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LETTER TO THE EDITOR

Reply: Multiple imputation models should incorporate the outcome in the model of interest

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Sir, We thank you for the opportunity to respond to Barlett, Frost and Carpenter who make the important point that the best statistical practice involves considering the outcome when imputing values for a covariate. This also makes sense informally as the goal of imputation is to use as much information as possible to 'fill-in' the unknown values yet still account for the uncertainty in the imputed values. In our separate detailed report describing the method for transforming CSF amyloid-β_{42} to Pittsburgh compound B positron emission tomography imaging (PIB-PET) (Weigand *et al*., 2011), we indicate that we used all available Alzheimer's Disease Neuroimaging Initiative subjects with simultaneous PIB-PET and CSF amyloid-β_{42}, a sample that included nine cognitively normal subjects, 22 with mild cognitive impairment and 10 with Alzheimer's disease dementia. Including cognitively normal subjects and subjects with Alzheimer's disease dementia not only increased the sample size in the calibration data set, but also expanded the range of values to encompass the full dynamic range of amyloid biomarker values seen in the disease of interest. We felt this was an important feature of the calibration data set. With cognitively normal subjects and subjects with Alzheimer's disease in the calibration data set, incorporating the outcome, time from mild cognitive impairment to Alzheimer's disease, in the imputation model was not possible.

However, the larger point about whether the imputation model was correctly specified is an important one that we carefully considered. In our imputation model, R^2 was indeed high (found to be 0.77), residuals approximately normal and no data point particularly influential. In other words, the model described the data quite well. In terms of applicability of the model to the larger sample of mild cognitive impairments, we note that CSF and PIB-PET imaging methods were identical for subjects regardless of clinical classification and we do not believe that the relationship between CSF amyloid-β_{42} and PIB-PET would differ appreciably by clinical group. Overall, while we recognize that statistical models are always going to be rough approximations of the underlying biology, we think that in our application the model provides a useful way of estimating PIB-PET given CSF and Apolipoprotein E genotype.

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Reference

Weigand SD, Vemuri P, Wiste HJ, Senjem ML, Pankratz VS, Aisen PS, et al. Transforming cerebrospinal fluid Abeta42 measures into calculated Pittsburgh compound B units of brain Abeta amyloid. Alzheimers Dement 2011. Advance Access published on Jan 29 2011, doi:10.1016/j.jalz.2010.08.230.

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