Reply to: "An Exponential Rather Than Multistep Model of Parkinson's Disease Pathogenesis"

A mantra of statistics is "All models are wrong, but some are useful."[1] We therefore welcome Dr. Fofffani's challenge to our multistep model of Parkinson's disease (PD) pathogenesis.[2] As we stated, our model's ability to fit the data well is not sufficient to imply that it truly explains the underlying processes. As Foffani shows, an alternative exponential function also fits the data. Both approaches perform quite well in that regard, so we contend that the real test of the competing models' usefulness is not statistical, but more broadly scientific. That is, how interpretable are the model coefficients, how well do they account for knowledge beyond the incidence data from which they were generated, and do they generate new testable hypotheses? On those grounds, we continue to prefer a discrete multistep model of PD pathogenesis, compared to an exponential model that relates it to a continuous aging-related process.

Foffani begins by applying multistep modeling to age-related mortality in the general population, contending that such models can too easily be used in situations where they clearly do not have validity. Although both models fit the data reasonably, tellingly his Bayesian model comparison showed that an exponential process was decisively better at accounting for age-at-mortality (Bayes factor [BF] = 2518). This is what one would expect, as a multistep model is a straw person in this situation and, a priori, an exponential process should provide a better explanation. Rather than showing that multistep models can be applied in any setting, we contend this actually demonstrates that when clearly inappropriate, they can be discounted by comparison to more credible alternatives.

We were less convinced by the comparison suggesting an exponential process also provides a better fit to our PD age-of-incidence data. Foffani limited his analysis to age 75 years, whereas if the comparison is performed over the original range, and accounting for the uncertainty in the underlying data, there is no evidence for one model over the other (BF = 0.98). Furthermore, Foffani's model postulates a uniform exponential time constant across all ages, whereas we found strong evidence favoring a process that varies by age (BF in favor of the original multistep broken-stick model over the uniform exponential model = 2.9). This is consistent with evidence of a greater genetic predisposition in early-onset PD.[3] The multistep approach also allowed us to test specific hypotheses about factors underlying the robust finding of lower PD incidence in women, whilst Foffani did not extend his model to address these sex differences. Foffani did extend his exponential model to account for the incidence drop-off at older ages, but again did not include all data points (ie, those >90 years). Visual inspection suggests that the exponential susceptibility model would not have produced such a close fit if the full data range was included. Furthermore, the coefficients of this model do not correspond well with other evidence. For example, the estimated 2.6% of the population with a pre-existing susceptibility to PD seems low, given that ~2.3% of people in their late eighties will be living with PD and presumably many other susceptible individuals will have died earlier from competing causes.[4]

We welcome further competition between models that seek to explain PD pathogenesis from population age-specific-incidence. However, the ability to statistically account for variability in the data is a necessary but not a sufficient criterion for model credibility. The true contest lies in their explanatory power. We look forward to attempts to extend models (whether Fofffani's, our own, or another) to match or exceed the current multistep approach in that regard.

Data Availability Statement

All data is available via our recent publication.

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