Mediation analysis with a time-to-event outcome and time-varying mediator: an application to cystic fibrosis-related diabetes

Kamaryn T. Tanner[1] , Ruth H. Keogh[1] , Linda D. Sharples[1], Rhian M. Daniel[2]

[1] The London School of Hygiene and Tropical Medicine, Dept of Medical Statistics, London, UK

[2] Cardiff University, Division of Population Medicine, Cardiff, UK

E-mail for correspondence: kamaryn.tanner1@lshtm.ac.uk

Abstract: Cystic fibrosis-related diabetes (CFRD) is a common comorbidity of cystic fibrosis (CF). CFRD negatively affects survival but the mechanism is not well understood. We investigate different approaches to estimating how much of the impact of CFRD on mortality is mediated by lung function using the UK CF Registry.

The time-dependent nature of the mediator and some covariates poses identification and analytical challenges. The time-to-event outcome provides an additional definitional challenge since the length of the mediator process differs under hypothetical assignment to different exposures. We compare two recently proposed methods. Aalen et al. (2018) described a method based on *exposure splitting*, combining a sequential linear model, an additive hazards model and a mediational g-formula. Vansteelandt et al. (2019) use a nested counterfactual framework that allows for time-dependent confounding and accommodates Cox regression or flexible parametric outcome models.

We discuss the results of both methods when applied to the UK CF Registry, including the sensitivity of each to model misspecification and data availability. Finally, we outline areas for future methodological developments.

Key words: Cystic fibrosis; Mediation analysis; Longitudinal data; Survival outcome

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