# Causal mediation analysis with a binary outcome and multiple continuous/ordinal mediators

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(joint work with Yenny Webb-Vargas, Ina Koning and Elizabeth Stuart)

# Overview

- Background: causal vs. conventional approach to mediation
- The challenge: binary outcome + multiple mediators
- The proposed method
- Simulation results
- Application to an alcohol intervention study

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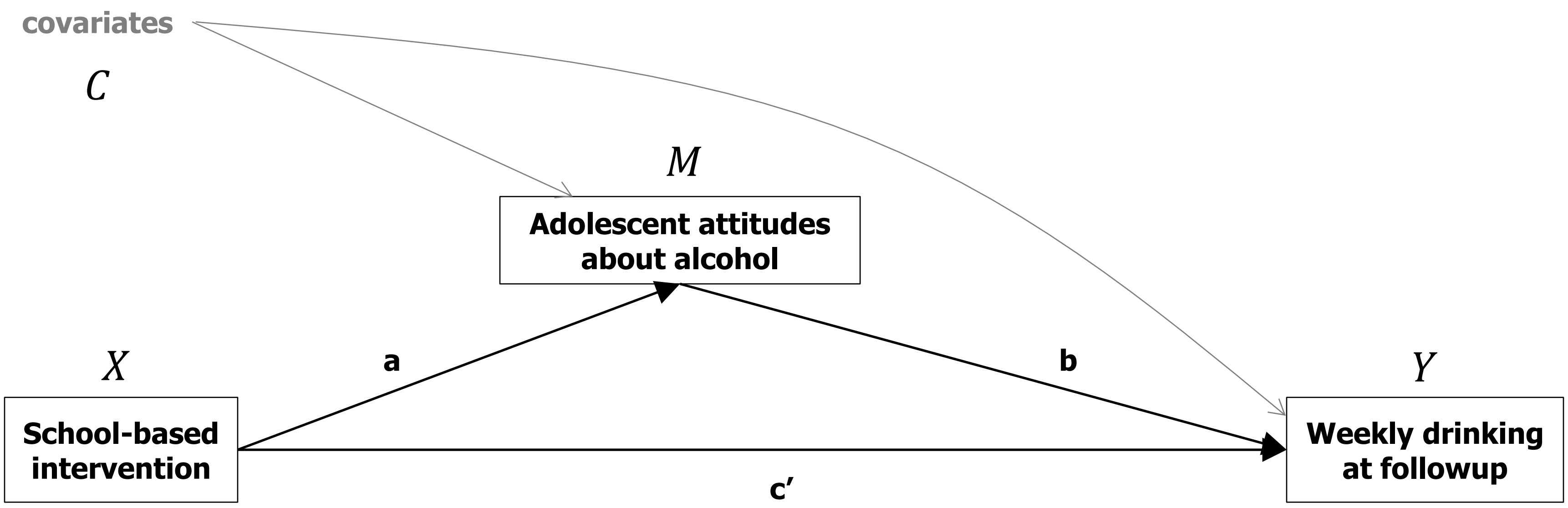
Usually, when considering mediation, we are interested in causation.

$$X \longrightarrow M \longrightarrow Y$$

# Conventional analysis: product of coefficients




Fit linear model.

Direct effect $= c'$, indirect effect $= ab$, total effect $= ab + c'$

Intepretation as <u>association</u>, i.e., difference in mean outcome between different people

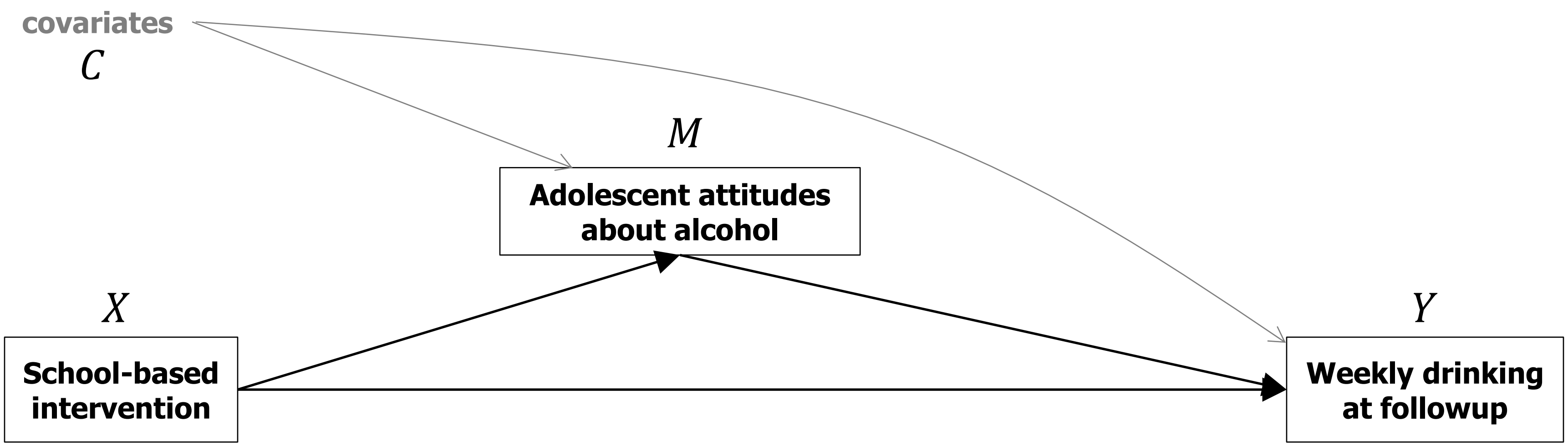
- Holding all covariates equal, on average students in the intervention arm had lower outcome than students in the control arm (TE).
- This difference consists of two parts: one explained by the intermediate variable (IE), the other not (DE).

Association $\neq$ Causation

How can we make the leap from association to causation?

First step: Define what we mean by causal effects.

# Mediation effect causally defined




**Causal effects on the individual** (adolescent $i$):

Potential outcomes $Y_i(1)$, $Y_i(0)$ and potential mediator levels $M_i(1)$, $M_i(0)$

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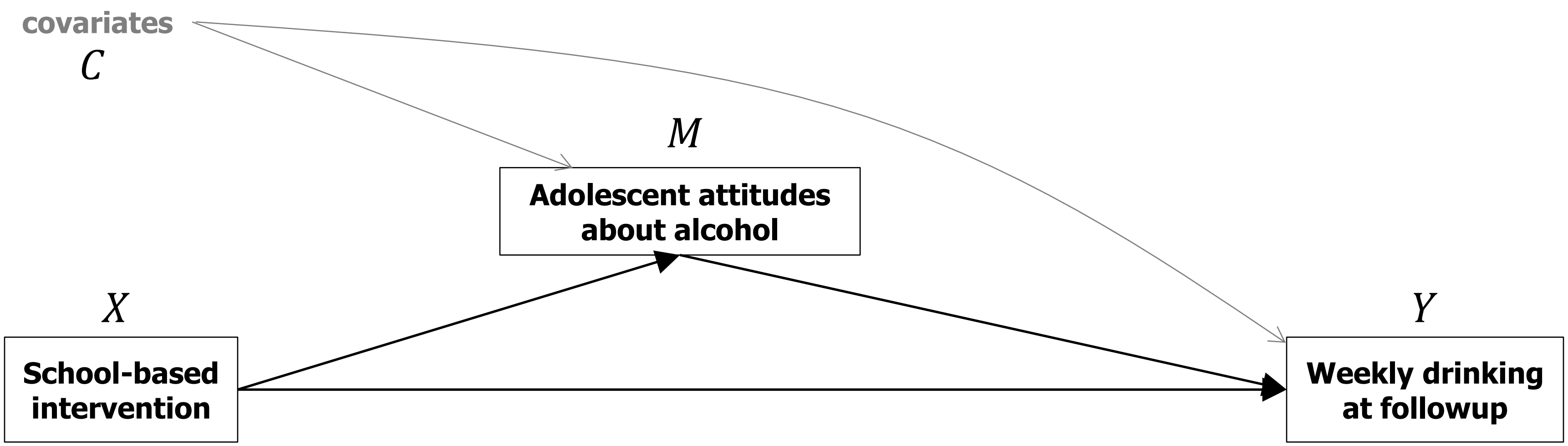


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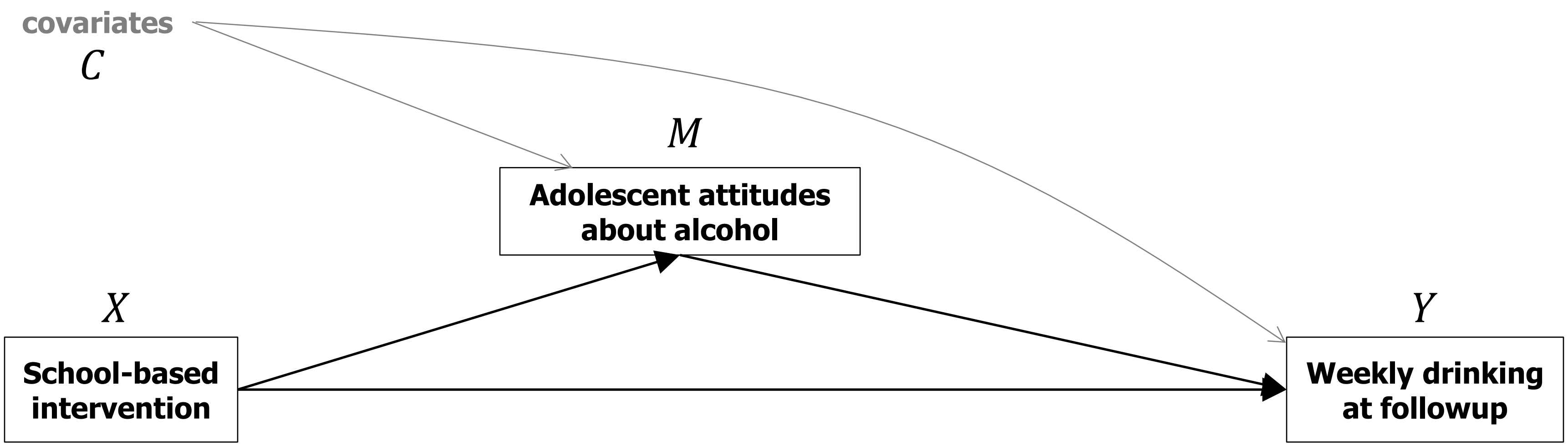
Potential outcomes $Y_i(1)$, $Y_i(0)$ and potential mediator levels $M_i(1)$, $M_i(0)$

Intervention effect: $Y_i(1) - Y_i(0) \rightarrow$ **total effect**

# Mediation effect causally defined

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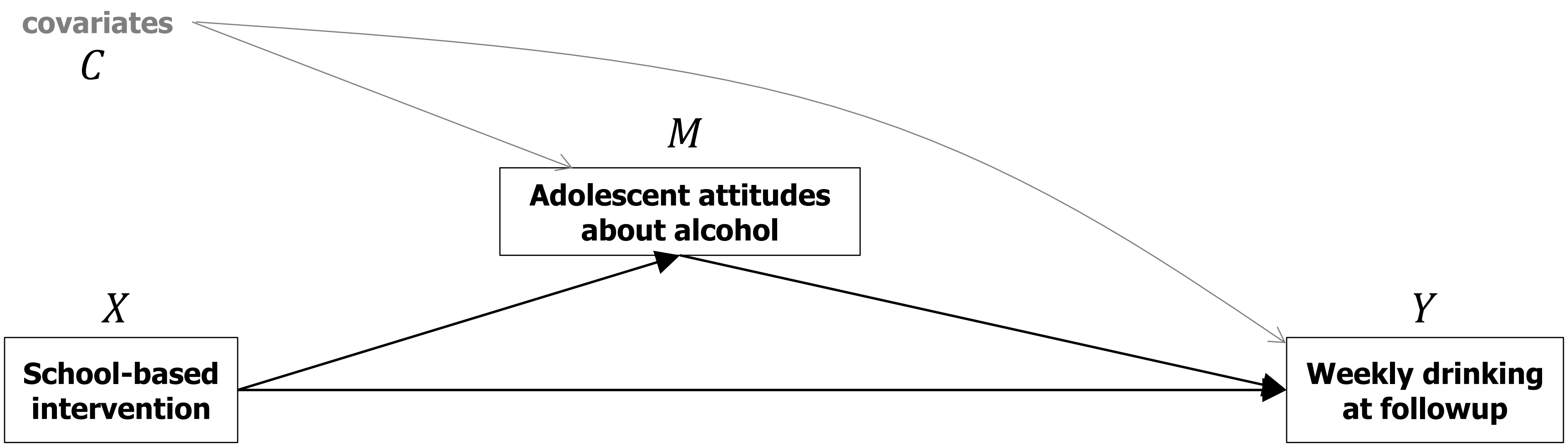


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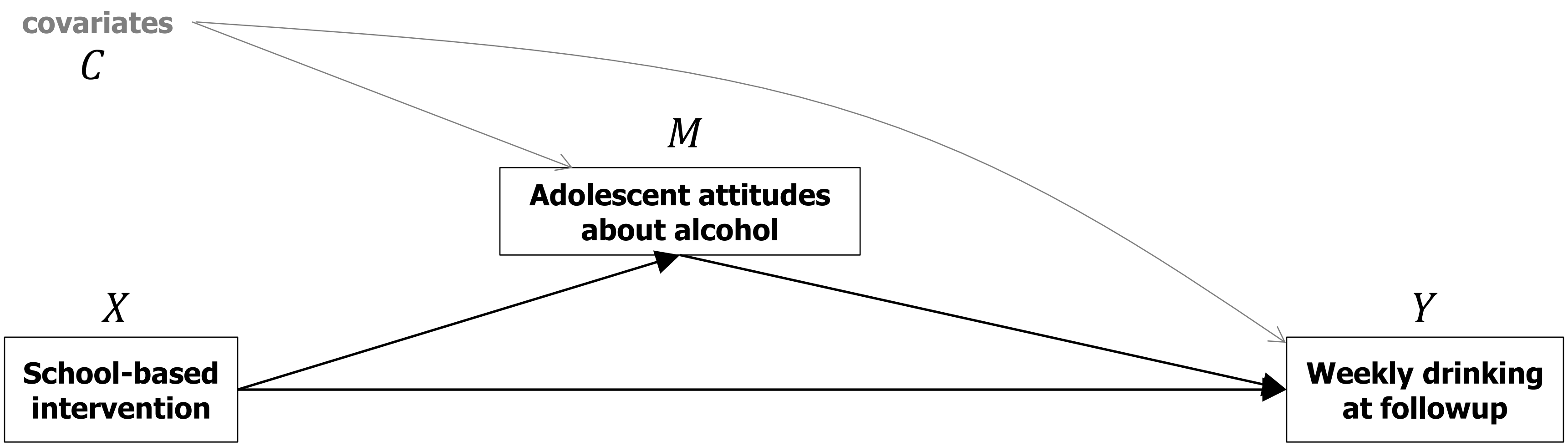
**Natural direct effect** and **natural indirect effect**:

NDE = effect fixing the mediator at natural level under one intervention condition

e.g., $Y_i\big(1, M_i(0)\big) - Y_i\big(0, M_i(0)\big)$

# Mediation effect causally defined

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**Natural direct effect** and **natural indirect effect**:

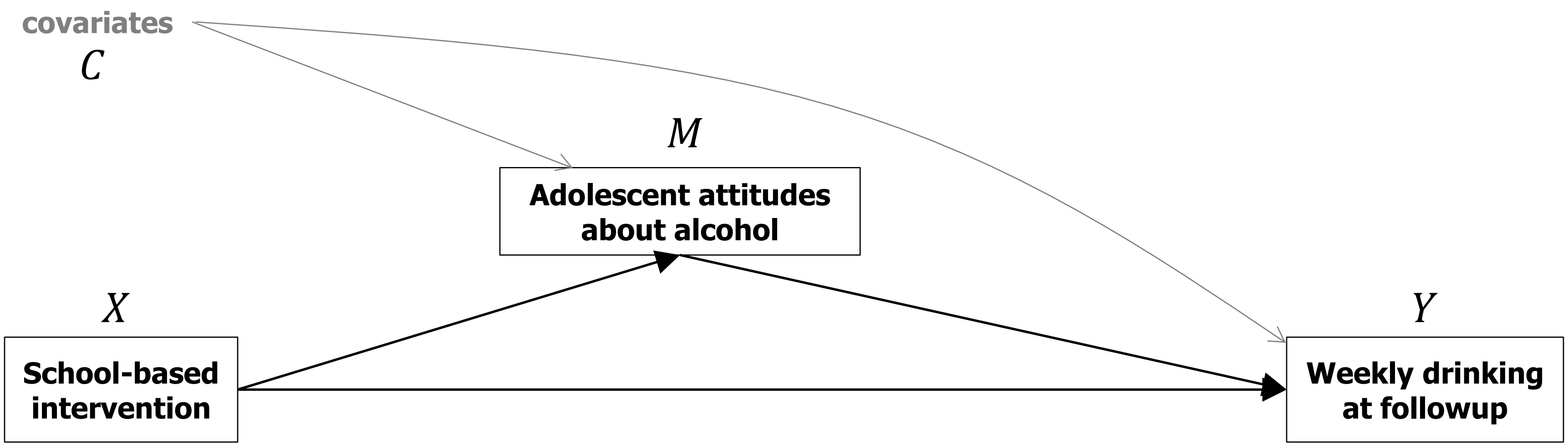
NDE = effect fixing the mediator at natural level under one intervention condition

$$\text{e.g., } Y_i\big(1, M_i(0)\big) - Y_i\big(0, M_i(0)\big)$$

NIE = effect due to switching mediator level but fixing intervention condition

$$\text{e.g., } Y_i\big(1, M_i(1)\big) - Y_i\big(1, M_i(0)\big)$$

# Mediation effect causally defined




**<u>Causal effects on the group/population</u>**

TE: $\mathrm{E}[Y(1)] - \mathrm{E}[Y(0)] =$
$\mathrm{E}[Y(1, M(1))] - \mathrm{E}[Y(0, M(0))]$

NDE: $\mathrm{E}[Y(1, M(0))] - \mathrm{E}[Y(0, M(0))]$

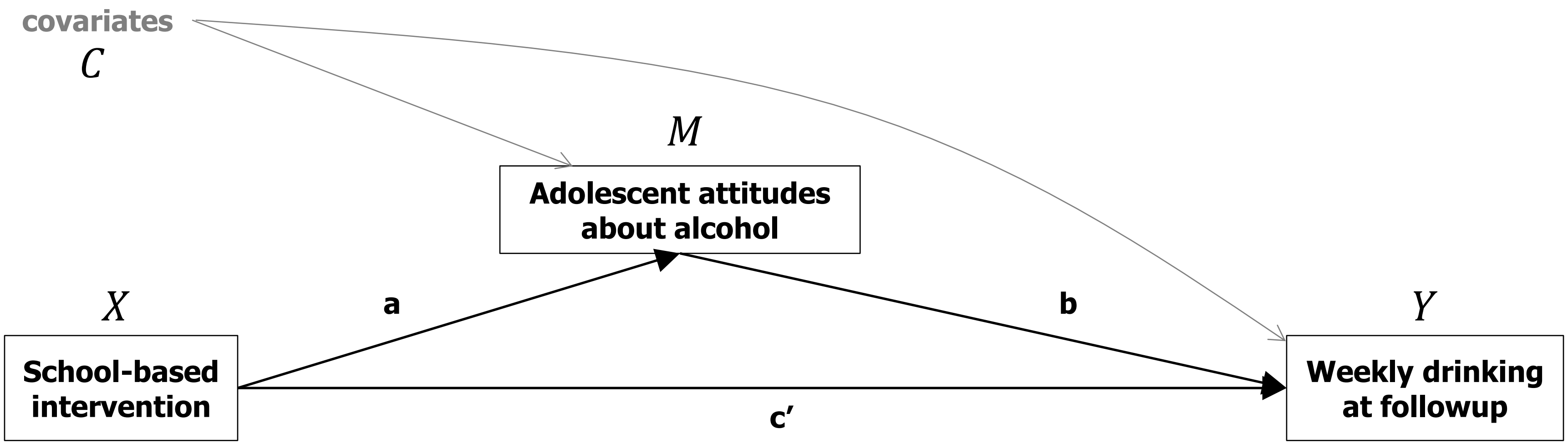
NIE: $\mathrm{E}[Y(1, M(1))] - \mathrm{E}[Y(1, M(0))]$

This refers to the whole group/population being under one condition versus another.

When the system is linear (and all confounding is controlled), NIE and NDE match effects from conventional analysis.

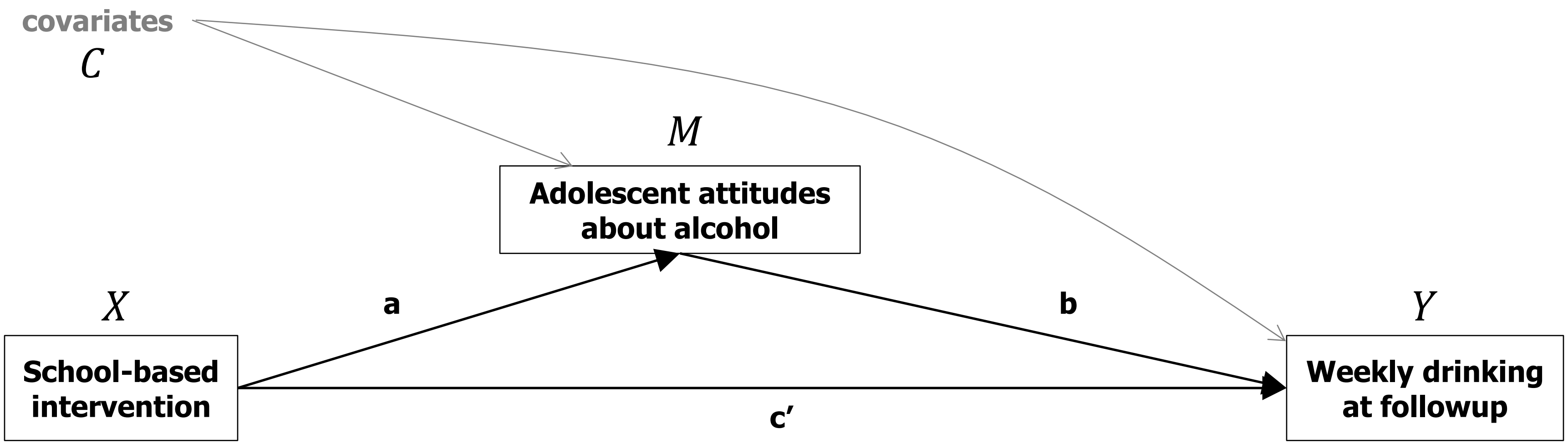
With non-linearity (e.g., binary outcome, interaction), they do not match.

# Binary outcome




Conventional approach: if probit/logit model to reflect non-linearity, effects reflect differences in the means of a latent continuous variable underlying the outcome.

# Binary outcome




Conventional approach: if probit/logit model to reflect non-linearity, effects reflect differences in the means of a latent continuous variable underlying the outcome.

Causal approach: TE, NDE and NIE are expressed using a measure of effect for a binary outcome, e.g., risk differences or risk ratios

Potential outcome probabilities

(potential prevalence of weekly drinking)

$$p_{11} = \mathrm{P}\big[Y\big(1, M(1)\big) = 1\big]$$

$$p_{00} = \mathrm{P}\big[Y\big(0, M(0)\big) = 1\big]$$

$$p_{10} = \mathrm{P}\big[Y\big(1, M(0)\big) = 1\big]$$

Causal effects

(reduction in weekly drinking prevalence)

TE $= p_{11} - p_{00}$ or $p_{11}/p_{00}$

NDE $= p_{10} - p_{00}$ or $p_{10}/p_{00}$

NIE $= p_{11} - p_{10}$ or $p_{11}/p_{10}$

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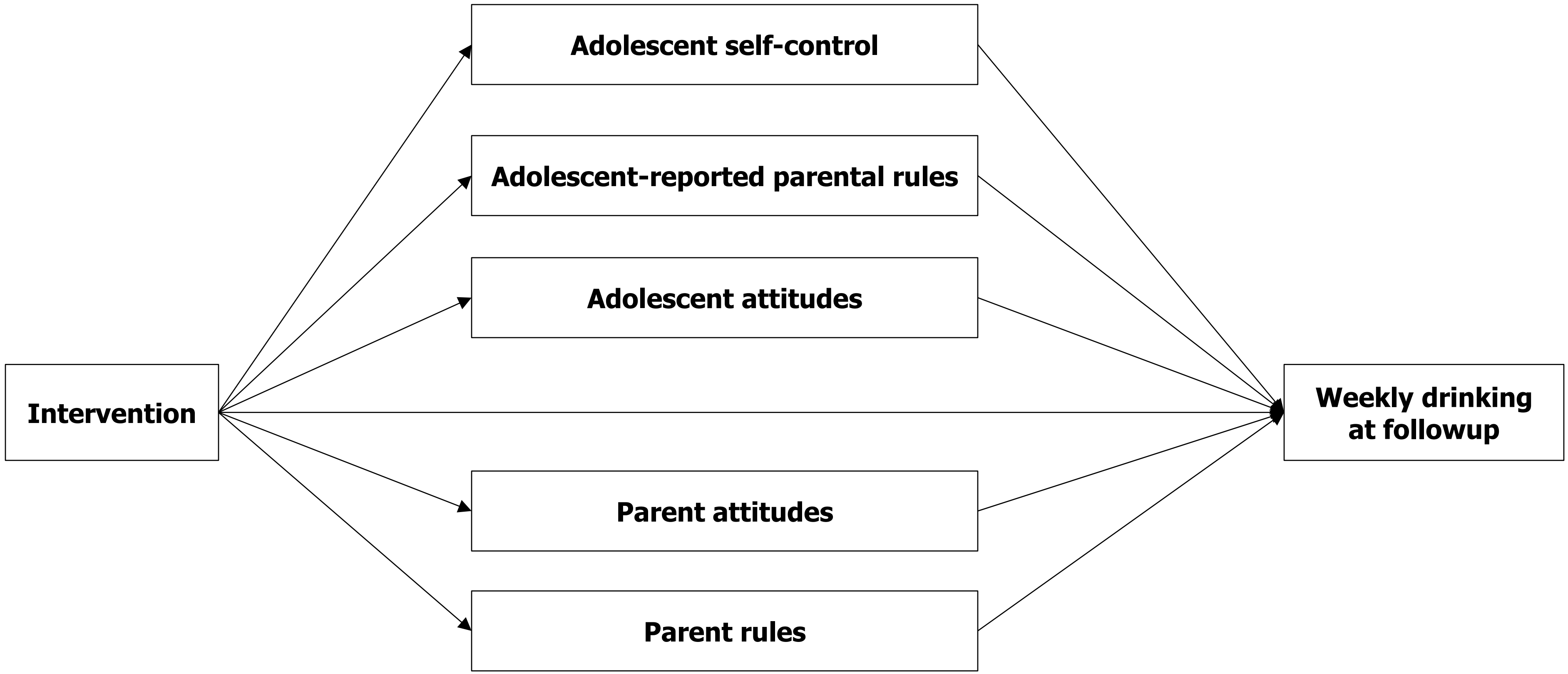
The causal mediation literature was focused on the single mediator case.

However, we are often faced with multiple mediators.

We may be interested in:

- path specific effects
- combined mediation effect of the multiple mediators

# Motivating example: Parent-and-student (PAS) intervention to reduce adolescent drinking, in the Netherlands



# Overview

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Would like to

- Estimate/predict $p_{11}$, $p_{00}$, $p_{10}$ (for the whole sample)
- Use those to compute TE, NDE, NIE

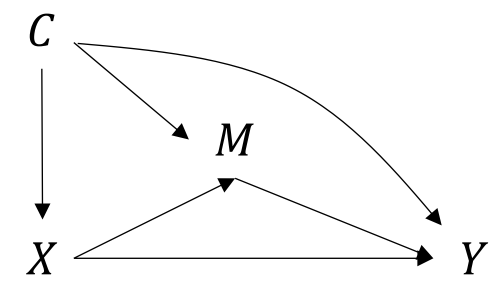
| | | | |
|---|---|---|---|
| $X = 1$ | $Y(1, M(1))$ | $Y(0, M(0))$ | $Y(1, M(0))$ |
| $X = 0$ | $Y(1, M(1))$ | $Y(0, M(0))$ | $Y(1, M(0))$ |

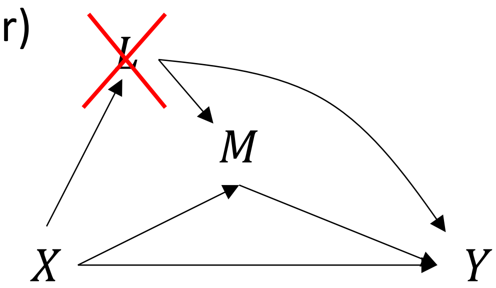
Need assumptions

and need to be clear about the assumptions

# Assumptions of the proposed method

- The usual identifying assumptions
  - No unmeasured exposure-outcome confounding
  - No unmeasured exposure-mediator confounding
  - No unmeasured mediator-outcome confounding
  - No mediator-outcome confounder influenced by exposure (but ok for the mediators in the set to influence one another)




- Method-specific assumptions:
  - Multivariate normal/probit model for the potential mediators
  - Probit model for the potential outcomes
  - No mediator-mediator interaction (exposure-mediator interaction is ok)

# How the method works

## Example with 2 continuous mediators $M_1, M_2$, 1 covariate $C$, and no $X$-$M$ interaction

(method accommodates more $M$s & $C$s, ordinal $M$s, and $X$-$M$ interaction)

# How the method works

## Example with 2 continuous mediators $M_1, M_2$, 1 covariate $C$, and no $X$-$M$ interaction

Assume that the model for the potential mediators is linear with multivariate normal errors

$$M_1(x) = \mu_1 + \alpha_1 x + \lambda_1 C + \epsilon_{M_1}$$
$$M_2(x) = \mu_2 + \alpha_2 x + \lambda_2 C + \epsilon_{M_2}$$

$$\binom{\epsilon_{M\,1}}{\epsilon_{M\,2}} \sim \mathrm{MVN}\left(\mathbf{0}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix}\right)$$

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Assume a probit model for the potential outcomes

$$\mathrm{P}(Y(x, m_1, m_2) = 1) = \phi(-\tau + \beta x + \gamma_1 m_1 + \gamma_2 m_2 + \delta C)$$

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which is equivalent to

a linear normal model on a latent continuous variable underlying the potential outcome

$$Y^*(x, m_1, m_2) = -\tau + \beta x + \gamma_1 m_1 + \gamma_2 m_2 + \delta C + \epsilon_Y \qquad \epsilon_Y \sim \mathrm{N}(0,1), \;\; \epsilon_Y \perp \left(\epsilon_{M_1}, \epsilon_{M_2}\right)$$

$$Y = \begin{cases} 1 & \text{if} \;\; Y^* > 0 \\ 0 & \text{if} \;\; Y^* \leq 0 \end{cases} \qquad \mathrm{P}(Y = 1) = \phi(\mathrm{E}[Y^*])$$

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$$\begin{pmatrix} \epsilon_{M1} \\ \epsilon_{M2} \end{pmatrix} \sim \mathrm{MVN}\left(\mathbf{0}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix}\right)$$

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Want $\quad p_{xx'} = \mathrm{P}\Big(Y\big(x, M_1(x'), M_2(x')\big) = 1\Big)$.

Strategy: get to $p_{xx'}$ via $\quad Y^*\big(x, M_1(x'), M_2(x')\big) = Y^*_{xx'}$.

# How the method works

Replace $m_1, m_2$ with $M_1(x'), M_2(x')$ in the potential outcomes model:

$$Y^*_{xx'} = -\tau + \beta x + \gamma_1 M_1(x') + \gamma_2 M_1(x') + \delta c + \epsilon_Y$$
$$= (-\tau + \gamma_1\mu_1 + \gamma_2\mu_2) + \beta x + (\gamma_1\alpha_1 + \gamma_2\alpha_2)x' + (\delta + \gamma_1\lambda_1 + \gamma_2\lambda_2)C + \left(\epsilon_Y + \gamma_1\epsilon_{M_1} + \gamma_2\epsilon_{M_2}\right)$$

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Replace $m_1, m_2$ with $M_1(x'), M_2(x')$ in the potential outcomes model:

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Want to convert $\mathrm{E}\left(Y^*_{xx'}\right)$ to $p_{xx'}$,

but $\mathrm{Var}\left(\epsilon_Y + \gamma_1\epsilon_{M_1} + \gamma_2\epsilon_{M_2}\right) = 1 + (\gamma_1^2\sigma_1^2 + \gamma_2^2\sigma_2^2 + 2\gamma_1\gamma_2\sigma_{12}) > 1.$

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Want to convert $\mathrm{E}\left(Y^*_{xx'}\right)$ to $p_{xx'}$,

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No problem!

Rescale $Y^{**}_{xx'} = Y^*_{xx'} / \sqrt{\mathrm{Var}\left(\epsilon_Y + \gamma_1\epsilon_{M_1} + \gamma_2\epsilon_{M_2}\right)}$ then convert $p_{xx'} = \phi\left(\mathrm{E}\left[Y^{**}_{xx'}\right]\right)$.

# Implementation

- Evaluate plausibility of assumptions
- Fit regression model including a multivariate normal model for the mediators and a probit model for the outcome

(easily done in Mplus, Stata, etc.)

  - Check normality of mediator residuals (if continuous mediators)
  - Harvest unstandardized coefficients and residual mediator variances & covariances
- Compute $\hat{p}_{11}$, $\hat{p}_{00}$, $\hat{p}_{10}$ using

$$p_{xx'} = \phi\left(\frac{(-\tau + \gamma_1\mu_1 + \gamma_2\mu_2) + \beta x + (\gamma_1\alpha_1 + \gamma_2\alpha_2)x' + (\delta + \gamma_1\lambda_1 + \gamma_2\lambda_2)C}{\sqrt{1 + (\gamma_1^2\sigma_1^2 + \gamma_2^2\sigma_2^2 + 2\gamma_1\gamma_2\sigma_{12})}}\right)$$

- Compute NDE, NIE, TE
- Bootstrap for confidence intervals

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Please see paper.

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# Causal Mediation Analysis With a Binary Outcome and Multiple Continuous or Ordinal Mediators: Simulations and Application to an Alcohol Intervention

Trang Quynh Nguyen,[1] Yenny Webb-Vargas,[1] Ina M. Koning,[2] and Elizabeth A. Stuart[1]

[1] *Bloomberg School of Public Health, Johns Hopkins University*
[2] *University of Utrecht*

We investigate a method to estimate the combined effect of multiple continuous/ordinal mediators on a binary outcome: (a) fit a structural equation model with probit link for the outcome and identity/probit link for continuous/ordinal mediators, (b) predict potential outcome probabilities, and (c) compute natural direct and indirect effects. Step 2 involves rescaling the latent continuous variable underlying the outcome to address residual mediator variance and covariance. We evaluate the estimation of risk-difference- and risk-ratio-based effects (RDs, RRs) using the maximum likelihood (ML), mean-and-variance-adjusted weighted least squares (WLSMV) and Bayes estimators in M*plus*. Across most variations in path-coefficient and mediator-residual-correlation signs and strengths, and confounding situations investigated, the method performs well with all estimators, but favors ML/WLSMV for RDs with continuous mediators, and Bayes for RRs with ordinal mediators. Bayes outperforms ML/WLSMV regardless of mediator type when estimating RRs with small potential outcome probabilities and in two other special cases. An adolescent alcohol prevention study is used for illustration.

**Keywords**: binary outcome, causal mediation analysis, causal inference, continuous mediators, multiple mediators, ordinal mediators, structural equation modeling

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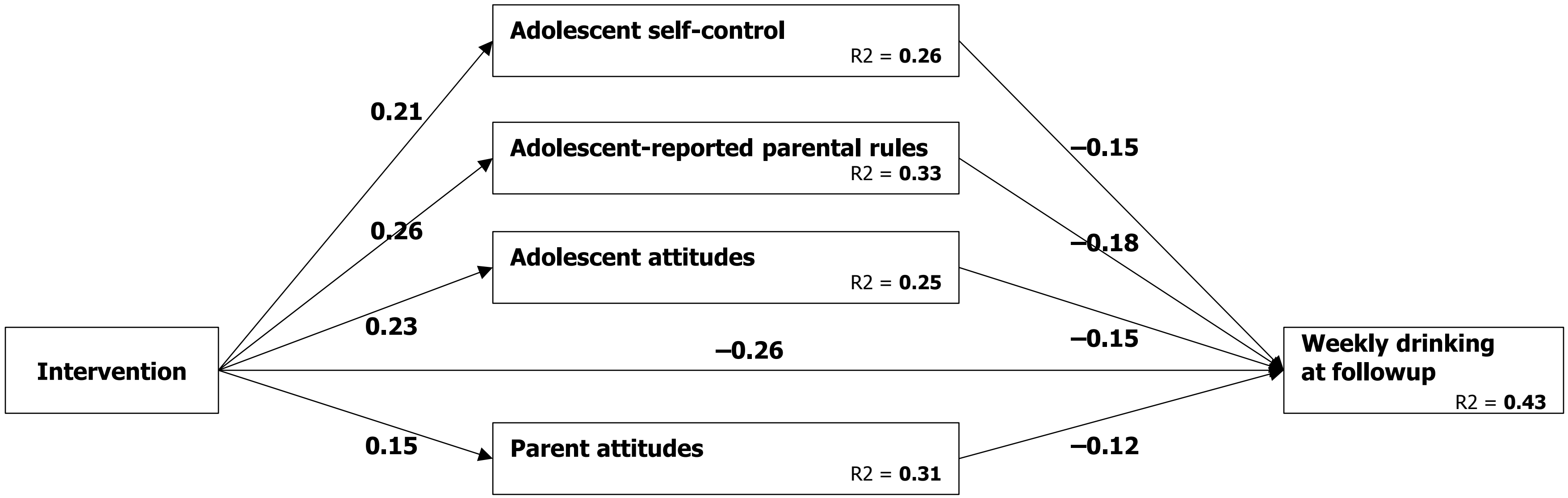
# Conventional analysis

Coefficients from SEM, standardized with respect to mediators & outcome:



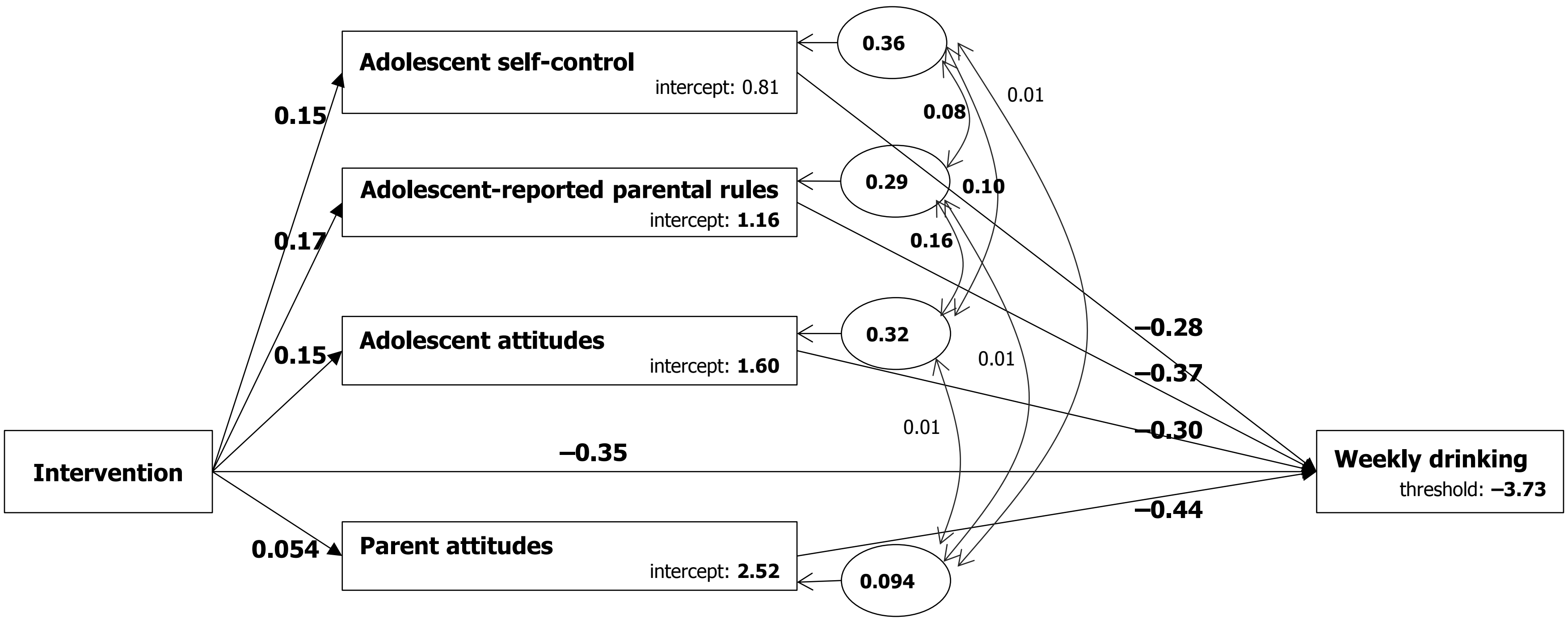

(covariates left out of diagram)

total indirect effects $= -.13$ $(\text{SE} = .03)$

direct effect $= -.26$ $(\text{SE} = .09)$ unit of effects is SD of $Y^*$

# Causal analysis using the proposed method

Same SEM: unstandardized coefficients and residual mediator variances & covariances:




Estimated potential outcome probabilities:

$\color{red}{\hat{p}_{11} = 18.1\%}$ (95% CI $= 14.3, 21.7\%$)

$\color{blue}{\hat{p}_{00} = 31.4\%}$ (95% CI $= 27.8, 35.5\%$)

$\color{green}{\hat{p}_{10} = 22.0\%}$ (95% CI $= 17.3, 26.3\%$)

Estimated effects on the RR scale:

TE $= \color{red}{\hat{p}_{11}}/\color{blue}{\hat{p}_{00}} = 0.58$ (95% CI $= .45, .72$)

NDE $= \color{green}{\hat{p}_{10}}/\color{blue}{\hat{p}_{00}} = 0.70$ (95% CI $= .55, .87$)

NIE $= \color{red}{\hat{p}_{11}}/\color{green}{\hat{p}_{10}} = 0.82$ (95% CI $= .76, .88$)

# Acknowledgements

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Thank you!

Questions, comments,
suggestions for further work
or potential applications
welcomed!

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