# Mediation effects that emulate a target randomized trial
# *Evaluation of ill-defined interventions on multiple mediators*


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Joint work with Paul Moran, Denise Becker, Carolyn Coffey, George Patton, John B Carlin


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# Outline

- Motivating example and two challenges arising
- Proposed approach
- Results in the example
- Concluding remarks

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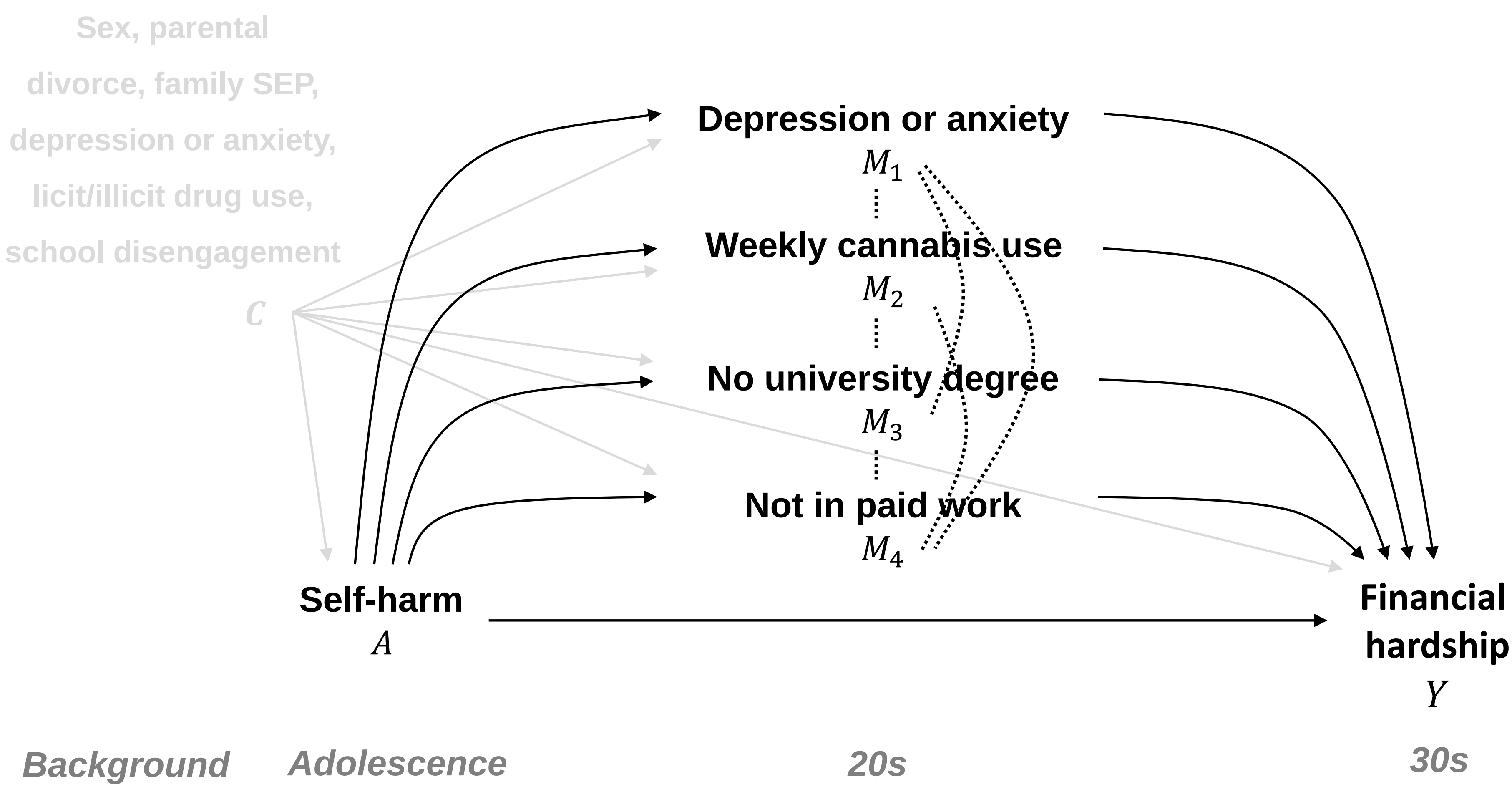
# Motivating example

Victorian Adolescent Health Cohort Study (VAHCS; n=1943, 20yr follow-up)
[Borschmann et al. 2017]

***"To what extent would mediator interventions alter the path from adolescent self-harm to poor psychosocial outcomes?"***



# Two methodological challenges

**Challenge 1: Causal mediation methods not adapted to address such questions**

**Challenge 2: Ill-defined mediator interventions**

# Causal mediation: what is the question?

1. Discovering causal mechanistic pathways ("**explanation**")
2. Evaluate impact of pathway interventions ("**intervention evaluation**")

**Is there a difference between these?**

| **Philosophically** | **Substantively** | **Methodologically** |
| --- | --- | --- |
| Can we conceive of causal mechanisms without interventions? | What is the translational intent of the mediation question? | Are different estimands suited to different types of question? |

Question 2 probably most feasibly and practically relevant but current methods not suited to multiple-mediator intervention questions

# Causal mediation estimands: overview

**Historical Baron-Kenny/SEM approaches**

- Model-based, estimand not clearly defined
- Interpretation and use unclear, strong causal and parametric assumptions

**Controlled direct effects** [Pearl 2001; VanderWeele 2011]

- Effect remaining after setting the mediator to be the same for everyone
- Unrealistic intervention and not amenable to multiple mediators

**Natural effects** [Robins and Greenland, 1992; Pearl 2001]

- Effects under individual-level interventions that could never be performed unless treatment is *separable* into components acting via distinct pathways [Robins & Richardson 2011; Didelez 2018; Aalen et al. 2019]
- Separability is rarely justified and extension to multiple mediators raises major complexities

# Causal mediation estimands: overview

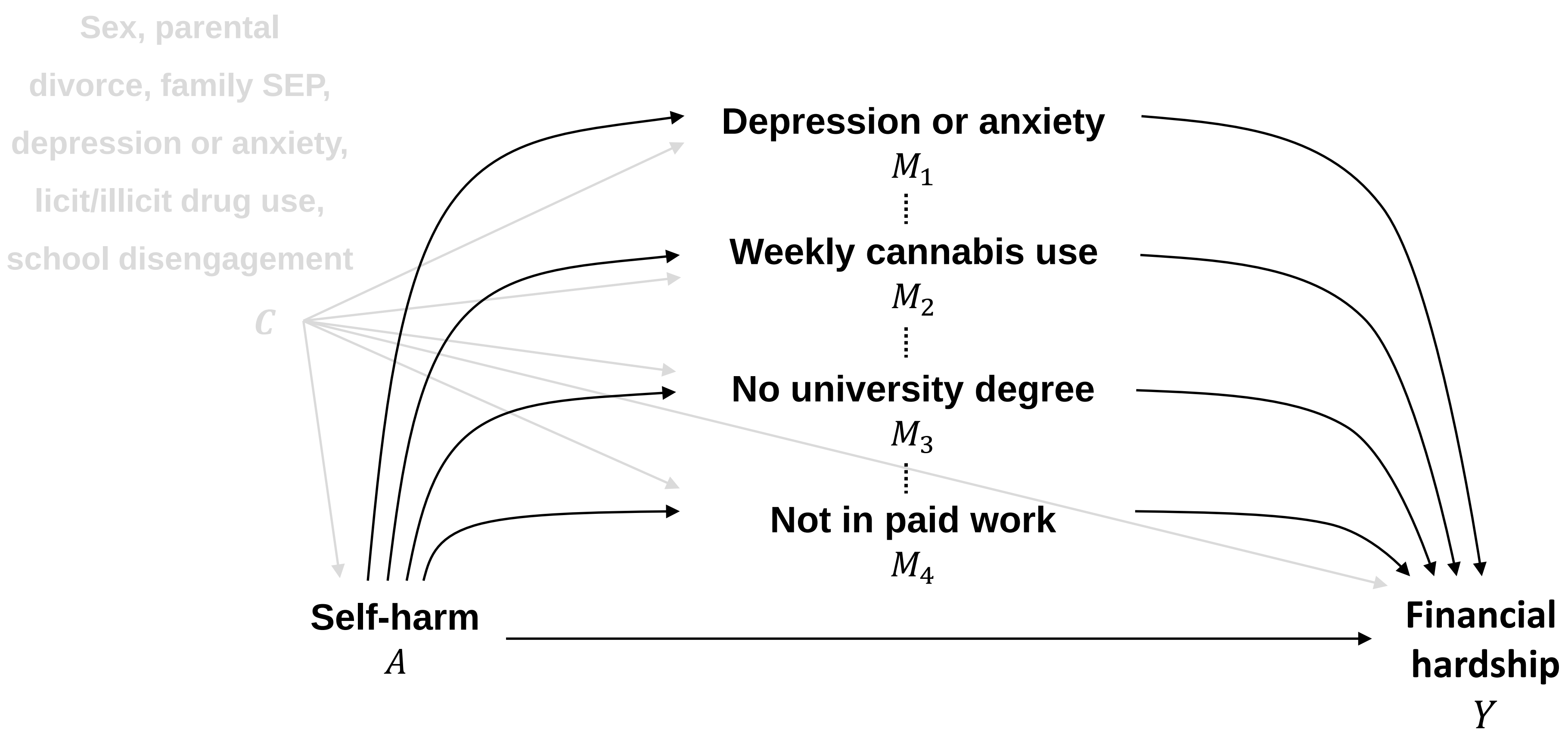
**Interventional effects** [Geneletti, 2007; Didelez et al, 2006; Zheng & van der Laan 2012; VanderWeele et al 2014; Lok 2015; Vansteelandt & Daniel 2017]

(a.k.a randomised interventional analogues, standardised/stochastic/organic effects)

- Effects implicitly emulate interventions that shift mediator distributions [Moreno-Betancur & Carlin 2018]
- Multiple mediators: several versions proposed

**Initial goal of this work:** To define mediation effects in explicit correspondence to a target trial that directly addresses relevant questions relating to mediator interventions

# Example policy-relevant question




If targeting only one mediator ("one-policy premise"), which of these separate interventions would provide the "biggest bang for the buck"?

# Two methodological challenges

**Challenge 1: Causal mediation methods not adapted to address such questions**

**Challenge 2: Ill-defined mediator interventions**

# Ill-defined interventions

- Intervention evaluation presupposes **well-defined interventions**, e.g. actual programs, policies, treatments

- Often there are no data on well-defined interventions also capturing the **populations**, **time-spans** and **outcomes** of interest
  - Self-harm example: Victorian population, 3 decades in the life-course, with outcomes 20 years after exposure

- "Exposure" data from long-term longitudinal cohort studies: only avenue to start addressing these complex questions, a first step to future intervention development

- Recent push for addressing, rather than shunning, the methodological challenge of ill-defined interventions [Galea & Hernan, AJE, 2019]

# Two scenarios

*Which mediator intervention would provide the "biggest bang for the buck"?*

Scenario 1: When **actual interventions** $B_k$ for $k = 1, \dots, K$ have been developed (e.g. a mental health care program targeted at adolescent self-harmers)

- Evaluate and compare effects in actual trials or with observational data by comparing self-harmers receiving and not receiving the interventions

$$E\left(Y_{B_k=1} | A = 1\right) - E\left(Y_{B_k=0} | A = 1\right), \; k = 1, \dots, K.$$

- Unexposed group and concept of mediation not relevant: we're done!

# Two scenarios

<u>Scenario 2:</u> When **no actual interventions** on mediators have been developed

- Simple approach: Estimate $E\left(Y_{M_k=1}|A=1\right) - E\left(Y_{M_k=0}|A=1\right)$

  Unsatisfactory because:
  - Potential outcomes $Y_{M_k=m_k}$ are ill-defined
  - Scenario $M_k = 0$ for all exposed (e.g. depression eliminated) is unrealistic as these conditions remain prevalent in the unexposed
  - Order of the mediators unknown, but needed for confounding adjustment

# Two scenarios

- Proposed approach:
  - o Explicitly acknowledge cannot inform actual interventions, but can inform “intervention targets” for future hypothetical interventions
  - o Conceptualise effect of hypothetical interventions by simulating the mediator distributional shifts that they might achieve
    - Amounts to setting mediators to random draws from distributions specified to reflect realistic benchmarks
  - o Unexposed group and concepts of mediation regain relevance: natural benchmark provided by levels in the unexposed

**Simulation of hypothetical interventions: need more assumptions, so a lower-level evidence than with well-defined interventions**
**→ as expected! [Galea & Hernan 2020]**

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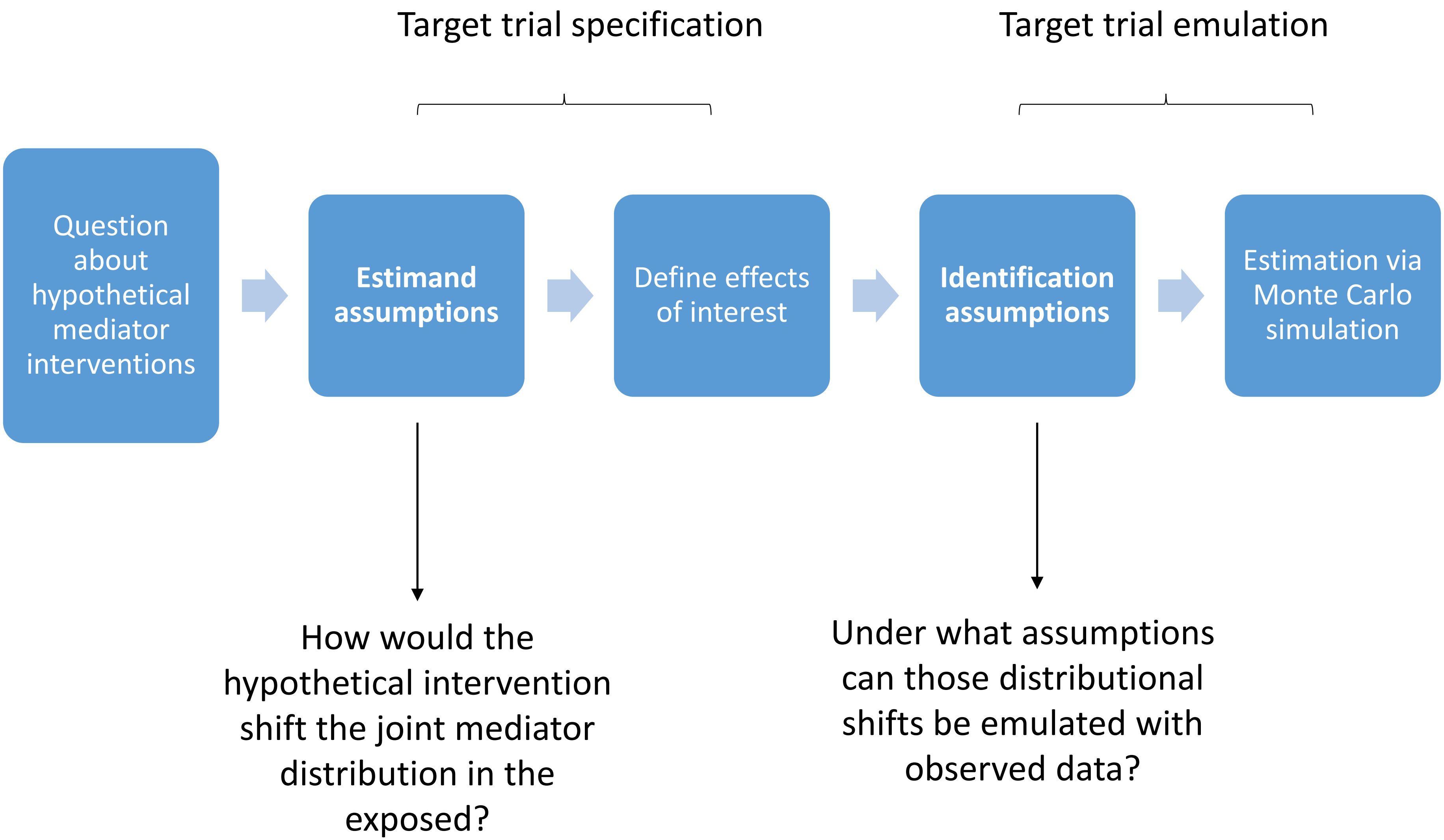
# Conceptual overview



# Notation

**Observed data**

- $A = 1$ if self-harm, $A = 0$ if not
- $M_k = 1$ if present, $M_k = 0$ if not ($k = 1, \ldots, 4$)
- $Y = 1$ if financial hardship, $Y = 0$ if not
- $\boldsymbol{C}$ : pre-exposure confounders

**Potential outcomes**

- $M_{ka}$ : status of $M_k$ if set $A = a$
- $Y_{ab}$: financial hardship if set $A = a$, $B = b$
- $\boldsymbol{M}_{\cdot a} = (M_{1a}, \ldots, M_{4a})$
- $\boldsymbol{M}_{(-k)a}$ : above vector without $k$th component

**Generic hypothetical intervention**

- $B = 1$ if received, $B = 0$ if not

# Self-harm example

**Questions about hypothetical mediator interventions**

- Question 1: Which mediator intervention would provide the “biggest bang for the buck”?
- Question 2: Remaining disparities between exposure groups if it were possible to jointly target all the mediators?
- Question 3: What would be the benefit of sequential policies, applying mediator interventions sequentially?

# Estimand assumptions

Shift in joint mediator distribution effected by hypothetical intervention in exposed

- Question 1: Which mediator intervention would provide the “biggest bang for the buck”?

$$B_k \text{ shifts to } P(M_{k0} = m_k|\boldsymbol{C}) \times P\left(\boldsymbol{M}_{(-k)1} = \boldsymbol{m}_{(-k)}|\boldsymbol{C}\right)$$

- Question 2: Remaining disparities between exposure groups if it were possible to jointly target all the mediators?

$$B_{all} \text{ shifts to } P(\boldsymbol{M}_{\cdot 0} = \boldsymbol{m}|\boldsymbol{C}).$$

- Question 3: What would be the benefit of sequential policies, applying mediator interventions sequentially?

$$B_{\{k\}} \text{ to } P(M_{10} = m_1|\boldsymbol{C}) \times \cdots \times P(M_{k0} = m_k|\boldsymbol{C}) \times P\left(\boldsymbol{M}_{(-1,\ldots,-k)1} = \boldsymbol{m}_{(-1,\ldots,-k)}|\boldsymbol{C}\right)$$

# Target trial for Questions 1 & 2

| | Arm | Exposure intervention | Hypothetical Intervention | Joint mediator distribution (given $C$) | Expected outcome |
|---|---|---|---|---|---|
| 1 | Unexposed group | $A = 0$ | | $M_{10}$ $M_{20}$ $M_{30}$ $M_{40}$ | $p_{ctr}$ |
| 2 | Exposed group | $A = 1$ | | $M_{11}$ $M_{21}$ $M_{31}$ $M_{41}$ | $p_{trt}$ |
| 3 | Exposed and shift $M_1$ distribution | $A = 1$ | $B_1 = 1$ | $M_{10}$ $M_{21}$ $M_{31}$ $M_{41}$ | $p_1$ |
| 4 | Exposed and shift $M_2$ distribution | $A = 1$ | $B_2 = 1$ | $M_{20}$ $M_{11}$ $M_{31}$ $M_{41}$ | $p_2$ |
| 5 | Exposed and shift $M_3$ distribution | $A = 1$ | $B_3 = 1$ | $M_{30}$ $M_{11}$ $M_{21}$ $M_{41}$ | $p_3$ |
| 6 | Exposed and shift $M_4$ distribution | $A = 1$ | $B_4 = 1$ | $M_{40}$ $M_{11}$ $M_{21}$ $M_{31}$ | $p_4$ |
| 7 | Exposed and shift joint distribution | $A = 1$ | $B_{all} = 1$ | $M_{10}$ $M_{20}$ $M_{30}$ $M_{40}$ | $p_{all}$ |

**Legend**

$X$ $W$ Joint distribution of $X$ & $W$ as in unexposed group (given $\boldsymbol{C}$)

$X$ $W$ Joint distribution of $X$ & $W$ as in exposed group (given $\boldsymbol{C}$)

$X$ $W$ $X$ & $W$ independent (given $\boldsymbol{C}$)

# Target trial for Questions 1 & 2

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| 7 | Exposed and shift joint distribution | $A = 1$ | $B_{all} = 1$ | $M_{10}$ $M_{20}$ $M_{30}$ $M_{40}$ | $p_{all}$ |

Standard 2-arm trial
Total causal effect (TCE)

**Legend**

$X$ $W$ Joint distribution of $X$ & $W$ as in unexposed group (given $\boldsymbol{C}$)

$X$ $W$ Joint distribution of $X$ & $W$ as in exposed group (given $\boldsymbol{C}$)

$X$ $W$ $X$ & $W$ independent (given $\boldsymbol{C}$)

# Effects Questions 1 & 2

- **Impact of intervention targeting mediator $\boldsymbol{k}$**
  *(a type of interventional indirect effect via mediator* $k$*)*

$$\mathrm{IIE}_k = p_{trt} - p_k$$

- **Remaining disparities if intervene on all mediators jointly**
  *(a type of interventional direct effect not via any mediator)*

$$\mathrm{IDE} = p_{all} - p_{ctr}$$

# Other effects and TCE decomposition

- **Effect remaining if after intervention on $\boldsymbol{M_k}$**
  *(a type of interventional direct effect)*

$$\mathrm{IDE}_k = p_k - p_{ctr}$$

- **Impact of joint intervention vs cumulative impact of individual interventions**
  *(a type of interventional indirect effect via the mediators' interdependence)*

$$\mathrm{IIE}_{\mathrm{int}} = (p_{trt} - p_{all}) - (\mathrm{IIE}_1 + \mathrm{IIE}_2 + \mathrm{IIE}_3 + \mathrm{IIE}_4)$$

  $\mathrm{IIE}_{\mathrm{int}}$ not nice interpretation (another version in two slides)

- **Decomposition of the total causal effect (TCE) based on these effects**

$$\mathrm{TCE} = p_{trt} - p_{ctr} = \mathrm{IDE} + \mathrm{IIE}_1 + \mathrm{IIE}_2 + \mathrm{IIE}_3 + \mathrm{IIE}_4 + \mathrm{IIE}_{\mathrm{int}}$$

# Target trial extension for Question 3

| | Arm | Exposure | Hypothetical Intervention | Joint mediator distribution (given $C$) | | | | Expected outcome |
|---|---|---|---|---|---|---|---|---|
| 8 | Exposed and<br>shift $M_1$ distribution<br>shift $M_2$ distribution | $A = 1$ | $B_{\{2\}} = 1$ | $M_{10}$ | $M_{20}$ | $M_{31}$ | $M_{41}$ | $p_{\{2\}}$ |
| 9 | Exposed and<br>shift $M_1$ distribution<br>shift $M_2$ distribution<br>shift $M_3$ distribution | $A = 1$ | $B_{\{3\}} = 1$ | $M_{10}$ | $M_{20}$ | $M_{30}$ | $M_{41}$ | $p_{\{3\}}$ |
| 10 | Exposed and<br>shift $M_1$ distribution<br>shift $M_2$ distribution<br>shift $M_3$ distribution<br>shift $M_4$ distribution | $A = 1$ | $B_{\{4\}} = 1$ | $M_{10}$ | $M_{20}$ | $M_{30}$ | $M_{40}$ | $p_{\{4\}}$ |

**Legend**

$X$ $W$ Joint distribution of $X$ & $W$ as in unexposed group (given $\boldsymbol{C}$)

$X$ $W$ Joint distribution of $X$ & $W$ as in exposed group (given $\boldsymbol{C}$)

$X$ $W$ $Z$ $X, W$ & $Z$ Independent (given $\boldsymbol{C}$)

# Effects Question 3: sequential policies

- **Effect of the $k$th intervention in the sequence & overall impact**
  *(other types of interventional indirect effects via mediator $k$ and overall)*

$$\mathrm{IIE}_{\{\mathrm{k}\}} = p_{\{k-1\}} - p_{\{k\}}$$

$$\mathrm{IIE}_{\{\mathrm{seq}\}} = p_{trt} - p_{\{K\}}$$

# Other effects and TCE decomposition

- **Impact of joint intervention vs sequential intervention**
  *(a nicer type of interventional indirect effect via the mediators' interdependence)*

$$\mathrm{IIE}_{\{\mathrm{int}\}} = (p_{trt} - p_{all}) - \left(\mathrm{IIE}_{\{\mathrm{seq}\}}\right) = p_{\{K\}} - p_{all}$$

- **Decomposition of the TCE based on effects for sequential policies**

$$\mathrm{TCE} = \mathrm{IDE} + \mathrm{IIE}_{\{\mathrm{seq}\}} + \mathrm{IIE}_{\{\mathrm{int}\}}$$

# Identification assumptions & estimation

- With confounders, all effects are averaged over empirical distribution of $\boldsymbol{C}$

- Identifiability assumptions ($B$ one of the hypothetical interventions)
  - [A0] Standard positivity assumptions
  - [A1] No causal effect of $B$ on the outcome other than through mediator shifts
  - [A2] All common causes of $A$, $B$, the mediators and the outcome (excluding $A$) are in $\boldsymbol{C}$
  - [A3] $Y_{ab} = Y$ when $A = a$ and $B = b$; $M_{ka} = M_k$ when $A = a$ for $k = 1, \dots, K$

  A1-A3 similar to those in VanderWeele & Hernan (2013)

  It is not possible to assess whether A1-A3 are plausible, except aspects not pertaining to $B$, which are like assumptions in Vansteelandt & Daniel (2017).

- Estimation possible via g-computation using Monte Carlo simulation

# Results for self-harm example

| 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** | | | | |
| $IIE_1$ | (depression or anxiety) | 0.002 | (-0.015; 0.019) | 3 |
| $IIE_2$ | (weekly cannabis use) | 0.005 | (-0.011; 0.020) | 7 |
| $IIE_3$ | (no university degree) | 0.009 | (-0.013; 0.032) | 13 |
| $IIE_4$ | (not in paid work) | 0.006 | (-0.011; 0.023) | 9 |
| $IIE_{int}$ | (mediators' interdependence) | -0.006 | (-0.021; 0.009) | -8 |
| **Effects under sequential policies** | | | | |
| $IIE_{\{seq\}}$ | (full sequence) | 0.019 | (-0.014; 0.052) | 27 |
| $IIE_{\{1\}}$ | (depression or anxiety) | 0.002 | (-0.015; 0.019) | 3 |
| $IIE_{\{2\}}$ | (weekly cannabis use) | 0.004 | (-0.010; 0.018) | 5 |
| $IIE_{\{3\}}$ | (no university degree) | 0.009 | (-0.012; 0.030) | 12 |
| $IIE_{\{4\}}$ | (not in paid work) | 0.005 | (-0.010; 0.020) | 7 |
| $IIE_{\{int\}}$ | (mediators' interdependence) | -0.003 | (-0.008; 0.002) | -4 |

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

Adjusted for pre-exposure confounders. Multiple imputation used for missing data.

# Summary

- Avoiding previous “axiomatic” definitions of mediation, we show that mediation interventional effects help tackle the pervasive issue of ill-defined interventions
- Novel definitions that explicitly emulate target trials of hypothetical interventions resulting in individualised mediator distributional shifts (i.e. given $\boldsymbol{C}$)
- Simulating hypothetical interventions is like an ‘in silico’ experiment. Relative to causal inference with well-defined interventions,
  - Addresses a more modest goal (inform ‘intervention targets’)
  - Relies on expanded assumptions

  →Lower-level evidence and increased subtlety in interpretation as expected

- Self-harm example showed one possible target trial, other options possible

Our proposal opens up a whole realm of possibilities for the definition and estimation of relevant effects, tailored to each specific problem

# Discussion

- Approach helps prioritise mediator intervention targets, not interventions that are well-defined. However, not necessary that a well-defined intervention on the exposure exists to get interpretable results [VanderWeele & Robinson 2014; Micali et al 2018; Jackson & VanderWeele 2018]

- Assumptions about causal ordering of mediators not needed for defining and identifying effects because estimand assumptions pertain to joint distribution and what the policy-maker's question is (e.g. which sequence of policies is of interest?)
    - Price to pay: Need unverifiable assumptions about correlation between the mediators under interventions which would differ from those in observed data

- Potential for parametric misspecification bias in estimation step: Sequential parametric regression approach which required a non-causal ordering to be chosen (although highly flexible regression models were used)

- Defining estimands is only first step of "target trial" approach, broader principles not considered here

# Thank you!

- Co-authors: Paul Moran, Denise Becker, Carolyn Coffey, George Patton, John B Carlin
- ARC DECRA
- ViCBiostat
- Collaborators across various cohort studies

# Thank you!

- Pre-print:

  Moreno-Betancur et al.” https://arxiv.org/abs/1907.06734

- Software:
  - R medRCT function: https://github.com/moreno-betancur/medRCT

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