Mechanisms and uncertainty in randomized controlled trials: A commentary on Deaton and Cartwright

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Uncertainty is Rampant in Biomedical and Social Sciences

The human body is extraordinarily complex. Even genetic apparatus of a cell is an extremely complex, self-regulating biochemical system. While much is now understood, a great deal remains to be studied. The deterministic behavior of biochemical systems is ultimately, however, the collective result of a very large number of random events governed by the laws of quantum mechanics (Hanin, 2017). The human person is yet more complex still. Uncertainty stems from human nature: from free actions, from our free will or ability to both follow and yet also abandon principles, from being rational creature, who yet reason imperfectly, and from the uncertainty in human interactions as well. Undeniably, life is unpredictable. From biology to human behavior, uncertainty and complexity is rampant in biomedical and social sciences. Deaton and Cartwright (2018) have done an impressive job of extensively describing what randomized controlled trials (RCTs) can and cannot do in face of that uncertainty and that complexity.

Randomization is powerful and, as documented by Deaton and Cartwright (2018) can allow for progress in the estimation of average causal effects even in the face of extraordinary complexity and substantial uncertainty. Much of their discussion as to what RCTs cannot do in addressing issues of uncertainty is largely obviated by trials that are themselves sufficiently large, but it is of course the case that many trials are small and many of the concerns they raise must be thought about and evaluated carefully. Here we would like to focus upon questions of mechanisms in RCTs and their relevance to the interpretation of, extrapolation from, and inferences made from the results of such trials.

Mechanisms and Sufficient Causes in Randomized Controlled Trials

Deaton and Cartwright (2018) write, "[m]echanisms are particularly important in understanding the explanation of causal processes in biology". Although the meaning of mechanisms may substantially vary across disciplines, a careful scrutiny of the concept of mechanism gives us further insight to understand why uncertainty or randomness is so rampant in biomedical and social sciences. In this regard, the sufficient cause model has provided a useful framework. This model was described within epidemiology by Rothman (1976), and it has shaped our understanding of causation in biomedical science. Similar models arise in philosophy (Mackie, 1965), law (Wright, 1988), and psychology (Novick & Cheng, 2004). In this model, causation is conceptualized as a collection of different causal mechanisms, each sufficient to bring about the outcome. These causal mechanisms are called ‘‘sufficient causes’’, and each sufficient cause would consist of a minimal set of conditions or ‘‘component causes’’ such that, whenever all the component causes for a particular causal mechanism were present, the mechanism would operate and the outcome would inevitably occur.

Importantly, the sufficient cause model makes clear that causation is a multifactorial

phenomenon. It is the combination of numerous conditions that gives rise to the health or social outcomes that we seek to study. In most population health settings, it consequently does not make sense to try to identify "the" cause; rather we study "causes" (VanderWeele, 2017). Furthermore, when many conditions are required for a particular causal mechanism to be operative, it will sometimes suffice to eliminate just one of them to prevent disease occurrence. If multiple conditions are required for a sufficient cause, then they effectively interact in this sufficient cause sense; each needs the other to set a particular mechanism into motion. We can thus sometimes study and identify the numerous causes that, if eliminated, may be sufficient to substantially reduce a disease. When many causes are present in the same sufficient cause, the elimination of any of them suffices, by definition, to render that sufficient cause inoperative, giving rise to important distinctions between "attributable fractions" and "etiologic fractions" (Greenland & Robins, 1988; Suzuki et al., 2012).

Within the sufficient cause framework, we usually include one component cause to represent unspecified events, conditions, and characteristics that must be present or must have occurred at the instance of the health outcome of interest. The necessity of the unknown or unmeasured component cause reminds us that uncertainty is rampant in biomedical and social sciences. It can also be used to help distinguish and relate concepts of confounding and of covariate balance (Suzuki et al., 2018). Even in the era of DNA-based typing, no matter how diligently one tries to observe the entire set of sufficient causes or causal mechanisms in individuals, it is impossible. Indeed, identifying all component causes within even one sufficient cause in one individual is beyond human reach. Besides, the configuration of a sufficient cause in an individual may well alter from moment to moment, and an individual can be at risk of, or susceptible to, several sufficient causes. This sometimes overwhelming conceptualization well illustrates the fact that there are many inter-personal as well as intra-personal variations in biomedical and social sciences.

Understanding causation in this multifactorial way helps us to grasp the complexity of causal systems. An RCT typically examines the effects of but one cause, but it does so in the context of the presence or absence of many others. Understanding this complexity helps us also to see that if the distribution of the other component causes varies across populations then so will the average causal effect (Rothman, 1976); and moreover different patterns of the underlying component causes across different individuals within a population will give rise to effect heterogeneity. The multitude of component causes potentially involved in the causation of outcomes of interest makes clear also then the difficulty in extrapolating effect estimates.

Mechanisms and Pathways in Randomized Controlled Trials

Another understanding of mechanism concerns chains of causal events: the treatment T alters some variable M which then goes on to affect the outcome Y. That variable M is sometimes said to be a

mediator of the effect of treatment *T* on outcome *Y*. Alternatively, it is sometimes said that *M* is a mechanism for the effect of *T* on *Y*. The analytic tools sometimes described as "mediation analysis" attempt to assess such mechanisms or pathways or causal chains and estimate the magnitude of the so-called "indirect effects" operating through the mediator, and the "direct effects" independent of the mediator (MacKinnon, 2008; VanderWeele, 2015). Such mediation analyses techniques are rather underdeveloped within economics but have been used for decades in psychology (Baron & Kenny, 1986) and in the social sciences. They have more recently been developed and placed within the counterfactual or potential outcomes framework in statistics and epidemiology (Pearl, 2001; Robins & Greenland, 1992; VanderWeele, 2015). Such mediating mechanisms can also likewise be formulated in terms of a series of sufficient causes (Hafeman, 2008; Suzuki et al., 2011; VanderWeele, 2009).

The framing of questions of mediating mechanisms within the potential outcomes framework also makes clear what RCTs do and do not contribute towards the understanding of mechanisms. It is now well-documented that even in a perfect and large RCT of treatment *T*, one must make additional untestable assumptions, to assess these questions of mediation (Pearl, 2001; Robins & Greenland, 1992; VanderWeele, 2015). Specifically, even if treatment *T* is randomized, it is still the case that to assess direct and indirect effects, one must control for covariates that suffice to adjust for mediator-outcome confounding (Judd & Kenny, 1981; Pearl, 2001; Robins & Greenland, 1992; VanderWeele, 2015). The treatment *T* may be randomized, but the mediator *M* generally is not. When we talk about mediation, mechanisms, and indirect effects, we are making causal claims; we must then take into account whether associations can be interpreted causally not only with respect to the treatment *T* but also with respect to the mediator *M*. The complexities raised by Deaton and Cartwright (2018) are then compounded further. Progress can sometimes be made but our inferences about mediation are generally only tentative, even from perfect and large RCTs.

But what do such mediation analyses themselves add to RCTs? First, if we can identify relevant mechanisms it might help us understand why a particular treatment succeeded, or failed. It can help strengthen and confirm, or alternatively refute, theories. If a particular treatment failed, it can also help us understand whether the treatment had little effect because it failed to alter the primary mechanism that was hypothesized, or whether it did in fact affect the mechanism that was hypothesized but that mechanism itself had little effect on the outcome. Understanding the mechanisms can also in some circumstances make the case for causality of an effect of the treatment on the outcome stronger. If we know that the treatment altered a number of other variables that are themselves related to the outcome, it becomes more difficult to explain away causal effect estimates as being spurious due to uncertainty. Also, as discussed further below, understanding the mechanisms might also help in cases of trying to extrapolate results from RCTs to other populations. If we have an understanding of the mechanisms for a causal effect, we can ask if we think, or if we have evidence for, those same mechanisms being operative in other populations and contexts.

Knowledge from Randomized Controlled Trials and from Mechanisms

An understanding of mechanisms might thus help better locate RCTs within the broader structure of knowledge and inference. What do we know when we have the results from an RCT? If carried out well, and reported honestly, without intentional or unintentional analytic errors, we have, subject to often substantial uncertainty, an unbiased estimate of the causal effect for the sample under study (Suzuki et al., 2016). As noted by Deaton and Cartwright (2018), however, we often want to know more than that. We want to extrapolate – often either through an argument about the generality of, or through the numerical transforming/transporting of causal effect estimates (Stuart et al., 2018). We want to know if our estimates, or at least the direction of effects, is consistent across populations and settings. A further understanding of mechanisms in the sense of mediation may give us greater confidence in extrapolating the direction of the effect to new populations; a greater understanding of mechanisms in the sense of sufficient causes may make us more humble in extrapolating the magnitude of causal effects to different populations.

Meta-analyses can sometimes take us one step further (Borenstein et al., 2009; DerSimonian & Laird, 1986). With a sufficient number of well-designed RCTs we can sometimes make statements along the lines of, "In a new setting and population, drawn at random from the types of settings employed in the meta-analysis, we would expect the causal effect for that population to be between *x* and *y* at least 95% of the time" (IntHout et al., 2016; Riley et al., 2011). However, often there is considerable ambiguity into the types and distribution of studies included in the meta-analysis to generate such statements and thus considerable uncertainty still with regard to whether such statements are truly relevant to new setting at hand. Moreover, often such prediction intervals from meta-analysis are too wide to be of much use in decision-making priorities or cost-effectiveness analysis. We are brought back to a position of humility with respect to our knowledge of the magnitude of effects.

This circumstance perhaps motivates the issue touched upon by Deaton and Cartwright (2018) of seeking out effect measures that might be able to be extrapolated across settings. They comment on how this was done by others, perhaps without adequate justification, for elasticity of medical expenditures with varying levels of co-payments. There is widespread belief in the biomedical world, that for many disease processes, the risk ratio relating exposures to disease outcomes is homogenous across populations (Fletcher & Fletcher, 2005; Schulz et al., 2010). Social scientists sometimes wonder why epidemiologists use risk ratios. That is perhaps at least a part of the reason why. Evidence put forward for this claim typically comes from surveys of meta-analyses suggesting that tests for homogeneity reject more often on the difference scale than on the ratio scale (Deeks, 2002; Deeks & Altman, 2001; Engels et al., 2000; Sterne & Egger, 2001). Such evidence is, however, flawed because the power of these tests can differ dramatically across settings, even when both measures are

heterogeneous and arguably to the same extent (Poole et al., 2015).

More compelling evidence perhaps comes from careful modeling of numerous exposures simultaneously in settings in which such modeling suggests that the effect of one exposure across strata of many others is often indeed close to constant on the risk ratio scale (Maas et al., 2016). If this were true as well of all relevant unmeasured covariates, it would indeed suggest also a homogeneity of the risk ratio across populations. However, this type and strength of empirical evidence is still at present relatively limited. Further work might help delineate when it is, and is not reasonable, to expect risk ratios, or other effect measures, to be constant across settings. It has been proposed that certain mechanistic patterns in biological systems may themselves give rise to homogeneous risk ratios or risk differences (Thompson, 1991; VanderWeele & Knol, 2014). This is ultimately the sort of knowledge that would be useful for extrapolation not only of the presence of causal effects, but also of their magnitude. We arguably have a long way to go in establishing such knowledge. And it may turn out that such patterns of homogeneity are more common in biomedical settings, with relatively universal laws governing phenomena, than in social science settings where social interactions and the meaning of social exposures are more likely to vary across contexts and cultures. Without this more developed understanding, we are left still with a great deal of uncertainty about extrapolation and about the generalizability of our knowledge, even that obtained from using multiple RCTs.

Uncertainty and Awareness

Although uncertainty is often not desirable, it is even less desirable to remain ignorant of uncertainty. Unquestionably, each of us should constantly strive to understand uncertainty and to understand also the numerous potential misunderstandings concerning RCTs, as documented in a paper by Deaton and Cartwright (2018). Only in so doing can researchers, despite prevailing uncertainty, make more reliable causal inferences. We very much believe that this awareness is essential to progress but we nevertheless believe also that RCTs will remain an essential asset in the accumulation of knowledge within the biomedical and social sciences.

In their conclusion, Deaton and Cartwright (2018) claim to respond to the following two challenges posed in the form of questions; “If you are being prescribed a new drug, wouldn’t you want it to have been through an RCT?” and, “OK, you have highlighted some of the problems with RCTs, but other methods have all of those problems, plus problems of their own.” We would give unequivocal, affirmative answers to both of these questions. While not every RCT is preferable to an observational study, and while RCTs are subject to misunderstanding and potential problems as documented by Deaton and Cartwright (2018), we believe the power of randomization will remain important in addressing uncertainty, in helping to ensure unconfoundedness, in building trust in conclusions, and therefore in the continued development of scientific knowledge.

Declarations of interest

None.

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