Metales, calcio coronario y riesgo cardiovascular: Análisis de mediación longitudinal en presencia de riesgos competitivos.

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7 de mayo de 2026

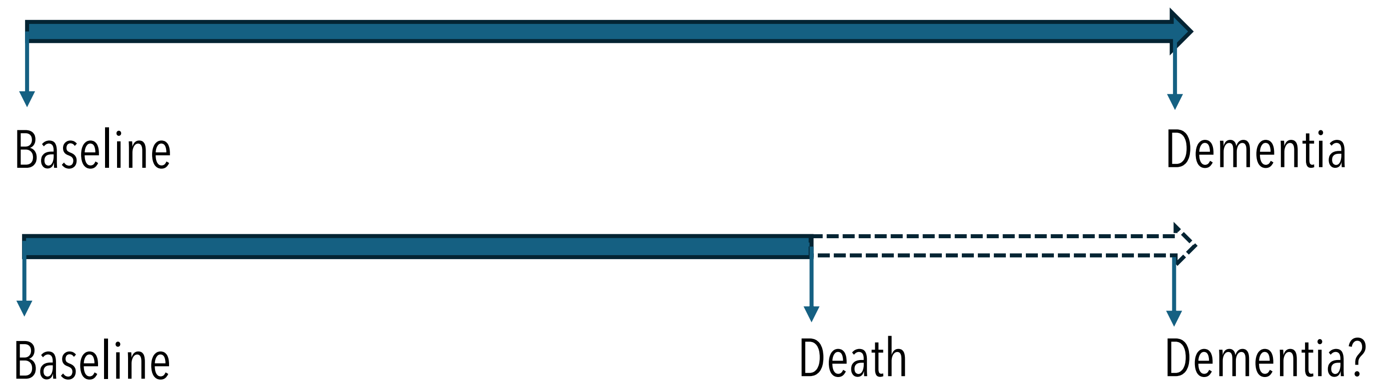
Introduction to competing risks

Competing risks: why do we care?

Competing events: any event that makes it impossible for the event of interest to occur

No competing risks

Competing risks by death



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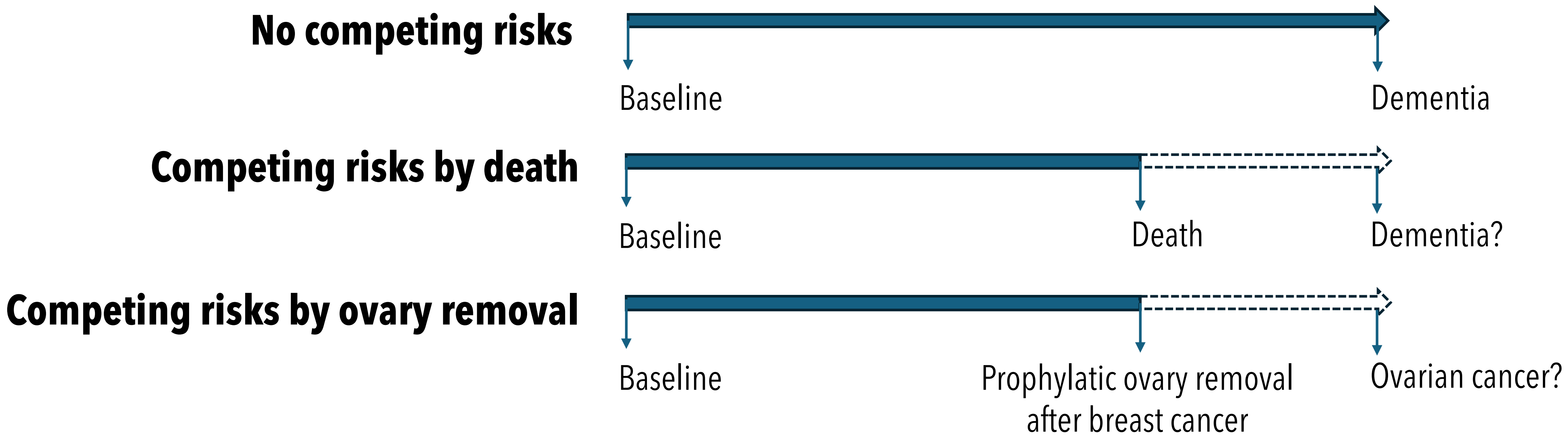
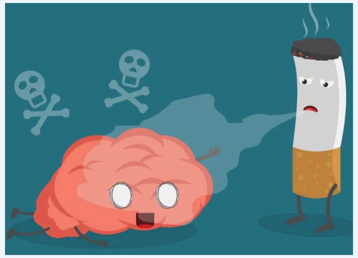


Competing risks: why do we care?

SMOKING, CANCER AND DEMENTIA



- Smoking and cancer history inversely associated with dementia risk.
- Smokers and those who suffer cancer die before being able to develop dementia

Image sources: Altoida, Orthoinfo

Competing risks: why do we care?

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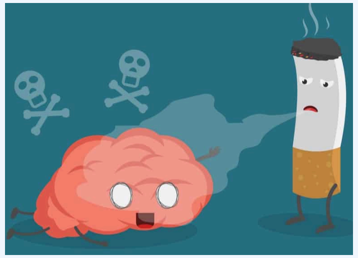

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INCIDENCE OF SECOND HIP FRACTURE IN OLDER INDIVIDUALS

- Overestimation of risk of second hip fracture because many people die after the first hip fracture

Image sources: Altoida, Orthoinfo

Causal effects in presence of competing risks

- Various statistical estimands proposed on competing risks survival settings
- No formal framework for causal effects identification / identifying conditions
- **Young et al 2020**: formal causal definition treating competing events as mediators

A causal framework for classical statistical estimands in failure time settings with competing events

Jessica G. Young[*,1], Mats J. Stensrud[2,3], Eric J. Tchetgen Tchetgen[4], Miguel A. Hernán[2,5,6]

Young et. al 2020, *Statistics in Medicine*

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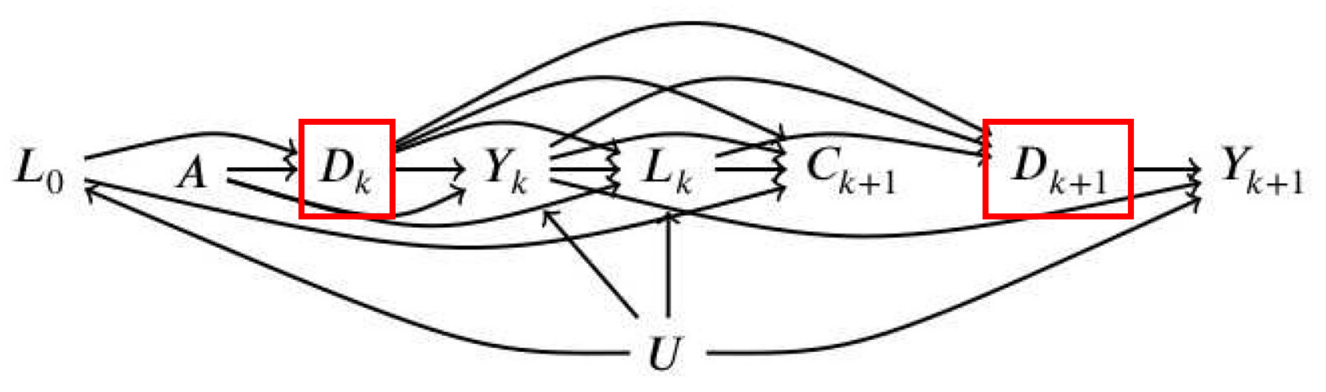

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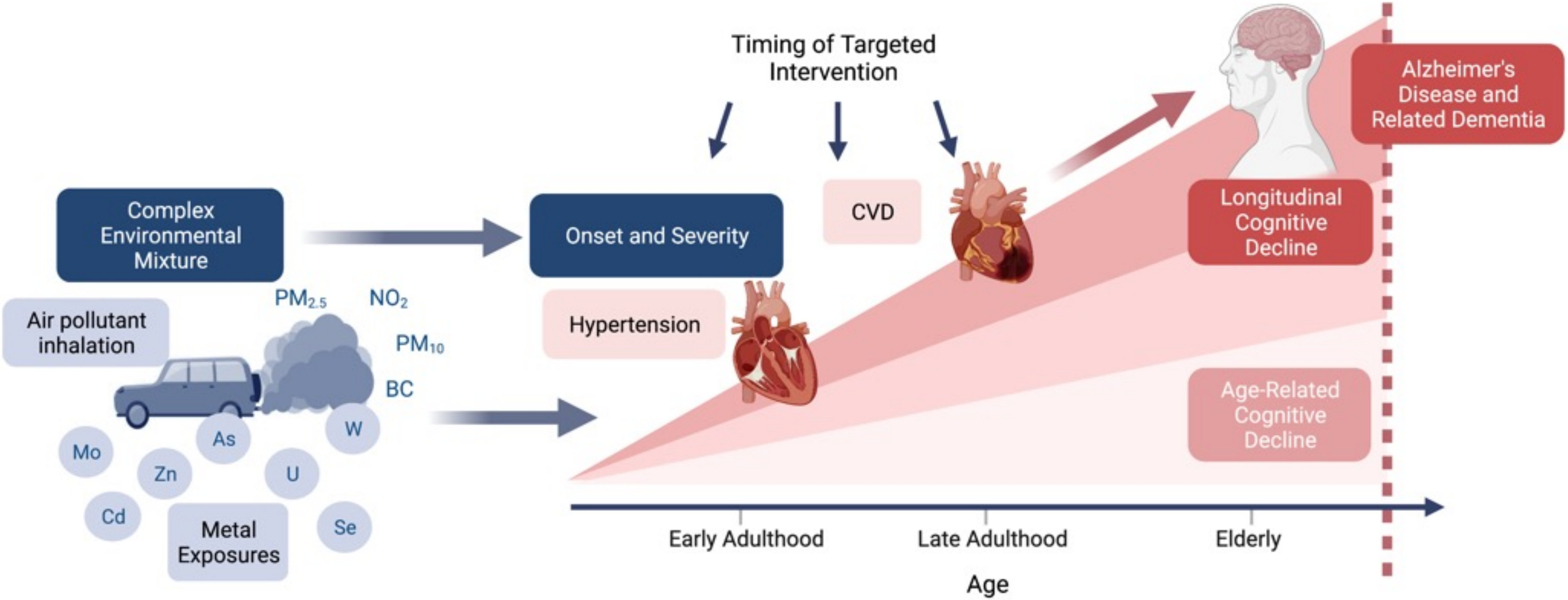
Objective

- To develop a statistical method able to conduct **mediation analysis** in presence of:
  - Longitudinal mediators
  - Time to event outcomes
  - Competing risks
- To apply this method to assess the mediating role of coronary artery calcification on the association between metals and CVD in the Multi-Ethnic Study of Atherosclerosis

A multivariate disease perspective to the mixtures & ADRD link



Slide by Linda Valeri

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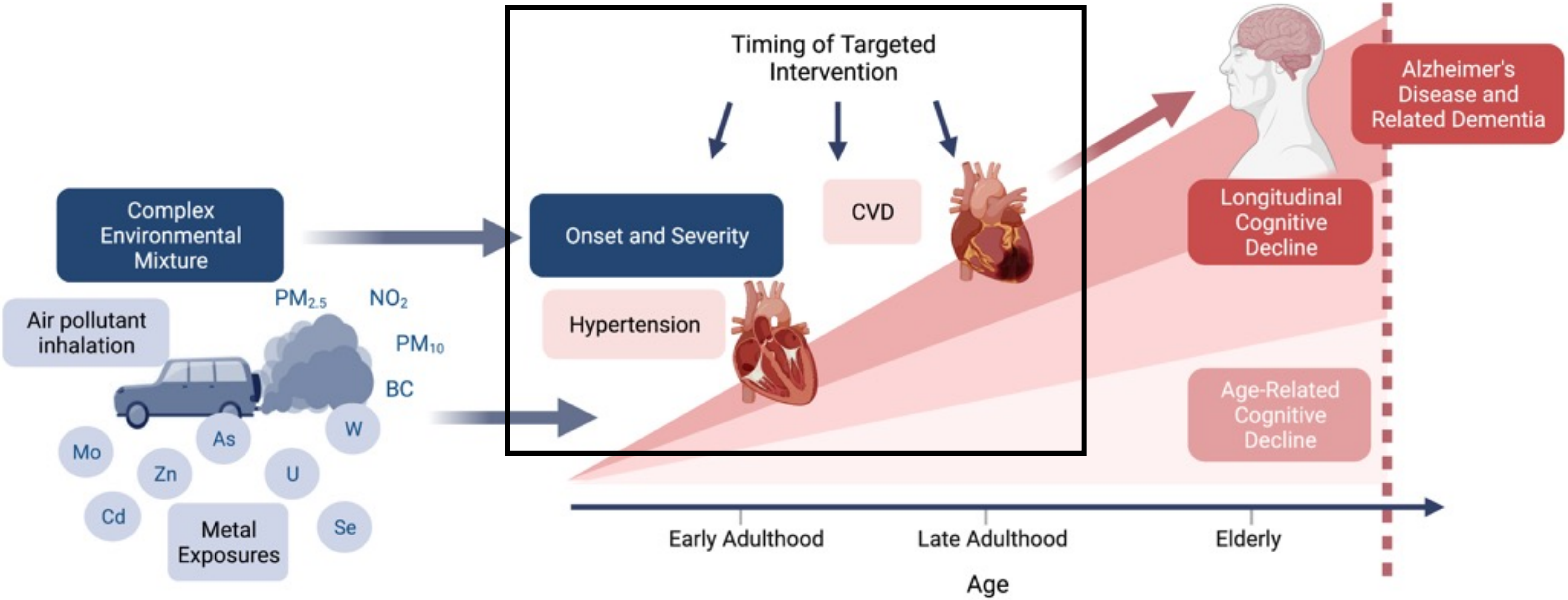

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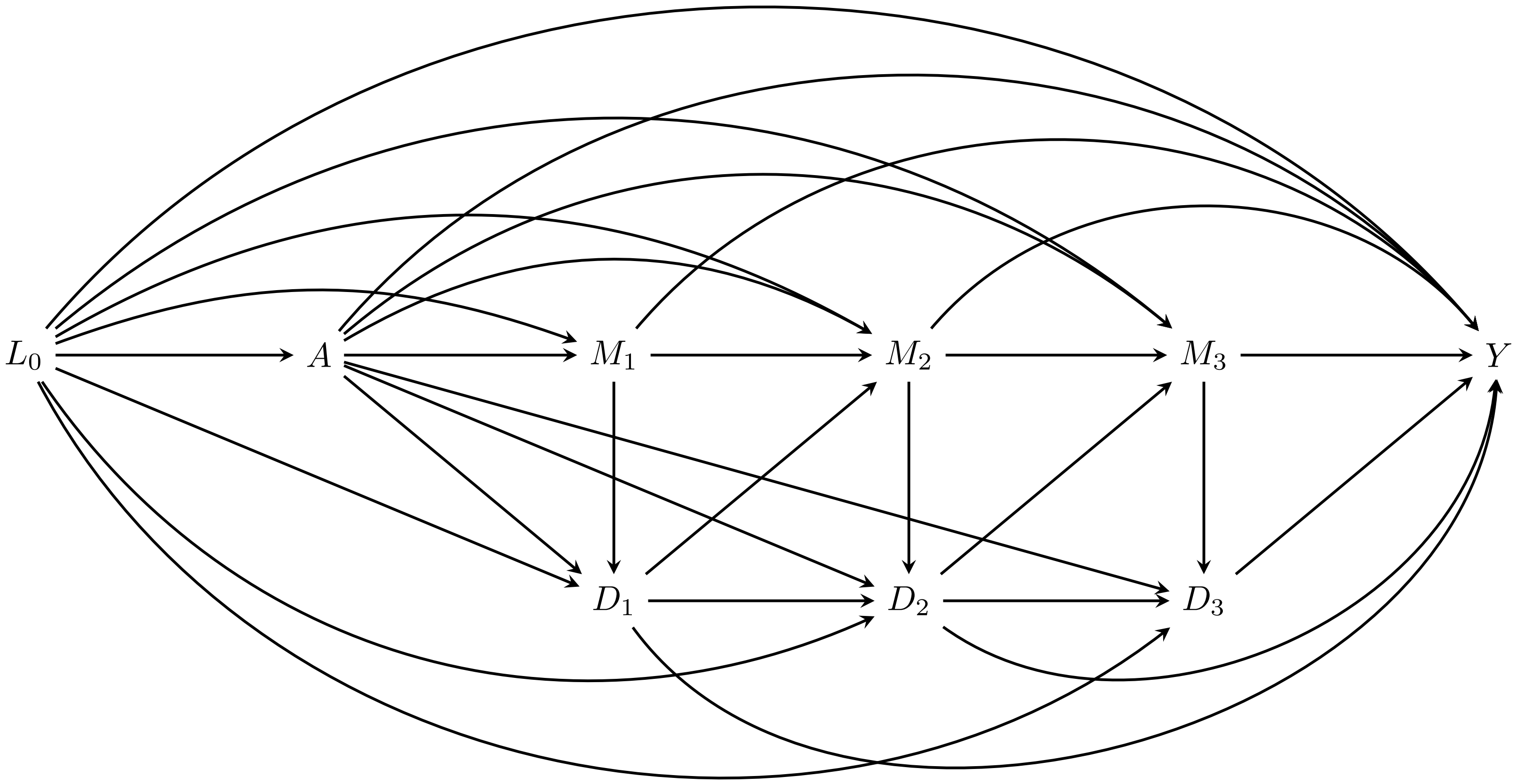
A path-specific effects approach to mediation analysis with competing risks

Directed acyclic graph



L_0: baseline confounders

A: exposure

M_i: longitudinal mediator

D_i: death indicators

Y: survival outcome

Causal estimands

- **Direct effect**:

$$\mathbb{E}\left[Y\left(a^*, S_{K+1}(a, M_K(a)), M_K(a, S_K(a))\right)\right] - \mathbb{E}\left[Y\left(a, S_{K+1}(a, M_K(a)), M_K(a, S_K(a))\right)\right]$$

- **Indirect effect through the trajectory of M** (the mediator of interest):

$$\mathbb{E}\left[Y\left(a^*, S_{K+1}(a, M_K(a^*)), M_K(a^*, S_K(a))\right)\right] - \mathbb{E}\left[Y\left(a^*, S_{K+1}(a, M_K(a)), M_K(a, S_K(a))\right)\right]$$

- **Indirect effect through death**:

$$\mathbb{E}\left[Y\left(a^*, S_{K+1}(a^*, M_K(a^*)), M_K(a^*, S_K(a^*))\right)\right] - \mathbb{E}\left[Y\left(a^*, S_{K+1}(a, M_K(a^*)), M_K(a^*, S_K(a))\right)\right]$$

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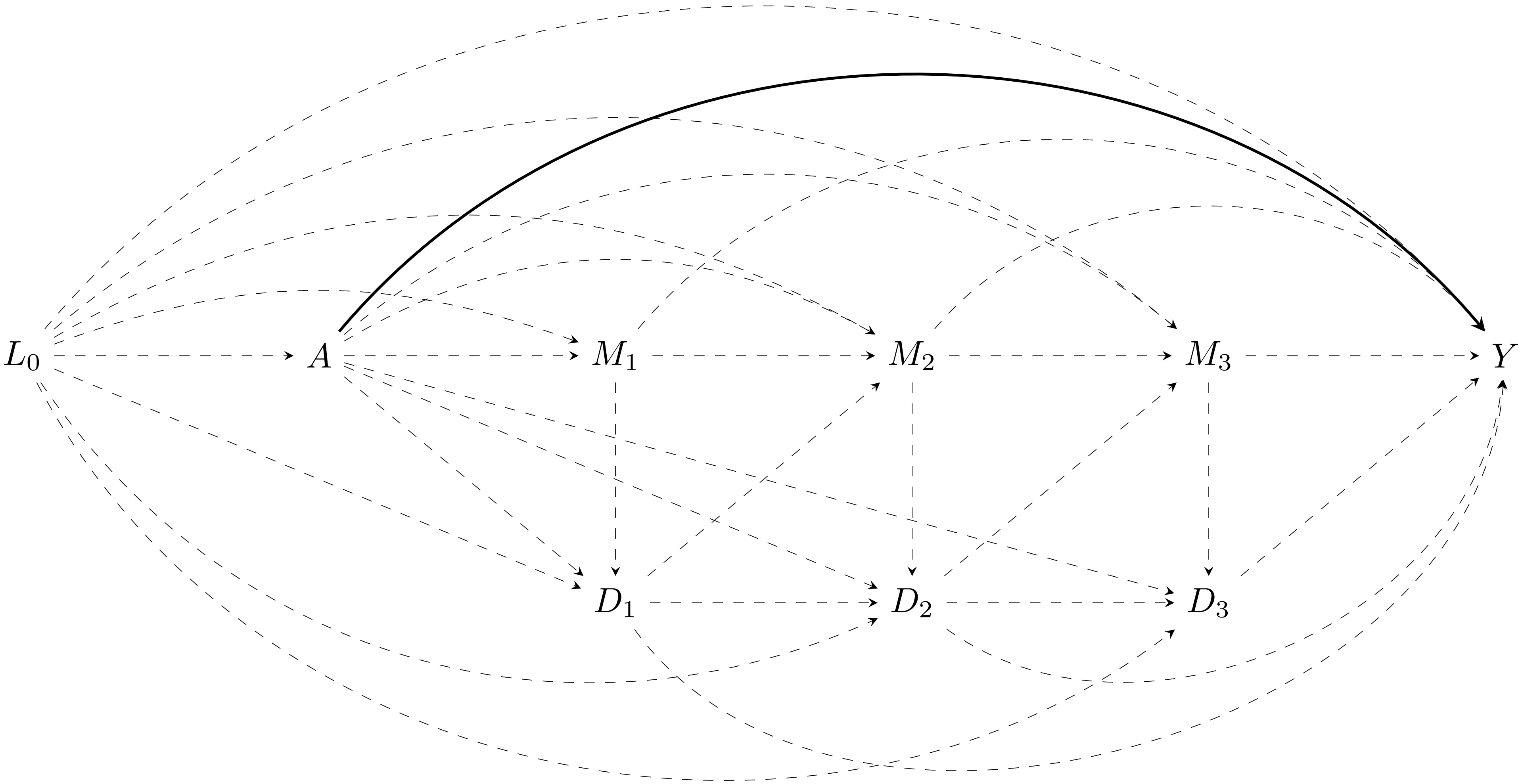

Indirect effect through the trajectory of the mediator of interest

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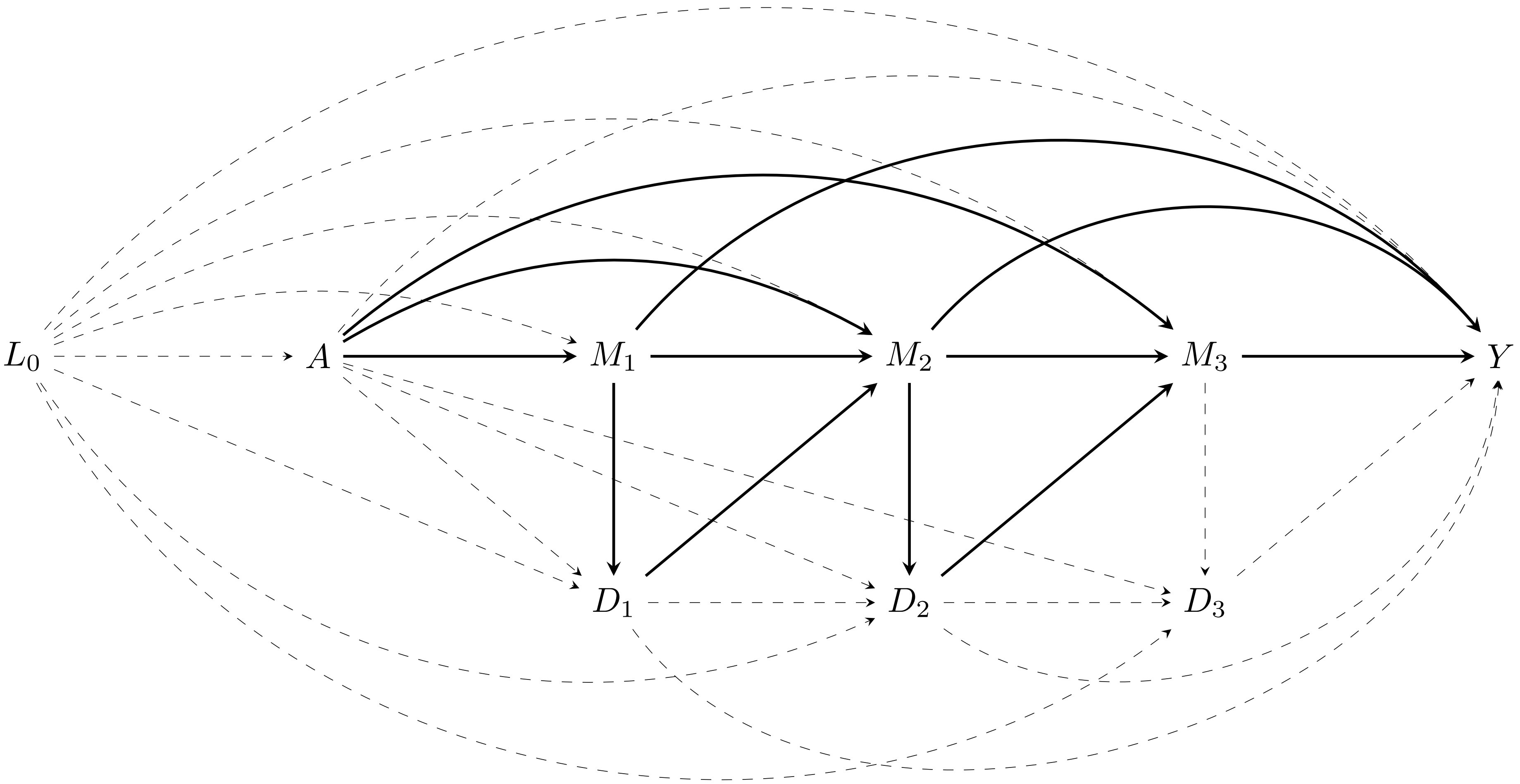

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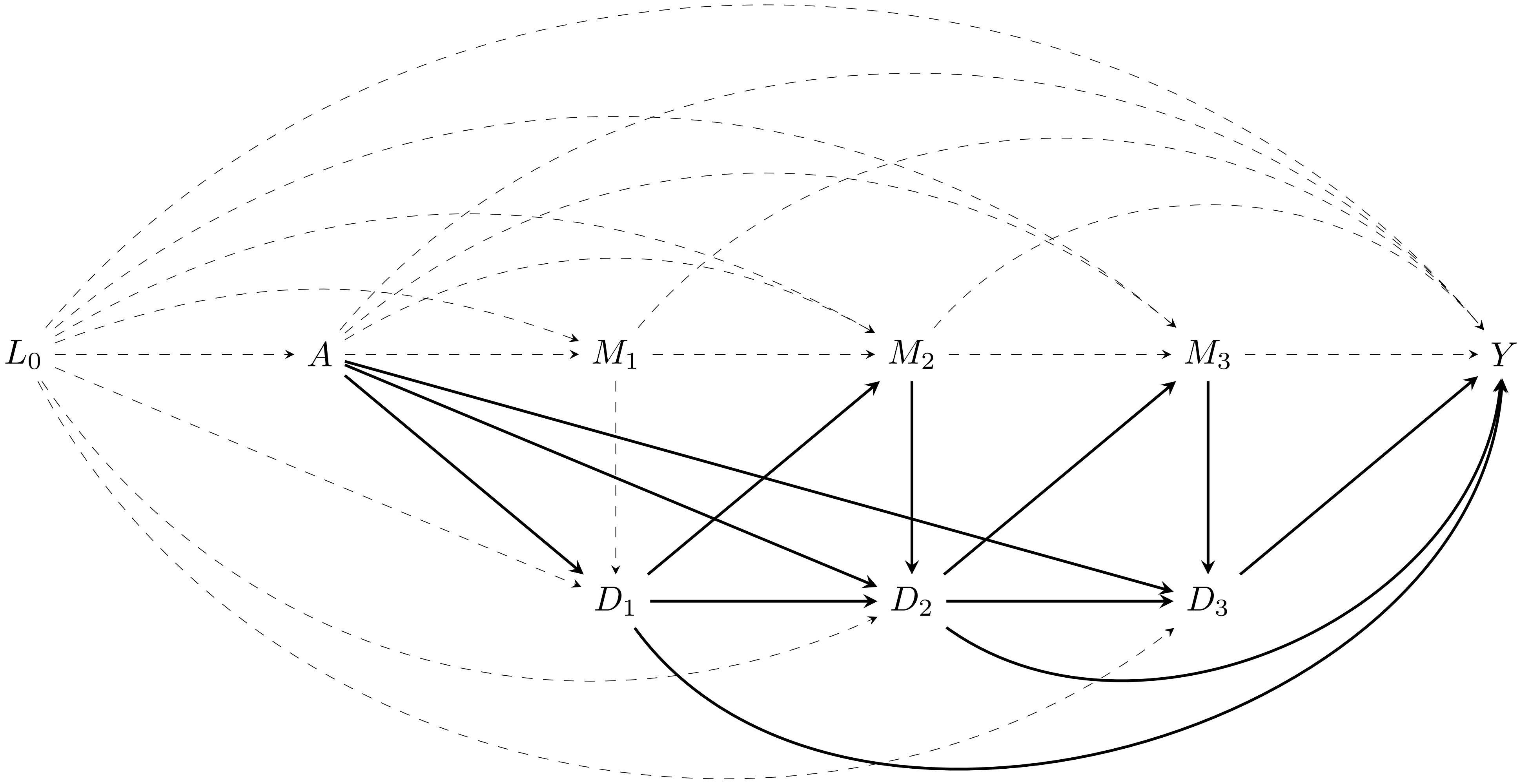

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Identifiability conditions

- **Exchangeability**:
  - $\bar{Y}_{k+1}(a, \bar{m}, \bar{s}=1) \perp A \big| L_0$
  - $\big(Y_{k+1}(a^*, \bar{s}_k = 1, \bar{m}_k), \bar{S}_k(a^*, \bar{m}_k)\big) \perp \bar{M}_k | A, L_0$
  - $\bar{S}_{k+1}(a, \bar{m}) \perp \bar{M}_{k+1}(a, \bar{s}=1) \big| A = a, \bar{M}_k = \bar{m}_k, \bar{Y}_k = 0, \bar{S}_k = 1, L_0$
  - $\bar{M}_{k+1}(a, \bar{s}=1) \perp A \big| L_0, \bar{Y}_k = 0, \bar{S}_k = 1$
  - $\bar{S}_{k+1}(a, \bar{m}) \perp A \big| L_0, \bar{Y}_k = 0, \bar{S}_k = 1$
  - $Y_{k+1}(a, \bar{m}, \bar{s}=1) \perp \big(\bar{M}_k(a^*, \bar{s}=1), \bar{S}_k(a^*, \bar{m})\big) \big| \bar{Y}_k = 0, \bar{S}_{k-1} = 1, A = a, L_0$
- **Positivity:** $P\big(A = a \big| L_0 = l_0\big) > 0$, and $P\big(\bar{M}_{k+1} = \bar{m}_{k+1}, \bar{S}_{k+1} = \bar{s}_{k+1} \big| A = a, L_0 = l_0, \bar{Y}_k = 0, \bar{S}_k = 1\big) > 0$, $\forall k = 1, \dots, K$
- **Consistency:** If $A = a$ and $S_k = 1$ then $\bar{M}_{k+1} = \bar{M}_{k+1}(a, \bar{s}=1)$, $S_{k+1} = \bar{S}_{k+1}(a, \bar{m})$, $\bar{Y}_{k+1} = \bar{Y}_{k+1}(a, \bar{m}, \bar{s}=1)$

Effect estimation: the mediational g-formula

Under identifiability conditions of positivity, consistency and exchangeability, the expected value of the outcome at time $k+1$, $\mathbb{E}[Y_{k+1}(a, \bar{M}_k, \bar{S}_k)]$ is identified using the **mediational g-formula.**

Algorithm: mediational g-formula

1. Choose two exposure values a and a* (ex: percentiles 25 and 75)
2. Fit models with observed data for mediators and outcome
3. **Counterfactual prediction of the mediators**:
   3.1. Predict M_i under a, $M_{i-1}(a)$, $S_{i-1}(a)$; under a, $M_{i-1}(a)$, $S_{i-1}(a^*)$; and under a*, $S_{i-1}(a^*)$, $M_{i-1}(a^*)$
   3.2. Predict S_i under a, $M_i(a)$, $S_{i-1}(a)$; under a*, $M_i(a)$, $S_{i-1}(a^*)$; and under a*, $M_i(a^*)$ $S_{i-1}(a^*)$
4. **Counterfactual prediction of the outcome**:
   4.1. Prediction of Y under a^*, $\bar{M}_i(a)$, $\bar{S}_i(a)$
   4.2. Prediction of Y under a, $\bar{M}_i(a)$, $\bar{S}_i(a)$
   4.3. Prediction of Y under a^*, $\bar{M}_i(a^*)$, $\bar{S}_i(a)$
   4.4. Prediction of Y under a^*, $\bar{M}_i(a^*)$, $\bar{S}_i(a^*)$
5. **Calculate the effects of interest subtracting counterfactual values of the outcome**, for example, the mediated effect through M would be $Y(a^*, a, a^*) - Y(a^*, a^*, a^*)$
6. **Calculate confidence intervals using bootstrap**

Comparison to traditional total effect

	Interpretation	Formula
Total effect (classical survival analysis)	Effect of the exposure on the outcome conditional on survival under the observed exposure: **we treat death as a non-informative censoring event.**	$\mathrm{E}(Y_{k+1}(a^*) \mid \bar{S}_{k+1} = 1) - \mathrm{E}(Y_{k+1}(a) \mid \bar{S}_{k+1} = 1)$
Total effect (accounting for competing risks)	Effect of the exposure on the outcome: **intervention on both exposure and survival**	$\mathrm{E}\left(Y_{k+1}(a^*, \bar{S}_{k+1}(a^*))\right) - \mathrm{E}\left(Y_{k+1}(a, \bar{S}_{k+1}(a))\right)$

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Stat Med. 2026 Feb 4;45(3-5):e70425. doi: 10.1002/sim.70425

A Path-Specific Effect Approach to Mediation Analysis With Time-Varying Mediators and Time-to-Event Outcomes Accounting for Competing Risks

Arce Domingo-Relloso [1,2,3,✉], Yuchen Zhang [1], Ziqing Wang [1], Astrid M Suchy-Dicey [4], Dedra S Buchwald [5], Ana Navas-Acien [2], Joel Schwartz [6], Kiros Berhane [1], Brent A Coull [7], Linda Valeri [1,8]

Application: Urinary Metals, Coronary Artery Calcification and Cardiovascular Disease in the Multi-Ethnic Study of Atherosclerosis (MESA)

Study Population: Multi-Ethnic Study of Atherosclerosis

MESA

- 6,814 men and women 45-84 years
- Started in 2000
- White, African American, Hispanic, Chinese

Exposures

Urinary metals measured at baseline

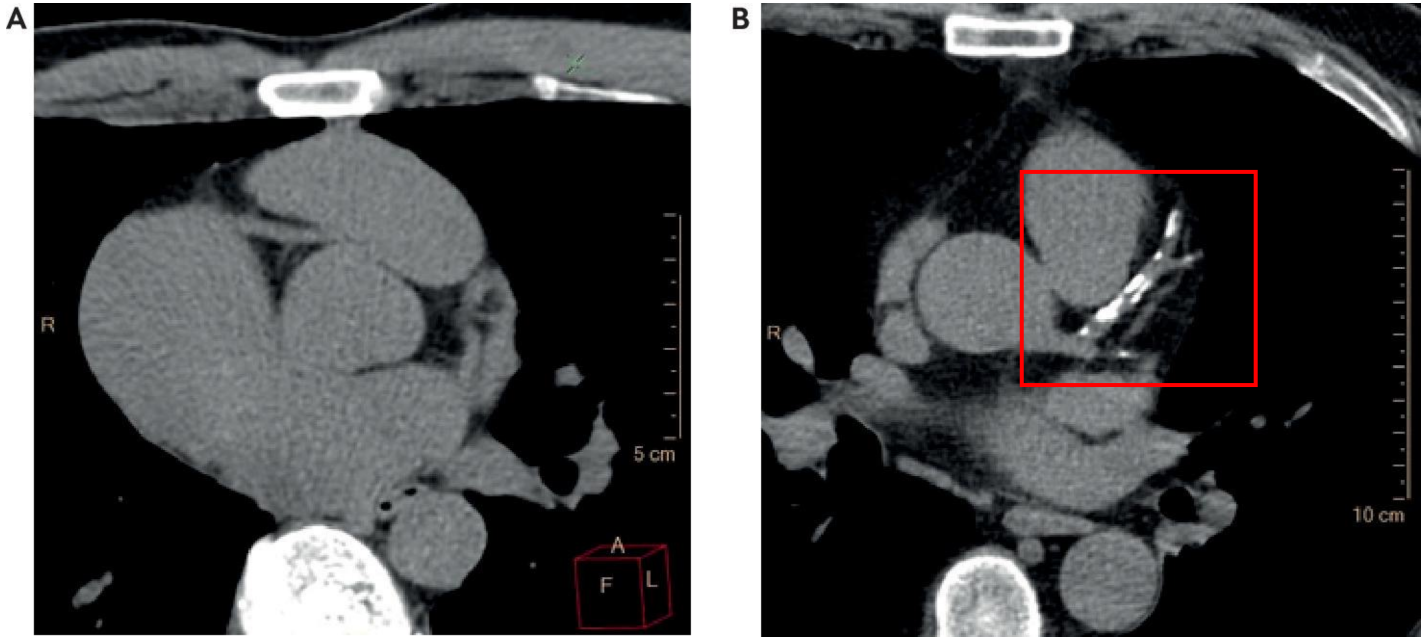
- Cadmium
- Copper
- Cobalt
- Tungsten
- Uranium
- Zinc

Measured at the Trace Metals Core Laboratory at Columbia University

Coronary artery calcification

- Atherosclerosis induces calcification in the coronary arteries
- Calcium builds up in the plaque found in the walls of the arteries
- Indicator of early CVD, highly predictive of CHD events
- Measured using spatially weighted calcification score

Healthy **Calcification**



Metals and coronary artery calcification

Katlyn McGraw

- Atherosclerosis induces calcification in the coronary arteries
- Calcium builds up in the plaque found in the walls of the arteries
- Indicator of early CVD, highly predictive of CHD events
- Measured using spatially weighted calcification score
- **Exposure to metals has been associated with coronary artery calcification in our prior work**

ELSEVIER

Journal of the American College of Cardiology

Volume 84, Issue 16, 15 October 2024, Pages 1545-1557

Original Research

Urinary Metal Levels and Coronary Artery Calcification: Longitudinal Evidence in the Multi-Ethnic Study of Atherosclerosis

Katlyn E. McGraw PhD [a], Kathrin Schilling PhD [a], Ronald A. Glabonjat PhD [a], Marta Galvez-Fernandez MD, PhD [a], Arce Domingo-Relloso PhD [b], Irene Martinez-Morata MD, PhD [a], Miranda R. Jones PhD [c d], Anne Nigra PhD [a], Wendy S. Post PhD [c d], Joel Kaufman MD [e], Maria Tellez-Plaza MD, PhD [f], Linda Valeri PhD [b], Elizabeth R. Brown ScD [e g], Richard A. Kronmal PhD [e], R. Graham Barr MD [h], Steven Shea MD [h], Ana Navas-Acien MD, PhD [a], Tiffany R. Sanchez PhD [a]

Cardiovascular disease and death

- **Cardiovascular Disease**: myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease, definite / probable angina, CVD death
- **All-cause mortality**: National Death Index database

Cardiovascular disease and death

Irene Martinez-Morata

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Circulation

RESEARCH ARTICLE | Originally Published 1 August 2024

Check for updates

Association of Urinary Metals With Cardiovascular Disease Incidence and All-Cause Mortality in the Multi-Ethnic Study of Atherosclerosis (MESA)

Irene Martinez-Morata, MD, PhD, Kathrin Schilling, PhD, Ronald A. Glabonjat, PhD, Arce Domingo-Relloso, PhD, Melanie Mayer, PhD, Katlyn E. McGraw, PhD, Marta Galvez Fernandez, MD, PhD, ... SHOW ALL ..., and Ana Navas-Acien, MD, PhD | AUTHOR INFO & AFFILIATIONS

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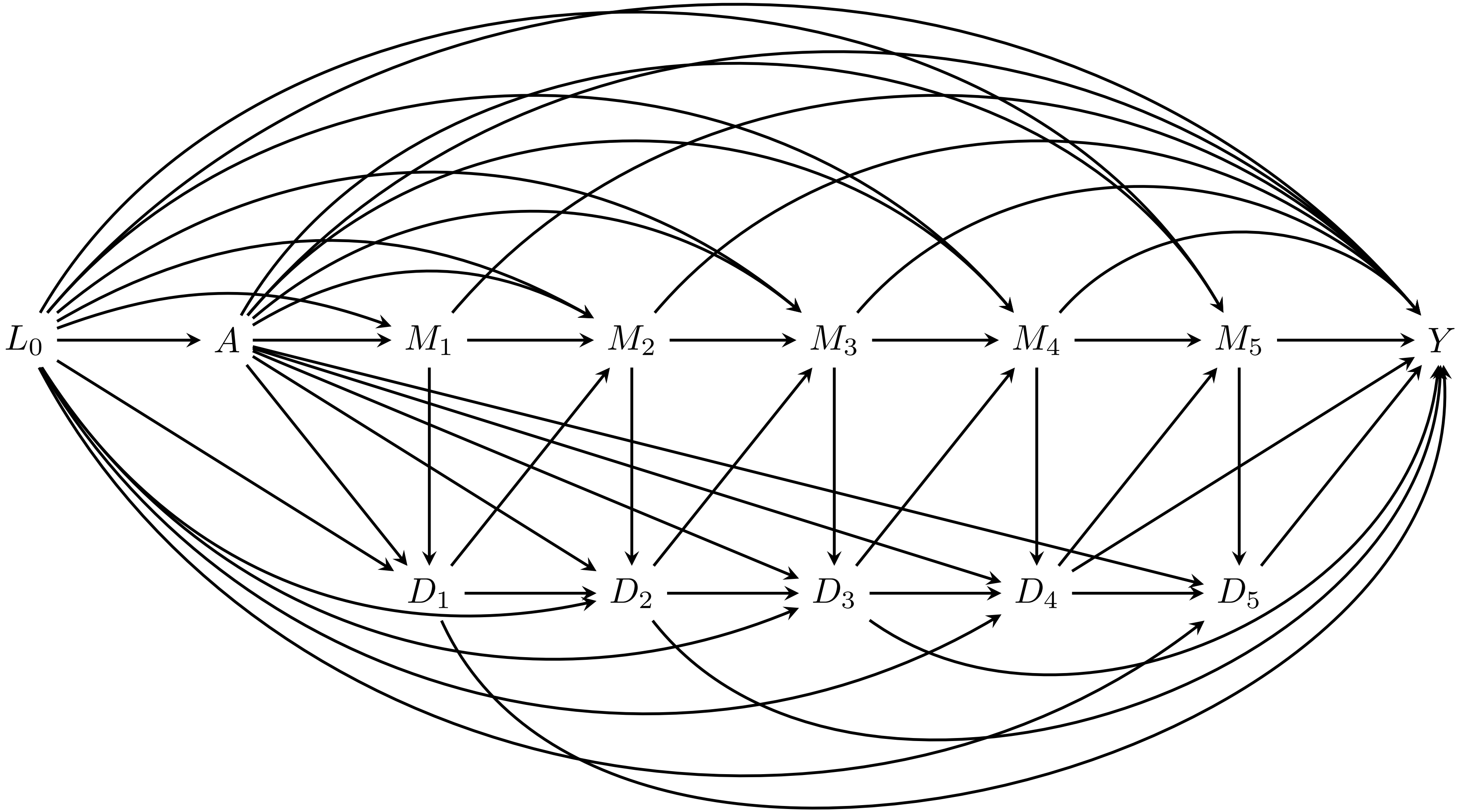
Directed Acyclic Graph



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Results

	Cadmium	Copper	Cobalt	Uranium	Tungsten	Zinc
Direct effect	73.0 (-48.6, 196.9)	309.7 (202.5, 418.1)	144.9 (47.6, 244.7)	76.3 (-48.7, 202.9)	122.2 (26.9, 217.0)	158.9 (67.1, 250.8)
Indirect effect through CAC	54.8 (37.1, 74.3)	19.7 (7.5, 32.9)	22.1 (8.6, 36.4)	19.8 (3.6, 37.5)	19.9 (6.9, 34.0)	45.6 (32.3, 60.3)
Indirect effect through death	-11.5 (-16.3, -6.8)	-4.6 (-9.1, -0.1)	-5.5 (-10.1, -1.1)	-2.9 (-7.5, 1.6)	-0.3 (-4.9, 4.3)	-2.5 (-6.9, 1.9)
Total effect	116.4 (-6.1, 239.9)	325.1 (216.4, 434.5)	161.9 (62.6, 263.2)	93.4 (-33.8, 222.1)	141.9 (45.5, 237.5)	202.1 (109.7, 293.7)

Models adjusted for age, sex, race/ethnicity, study site, education level, body mass index, eGFR and smoking status.
Metals were log-transformed and divided by creatinine to correct for urine dilution.

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Indirect effect through CAC	54.8 (37.1, 74.3)	19.7 (7.5, 32.9)	22.1 (8.6, 36.4)	19.8 (3.6, 37.5)	19.9 (6.9, 34.0)	45.6 (32.3, 60.3)
Indirect effect through death	-11.5 (-16.3, -6.8)	-4.6 (-9.1, -0.1)	-5.5 (-10.1, -1.1)	-2.9 (-7.5, 1.6)	-0.3 (-4.9, 4.3)	-2.5 (-6.9, 1.9)
Total effect	116.4 (-6.1, 239.9)	325.1 (216.4, 434.5)	161.9 (62.6, 263.2)	93.4 (-33.8, 222.1)	141.9 (45.5, 237.5)	202.1 (109.7, 293.7)

Models adjusted for age, sex, race/ethnicity, study site, education level, body mass index, eGFR and smoking status.
Metals were log-transformed and divided by creatinine to correct for urine dilution.

Results

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Metals, coronary artery calcification, and CVD

- **Association of urinary metals with CVD partially mediated by CAC over time.**
- Cadmium showed a strong association with mortality for causes other than CVD: competing risks
- Other biological pathways unrelated to CAC might mediate the association between copper and zinc and CVD.

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Full length article

The role of coronary artery calcification in metal-related cardiovascular disease

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Conclusions

- Part of the association between urinary metals and CVD was attributable to changes in CAC, a subclinical atherosclerosis marker, over time.
- Our results highlight the importance of accounting for competing risks due to death for those exposures that have a strong association with mortality.
- The effect of copper and zinc on CVD was largely attenuated after adjustment of CVD risk factors: other CVD risk factors might be contributing to this effect.
- **Being able to decompose the effect of metals on CVD and death provides a better insight on the biological pathways involved in the harmful effects of elevated urinary metal levels.**

Limitations

- Limitation: death is discretized
- Ongoing work: multi-state models for time-to-event mediators
- Unmeasured confounding cannot be ruled out
- Future work: multiple mediators of different types / extension to machine learning to evaluate mixtures

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Questions?

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