Calculation of the effect of exposure at time points 15 and 50 in Simulation 1D of Tian and Burgess 2023.

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Tian and Burgess[1] claim that the results they find show that multivariable MR with time-varying exposures is misleading if the model is even slightly misspecified regarding the time point of interest. However, the structure they give the association between the genetic variants and the exposure over time gives no reason for effects in close time periods to be highly corrected, or even act in the same direction. The function used for the relationship between the genetic variants and the exposure over time includes a cosign term multiplied by the time point, leading to a sinusoidal pattern to the association between the genetic variants and the exposure over time. Using the expressions for this relationship given in equation 2 in their paper and parameters for scenario 1 given in Supplementary table 1, **Fig. 1** simulates what the pattern of the association between the genetic variants and the exposure would look like across 1000 repetitions and for a randomly selected single repetition within that simulation.

Here we estimate the expected effect estimates for Simulation 1D in Tian and Burgess, taking this pattern of the association between the genetic variant and the exposure into account.
This pattern gives a negative correlation between the association between the genetic variants and the exposure at time point 10 and the genetic variant and the exposure at time point 15. The effect estimate at time point 15, conditional on time point 50, will be the effect at time point 10 multiplied by the correlation between the genetic effects at time point 10 and time point 15. Therefore, the effect estimate obtained would be expected to be in the opposite direction to the direct effect at time point 10. Using the mean estimated genetic variant exposure associations across our simulations, we calculated the expected effect estimates for a model including periods 15 and 50 when there is a direct effect of periods 10 and 50 as;

$$\tilde{\beta}_{15} = cor(g_{10}\, g_{15}) \times \beta_{10}$$
$$\tilde{\beta}_{50} = \beta_{50} + cor(g_{10}\, g_{50}) \times \beta_{10}$$

i.e. the effect of the included time point plus the effect of the excluded time point scaled by the correlation between the genetic effects on the included and excluded time point. The estimated correlation between the genetic effects at time 10 and time 15, $cor(g_{10}\, g_{15})$, from our simulation is -0.35 and between time 10 and time 50, $cor(g_{10}\, g_{50})$, is 0.78. The direct effects of the exposure at time points 10 and 50 are $\beta_{10} = 0.4$ and $\beta_{50} = -0.8$. Combining these gives values of $\tilde{\beta}_{15} = -0.14$ and $\tilde{\beta}_{50} = -0.49$, remarkably close to the mean values obtained by Tian and Burgess.

References:

1. Tian, H. and S. Burgess, *Estimation of time-varying causal effects with multivariable Mendelian randomization: some cautionary notes.* International Journal of Epidemiology, 2023. **52**(3): p. 846-857.