Clinical outcome and drugs at SDC

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Bendix Carstensen Steno Diabetes Center, Gentofte, Denmark
& Department of Biostatistics, University of Copenhagen
bxc@steno.dk
http://BendixCarstensen.com

Contents

1 Patient follow-up

at SDC patients are followed through the T2 clinic, recording the baseline status and the status at the end.

The purpose of this analysis is to estimate the effect of different treatments on the outcome, defined as the HbA_{1c}, or specifically the *change* in HbA_{1c}. This is done by taking the baseline HbA_{1c} as a covariate in the analysis of the HbA_{1c} at follow-up. In this type of analysis, coefficients to any other covariate included in the model will represent the effect of that variable on the outcome (follow-up) variable *conditional* on the baseline value.

Thus for individual i with baseline and follow-up values of HbA_{1c} of y_{bi} and y_{fi}, respectively, we might use a statistical model of the form:

$$y_{fi} = \mu + \beta y_{bi} + \gamma x_i + \cdots$$

Thus, comparing two persons with the *same* baseline value and a difference in x of 1, predicts a difference of γ in the outcome. Thus γ is the effect of x on the change in y between baseline and follow-up. But assuming that the effect of x is the same regardless of the baseline value y_b.

In the particular analysis we do not only want to condition on the baseline value of y, but also on the baseline value of other clinical variables, such as BMI, blood pressure, cholesterol, etc.

2 Effect of drug exposure

The core of the analysis will be to assess the effect of the drug exposure during follow-up on the outcome of interest. The aim is formally to identify the "best treatment" for a given baseline status.

Now if we include treatment at baseline (see below for definition of this) we are conditioning on this when assessing the effect of treatment at follow-up through the inclusion of variables for this in the model.

But that analysis will, as explained above in the simple case with a single x, assume that the effect of the drugs during FU is *the same* regardless of the value of any of the baseline variables.

However, if we want to identify treatment modalities (drugs, say) that are particularly suited for some patients (as defined by some summary baseline constitution), and not other, we must believe that the effect of treatment modalities are different for different baseline constitutions.

So we should be looking for *interactions* between baseline and treatment modality. This will potentially identify different treatment modalities that are preferable for some baseline constitutions but not for other. Thus we should for a given baseline constitution look across treatment modalities to see which ones gives the better outcome.

The problem here is of course to define a suitable description of baseline, and in particular to describe the type of interactions to look for.

3 Drug use information

We have records from the prescription register (RMS) for all persons in the study. Thus based on

- grouping of drugs
- date of purchase
- assumptions of duration of drugs use from amount purchased

we can at any time we wish determine whether a person is on a given drug or not.

4 Concepts used

In the previous sections we used:

- baseline constitution — the pattern of clinical variables measured on patients at baseline.
- treatment at baseline — the drugs that the patient is exposed to a baseline. This could be defined as the drugs the patients is taking at the date of baseline or as the drugs the patients has been taking during some, say 6 month, window before baseline.
- treatment at follow-up — the drugs that the patient is exposed to at the follow-up date or rather at a certain time *before* follow-up. If it is believed that it takes some time for drugs show clinical effect this time-lag should be 30 or 40 days.

These will be the three groups of variables that we should have in the model, and the core of the analysis would be the interaction between the last and first two.

Thus we will term the first two groups of variable *baseline* variables (denoted by x), and the last group *intervention* variables (denoted by z).

5 Drug exposure

There are two groups of druge exposure that must be fixed:

- What are the relevant groups of drugs *at entry* — and what window do we want to consider.
- What are the relevant groups of drugs *at exit* — and what window do we want to consider.

And in particular do we foresee any interactions worth exploring.

6 Clinical status

In order to devise sensible interactions it is necessary to pinpoint the clinical variable of interest (beyond $\mathrm{HbA_{1c}}$):

- blood pressure
- renal complications
- ...

This set of variable needs to be expanded, and in particular variables clearly defined relative to the baseline date.

7 Analysis

7.1 Rationale behind analyses

The analysis will be some kind of interaction model controlling for baseline $\mathrm{HbA_{1c}}(y)$.

We want to look after effects where a given clinical value (x) is predictive of the effect of an intervention, producing statements such as:

- Large values of x implies positive effect of z
- Small values of x implies no or negative effect of z

In practical terms this type of conclusion would imply that patients with high x should be treated with z, and patients with low x should not be treated with x.

Thus this is not just a traditional interaction term with increasing effect of z by increasing values of x — that would just be accommodated by including a product term xz. In a clinically meaningful setting we should be able to judge the z-effect across the spectrum of x.

7.2 Practical implementation in models

Looking at interactions between baseline and follow-up variables tend to answer the wrong question accurately, instead of answering the right question approximately. The right question is really to classify baseline characteristics in groups where we can identify regimens that are superior to other regimens.

The identification of interactions between (pairs of) baseline variables and treatment variables is the first step in this. If no interactions are detectable, then we may be convinced that not much information on treatment modalities can be extracted. If we have strong interactions, then one end of the clinical variable distribution may be of particular interest as a target.

7.2.1 Simple product interaction

Now suppose we have fitted a model of the form:

$$y_{fi} = \mu + \beta y_{bi} + \gamma x_i + \delta x_i z_i + e_i$$

where x_i is some baseline characteristic and z_i is a measure of treatment in the period — drug or other.

The z-effect for a given x, is δx, but we must judge it in the context of the magnitude of the x-effect; thus we want to see a plot of $\gamma x + \delta x$ versus x. This will show how the change in y (beyond that governed by the baseline y, y_b) depend on x.

The reason that we want to see this as a function of x is that x is considered a *given* baseline value, and we want to evaluate the *absolute* effect of z across the spectrum of x.

7.2.2 General interaction

However, since we are interested in the totality of the terms involving x and z, there is no particular reason to assume the particular form above (although it is parsimonous with only 2 parameters). In principle any scalar function of x and z would do:

$$y_{fi} = \mu + \beta y_{bi} + f(x_i, z_i)$$

and if we based on the available data produce a parametric estimate of f we would simply want to plot $(x, \hat{f}(x, z))$ for different values of z. This would give a whole family of curves (one for each chosen value of z), whereas the simple approach above assumes a linear effect of z for any given value of x.

A practical choice would be to use natural splines with three knots for the effects of x and z, thus with three parameters each, and so an interaction with 8 parameters (the intercept is out).

7.3 Using binary / categorical intervention variables

7.3.1 Baseline variables

If a baseline variable x is binary we can then just graph the z-effect for each level of the intervention and see of they are substantially different.

7.3.2 Intervention variables

If an intervention variable z is binary we can then just graph the x-effect for each level of the intervention and see of they are substantially different.

8 Variables

Thus the practical problem boils down to defining the variables of interest, between which we will explore the interactions:

- Clinically relevant baseline variables:

  - HbA_{1c} — note that even if we have the baseline value of HbA_{1c} in the model already, there is no hindrance to inclusion of an interaction with the intervention variables
  - blood pressure
  - ...

- Intervention variables:
  - Metformin dosage
  - Insulin dosage
  - Adding insulin
  - ...