show that sensitivity to background conditions
59 makes constructing apt mooted model impossible in practice. Consider studies on correlations
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4 between *H. pylori* infections and obesity for instance. Some find substantive correlations (see,
5 e.g., Chen et al. 2018). Others find that *H. pylori* abundance has no relation to BMI in particular
6 demographics (Kawano *et al* 2001; Kyriazanos *et al* 2002; Archimandritis *et al* 2003). And still
7 others find no relationship at all between *H. pylori* and being overweight (see, e.g., Ioannou *et al*
8 2005; Cho *et al* 2005).
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10 11 **1.3. Microbiomes and Mental Conditions**

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14 The above points all apply equally well to the example of FMT experiments and probiotic
15 manipulations used to establish causal connections between features of microbiomes and
16 mental conditions. Lynch, Parke, and O'Malley acknowledge that both the nature of
17 microbiomes (as a group of interacting microbial species) and the nature of mental health states
18 (as complex traits affected by multiple genes, the environment, and their interactions)
19 contribute to a multifactorial range of possible developmental pathways. They argue,
20 convincingly, that claims about the causal role of any microbiome as a whole are thus unlikely to
21 fulfill the Proportionality or Specificity criteria. Depression and anxiety, they suggest, are
22 multifactorial traits which involve complex interactions between microbiomes, hosts, and their
23 environments. It's therefore unlikely that claims involving entire microbiomes could be specific,
24 since a given microbiome-type is unlikely to be in 1-1 correspondence with a particular
25 psychological profile. We believe it is also unlikely that they will be stable, since a given
26 microbiome-type will probably not produce a specific set of psychological traits across a range of
27 background conditions.
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34 It is also unclear how following Lynch, Parke, and O'Malley's suggestions, and adopting more
35 highly specific accounts of microbiomes or focusing on specific behavioral components, will help
36 overcome either of these problems for microbiome research on mental conditions. Since
37 psychological traits are due to complex interactions between a microbiome, a host (even down
38 to epigenetic artifacts), and their environment, there's just no reason to expect that there will be
39 specific or stable relationships between any given microbiome components and specific mental
40 conditions. There are just too many confounds and background influences to develop apt
41 mooted models to establish such relationships.
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45 46 47 **2. Flawed Causal Inferences about Microbiomes can be Valuable**

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49 We agree that researchers should aspire to explanations that fulfill the Specificity, Stability, and
50 Proportionality criteria. Yet, even explanations that fall short can be, and are often,
51 pragmatically and heuristically useful. For instance, learning that FMT transplants can cause
52 obesity in germ-free mice tells us something about where to look for relevant causal
53 mechanisms, even though it does not fulfill the Stability criterion. Finding out that this effect is
54 moderated by the level of dietary fat also gives us information about which causal models might
55 be plausibly hypothesized. Flawed models can be valuable for developing and refining
56 hypotheses that can help generate more and more refined causal models. We contend that it is
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4 therefore crucially valuable, especially at early stages of a research program, to value crude and
5 flawed hypotheses and models of potential causal mechanisms.
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8 Flawed models can also have value for helping evaluate particular cases and potential courses of
9 disease treatment. We know that in *some* cases, antibacterials and means of changing the
10 composition of gut microbiomes can be used to effectively treat and/or prevent ulcers. In *some*
11 cases, such interventions can help treat and/or prevent obesity. And in *some* cases, they can be
12 used to effectively treat and/or prevent certain mental conditions. Knowing these things is
13 obviously useful in particular cases, even though the mooted models these conclusions derive
14 from are wrong and even if generalizable mooted models are impossible.
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18 In view of the complexity of microbiomes and the broader networks of which they are parts, we
19 believe that it is at this stage practically impossible to produce apt mooted models to found
20 generalizable microbiome explanations. The appeal to more rigorous interventionist explanatory
21 criteria at this stage of our understanding is thus a step in the right direction but at once
22 quixotic. But all is not lost. Interventionist explanatory criteria are no doubt useful and
23 explanatory models that fail interventionist criteria can be crucially valuable nevertheless.
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