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Effects of Aspirin in the Healthy Elderly

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THE AUTHORS REPLY:

Li and Shu raise the issue of weight-adjusted dosing of aspirin, and they refer to a recent meta-analysis that showed that low-dose aspirin was less effective in participants who weighed 70 kg or more than in those who weighed less than 70 kg. In the ASPREE trial, participants were stratified according to body-mass index (BMI) rather than according to body weight, and they were categorized as being under-weight, normal weight, overweight, or obese. Forest-plot analyses showed that these BMI categories did not modify the lack of effect of aspirin on disability-free survival (Fig. S1 in the Supplementary Appendix of the article on disability-free survival, available with the full text of the article at [NEJM.org](https://www.nejm.org)) or on cardiovascular disease (Fig. S5 and S7 in the Supplementary Appendix of the article on cardiovascular events and bleeding, available at [NEJM.org](https://www.nejm.org)).

Xin et al. refer to the increase in all-cause mortality that we found in our trial after a median of 4.7 years of intervention. They note that in two major U.S. studies, mortality from cancer was reduced after 10 years of aspirin use. They suggest that a longer duration of aspirin intervention and observation might be required to identify a net beneficial effect. We acknowledge this point, and a study is under way to track health events in the ASPREE cohort over at least the next 5 years to address the question of a possible “legacy effect” of aspirin on long-term prevention of cancer, as reported by Rothwell and colleagues.¹

McCaw and colleagues raise the issue of competing causes of death and query whether a reduction in deaths from cardiovascular causes might have led to an increase in the next most common cause of death — cancer. During our trial, in absolute terms there were 21 fewer deaths from cardiovascular causes in the aspirin group than in the placebo group, but there were 68 more deaths from cancer; this makes this proposal unlikely. With regard to an intention-to-treat versus an on-treatment analysis, we stated that “most participants would have stopped taking the trial intervention in advance of the terminal phase of their last

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Since publication of their articles, the authors report no further potential conflict of interest.

illness”; we did not suggest that most participants had discontinued the trial medication “long before death.” Our prespecified approach to our per-protocol analysis was outlined in a previously published statistical analysis plan² and includes the estimation of complier average causal effect. One challenge with restricted mean survival time is the need to make an a priori choice of the follow-up time point of interest at which to calculate this quantity; the range of participant follow-up times was approximately 3 to 7 years in our trial. Finally, our cumulative-incidence curves² were based on a competing-risks model, stratified according to trial group, with the remaining causes of death as competing events. Subdistribution hazard ratios were not explicitly reported; cause-specific hazard ratios were preferred because of their enhanced interpretability.

References

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