illness-death model should be preferred to the standard Cox regression analysis (10). The bias resulting from such a naive Cox analysis and its relevance has been characterized elsewhere (11). Finally, we note that the importance of taking competing risks into account has also been pointed out in this journal (12, 13).

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TWO AUTHORS REPLY

We thank Binder et al. (1) for their interest in and careful review of our article (2). First, we apologize that the column headings in Table 2 (2, p. 419) were mislabeled with “%,” but it should be clear from the table title that the incidence rates refer to events per 1,000 person-years of follow-up. Second, we did not use the Kaplan-Meier approach to draw our conclusions about cumulative incidence differences. Rather, we used the simple (and well-understood) plot in Figure 2 (2, p. 420) to illustrate the very small differences in dementia-specific survival between participants and nonparticipants. We used incidence density estimates (numbers of events per 1,000 person-years of follow-up) as our measures of dementia incidence, and we used these well-understood and -accepted epidemiologic estimates to make the primary comparisons of incidence between participant groups (3). We recognize that these estimators will produce higher estimates of incidence than will result from analyses that account for competing risks—for exactly the reasons outlined by Binder et al. (1).

The concerns about interval censoring and competing risks are integrally related and are certainly important issues. We had previously performed a variety of analyses in an attempt to evaluate the degree to which directly accounting for interval censoring might affect the results of assessments of associations in time-to-event outcomes that were observed as we described in our study. For every comparison we examined, we found that using the midpoint of the time interval between visits for persons with incident illness resulted in hazard ratio estimates that were very comparable to those obtained with more sophisticated analytical approaches used for interval censoring. Therefore, we chose to use the simpler approach in our primary analyses.
Our analyses were somewhat different from the usual situation in which the same assessment methods are used to compare different treatments or different diseases, in that we were comparing dementia incidence in persons who were under active surveillance with that in persons who were being followed passively through medical record review because they had declined to participate in our observational study (2). The key outcome in our analyses was the difference between the active surveillance and passive surveillance groups. Thus, we were comparing 2 different methodologies, one of which was subject to interval censoring but had a higher likelihood of detection (active surveillance) and one in which interval censoring was not an issue but had a lower likelihood of detection (passive surveillance through medical record review). We agree that the illness-death model, by minimizing the impact of competing mortality, has advantages over the Cox model in this situation.

Therefore, we followed the suggestion of Binder et al. (1) and used the SmoothHazard package in R (4) to rerun our analyses. Using the illness-death model with interval censoring, incidence rates in both the active surveillance and passive surveillance groups were lower than the estimates from the Cox models. There was no difference between the nonparticipant group and the active surveillance group (hazard ratio = 0.77, 95% confidence interval: 0.55, 1.08), with the point estimate being consistent with a higher rate of incident dementia in the active surveillance group. Nonetheless, the 95% confidence interval included 1. Recall that our primary analysis (2) also showed that there was no difference between the nonparticipant group and the active surveillance group (hazard ratio = 1.16, 95% confidence interval: 0.95, 1.43), with the estimate pointing in the opposite direction.

The finding from additional analysis using the illness-death model is very gratifying, since it produces the same conclusion that we reported (2). We thank Binder et al. for their suggestion to perform this additional analysis, as it supports our original conclusion (obtained using Cox modeling) that nonparticipation did not have an impact on incident dementia.

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