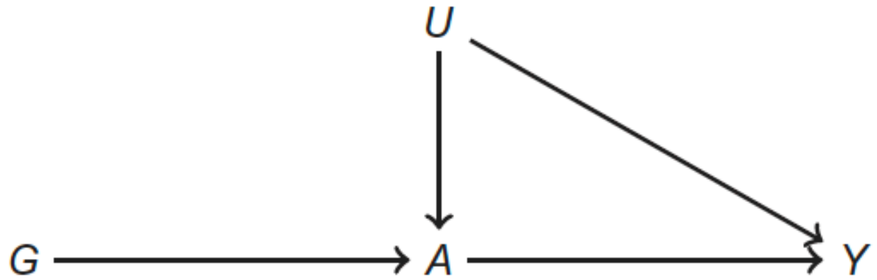
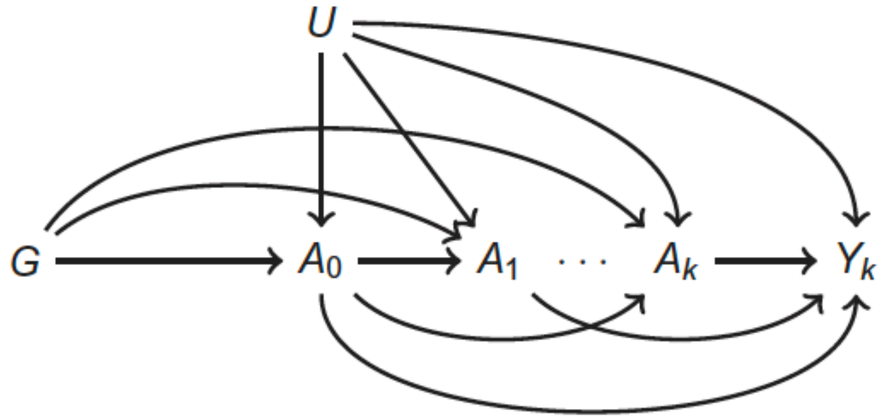
# Genetic instruments that can’t keep time

## Evidence for Genes with Time-Varying Effects and How to Use Them in Mendelian randomization





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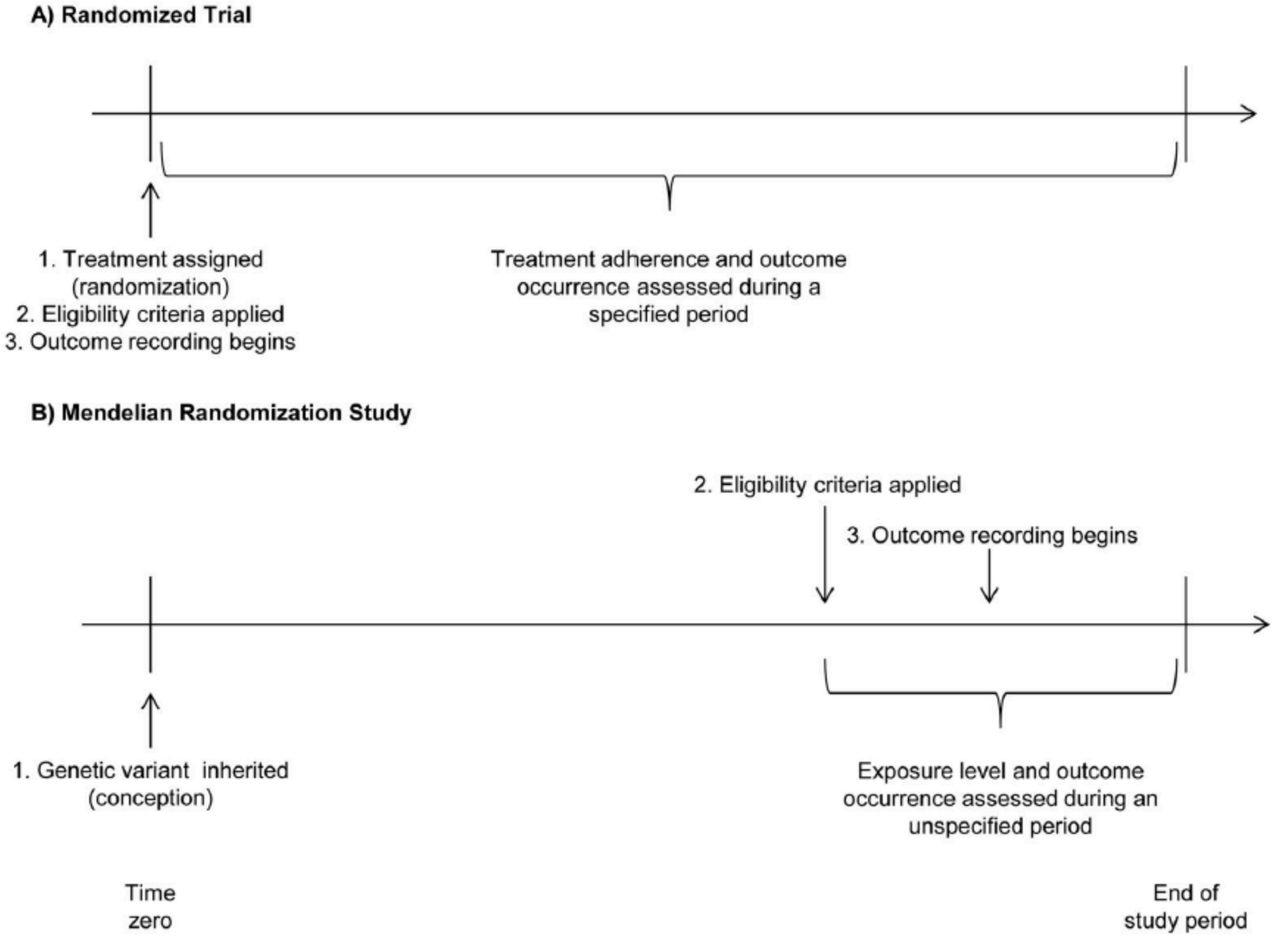
Causal Inference Group, Erasmus MC


SER - Causal inference and molecular epidemiology

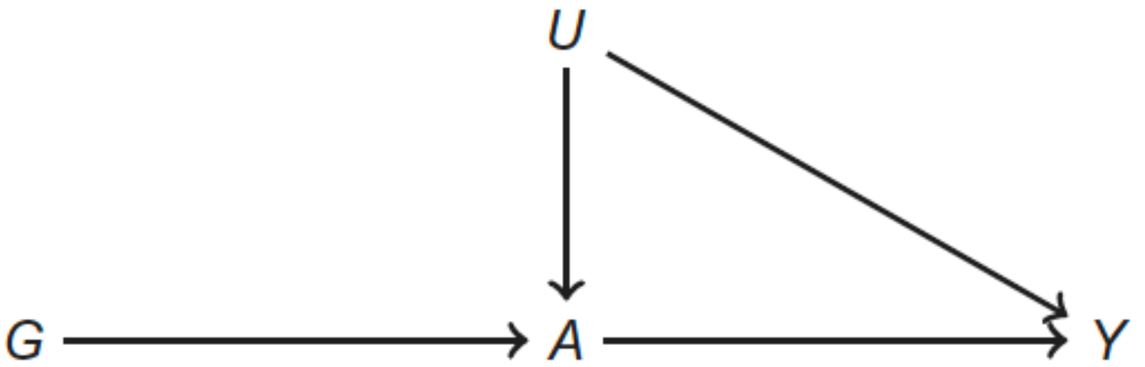
Erasmus MC
Universitair Medisch Centrum Rotterdam

Have you ever wondered how Mendelian randomization can estimate a lifetime effect when the exposure is only measured once?

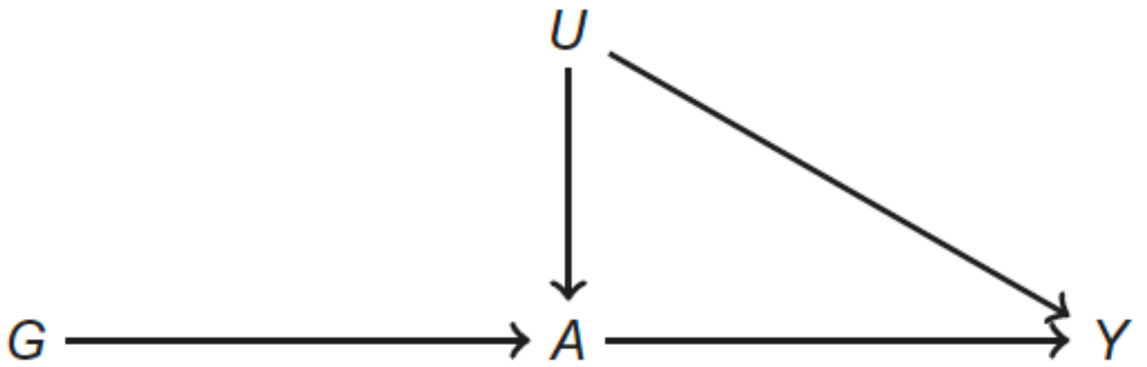
Labrecque and Swanson, IJE, 2020

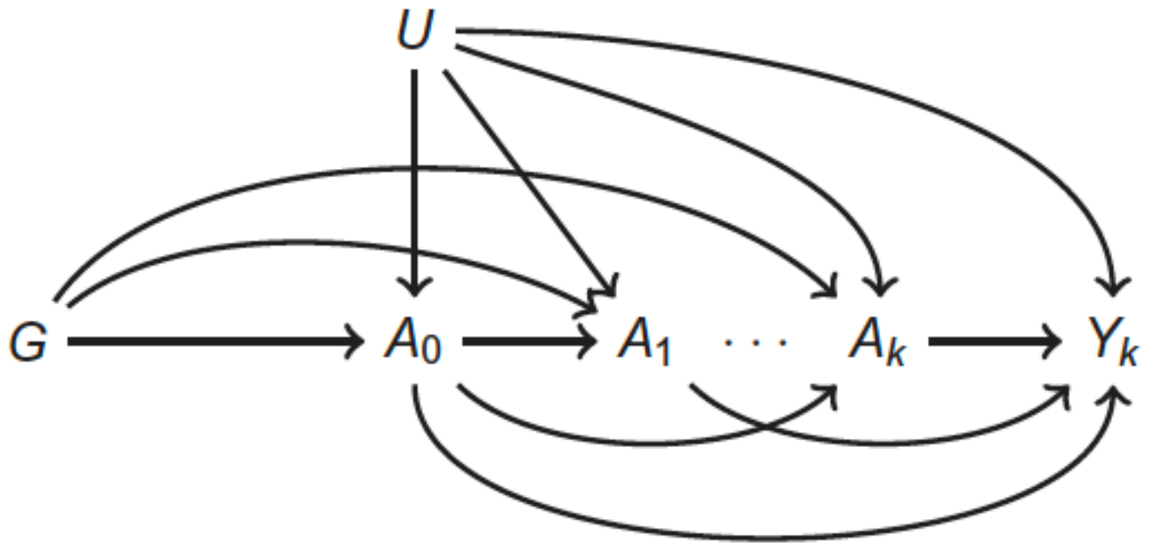



Swanson et al, EPIDEMIOLOGY, 2017



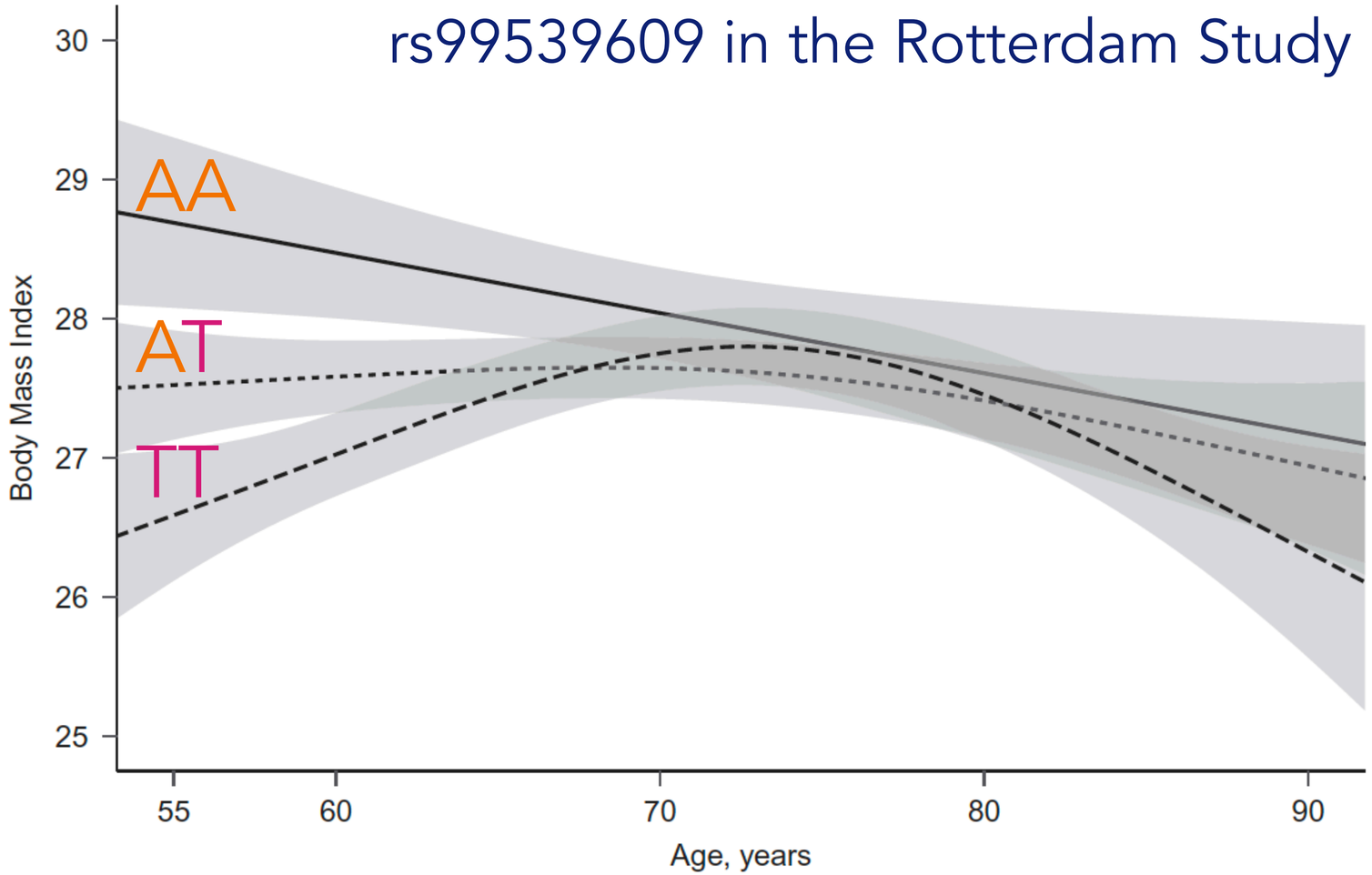

Labrecque and Swanson, AJE, 2019




Labrecque and Swanson, AJE, 2019

# rs99539609 in the Rotterdam Study

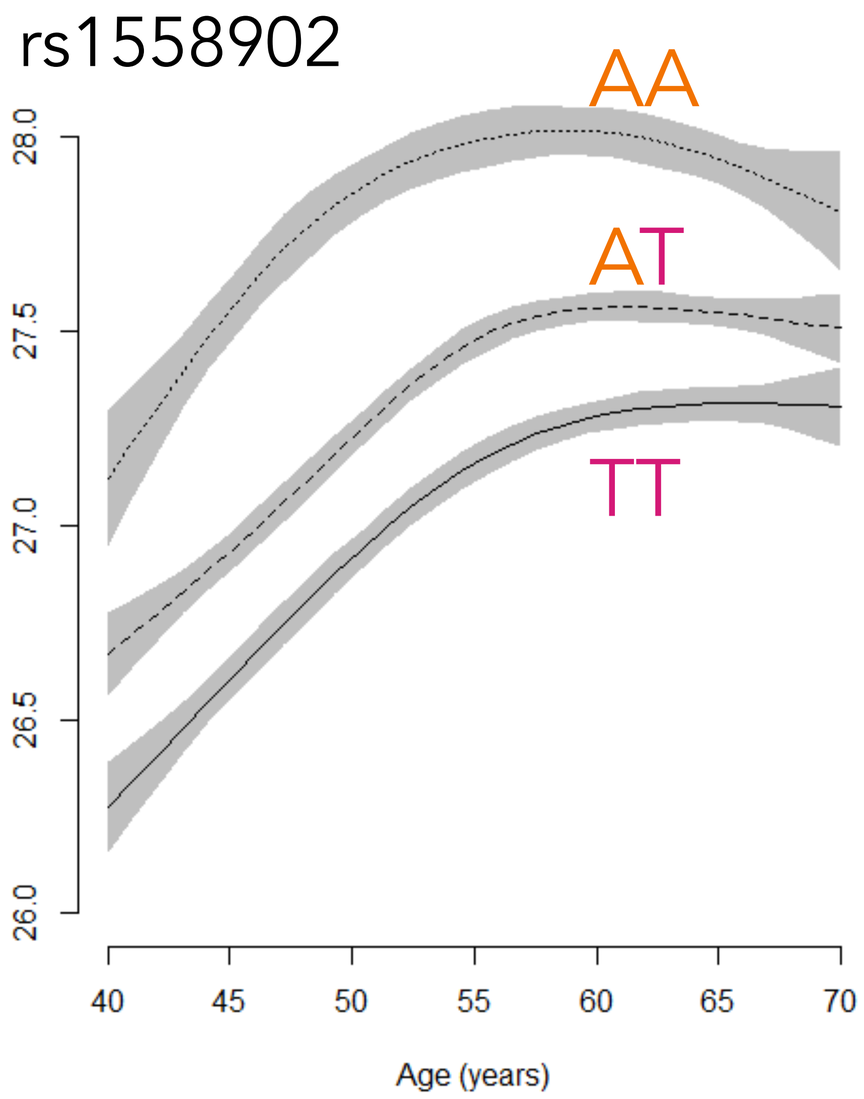



Labrecque and Swanson, AJE, 2019

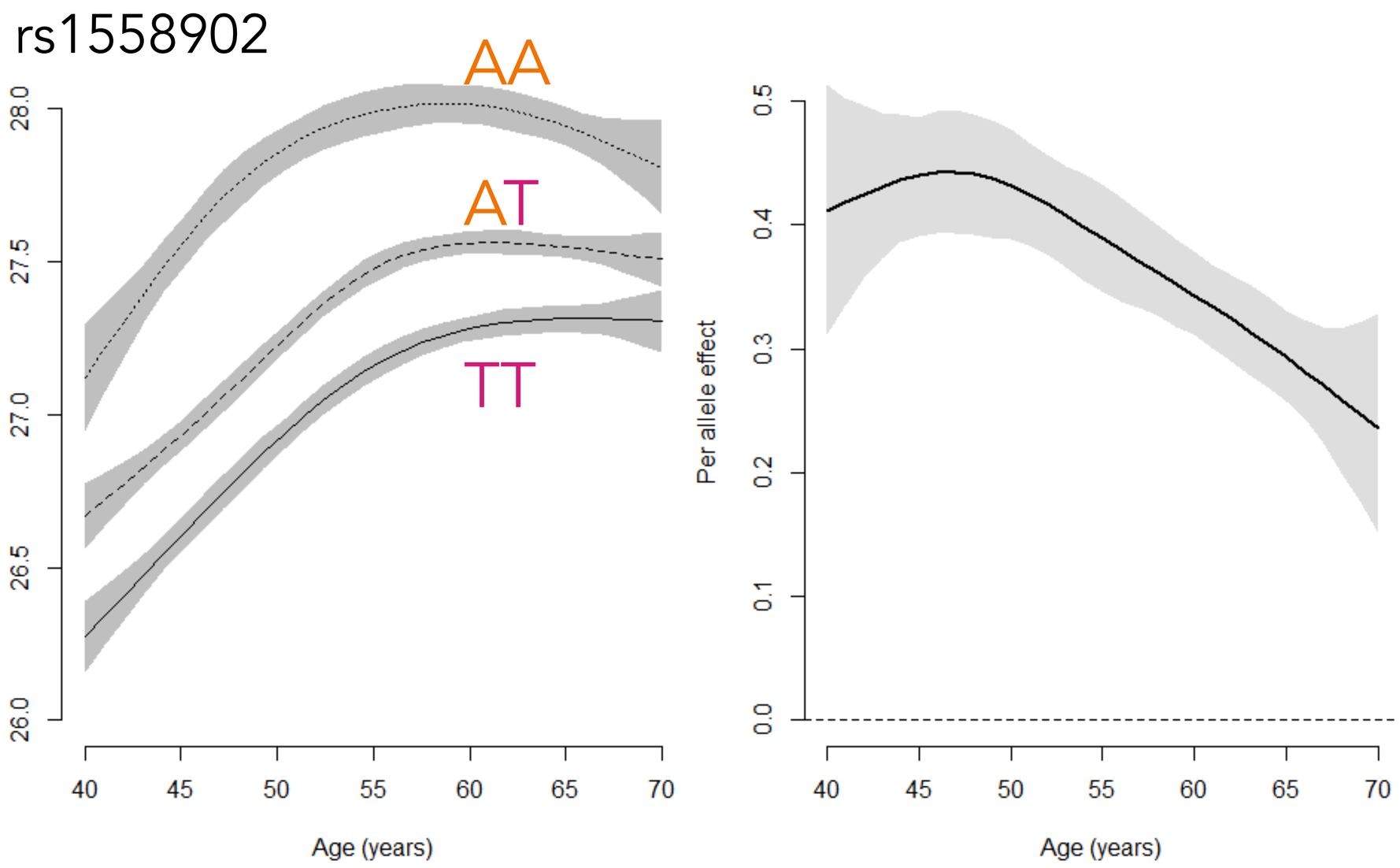
# So we looked at the UK Biobank

- 355,655 people
- Age 40 to 70
- 4 phenotypes commonly used in MR:
  - BMI
  - alcohol consumption
  - C-reactive protein
  - LDL cholesterol
- Genetic variants commonly used in MR using these phenotypes as exposure
- Modeled using restricted B-splines

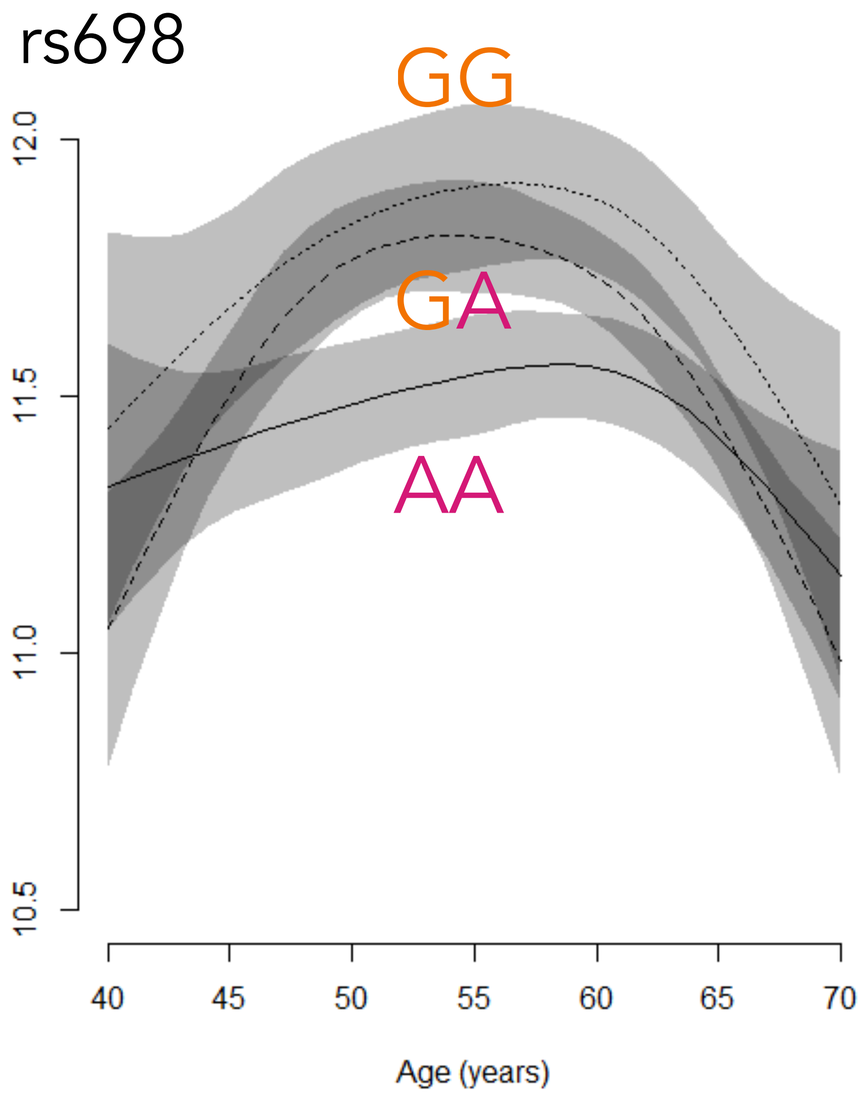
BMI


rs1558902
AA
AT
TT
28.0
27.5
27.0
26.5
26.0
40
45
50
55
60
65
70
Age (years)

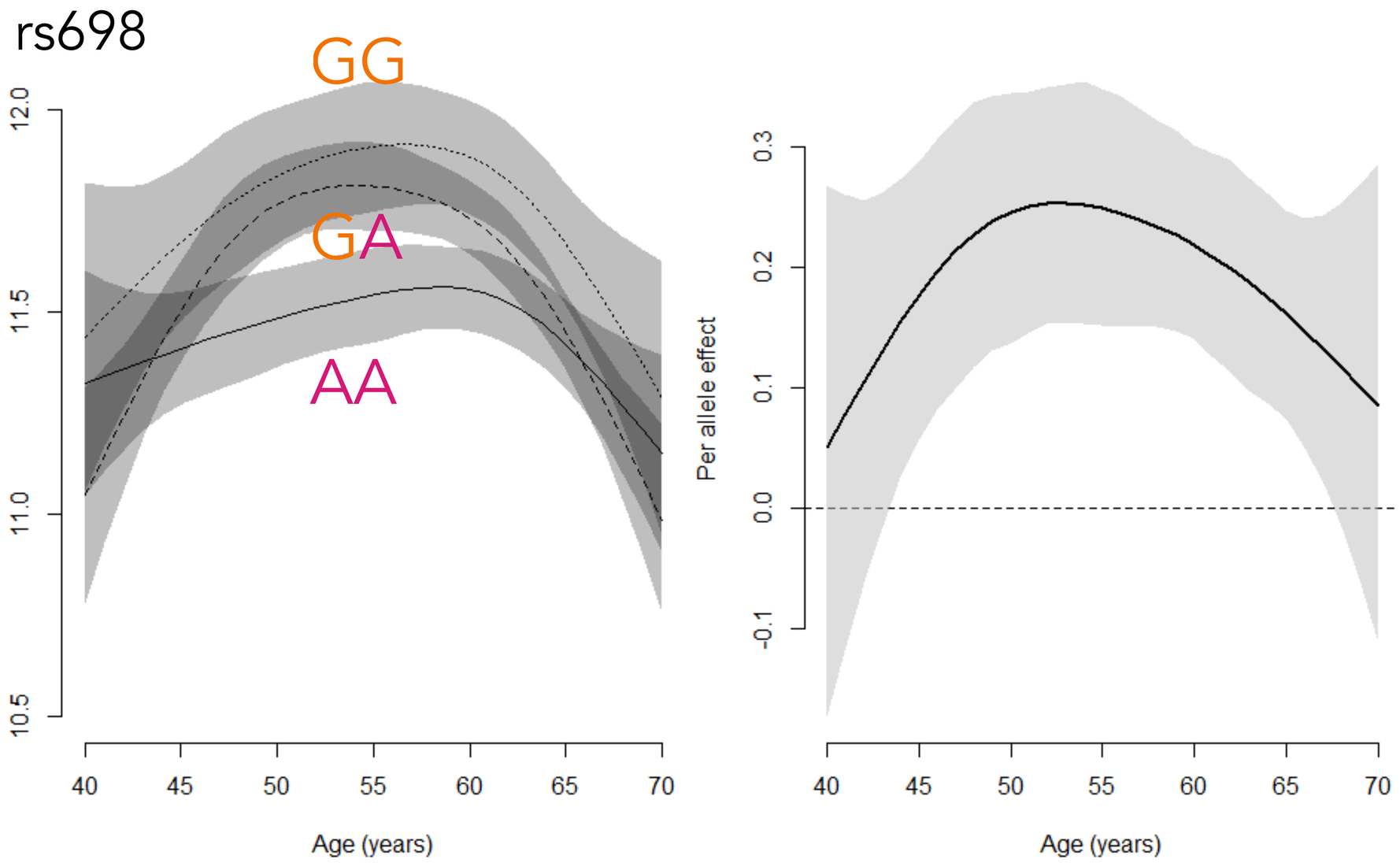
BMI


rs1558902
AA
AT
TT
28.0
27.5
27.0
26.5
26.0
40
45
50
55
60
65
70
Age (years)
Per allele effect
0.5
0.4
0.3
0.2
0.1
0.0
40
45
50
55
60
65
70
Age (years)

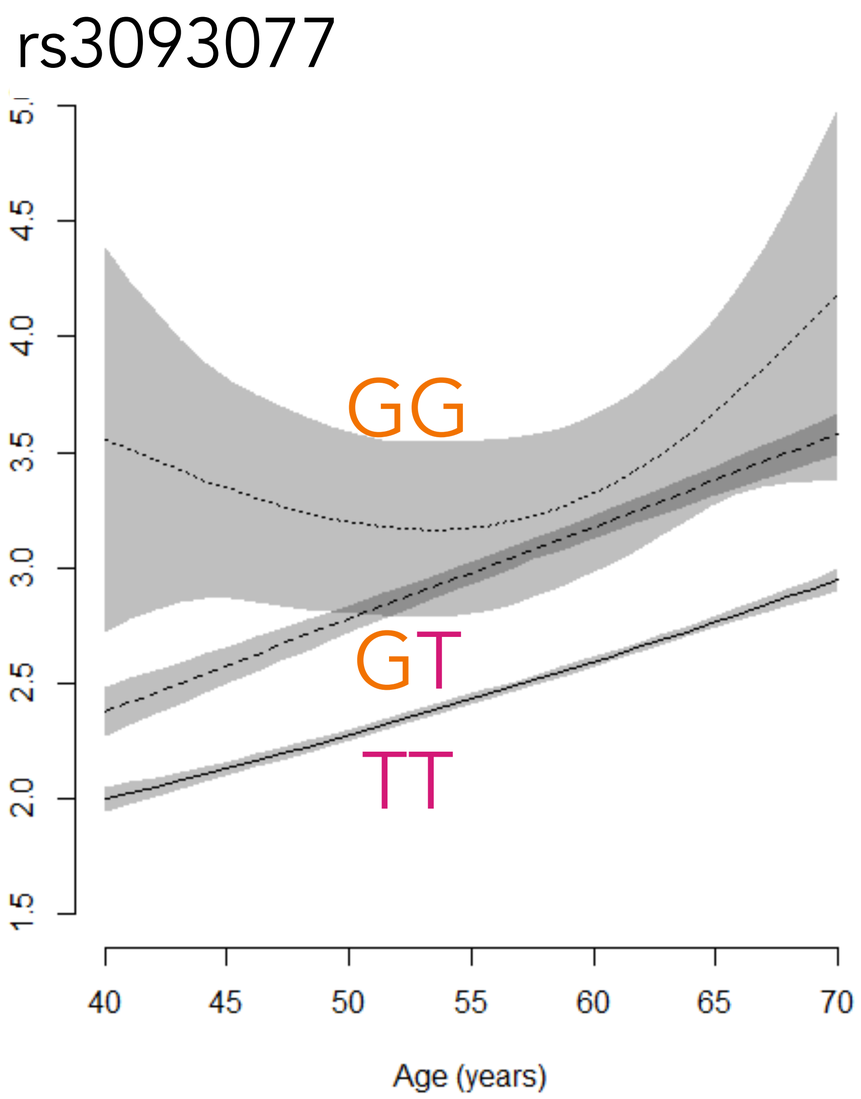
Alcohol consumption



Alcohol consumption

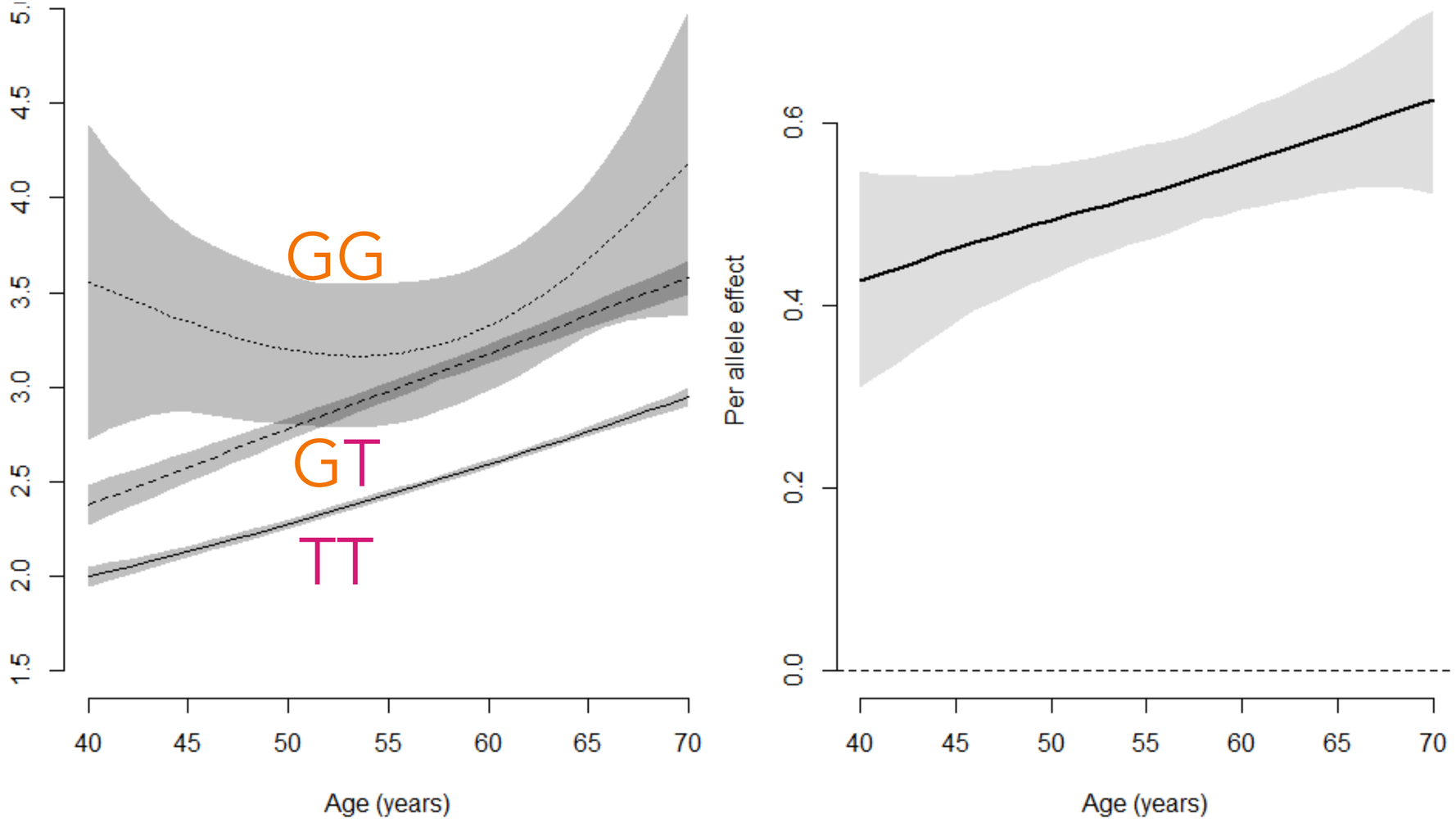


C-reactive protein

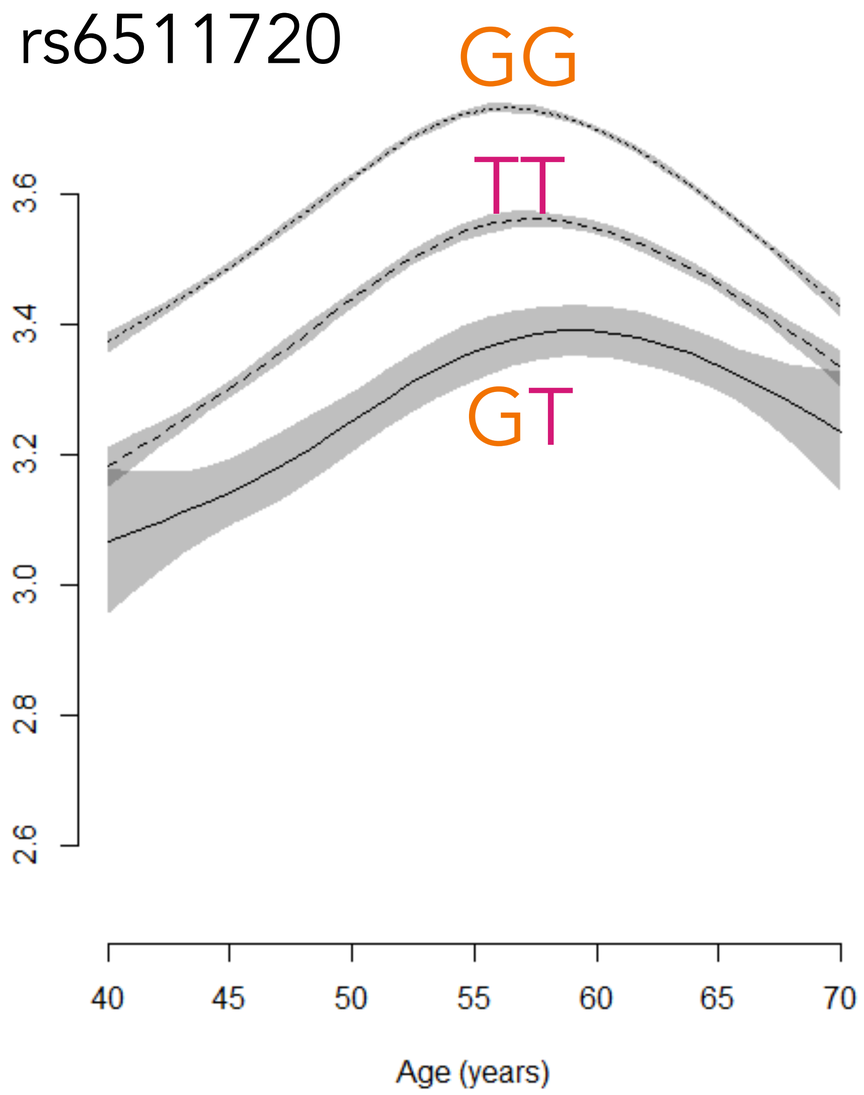


C-reactive protein

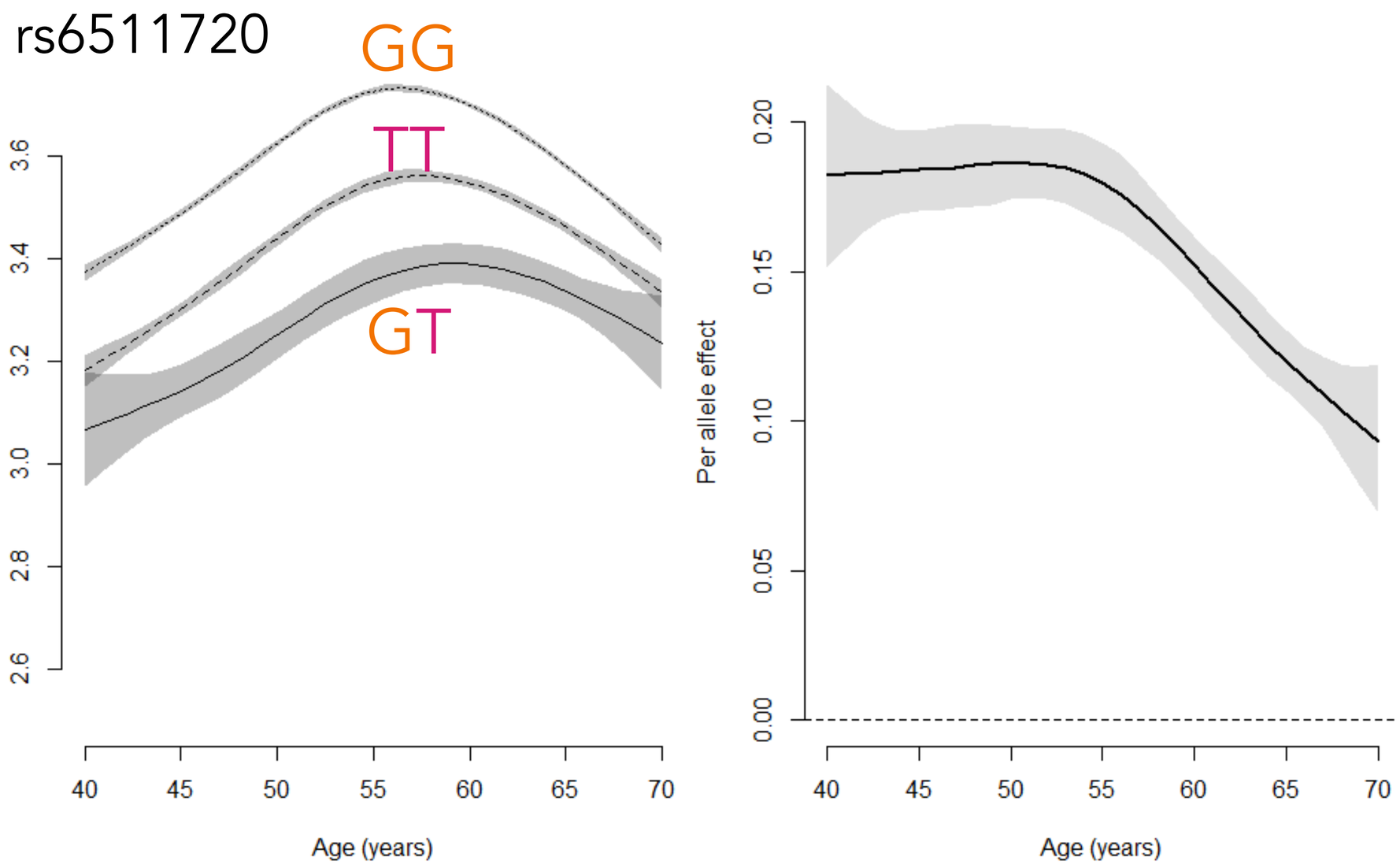
rs3093077



LDL cholesterol



LDL cholesterol



# But how much bias are we talking about here?

- Plasmode simulation

| rs1558902 | age | BMI | CVD |
|---|---|---|---|
| 0 | 55 | 25.6 | 0 |
| 2 | 46 | 30.7 | 1 |
| 1 | 67 | 32.4 | 1 |
| 1 | 65 | 23.3 | 0 |
| 2 | 51 | 25.8 | 0 |
| 2 | 40 | 27.2 | 1 |
| 0 | 46 | 30.1 | 0 |
| 1 | 61 | 33.2 | 1 |

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- Plasmode simulation

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|---|---|---|---|
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| 1 | 67 | 32.4 | 1 |
| 1 | 65 | 23.3 | 0 |
| 2 | 51 | 25.8 | 0 |
| 2 | 40 | 27.2 | 1 |
| 0 | 46 | 30.1 | 0 |
| 1 | 61 | 33.2 | 1 |

Pretend everyone is
65 years old

| rs1558902 | age | BMI | CVD |
|---|---|---|---|
| 0 | 65 | 27.5 | 0 |
| 2 | 65 | 32.0 | 1 |
| 1 | 65 | 33.1 | 1 |
| 1 | 65 | 26.5 | 0 |
| 2 | 65 | 25.9 | 0 |
| 2 | 65 | 28.4 | 1 |
| 0 | 65 | 29.3 | 0 |
| 1 | 65 | 31.2 | 1 |

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- Plasmode simulation

| rs1558902 | age | BMI | CVD |
|---|---|---|---|
| 0 | 55 | 25.6 | 0 |
| 2 | 46 | 30.7 | 1 |
| 1 | 67 | 32.4 | 1 |
| 1 | 65 | 23.3 | 0 |
| 2 | 51 | 25.8 | 0 |
| 2 | 40 | 27.2 | 1 |
| 0 | 46 | 30.1 | 0 |
| 1 | 61 | 33.2 | 1 |

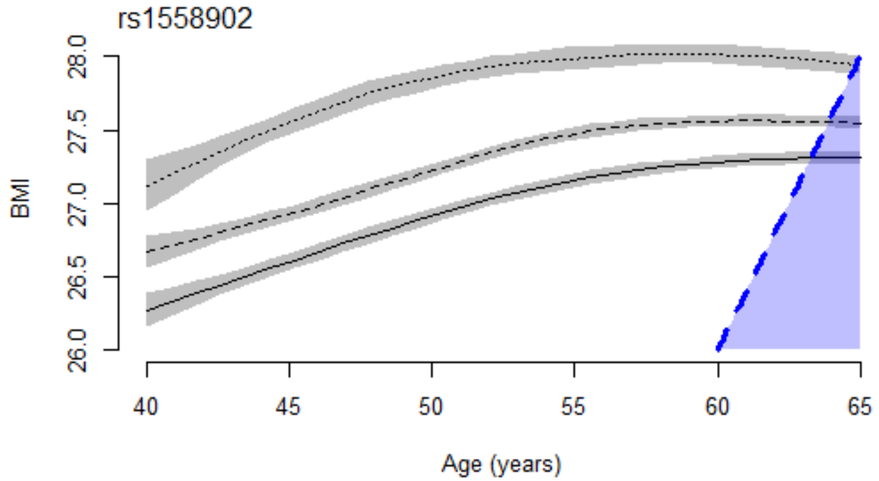
**Pretend everyone is 65 years old**

| rs1558902 | age | BMI | CVD |
|---|---|---|---|
| 0 | 65 | 27.5 | 0 |
| 2 | 65 | 32.0 | 1 |
| 1 | 65 | 33.1 | 1 |
| 1 | 65 | 26.5 | 0 |
| 2 | 65 | 25.9 | 0 |
| 2 | 65 | 28.4 | 1 |
| 0 | 65 | 29.3 | 0 |
| 1 | 65 | 31.2 | 1 |

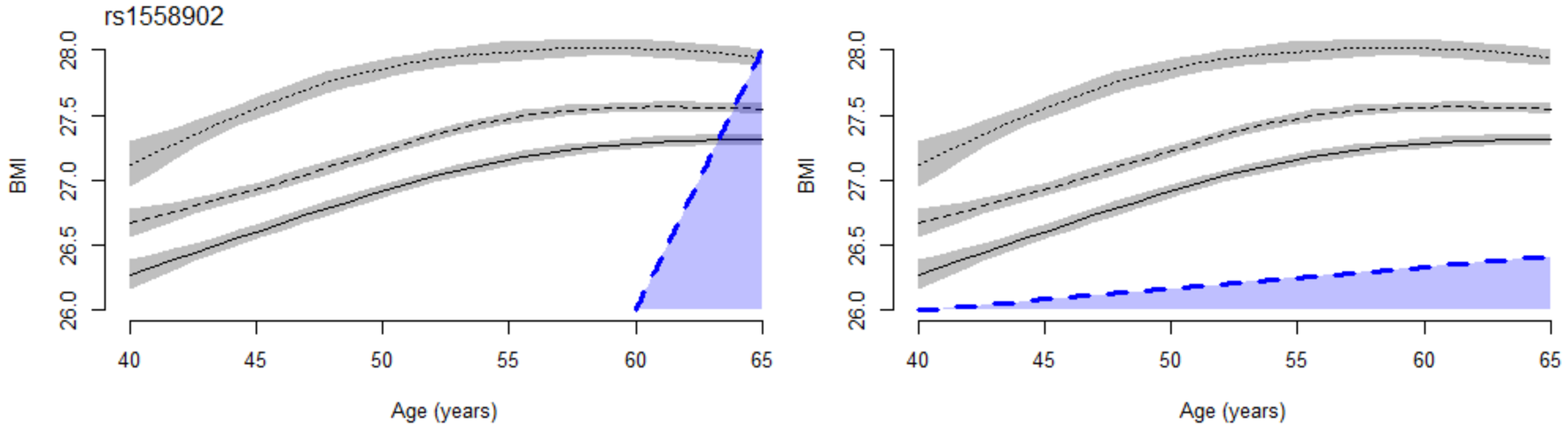
**Simulate outcome based on BMI only**

| rs1558902 | age | BMI | Y |
|---|---|---|---|
| 0 | 65 | 27.5 | 2.5 |
| 2 | 65 | 32.0 | 4.6 |
| 1 | 65 | 33.1 | 6.3 |
| 1 | 65 | 26.5 | 1.7 |
| 2 | 65 | 25.9 | 1.4 |
| 2 | 65 | 28.4 | 3.1 |
| 0 | 65 | 29.3 | 3.5 |
| 1 | 65 | 31.2 | 4.0 |

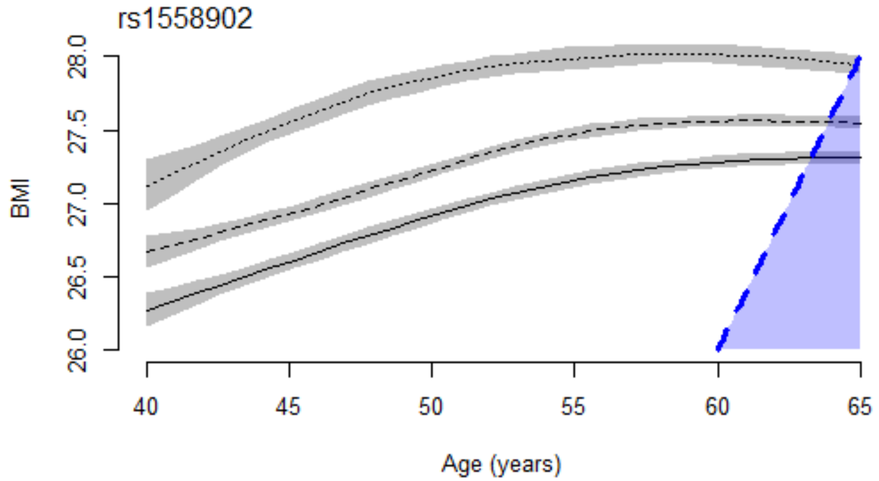
# Exposure windows

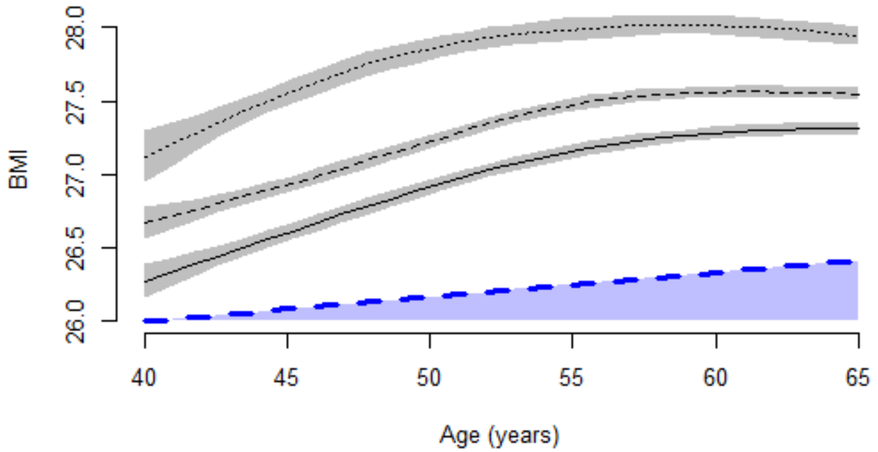


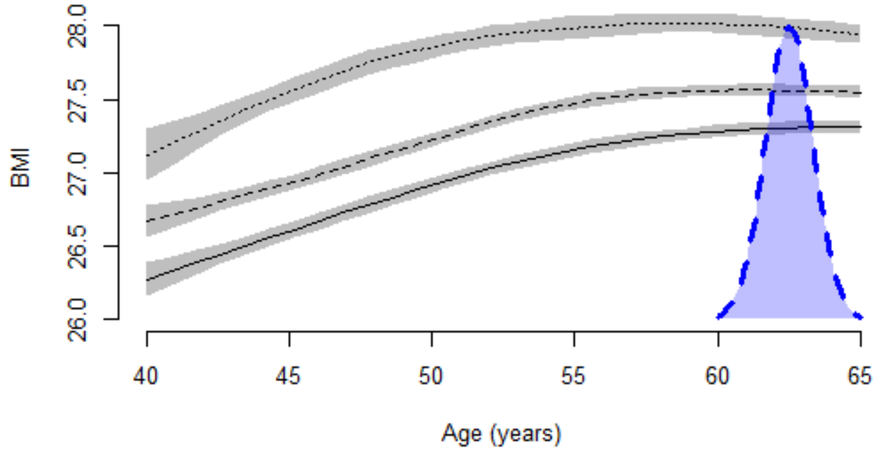
# Exposure windows



# Exposure windows



# Exposure windows