Meditations on mediation analysis

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Acknowledgements

This presentation has been influenced by conversations with many people, including Michelle C. Carlson, Ilya Shpitser, and Vanessa Didelez.

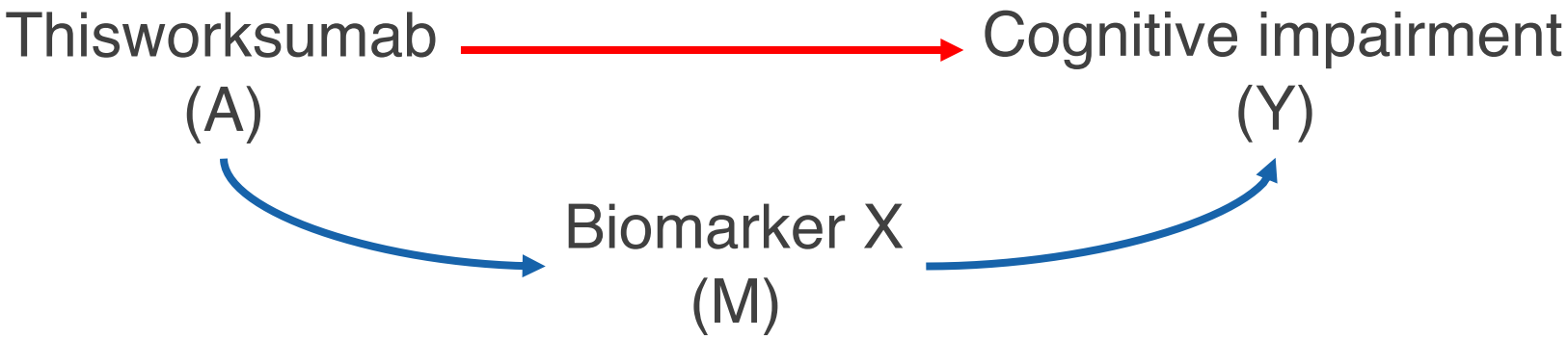
Disclaimers

I cannot cover everything in a 30-40 minute presentation; this is not meant to be comprehensive.

I focus on single mediator cases for simplicity; multiple mediator methods do exist, and they do require thought before use.

All opinions and errors are my own.

Crash course in mediation analysis



The treatment/exposure has two (or more) pathways by which it affects the outcome. The pathway not involving the mediator(s) is the direct effect, and the pathway involving the mediator is the indirect effect.

“Baron & Kenny” mediation analysis, usually via series of linear regressions

Crash course in causal inference

Randomized controlled trials = gold standard

…but we often cannot carry out an RCT

…and even if we could, RCTs do not randomize mediators

Causal inference = a principled way of thinking about scientific questions, interventions, and data to extract causal effects under suitable assumptions.

Crash course in causal inference

For any outcome of interest, we assume the existence of potential/counterfactual outcomes under different interventions

Example: What is causal effect of thisworksumab (A=1) on cognitive impairment?

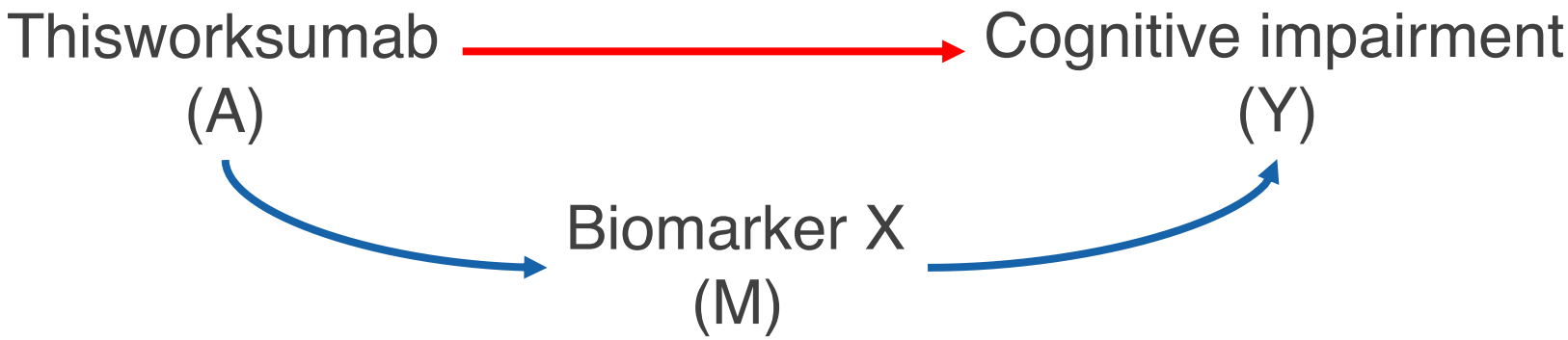
	Potential outcomes for cognitive impairment		Observed variables	
	Received A=1	**Received A=0**	**Received A=1**	**Cognitive impairment**
Bob	Not impaired	Impaired	Yes	Not impaired
Sally	Not impaired	Not impaired	No	Not impaired
Judith	Impaired	Impaired	No	Impaired
Marco	Impaired	Not impaired	Yes	Impaired

Let $Y(a)$ be one's counterfactual outcome under $A = a$ and $Y(a')$ be one's counterfactual outcome under $A = a'$

The average causal effect of $A = a$ versus $A = a'$ is given by

$$E\{Y(a) - Y(a')\}$$

In mediation analysis, the ACE is often referred to as the "total effect"



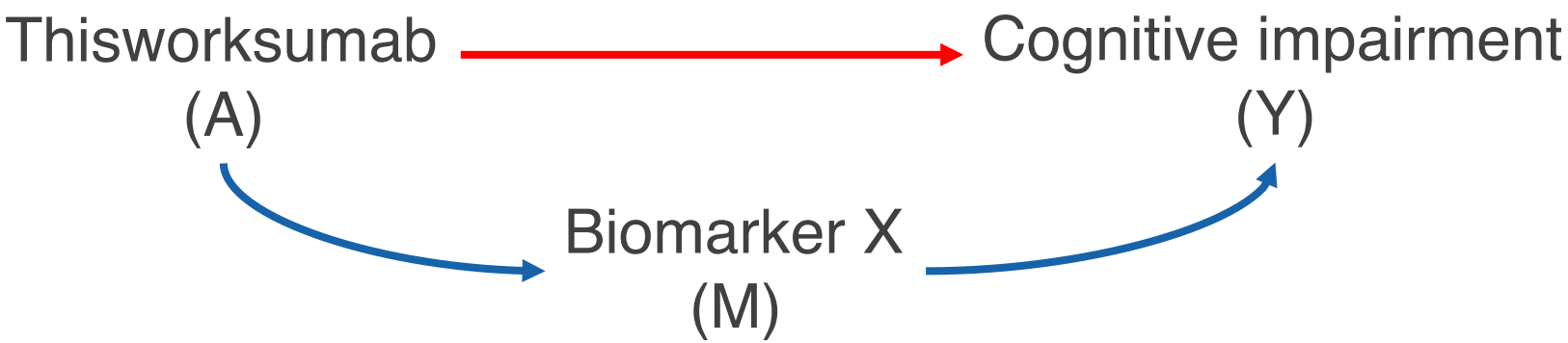
Let $M(a)$ denote the counterfactual mediator value under $A = a$.

In causal mediation, we usually employ “nested counterfactuals” to capture path-specific interventions

$$Y\left(a, M(a')\right)$$

Exposure assignment
$A \rightarrow Y$ pathway

Exposure assignment
$A \rightarrow M \rightarrow Y$ pathway



Common causal mediation estimands:

Natural direct effect (NDE): $E\{Y(a, M(a')) - Y(a', M(a'))\}$

Natural indirect effect (NIE): $E\{Y(a, M(a)) - Y(a, M(a'))\}$

Under various assumptions, these effects are identified from observed data

Note: No where have we assumed a (parametric) model!

Meditation #1: Why do you want to do a mediation analysis?

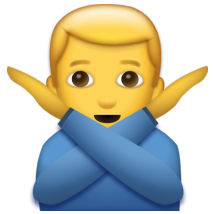
Various motivations for mediation

"I have an *a priori* theory for why it exists"

"I want to know how the exposure 'works'"

"A member of my thesis committee does mediation"

"I want to be a member of the 'causal club'"



Causal mediation analysis “checklist”

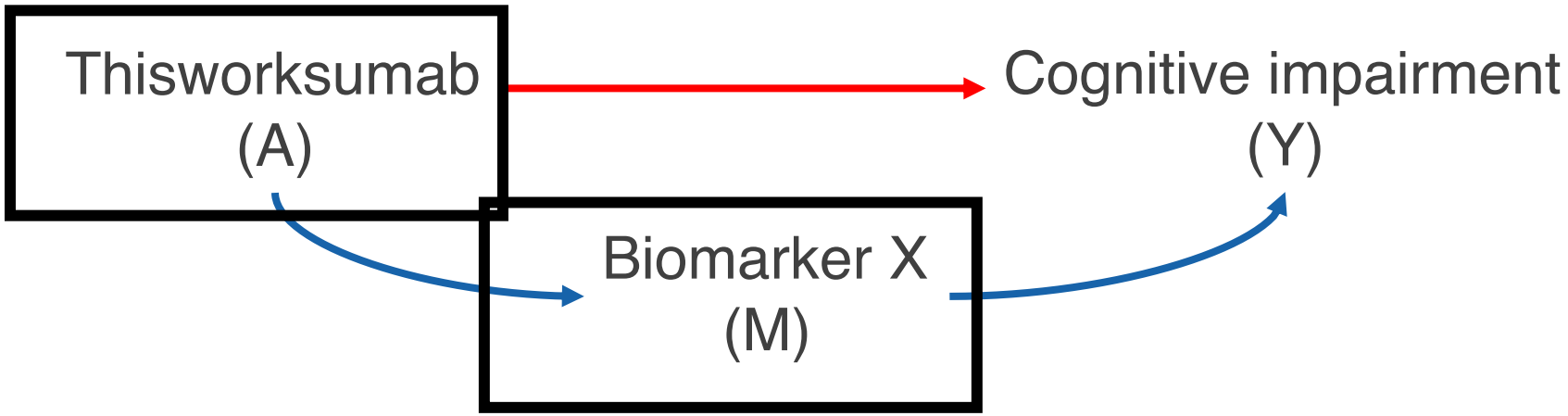
1. You have a theory for why the effect of a treatment/exposure on the outcome is mediated by > 1 variables

   Thisworksumab contains chemicals known to affect Biomarker X, which is a known contributor to cognitive function. At the same time, in an RCT, factors like adherence to treatment, the placebo effect, and other biological processes could also lead to cognitive function benefits.

2. You wish to frame your study in terms of causal questions, including hypothetical interventions

   I can change the formula of thisworksumab; I can enforce 100% adherence; I can tell people when they are taking the placebo, etc.

What are ***NOT*** mediation questions

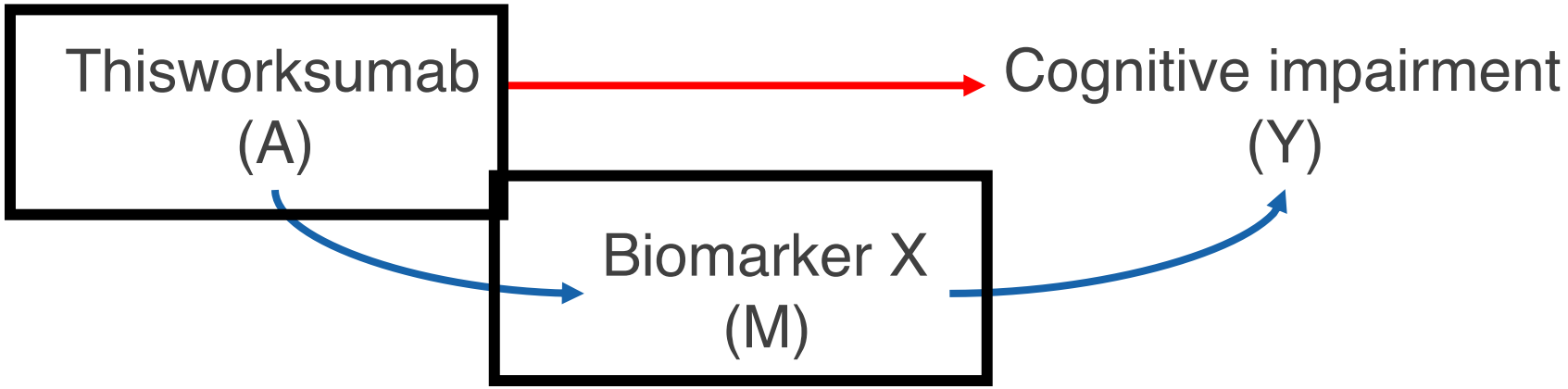


Is it better to intervene on the treatment…

…or the mediator (if you cannot do both)?

Courtesy of Vanessa Didelez

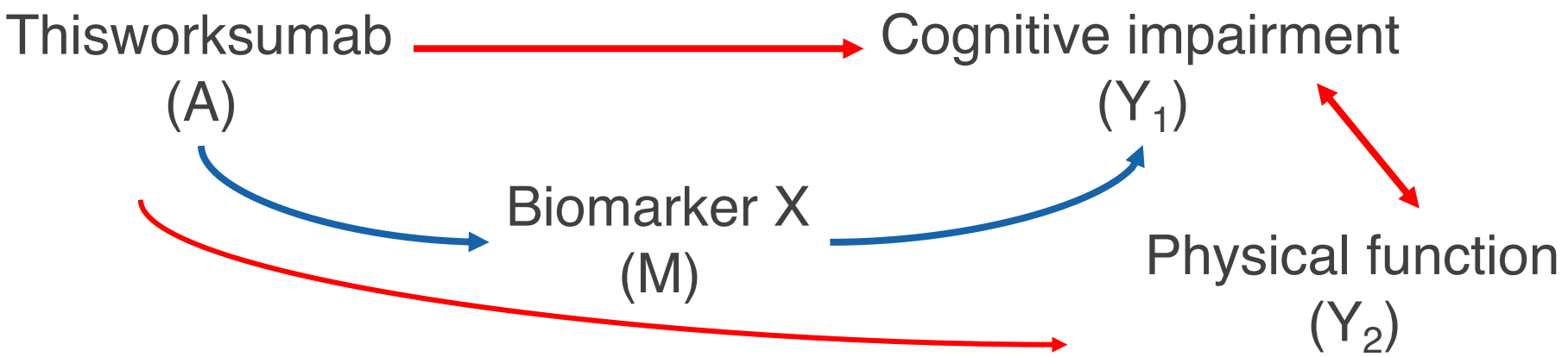
What are ***NOT*** mediation questions



Is it better to intervene on both the treatment and mediator jointly, versus intervene separately?

Courtesy of Vanessa Didelez

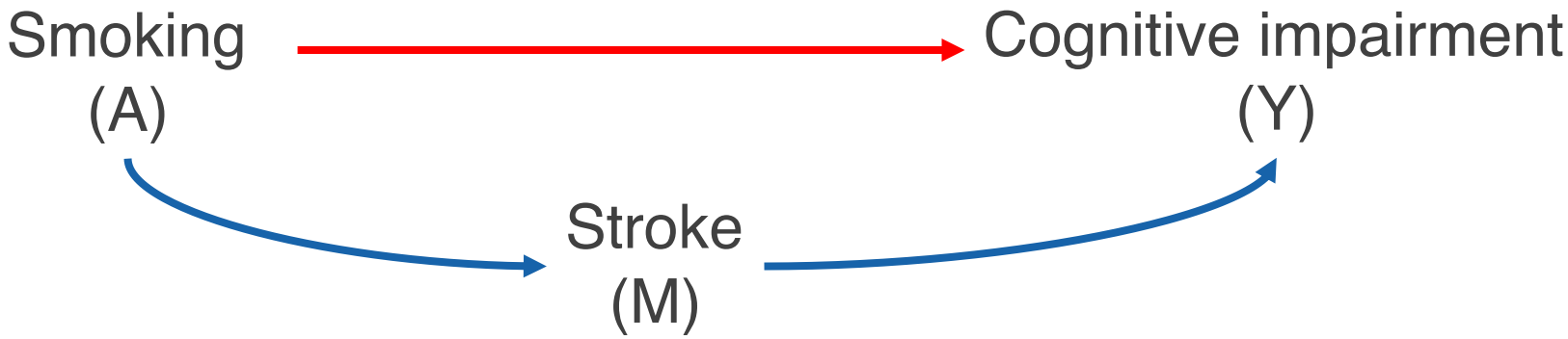
What are ***NOT*** mediation questions



What are the various effects of treatment?

Courtesy of Vanessa Didelez

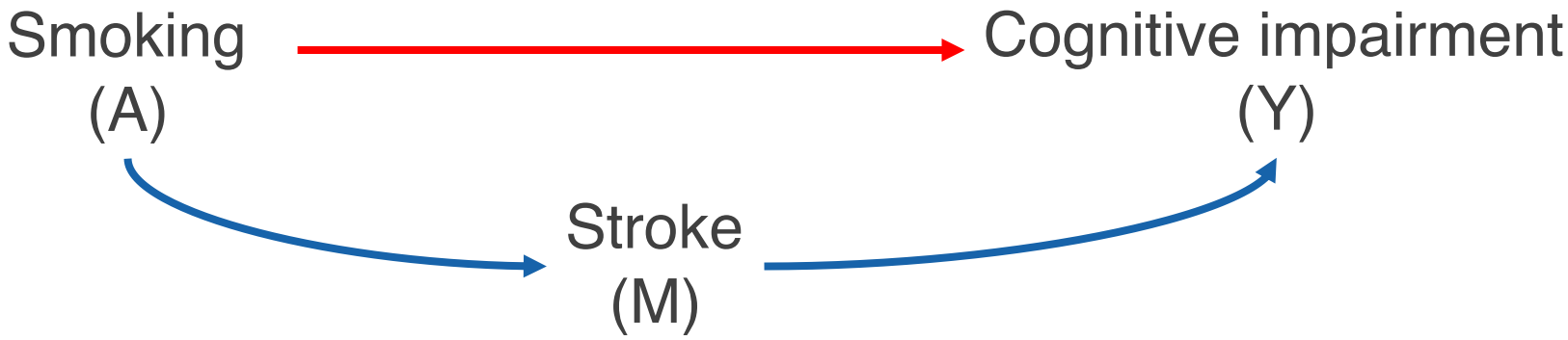
Intervention-related mediation



We are interested in interventions to prevent cognitive impairment, and we plan a mediation analysis. Our DAG is above.

What do we want this mediation analysis to mean?

Intervention-related mediation



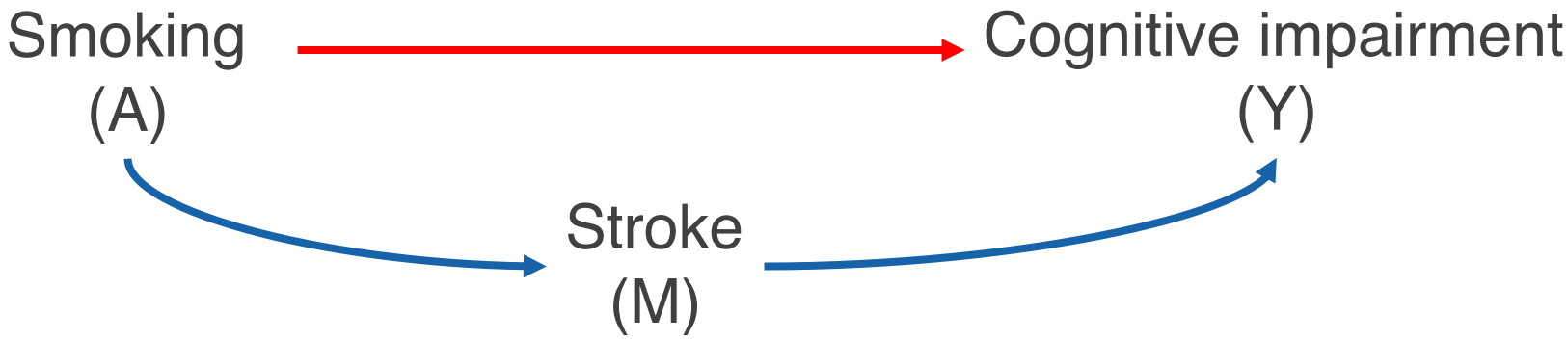
Suppose we find a “significant” indirect effect.

Should we design an intervention to lower stroke risk among smokers?

Is this even possible? What does this mean?

What about the non-smokers?

Intervention-related mediation

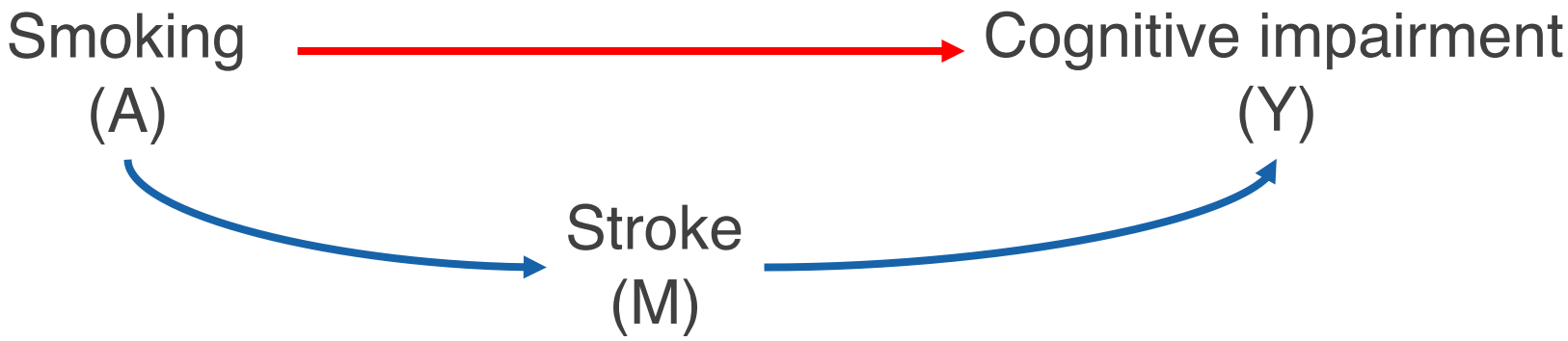


Suppose we find a “significant” indirect effect.

Should we design an intervention to prevent stroke?

Interesting idea…but you did not need mediation analysis

Intervention-related mediation



Suppose we find a ”significant” direct effect

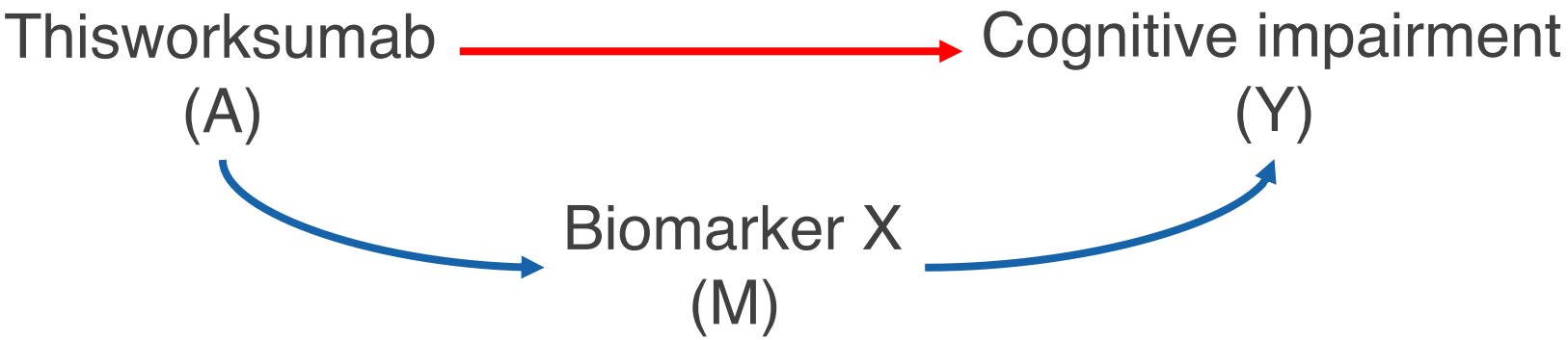
Should we design an intervention to prevent smoking?

Okay, but you did not need a mediation analysis

Meditation #2:

Be careful about describing causal mediation assumptions

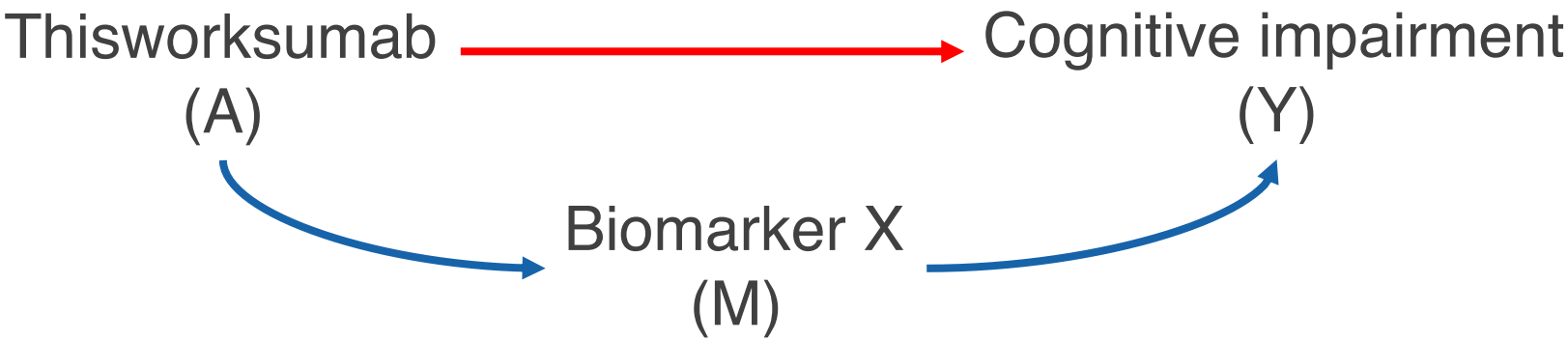
Time is an integral part of mediation analysis



By planning a mediation analysis, you believe that A first affects M, and then both A and M affect Y. ***Otherwise, you do not have direct and indirect effects.***

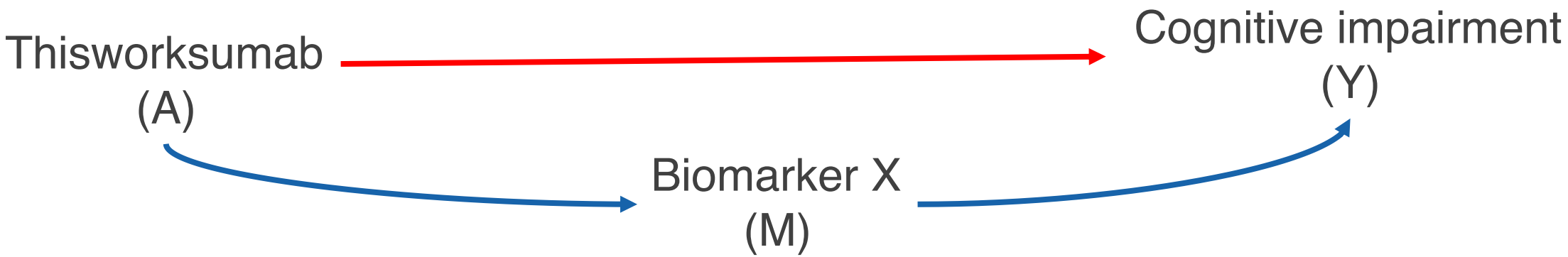
Belief in a time ordering is therefore a necessary assumption for mediation analysis. ***The use of cross-sectional data is not appropriate without extremely strong assumptions.***

Time is an integral part of mediation analysis



By planning a mediation analysis, you also assume something about the time scale of the effects

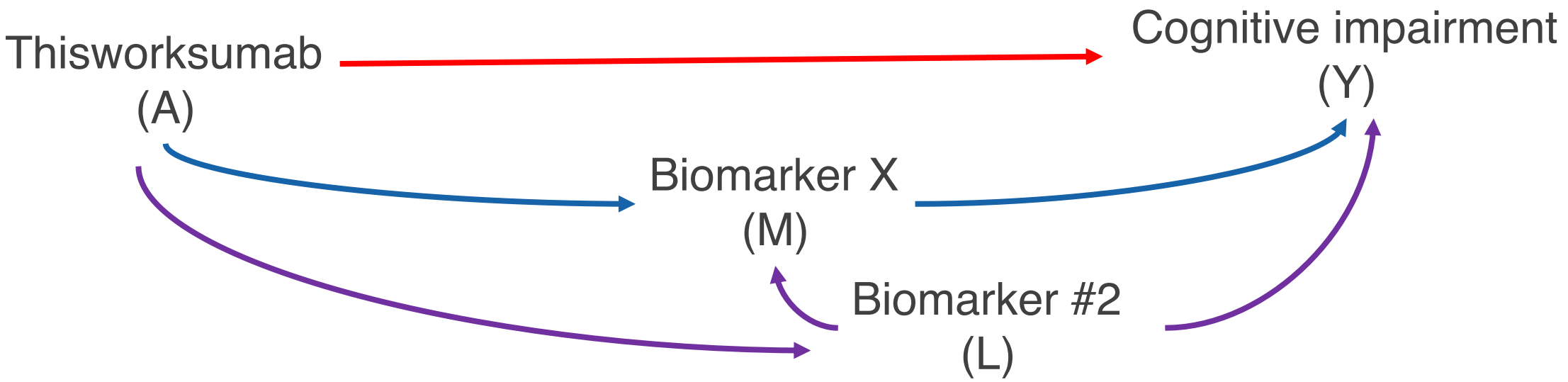
e.g., if thisworksumab takes 6 months to work, don't use mediator and outcome measurements at 1 and 3 months, etc.



It is difficult to put precise mathematical assumptions into English words.

Example: The "cross-world" assumption is that $Y(a, m) \perp M(a')$. Two subtle points:

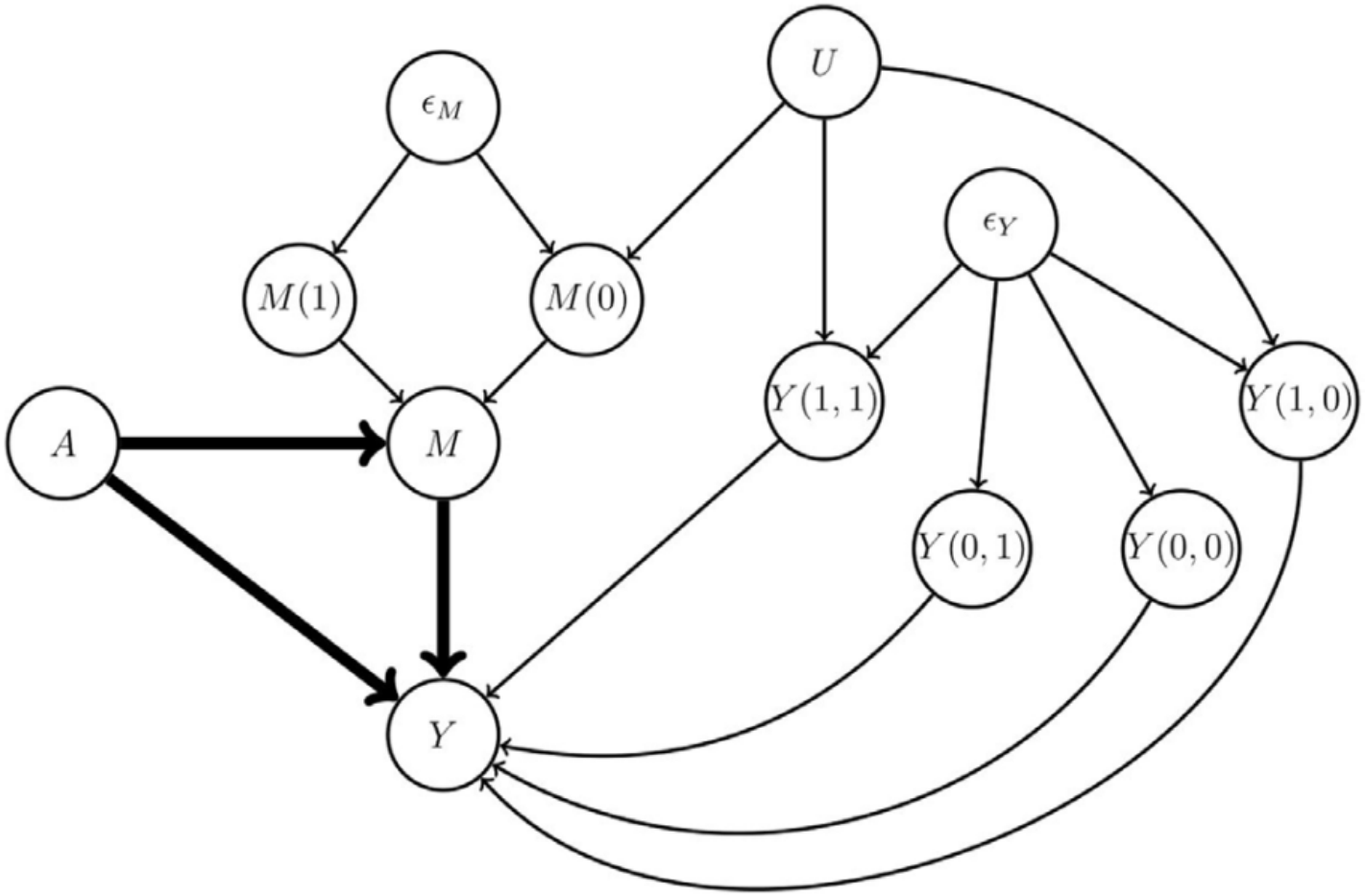
1. "This assumption must hold" (or variations, like "is required," etc.). It is a ***sufficient*** assumption, but it is not a ***necessary*** assumption.



Example: The "cross-world" assumption is that $Y(a, m) \perp M(a')$. Two subtle points:

2. "It is equivalent to the absence of mediator-outcome confounders affected by treatment" (also known as "recanting witnesses"). ***This is only true if you first assume a NPSEM-IE model.***

Andrews & Didelez (2021)



Adapted from Robins & Richardson (2011)

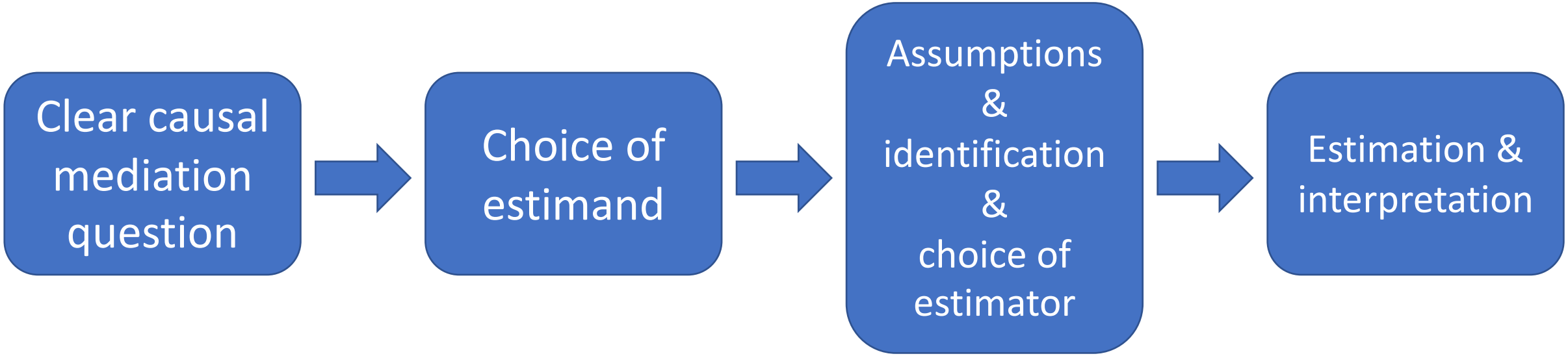
There is no recanting witness on this graph…

…but the cross-world assumption
is still violated

<u>Take-away</u>: Assessing the cross-world assumption is more than just identifying "recanting witnesses"

Meditation #4: Let your question drive your approach

The research pipeline should be:



…but often this is not followed in practice

Much like when the pipes break in your house, breakdowns in this pipeline can leave you with something that is messy, possibly smelly, and not what you want

Example: I am interested in the direct and indirect effects of thisworksumab on cognitive impairment through Biomarker X. I am worried about my assumptions, however, and instead decide to estimate the controlled direct effect. I think that is easier to do.

If you want certain effects, why move the goalpost because of non-identification?

(Better) solution: Sensitivity analyses and/or bounds on the effects ***+ motivating the collection of better/additional data in future studies.***

"Far better to have an approximate answer to the right question…than the exact answer to the wrong question" (John Tukey)

Example: I came to graduate school to do ”causal inference,” and your lecture on causal mediation was very inspiring. I want to do causal mediation analysis for my thesis. What is a problem I can work on?

Epidemiology is perhaps the only field where methods are put on a proverbial pedestal. This is probably not healthy.

If you start with a method, and then find a question, you are doing the exact opposite of what needs to be done

…this also includes letting an R package/Stata ADO/SAS macro drive your study question and approach

Meditation #5: “Separable effects” are an intuitive and useful approach to mediation analysis

Separable effects

What is the intuition of mediation analysis?

The treatment/exposure operates through 2+ pathways

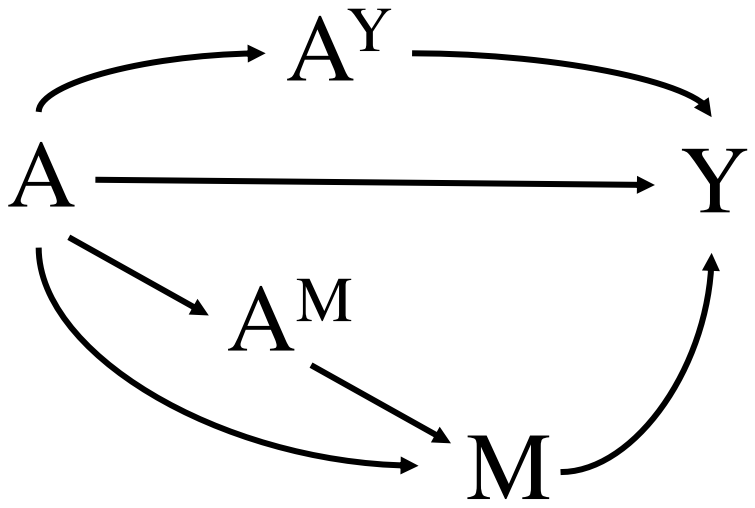
Intervening on the mediator is not usually the focus

Common approaches/estimands to mediation analysis do not capture this intuition, despite frequently being interpreted as doing so

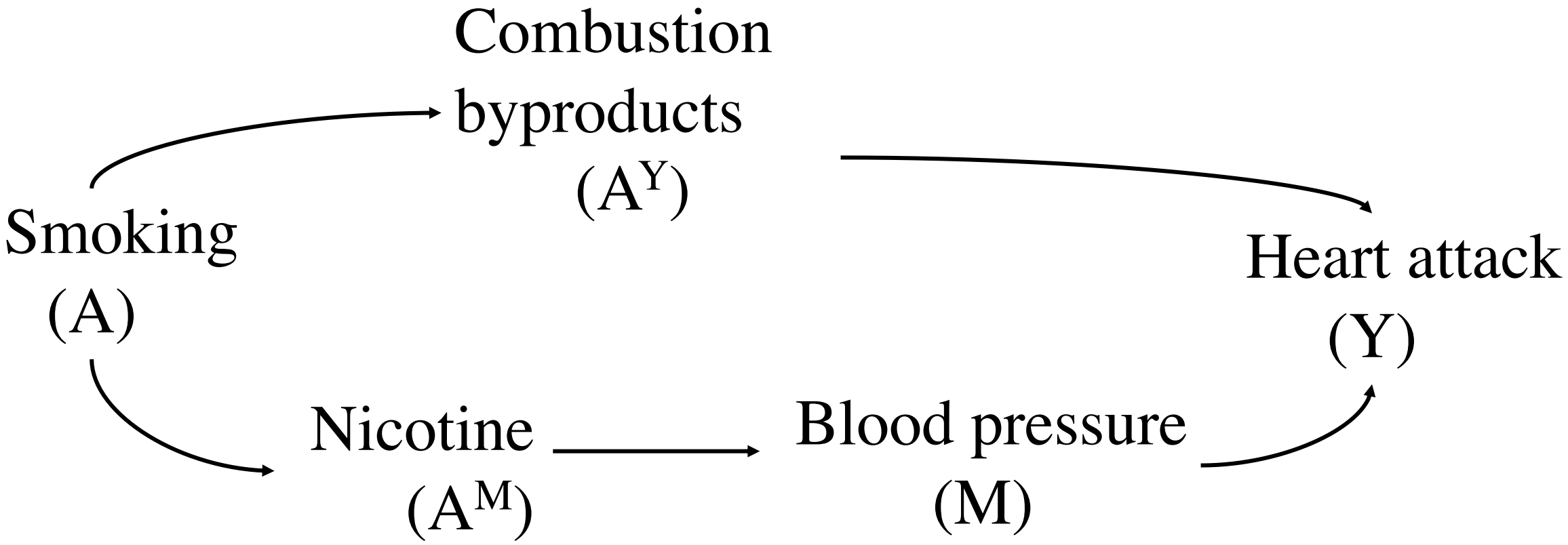
Example: Pearl's "nicotine-less" cigarettes

Separable effects

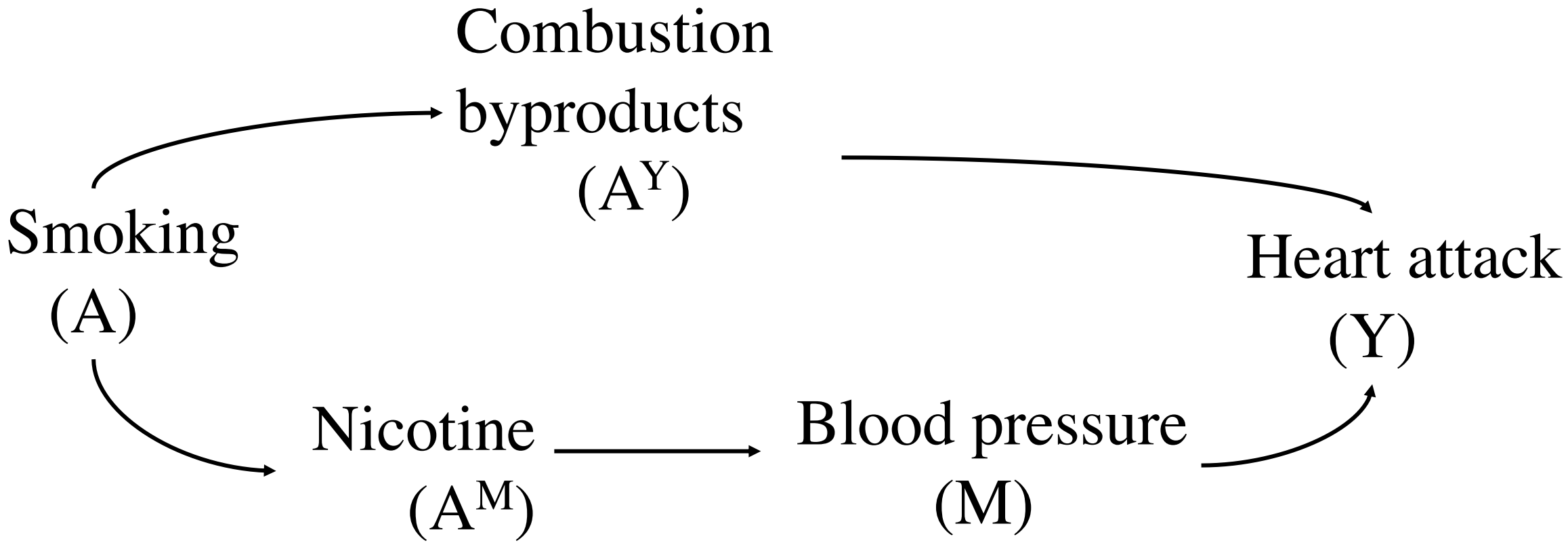
Assume that treatment has components (A^M, A^Y)



Observationally, $A = A^M = A^Y$. However, we can imagine intervening separately on each component (e.g., a 4 arm trial)

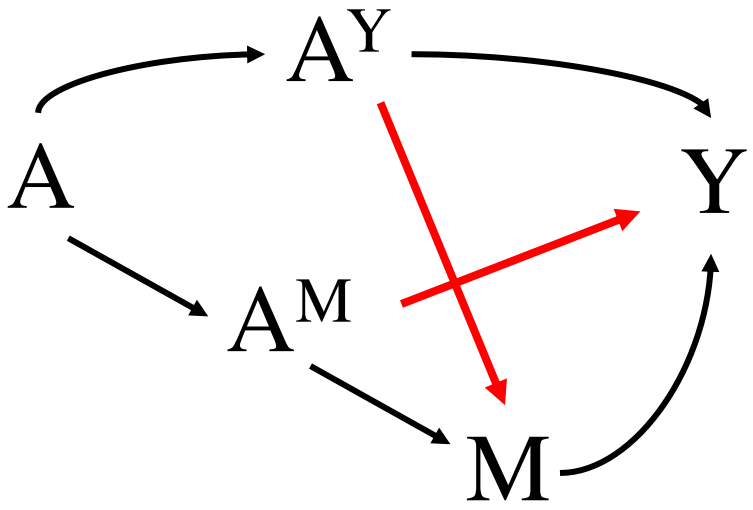


Observationally, $A = A^M = A^Y$. However, we can imagine intervening separately on each component (e.g., a 4-arm trial)



$$SDE := E\{Y(A^Y = a, A^M = a) - Y(A^Y = a', A^M = a)\}$$
$$SIE := E\{Y(A^Y = a', A^M = a) - Y(A^Y = a', A^M = a')\}$$

Identification



No need for nested counterfactuals

Assumptions are empirically testable

No interventions on the mediator

Conceptually, identification of the SDE and SIE hinge on:

1. $\mathrm{Y(a)} = \mathrm{Y}\left(\mathrm{A^M} = \mathrm{a}, \mathrm{A^Y} = \mathrm{a}\right)$ (i.e., a type of causal consistency)
2. Plausible interventions on A^M and A^Y (i.e., do you have a story?)
3. Absence of red arrows above (i.e., there is separability)

Identification functional

If these assumptions (plus the usual ones, like positivity, etc + no unmeasured M-Y confounding) hold:

$$E\{Y(A^Y = a, A^M = a')\} = \sum_m E(Y \mid A = a, M = m)P(M = m \mid A = a')$$

This is the mediational g-formula!

The popular methods for estimation are compatible with this approach

Take away points

Causal mediation is a useful tool, but like all tools, it requires careful attention and clear motivation for use

Is our research question unambiguous?

What do we want our mediation analysis to mean?

What is the interpretation?

Are we being theory-driven or data-driven?

Take away points

There is no such thing as assumption-free analyses. We need to be better about stating our assumptions and evaluating them.

- Can we link our choices to those in a “target trial?”
- Did we avoid obvious pitfalls (e.g., cross-sectional data)?
- What assumptions are we making?
  - Are they justified?
  - Can we test them?
  - Did we test them?
- Are the violations of our assumptions “interesting?”

Take away points

Separable effects mediation is a useful framework for mediation

- It forces you to justify the mediation theoretically
- It avoids cross-world assumptions
- In theory, its assumptions are empirically testable
- It is compatible with all software


Fin

Selected references

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