Heterogeneity's ruses: the neglected role of between-individual variability in longitudinal studies of COPD exacerbations

ABSTRACT

Studying the causal and temporal association between past and future exacerbations in COPD is an active area of research. Standard survival analysis techniques often used in such studies typically produce results that pertain to the overall population, whereas the greatest interest is in the study of associations within individuals. A factor that can lead to profound discrepancies between population-level and individual-level survival patterns is the between-individual heterogeneity in the rate of exacerbations. We briefly review two studies that, while reporting valid results for the overall population, drew conclusions at the individual level that could not be supported by the observations. We caution on the distinction between population and individual-level associations in survival analysis, and recommend accounting for heterogeneity in future studies.

There is great interest in studying the impact of exacerbations on the course of COPD. Such studies often rely on survival analysis of longitudinal data. Standard survival analysis techniques produce results that pertain to the population, whereas the real interest is in within-individual associations. A crucial issue in this context is the heterogeneity in the exacerbation rate across individuals. Estimates of hazard function from survival analysis are particularly associated with surprisingly conflicting and potentially misleading patterns when heterogeneity is not taken into account.¹ figure 1 provides an illustrative example.

We are concerned that the conventional wisdom about the role of exacerbations in the course of COPD might have been confounded by such phenomena. We illustrate this by replicating analyses from two previous studies using a simulated 'stylised cohort', in which there is no within-individual associations between exacerbations, but there is between-individual heterogeneity in exacerbation rates. Details of methods and additional results are provided in online supplementary material.

Figure 2A is the hazard function and median between exacerbation times after successive exacerbations from Suissa *et al.*² Based on this and similar results, the authors stated 'occurrence of every new exacerbation requiring hospitalisation

worsens the course of the disease and increases the risk of a subsequent exacerbation', and made recommendations, such as 'delaying the second severe exacerbation as a target of COPD management'. However, as seen in figure 2B, similar patterns can be generated by repeating the analysis in the stylised cohort, where such interpretations do not hold due to a lack of causal associations among exacerbations.

Similarly, Hurst *et al* estimated the population hazard function for time-to-next-exacerbation.³ The decreasing hazard was interpreted as an increased risk of exacerbation in the period after the previous one. They concluded that 'exacerbations are not random events but cluster together in time', a finding that they believed 'has important implications for the targeting of preventative interventions'. Nevertheless, heterogeneity per se can generate decreasing population hazard through the mechanism explained in figure 1, also observed in the stylised cohort (see online supplementary material), even in the absence of temporal clustering of exacerbations within individuals.

Figure 1 Heterogeneity's ruses: an illustrative example of discrepancies between the population and individual hazards. This is a hypothetical population consisting of two subgroups (each 50% of the population) with regard to the hazard of an absorbing event (such as death or 'next' exacerbation): a *frail* subgroup that experiences the event at a high rate and a *robust* subgroup that experiences the event at a lower rate. While the hazard is constant within each subgroup, the population hazard decreases over time. This is because at any given point in time, the population hazard is the weighted average of subgroup hazards, with weights being the proportion of each subgroup in the event-free population. At first, everyone is event free, so the overall hazard is the midpoint between the subgroups' hazards. As time passes, more individuals in the *frail* than the *robust* subgroup experience the event, thus, the event-free population becomes predominantly of the *robust* subgroup, lowering the population hazard. If the population hazard is interpreted at the individual level, one might erroneously conclude that the hazard of the event decreases over time. Phenomena similar to this can be responsible for the findings of both the studies discussed in this paper. For other examples refer to reference 1.

A key aspect of both studies is that the estimated hazard functions belong to the population but were interpreted at the individual level. These interpretations are not necessarily incorrect; however, given the chosen analytical framework, it is impossible to discern to what extent the observed results were because of within-individual associations or between-individual heterogeneity. This distinction is of paramount importance, as the existence of within-individual associations can change priorities, for example, by shifting the attention from the prevention of COPD to the prevention of exacerbations.

Our intent is not to provide solutions to enable within-individual inference in this particular context. Generally, a class of survival analysis called frailty models,⁴ or recurrent-event models that allow comparison of hazard within the same person,⁵ might hold some promise. We invite the respiratory research community to harness the power of such techniques towards better understanding the role of exacerbations in the natural history of COPD.

Figure 2 Hazard function and median between exacerbation times of successive exacerbations from Suissa *et al* (A) and the stylised cohort (B). The authors of the original study mentioned three features of their figure (A): high risk of subsequent exacerbations in the immediate period after each exacerbation (spikes followed by a downward curve), the decreasing between-exacerbation times (spikes getting closer to each other), and the increasing hazard of a future exacerbation after a previous one (the general upward slope). All three features can be explained by heterogeneity: the downward curves after spikes are manifestations of the mechanism explained in figure 1. As one moves along the X-axis, the observations that contribute to the curve come from individuals with higher number of previous exacerbations. In the presence of heterogeneity, these individuals are a selected subgroup of the population with high background rate of exacerbation, explaining the higher hazard and shorter time-to-next-exacerbation.

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