## Reply to letter Yates et al

To the Editor—We thank Yates et al [1] for their interest in our article and positive comments regarding careful control of potential confounding variables in the analyses [2]. In addition to confounding, other types of bias—including collider bias (the subject addressed by Yates et al) as well as recall bias, regression dilution, and reverse causation bias (which are not mentioned)—are important to consider when interpreting the results of the association between human cytomegalovirus (HCMV) and cardiovascular disease (CVD).

A key premise of the suggestion by Yates et al that collider bias could substantially affect the null association found in our study is that the seroprevalence of HCMV is much lower in the UK Biobank (UKB) than in the general population. This is owing to the overall younger age profile of UKB participants; the age-specific prevalence of HCMV in UKB participants is actually very similar to findings from the national survey by the Public Health Laboratory Services serological surveillance program cited by Yates et al [3].

The second study [4] Yates et al provide as evidence that HCMV seroprevalence is lower than expected in the UKB is from the Born in Bradford cohort, a highly selected cohort of pregnant women recruited from areas with high levels of socioeconomic deprivation. Given the known inverse association between HCMV and socioeconomic status, this study is not an appropriate comparator, as one would expect HCMV seroprevalence to be higher in the Born in Bradford cohort than in both the general population and the UKB.

Yates et al [1] argue that the lower prevalence of CVD risk factors and CVD mortality rates in the UKB compared with the general population could introduce collider bias [5, 6]. However, the direction and magnitude of the majority of associations between established cardiovascular risk factors and CVD mortality rates are similar in the UKB and the Health Survey for England cohort, which is more representative of the national population [5]. However, it is worth noting that neither of these analyses accounted for regression dilution bias, which may attenuate true associations. Nonetheless, this provides further evidence that, despite the more favorable sociodemographic, behavioral, and health-related characteristics of UKB participants, these specific exposure-outcome associations are largely generalizable to the general population.

We agree with Yates et al that investing in making research participation more broadly available is an important endeavor. From the outset, selection into the UKB aimed to be as inclusive as reasonably possible, with everyone aged 40–69 years who was registered with the National Health Service and lived within about 25 miles of any of 22 assessment centers being eligible for invitation (a sampling frame of 9.2 million individuals). To help increase the cohort's socioeconomic and ethnic heterogeneity, the assessment centers were set up in convenient locations with easy travel links and in different parts of the United Kingdom [7]. Having sufficiently large numbers of individuals represented across the full range of participant characteristics, with repeated measures over time and extended follow-up, ensures the performance of research that considers a range of biases, allowing full interpretation of results.

In conclusion, we believe that the best approach to interpreting epidemiological findings is to carefully consider the relative strengths and limitations of different studies and acknowledge the potential sources of bias inherent to all population-based observational studies (including those that are representative of the general population). When contextualizing our findings within the existing literature [8, 9], we maintain our conclusion that there is limited evidence for a positive association between HCMV exposure and CVD risk.


### Notes

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