Interpretation of Mendelian randomization estimates with time-varying exposures

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The importance of interpretation

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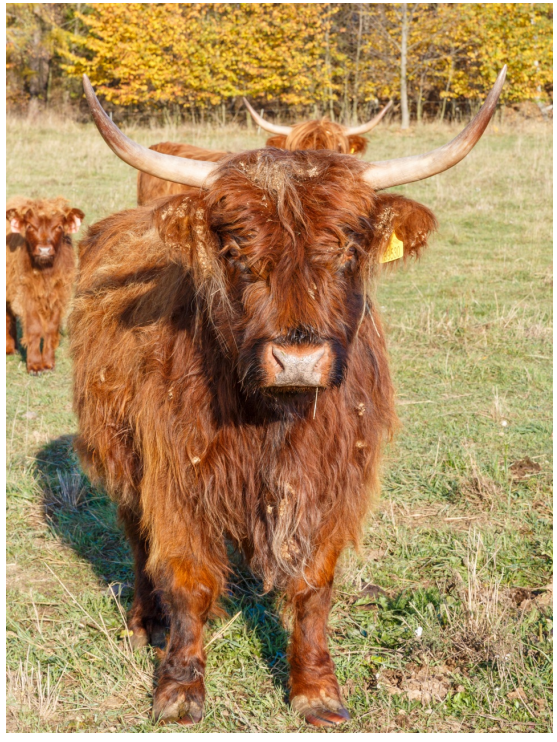

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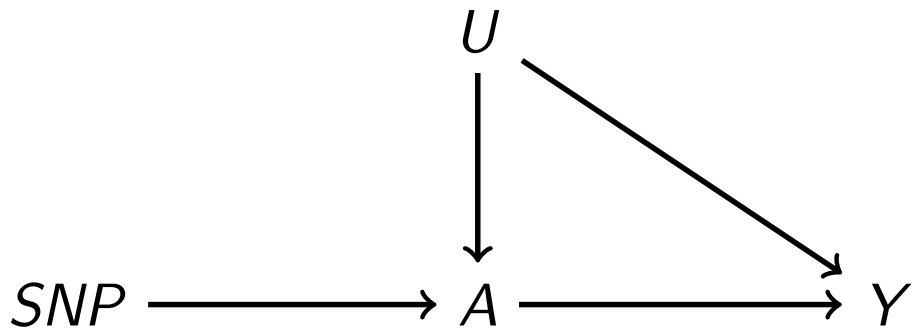
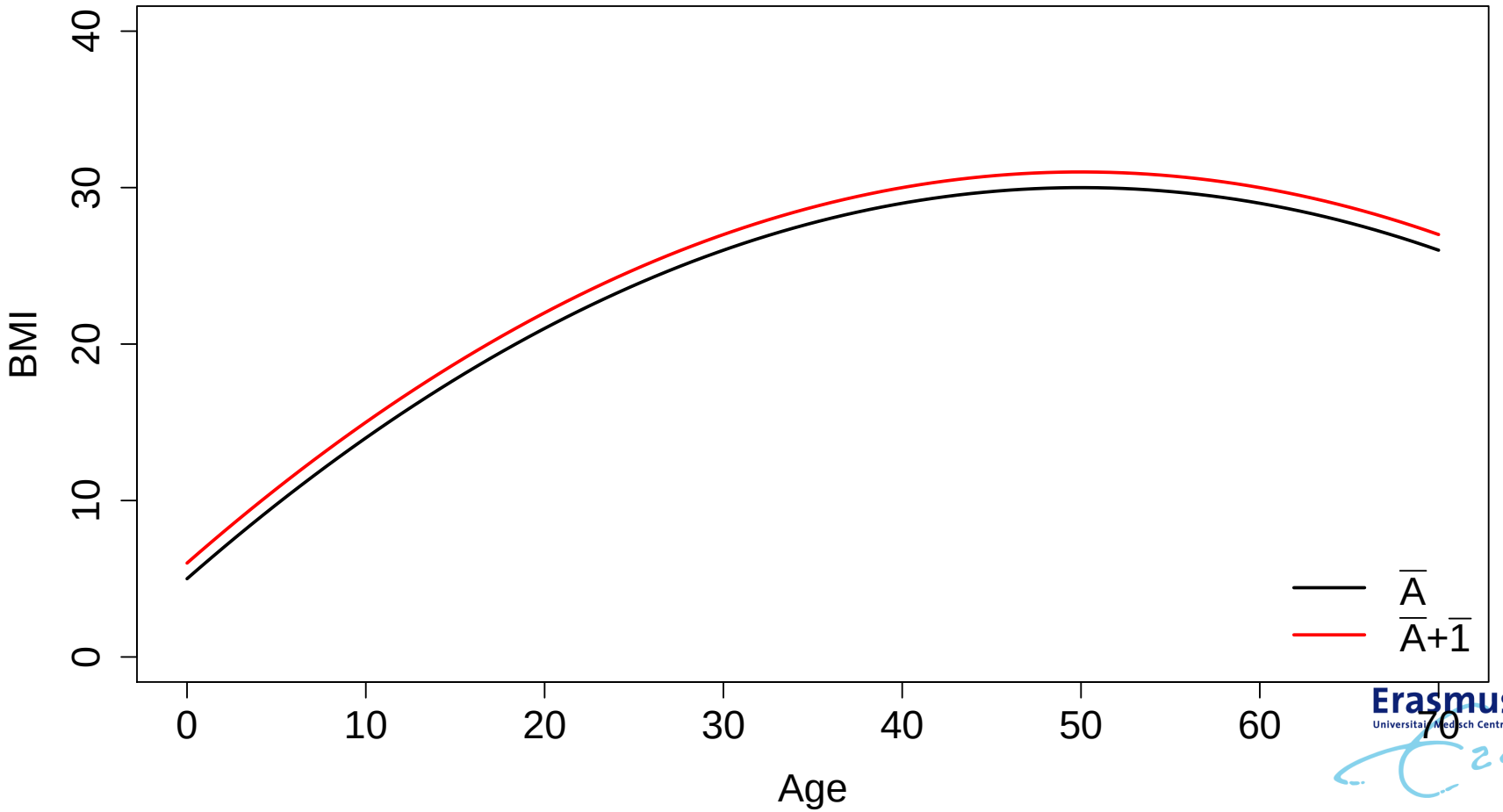
What is the interpretation of Mendelian randomization?

- 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?

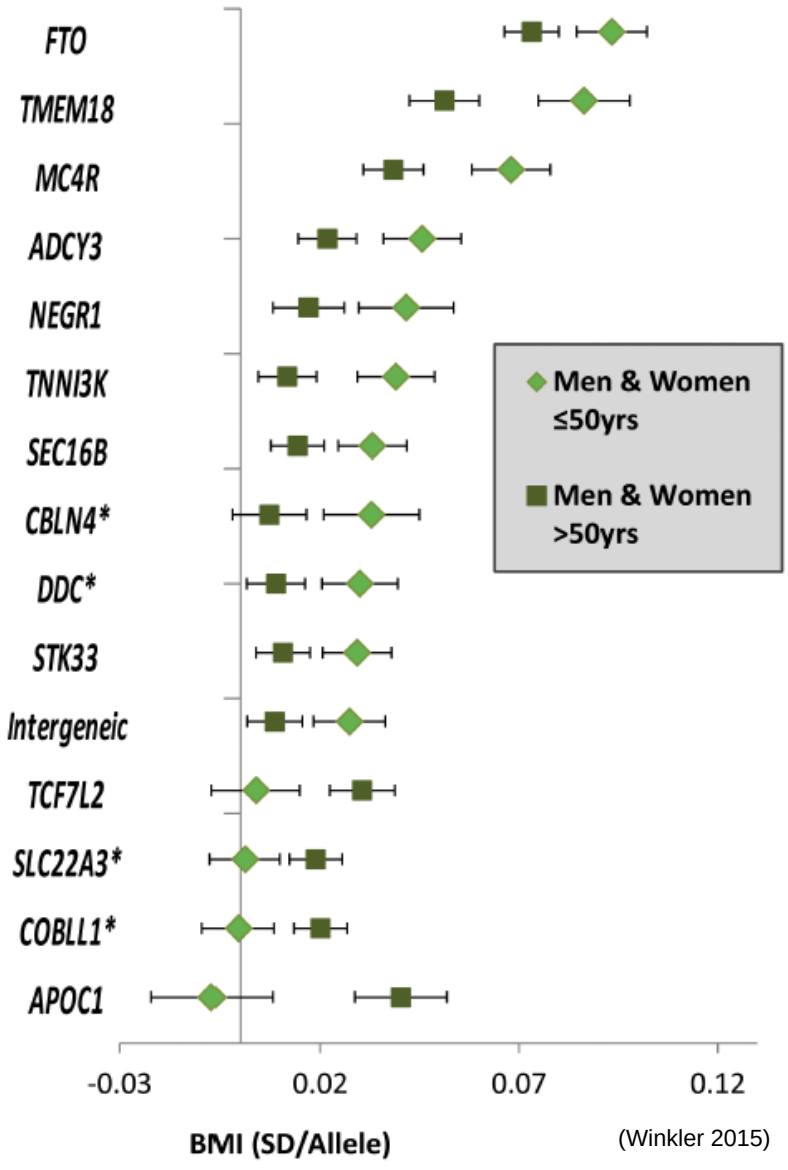


A precise definition of what MR estimates

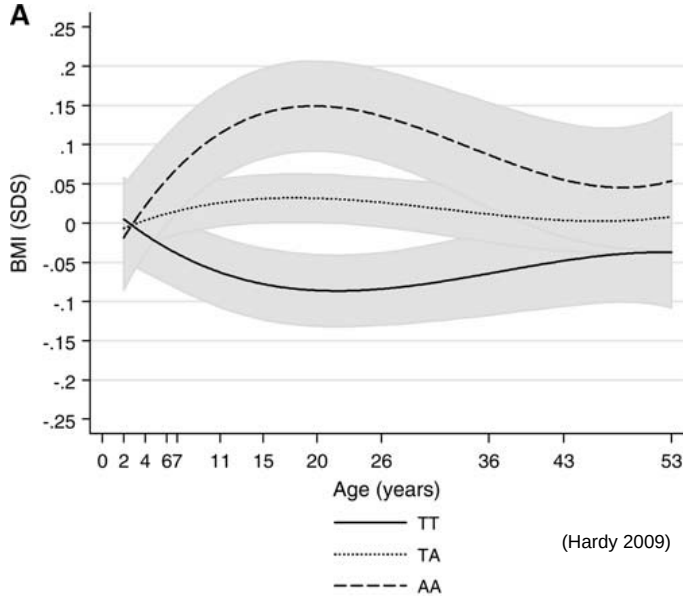
- We propose: $\mathrm{E}[Y_K^{\bar{A}+\bar{1}}] - \mathrm{E}[Y_K^{\bar{A}}]$
- In words, this is the lifetime effect of shifting the exposure history $\bar{A}$ by one unit on Y at time K.
- Notice that the lifetime effect depends on k, i.e. varies with age



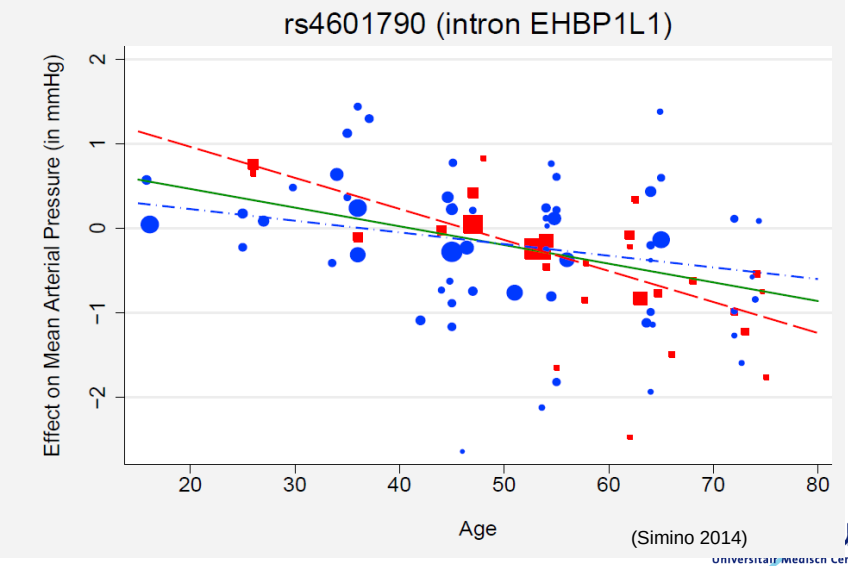
MR with SNPs whose effects change with time



(Winkler 2015)



(Hardy 2009)



(Simino 2014)

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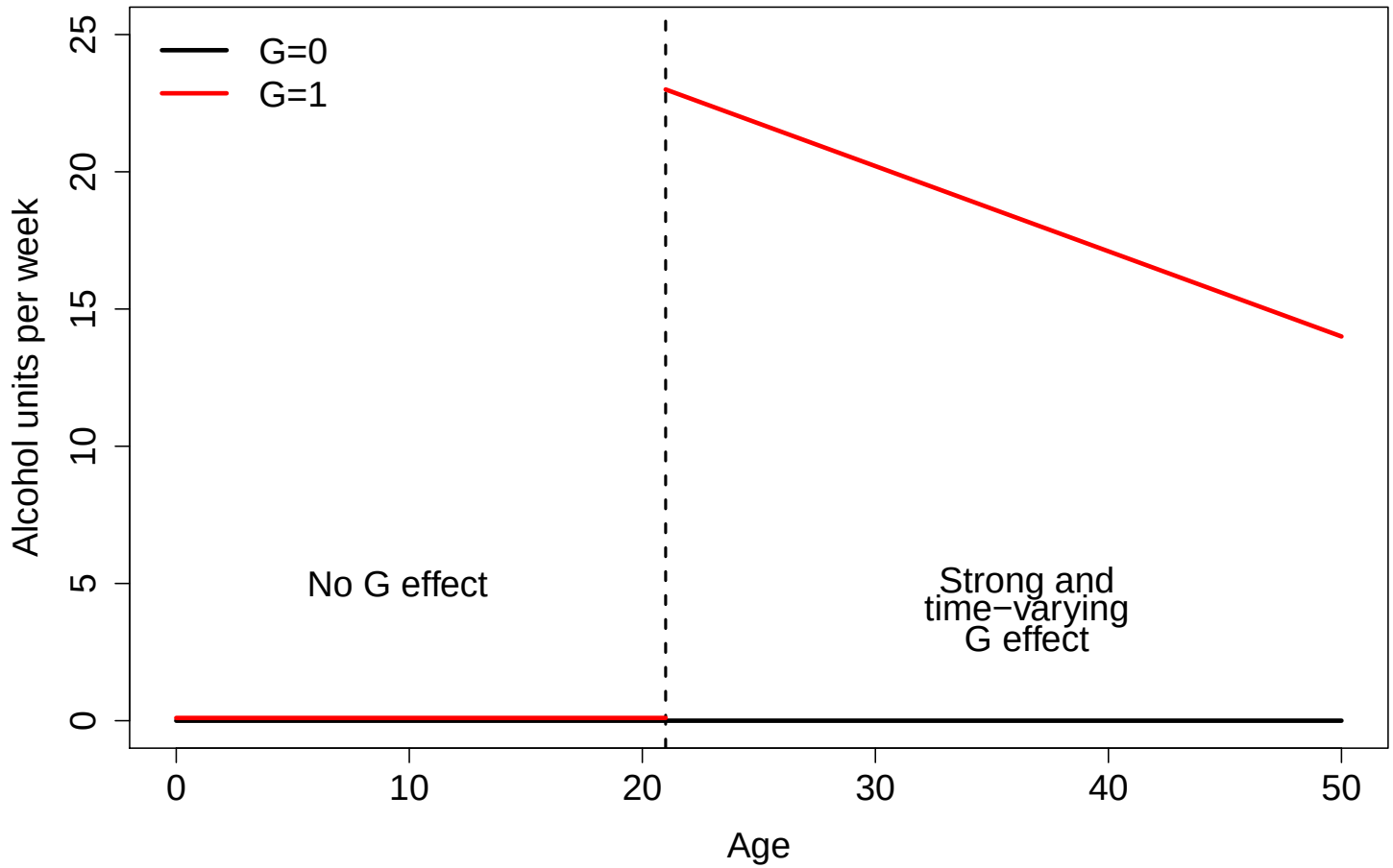
Inferring time-varying genetic effects

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



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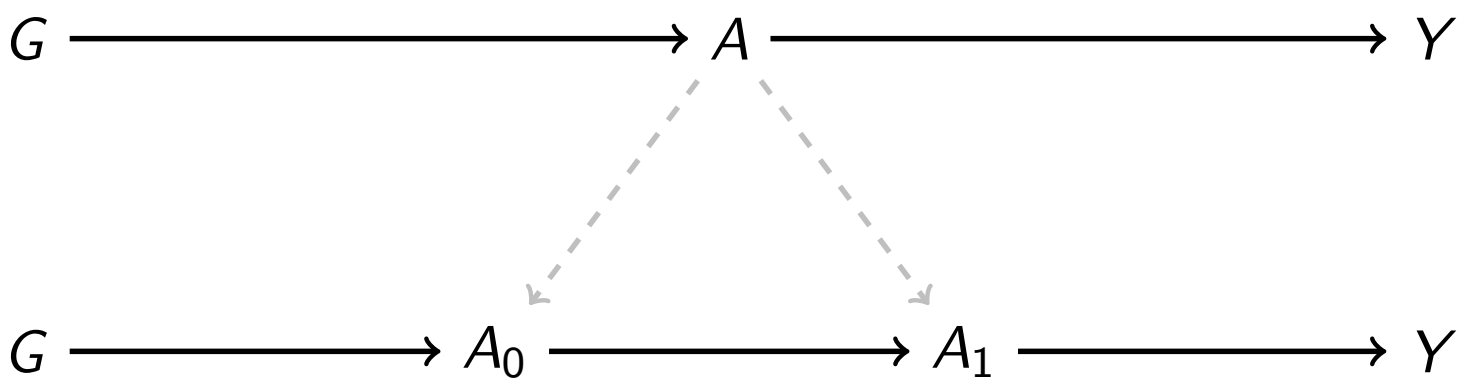
A simple explanation for why time-varying SNPs bias MR

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



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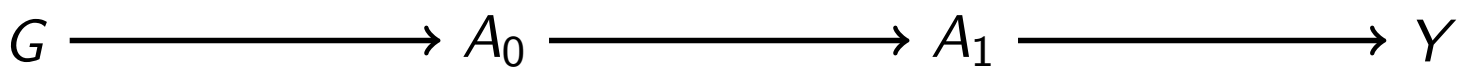
A simple explanation for why time-varying SNPs bias MR



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

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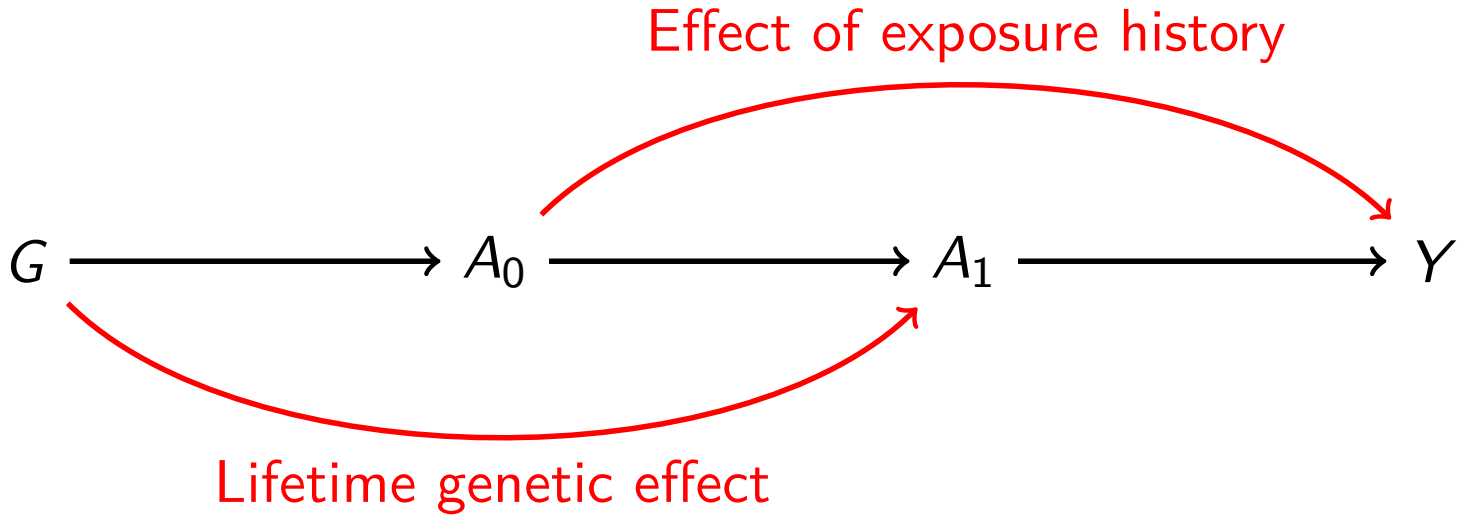
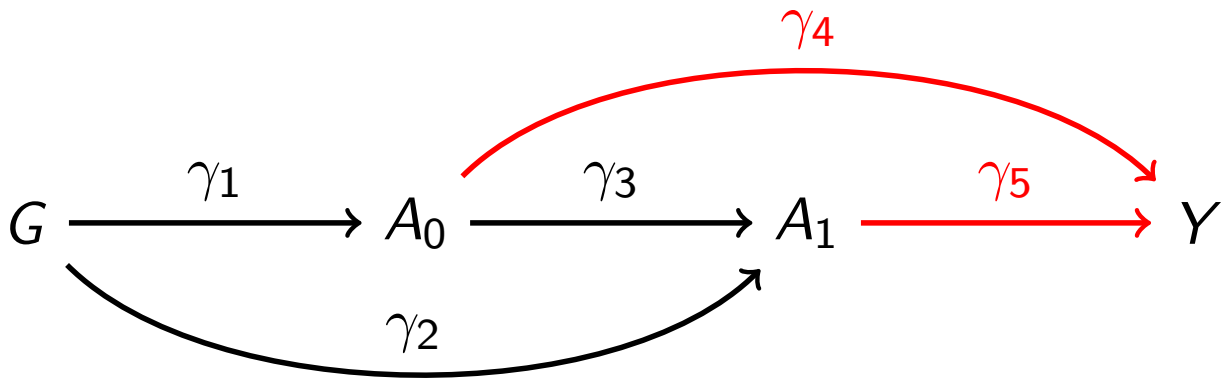
A simple explanation for why time-varying SNPs bias MR



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

A simple explanation



$$\text{True lifetime effect} = \gamma_4 + \gamma_5$$

$$MR_1 = \frac{\gamma_1 * \gamma_4 + \gamma_1 * \gamma_3 * \gamma_5 + \gamma_2 * \gamma_5}{\gamma_1 * \gamma_3 + \gamma_2}$$

$$= \left(\frac{\gamma_1}{\gamma_1 * \gamma_3 + \gamma_2}\right) * \gamma_4 + \gamma_5$$

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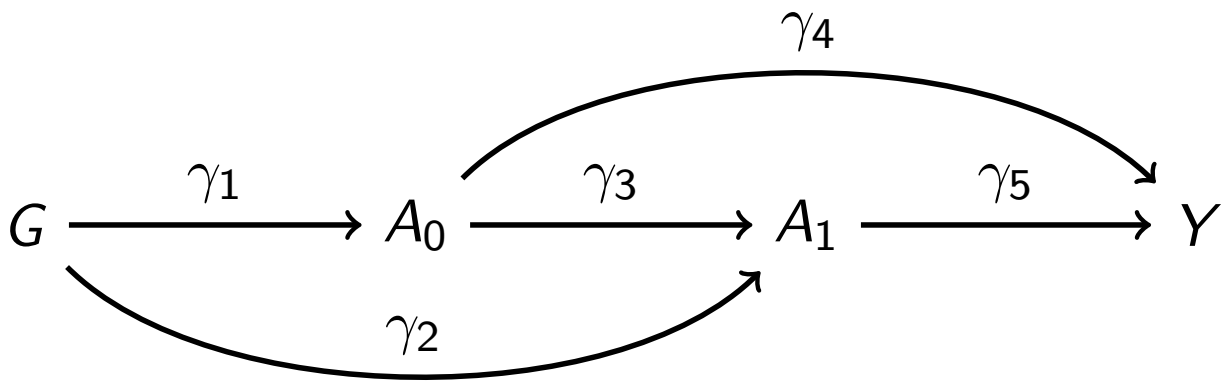
But if $\gamma_1 = \gamma_1 * \gamma_3 + \gamma_2 \ldots$



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

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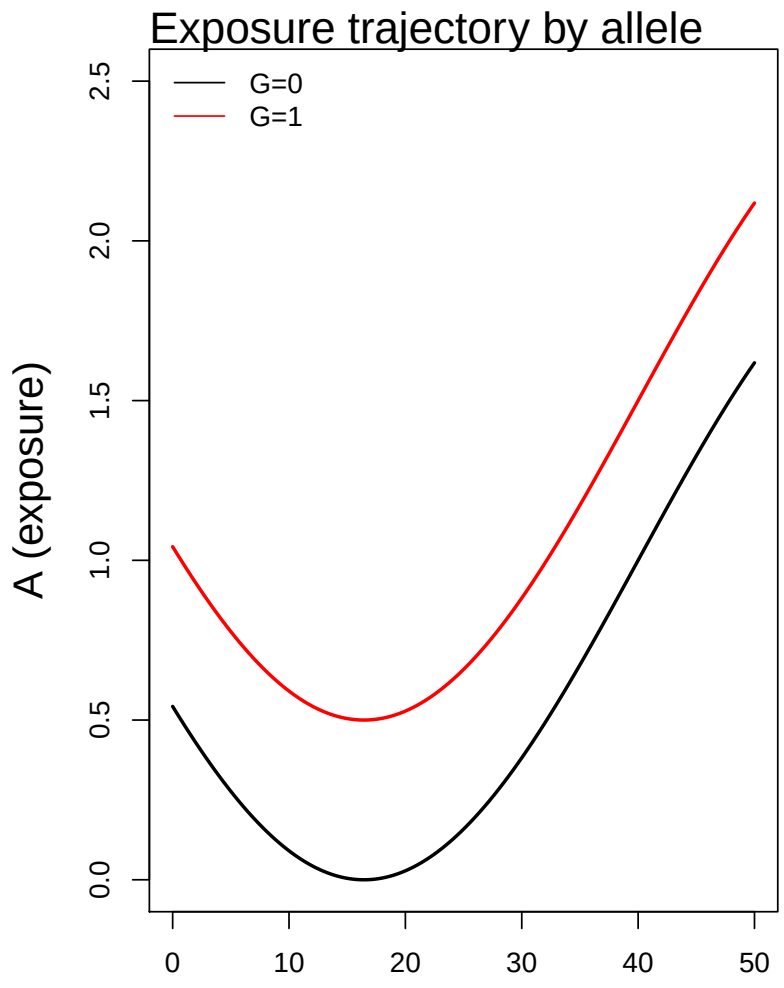
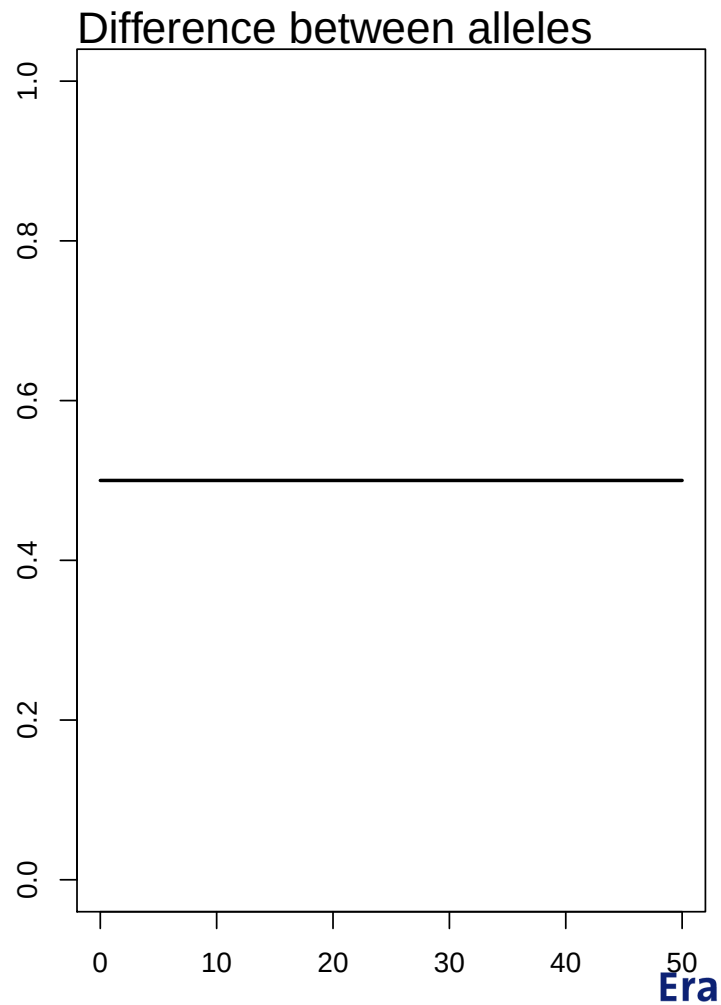
But how much bias are we talking here?

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





Age

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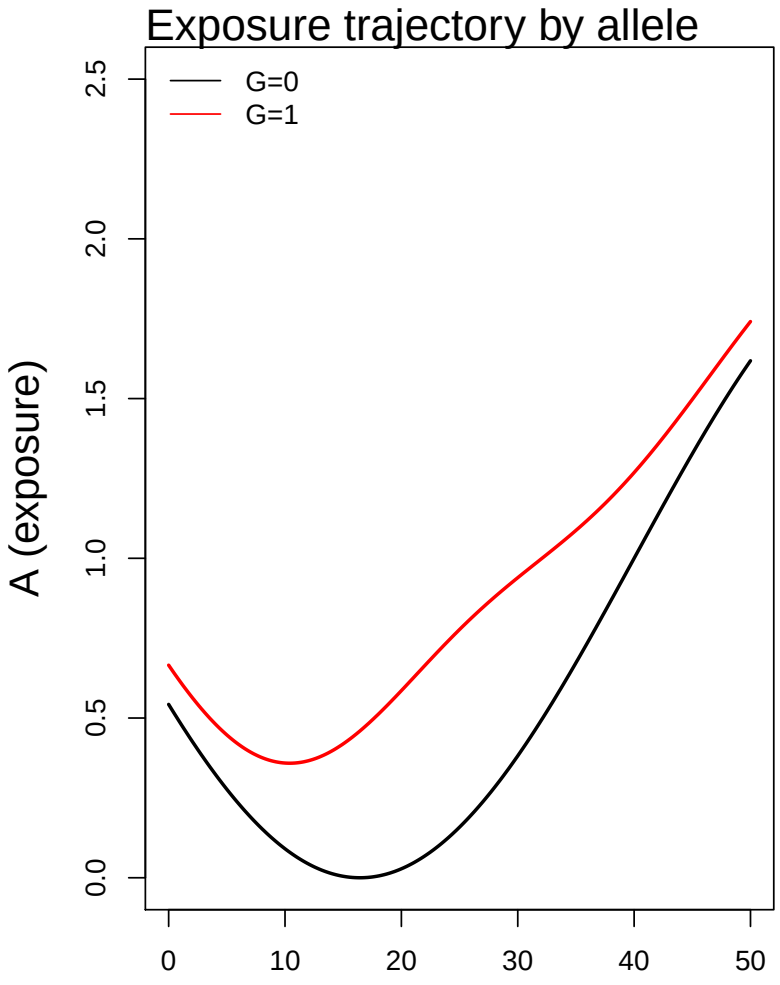
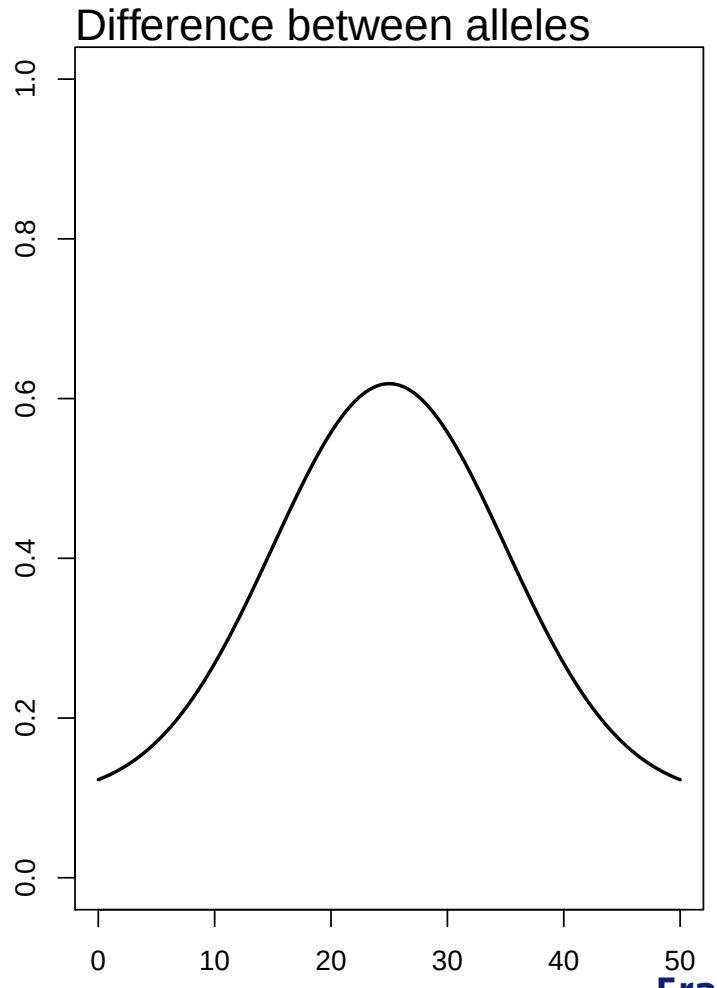
1. Relationships between G and A

2. Similar to FTO





Age

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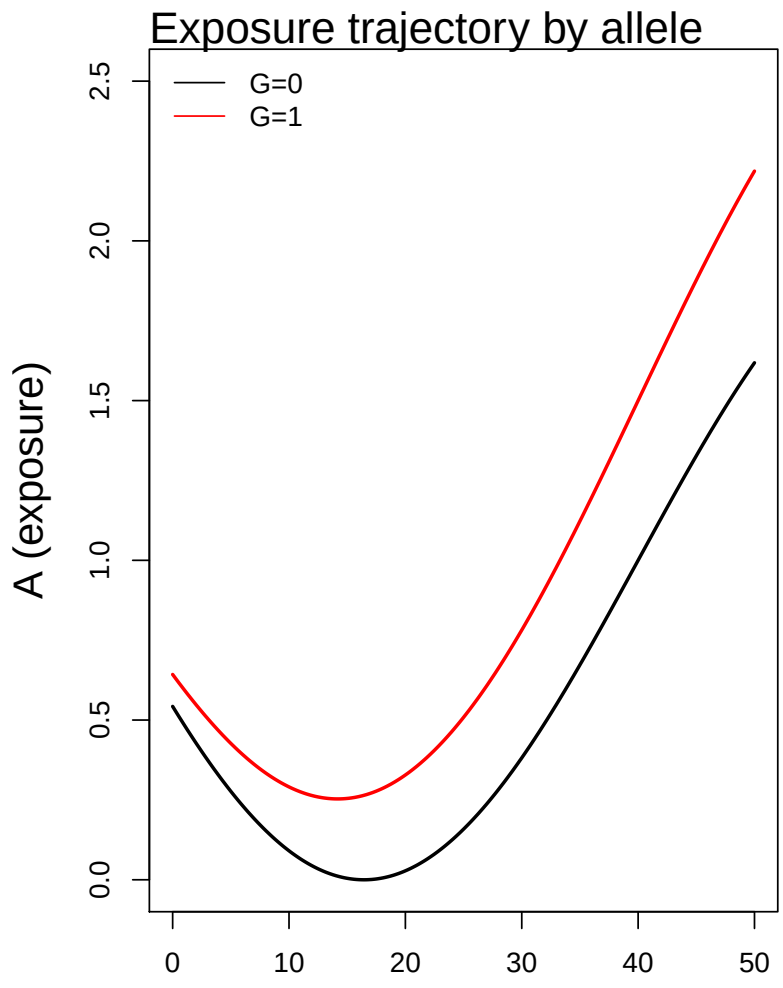
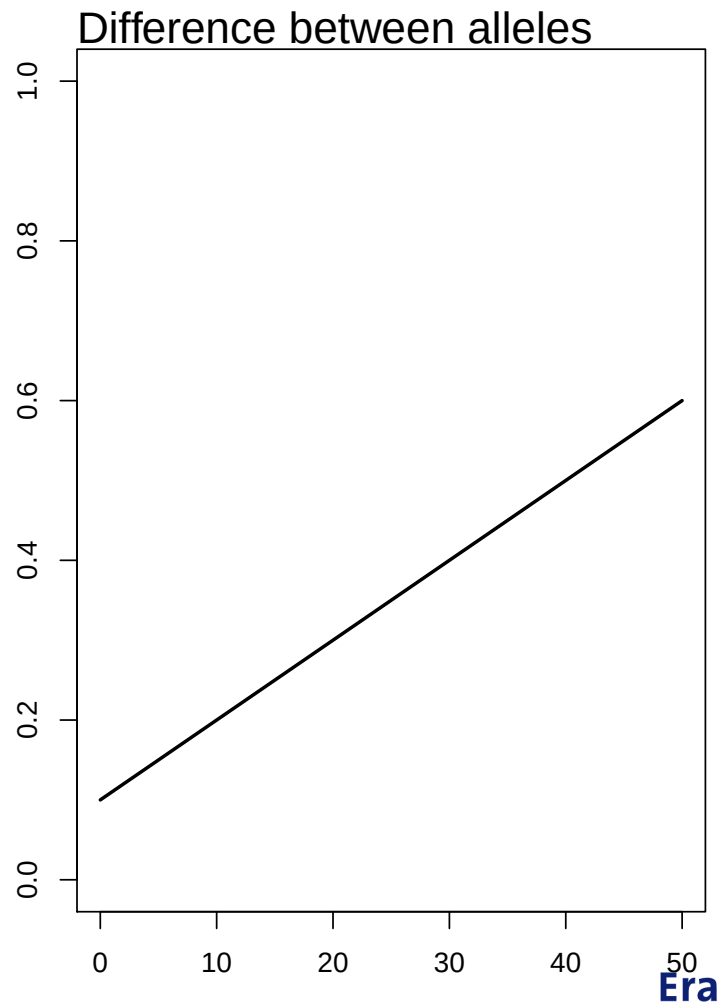
1. Relationships between G and A

3. Increasing genetic effect





Age

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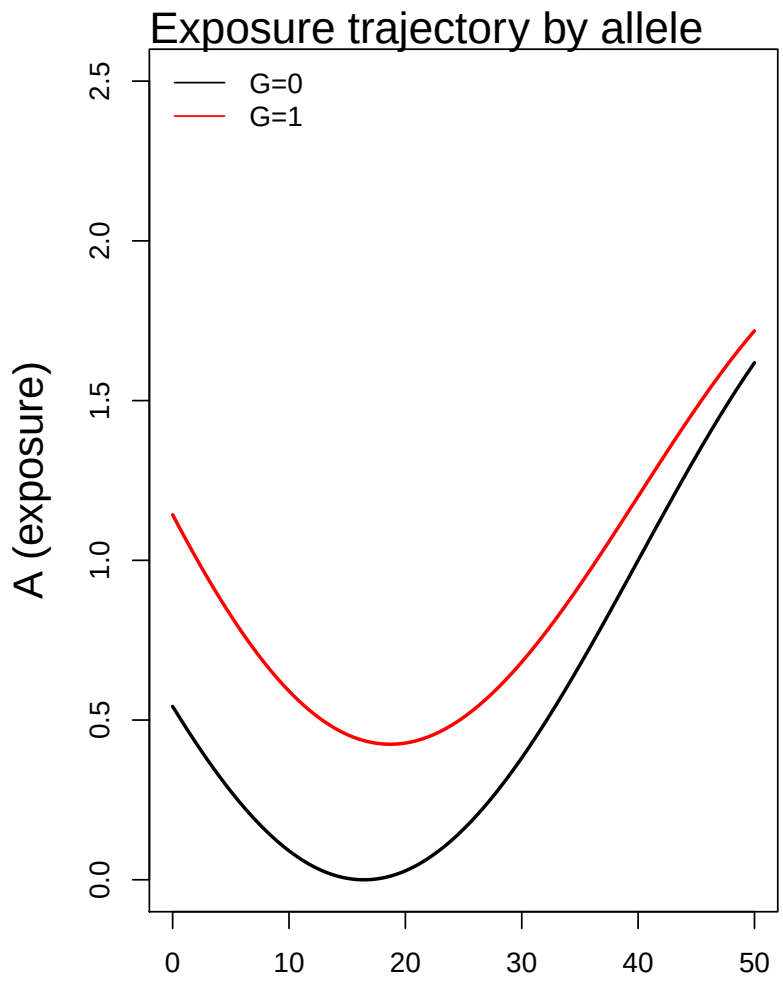
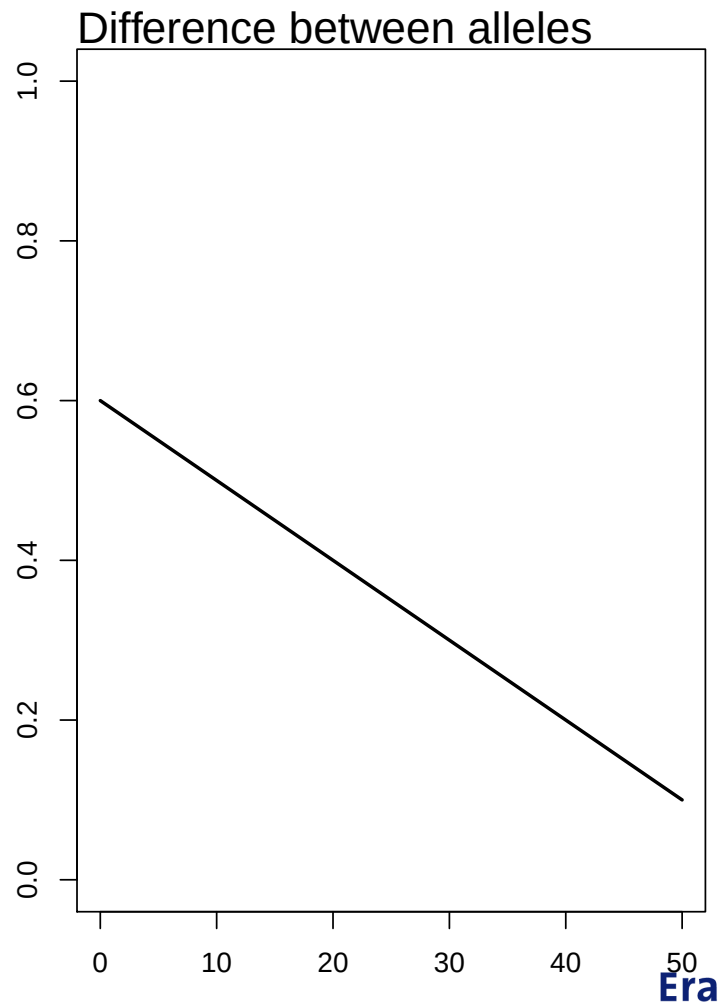
1. Relationships between G and A

4. Decreasing genetic effect





Age

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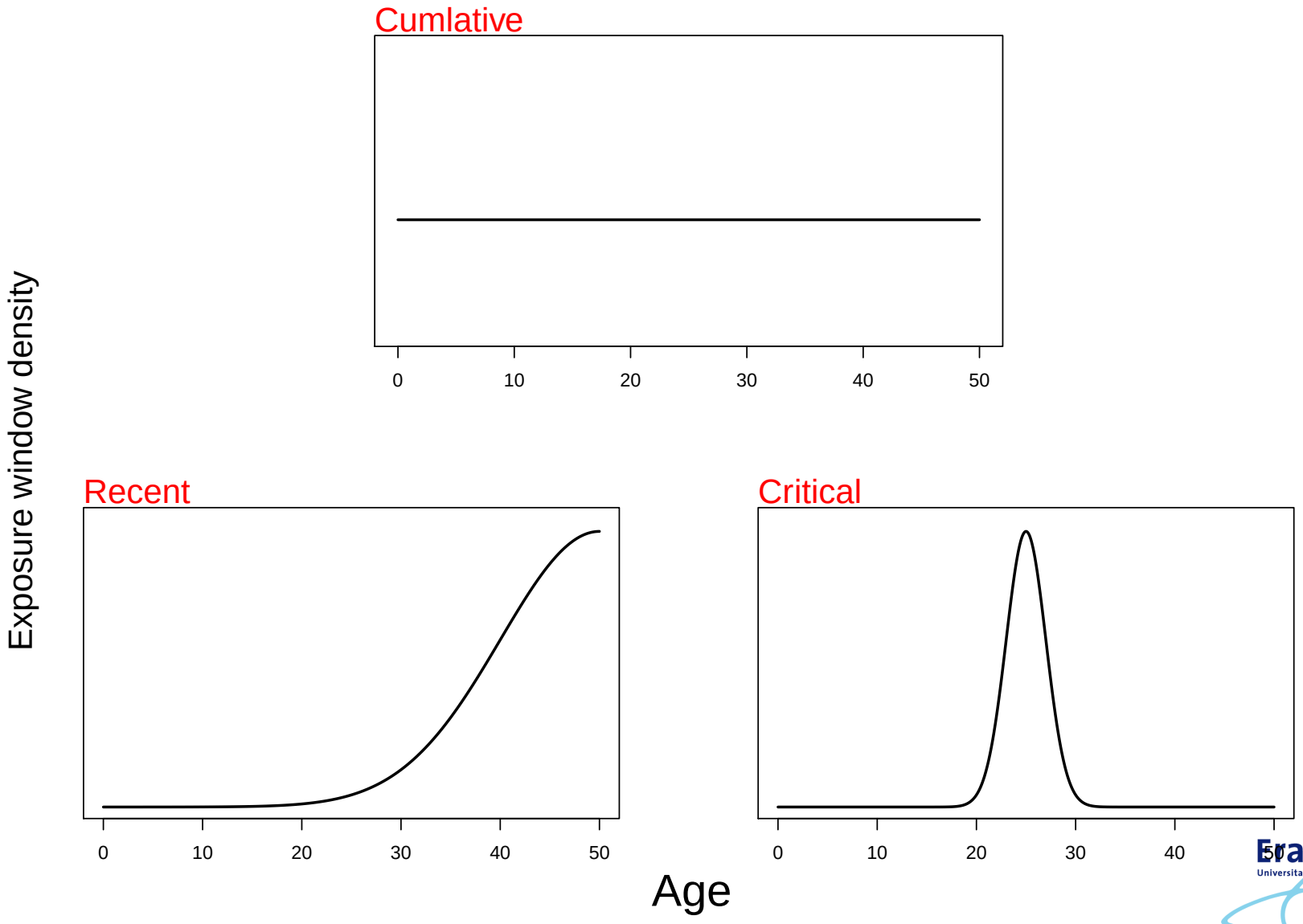
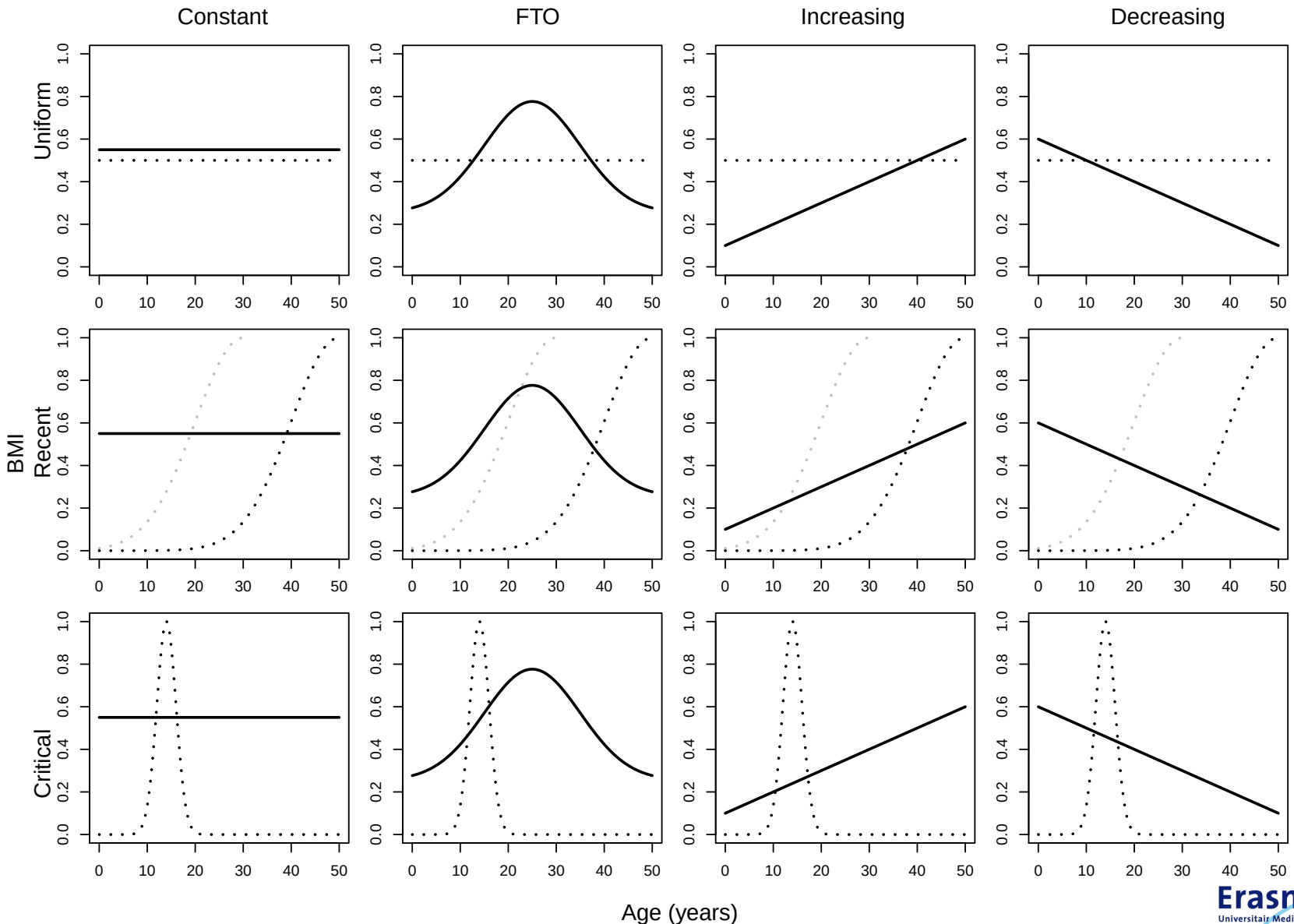
2. Exposure windows

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



12 scenarios



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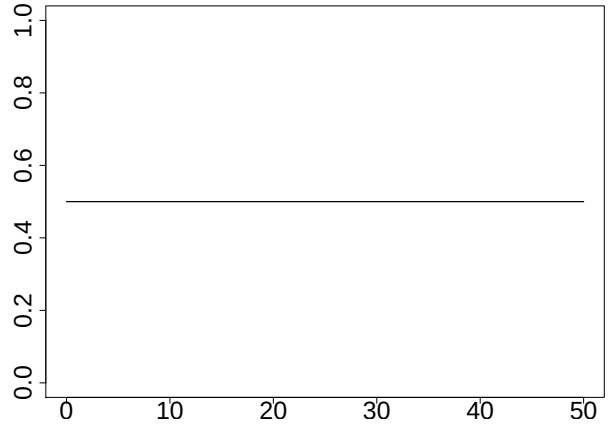
Analytic solution

- 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

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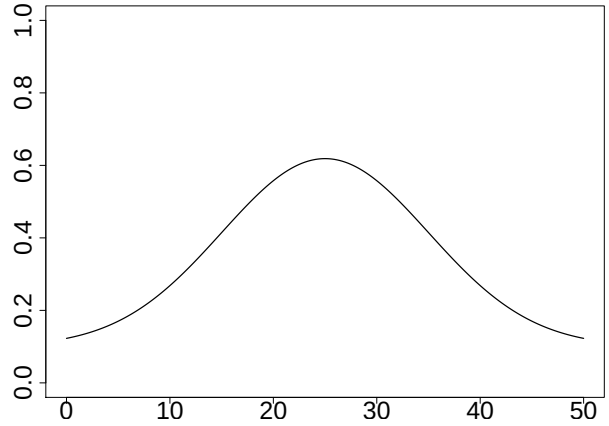
Results: Similar to FTO



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

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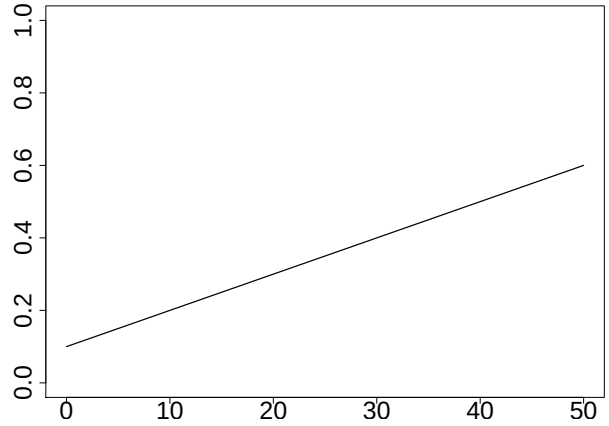
Results: Increasing genetic effect



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

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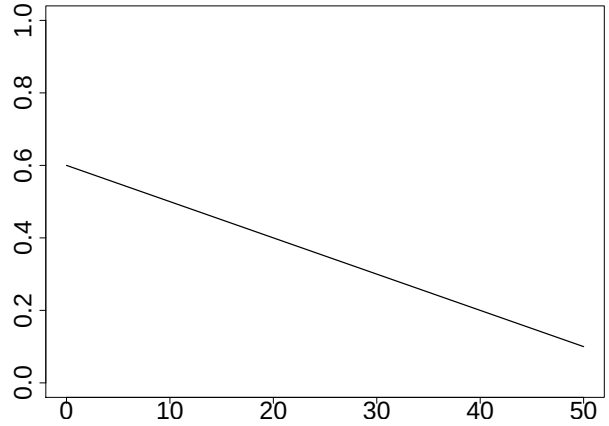
Results: Decreasing genetic effect



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

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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 al[1] for what can be tested
- Sensitivity analyses to see how much variations in effect size could change results (weaker instruments will be more biased)

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

Take home message

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

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Thank you

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- Slides, simulation and other materials available at: github.com/jerbreck

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