

Interpretation of Mendelian randomization estimates with time-varying exposures

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The importance of interpretation



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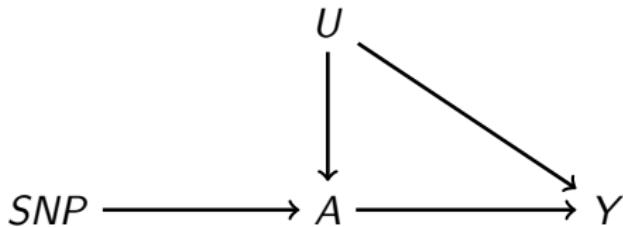


The importance of interpretation



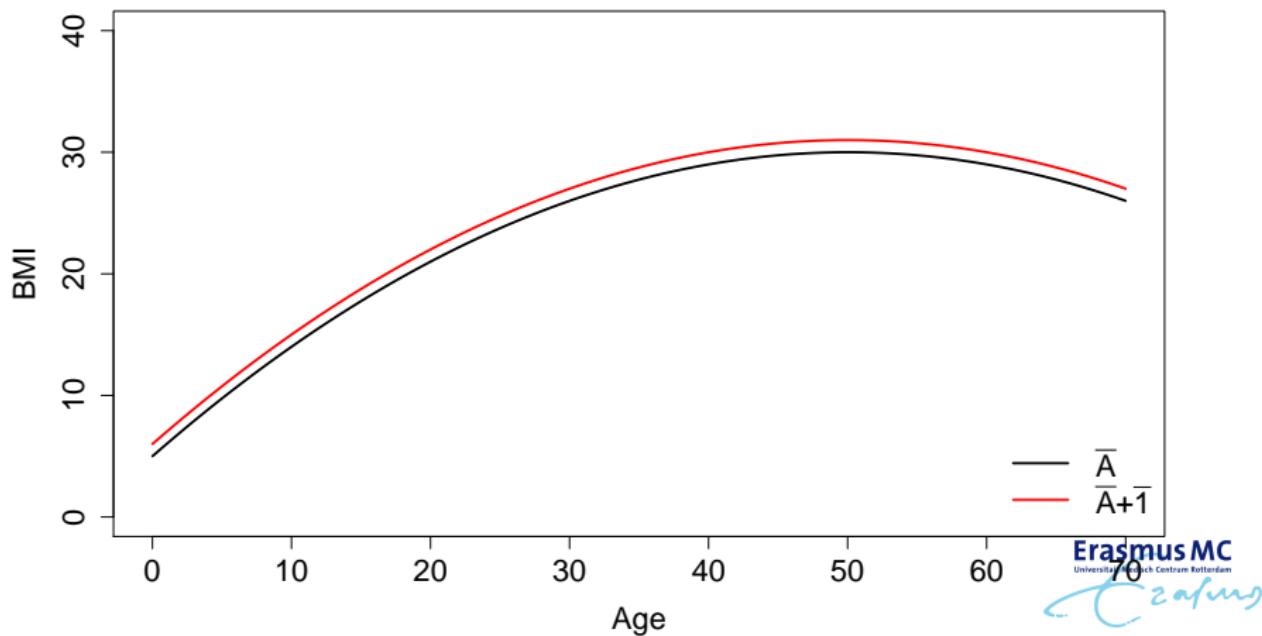
What is the interpretation of Mendelian randomization?

- ▶ MR uses IV which comes from econometrics and economists don't think about time (as much as epidemiologists anyway)
- ▶ Typical answer: "...the effects of long-term differences in exposures on disease risk."
- ▶ What does this mean?
 - ▶ Intervening at birth?
 - ▶ Average long-term differences?
 - ▶ How big are the differences?
 - ▶ What does long-term mean?

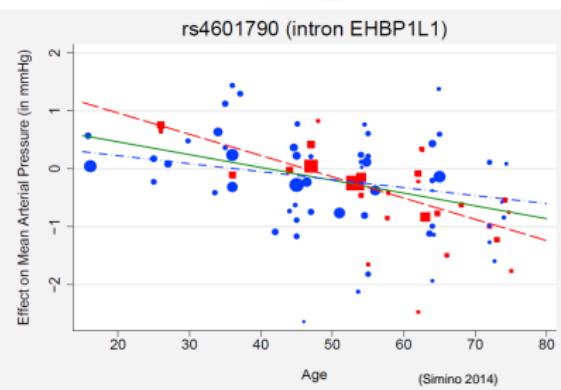
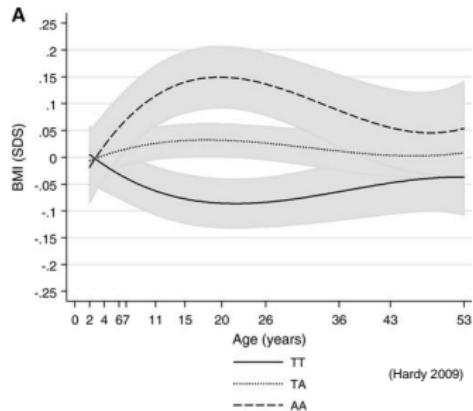
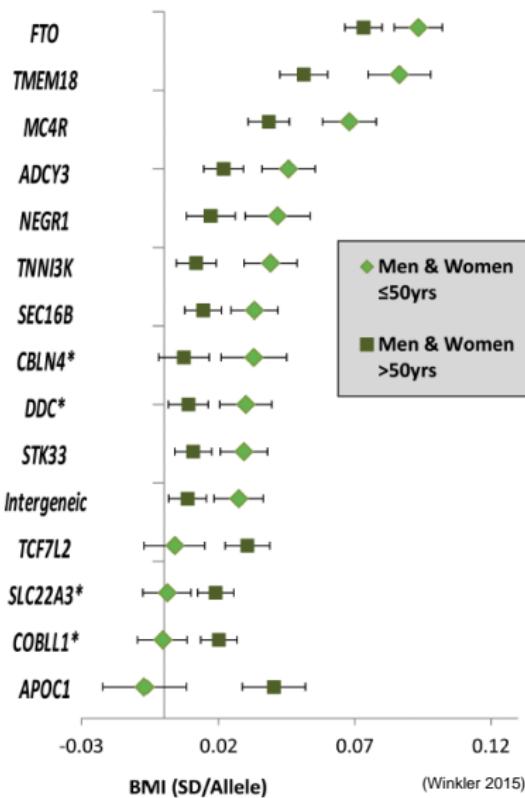


A precise definition of what MR estimates

- ▶ We propose: $E[Y_K^{\bar{A}+1}] - E[Y_K^{\bar{A}}]$
- ▶ In words, this is the lifetime effect of shifting the exposure history \bar{A} by one unit on Y at time K .
- ▶ Notice that the lifetime effect depends on k , i.e. varies with age

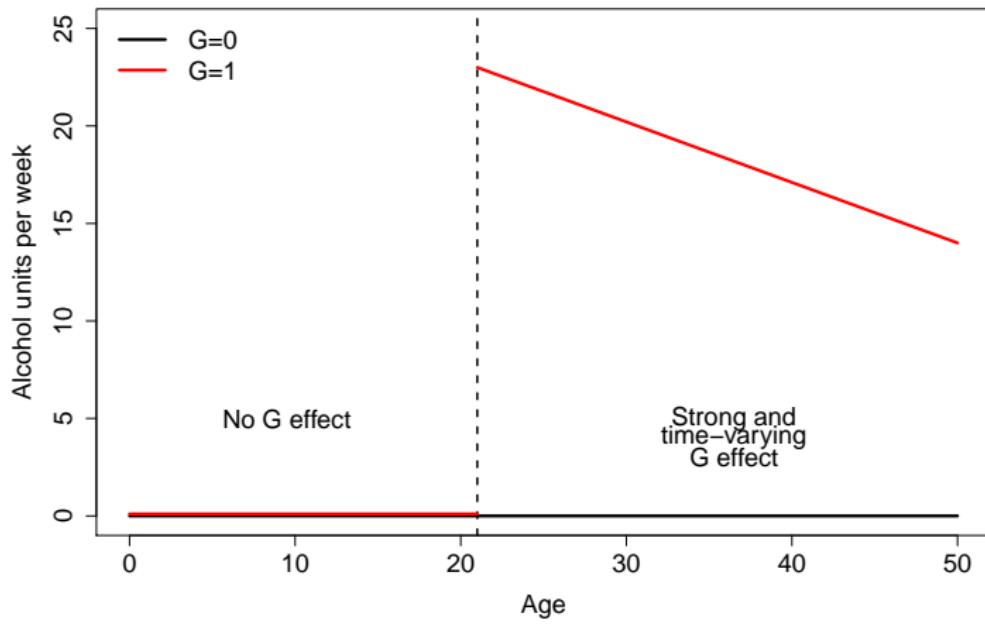


MR with SNPs whose effects change with time



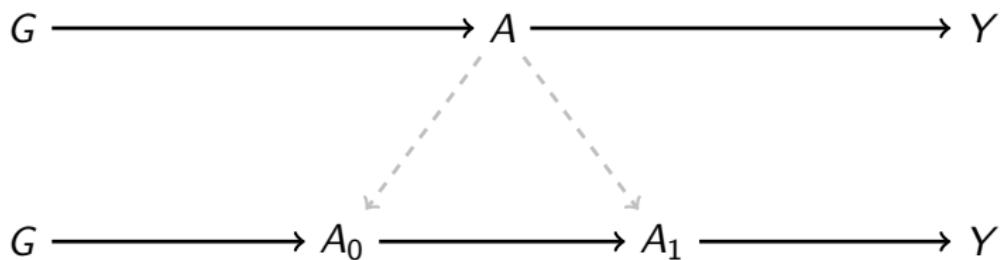
Inferring time-varying genetic effects

- ▶ We can infer time-varying genetic effects when one genetic variant abstains from exposure (alcohol, dairy) and another level changes with time:



A simple explanation for why time-varying SNPs bias MR

- ▶ Split A node to allow it to change with time.

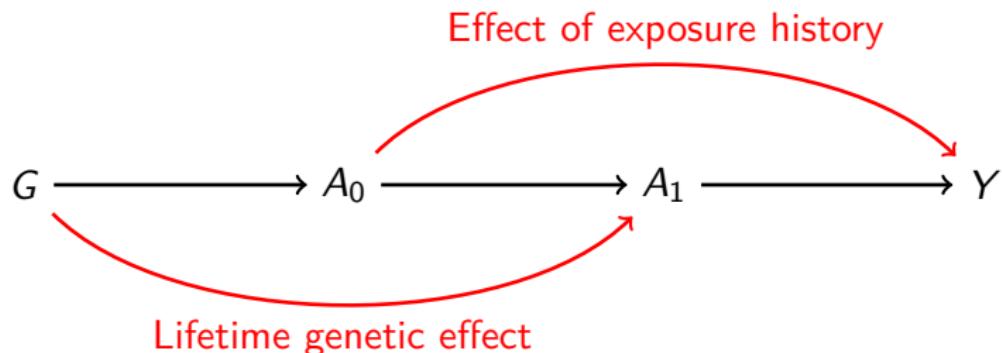


A simple explanation for why time-varying SNPs bias MR



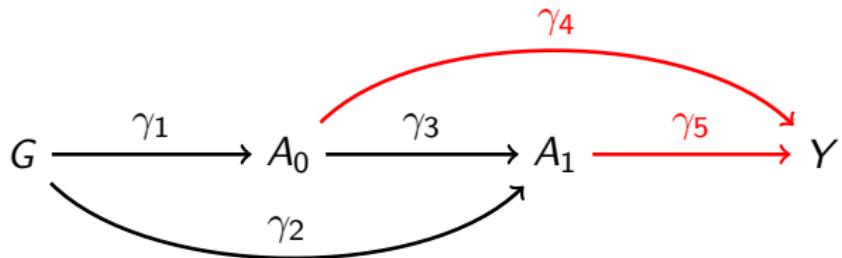
- ▶ Under this causal structure, everything is ok
- ▶ But is this causal structure realistic?

A simple explanation for why time-varying SNPs bias MR



- ▶ NB: the exclusion restriction can hold for A as a whole but not for A at specific points in time

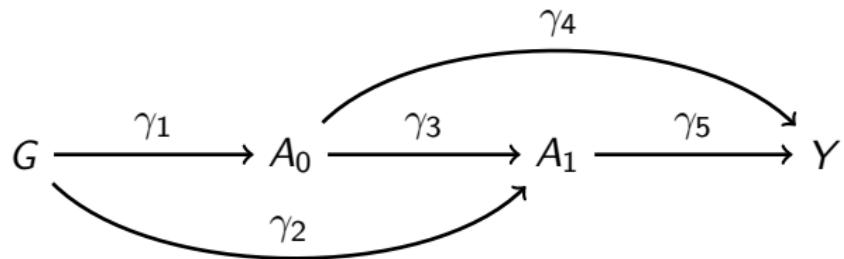
A simple explanation



True lifetime effect = $\gamma_4 + \gamma_5$

$$\begin{aligned} MR_1 &= \frac{\gamma_1 * \gamma_4 + \gamma_1 * \gamma_3 * \gamma_5 + \gamma_2 * \gamma_5}{\gamma_1 * \gamma_3 + \gamma_2} \\ &= \left(\frac{\gamma_1}{\gamma_1 * \gamma_3 + \gamma_2} \right) * \gamma_4 + \gamma_5 \end{aligned}$$

But if $\gamma_1 = \gamma_1 * \gamma_3 + \gamma_2 \dots$



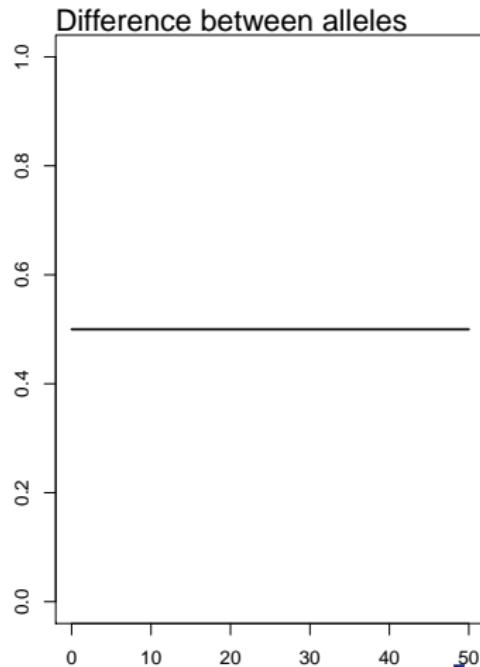
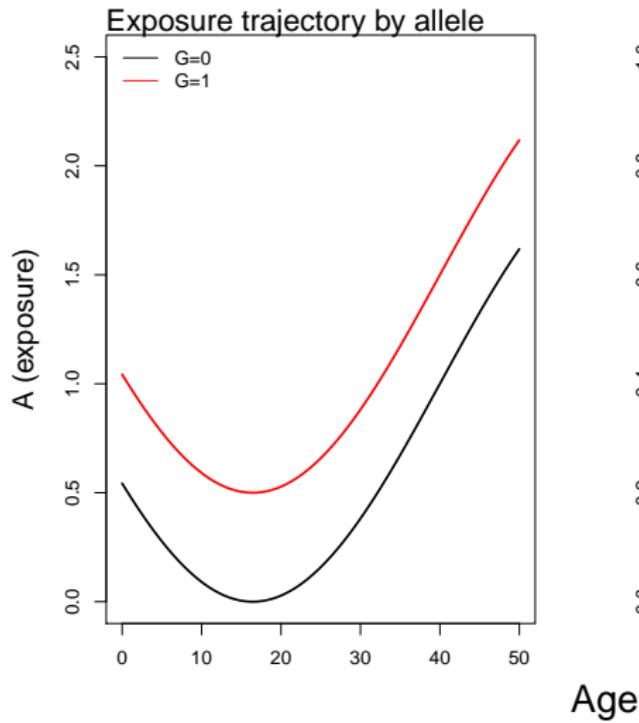
$$\begin{aligned}MR_1 &= \left(\frac{\gamma_1}{\gamma_1 * \gamma_3 + \gamma_2} \right) * \gamma_4 + \gamma_5 \\&= \left(\frac{\gamma_1}{\gamma_1} \right) * \gamma_4 + \gamma_5 \\&= \gamma_4 + \gamma_5\end{aligned}$$

But how much bias are we talking here?

1. Choose relationship between G and A
2. Choose exposure window
3. Calculate MR estimate and true lifetime effect

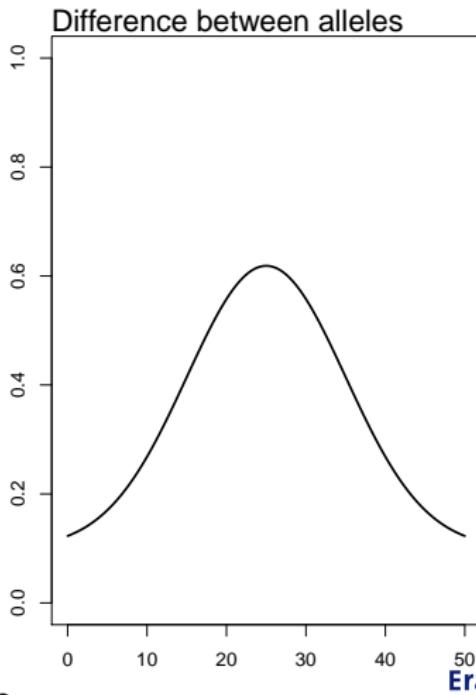
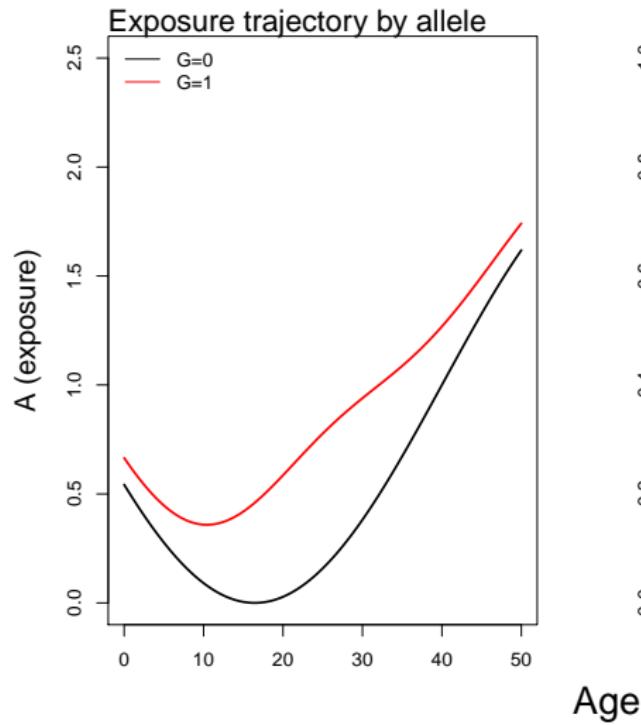
1. Relationships between G and A

1. Constant genetic effect



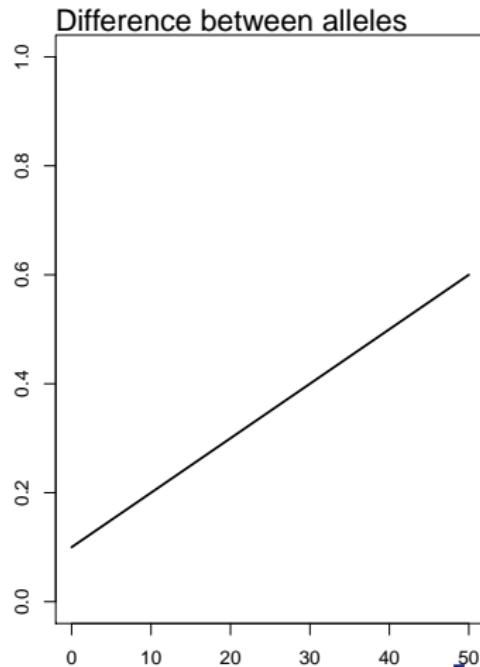
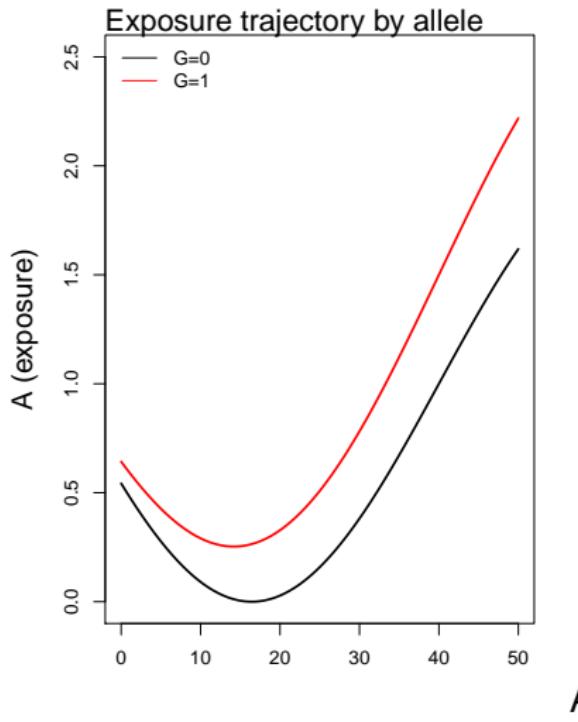
1. Relationships between G and A

2. Similar to FTO



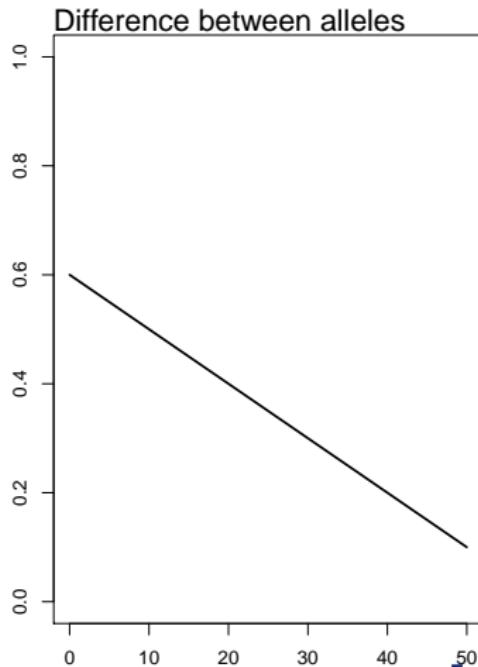
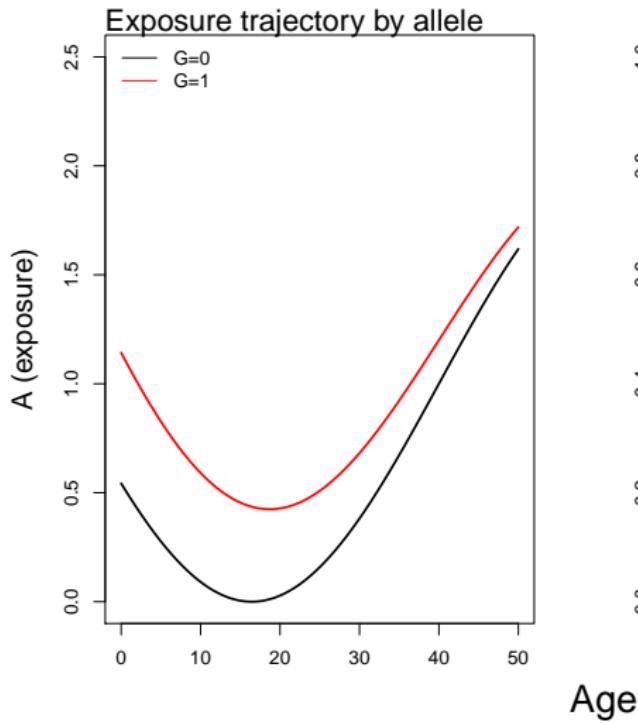
1. Relationships between G and A

3. Increasing genetic effect



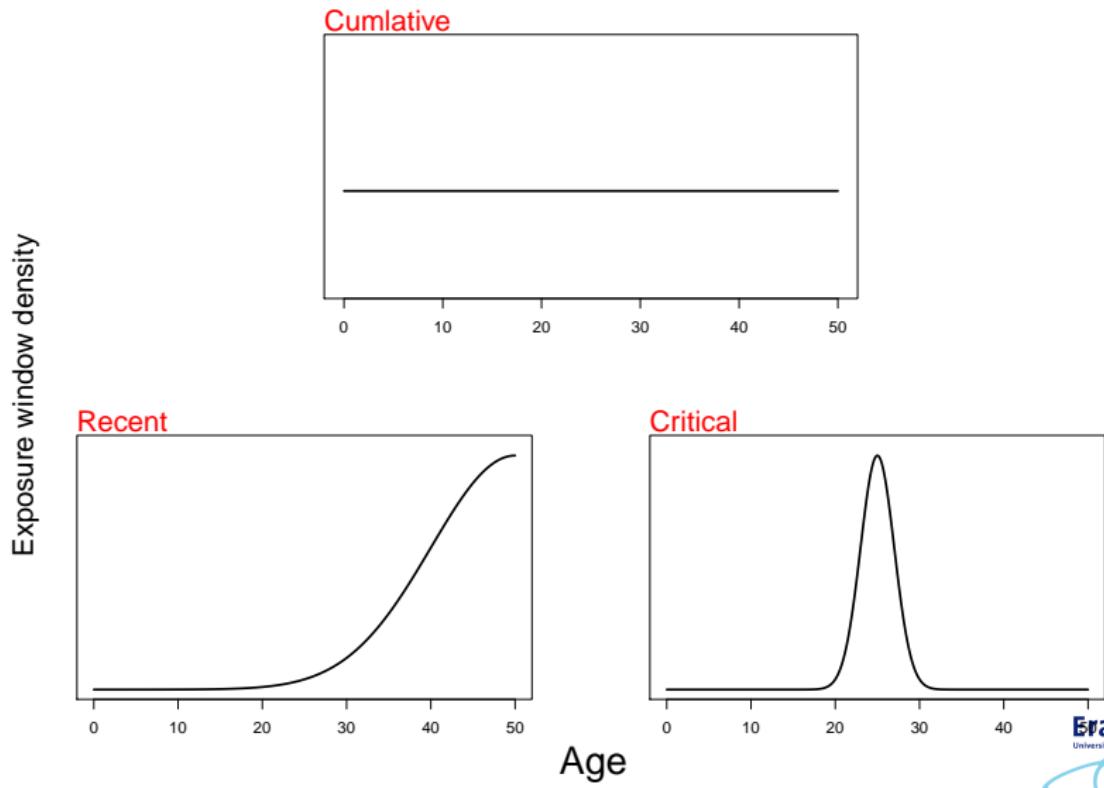
1. Relationships between G and A

4. Decreasing genetic effect

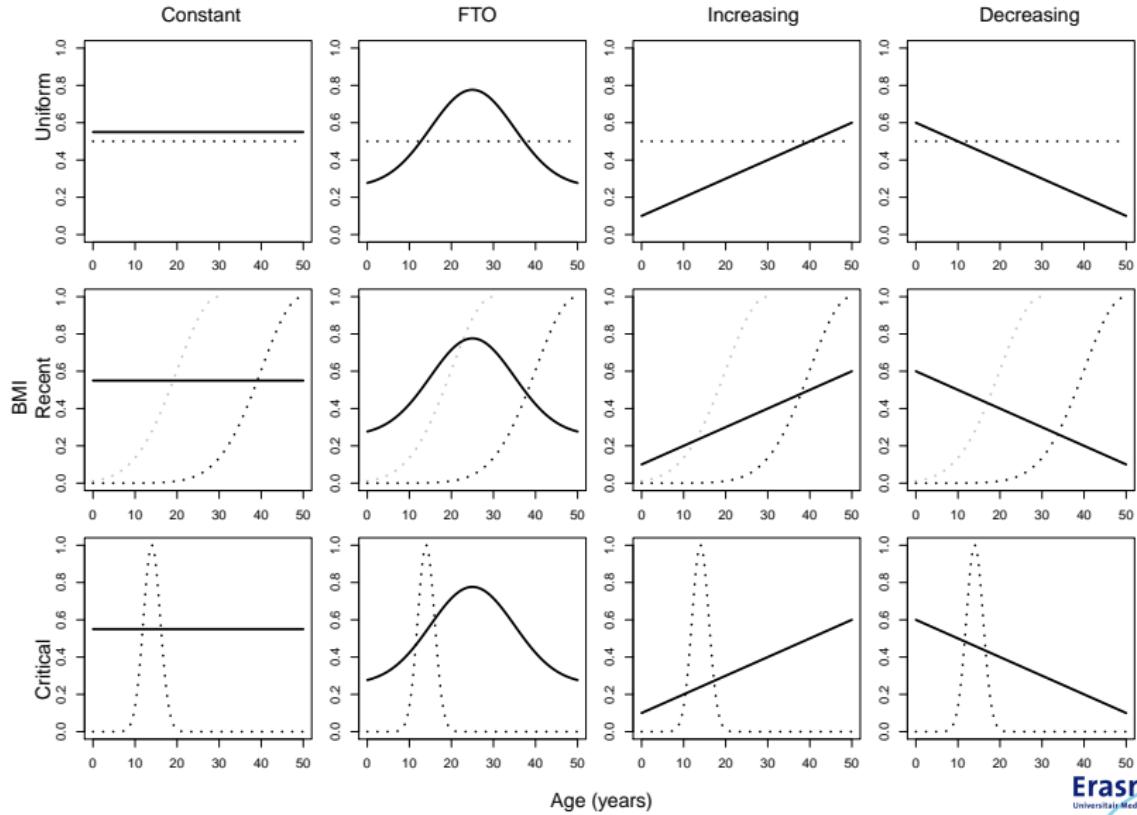


2. Exposure windows

We used three exposure windows and set the lifetime effect to 2:



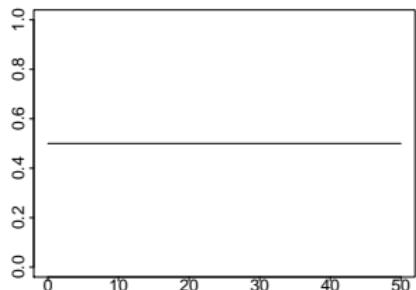
12 scenarios



Analytic solution

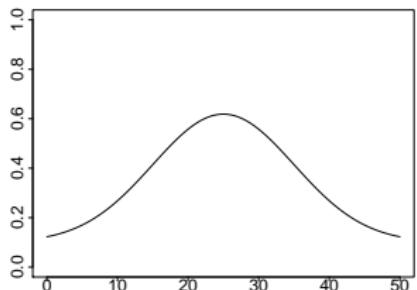
- ▶ Using the previous graphs above we can calculate (at age 50):
 - ▶ Reduced form estimate ($E[Y|G = 1] - E[Y|G = 0]$)
 - ▶ Instrument strength ($E[A|G = 1] - E[A|G = 0]$)
 - ▶ MR estimate
- ▶ We then calculate the absolute and relative bias by comparing the MR estimate to the lifetime effect (which we set to 2)

Results: Constant genetic effect



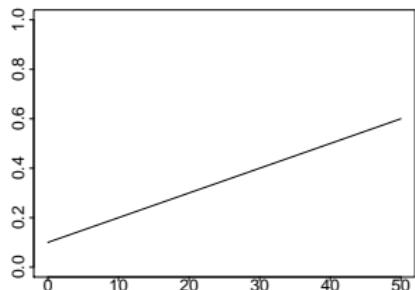
Exposure window	True effect	MR estimate	Absolute bias	Relative bias (%)
Uniform	2.0	2.0	0.0	0
Recent	2.0	2.0	0.0	0
Critical	2.0	2.0	0.0	0

Results: Similar to FTO



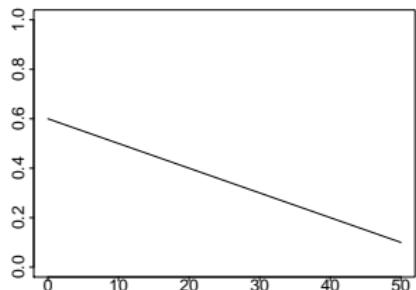
Exposure window	True effect	MR estimate	Absolute bias	Relative bias (%)
Uniform	2.0	3.7	1.7	85
Recent	2.0	2.9	0.9	46
Critical	2.0	3.9	1.9	95

Results: Increasing genetic effect



Exposure window	True effect	MR estimate	Absolute bias	Relative bias (%)
Uniform	2.0	1.5	-0.5	-25
Recent	2.0	1.8	-0.2	-8
Critical	2.0	1.3	-0.7	-36

Results: Decreasing genetic effect



Exposure window	True effect	MR estimate	Absolute bias	Relative bias (%)
Uniform	2.0	3.0	1.0	50
Recent	2.0	2.3	0.3	16
Critical	2.0	3.4	1.4	72

Results summary

- ▶ MR with time-varying exposures remains unbiased if genetic effect is constant
- ▶ Whenever the genetic effect itself is time-varying, the MR estimate will be biased
- ▶ The bias is related to how much A varies relative to the strength of the instrument in the exposure window
- ▶ If MR estimates are truly bidirectional, both estimates will be biased (see appendix on github)

Solutions?

- ▶ There is no fix because you can't summarize a longitudinal relationship with one number
- ▶ Don't estimate effects with SNPs whose effects vary with age/time (FTO, MC4R, ALDH2, etc)
- ▶ Can still test but see Swanson et al¹ for what can be tested
- ▶ Sensitivity analyses to see how much variations in effect size could change results (weaker instruments will be more biased)

¹Swanson, Labrecque and Hernan 2018. Eur J Epi.

Take home message

- ▶ Our proposed definition of a lifetime effect in MR:
 $E[Y_K^{\bar{A}+1}] - E[Y_K^{\bar{A}}]$
- ▶ Estimation of lifetime effects with MR requires:
 - ▶ Relevance
 - ▶ Exclusion restriction
 - ▶ Exchangeability
 - ▶ Homogeneity or monotonicity
 - ▶ SNP(s) with non-time-varying effects

Thank you

- ▶ Thanks to Sonja and the rest of Causal Inference Group at Erasmus MC.
- ▶ This work was partly supported by a DynaHEALTH grant [European Union H2020-PHC-2014; 633595]. Dr. Swanson is supported by a NWO/ZonMW Veni grant [91617066]
- ▶ Slides, simulation and other materials available at:
github.com/jerbreck/MR_interpretation

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