THE AUTHORS REPLY

We thank Bartlett et al. (1) for their interest in our paper (2). We agree with them that keeping the assumptions behind models in mind is essential in interpreting the results. Bartlett et al. are concerned about our assumption that measurement error (\(e\) in our formulae) was nondifferential with regard to the outcome. We do not share this concern, as we do not see how the “true” measurement error (due to short-term biologic fluctuations and instrumental/protocol measurement errors) in blood pressure and serum cholesterol values could depend on future cause or age of death. However, after extensively studying Bartlett et al.’s description (1) of possible bias in our table 4 (2), we came to understand that they are referring not to nondifferential measurement error \(e\) but rather to possible nondifferentiality with regard to the outcome in the difference between “true” exposure and the empirical Bayesian estimate of exposure included in the Cox model. Although one could make an argument that this difference should also be regarded as “measurement error,” we prefer to make a clear distinction and to use the term “measurement error” only when it refers to the original measurements. However, the issue at hand is whether such a bias exists in table 4 and whether it is of practical importance.

Bartlett et al. assume that the purpose of table 4 is to present unadjusted relative risks, that is, relative risks for recent blood pressure unadjusted for past blood pressure and vice versa, and that we present these results because we find these unadjusted relative risks interesting in their own right. However, that is not the case. The objective of our study was to determine whether cardiovascular mortality depended on recent blood pressure, past blood pressure, or both. Figure 1 gives the causal graph (3) associated with our problem, and the three hypotheses imply that either causal path I (arrow) exists, causal path II exists, or both exist. Our objective in table 4 was to present the results of analyses partly carried out under the working hypothesis that only path I exists and partly under the assumption that only path II exists. We agree with Bartlett et al. that these results would not be valid if both paths existed. This is not only for the reason they give but, more importantly, also because then the relative risks would be confounded by (unadjusted for) the effect of blood pressure at the other time point.

The results given in tables 5 and 6 (2), in contrast, are valid (given the usual provisions of no unaccounted-for confounding and correctness of model specification) under all three hypothesized causal mechanisms. So why did we not restrict ourselves to tables 5 and 6? There are two reasons. First, although the models used in tables 5 and 6, in theory,
are unbiased (again, given no confounding and correct model specification), they are not very powerful, because of the causal relation between true blood pressure (BP) 1 and true BP 2. Given the presence of considerable measurement error, the correlation between these two variables is much stronger than the correlation between measured BP 1 and measured BP 2. Therefore, if one of the first two hypotheses were true, the appropriate model from table 4 would be the better model. Second, because of the high correlation between true blood pressures measured at different time points, we felt it might improve understanding if the results arrived at in tables 5 and 6 were also presented without the variables that might cause collinearity.

Summarizing, we agree with Bartlett et al. (1) that if both causal paths are present, the relative risks shown in our table 4 are not unbiased estimates of the unadjusted relative risks. However, estimating such unadjusted relative risks was not our aim, and the table was included in the paper for other reasons.

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