The Big Question: What types of studies, and study results, should compel a scientist (or agency) to adopt or advocate for a nutritional intervention?

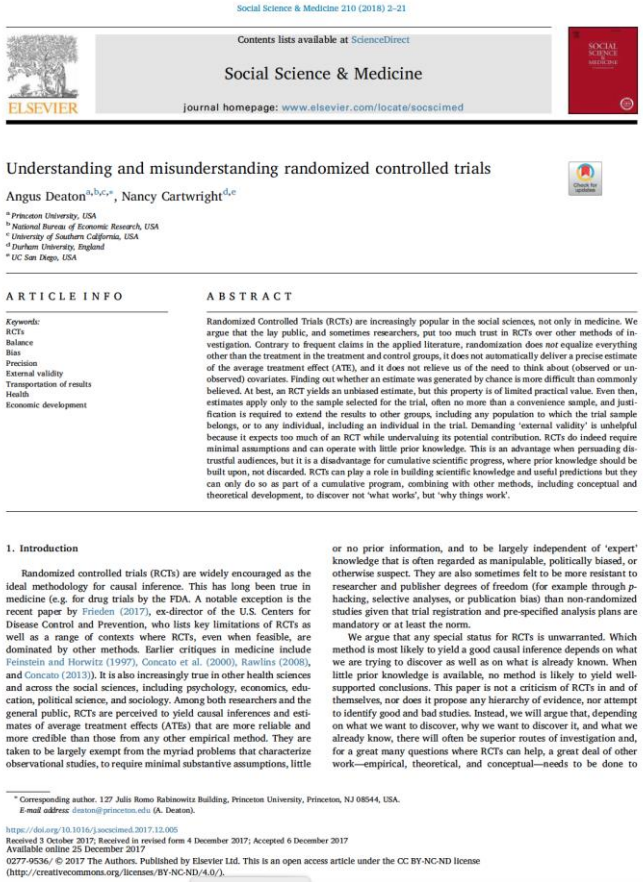
The Default Answer: A traditional phase III-like comparative randomized clinical trial

The 'traditional phase III-like RCT' straw man:

- Randomization is used to enable causal claims to be made about the intervention and response
- Inclusion and exclusion criteria are used to avoid confounding and outlier effects
- Relatively few arms if more than just, e.g., a single active intervention and placebo arm
- Focus is on population-level efficacy (e.g., group differences between, e.g., active and placebo arms; use of interpretable, though not unproblematic, population metrics like the number needed to treat (NNT) to characterize utility, etc.)
- Relatively few measures taken on each individual to maximize the number of individuals studied

Limitations of the traditional phase III-like comparative randomized clinical trial:

- Randomization does not guarantee **balanced covariate profiles** for any one trial (block randomization can mitigate imbalance to a certain extent)
- Inclusion and exclusion criteria **limits generalization** of the effects of the intervention to a relevant population
- Traditional trials focus on efficacy and **not effectiveness** (i.e., 'real world' deployment utility)
- Limited number and range of measurements on any individual and length of intervention period restrict **individual response evaluation** (e.g., event rates)
- The 'average' effect difference between trial arms is not always a **good metric for assessing utility**
- **Many more criticisms**, including those specific to nutrition research, to be discussed during the meeting (e.g., assessment background exposure, differences among individuals in background exposure, lack of adherence measures, multiple biologically active forms of some bioactive compounds)


Social Science & Medicine 210 (2018) 2–21
Contents lists available at ScienceDirect
Social Science & Medicine
journal homepage: www.elsevier.com/locate/socscimed

Understanding and misunderstanding randomized controlled trials

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ARTICLE INFO

Keywords:
RCTs
Balance
Bias
Precision
External validity
Transportation of results
Health
Economic development

ABSTRACT

Randomized Controlled Trials (RCTs) are increasingly popular in the social sciences, not only in medicine. We argue that the lay public, and sometimes researchers, put too much trust in RCTs over other methods of investigation. Contrary to frequent claims in the applied literature, randomization does not equalize everything other than the treatment in the treatment and control groups, it does not automatically deliver a precise estimate of the average treatment effect (ATE), and it does not relieve us of the need to think about (observed or unobserved) covariates. Finding out whether an estimate was generated by chance is more difficult than commonly believed. At best, an RCT yields an unbiased estimate, but this property is of limited practical value. Even then, estimates apply only to the sample selected for the trial, often no more than a convenience sample, and justification is required to extend the results to other groups, including any population to which the trial sample belongs, or to any individual, including an individual in the trial. Demanding 'external validity' is unhelpful because it expects too much of an RCT while undervaluing its potential contribution. RCTs do indeed require minimal assumptions and can operate with little prior knowledge. This is an advantage when persuading distrustful audiences, but it is a disadvantage for cumulative scientific progress, where prior knowledge should be built upon, not discarded. RCTs can play a role in building scientific knowledge and useful predictions but they can only do so as part of a cumulative program, combining with other methods, including conceptual and theoretical development, to discover not 'what works', but 'why things work'.

1. Introduction

Randomized controlled trials (RCTs) are widely encouraged as the ideal methodology for causal inference. This has long been true in medicine (e.g. for drug trials by the FDA. A notable exception is the recent paper by Frieden (2017), ex-director of the U.S. Centers for Disease Control and Prevention, who lists key limitations of RCTs as well as a range of contexts where RCTs, even when feasible, are dominated by other methods. Earlier critiques in medicine include Feinstein and Horwitz (1997), Concato et al. (2000), Rawlins (2008), and Concato (2013)). It is also increasingly true in other health sciences and across the social sciences, including psychology, economics, education, political science, and sociology. Among both researchers and the general public, RCTs are perceived to yield causal inferences and estimates of average treatment effects (ATEs) that are more reliable and more credible than those from any other empirical method. They are taken to be largely exempt from the myriad problems that characterize observational studies, to require minimal substantive assumptions, little or no prior information, and to be largely independent of 'expert' knowledge that is often regarded as manipulable, politically biased, or otherwise suspect. They are also sometimes felt to be more resistant to researcher and publisher degrees of freedom (for example through *p*-hacking, selective analyses, or publication bias) than non-randomized studies given that trial registration and pre-specified analysis plans are mandatory or at least the norm.

We argue that any special status for RCTs is unwarranted. Which method is most likely to yield a good causal inference depends on what we are trying to discover as well as on what is already known. When little prior knowledge is available, no method is likely to yield well-supported conclusions. This paper is not a criticism of RCTs in and of themselves, nor does it propose any hierarchy of evidence, nor attempt to identify good and bad studies. Instead, we will argue that, depending on what we want to discover, why we want to discover it, and what we already know, there will often be superior routes of investigation and, for a great many questions where RCTs can help, a great deal of other work—empirical, theoretical, and conceptual—needs to be done to

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https://doi.org/10.1016/j.socscimed.2017.12.005
Received 3 October 2017; Received in revised form 4 December 2017; Accepted 6 December 2017
Available online 25 December 2017
0277-9536/


Social Science & Medicine 210 (2018) 22–25
Contents lists available at ScienceDirect
Social Science & Medicine
journal homepage: www.elsevier.com/locate/socscimed

Introduction. What works? And for whom?

Lots of opinions… especially about the role of counterfactuals in making causal claims, historical precedents, etc.


Social Science & Medicine 210 (2018) 53–56
Contents lists available at ScienceDirect
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Commentary

Randomized controlled trials: Often flawed, mostly useless, clearly indispensable: A commentary on Deaton and Cartwright

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We need more traditional RCTs!


Social Science & Medicine 210 (2018) 60–62
Contents lists available at ScienceDirect
Social Science & Medicine
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Challenging the hegemony of randomized controlled trials: A commentary on Deaton and Cartwright

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Alternatives include propensity score-based comparisons in observational studies; Mendelian Randomization studies; etc.


Social Science & Medicine 210 (2018) 71–73
Contents lists available at ScienceDirect
Social Science & Medicine
journal homepage: www.elsevier.com/locate/socscimed

Randomized clinical trials and personalized medicine: A commentary on deaton and cartwright

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Better designs that may include randomization (e.g., adaptive, aggregated N-of-1, bucket and umbrella trials, etc.)

NASEM Meeting: 08/31/2021