$$A_{t=e^{i\pi}} \longrightarrow A_{t=0} \longrightarrow A_{t=1} \longrightarrow A_{t=\sqrt{2}} \longrightarrow A_{t=e} \longrightarrow A_{t=\pi} \longrightarrow$$

The only reason for time is so that everything doesn’t happen at once.

$$Y_{t=e^{i\pi}} \longrightarrow Y_{t=0} \longrightarrow Y_{t=1} \longrightarrow Y_{t=\sqrt{2}} \longrightarrow Y_{t=e} \longrightarrow Y_{t=\pi} \longrightarrow$$

$$M_{t=e^{i\pi}} \longrightarrow M_{t=0} \longrightarrow M_{t=1} \longrightarrow M_{t=\sqrt{2}} \longrightarrow M_{t=e} \longrightarrow M_{t=\pi} \longrightarrow$$

$$Z_{t=e^{i\pi}} \longrightarrow Z_{t=0} \longrightarrow Z_{t=1} \longrightarrow Z_{t=\sqrt{2}} \longrightarrow Z_{t=e} \longrightarrow Z_{t=\pi} \longrightarrow$$

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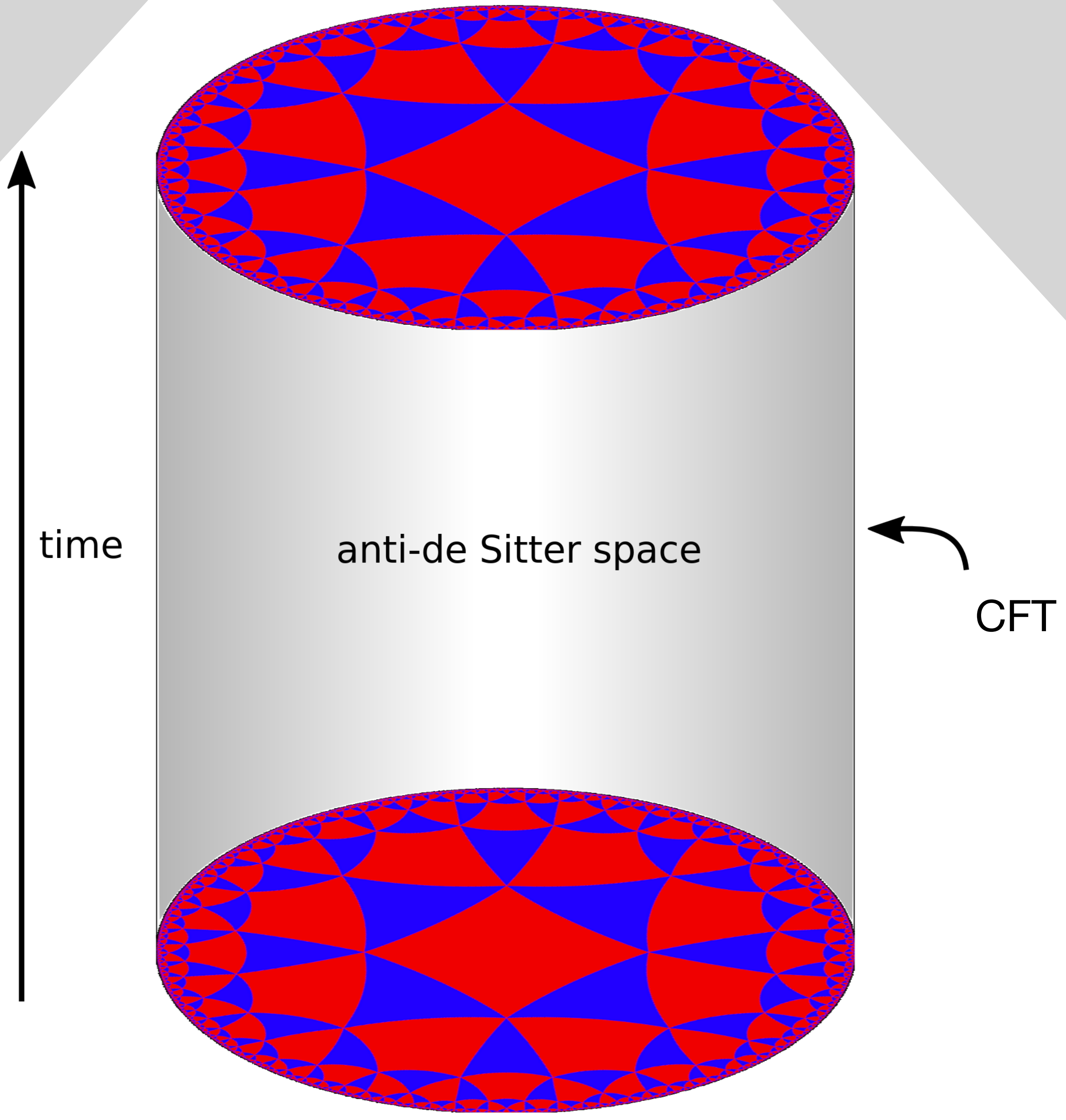
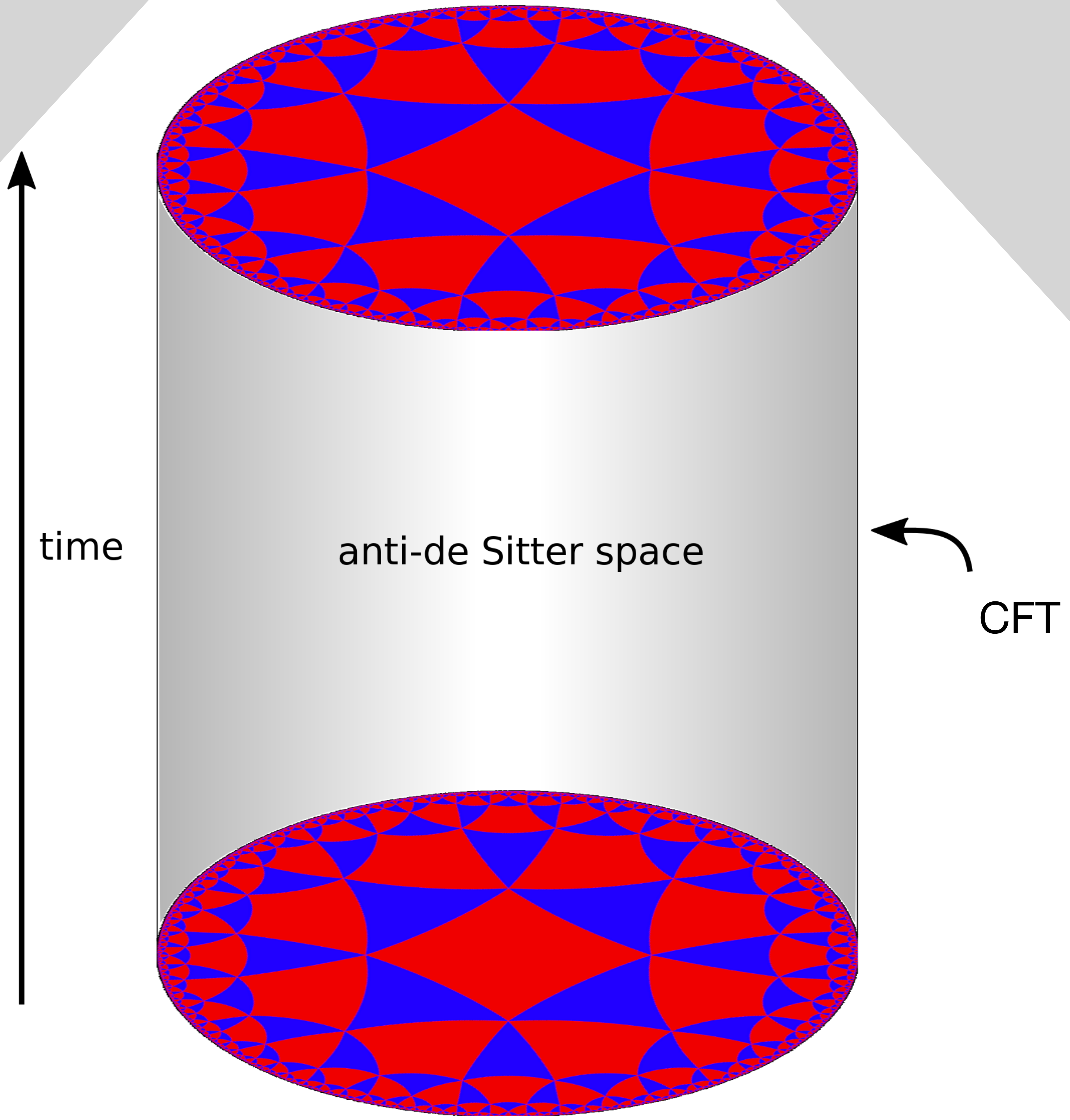
Erasmus MC
Universitair Medisch Centrum Rotterdam


THIS IS WHERE YOU LOST YOUR WALLET?


THIS IS WHERE YOU LOST YOUR WALLET?
NO, I LOST IT IN THE PARK. BUT THIS IS WHERE THE LIGHT IS.


time
anti-de Sitter space
CFT

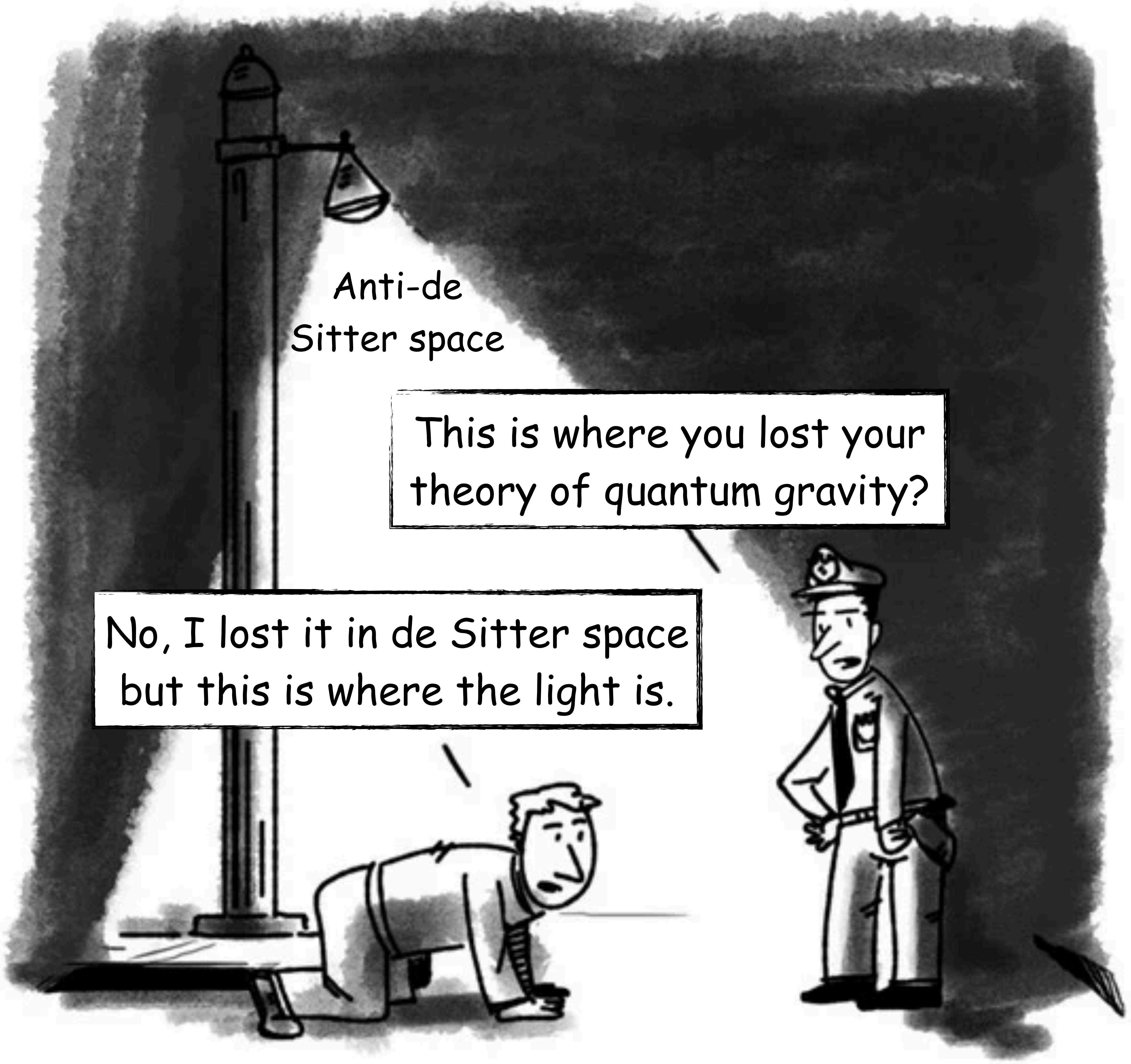
“…there have been **thousands or maybe tens of thousands of papers** working out details of this. It’s been a great source of kind of inspiration of how quantum systems might be related to one another…

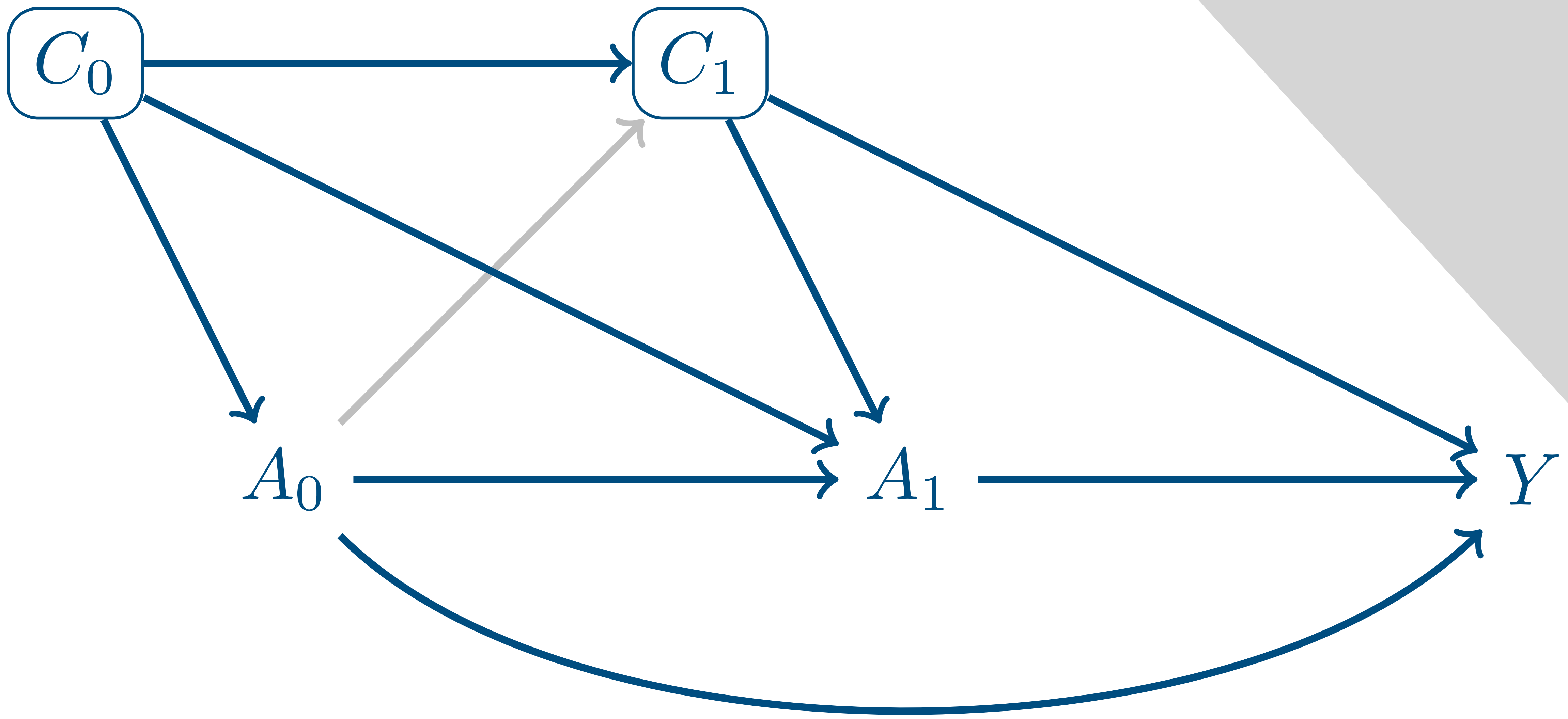


"...there have been **thousands or maybe tens of thousands of papers** working out details of this. It's been a great source of kind of inspiration of how quantum systems might be related to one another...

...**but it's not the real world.** So of the three possibilities, negative curvature, zero curvature and positive curvature, **the one that we've understood is the furthest from observable physical reality**."

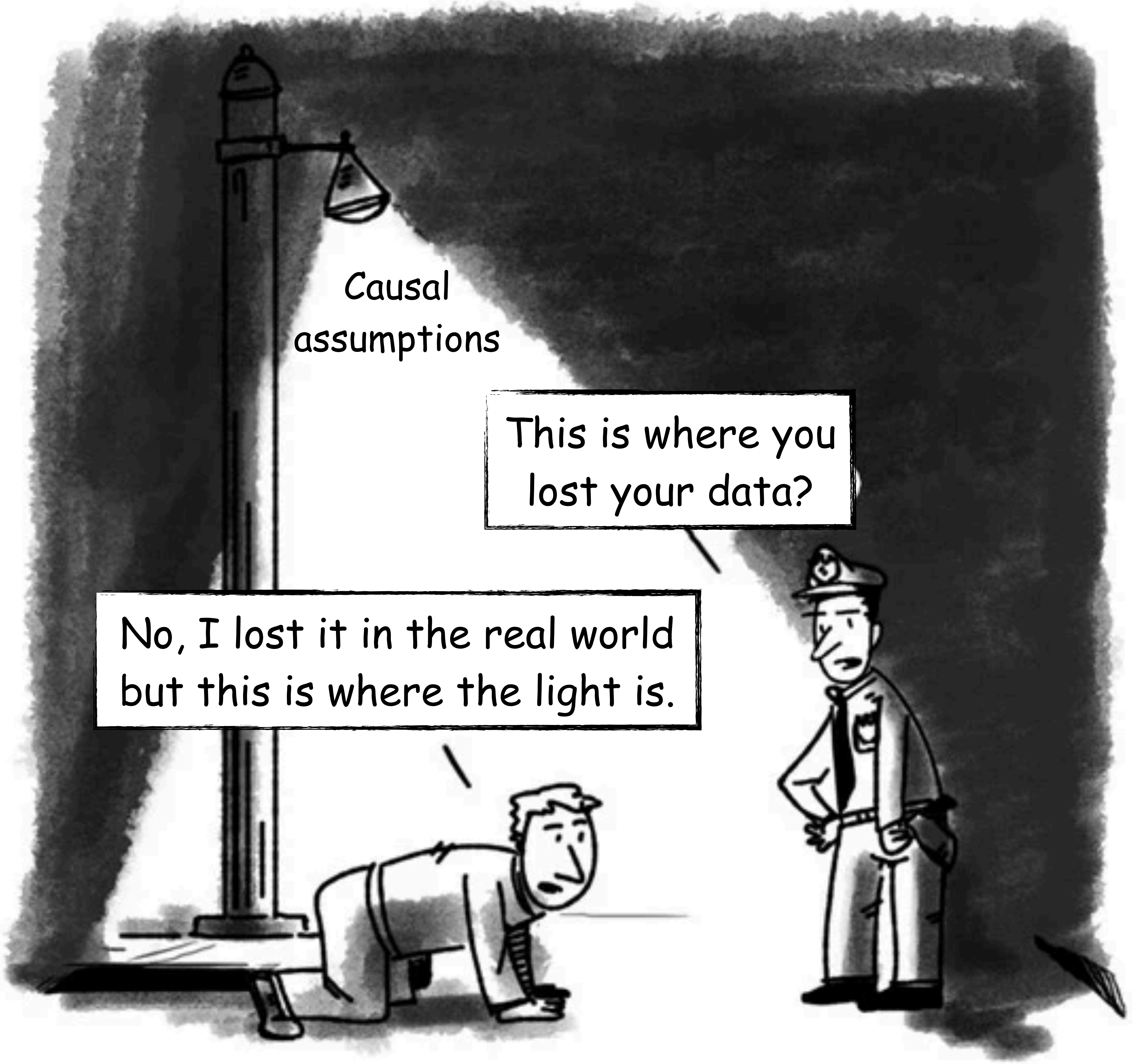
- Andrew Strominger


Anti-de Sitter space
This is where you lost your theory of quantum gravity?
No, I lost it in de Sitter space but this is where the light is.



- ☑ Conditional exchangeability
- ☑ Positivity
- ☑ Consistency
- ☑ No measurement error
- ☑ Well-specified models


C_0
C_1
A_0
A_1
Y
Conditional exchangeability
Positivity
Consistency
No measurement error
Well-specified models
C_0^*
C_1^*
C_0
C_1
A_0
A_1
Y
U
Conditional exchangeability
Positivity
Consistency
No measurement error
Well-specified models

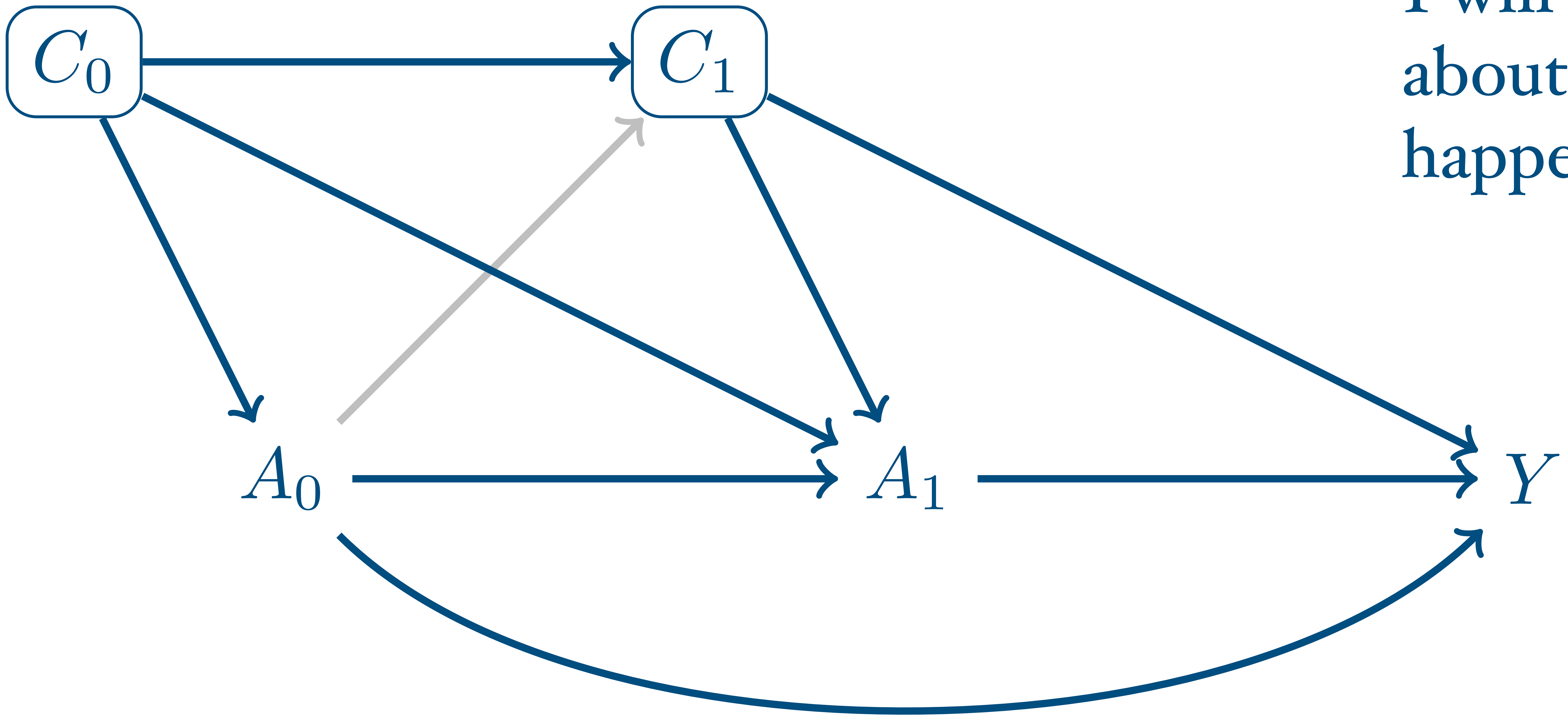

Causal assumptions
This is where you lost your data?
No, I lost it in the real world but this is where the light is.

[illegible]

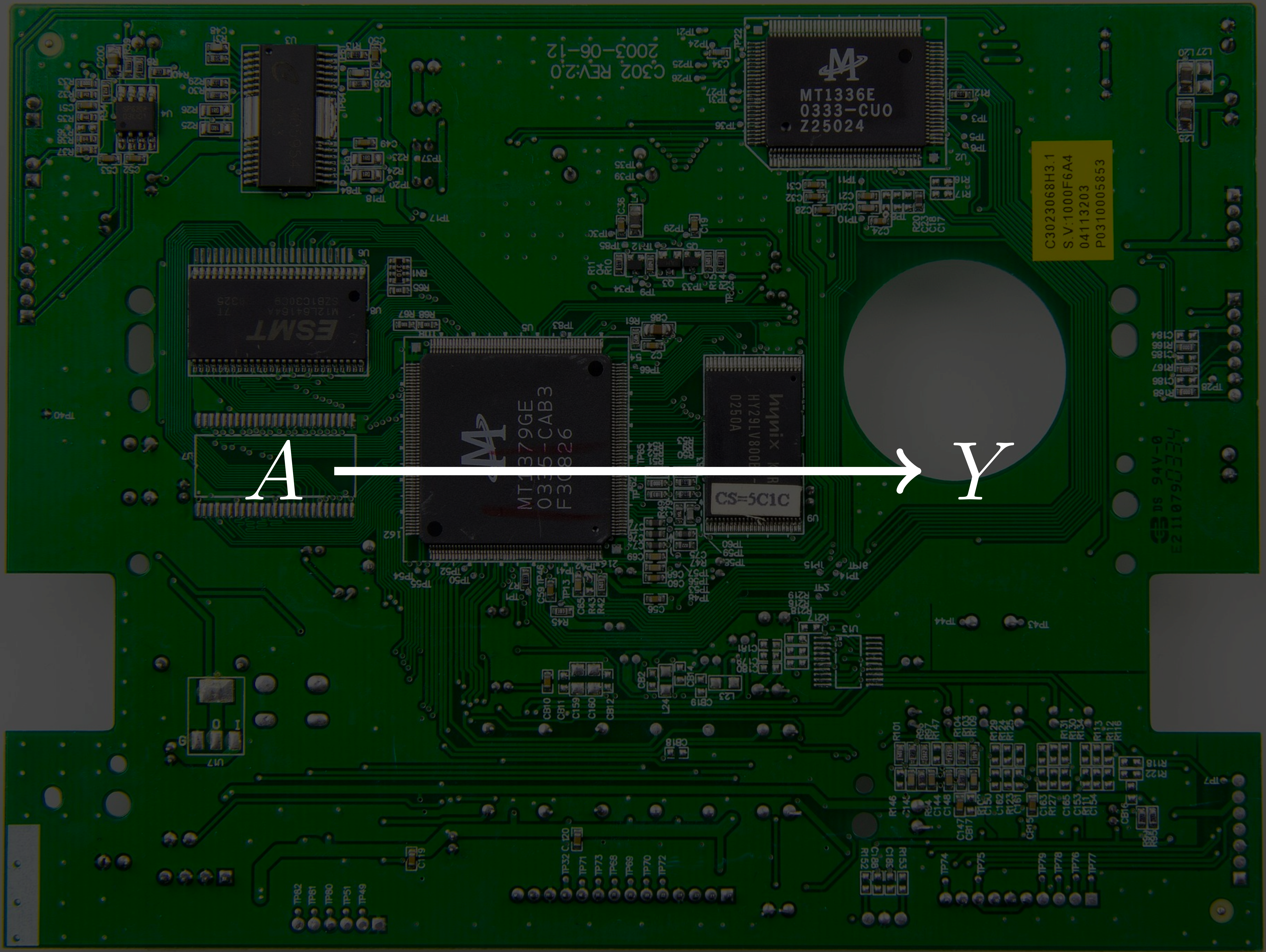
The only reason for time is so that everything doesn't happen at once.

We are good at thinking about time in certain contexts (e.g., time-varying effects).

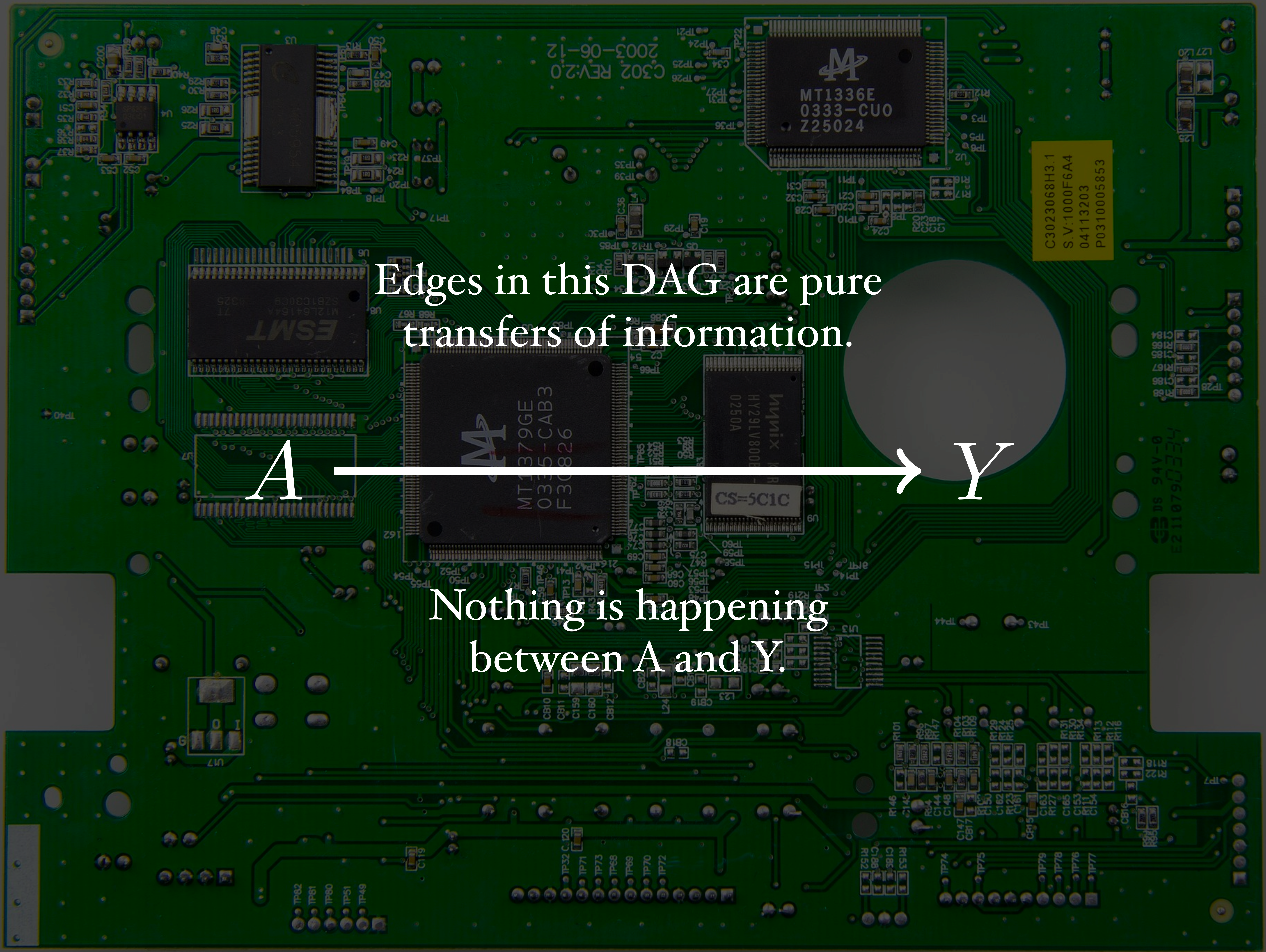
I will argue that, sometimes, we forget about time and act as though "everything happens at once".



$$
\begin{tikzcd}
C \arrow[d] \arrow[dr] & \\
A \arrow[r] & Y
\end{tikzcd}
$$



$A \longrightarrow Y$



Edges in this DAG are pure transfers of information.

$$A \longrightarrow Y$$

Nothing is happening between A and Y.

$$\text{Smoking}_{t=0} \longrightarrow \text{Time to death}$$

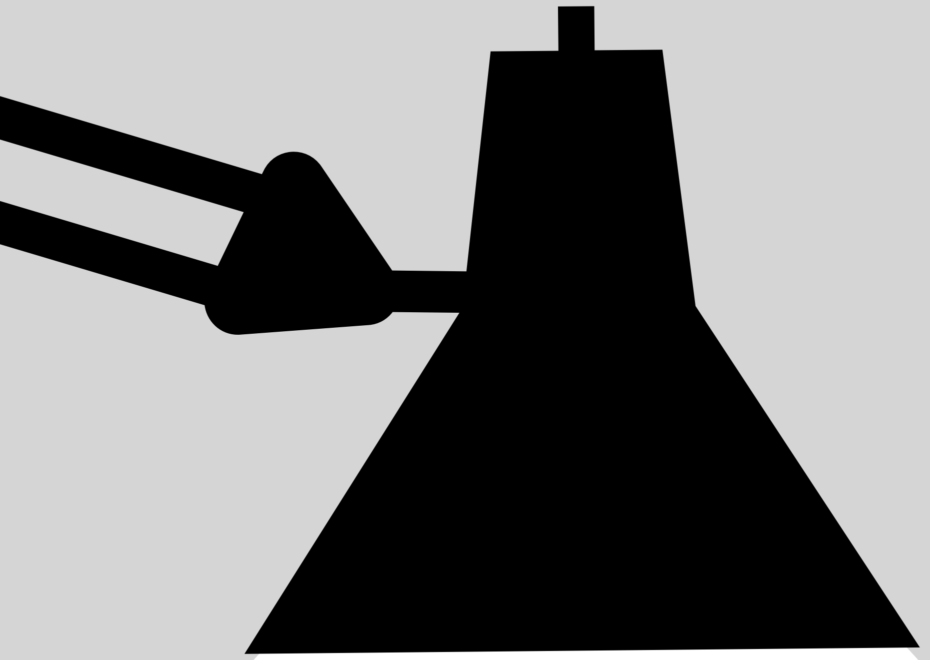
How does information get from
Smoking to death?

$$\text{Smoking}_{t=0} \longrightarrow \text{Time to death}$$

How does information get from Smoking to death?

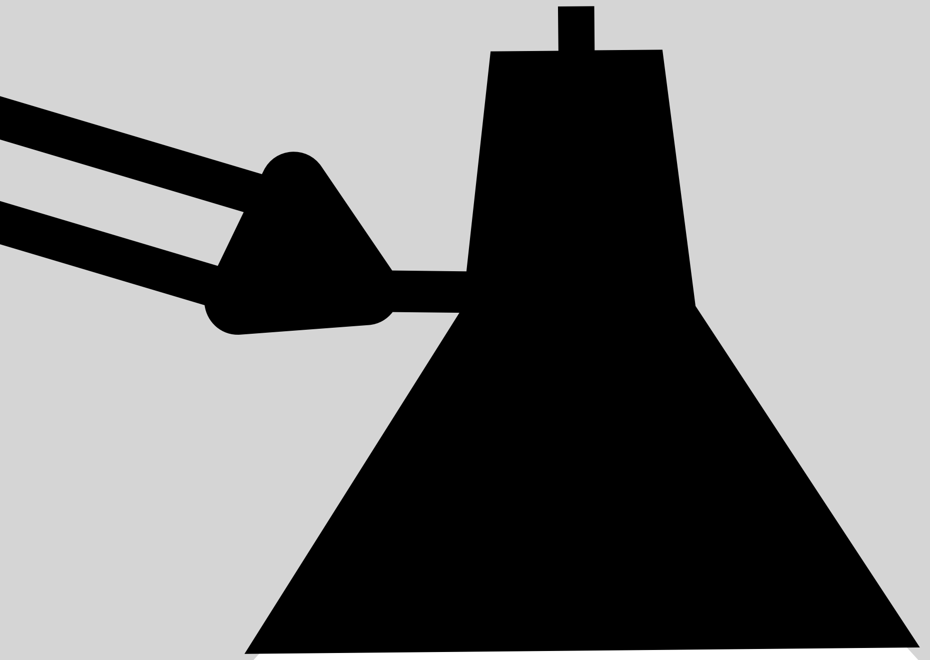
$$\begin{tikzcd}
& S_{t=1} \arrow[r] & S_{t=2} \arrow[r] & \cdots \arrow[r] & S_{t=i} \arrow[dr] & \\
S_{t=0} \arrow[ur] \arrow[dr] & & & & & \text{Time to death} \\
& M_{t=1} \arrow[r] & M_{t=2} \arrow[r] & \cdots \arrow[r] & M_{t=j} \arrow[ur] &
\end{tikzcd}$$

And this is still a huge oversimplification...



$$\begin{tikzcd}
 & S_{t=1} \arrow[r] & S_{t=2} \arrow[r] & \cdots \arrow[r] & S_{t=i} \arrow[dr] & \\
S_{t=0} \arrow[ur] \arrow[dr] & & & & & \text{Time to death} \\
 & M_{t=1} \arrow[r] & M_{t=2} \arrow[r] & \cdots \arrow[r] & M_{t=j} \arrow[ur] &
\end{tikzcd}$$

$$\text{Smoking}_{t=0} \longrightarrow \text{Time to death}$$



$$\begin{tikzcd}[column sep=small]
 & S_{t=1} \arrow[r] & S_{t=2} \arrow[r] & \cdots \arrow[r] & S_{t=i} \arrow[dr] & \\
S_{t=0} \arrow[ur] \arrow[dr] & & & & & \text{Time to death} \\
 & M_{t=1} \arrow[r] & M_{t=2} \arrow[r] & \cdots \arrow[r] & M_{t=j} \arrow[ur] &
\end{tikzcd}$$

The only reason for time is so that everything doesn't happen at once.

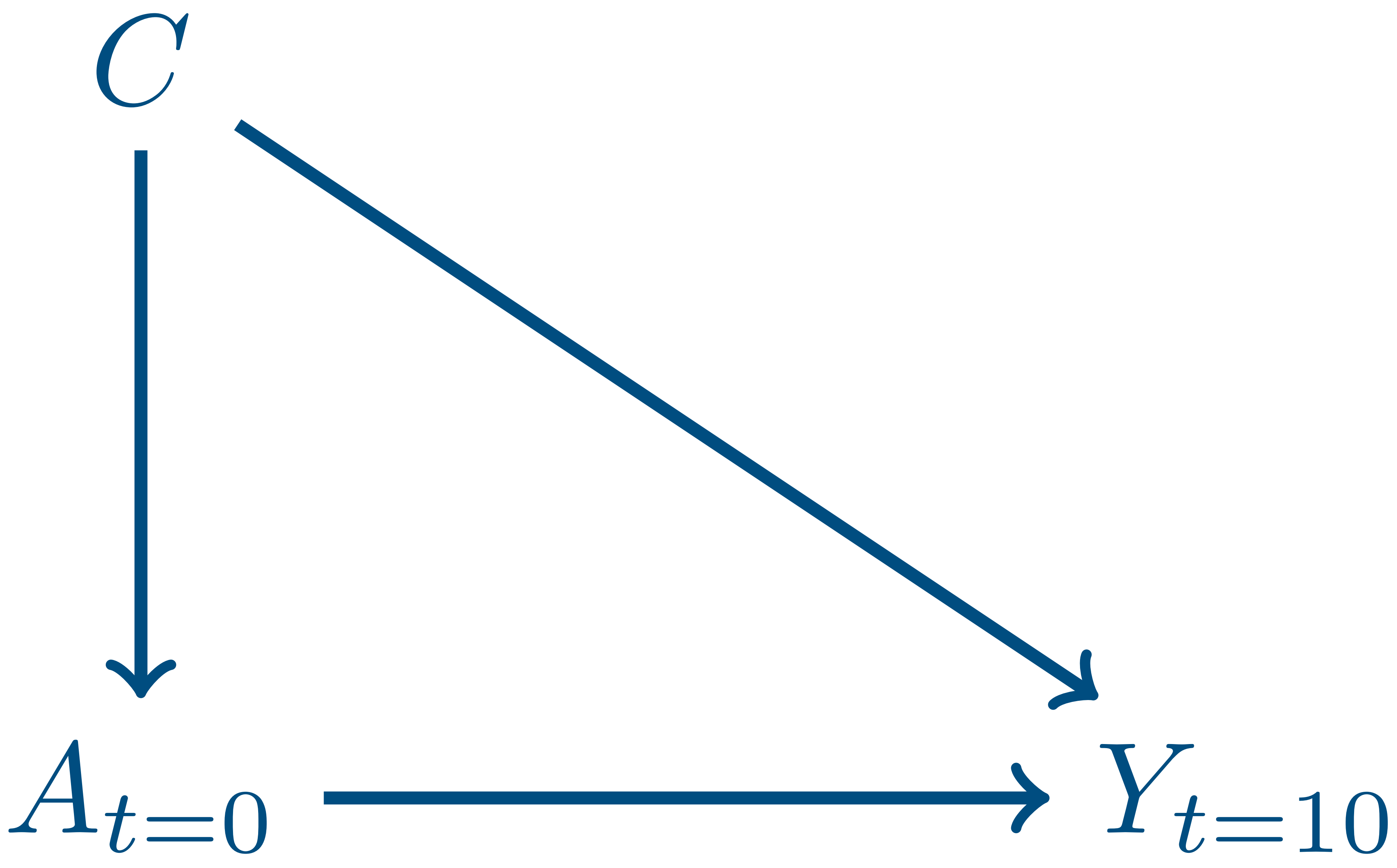
$$\text{Smoking}_{t=0} \longrightarrow \text{Time to death}$$

Example 1

$$
\begin{tikzcd}
C \arrow[d] \arrow[dr] & \\
A_{t=0} \arrow[r] & Y_{t=10}
\end{tikzcd}
$$

"…control for each covariate that is a cause of the exposure, or of the outcome, or of both; exclude from this set any variable known to be an instrumental variable"

- Vanderweele (2019)



"...control for each covariate that is a cause of the exposure, or of the outcome, or of both; exclude from this set any variable known to be an instrumental variable"

- Vanderweele (2019)

$$
\begin{tikzcd}
Z \arrow[d] & \\
A_{t=0} \arrow[r] & Y_{t=10}
\end{tikzcd}
$$

"…control for each covariate that is a cause of the exposure, or of the outcome, or of both; exclude from this set any variable known to be an instrumental variable"

\- Vanderweele (2019)

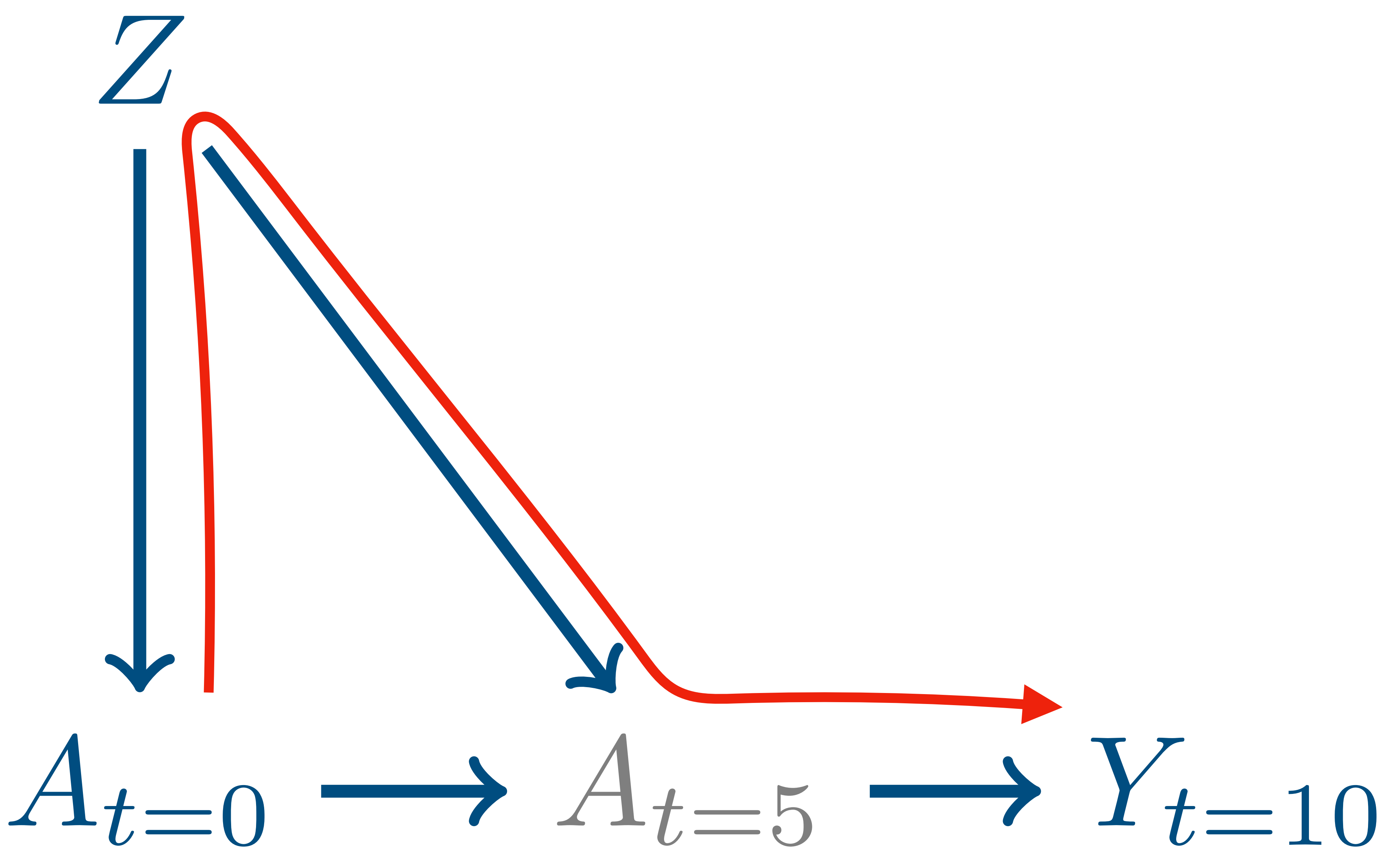
$$\begin{tikzcd} Z \arrow[d] \arrow[dr] & & \\ A_{t=0} \arrow[r] & A_{t=5} \arrow[r] & Y_{t=10} \end{tikzcd}$$

Grey variables are not measured

“...control for each covariate that is a cause of the exposure, or of the outcome, or of both; exclude from this set any variable known to be an instrumental variable”

- Vanderweele (2019)

- If our causal question is the effect of $A_{t=0}$ on Y, we must adjust for Z
- Z is an IV when A is considered as a whole, is not an IV for $A_{t=0}$
- The null hypothesis of no effect of A at any time is still testable even without adjusting for Z



Grey variables are not measured

Example from genetics

$$
\begin{tikzcd}
SNP \arrow[d] \arrow[dr] & & \\
BMI_{t=0} \arrow[r] & BMI_{t=5} \arrow[r] & \text{Body Image Disorder}_{t=10}
\end{tikzcd}
$$

Grey variables are not measured

Example from genetics

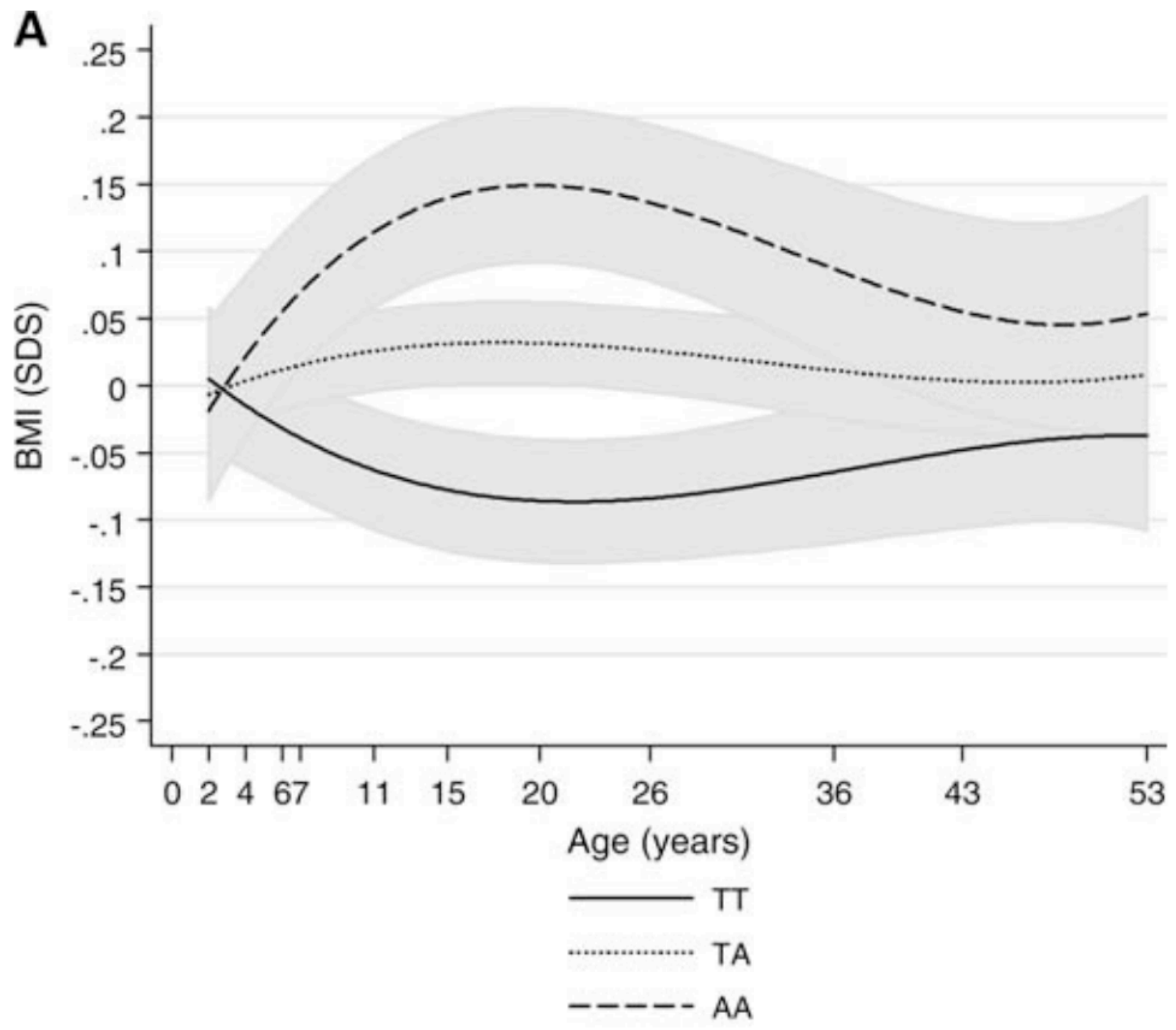
$$
\begin{tikzcd}
SNP \arrow[d] \arrow[dr] & & \\
BMI_{t=0} \arrow[r] & BMI_{t=5} \arrow[r] & \text{Body Image Disorder}_{t=10}
\end{tikzcd}
$$

- A SNP that only affects the outcome through the exposure can still be confounder

Grey variables are not measured

$$\begin{tikzcd}
SNP \arrow[d] \arrow[dr] & & \\
BMI_{t=0} \arrow[r] & BMI_{t=5} \arrow[r] & \text{Body Image Disorder}_{t=10}
\end{tikzcd}$$

- A SNP that only affects the outcome through the exposure can still be confounder



Grey variables are not measured

Example from RCTs

$$
\begin{tikzcd}
Z \arrow[d] \arrow[dr] & & \\
PSA_{t=0} \arrow[r] & PSA_{t=5} \arrow[r] & Y_{t=10}
\end{tikzcd}
$$

Example from RCTs

$$
\begin{tikzcd}
Z \arrow[d] \arrow[dr] & & \\
PSA_{t=0} \arrow[r] & PSA_{t=5} \arrow[r] & Y_{t=10}
\end{tikzcd}
$$

- Must adjust for Z to estimate the point per protocol effect of $PSA_{t=0}$
- Should NOT adjust for Z if you're estimating the joint effect of $PSA_{t=0}$ and $PSA_{t=5}$

Example from RCTs

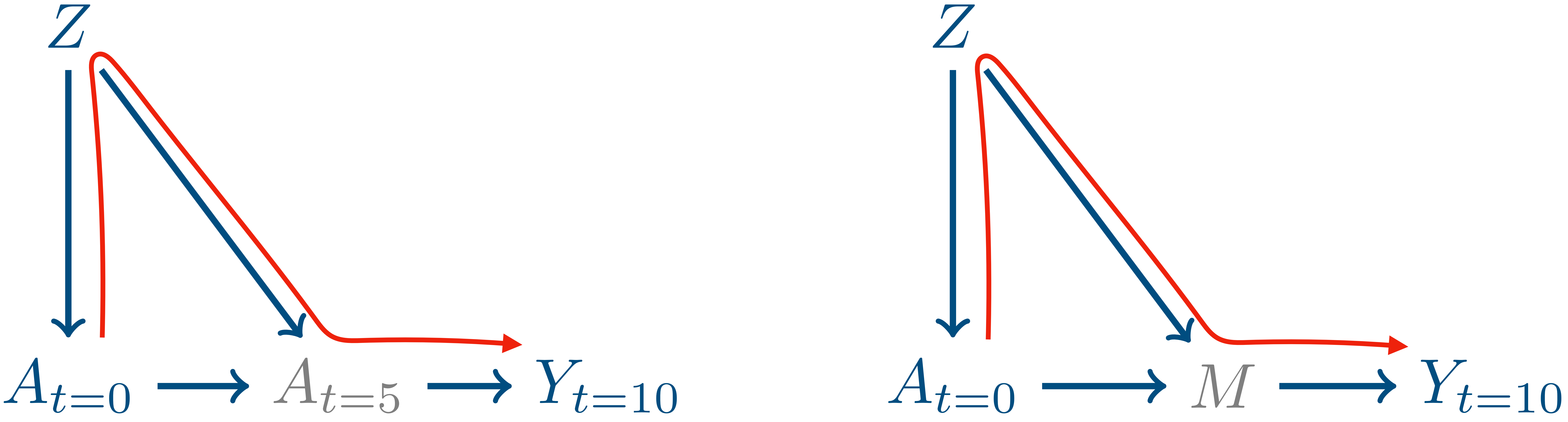
$$\begin{tikzcd}
Z \arrow[d] \arrow[dr] & & \\
PSA_{t=0} \arrow[r] & PSA_{t=5} \arrow[r] & Y_{t=10}
\end{tikzcd}$$

- Must adjust for Z to estimate the point per protocol effect of $PSA_{t=0}$
- Should NOT adjust for Z if you're estimating the joint effect of $PSA_{t=0}$ and $PSA_{t=5}$

One option for validly estimating the per-protocol effect in a pragmatic trial with a point intervention is to directly adjust for baseline prognostic factors that are also predictors of adherence, i.e. baseline confounders. Many statistical approaches are valid to adjust for confounders in per-protocol analyses.

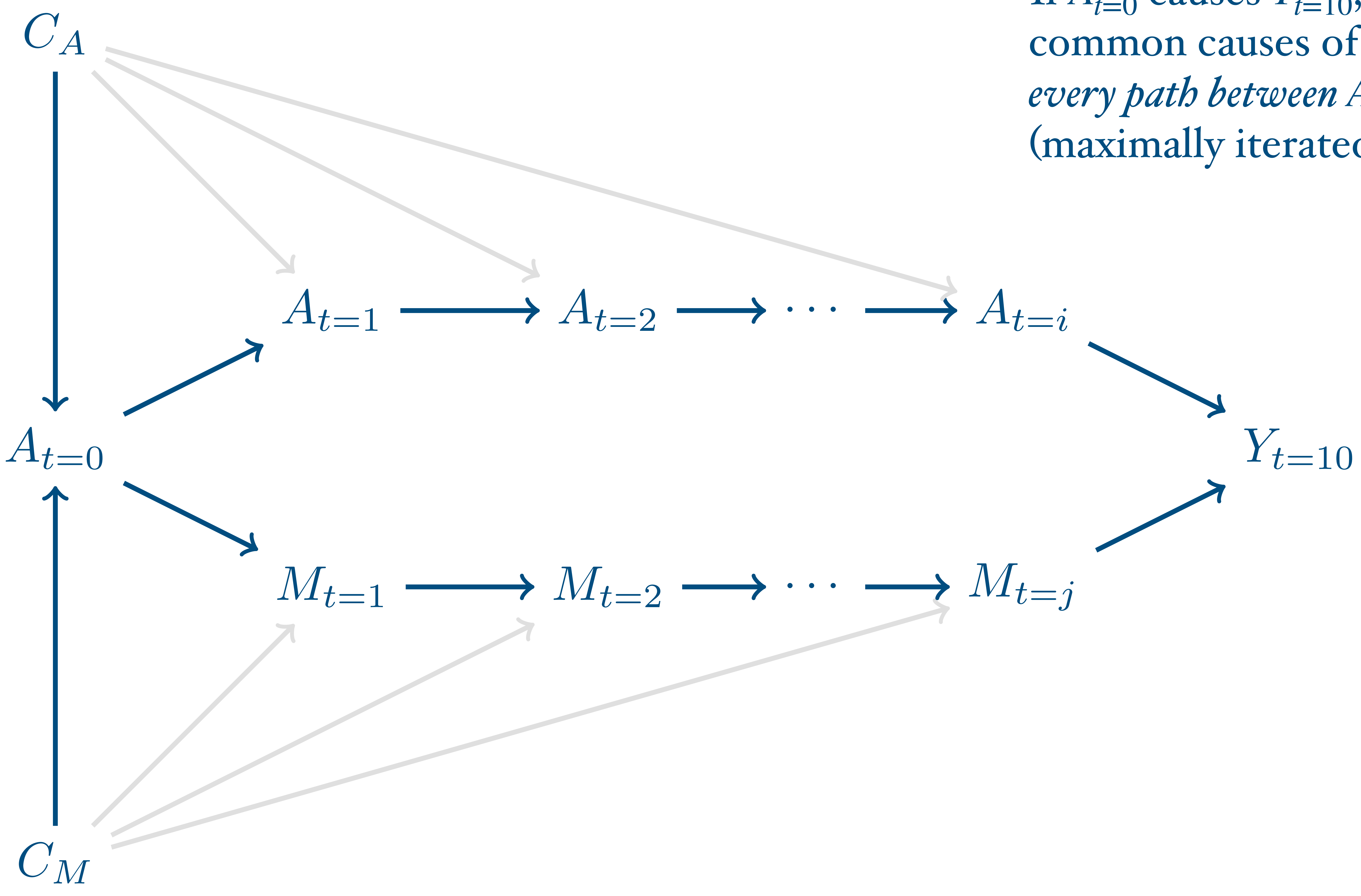
Murray et al 2019

Can replace $A_{t=5}$ with any mediator



Grey variables are not measured

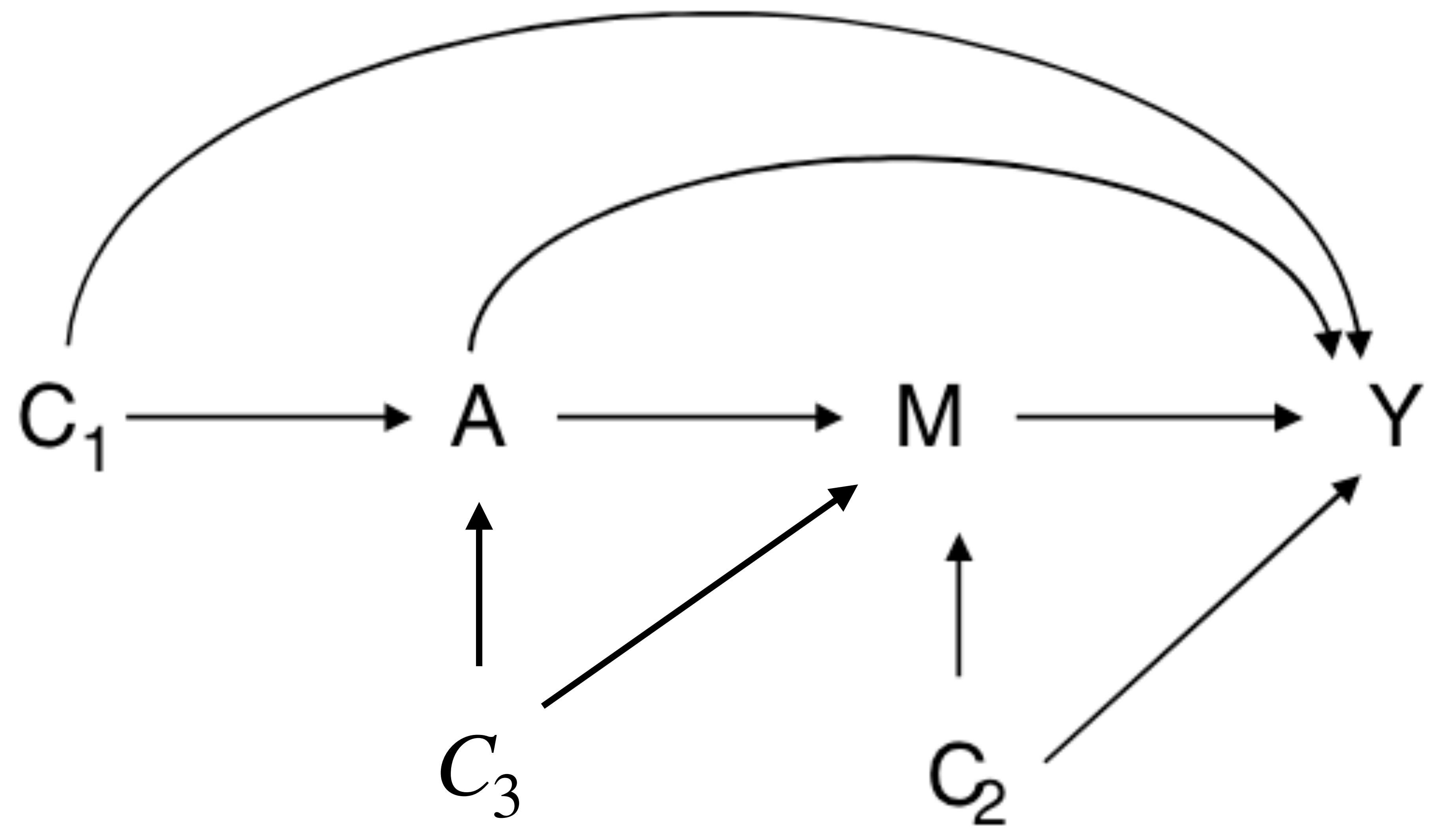
If $A_{t=0}$ causes $Y_{t=10}$, we have to adjust for all common causes of $A_{t=0}$ and *every variable on every path between* $A_{t=0}$ *and* $Y_{t=10}$
(maximally iterated paths)



Some consequences:

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship

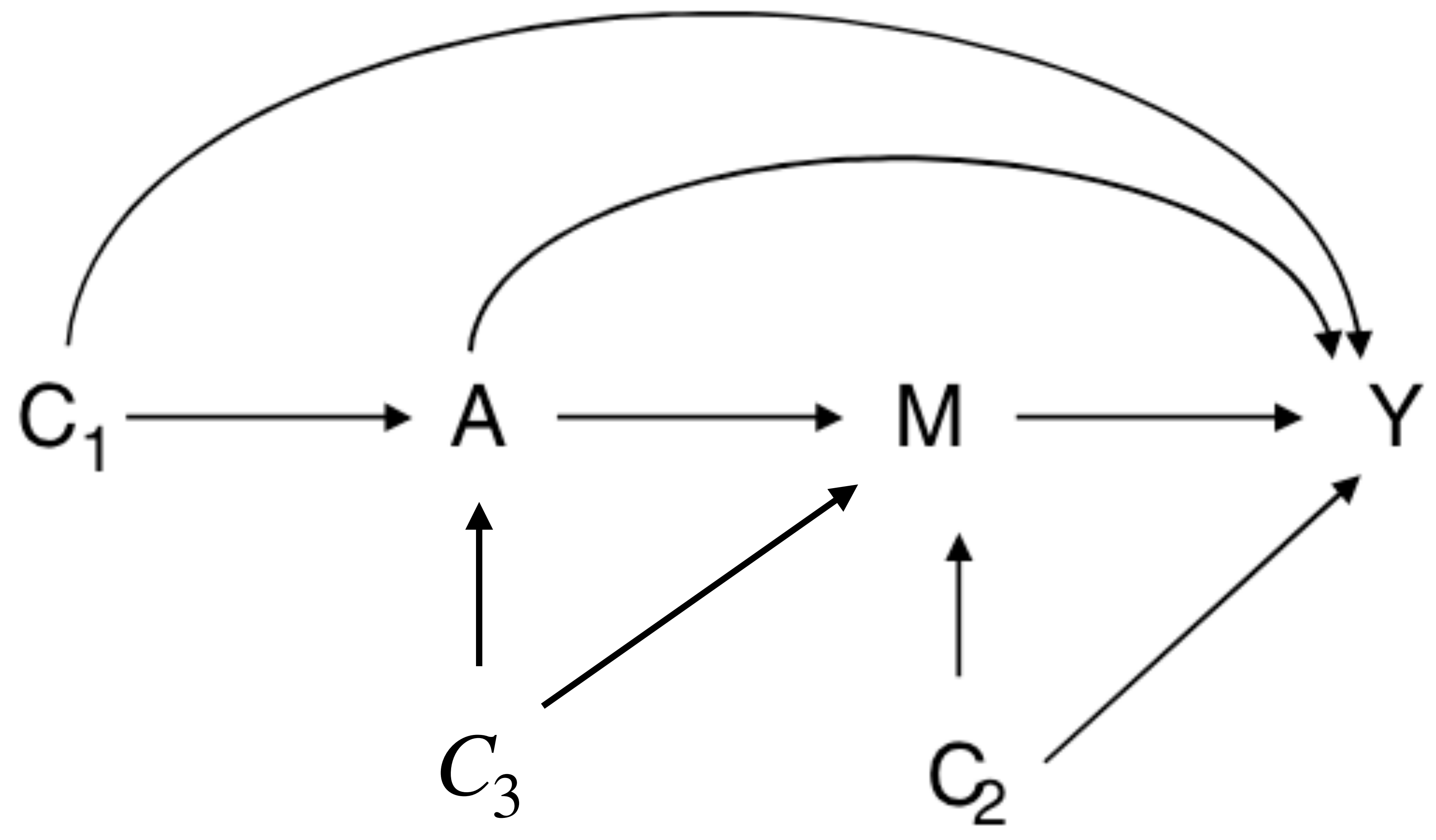
A2.1: What do you need to adjust for?



Some consequences:

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship

A2.1: What do you need to adjust for?
C_1 and C_3

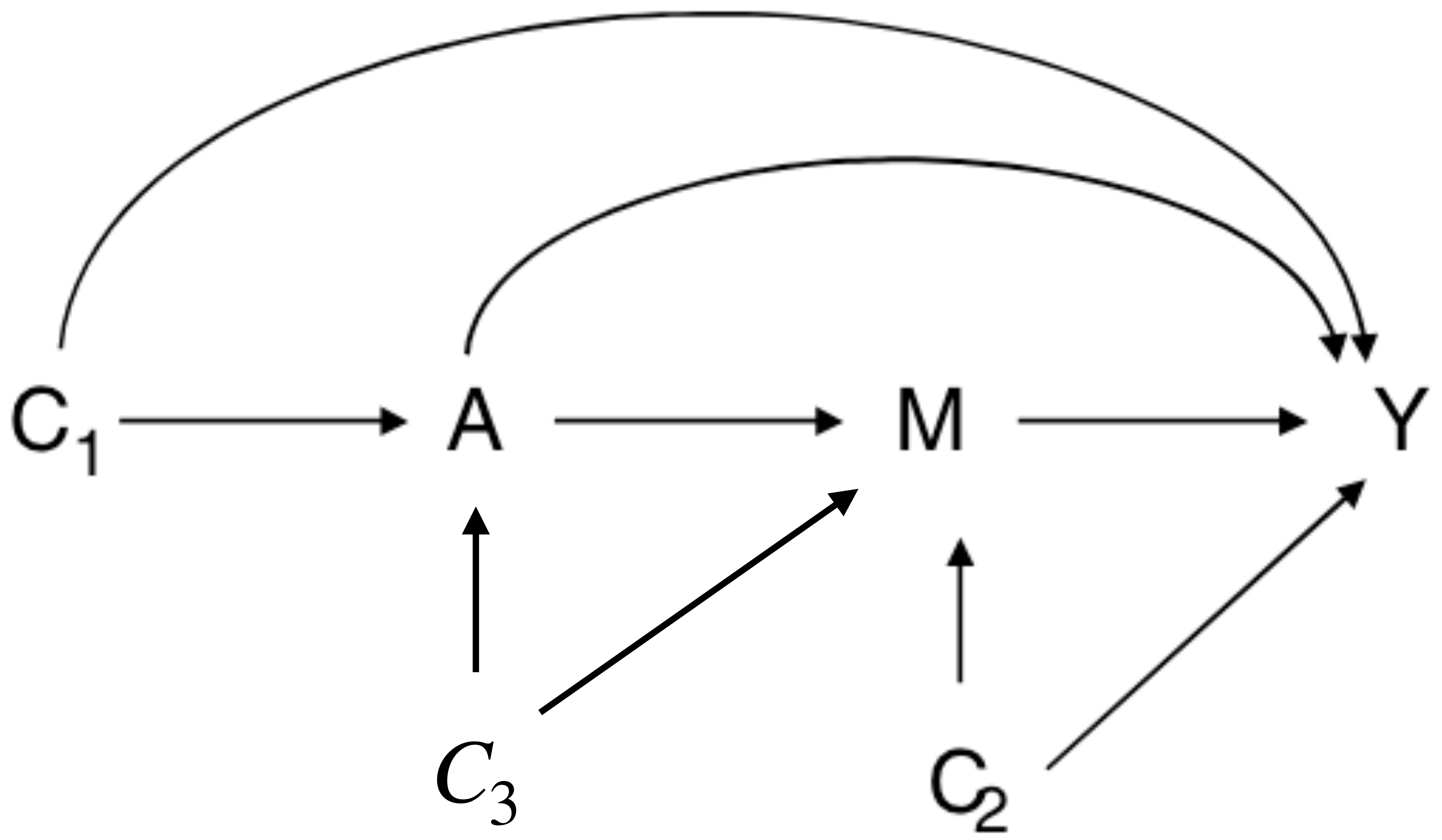


Some consequences:

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship and [assumption (A2.2)] no unmeasured confounding of the mediator–outcome relationship. The measured covariates C included in the models need to

A2.1: What do you need to adjust for?
C_1 and C_3

A2.2: What do you need to adjust for?

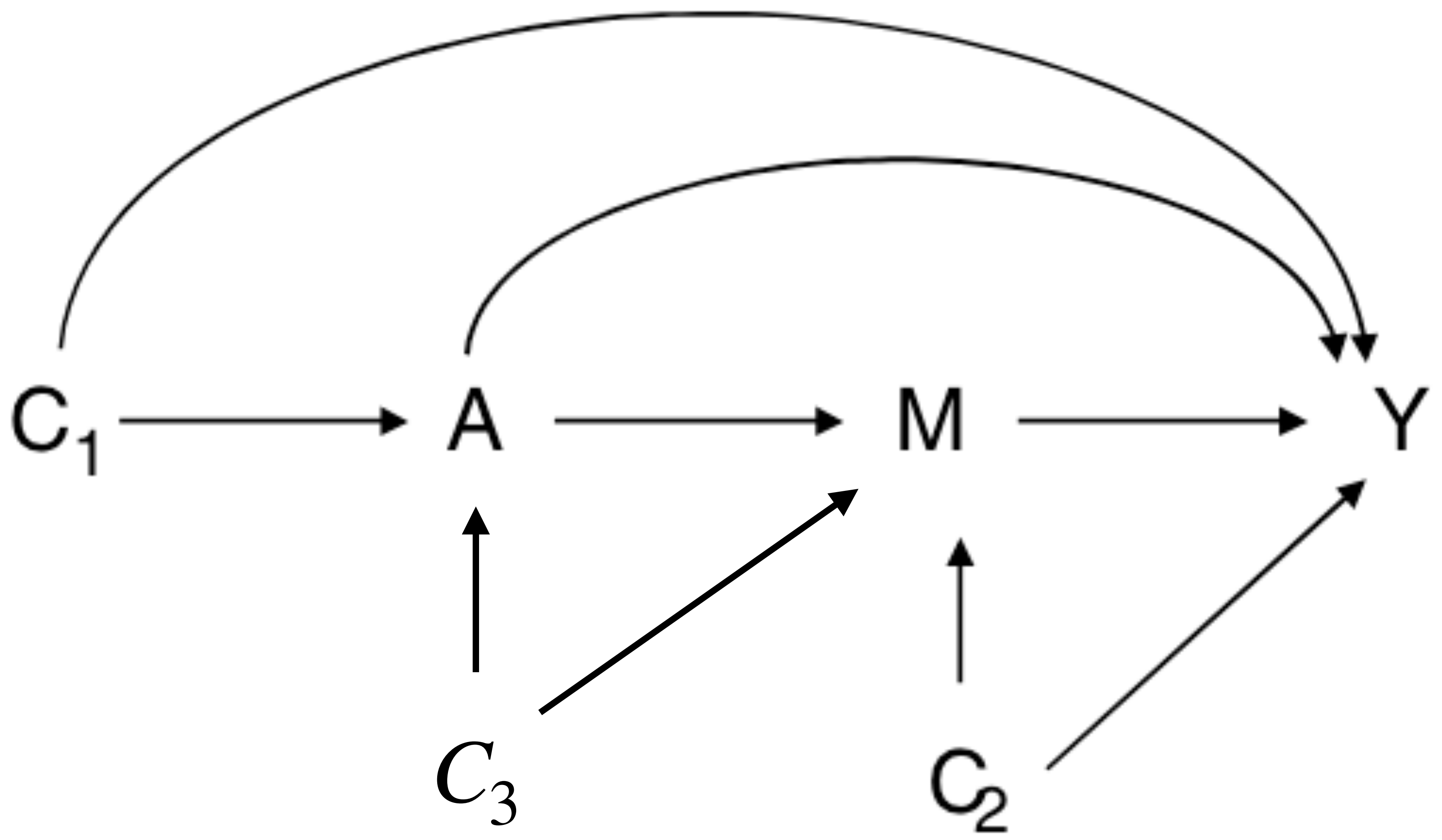


Some consequences:

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship and [assumption (A2.2)] no unmeasured confounding of the mediator–outcome relationship. The measured covariates C included in the models need to

A2.1: What do you need to adjust for?
C_1 and C_3

A2.2: What do you need to adjust for?
C_2



Some consequences:

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship and [assumption (A2.2)] no unmeasured confounding of the mediator–outcome relationship. The measured covariates C included in the models need to

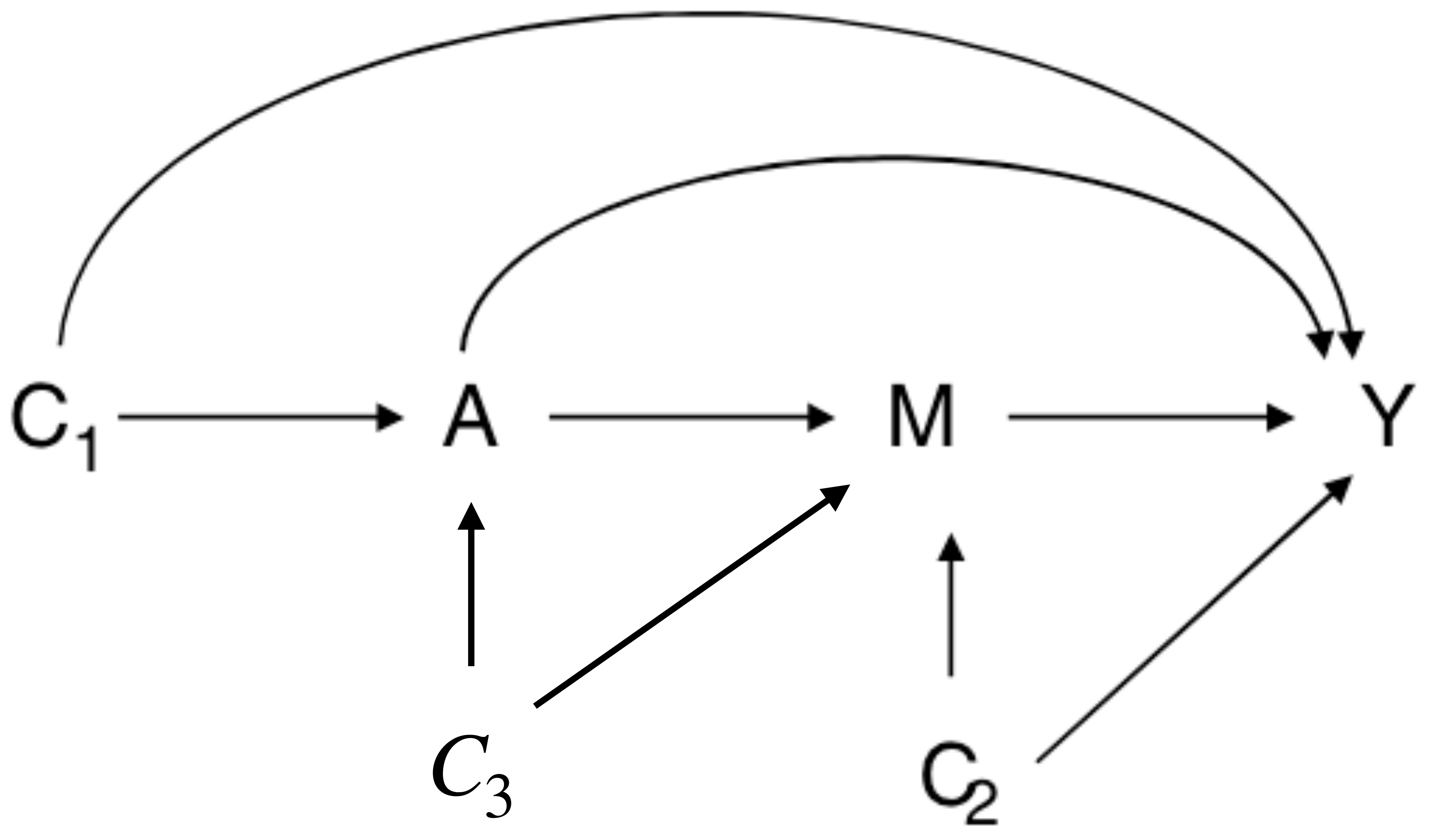
effects to be identified from the data, there must also be [assumption (A2.3)] no unmeasured confounding of the treatment–mediator relationship. Control must

Vanderweele 2016

A2.1: What do you need to adjust for?
C_1 and C_3

A2.2: What do you need to adjust for?
C_2

A2.3: What do you need to adjust for?



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C_2

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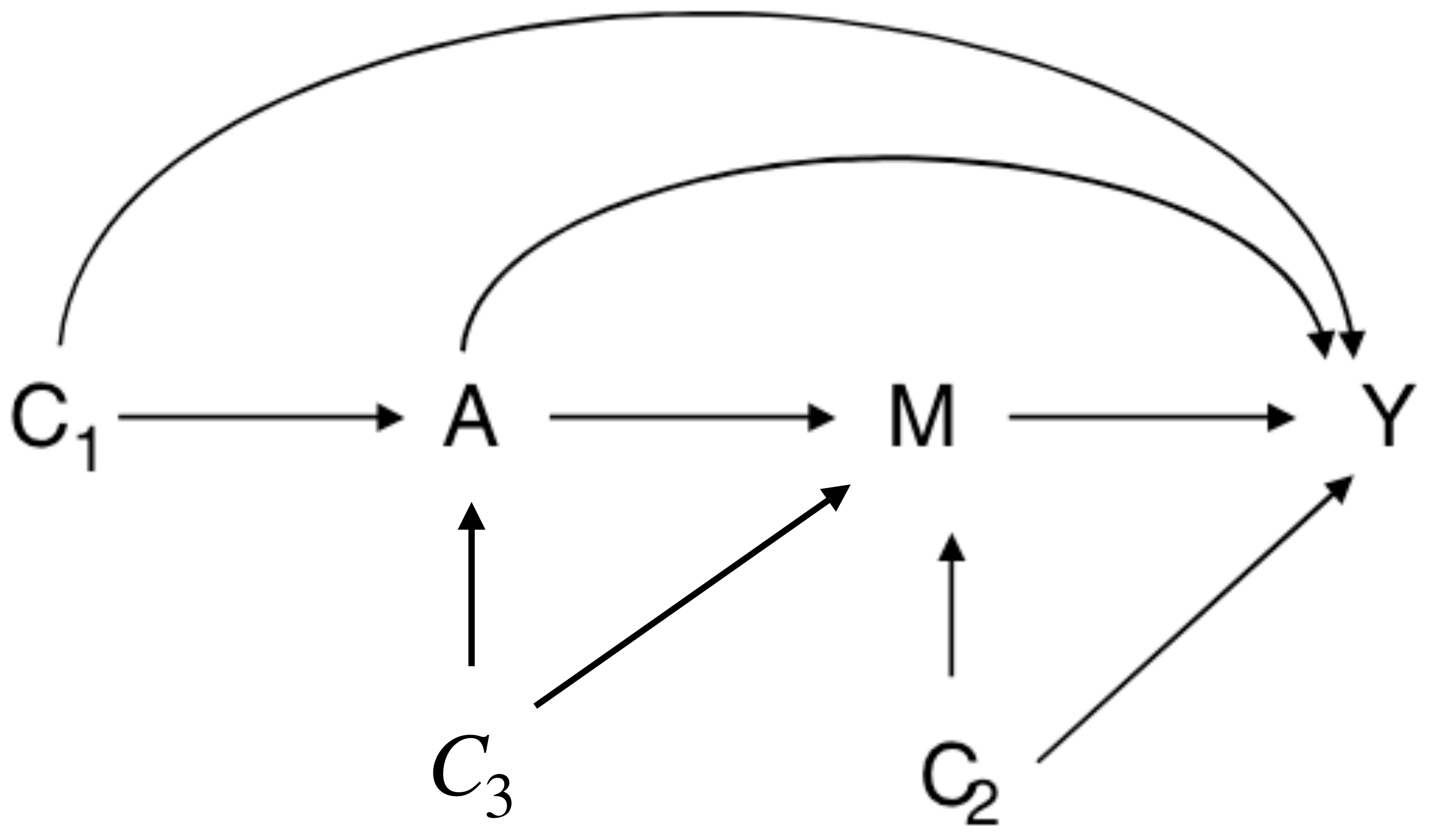
C_3



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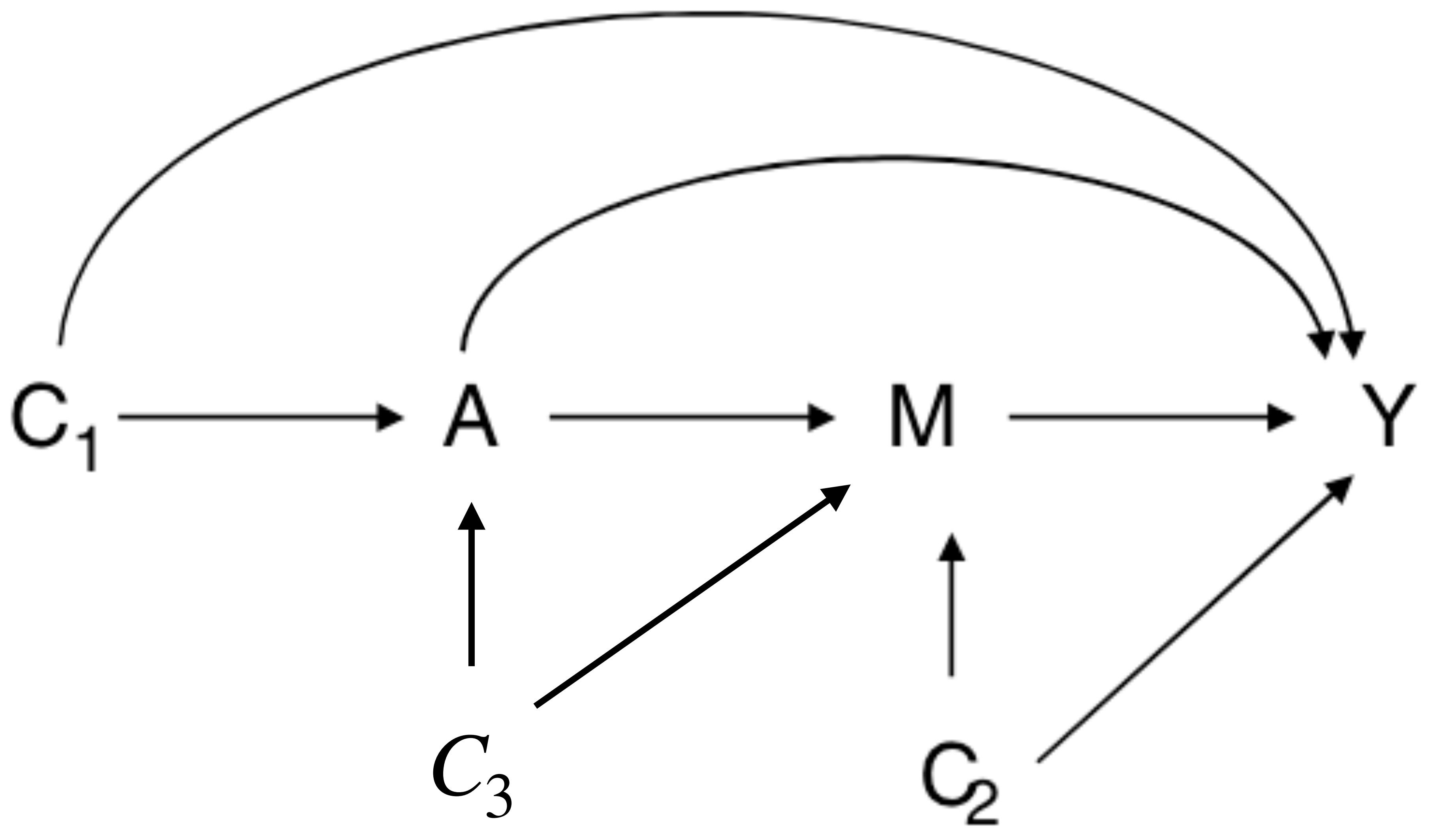
Vanderweele 2016

A2.1: What do you need to adjust for?
C_1 and C_3

A2.2: What do you need to adjust for?
C_2

A2.3: What do you need to adjust for?
C_3

Adjusting for C_3 is mentioned twice!



Some consequences:

C_1 and C_3

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship and [assumption (A2.2)] no unmeasured confounding of the mediator–outcome relationship. The measured covariates C included in the models need to C_2

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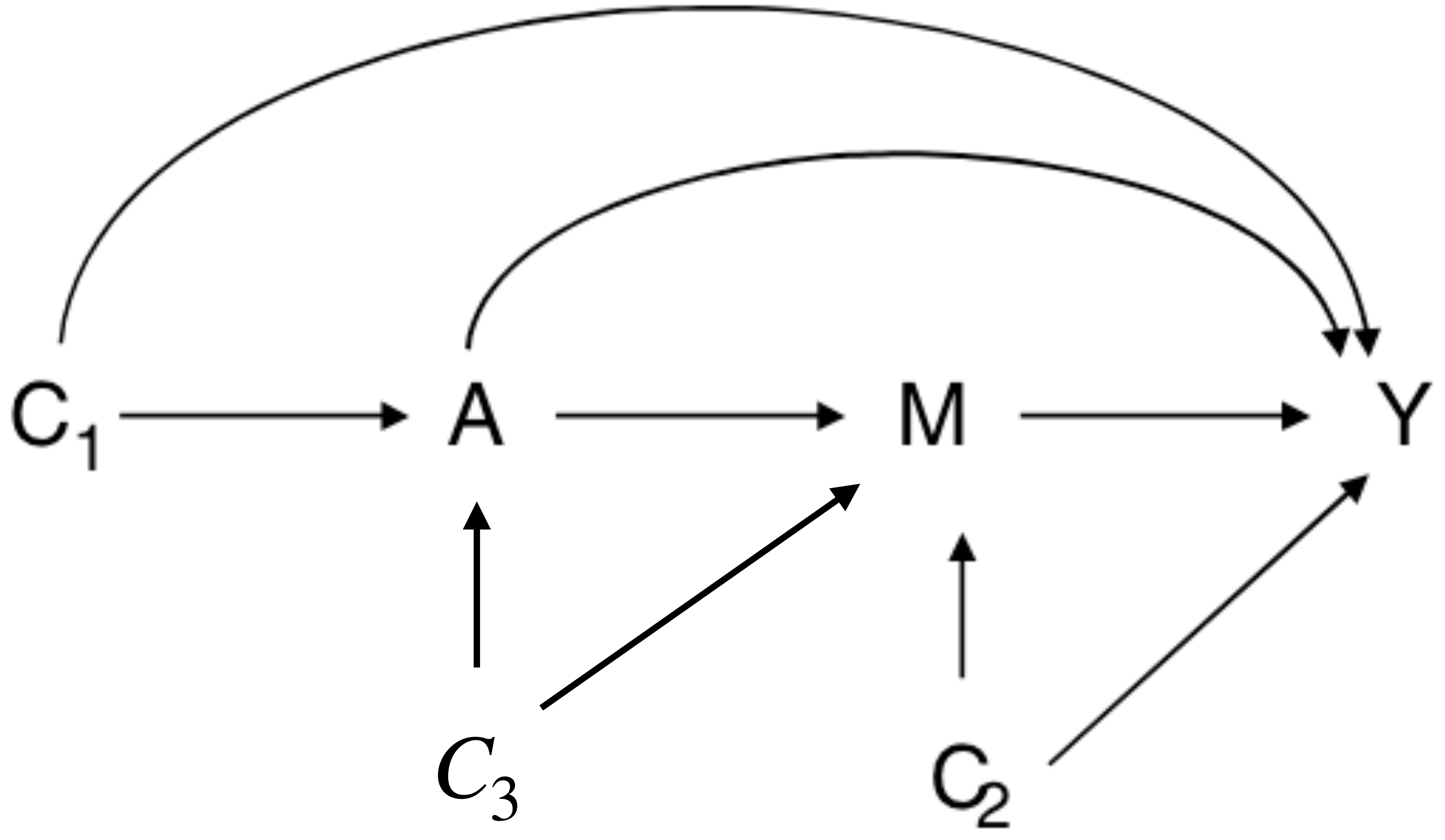
Vanderweele 2016

In summary, controlled direct effects require [assumption (A2.1)] no unmeasured treatment–outcome confounding and [assumption (A2.2)] no unmea-

Implied: C_1, C_2 and C_3



Some consequences:

C_1 and C_3

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship and [assumption (A2.2)] no unmeasured confounding of the mediator–outcome relationship. The measured covariates C included in the models need to C_2

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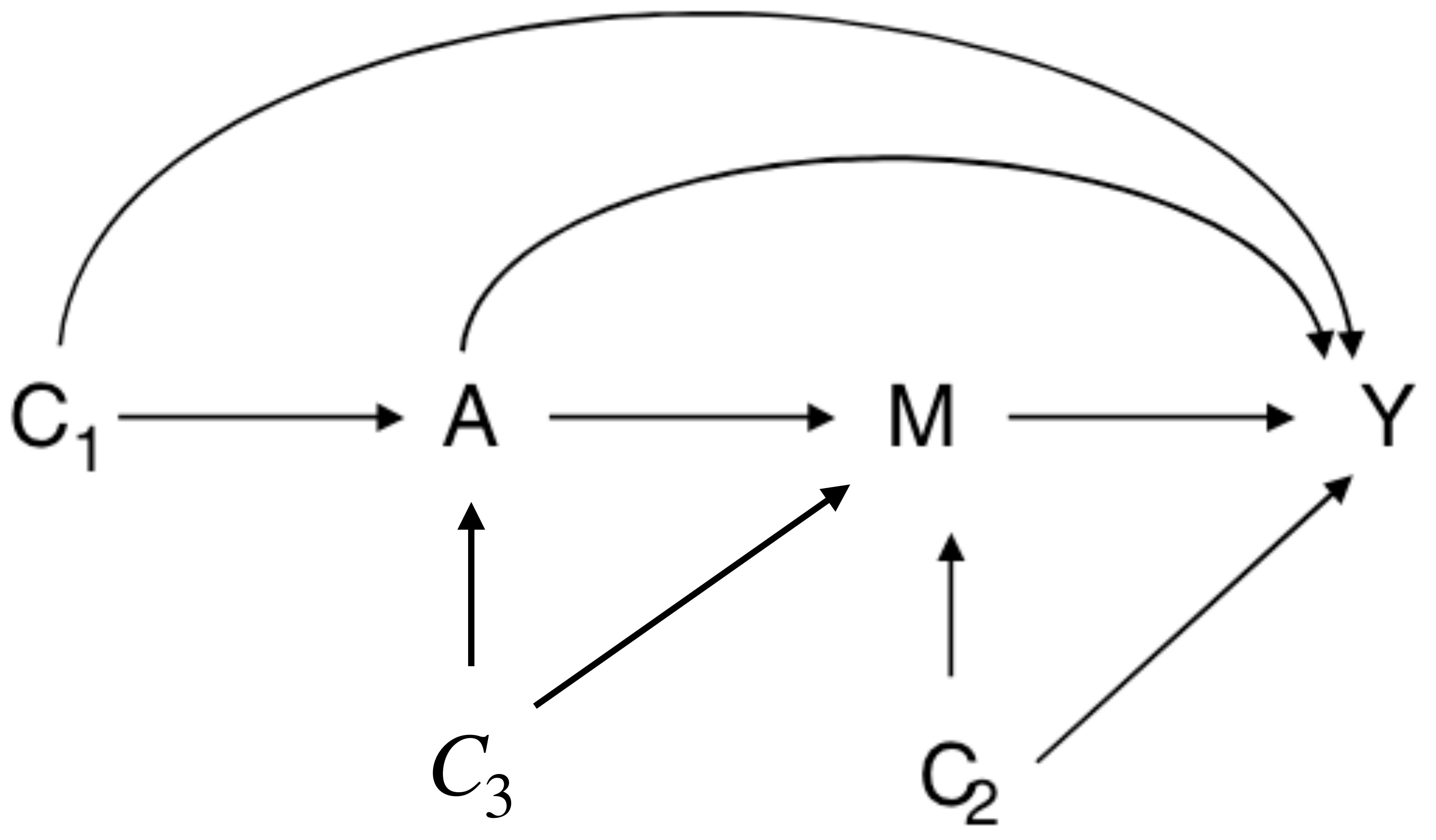
Vanderweele 2016

In summary, controlled direct effects require [assumption (A2.1)] no unmeasured treatment–outcome confounding and [assumption (A2.2)] no unmea-

Implied: C_1, C_2 and C_3

Actual: C_1 and C_2



Some consequences:

C_1 and C_3

[assumption (A2.1)] no unmeasured confounding of the treatment–outcome relationship and [assumption (A2.2)] no unmeasured confounding of the mediator–outcome relationship. The measured covariates C included in the models need to C_2

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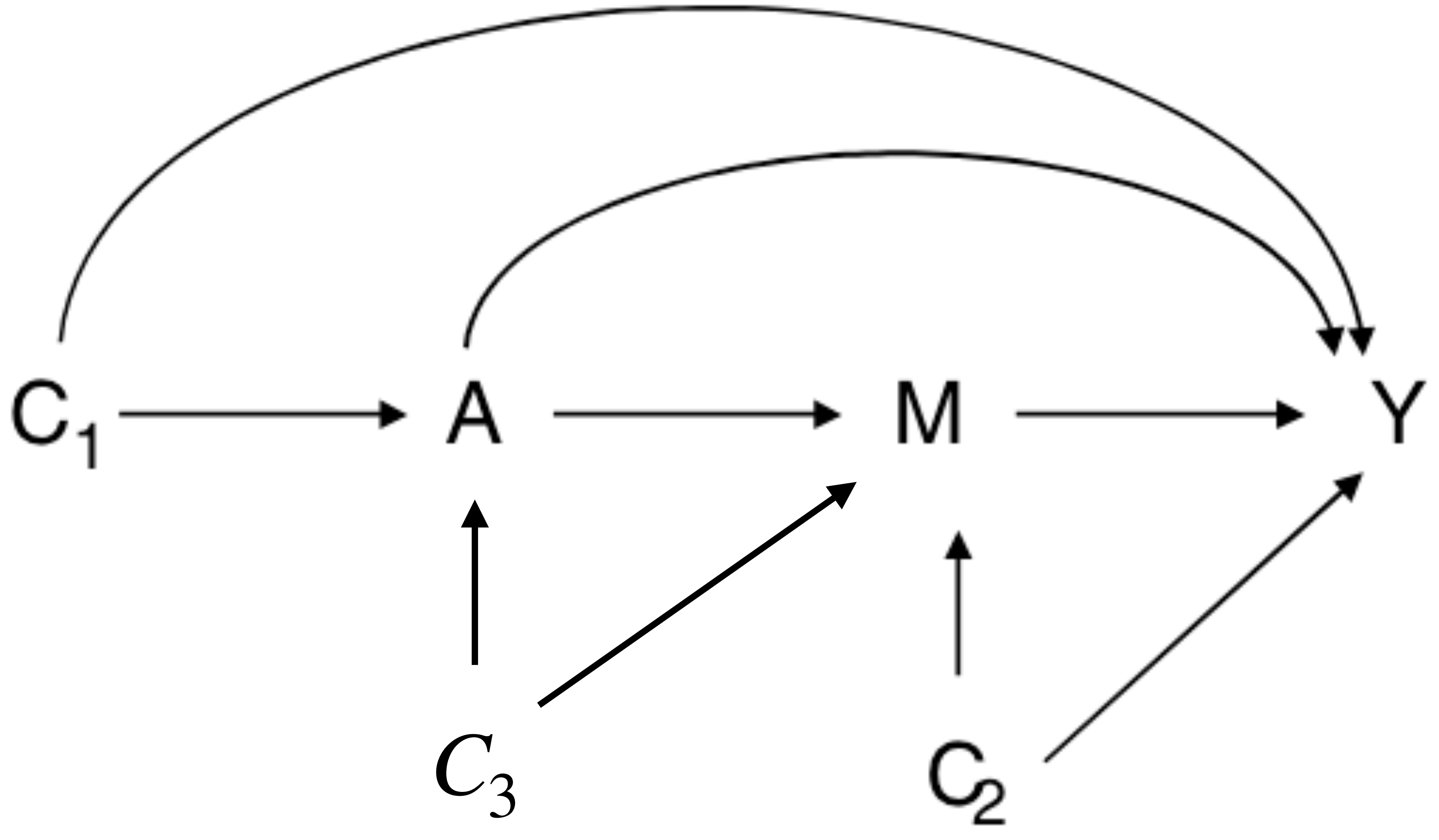
Vanderweele 2016

In summary, controlled direct effects require [assumption (A2.1)] no unmeasured treatment–outcome confounding and [assumption (A2.2)] no unmea-

Implied: C_1, C_2 and C_3

Actual: C_1 and C_2



A2.1 should be: "no unmeasured confounding of the treatment-outcome relationship through paths that do not go through M"

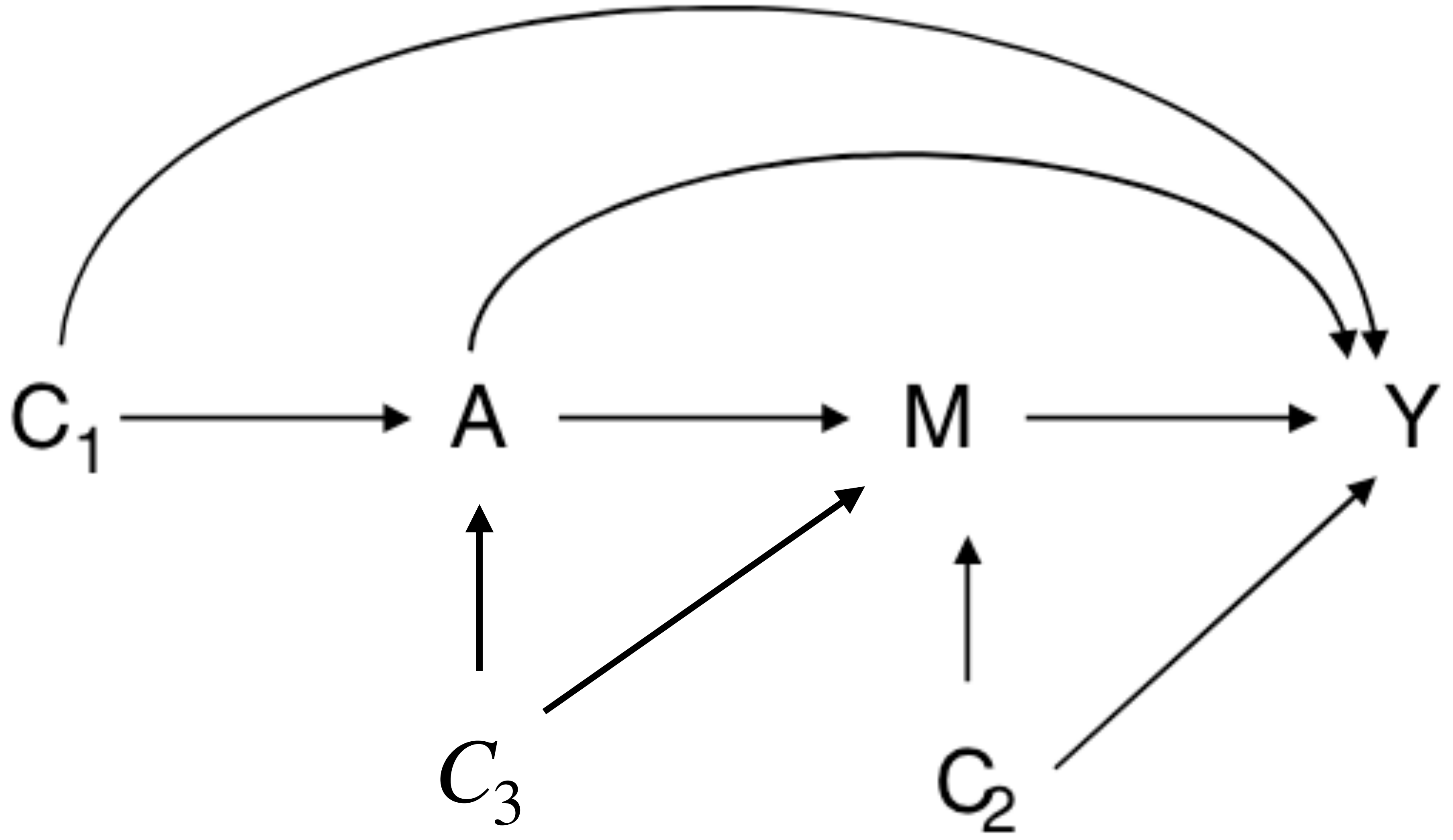
Some consequences:

for all levels of a and m. However, controlled direct effects in general require stronger conditions for identification than do total causal effects. This is because the definition of a con-

Vanderweele and Vansteelandt 2009

chapter, when we are interested in pathways and direct and indirect effects, the assumptions about confounding that are needed to identify these direct and indirect effects are even stronger than for total effects. We might often, perhaps almost

Vanderweele 2016



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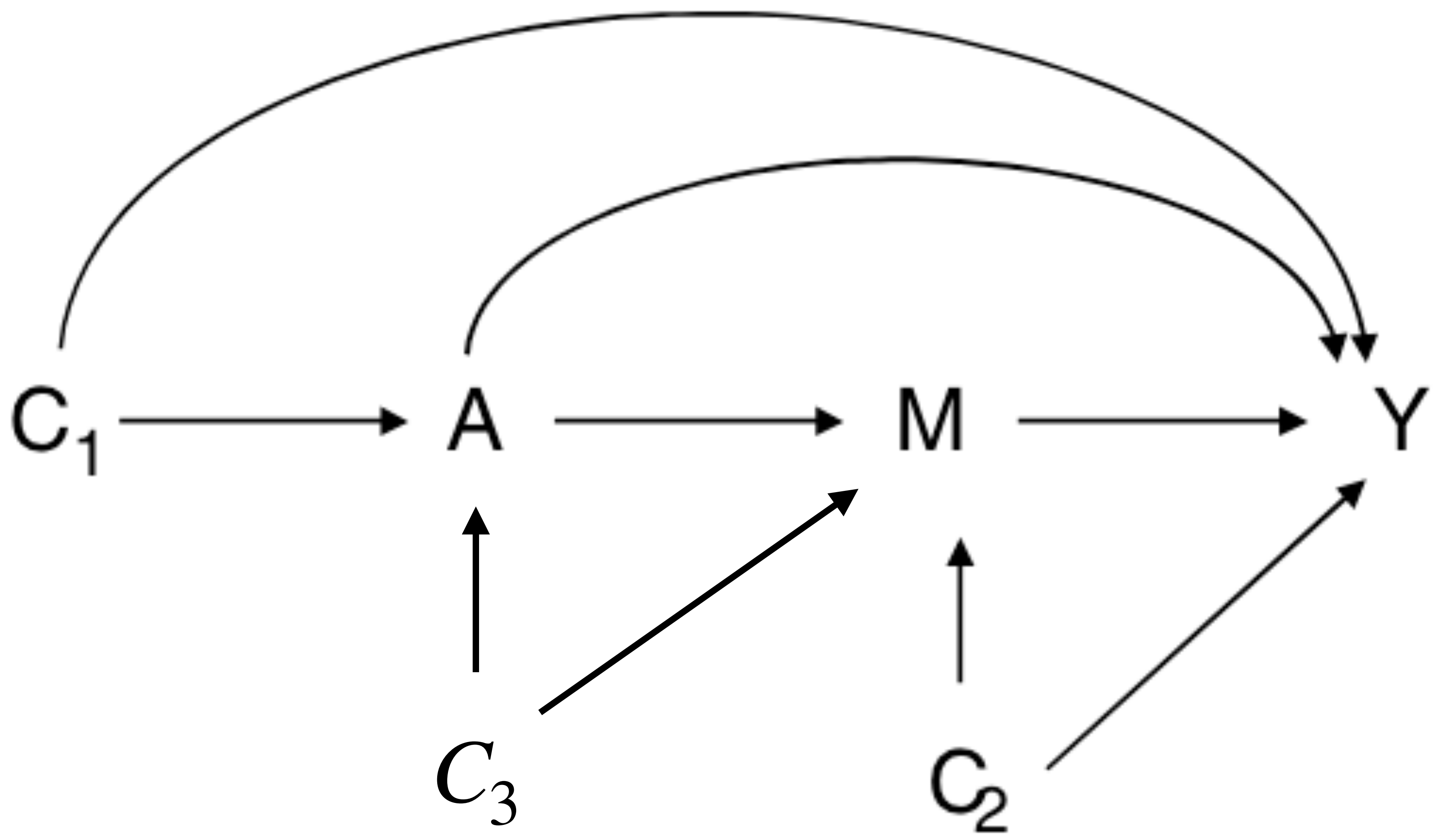
Vanderweele and Vansteelandt 2009

chapter, when we are interested in pathways and direct and indirect effects, the assumptions about confounding that are needed to identify these direct and indirect effects are even stronger than for total effects. We might often, perhaps almost

Vanderweele 2016

This is only true in general if assumptions for CDE are the assumptions for total effects plus adjusting for C_2

- CDE requires adjusting for C_1 and C_2
- Total effect requires adjusting for C_1 and C_3

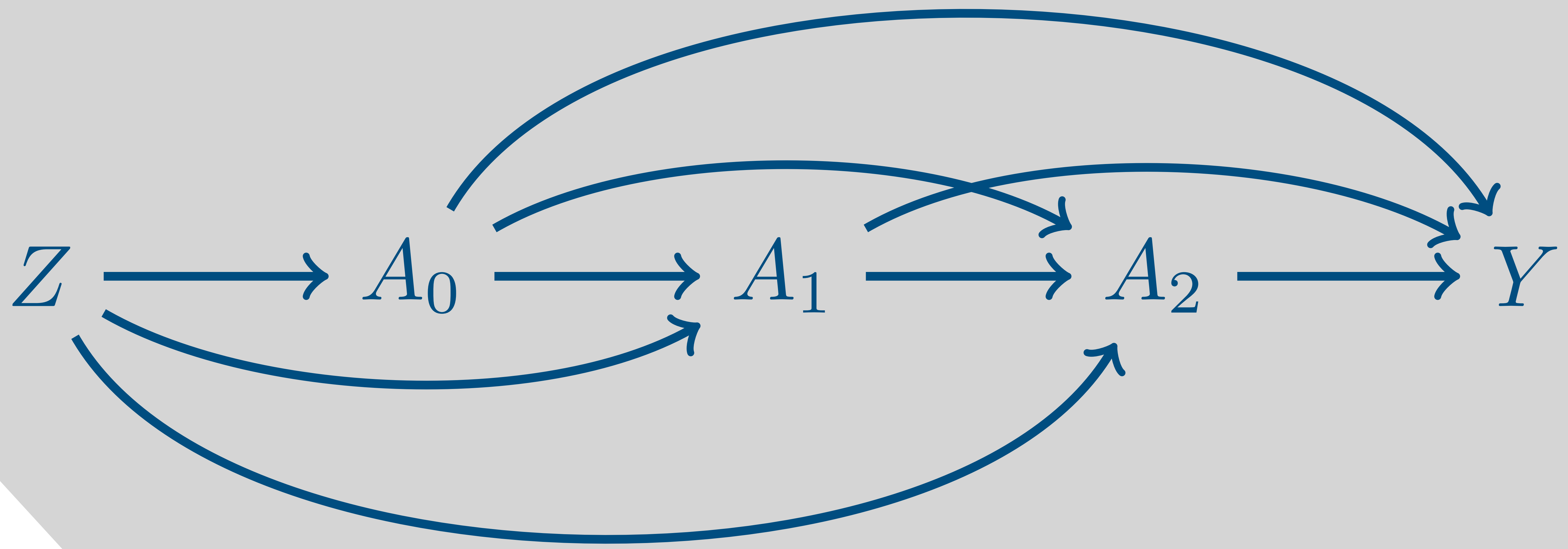


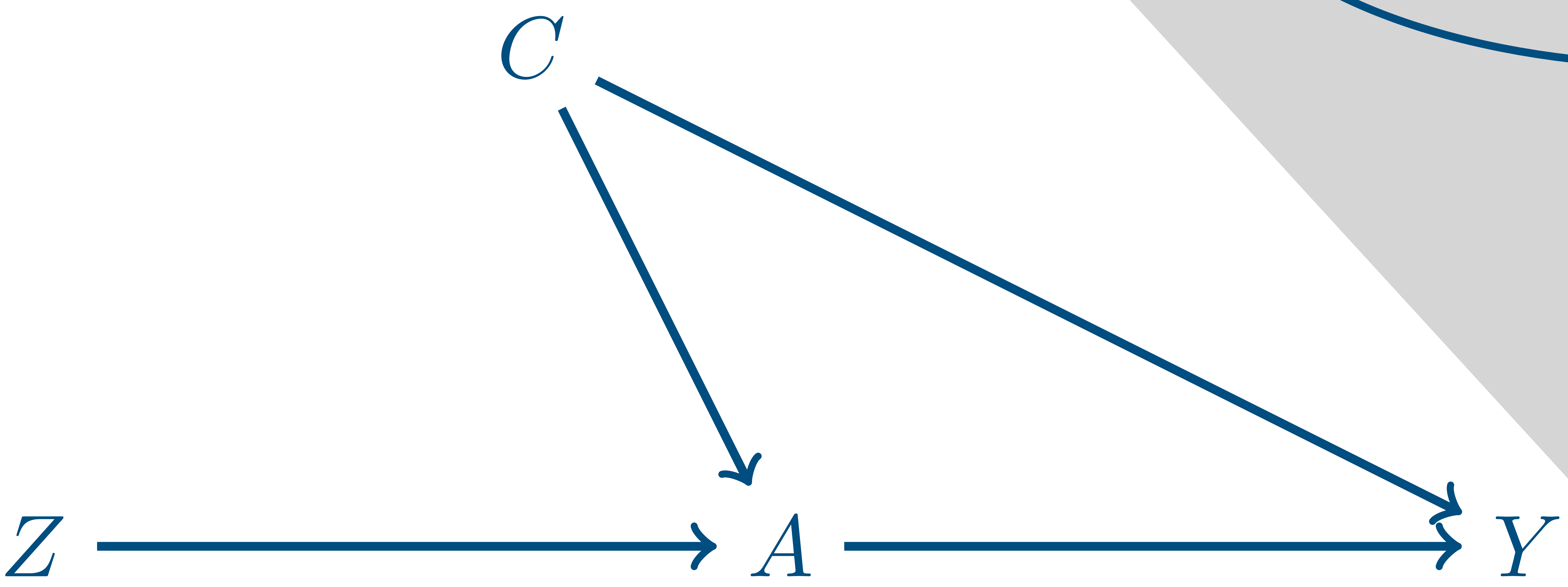
Example 2

$$\begin{tikzcd}
 & C \arrow[d] \arrow[dr] & \\
Z \arrow[r] & A \arrow[r] & Y
\end{tikzcd}$$

...standard IV setup

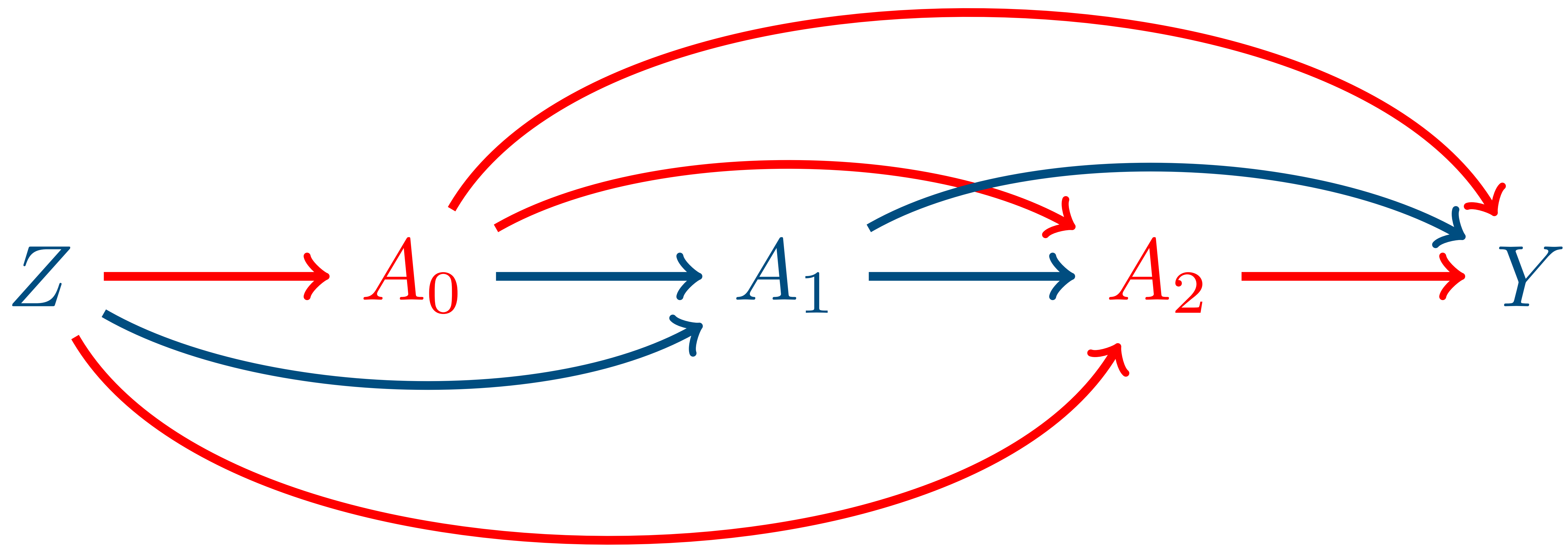
...Z does not have instantaneous effect on A



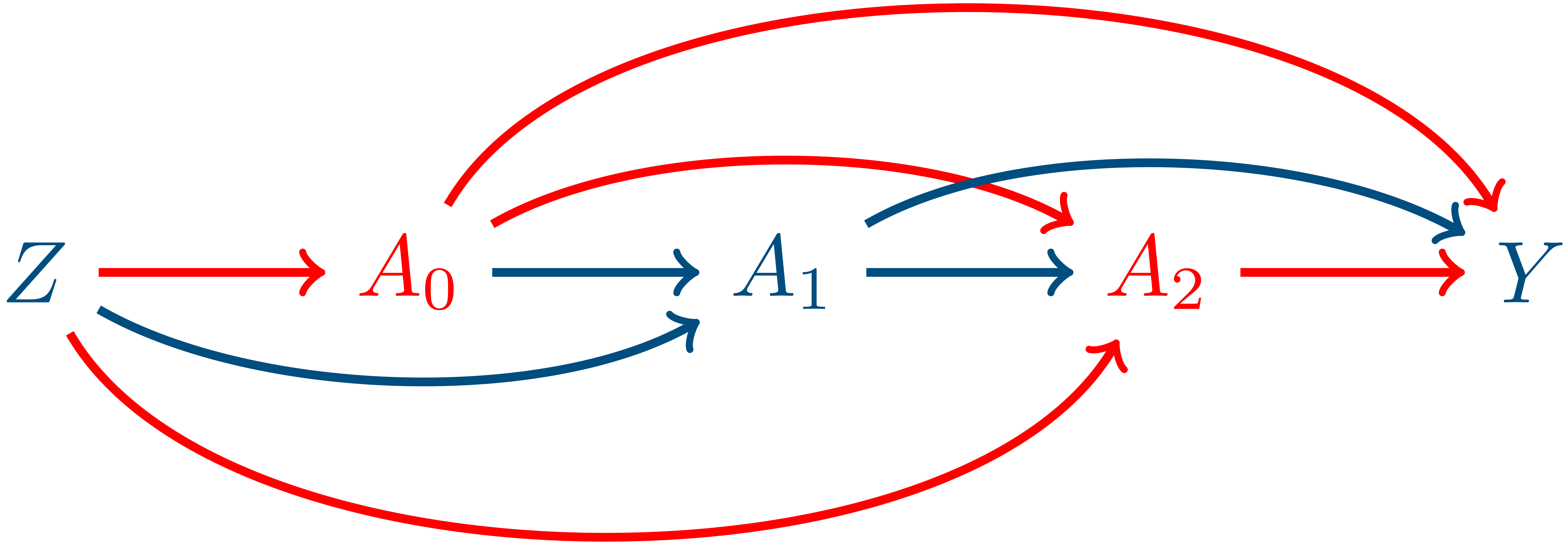


...standard IV setup

Exclusion restriction assumption: The instrument only affects the outcome through its effect on the exposure.

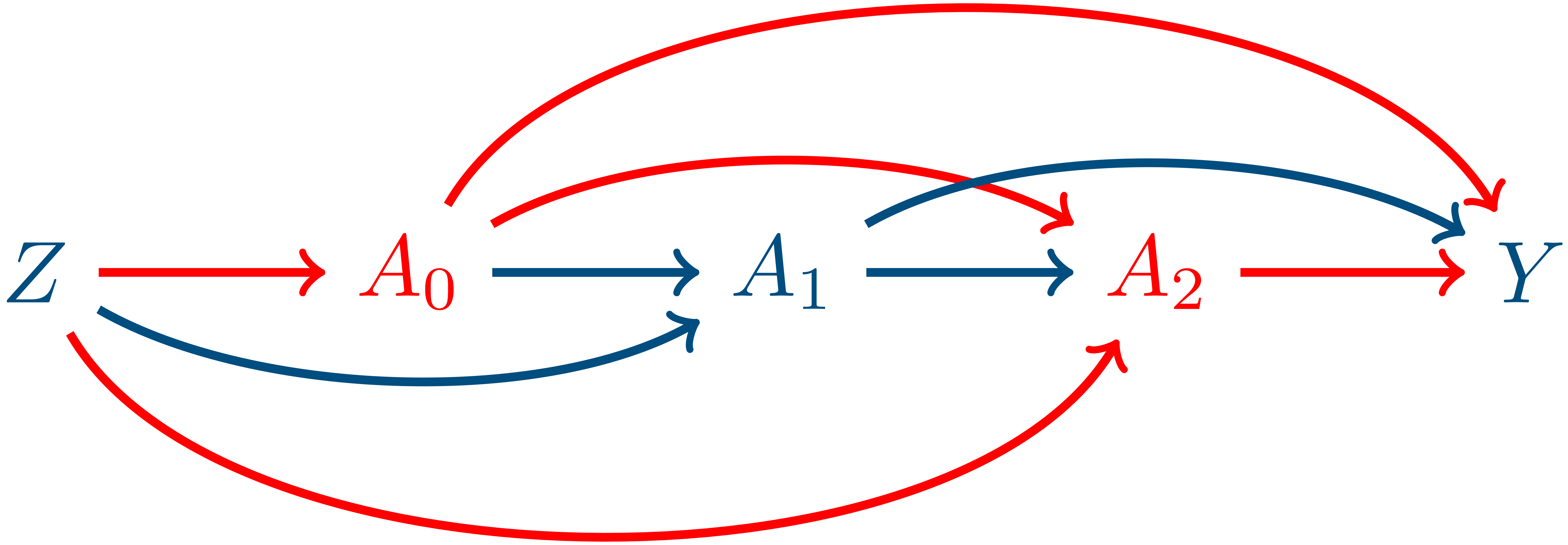


Exclusion restriction assumption: The instrument only affects the outcome through its effect on the exposure.



If you've only measured A_1, the red paths violate the exclusion restriction.

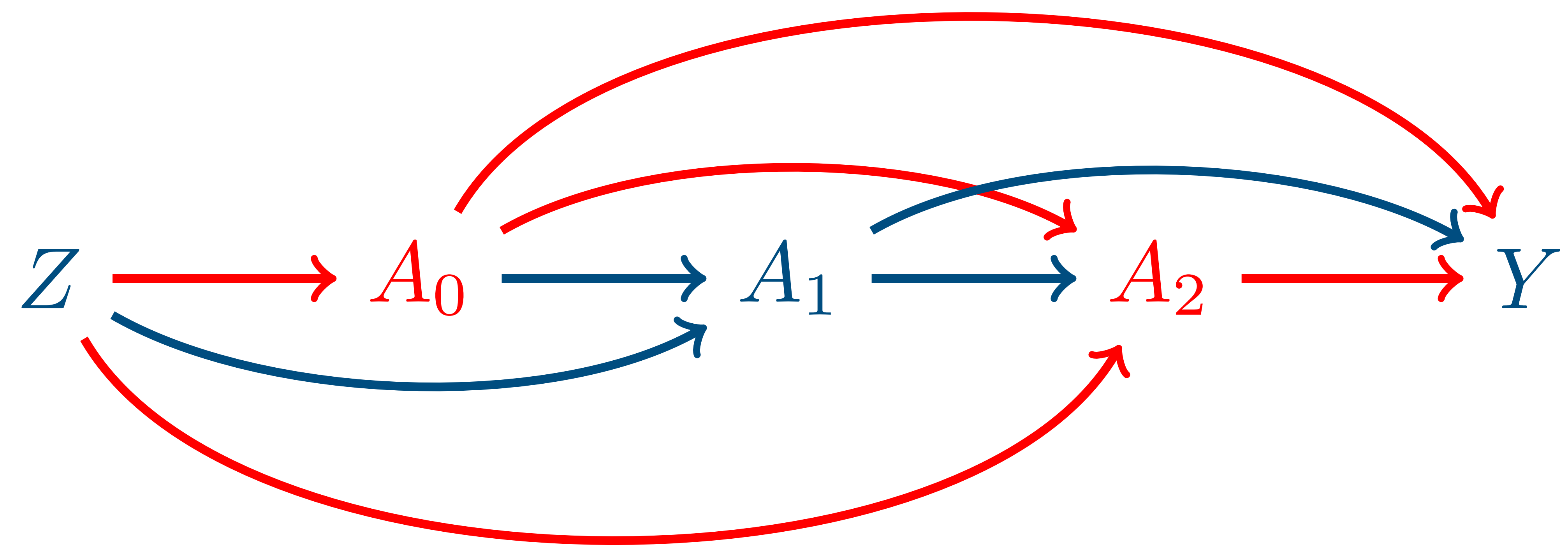
Exclusion restriction assumption: The instrument only affects the outcome through its effect on the exposure.



If you've only measured A_1, the red paths violate the exclusion restriction.

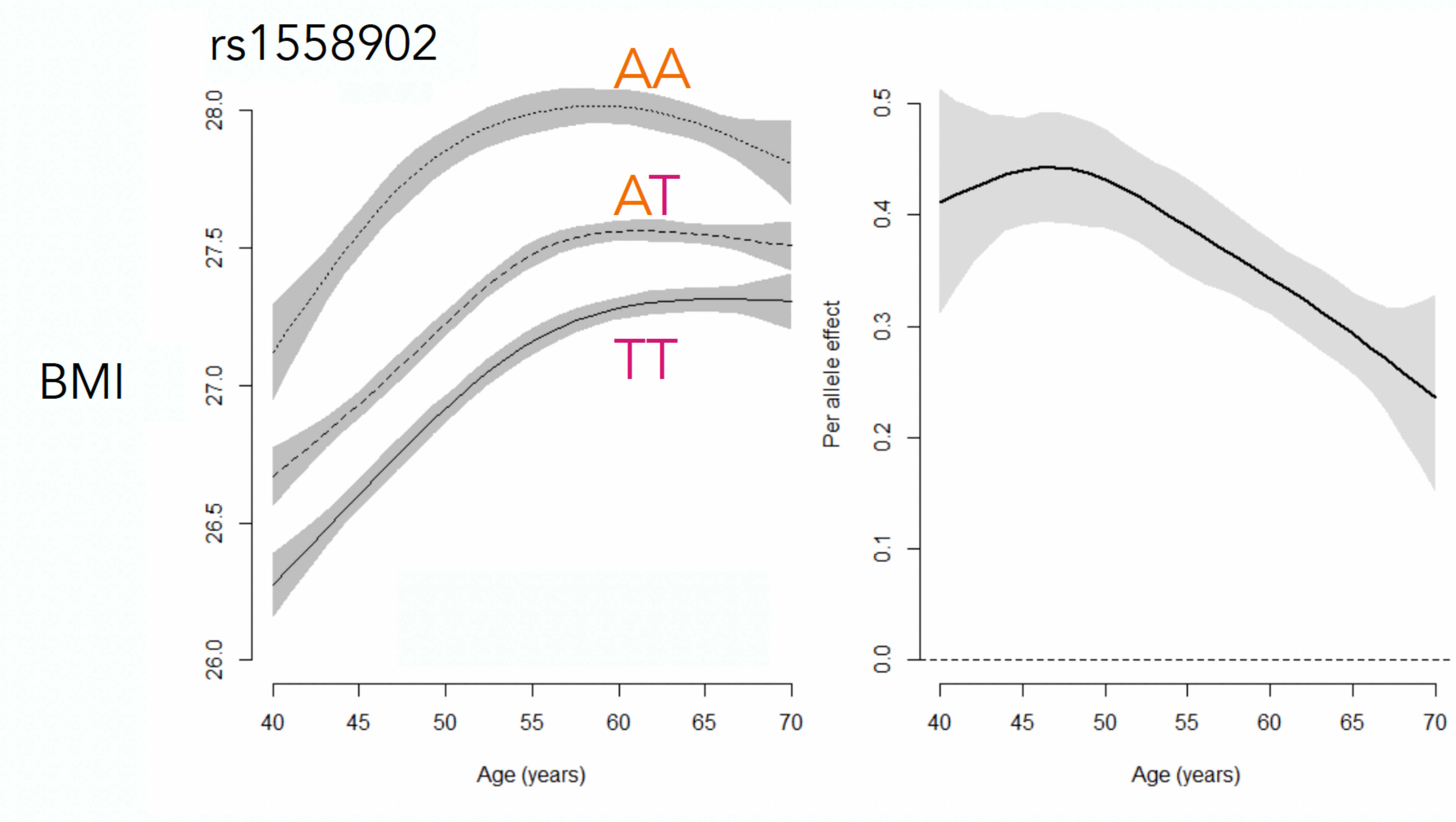
What is our causal question??

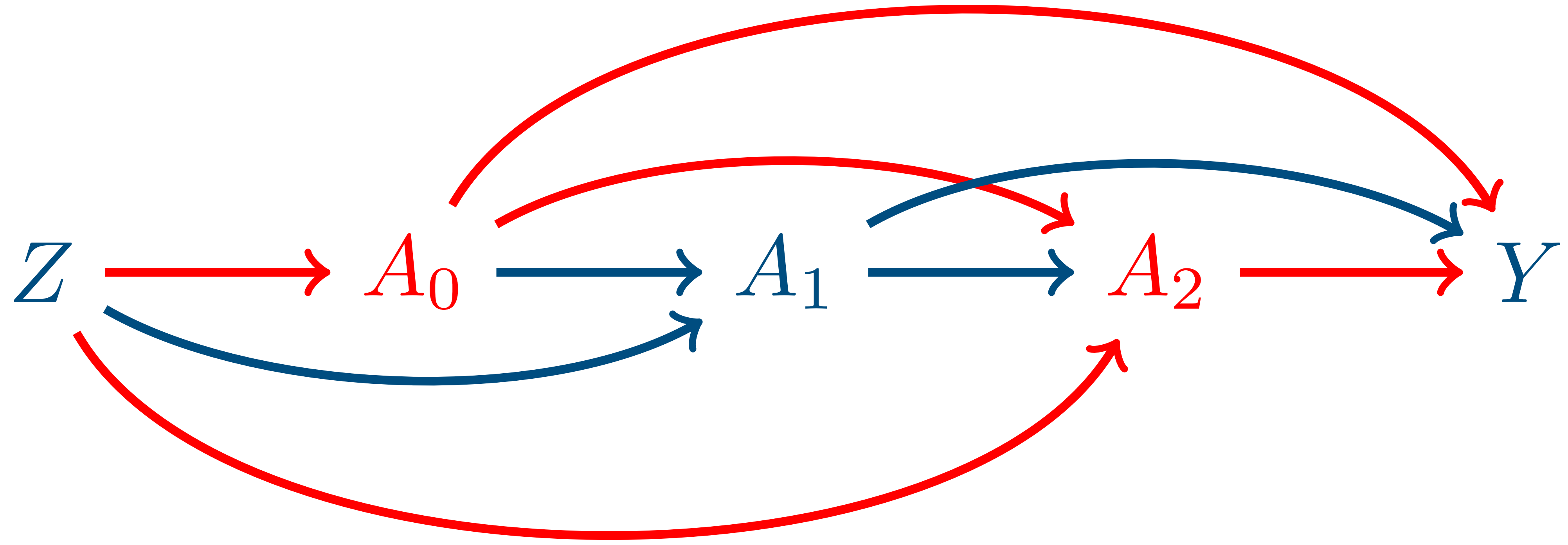
- Effect of A_1?
- Effect of A at all times



What is our causal question??

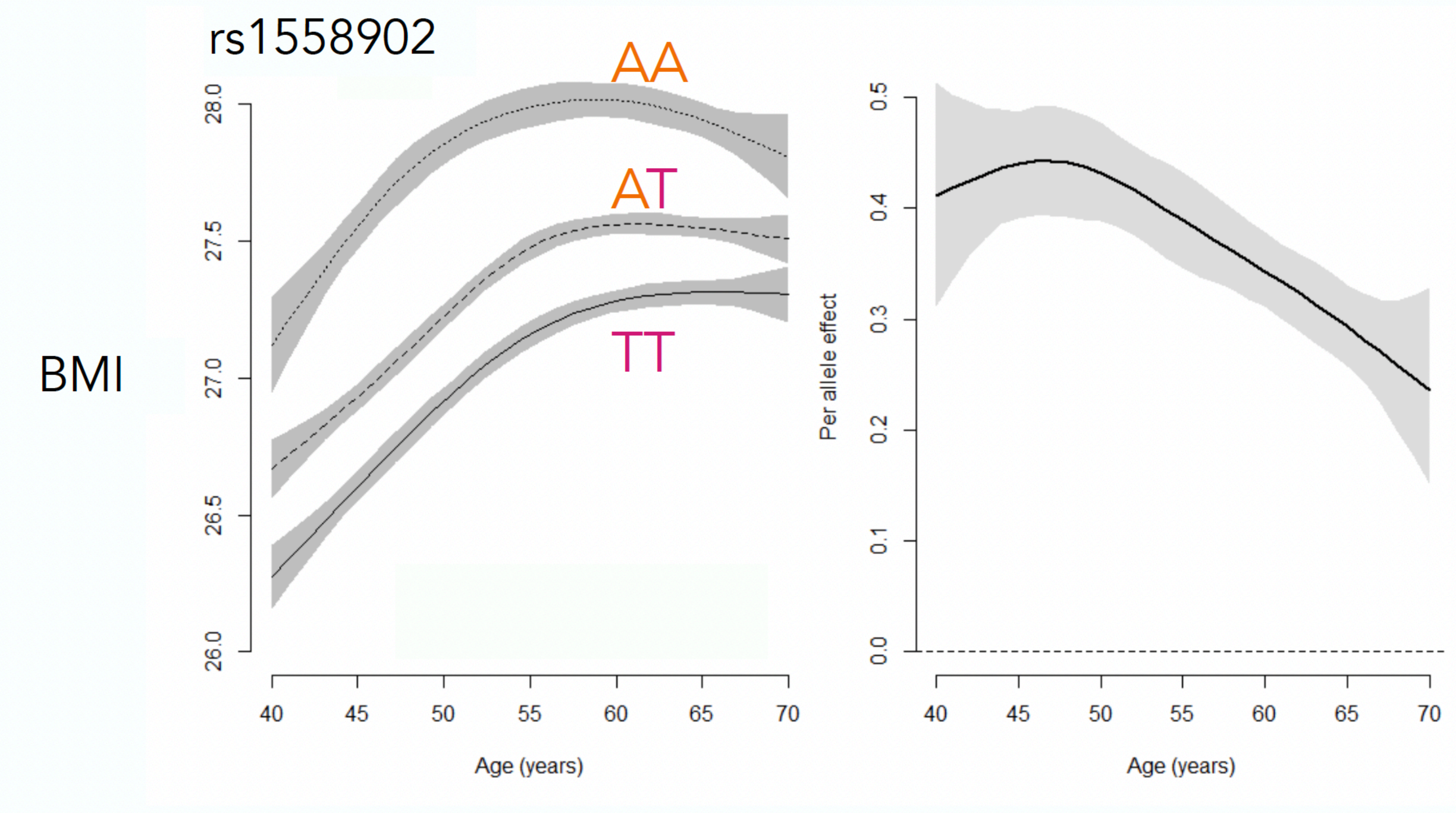
- ~~Effect of A_T?~~
- Effect of A at all times (assuming the relationship between Z and A is constant)



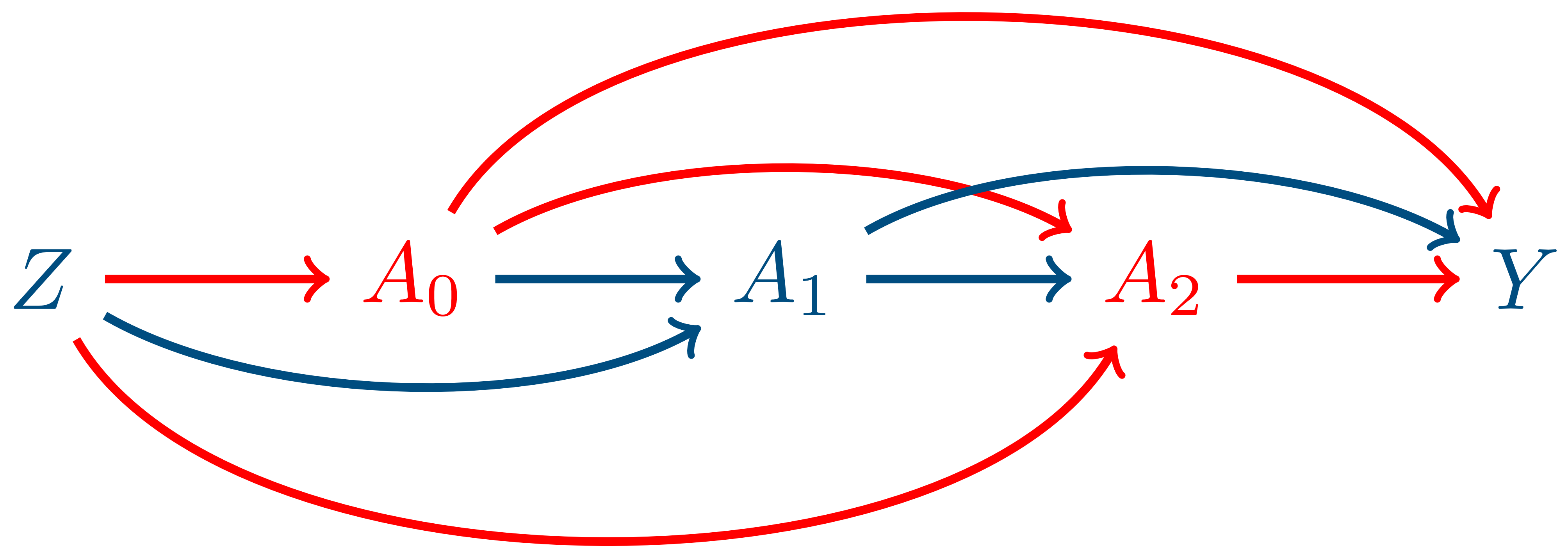


What is our causal question??

- ~~Effect of A_T?~~
- Effect of A at all times (assuming the relationship between Z and A is constant)

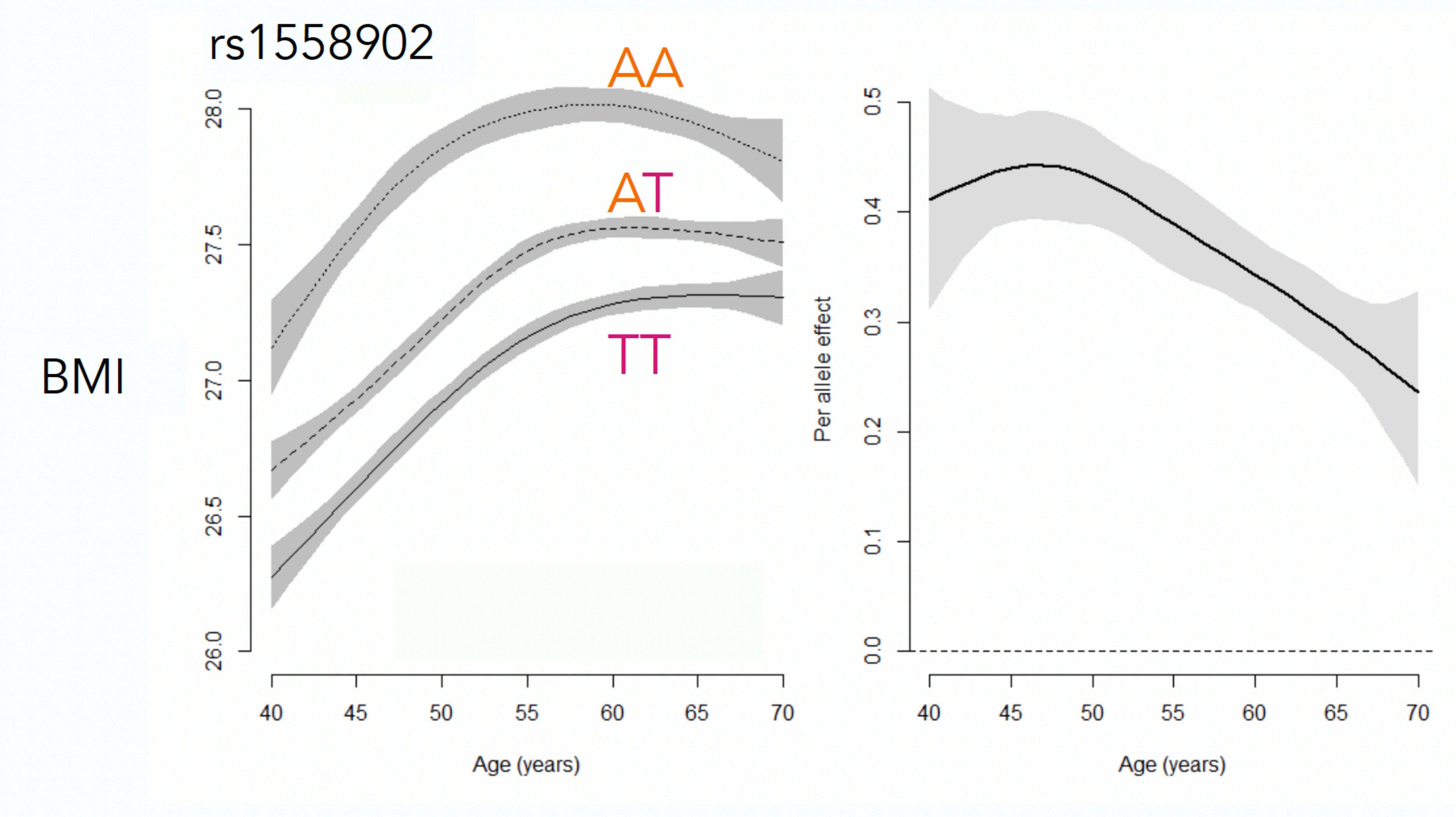


	Linear exposure window		
	5 year	10 year	25 year
BMI			
rs1558902	5 (0,9)	10 (3,19)	25 (12,39)
rs6567160	6 (-1,14)	10 (-1,24)	19 (1,43)
rs13021737	15 (6,28)	33 (15,59)	65 (31,116)
rs10938397	11 (1,25)	15 (-3,38)	23 (-6,64)
rs543874	6 (-3,18)	19 (2,42)	51 (19,101)
rs2207139	10 (-1,20)	13 (-3,32)	29 (3,66)
rs11030104	0 (-9,9)	2 (-12,22)	8 (-13,40)
rs3101336	18 (-2,52)	39 (1,107)	79 (13,216)
rs7138803	2 (-9,13)	6 (-11,29)	19 (-11,65)
rs10182181	12 (4,24)	26 (10,48)	41 (14,80)
Score	4 (3,5)	9 (7,11)	23 (18,29)



What is our causal question??

- ~~Effect of A_T?~~
- Effect of A at all times (assuming the relationship between Z and A is constant)



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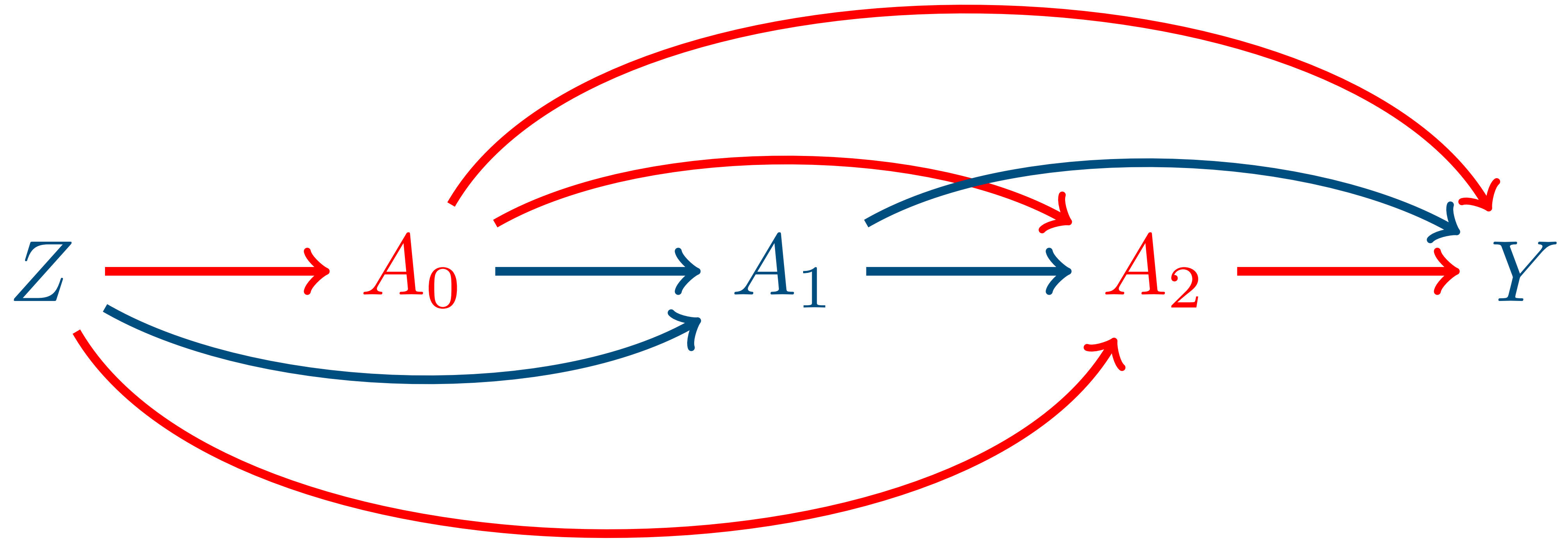
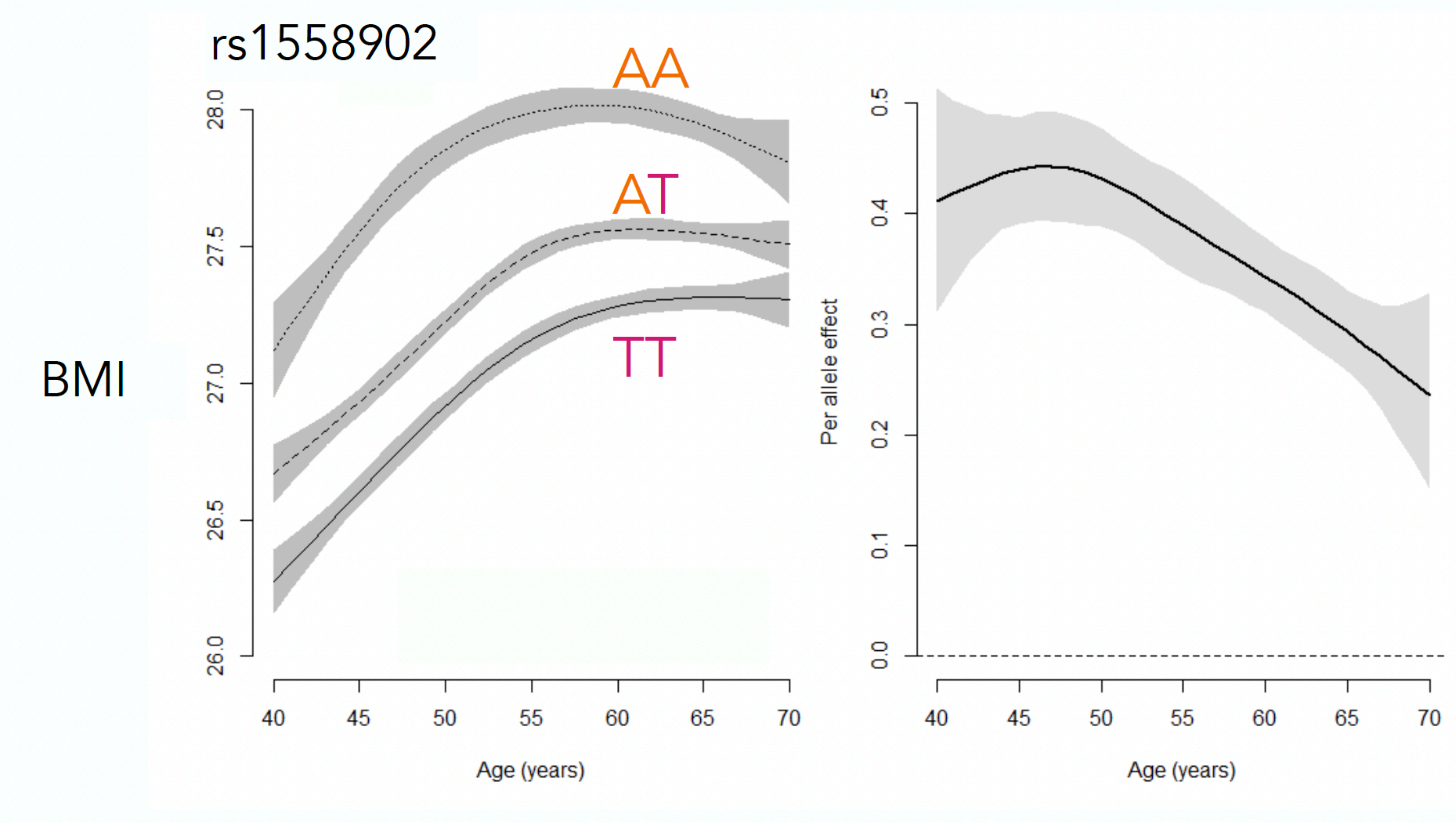
rs10182181	12 (4,24)	26 (10,48)	41 (14,80)
Score	4 (3,5)	9 (7,11)	23 (18,29)



What is our causal question??

- ~~Effect of A_T?~~
- Effect of A at all times (assuming the relationship between Z and A is constant)



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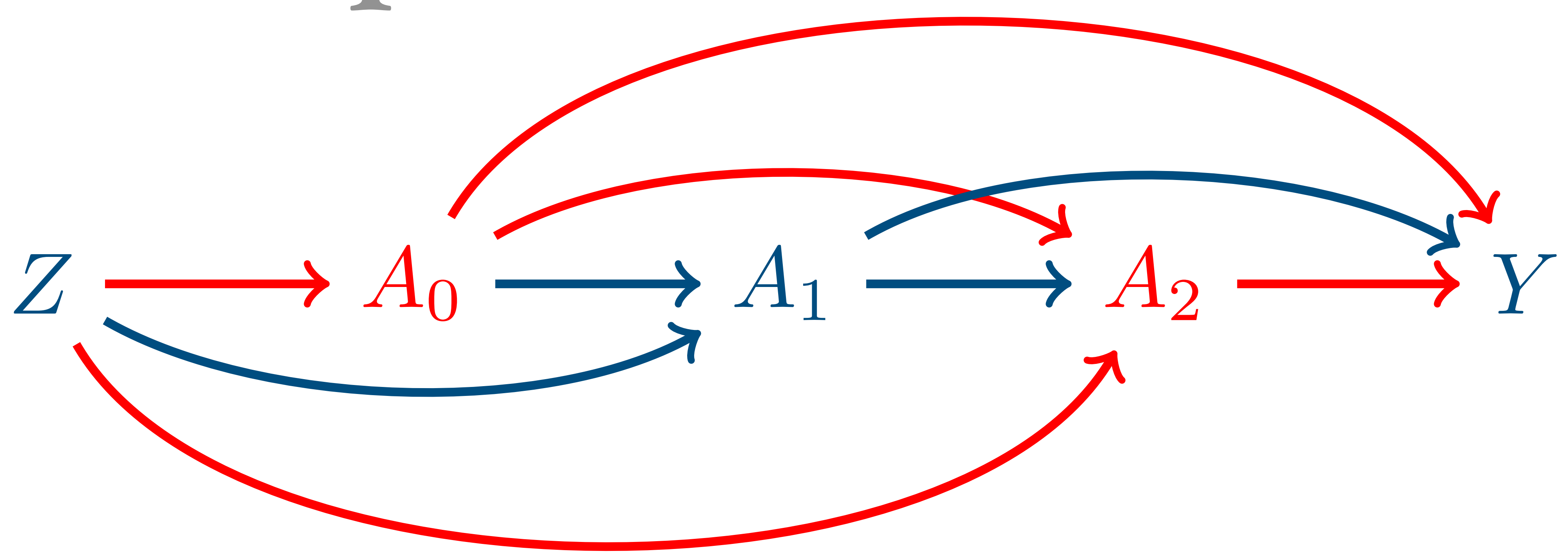
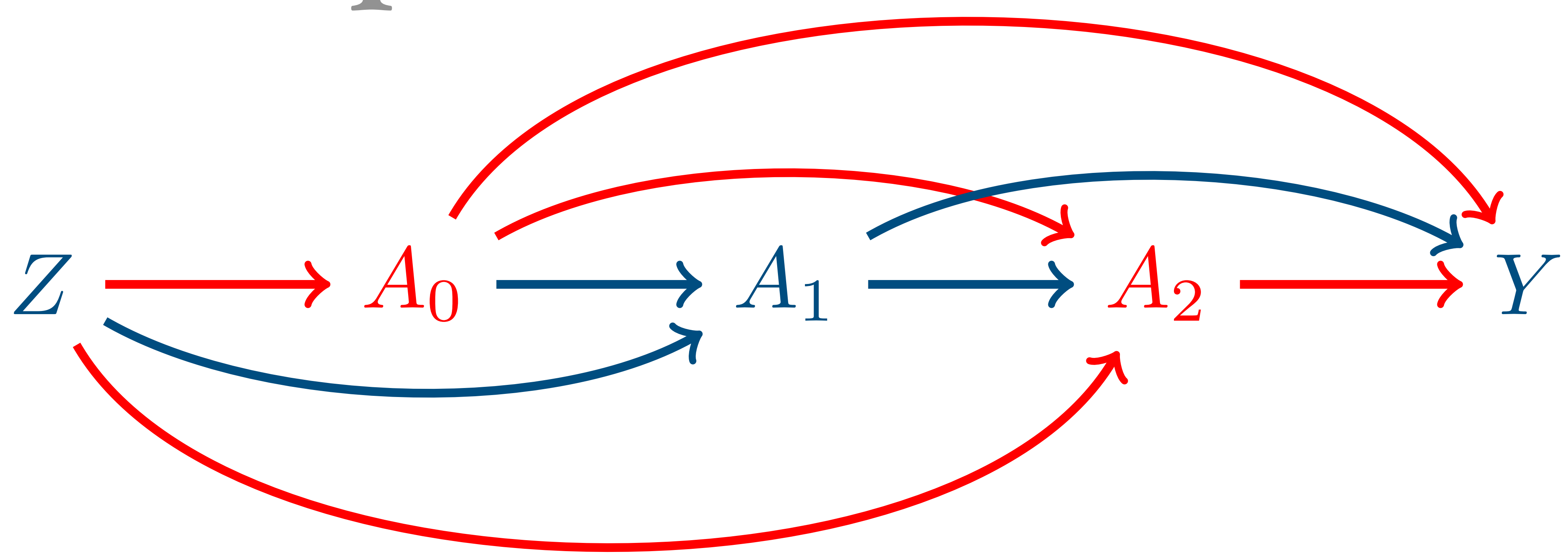
IV setup



What is our causal question??

- ~~Effect of A_1?~~
- Effect of A at all times (assuming the relationship between Z and A is constant)

IV setup

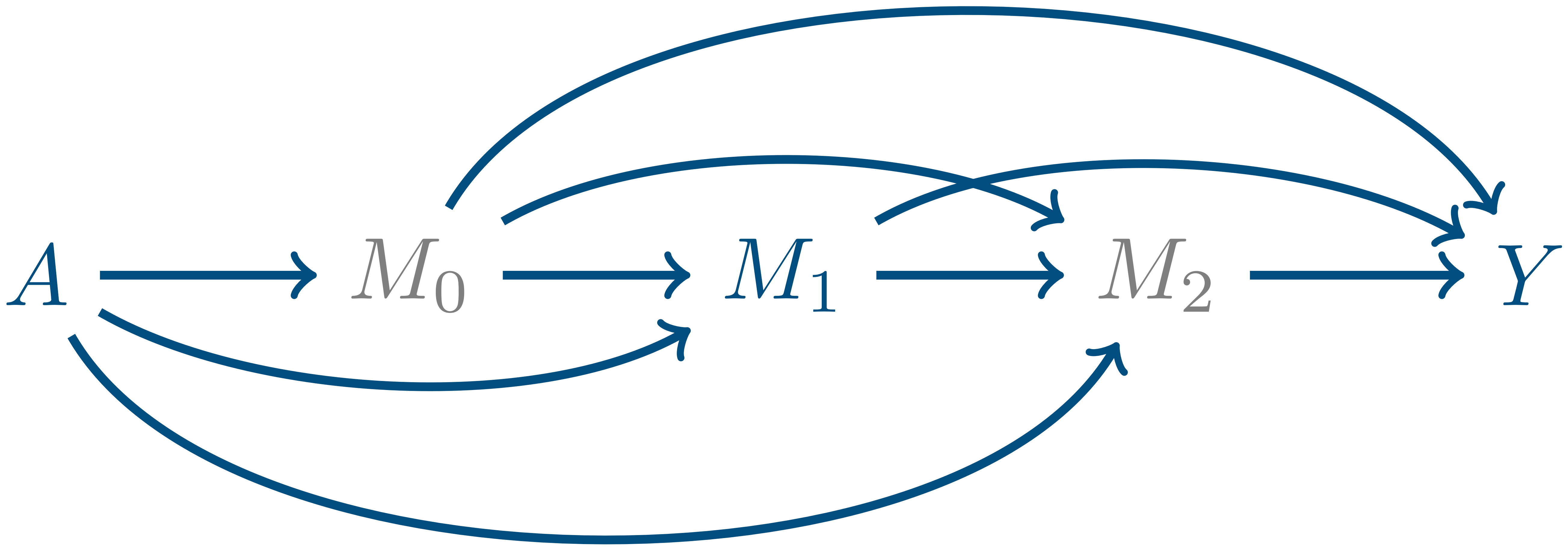


What is our causal question??

- ~~Effect of A_1?~~
- Effect of A at all times (assuming the relationship between Z and A is constant)

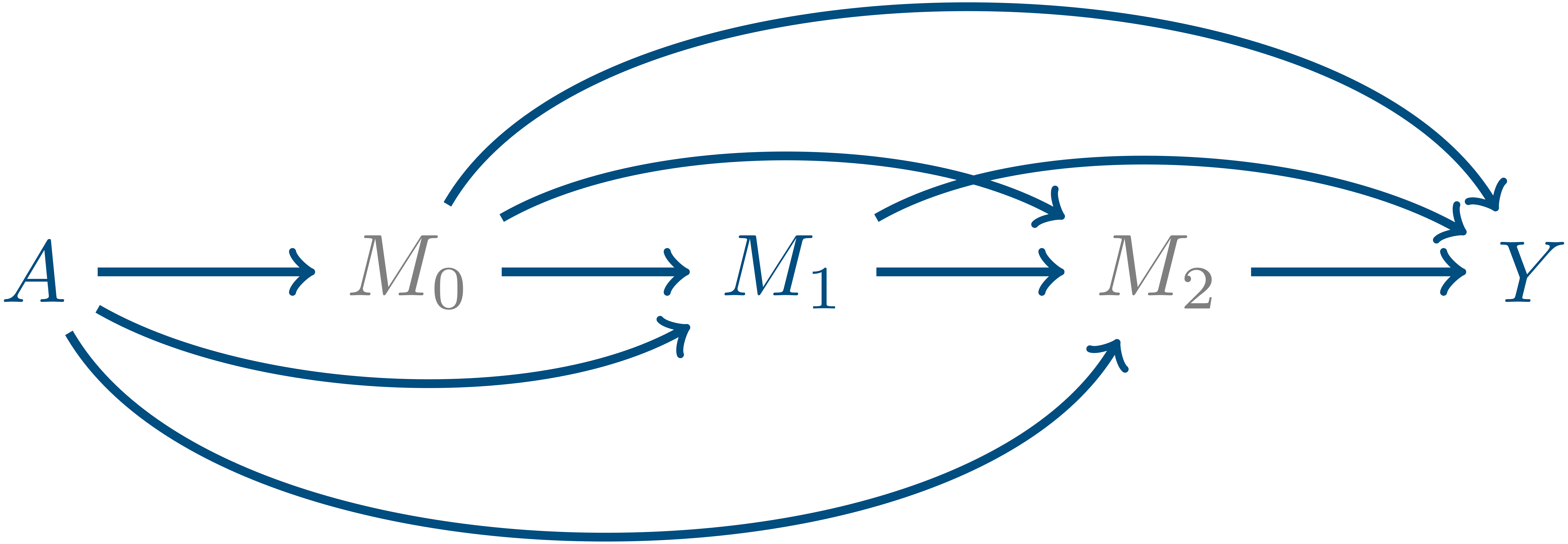
What is our direct effect??

- Effect of A on Y not passing through M_1?
- Effect of A on Y not passing through M at any time?



Mediation setup

Mediation setup



What is our direct effect??

- Effect of A on Y not passing through M_1?
- Effect of A on Y not passing through M at any time?

Example 3

<u>Estimand</u>: Effect of A_1 on Y_1

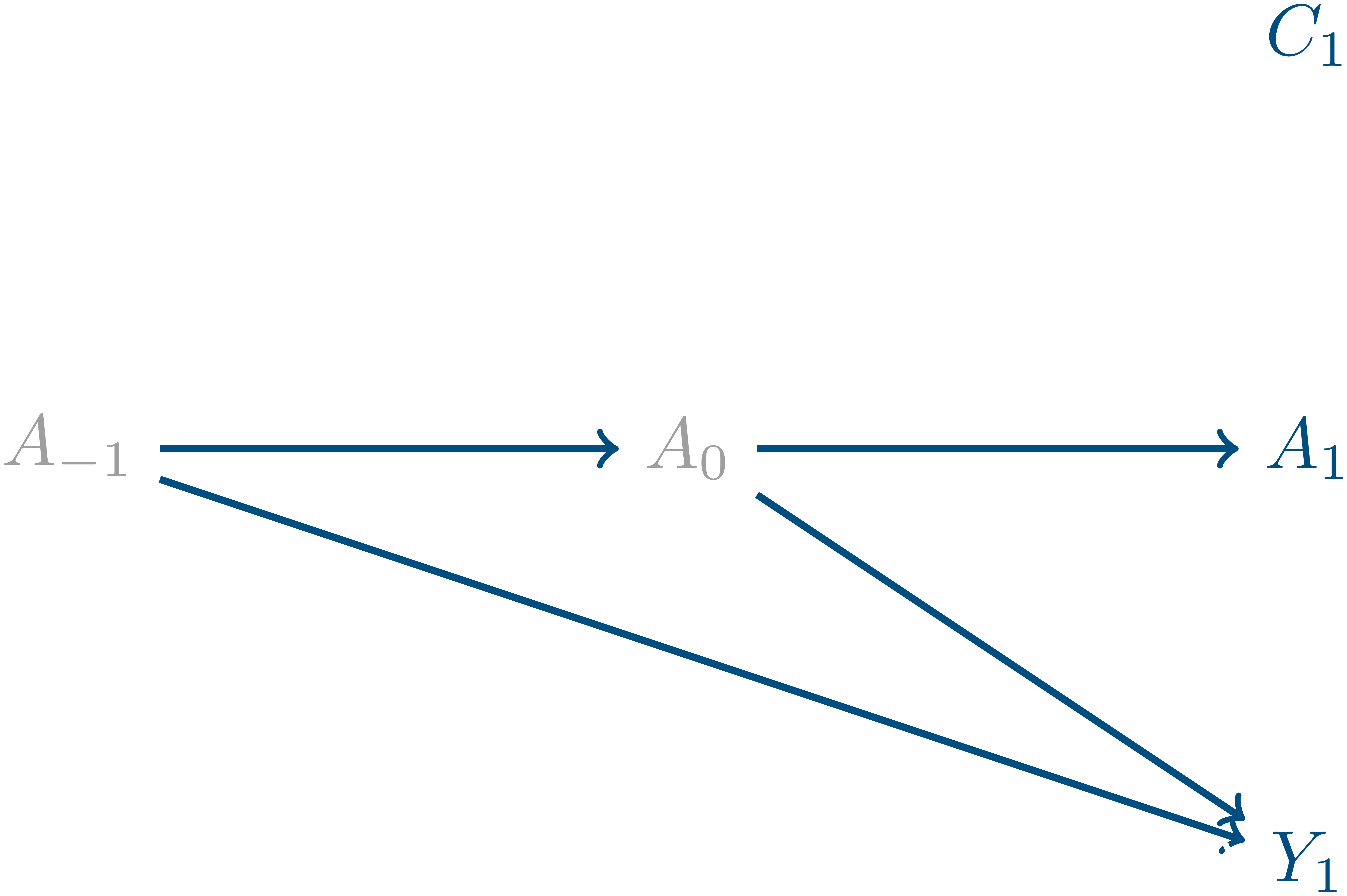
C_1

If C, A and Y are truly measured cross-sectionally, they cannot cause each other.

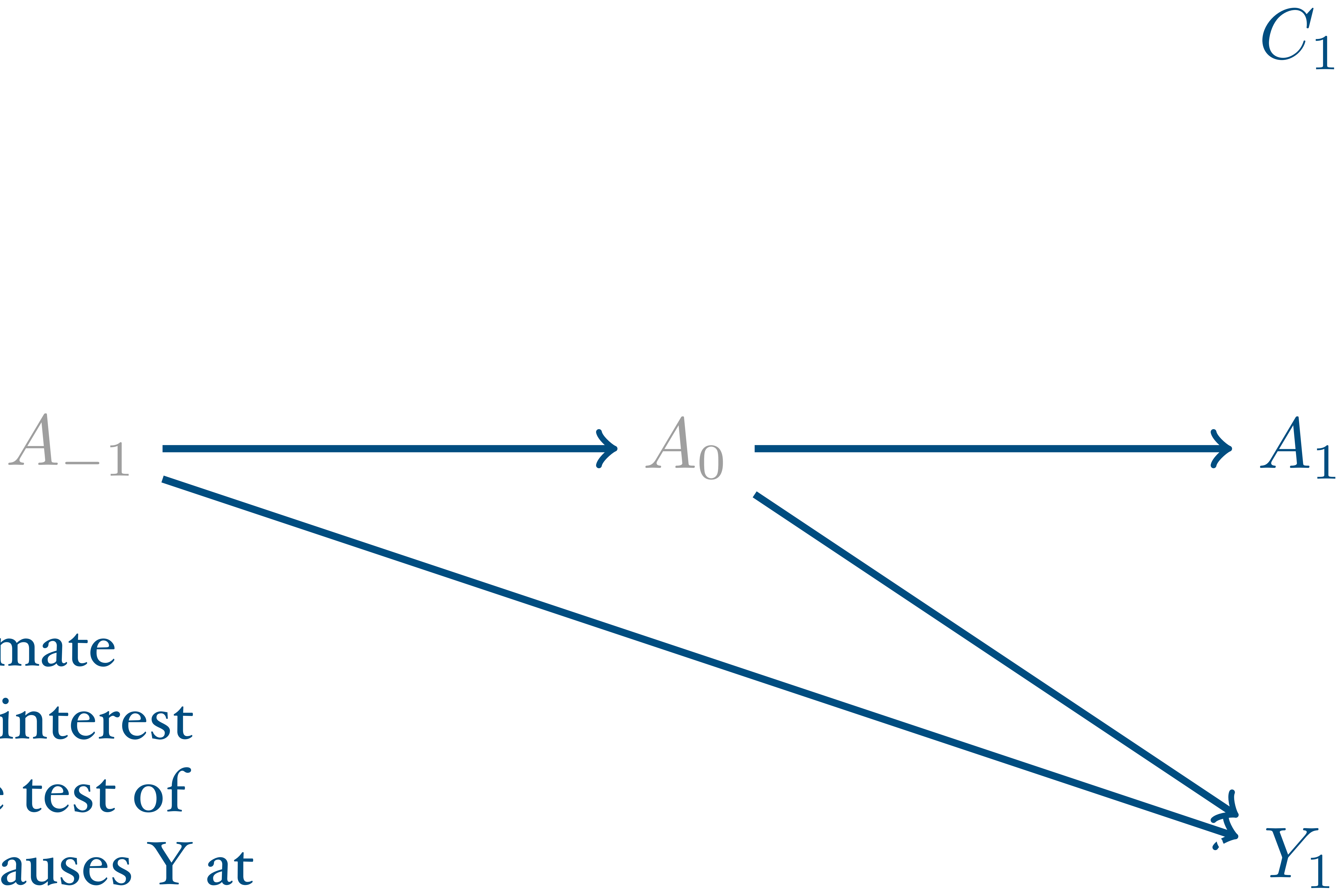
A_1

Y_1

Estimand: Effect of A_1 on Y_1

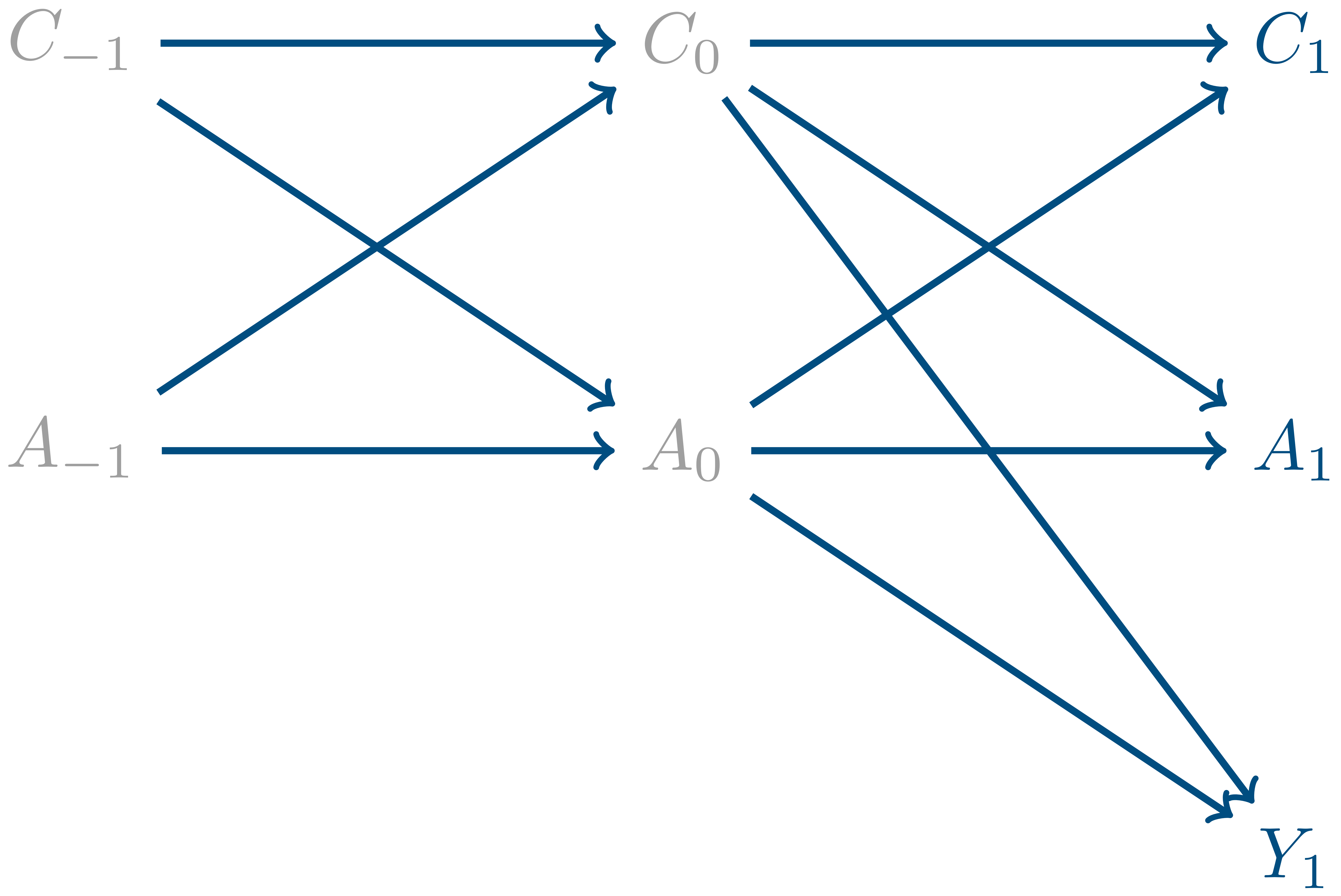


Estimand: Effect of A_1 on Y_1

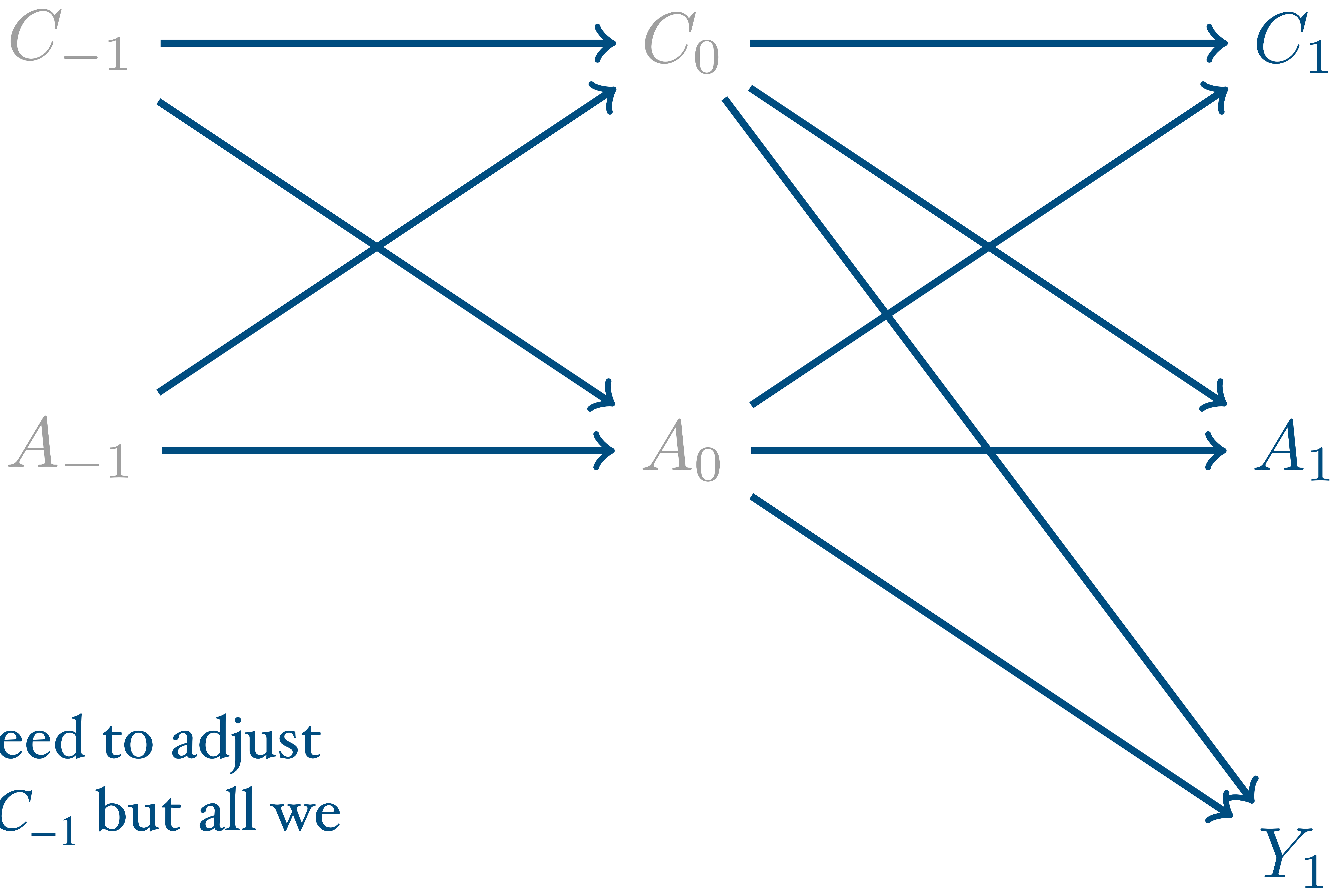


Cannot estimate anything of interest here but the test of whether A causes Y at any time is still valid.

<u>Estimand</u>: Effect of A_1 on Y_1

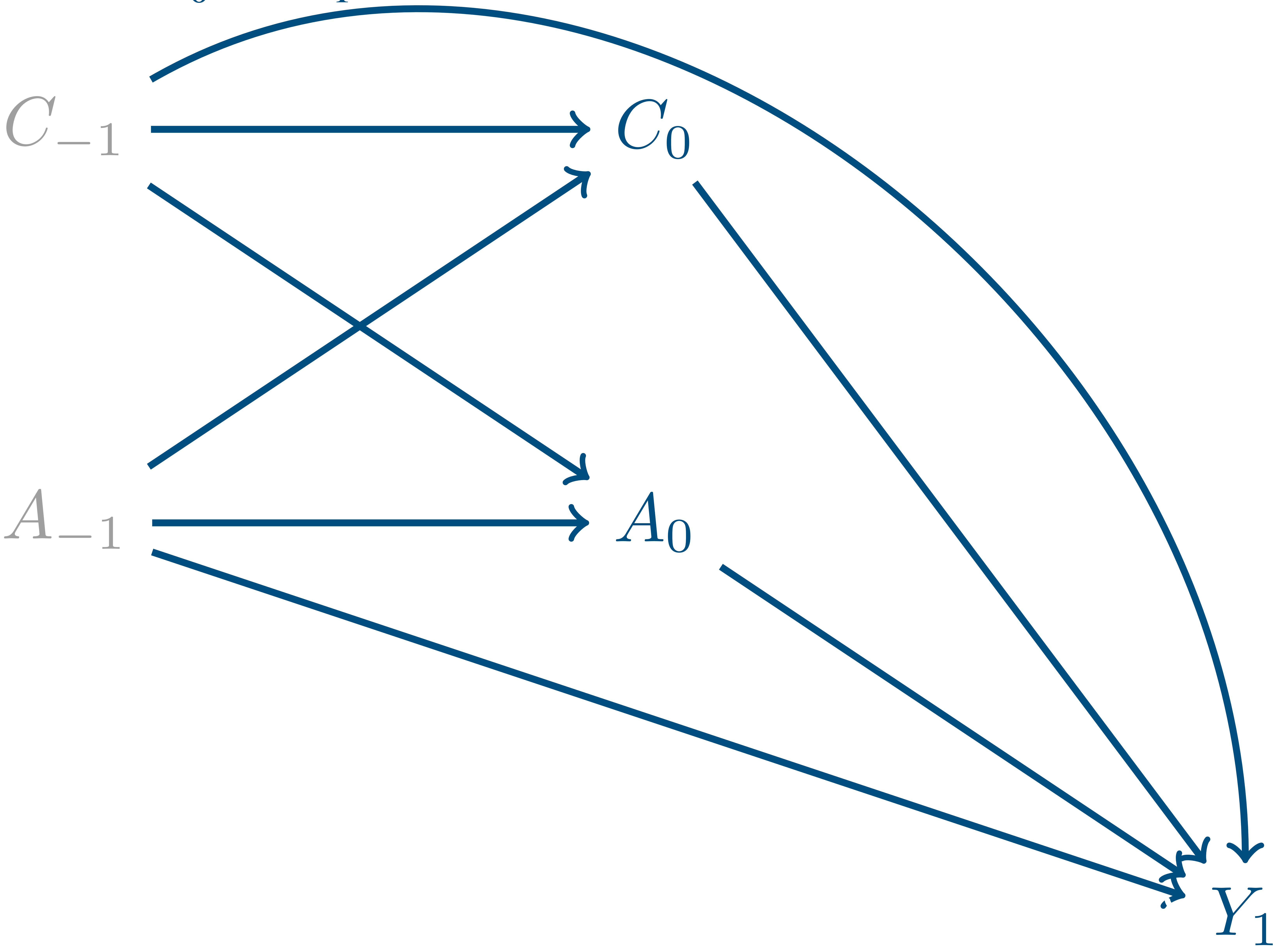


Estimand: Effect of A_1 on Y_1

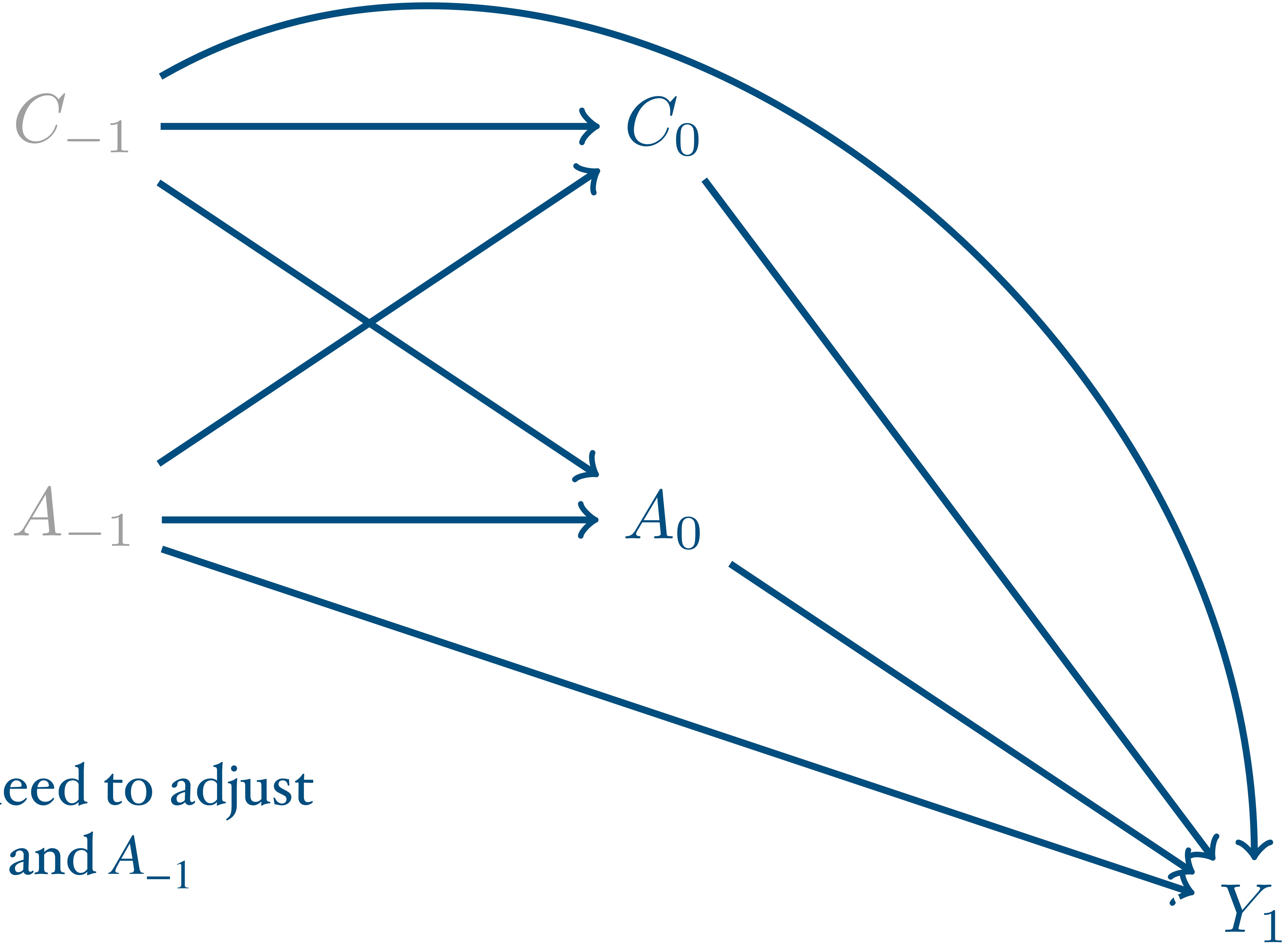


Here, we need to adjust for C_0 and C_{-1} but all we have is C_1

Estimand: Effect of A_0 on Y_1



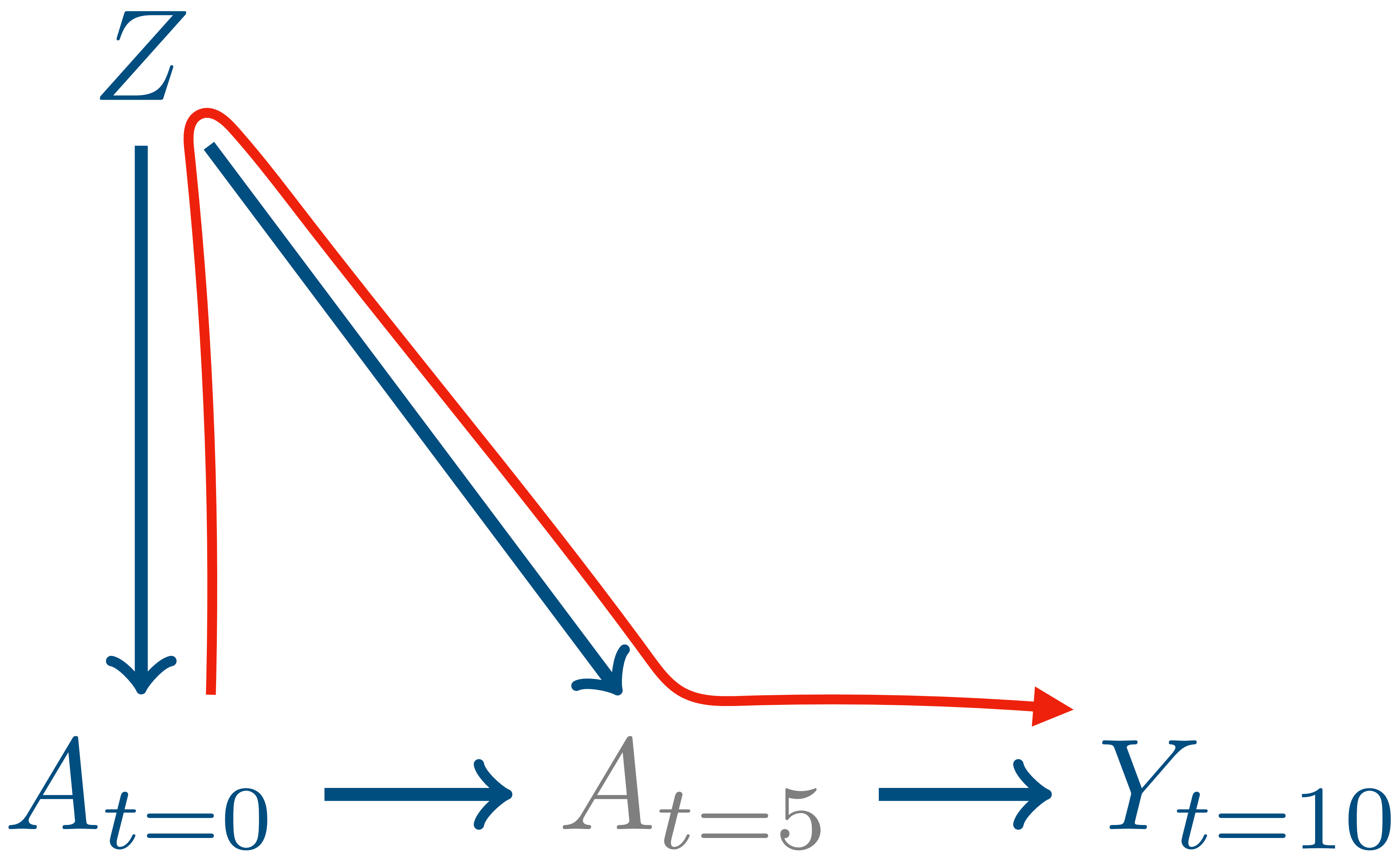
Estimand: Effect of A_0 on Y_1



Here, we need to adjust for C_0, C_{-1} and A_{-1}

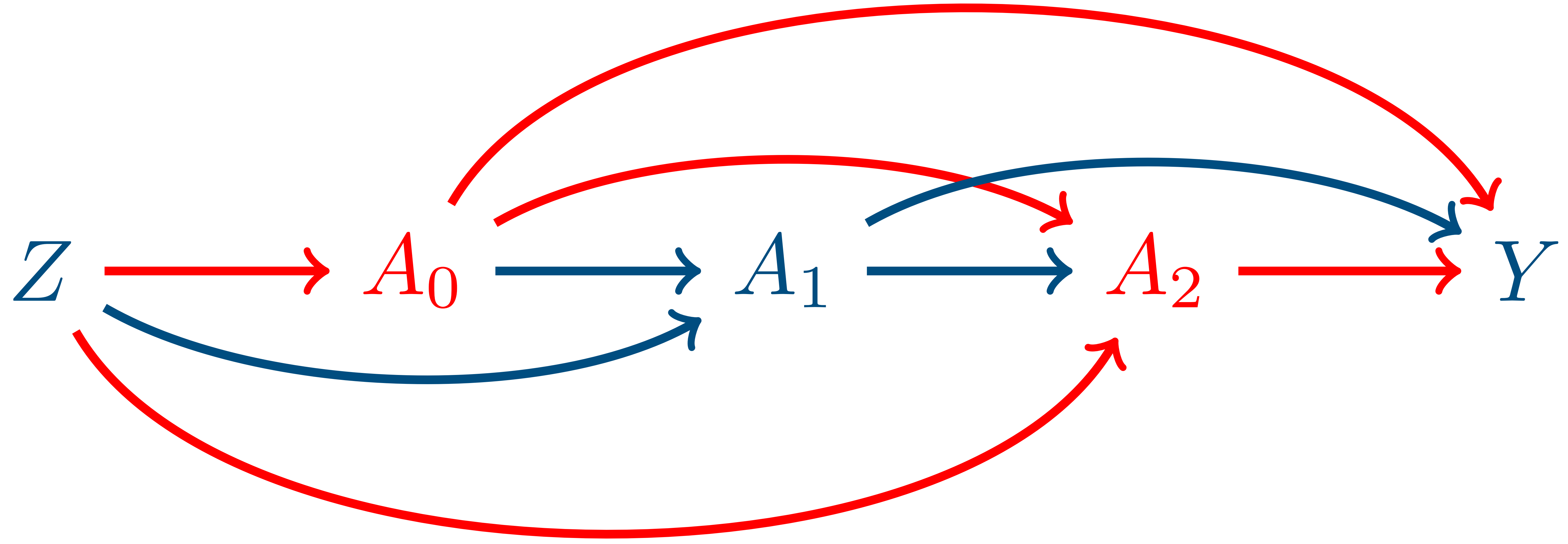
Acknowledging that "everything doesn't happen at once" can:

1. Help you identify biases

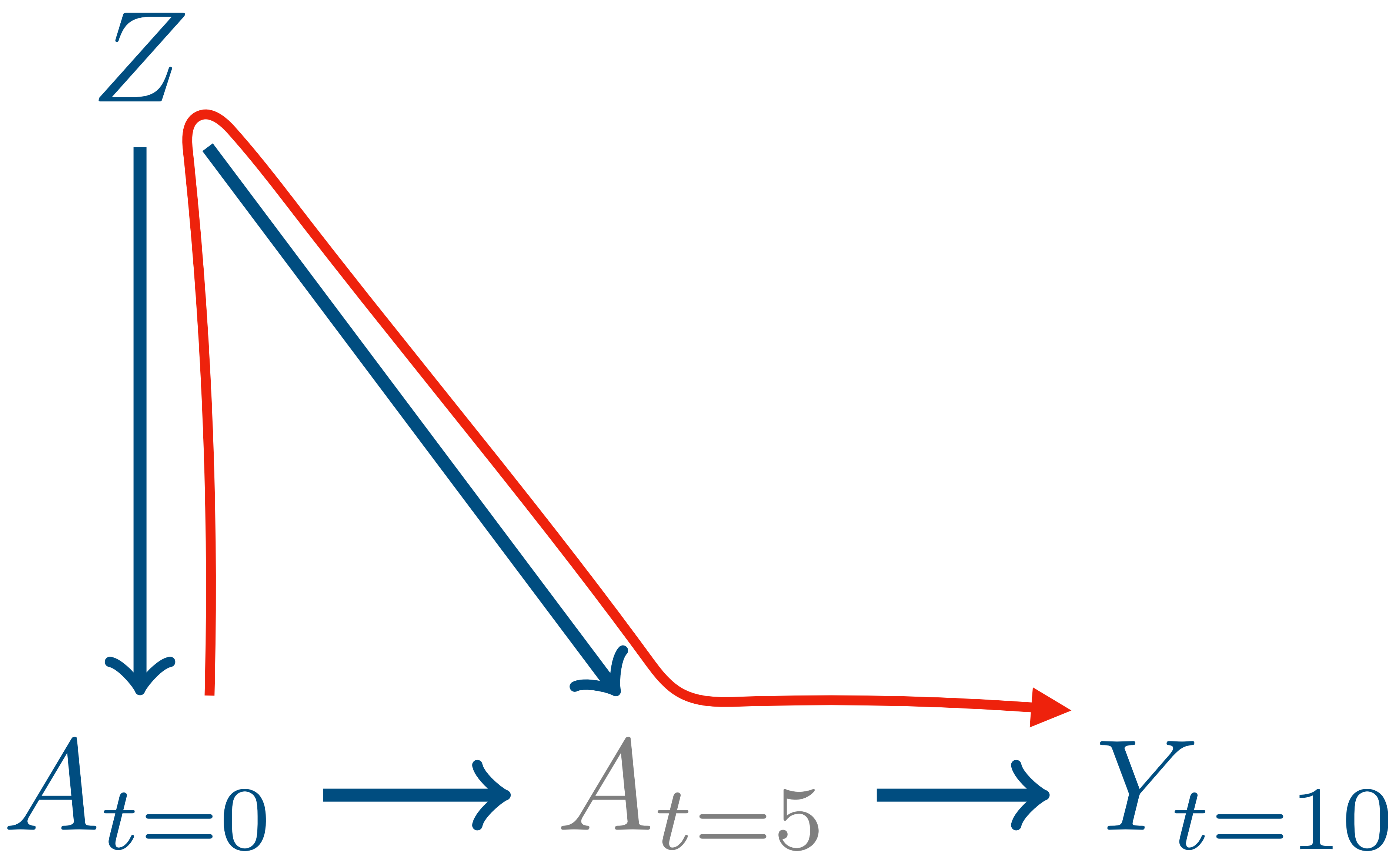


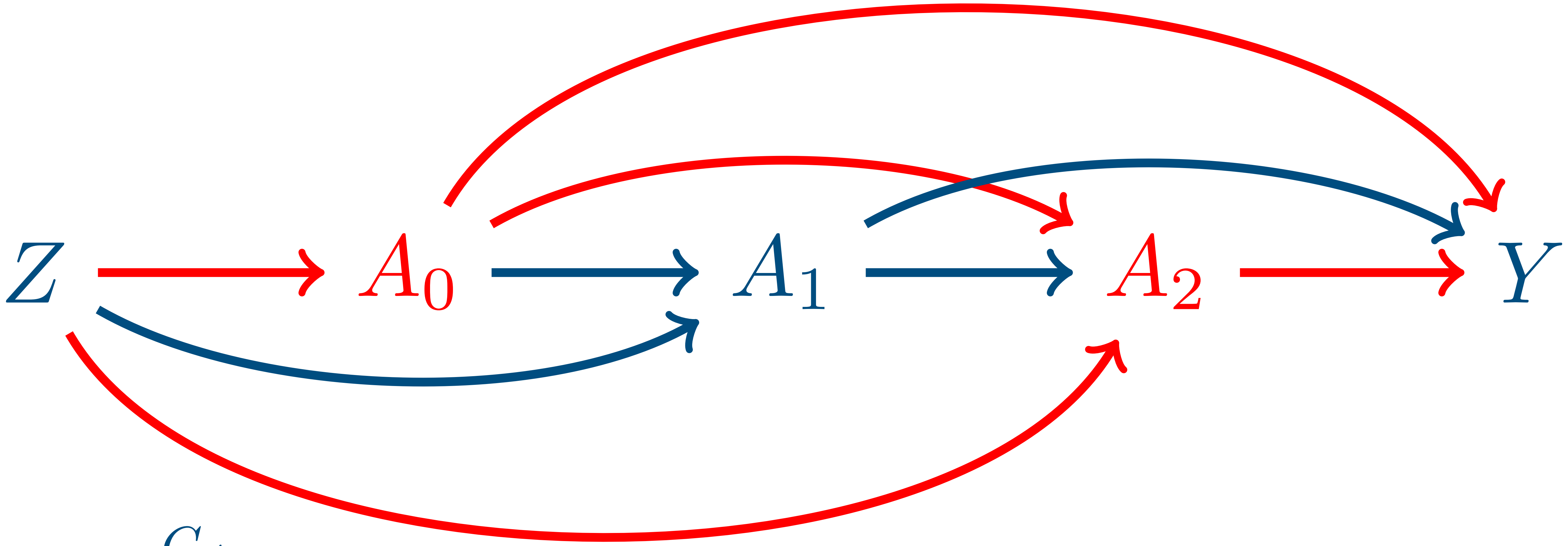
Acknowledging that “everything doesn’t happen at once” can:

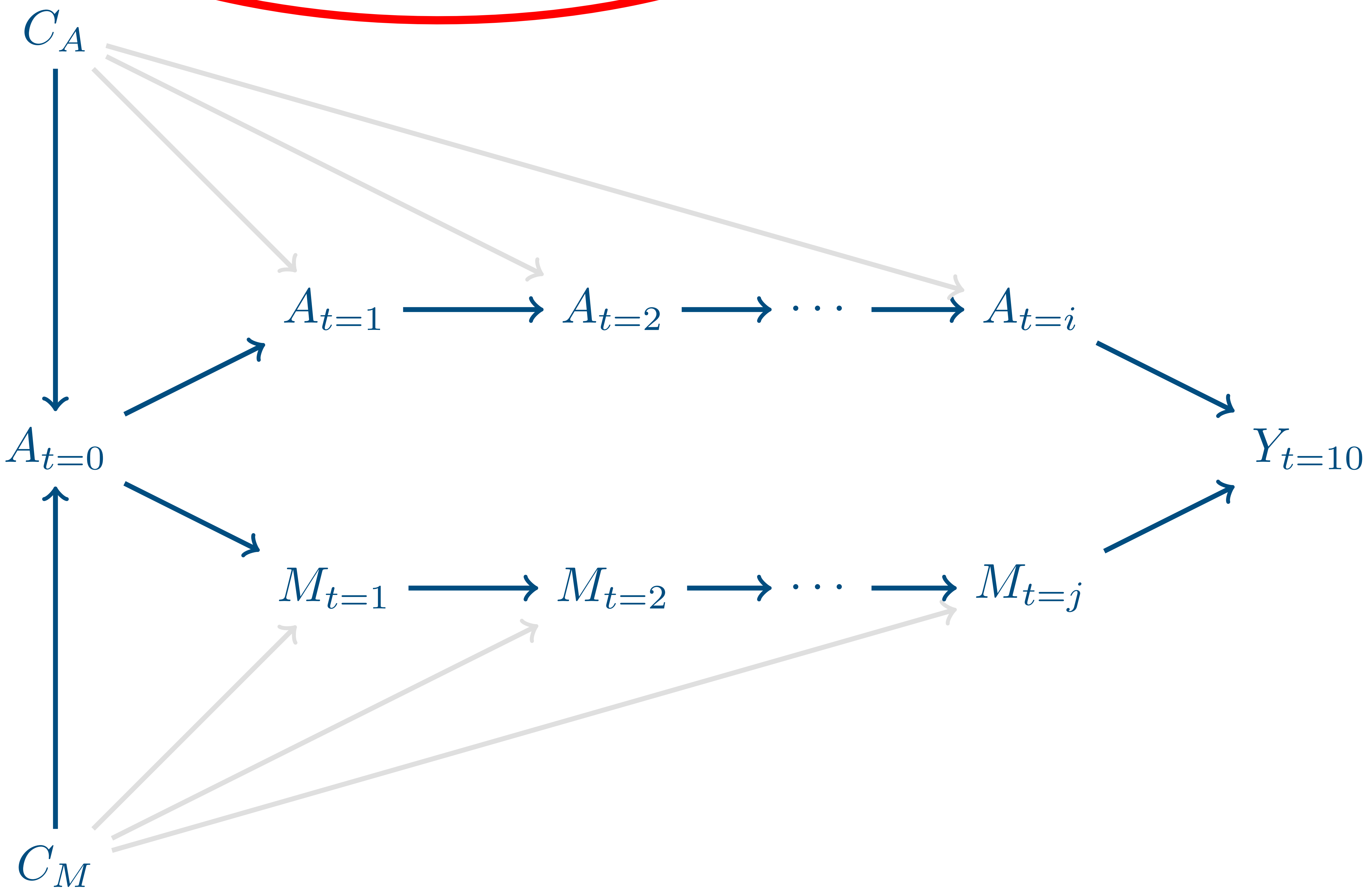
1. Help you identify biases
2. Make you recognize you’re answering a different causal question



Questions?







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