The reviewer does not comment directly on our paper but rather queries whether the underlying dataset is correct. His concerns are based on a routine surveillance report from Public Health Scotland, not written by us, which reported a rate ratio of 0.59 for all-cause mortality in the first 28 days after first vaccination dose. As the reviewer notes, this is unlikely to be a causal effect of vaccination. The report from Public Health Scotland noted that this could be explained by a number of factors but did not elaborate further.

A plausible explanation for lower total mortality shortly after vaccination in vaccine recipients is allocation bias. Specifically, people who are terminally ill and likely to die in the next few weeks are less likely to attend when they are sent an appointment for vaccination. Thus mortality in the first few weeks after vaccination will be lower than the average for people of the same age and sex. On this basis we would predict that mortality from cancer and other conditions that cause death after prolonged illness would be especially low in the first few weeks after vaccination, but mortality from causes where deaths are often sudden (circulatory disease, external causes) would be reduced less.

To examine this, we constructed a cohort from all 330614 individuals aged over 60 and not resident in care homes who were sampled as controls in the REACT-SCOT study before they had received their first vaccine dose. Of these 304447 received their first dose of vaccine and 10041 died before the end of follow-up. The deaths were grouped by ICD-10 codes for underlying cause on the death certificate as cancer (Chapter II), circulatory disease (Chapter IX), external causes (Chapter XX), and other. For each group of causes of death, a Cox regression model was fitted with age, sex, and clinical risk category as time-invariant covariates, and first vaccine dose in the last 28 days as a time-varying covariate updated at the start of each 7-day interval.

Results are shown in the table.

Underlying cause	**Odds ratio**
Cancer	0.46 (0.38, 0.56)
Circulatory	0.72 (0.59, 0.86)
External	0.71 (0.37, 1.36)
Other	0.40 (0.34, 0.46)

As expected, the odds ratio for mortality in the first 28 days after vaccination compared with all other person-time at risk is lowest for cancer, less reduced for circulatory disease, and for external causes the confidence interval overlaps 1.

This form of bias, where a pre-existing disease underlies the event and this disease also influences the exposure under study (vaccination) is well known to epidemiologists. Where the outcome under study studied has a rapid onset, this bias can be largely eliminated by excluding the early post-exposure period. In Scotland those who are sent appointments for vaccination are warned not to attend if they have symptoms of COVID-19. This is the most likely explanation for the low incidence of test-positive infections in the first 7 days after vaccination (1). In our study, individuals were classified as vaccinated only after at least 14 days have elapsed since vaccination. As the interval from COVID-19 symptoms to hospitalisation is typically less than 10 days (2), this is enough to exclude most hospitalised cases who who did not attend for vaccination because they were symptomatic at the time of their appointment.

1. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: A national prospective cohort study. Lancet (London, England). 2021 May;397(10285):1646–57.

2. Faes C, Abrams S, Van Beckhoven D, Meyfroidt G, Vlieghe E, Hens N. Time between Symptom Onset, Hospitalisation and Recovery or Death: Statistical Analysis of Belgian COVID-19 Patients. International Journal of Environmental Research and Public Health. 2020 Oct;17(20):7560.