Letter to the Editors

Author reply to Holford, Vu and Nutt regarding 'piecing together the puzzle of progression and mortality in Parkinson's disease'

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Drs Holford, Vu and Nutt have regrettably missed the point of our comment. The relevant question (as to mortality) for a patient faced with a choice of treatment is the overall mortality risk, under each possible treatment, for patients with similar clinical characteristics and history at the time the choice of treatment is to be made. It is not appropriate to use estimates adjusted for possible future consequences of the different treatments, such as post-treatment changes in Unified Parkinson Disease Rating Scale (UPDRS) scores, which is what is done in the calculation highlighted by the authors. Changes in UPDRS scores in this instance may be intermediaries in a causal pathway between selegiline treatment and mortality and would be inappropriate to include in any model of the effect of selegiline on mortality. Adjusting for post-treatment UPDRS scores would be analogous to adjusting for post-treatment cholesterol concentrations when examining the effect of statins on cardiovascular mortality. Including intermediate variables may cause real effects to go undetected (as in the statin example) or introduce spurious effects (as we suspect may be occurring in the analysis of Vu *et al.*)

The point is discussed in many texts in epidemiology and biostatistics, see for example Cox, p 48 [1], Rothman, Chapter 7 [2] and Kalbfleisch & Prentice, Section 6.3.2 [3]. The article by Weinberg [4] gives an excellent general discussion of the issue with many examples.

educational programmes and from Merck Serono for her services as a clinical trial site investigator. Her research coordinator has also been paid by Merck Serono for clinical trial services. DO was the chief biostatistician for the DATATOP study and its extension protocols. In the period 1992–1996 he received research support from Somerset Pharmaceuticals for some of this work.

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- 2 Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: Wiley, 2002.
- 3 Rothman KJ. Modern Epidemiology. Boston, MA: Little Brown, 1986.
- 4 Weinberg CR. Toward a clearer definition of confounding. Am J Epidemiol 1993; 137: 1–8.

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Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. CM has received honoraria from EMD Serono for participating in