Defining mediation effects for multiple mediators using the concept of the target randomized trial

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Abstract

Causal mediation approaches have been primarily developed for the goal of “explanation”, that is, to understand the pathways that lead from a cause to its effect. A related goal is to evaluate the impact of interventions on mediators, for example in epidemiological studies that seek to inform policies to improve outcomes for sick or disadvantaged populations by targeting intermediate processes. Previous methodological work on evaluating mediator interventions has been limited, in particular failing to utilize the key concept of defining target estimands in terms of a hypothetical randomized controlled trial: the “target trial”. In this paper, we define so-called interventional mediation effects in the framework of a target trial that evaluates a number of population-level mediator interventions, in the context of multiple interdependent mediators and real-world constraints of policy implementation such as limited resources, with extension to the evaluation of sequential interventions. We describe the assumptions required to identify these novel effects from observational data and a g-computation estimation method. This work was motivated by an investigation into alternative strategies for improving the psychosocial outcomes of adolescent self-harmers, based on data from the Victorian Adolescent Health Cohort Study. We use this example to show how our approach can be used to inform the prioritization of alternative courses of action. Our proposal opens up avenues for the definition and estimation of mediation effects that are policy-relevant, providing a valuable tool for building an evidence base on which to justify future investment of resources in the development and evaluation of interventions.

Keywords: mediation; interventional effects; natural effects; separable effects; target trial; multiple mediators; randomized controlled trial; causal inference
INTRODUCTION

Mediation analysis examines intermediate processes (“mediators”) presumed to lie on the path from an exposure (the “cause”) to an outcome (the “effect”). Specifically, it has commonly been used to answer two broad types of questions:

1. Questions aiming to explain causal effects, i.e. to understand the pathways that lead from an exposure to a later outcome.
2. Questions aiming to evaluate the effectiveness of interventions on mediators, i.e. to quantify the effect remaining after intervening on causal pathways.

Whether there is a difference between these two types of enquiry relates to the broader question of whether it is possible to conceive of or clearly define the concept of cause and effect without considering interventions. This question has in turn led some to proclaim “no causation without manipulation”, in a philosophical debate that has been ongoing since the inception of the field of causal inference [1–6]. In the context of mediation analysis, although there is an intuition about the notion of a mediating mechanism, it is similarly challenging to provide a formal definition without considering interventions, which in this case must relate to or affect the intermediate processes as well as the exposure. The debate about the need for interventions is central to criticisms of the “natural effects” framework [7–10] for defining mediation effects. Many authors have raised concerns regarding the impossibility of devising an experiment where the so-called “cross-worlds independence” assumptions required to identify these effects could be verified [5,11], and there are further complexities in the context of multiple mediators [12–15], although these challenges might be circumvented in specific scenarios [5,16,17]. These concerns suggest that a grounding in hypothetical experiments would make the concept of causal mediation more concrete.

More pragmatically, in approaching a mediation analysis it seems important to question the translational intent of the study at hand from a substantive perspective. That is, how will the conclusions of the study be used? Often, at least in population health and medical research, the ultimate aim of discovering or understanding causal pathways is to devise interventions for improving health, social and other outcomes [11]. For example, life-course epidemiological studies often seek to inform the development of policies or treatments to improve the outcomes of those vulnerable early in life [18]. Regardless of one’s philosophical
standpoint, it would be ideal in these settings to define mediation effects in such a way that they emulate the effects that might be found in the randomized trials that one would hypothetically conduct to evaluate such interventions. This “target trial” approach has proven useful for the estimation of total causal effects in other contexts [19,20].

A promising framework for developing such definitions is presented by so-called “interventional effects” [13,21–23]. These effects were originally proposed as an alternative to natural effects for the purpose of “explanation”, because of their reliance on less demanding identification assumptions, and Vansteelandt and Daniel [21] provided appealing definitions for the context of multiple mediators. Subsequently, Moreno-Betancur and Carlin [14] showed that interventional effects are population-average quantities that implicitly emulate randomized trials of population-level interventions on the mediators. However, those implicit interventions are not necessarily realistic in that they do not appear to correspond to actions that policy-makers would actually consider and would want to evaluate if they were able to run a trial. Other methods that have been proposed specifically to evaluate interventions on mediators or confounders can also be considered to fall under the “interventional effects” umbrella [24–29], but again, the lack of an explicit consideration of the target trial to be emulated limits their potential for informing real-world policies.

In this work, we propose the formulation of mediation questions explicitly in terms of a target trial reflecting real-world constraints of policy implementation, such as limited resource availability. From this we derive novel definitions of interventional effects for multiple mediators that differ from previous proposals (e.g. [13,21]). We describe how these definitions can serve to focus efforts of future intervention development and evaluation, determine identification assumptions and describe a g-computation estimation method, providing example R code. We motivate and illustrate our proposal in the context of an investigation into alternative strategies to change the life course of a particularly vulnerable group: adolescent self-harmers.

**MOTIVATING EXAMPLE**

Concerns have been raised around self-harming behavior during adolescence [30,31], the incidence of which appears to be on the rise, particularly among teenage girls [32]. Adolescent self-harm is associated with substantial global disease burden, through immediate
and long-term effects on health and mortality \cite{33,34}, as well as through persisting associations with poor health and social functioning in later life, including higher rates of substance use \cite{35}, depression \cite{35} and financial hardship \cite{36}. This raises the question of which intermediate processes, in young adulthood, could be targeted by policies aiming to reduce the longer-term impacts of adolescent self-harm. For illustration, we focus on financial hardship as outcome, which is intimately related to mental health and is a key risk factor for later poor health and mortality. Four putative mediating processes are of interest: young adulthood depression or anxiety, cannabis use, lack of higher education and unemployment \cite{36}.

To address this question we considered data from the Victorian Adolescent Health Cohort Study, a 10-wave longitudinal population-based cohort study of health across adolescence to the fourth decade of life in the state of Victoria, Australia (1992-2014). The eAppendix provides more details on study design, and the key measures of relevance for the present investigation, which are summarized next.

The exposure, denoted $A$, was adolescent self-reported self-harm across waves 3 to 6 (age 15–18 years). We define $A = 1$ if self-harm was present at any wave during adolescence and $A = 0$ otherwise, including when all wave-specific measures were either negative or missing. The outcome ($Y$) was financial hardship as self-reported at wave 10 (median age 35 years). We define $Y = 1$ if financial hardship was present and $Y = 0$ otherwise. The mediators, measured at wave 8 (median age 24 years), were depression or anxiety ($M_1$), weekly or more frequent cannabis use over the past year ($M_2$), not having completed a university degree ($M_3$), and not being in paid work ($M_4$). We define $M_k = 1$ if the mediator was present and $M_k = 0$ if it was absent ($k = 1, \ldots, 4$).

Pre-exposure confounders ($C$) were selected on an a priori basis considering potential confounders of the exposure-mediator, mediator-outcome and exposure-outcome associations. These were: participant sex, parental completion of high school (as a marker of socio-economic position), parental divorce or separation up to and including wave 6, and adolescent antecedents of the mediators where present, specifically participant completion of high school, adolescent depression or anxiety and cannabis use (weekly or more frequent). The latter two were summarized across waves 3-6 in the same way as the exposure. Figure 1
shows the assumed causal structure, which is agnostic to the directionality of causal relations between these interdependent mediators.

**TARGET TRIAL FOR MEDIATION EFFECTS**

**Interventions vs intervention targets**
The goal in our example is to evaluate the impact of intervening on four mediating processes in young adulthood on the risk of later financial hardship in adolescent self-harmers. This would be via interventions such as programs for mental health care, substance use reduction, and career development targeted at young adults who had previously self-harmed in adolescence. Stepping back momentarily from the idea of mediation analysis and the cohort study setting just described, we consider two quite distinct scenarios for how one might address this research question.

**Scenario 1: When seeking to build an evidence base for actual interventions.** This refers to the scenario where the programs alluded to above have been developed and there is sufficient time (more than a decade) and resources to compare and evaluate them. Evaluation can then be done by either running a randomized trial or rolling out the programs (or sufficiently similar interventions) and constructing a suitable observational database capturing data on adolescent self-harmers who receive and do not receive each of them. In either case the eligible population for recruitment would be the population of young adults who self-harmed in adolescence and it would be a question of estimating total causal effects in this group. The rest of the population, i.e. non-self-harmers, and concepts of mediation are irrelevant to this scenario.

**Scenario 2: When seeking to build an evidence base to inform the future development and evaluation of interventions targeting certain processes.** We focus on this scenario, which is where actual programs do not exist, or it is impossible to run a trial or access a suitable database to emulate a trial, at least not without considerable investment in time and funding. With an observational study like the Victorian Adolescent Health Cohort Study, an evidence base can be built on which to justify either the development of specific programs or the running of a trial or setting-up of an observational database, which would place us in Scenario 1 in the future. While this cohort study does not capture data on any actual interventions, it has data on the mediating constructs that those hypothetical programs would
target, e.g. cannabis use. Therefore, we can at least emulate the distributional mediator shifts that interventions with those “intervention targets” might achieve, and thereby obtain an initial estimate of their potential impact. It is in the context of this more modest goal that the non-self-harming group and ideas of mediation play a role, as will become clear in the next section.

**The target trial**

Following this rationale, we consider a target trial that evaluates the impact of shifts in the distribution of each mediator in the exposed, presumed to arise from hypothetical interventions. In settings like the self-harm example, it is reasonable to consider a trial under the following premises. First, a “one-policy premise” posits that the interventions are competing, such that only one would ultimately be implemented – this might be the case if there are limited resources. A second premise is that each intervention would at most shift the distribution of the corresponding mediator to what it would be in the unexposed population, as it would be unrealistic to consider improvements beyond that. A third premise is that the intervention to shift a mediator would be applied independently from other mediators (that is, to all exposed equally, regardless of other mediators), and would not have positive side-effects on their distributions. This last point might be considered to describe a worst-case scenario under the assumption that each intervention could potentially have beneficial, but not detrimental, effects on the other mediators.

Given these premises, the target trial for the self-harm example would have seven parallel arms as depicted in Figure 2. The first two arms, referred to as the unexposed and exposed groups, correspond to those in a classic two-arm parallel trial design: the intervention is only on the exposure, which is set to \( A = 0 \) and \( A = 1 \), respectively, leading to a naturally arising joint distribution of the mediators in each arm. For the remaining arms, the exposure is set to \( A = 1 \), and further intervention is conceived to shift the joint distribution of the mediators in different ways. For example, in the third arm, the distribution of \( M_1 \) is shifted to be as it is in the unexposed group independently of the other mediators, while the joint distribution of \( M_2, M_3 \) and \( M_4 \) is left as it naturally arises in the exposed group. In the final arm, the full joint distribution of the mediators is shifted to what it is in the unexposed group. This target trial extends in the natural way to the case of \( K \) mediators, with \( K + 3 \) arms, and considers distributional shifts that are different to those in the trials implicitly emulated by previously
proposed definitions of interventional effects [13,21], described in [14]. As in the thought experiment detailed in the appendix of [14], one can imagine any given distributional shift in the mediators as arising from a suite of policies or treatments (a so-called “intervention regime”). Even if largely hypothetical, as mentioned previously this appears to be a necessary step to conceptualizing effects that can inform the development of future interventions.

In some circumstances one might want to go beyond the one-policy premise, and explore the effects of sequential application of the policies. This can be done by adding arms to the trial, as depicted in Figure 3 for the case of four mediators. This again extends in the obvious way to the $K$-mediator case.

**MEDIATION EFFECT DEFINITIONS**

**Effects under one-policy premise**

Having defined the target trial we can derive interventional effects that provide an initial evaluation of the impact of hypothetical interventions targeting mediators. Consider the general case of $K$ mediators. The total causal effect (TCE) in the difference scale is given by the contrast between the outcome expectation in the first two arms: \( \text{TCE} = p_{trt} - p_{ctr}. \) We define a type of interventional indirect effect via the $k$th mediator, \( \text{IIE}_k (k = 1, ..., K) \), as the contrast between the outcome expectation in the exposed group and the arm in which the $M_k$ distribution is shifted:

\[
\text{IIE}_k = p_{trt} - p_k.
\]

This effect quantifies the impact of an intervention targeting $M_k$, while the joint distribution of the other mediators remains as it would be under exposure. In the example, for $M_2$ (weekly cannabis use), $\text{IIE}_2$ is the reduction in risk of financial hardship in self-harmers that would be achieved by reducing their rates of weekly cannabis to those in the non-self-harmers, while the joint distribution of all other mediators is left intact. These indirect effects differ from those proposed by Vansteelandt and Daniel [21] in that here the joint distribution of all other mediators is left as in the exposed group, which is intended to reflect what could feasibly be achieved under the one-policy premise. Our effects also reflect the realistic constraints that are expressed in the other premises.
Another effect of interest is the following interventional direct effect not via any mediator (IDE):

$$IDE = p_{att} - p_{ctr}$$

The IDE quantifies the effect of the exposure that would remain even if one devised a joint intervention for the mediators that would shift their joint distribution (mean levels and interdependence) to be as in the unexposed group.

The TCE is decomposed as:

$$TCE = IDE + IIE_1 + \cdots + IIE_K + IIE_{int}$$

where the last term is a type of interventional indirect effect via the mediators’ interdependence, contrasting the benefit of the aforementioned joint intervention with the sum of the benefits of individual interventions:

$$IIE_{int} = (p_{trt} - p_{att}) - (IIE_1 + \cdots + IIE_K).$$

The $IIE_{int}$ effect might not be the most policy-relevant effect as the second term pertains to a scenario where one would apply one policy, and then revert everything back to how it was before the policy was introduced before applying the next policy, and so on. A more intuitive definition of effect via the mediators’ interdependence arises under sequential policies (see next section).

More broadly, there are infinite possible decomposition of the TCE and what matters is that the effect components answer relevant questions. Under the one-policy premise, other contrasts that could be of interest, regardless of their role in a decomposition, are $IDE_k = p_k - p_{ctrl} = TCE - IIE_k$, for $k = 1, \ldots, K$, with $IDE_k$ quantifying the effect remaining after intervening on $M_k$.

Each effect can be expressed as a proportion of the TCE. For indirect effects $IIE_k$, these fractions represent the “proportion eliminated”, capturing how effective intervening on each
process would be in reducing the association; for direct effects, IDE and IDE\(k\), it is the fraction of the association that would remain after the corresponding intervention.

**Effects under sequential policies**

In the extended target trial (Figure 3), in order to examine the effect of shifting the distribution of each of \(M_1\) to \(M_K\), in that order, we define the interventional indirect effect of the \(k\)th intervention in the sequence, \(\text{IIE}_k\) \((k = 1, \ldots, K)\), as

\[
\text{IIE}_k = p_{(k-1)} - p_k.
\]

Here, \(p_0 = p_{\text{trt}}\) and \(p_1 = p_1\), and \(p_k\) for \(k > 1\) denotes the outcome expectation in the arm in which the interventions on \(M_1\) to \(M_k\) have been applied as described by the joint distributions depicted in Figure 3. The sum of these effects provides an overall interventional indirect effect quantifying the overall impact of the sequential intervention (\(\text{IIE}_{\text{seq}}\)) and is equal to:

\[
\text{IIE}_{\text{seq}} = p_{\text{trt}} - p_{(K)}
\]

The TCE may then be decomposed as:

\[
\text{TCE} = \text{IDE} + \text{IIE}_{\text{seq}} + \text{IIE}_{\text{int}}
\]

where \(\text{IIE}_{\text{int}}\) is another type of interventional indirect effect via the mediators’ interdependence, which contrasts the benefit of the aforementioned joint intervention with the benefit of the sequential intervention:

\[
\text{IIE}_{\text{int}} = (p_{\text{trt}} - p_{\text{all}}) - \text{IIE}_{\text{seq}} = p_{(K)} - p_{\text{all}}
\]

This effect thus answers a more relevant question than \(\text{IIE}_{\text{int}}\). Further, the expression after the second equality makes it clear that this effect captures what one would intuitively conceive as the effect via the overall interdependence between the mediators (contrasting the expected outcome under a shift in the joint mediator distribution to that when independent shifts are
made for each mediator). In contrast, while the IIEn int captures an effect via the mediators’ interdependence, it does so mediator by mediator in a way that is harder to interpret.

**IDENTIFICATION AND ESTIMATION**

Let \( M_{ka} \) be the status of \( M_k \) when \( A \) is set to \( a \) and \( Y_{am_1…m_K} \) be the outcome when setting \( A \) to \( a \), \( M_1 \) to \( m_1 \), ..., \( M_K \) to \( m_K \), for \( a = 0,1 \) and \( k = 1, ..., K \). Under a causal structure like that in Figure 1 but extended to \( K \) mediators, the effects defined above can be emulated using observational data under standard assumptions of positivity, consistency (i.e. \( Y_{am_1…m_K} = Y \) when \( A = a, M_1 = m_1, ..., M_K = m_K \) and \( M_{ka} = M_k \) when \( A = a \)) and unconfoundedness of the different effects given the pre-exposure confounders \( C \), similar to those of Vansteelandt and Daniel [21]:

(i) \( Y_{am_1…m_K} \perp A|C \)

(ii) \( Y_{am_1…m_K} \perp (M_1, ..., M_K)|C, A = a \)

(iii) \((M_{1a}, ..., M_{Ka}) \perp A|C \)

For instance, \( \text{IIE}_k \) can be expressed in terms of potential outcomes as follows

\[
\text{IIE}_k = E \left[ \sum_{m=(m_1, ..., m_K)} E(Y_{1m_1…m_K}|C = c) \right.
\]

\[
\times \left\{ P(M_{-1} = m|C = c) - P(M_{k0} = m_k|C = c) \times P(M_{(-k)1} = m_{(-k)}|C = c) \right\} \]

where the outer expectation is over the distribution of \( C; M_{a} = (M_{1a}, ..., M_{Ka}); \) and \( M_{(-k)a} \) is equal to \( M_a \) without the \( k \)th component, for \( a = 0,1 \) and \( k = 1, ..., K \). Denote the observed counterparts of these vectors by \( M_{i} = (M_{1}, ..., M_{K}) \) and \( M_{(-k)} \), respectively. Under the above assumptions, \( \text{IIE}_k \) can be expressed in terms of observed data as follows:
\[
IIE_k = E \left[ \sum_{m=(m_1, \ldots, m_K)} E(Y|A = 1, M_1 = m_1, \ldots, M_K = m_K, C = c) \times \left\{ P(M. = m|A = 1, C = c) - P(M_K = m_k|A = 0, C = c) \times P(M_{(-k)} = m_{(-k)}|A = 1, C = c) \right\} \right]
\]

Similarly, the IDE is expressed as

\[
IDE = E \left[ \sum_{m=(m_1, \ldots, m_K)} \left\{ E(Y_1 m_1 \ldots m_K|C = c) - E(Y_0 m_1 \ldots m_K|C = c) \right\} \times P(M. = m|C = c) \right]
\]

which under the assumptions is equal to:

\[
IDE = E \left[ \sum_{m=(m_1, m_2, m_3, m_4)} \left\{ E(Y|A = 1, M_1 = m_1, \ldots, M_K = m_K, C = c) - E(Y|A = 0, M_1 = m_1, \ldots, M_K = m_K, C = c) \right\} \times P(M. = m|A = 0, C = c) \right]
\]

Identification can be shown in a similar fashion for the other effects described above.

Estimation can be performed using a Monte Carlo simulation-based g-computation approach as described by Vansteelandt and Daniel [21] (see eAppendix). Example R code for implementing the method, including a worked example on simulated data, can be accessed at the first author's GitHub repository (https://github.com/moreno-betancur/medRCT).

**SELF-HARM EXAMPLE**

**Preliminary analyses**

We applied the proposed method to the self-harm example. Descriptive statistics for all variables are provided in Table 1, based on the 1786 participants (out of 1943 in the cohort study) with the adolescent self-harm exposure available. As all other analysis variables had missing data, subsequent analyses were based on multiple imputation using 40 imputations (see eAppendix for details). Table 2 shows preliminary estimates of unadjusted and
regression-adjusted exposure-outcome, exposure-mediator and mediator-outcome associations, obtained using main-effects multivariable logistic regression models. These provide an idea of the strength of the hypothesized pathways in Figure 1 for this example.

**Plausibility of assumptions**

We selected a rich set of putative pre-exposure confounders to make exchangeability plausible. The consistency assumption relies on the possibility of identifying the exposure with a well-defined intervention that would set the self-harm status of an individual. However, with the main goal being to evaluate mediator interventions to assess their potential for reducing disparities between the two exposure groups, it can be argued that application of the proposed method remains meaningful regardless of the existence of such an intervention, as others have proposed in related settings [24,26,37]. On the other hand, the question of well-defined interventions for the mediators is tackled by considering shifts in the mediator distributions rather than individual-level interventions, with the proposed interpretation focusing on the relatively modest goal of learning about intervention targets that could be the focus of future actual interventions.

**Implementation of estimation method**

The estimation procedure (see eAppendix) was implemented in R [38] using logistic regression for all the required models, with model complexity limited to all two-way interactions. We conducted 200 simulations and standard errors were obtained using 1000 nonparametric bootstrap samples under a “multiple imputation then bootstrap” approach. The latter is theoretically valid when estimators are normally distributed [39], which we both expected given that the effects are contrasts of means and verified via inspection of histograms of the bootstrap samples.

**Results of mediation analysis**

Table 3 shows the results. There was some evidence that adolescent self-harmers had an increased risk of financial hardship in adulthood compared to non-self-harmers: TCE=7.2% (95%CI: -1.7 to 16.1%). Shifting the joint distribution of the mediators in the self-harm group to be as under no self-harm would still leave 77% of the difference between the two groups remaining: IDE=5.6% (-3.1 to 14.3%). Under the one-policy premise, we estimated that the highest impact would be achieved by an intervention that would improve the rates of
university completion in adolescent self-harmers (IIE$_3$=0.9%; -1.3 to 3.2%). This corresponds to a 13% reduction in the between-group difference, with the remaining difference being IDE$_3$=TCE – IIE$_3$=6.3%. Other intervention targets have lower impact. The IIE$_{\text{int}}$ is negative, which might be expected as adding the individual intervention effects is likely to overestimate what can genuinely be achieved.

Considering the sequential application of these policies in the order $M_1$, $M_2$, $M_3$, $M_4$, we see that the overall sequence could, in principle, achieve an overall reduction of 27% of the total effect (IIE$_{\text{seq}}$=1.9%; -1.4 to 5.2%). This is decomposed into the effects of applying each policy on top of the previous ones in the sequence. Each of the effects from $M_2$ onwards is seen to be of slightly lower magnitude than when only one is applied (i.e. under the one-policy premise). The effect via the interdependence IIE$_{\text{int}}$ is negative like IIE$_{\text{int}}$, though of lesser magnitude. Although this effect has a clearer interpretation, it can still overestimate what can genuinely be achieved since the sequential policy regime we consider assumes that the individual policies have no benefits on the other mediators, which might not be the case when these are correlated.

**DISCUSSION**

Previous work described the randomized trials *implicitly* emulated by different versions of interventional effects that may be defined for multiple mediators [14]. In this work we define novel interventional effects *explicitly in terms of the target trial(s) one may wish to emulate, which is particularly appealing when the aim is mediator intervention evaluation. Our approach can be used to build an evidence base for the future design and evaluation of interventions. The self-harm example illustrated how our proposal can provide insights into which single intervention target is most promising as well as into the potential benefit of targeting multiple intermediates in a sequence.

It is of interest to contrast the proposed effects with natural effects in the special situation where the exposure is “separable” into components acting through distinct pathways [5,16,17], as it has been shown that the aforementioned cross-worlds independence assumption can be circumvented in that setting. Actually, in that situation natural effects emulate effects from a hypothetical experiment evaluating intervention regimes on the exposure components. This seems to capture our intuitive notion of mediation, although
assumptions regarding effect separability presume knowledge of the mechanisms of action of the exposure. This might be very poor in certain settings, or might be exactly what we are trying to discern in a mediation analysis. In settings like the self-harm example the relevance of the concept of treatment separability seems limited, not necessarily because of the difficulty in ascertaining separability but because the research question is not about interventions to change the self-harm status per se.

In contrast, interventional effects consider target trials with intervention regimes on the mediators. This could be seen as a general problem of static (i.e. predetermined) intervention regime evaluation, except that the unexposed group and ideas of mediation become relevant because they provide a benchmark for the emulated mediator shifts. As mentioned previously, having the unexposed group as a reference point is important in the “intervention targets” setting.

Importantly, we explicitly defined one target trial and a potential extension, under reasonable premises that would make sense in the context of the self-harm example. Grounding in an example is critical as the relevant target trial must reflect realistic conditions, so is inherently context-dependent. Nevertheless, the design of the target trial described for this example is likely to be of relevance in a range of settings. In other contexts it might be of interest to consider other target trials, or one could simply extend the target trial here by adding more trial arms. In this way, our proposal opens up a whole realm of possibilities for the definition and estimation of relevant mediation effects, tailored to each specific problem.

**Software implementation:** Example R code for implementing the method, including a worked example on simulated data, can be accessed at the first author's GitHub repository ([https://github.com/moreno-betancur/medRCT](https://github.com/moreno-betancur/medRCT)).
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**FIGURES**

Figure 1. Directed acyclic graph portraying the assumed causal structure, conceptualizing the pathways from adolescent self-harm to financial hardship, via the four mediators of interest. Dotted undirected arrows indicate where we are agnostic about the directionality of causal influences. Pre-exposure confounders and arrows from these are shown in grey to improve clarity.
Figure 2. Graphical depiction of arms in the “target trial” designed to examine the potential effects of interventions shifting the distributions of four interdependent mediators.
**Figure 3.** Extension of target trial to evaluate the effects of sequentially applying interventions shifting mediator distributions.
### Table 1. Descriptive statistics by exposure group in the self-harm example

|                      | Adolescent self-harm<sup>b</sup> | Missing (%)<sup>c</sup> |
|----------------------|----------------------------------|--------------------------|
|                      | No  | Yes |                  |
| Number<sup>a</sup>   | 1638| 148 |                  |
| Pre-exposure confounders |      |     |                  |
| Sex of participant: Female (%) | 846 (51.6) | 95 (64.2) | 0.0 |
| Parental divorce or separation (%) | 339 (20.7) | 45 (30.4) | 0.0 |
| Neither parent completed secondary school (%) | 515 (32.7) | 46 (33.3) | 4.1 |
| Adolescent depression or anxiety (%) | 495 (30.2) | 111 (75.0) | 0.0 |
| Adolescent weekly cannabis use (%) | 155 (9.5) | 41 (27.9) | 0.5 |
| Participant did not complete secondary school (%) | 232 (14.8) | 32 (23.2) | 4.6 |
| Mediators (at age 24 years) |      |     |                  |
| Depression or anxiety (%) | 263 (20.0) | 32 (26.0) | 19.6 |
| Weekly cannabis use (%) | 143 (10.9) | 25 (20.3) | 19.7 |
| No university degree (%) | 805 (61.3) | 96 (78.0) | 19.5 |
| Not in paid work (%) | 140 (10.6) | 22 (17.9) | 19.5 |
| Outcome (at age 35 years) |      |     |                  |
| Financial hardship | 258 (21.9) | 41 (38.3) | 28.0 |
| Any analysis variable missing (%) | 546 (33.3) | 47 (31.8) | 0 |

<sup>a</sup> The total number of participants in each exposure group

<sup>b</sup> Descriptive statistics for each characteristic are based on the records with available data for that variable in the given exposure group

<sup>c</sup> Proportion of missing data across both exposure groups for that variable
Table 2. Associations amongst exposure, outcome and mediators estimated using multivariable logistic regression models and multiple imputation (40 imputations)

| Associations                                                                 | Crude OR | 95% CI     | Adjusted OR | 95% CI    |
|------------------------------------------------------------------------------|----------|-------------|-------------|-----------|
| Exposure (adolescence) - Outcome (35yrs)                                     |          |             |             |           |
| Self-harm - Financial hardship                                               | 2.20     | (1.49; 3.25)| 1.56        | (1.01; 2.42) |
| Exposure (adolescence) - Mediators (24yrs)                                  |          |             |             |           |
| Self-harm - Depression or anxiety                                           | 1.46     | (0.96; 2.22)| 0.93        | (0.59; 1.45) |
| Self-harm - Weekly cannabis use                                             | 2.06     | (1.31; 3.23)| 1.29        | (0.76; 2.19) |
| Self-harm - No university degree                                            | 2.07     | (1.34; 3.20)| 1.56        | (0.95; 2.53) |
| Self-harm - Not in paid work                                                | 1.89     | (1.16; 3.08)| 1.42        | (0.84; 2.40) |
| Mediators (24yrs) - Outcome (35yrs)                                         |          |             |             |           |
| Depression or anxiety - Financial hardship                                   | 1.64     | (1.17; 2.30)| 1.37        | (0.96; 1.95) |
| Weekly cannabis use - Financial hardship                                     | 1.47     | (1.00; 2.16)| 1.34        | (0.87; 2.08) |
| No university degree - Financial hardship                                    | 2.97     | (2.16; 4.08)| 2.53        | (1.78; 3.59) |
| Not in paid work - Financial hardship                                        | 2.23     | (1.53; 3.26)| 1.77        | (1.18; 2.64) |

a Adjusted for pre-exposure confounders and, for mediators, the exposure
OR: Odds ratio
CI: Confidence Interval
Table 3. Estimates of proposed interventional mediation effects under the one-policy premise and under sequential policies, estimated using the Monte Carlo simulation-based g-computation approach (200 replications), along with the bootstrap (1000 runs) and multiple imputation (40 imputations)

| Effect                        | Estimate | 95% CI           | Proportion of TCE (%) |
|-------------------------------|----------|------------------|-----------------------|
| TCE                           | 0.072    | (-0.017; 0.161)  | 100                   |
| IDE                           | 0.056    | (-0.031; 0.143)  | 77                    |
| **Effects under one-policy premise** |          |                  |                       |
| IIE<sub>1</sub> (depression or anxiety) | 0.002    | (-0.015; 0.019)  | 3                     |
| IIE<sub>2</sub> (weekly cannabis use)   | 0.005    | (-0.011; 0.020)  | 7                     |
| IIE<sub>3</sub> (no university degree) | 0.009    | (-0.013; 0.032)  | 13                    |
| IIE<sub>4</sub> (not in paid work)    | 0.006    | (-0.011; 0.023)  | 9                     |
| IIE<sub>int</sub> (mediators’ interdependence) | -0.006   | (-0.021; 0.009)  | -8                    |
| **Effects under sequential policies** |          |                  |                       |
| IIE<sub>seq</sub> (full sequence)     | 0.019    | (-0.014; 0.052)  | 27                    |
| IIE<sub>1</sub> (depression or anxiety) | 0.002    | (-0.015; 0.019)  | 3                     |
| IIE<sub>2</sub> (weekly cannabis use)   | 0.004    | (-0.010; 0.018)  | 5                     |
| IIE<sub>3</sub> (no university degree) | 0.009    | (-0.012; 0.030)  | 12                    |
| IIE<sub>4</sub> (not in paid work)    | 0.005    | (-0.010; 0.020)  | 7                     |
| IIE<sub>int</sub> (mediators’ interdependence) | -0.003   | (-0.008; 0.002)  | -4                    |

TCE: Total Causal Effect  
IDE: Interventional Direct Effect  
IIE: Interventional Indirect Effect  
CI: Confidence Interval
APPENDIX

This appendix contains further details supplementing the main text of the paper. The contents are as follows:

- Study design, participants and ethics approval in the Victorian Adolescent Health Cohort Study.
- Measures of relevance for the self-harm example in the Victorian Adolescent Health Cohort Study.
- Description of Monte Carlo simulation-based g-computation estimation method.
- Implementation of multiple imputation in the analysis of the self-harm example.

Notation and terminology are as defined in the main text.

Study design, participants and ethics in the Victorian Adolescent Health Cohort Study

The Victorian Adolescent Health Cohort Study is a 10-wave longitudinal cohort study of health across adolescence to the fourth decade of life in the state of Victoria, Australia, conducted between August 1992 and March 2014. At baseline, a representative sample of mid-secondary school adolescents was selected with a two-stage cluster sampling procedure. At stage one, 45 schools were chosen at random from a stratified frame of government, Catholic, and independent schools, with a probability proportional to the number of Year 9 (aged 14–15 years) students in the schools in each stratum. At stage two, one single intact class was selected at random from each participating school in the latter part of the ninth school year (wave 1), and a second class from each school was selected 6 months later (wave 2). One school did not continue beyond wave 1, causing a loss of 13 participants and leaving 44 schools in the study. Participants were reviewed at four 6-month intervals between the ages of 15–18 years (waves 3–6) with four follow-up waves in adulthood, ages 20–21 years (wave 7), 24–25 years (wave 8), 28–29 years (wave 9), and 34–35 years (wave 10).

Data collection protocols were approved by the Ethics in Human Research Committee of the Royal Children’s Hospital, Melbourne. Informed parental consent was obtained before inclusion in the study. In the adult phase, all participants were informed of the study in writing and gave verbal consent before being interviewed.
Measures in the Victorian Adolescent Health Cohort Study

Exposure ($A$): Adolescent self-harm was assessed at each of waves 3 to 6 using the following question: “In the last [reference period] have you ever deliberately hurt yourself or done anything that you knew might have harmed you or even killed you?” The reference period was 1 year for wave 3 and 6 months for waves 4 to 6. Participants who responded positively to the main question were then asked to describe the nature and timing of each self-harm event. These detailed responses were coded into five subtypes of self-harm (by the study’s principal investigator, confirmed by a co-investigator: cutting or burning, self-poisoning, deliberate and potentially life-threatening risk-taking, self-battery, and other (including attempted self-drowning, hanging, intentional electrocution and suffocating). Participants were classified at each wave with “any self-harm” if they were identified to have reported one or more of these individual categories. A summary measure across adolescence was used in analyses, defined as any occurrence in waves 3–6, with a negative value assumed when all wave-specific measures were either negative or missing. We define $A = a$ if self-harm was present according to this summary measure and $A = a^*$ otherwise.

Outcome ($Y$): At age 35 years (wave 10), the outcome measure of financial hardship was assessed via a positive response to one or more of the following: [“Over the past 12 months, due to a shortage of money, you..”] 1) have been unable to pay gas, electricity, or telephone bills on time; 2) have been unable to pay mortgage or rent on time; 3) could not afford a night out once a fortnight; and/or 4) could not afford a holiday away for at least 1 week a year. We define $Y = 1$ if financial hardship was present and $Y = 0$ otherwise.

Mediators ($M_1, M_2, M_3, M_4$): Potential mediating factors, measured at age 24 (wave 8), were depression and/or anxiety ($M_1$), weekly or more frequent cannabis use over the past year ($M_2$), not having completed a university degree ($M_3$), and not being in paid work ($M_4$). At wave 8, symptoms of depression and anxiety were assessed with the 12-item General Health Questionnaire (“GHQ-12”), an extensively used screen for psychological disorders in general health care, dichotomised at the cut-off point of 3 or above to indicate a level of distress appropriate for clinical intervention. We defined $M_k = 1$ if the mediator is present and $M_k = 0$ if it is absent.
Pre-exposure confounders ($C$): These were selected on an a priori basis considering potential confounders of the exposure-mediator, mediator-outcome and exposure-outcome associations. We selected: participant sex, parental completion of high school, parental divorce or separation up to and including wave 6, and adolescent antecedents of the mediators where present, specifically participant completion of high school, adolescent depression and/or anxiety and cannabis use (weekly or more frequent). The latter two were summarised across waves 3-6 in the same way as the exposure. Symptoms of depression and anxiety were assessed using the revised Clinical Interview Schedule (“CIS-R”). The total scores on this scale were dichotomised at a cut-off point of 11 ($\leq 11$ vs $>11$) to delineate a mixed depression-anxiety state, at a lower threshold than syndromes of major depression and anxiety disorder but for which clinical intervention would still be appropriate.

Description of estimation method

As mentioned in the main text, estimation of the proposed effects can be conducted using a Monte Carlo simulation-based g-computation approach as described in Vansteelandt and Daniel [21]. It relies on the factorization of joint mediator distributions as the sequential product of conditional distributions. The procedure is described next and in each step we exemplify what it entails in the context of estimating the second term of $IIE_2$.

$$E[\sum_{m_1=m_1}^{m_K} E(Y | A = 1, M_1 = m_1, \ldots, M_K = m_K, C = c) \times P(M_2 = m_2 | A = 0, C = c) \times P(M_{(-2)} = m_{(-2)} | A = 1, C = c)].$$

Step 1. Fit regression models to the observed data to estimate the required distributions. In the example of the second term of $IIE_2$, these are $P(M_2 = m_2 | A, C = c)$, $P(M_1 = m_1 | A, C = c)$, $P(M_3 = m_3 | M_1, A, C = c)$, $\ldots$, $P(M_K = m_K | M_1, M_3, \ldots, M_{K-1}, A, C = c)$ and $E(Y | A, M_1, \ldots, M_K, C = c)$. All these models should include as many higher-order interactions amongst exposure and mediators as supported by the data.

Step 2. For each individual, sequentially draw mediator values from the fitted distributions, given their covariate vector $c$, the relevant exposure value (in the example, $A = 0$ for $M_2$, $A = 1$ for other mediators) and draws of previous mediators as required (in the example, required from $M_3$ onwards).
Step 3. Using the fitted outcome model, for each individual predict the outcome given their covariate vector $c$, the relevant exposure value (in the example, $A = 1$) and the mediator draws.

Step 4. Repeat steps 1 to 3 a large number of times and average the outcome predictions across the whole sample and these repetitions to obtain an estimate of the required term.

Steps 1 to 4 are a way of estimating a weighted average, where the weights reflect the required population-level intervention on the joint distribution of the mediators [14]. The estimated terms are then added or subtracted to obtain the required contrast i.e. effect estimate. The nonparametric bootstrap can be used to obtain standard errors, confidence intervals and p-values.

**Implementation of multiple implementation in self-harm example**

A multiple imputation approach, described next, was used to handle missing data for both the preliminary analyses of associations and the mediation analyses in the self-harm example.

Multiple imputation by chained equations [40] was used with 40 imputations and a logistic regression imputation model for each variable including all analysis variables, three auxiliary background variables associated in the sample with incomplete participation (school region on entry to study, at least one parent smokes cigarettes most days, no parent drinks alcohol most days), relevant auxiliary variables from the preceding wave (e.g. wave 7 mental health to impute wave 8 mental health), and all relevant interactions for the mediation analysis models as recommended [41]. The inclusion of auxiliary variables was intended to make the “missing at random” assumption more plausible, although we note that the missing at random assumption is a sufficient but not a necessary assumption for approximately unbiased estimation with multiple imputation [42].