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HINTS & KINKS

Segmented generalized mixed effect models to evaluate health outcomes

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Introduction

Randomized placebo-controlled trials (RCTs) are considered the gold standard for assessing the effect of exposures (e.g., treatments) or interventions (e.g., policies) on a variety of outcomes. By design, randomization "controls" for confounders to yield internally valid inference. However due to high costs, feasibility issues and/or ethical considerations, the RCT study design may be unable to answer pertinent public health-related research questions (West et al. 2008). Such questions include real-world effectiveness of newly marketed medications or the evaluation of health policies. Observational studies can bridge knowledge gaps left by RCTs. The following article will explain how to extend a pre–post study design using a segmented generalized mixed model to evaluate the impact of acute individual-level exposures on health outcomes. We describe the advantages of using repeated measures over traditional pre–post designs, what exposures are appropriate to analyze, and how different impact models can be parameterized. Like all methods, this approach comes with strengths, assumptions and limitations, which we discuss.

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Pre–post design

A simple pre–post study design compares outcomes at two periods in time: before and after the exposure. To understand how this design can measure the impact of an exposure, we introduce the notion of *counterfactual* or potential outcomes (Rubin 2005). We would like to compare outcomes in the same people simultaneously: had they been exposed and had they not. This would eliminate any factors that confound the relation between exposure and outcome, but of course this is not possible. Instead, we seek an analytic design that mimics a scenario where we can observe what *would have happened* in the absence of an exposure. When repeated measures are available for the same individual, and the only factor that changes over time is the exposure, then the pre-exposure observations can act as the *counterfactual* for the post-exposure outcomes. By design, since the same individual is observed before and after exposure, they act as their own control, meaning time-invariant confounders, both known (i.e., sex, ethnicity, socioeconomic status) and unknown/unmeasured (i.e., genetics, motivation, determination), are accounted for. A regression-based approach extends the simple pre–post design to model trends in outcomes as a function of time (or slopes); see Fig. 1. The difference between the estimated model for post-treatment slope based on the observed or "factual" data, and the counterfactual slope (extension of the pre-treatment slope) plus any immediate level change is attributed to the effect of the exposure.

Exposure and time

The pre–post study design combined with a segmented regression model requires systematic longitudinal data with precise dates of the exposure and outcomes. Since the main assumption is that nothing other than the exposure is

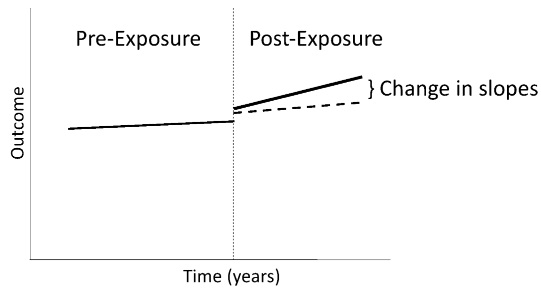

Fig. 1 Pre–post design. Vertical dashed line illustrates the time at which exposure occurred. Gray line illustrates the pre-exposure slope or trends in outcomes. The gray dashed line is the counterfactual extension of the pre-exposure trends to which the solid black line (the actual post-exposure trends) is compared. The difference between the two slopes (counterfactual and actual post-exposure) and the level shift at the intervention point combine to form the impact of outcome attributed to the exposure

changing over time, the exposure must be acute (abrupt or a shock) and uncorrelated with other covariates. Calendar time can be used as the time axis when an exposure impacts a population at a specific period in time, such as a policy change, and many published examples exist (Bernal et al. 2017; Dayer et al. 2015; Dennis et al. 2013; Jandoc et al. 2015; Kittel 2018; Lau et al. 2015; Lavergne et al. 2018; Penfold and Zhang 2013; Wagner et al. 2002). Alternatively, and less common in the literature, is when time is centered for a given individual or cluster at a specific event, also known as a multiple-baseline time series (Biglan et al. 2000; Fell et al. 2014). Examples include critical biological periods (e.g., puberty, menopause) (Naumova et al. 2001), acute physiological changes such as surgical transplants or viral clearance via curative treatments (the example we will use to illustrate this design).

Segmented regression impact model

The impact of the exposure on the outcome can be modeled in multiple ways. Figure 2 illustrates impact models (or expected outcomes) which may include: immediate changes, denoted as a jump or break between pre/post exposure (Fig. 2b, c, f) and/or a more gradual change over time (slope change) (Fig. 2a, b, d, e). The effect can also be modeled as a temporary (Fig. 2f) or a delayed (Fig. 2e) effect. The impact model should be determined a priori based on expert knowledge. A segmented model may also be called a piecewise or broken-stick model; when evaluating population-level exposures with panel data, the pre–post design combined with segmented regression is known as an interrupted time series design (Bernal et al. 2017; Wagner et al. 2002).

Statistical considerations

Generalized mixed models can be used in combination with a segmented design (French and Heagerty 2008). Clusters may refer to repeated measures of individual people or hierarchical groupings such as by jurisdictions, hospitals, or physicians. The use of random effects reflects natural heterogeneity across clusters, allowing for cluster-specific intercepts to be estimated efficiently by assuming that they arise from a normal distribution (Laird and Ware 1982), and by borrowing strength from those subjects with many data points to learn about individuals with fewer measurements. Fixed effects models are an alternative approach and require less stringent assumptions to produce consistent estimates (Strumpf et al. 2017), but are not statistically efficient since they require estimating separate parameters for each cluster. When models are linear,

Fig. 2 Segmented regression impact models. **a** Slope change; **b** level and slope change; **c** level change; **d** temporary slope change leading to a level change; **e** slope change following a lag; **f** temporary level change (Figure adapted from Bernal et al. 2017)

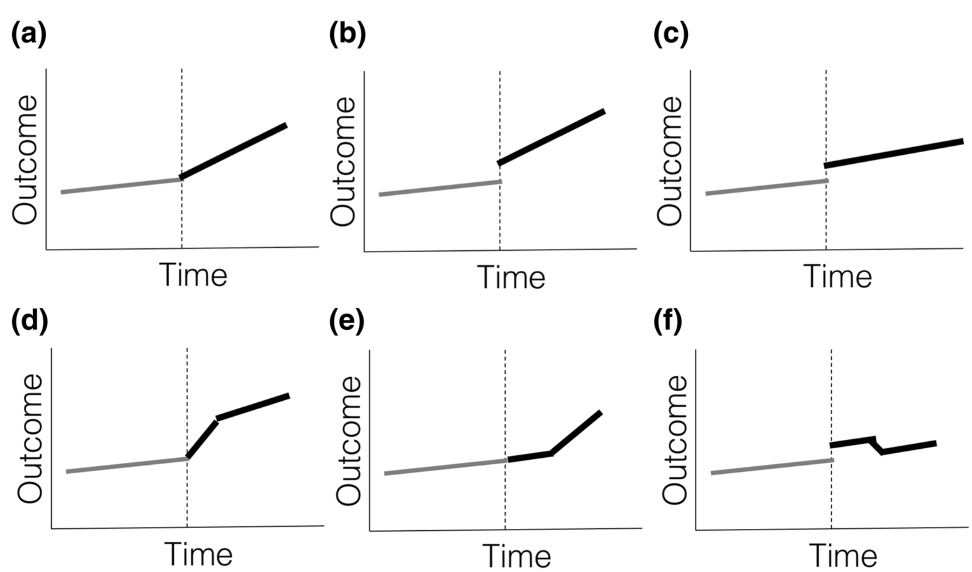

Fig. 3 Visualization of segmented regression coefficients

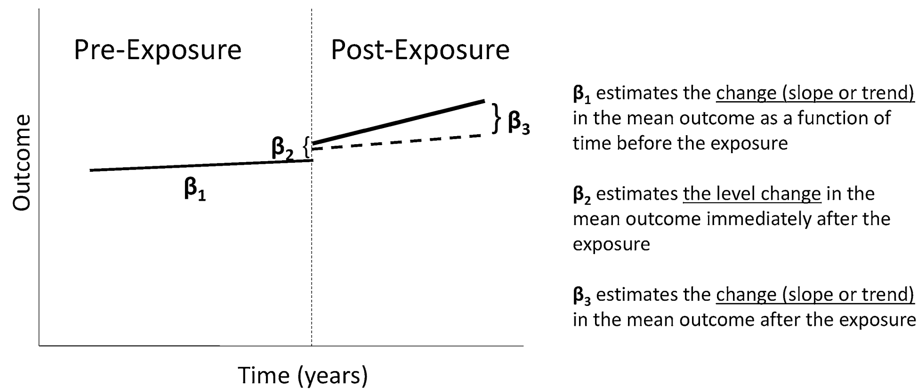

Table 1 Results from a generalized linear mixed regression model of the impact of DAAs on HR-QoL

		(VAS units, 95% CI)
Baseline HR-QoL	β_0	68.7 (66.8, 70.6)
Pre-treatment HR-QoL trends (change HR-QoL/year)	β_1	0.1 (− 0.3, 0.4)
Immediate or level change of HR-QoL	β_2	2.3 (0.0, 4.7)
Impact of DAAs on HR-QoL post-treatment (change HR-QoL/year)	β_3	0.4 (− 1.9, 2.6)

Table 2 Limitations and solutions

Potential limitations	Explanation or practical example	Solutions/sensitively analyses
Presence of a lead-time effect	Since the exposure is not randomly assigned, it is possible that outcomes may change in anticipation of the exposure	This can be assessed by evaluating whether changes in the trend had already started to occur during the pre-exposure period. *Sensitivity analysis* Change the time axis to begin at some fixed interval prior to the exposure. This would provide a pre-treatment slope excluding any artificial changes attributable to the exposure
Biased counterfactual	The impact of the exposure is dependent on the pre-exposure trends estimating an unbiased *counterfactual* of post-exposure trends	Pre-exposure trends need to be assessed by subject matter knowledge. *Sensitivity analysis* If there are concerns that outcomes may be changing over time, an external control group (a group of people not exposed) can be used to evaluate trends over time; this is known as a "difference-in-difference" approach (Strumpf et al. 2017)
Presence of time-varying confounding	Although time-invariant confounders are accounted for by design when using repeated measures, time-varying confounders are not. These include factors that change over time associated with the exposure and outcome and not captured by the pre-exposure trend	If time-varying confounders are measured, these can be included into the regression model, provided these variables themselves are not affected by the change in exposure
Exposure has a non-linear effect	The model equation described in this paper assumes a linear relationship of the outcome and time. However, this relationship may in fact be non-linear	Visually examining the data is a first step to evaluate non-linearity. Flexible modeling of time can be a solution. *Sensitivity analysis* A squared or cubic form of time can be included in the model. The use of splines or other more flexible modeling may also be explored if data permits; however, model interpretation becomes more difficult

estimates from fixed versus mixed models are very similar. However, the interpretations from each model, especially when models are non-linear, and the properties of the estimators—most notably power—differ.

The basic segmented regression model (consistent with Fig. 2a–c) that allows for immediate (level) and gradual (slope) changes has three model parameters relating to (1) $time_{ij}$, where each individual i has j observations; (2) pre–

$post_{ij}$, an indicator variable to divide observations before and after exposure; (3) interaction term ($time_{ij} \times$ pre–$post_{ij}$) to allow for the post-exposure slope to change. Additional variables may be incorporated, letting X_{ij} denote a vector of confounders. Figure 3 illustrates the following model:

$$E[Y_{ij}] = (\beta_0 + b_i) + \beta_1 \text{ time}_{ij} + \beta_2 \text{ pre} - \text{post}_{ij} + \beta_3 \text{ time}_{ij} \times \text{pre} - \text{post}_{ij} + \beta_4 X_{ij}$$

Additional parameters are needed to capture relationships like those shown in Fig. 2d–f.

Example Hepatitis C virus (HCV) is the first chronic viral infection that can be cured using direct acting antivirals (DAAs), in as little as 12 weeks. Although efficacious, it remains unknown what impact HCV cure will have on other health outcomes such as health-related quality of life (HR-QoL). Data were provided from a large prospective cohort of HIV–HCV co-infected individuals with repeated HR-QoL measures before and after treatment (Klein et al. 2010). Participants self-reported current health from 0 to 100 (worst to best health) using the visual analog scale (VAS) of the EQ-5D-3L. A priori, we assume the exposure/outcome relationship would resemble Fig. 3. Stata code is provided (appendix 1). Between 2014 and 2016, 231 individuals (i) initiated DAA (*exposure at time zero*). A total of 1765 observations (j) ; mean follow-up of 3.4 (SD 2.7) years, were collected before treatment (*pre-exposure*) and 523 observations (j); mean follow-up of 0.7 (SD 0.6) years were collected after treatment completion (*post-exposure*). The results are summarized in Table 1. Using a real-world population, we found evidence of an immediate improvement in HR-QoL following treatment: 2.3 units (95% CI, 0.0, 4.7). Following the end of treatment, HR-QoL continued to increase by 0.4 units/year (95% CI, − 1.9, 2.6), controlling for the immediate change and the pre-treatment trends.

Segmented regression assumes that any change in the outcome stems only from the exposure, and that the model correctly specifies the dependence of the outcome on time, exposure, and other variables. Table 2 summarizes the possible violations of these assumptions and solutions.

In this paper, we have demonstrated how a segmented generalized mixed model can be used to investigate the impact of acute individual-level exposures on health outcomes. We illustrated this method using a real-world example of the impact of a curative HCV treatment on HR-QoL. The approach can easily be applied with any standard statistical software. The major strength of this approach is that, by having repeated measures on the same individual before and after an exposure, by design both known and unknown time-invariant confounders are controlled. However, time-varying confounders and the possibility of lead-time effects may bias results. Therefore, caution should be exercised before interpreting the results causally.

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Compliance with ethical standards

Conflict of interest Authors SS, EEMM and ECS declare that they have no conflicts of interest. None of the authors have any conflict of interest with regard to this study and there was no pharmaceutical industry support to conduct this study although MBK has received research grants for investigator-initiated trials from Merck and ViiV Healthcare, and consulting fees from ViiV Healthcare, Bristol-Meyers Squibb, Merck, Gilead and AbbVie.

Ethical approval The data used to illustrate the study design come from the Canadian HIV–HCV Coinfection Study (CCC) which has been approved by the community advisory committee of the Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network and by all institutional ethics boards of the participating centers.

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