32
Three examples

This chapter describes three studies where the explanatory variables change with time and where the analysis has been helped by the statistical methods discussed in immediately preceding chapters. The first is a clinical follow-up study of heart transplant patients and has already been introduced in Exercise 31.1. The second is an epidemiological study into the effects of bereavement in old people. The third is concerned with the important problem of estimating the parameters of cancer screening programmes to help public health administrators in planning such services.

32.1 Mortality following heart transplantation

The first example concerns the survival of patients in the Stanford heart transplant program.* The basic nature of the data is illustrated in Fig. 32.1. The follow-up of patients starts as soon as they are enrolled in the program to await a suitable heart. In this phase of the follow-up, patients are in the *pre-transplant* state. When a heart becomes available, and if selected, transplantation takes place and the patient transfers into the *post-transplant* state. The diagram shows two patients, one of whom dies some time after transplantation while the other dies while awaiting a suitable heart.

The diagram also indicates (by the two vertical lines) a stratification by time in programme. In this time band there is some person-time pre-transplant and some post-transplant. This allows comparison of mortality in post-transplant patients with that in controls who are still awaiting transplantation. The possible biases in this comparison were the subject of Exercise 31.1. Here we are more concerned with the mechanics of the analysis. In this comparison it would be necessary to control for such variables as age (either itself, or at enrollment into the programme), date when enrolled, date when transplanted, and prognostic factors such as record of previous surgery. Multiplicative models fitted using Cox's method can be used to do this.

*Crowley, J. and Hu, M., *Journal of the American Statistical Association*, **72**, 27–36.

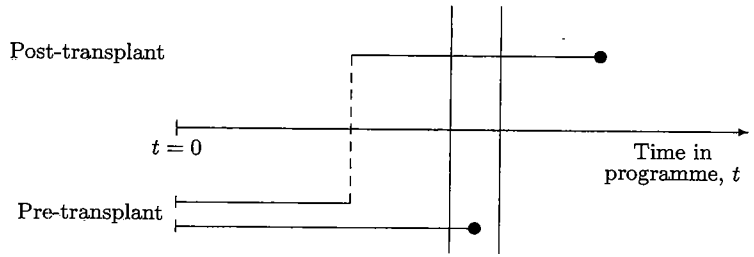

Fig. 32.1. Mortality following heart transplant.

These models are based on the assumption that

$$\frac{\text{Mortality rate for transplanted patient}}{\text{Mortality rate for untransplanted patient}} = \text{Constant},$$

that is, the rate ratio does not vary either with time since entry into the program or with time since transplantation. The latter seems very unlikely. We might even expect an initial adverse effect of transplantation (rate ratio greater than 1) which would later be replaced by a beneficial effect (rate ratio less than 1). The assumption can be relaxed by allowing the transplantation effect to vary with time since transplantation — a variable whose evolution over time can be demonstrated by adding a further axis to the follow-up diagram, as in Fig. 32.2.

Exercise 32.1. Time since transplant can be included in the model for the rate ratio in a number of ways. Perhaps the simplest is to include time since transplant as a quantitative variable as in

$$\log(\text{Rate}) = \text{Corner} + \text{Time} + \text{Transplant} + \text{Transplant} \cdot [\text{Time-since-transplant}],$$

where time is time in program. What signs would you expect for the two parameters of this model? Sketch the graph showing how the rate ratio would vary with time since transplant in this model. (You should assume that Time-since-transplant is coded zero until transplantation occurs.)

Other potential effect modifiers are age at transplantation, time spent awaiting transplantation, and closeness of matching of tissue type with the donor.

32.2 Bereavement in the elderly

The second example is drawn from a study of the effect of bereavement (death of spouse) in an elderly population.† There is some empirical evi-

†Jagger, C. and Sutton, C.J., *Statistics in Medicine*, **10**, 395–404.

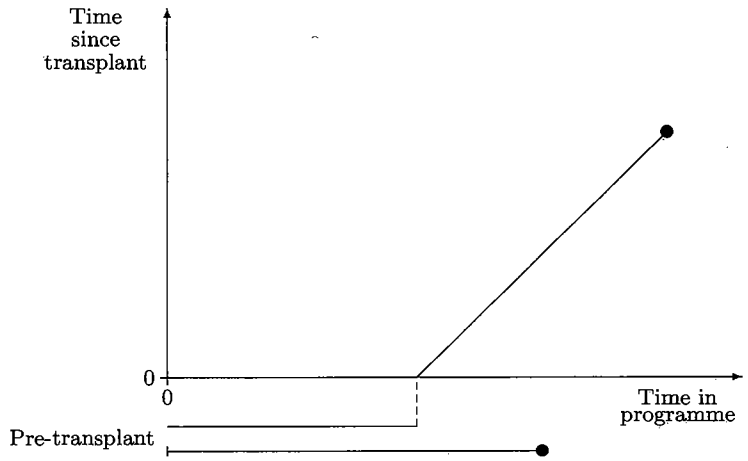

Fig. 32.2. Incorporating time since transplantation.

dence that, for a period following the death of a spouse, the mortality rate of the surviving partner is elevated. Fig. 32.3 shows a plausible relationship between mortality rate, expressed relative to mortality in persons with surviving partners, and time since death of spouse. Such a relationship can be modelled by a simple function such as

$$\text{Rate ratio} = \alpha + \beta \exp(-\gamma t),$$

where α, β, and γ are parameters. At $t = 0$ the rate ratio is $\alpha+\beta$ and, with the passage of time since bereavement, it falls away to α. The parameter γ controls how soon the rate ratio dies away.

Fig. 32.4 shows follow-up of four subjects in a cohort study by calendar time and by time since loss of spouse. Before bereavement, subjects are followed through time, thus allowing measurement of baseline mortality rates. Following death of a spouse, observation may be represented by diagonals in the Lexis diagram formed by plotting calendar time against time since bereavement. Our diagram shows the pattern of observation of two couples. For the sake of clarity, the diagram has been simplified by omitting age, although this must be included in the analysis. In a fuller representation, observation of subjects with living spouses would be represented by lines in an age by calendar time Lexis diagram, while bereaved subjects would be represented by lines in a three-dimensional diagram formed by age, calendar time and time since bereavement.

The analysis of this study must relate mortality rates to all three time

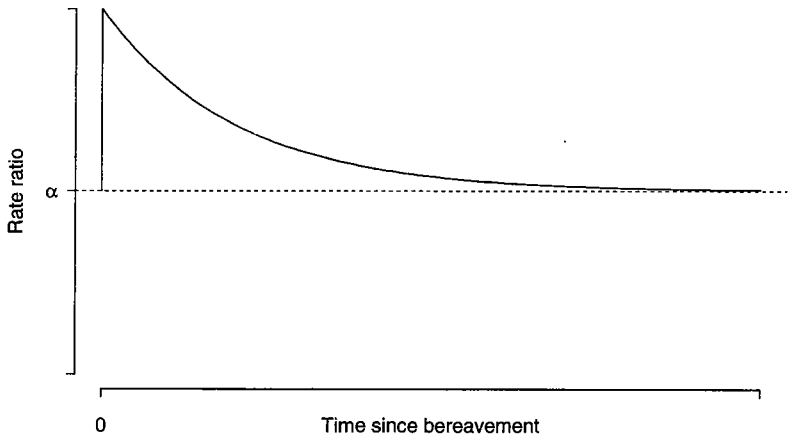

Fig. 32.3. Mortality following bereavement.

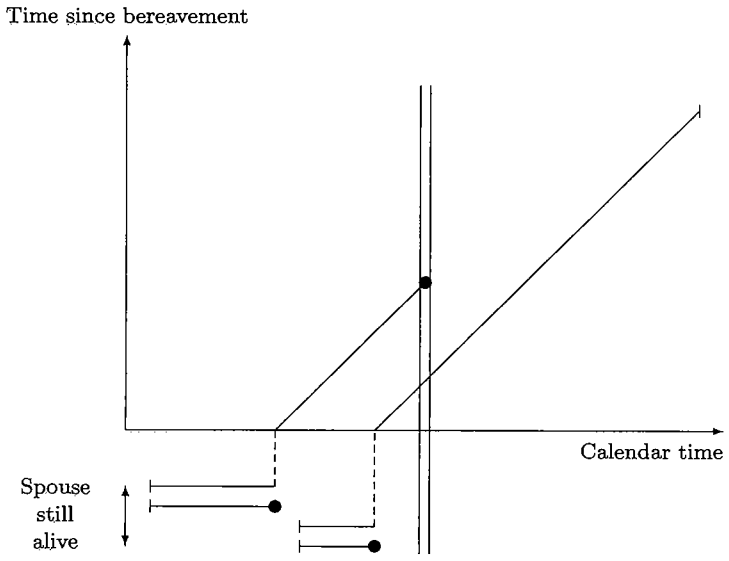

Fig. 32.4. A study of mortality following bereavement.

scales. The effect of time since bereavement is modelled by

$$\text{Rate ratio} = \alpha + \beta \exp(-\gamma t),$$

which describes the relationship using three parameters. For modelling the effects of age and calendar time, all three possibilities discussed in Chapter 31 are open to us. A frequent recommendation is that the scale used in the construction of risk sets should be that with the strongest relationship with event occurrence, and this would argue for age being dealt with in this way. However, mortality in the elderly also varies quite markedly with calendar time, owing to climatic fluctuations, influenza epidemics, and so on. While the age relationship is a smoothly increasing function and may easily be modelled by a linear or quadratic function, the relationship with calendar time is very irregular. It follows that a better strategy is to take calendar time as the scale for definition of risk sets, and to include age in the model as a time-dependent continuous quantitative variable.

Fig. 32.4 illustrates the construction of the risk set in calendar time. The risk set corresponding to each death consists of all those subjects under study in the time slice containing it — illustrated by the vertical band in the diagram. Two of our four subjects belong to the indicated risk set — one as the case. At the relevant date, both have been bereaved and the model would assign them different values of θ (> 1.0) according to the time since their bereavement.

The analysis could also be carried out by creating a nested case- control study by sampling risk sets. This possibility also suggests the design of a *true* case-control study.

Exercise 32.2. Describe a case-control study into mortality following bereavement which mirrors the analysis described above. What sources of bias can you foresee?

32.3 Estimating the parameters of a screening test

Our final example concerns the estimation of the parameters of a cancer screening programme.[‡] The aim of such programmes is to detect cancer during the *preclinical detectable phase* (PCDP) — the period, prior to the time at which the disease would have been detected symptomatically, during which there is some possibility of detecting the disease by screening. Two parameters which it is important to know are the *sojourn time* (the name given to the duration of the PCDP) and the *sensitivity*, defined as the probability of detecting disease by screening during the PCDP. We shall denote these parameters by τ and π respectively, so that π is the probability that screening would detect the disease if applied within a period of

[‡]Day, N.E. and Walter, S.D., *Biometrics*, **40**, 1–14.

duration τ before the time at which the disease would have been discovered anyway.

Interpretation of these parameters and comparisons between different population groups and screening tests requires some care. In general, a better test will lead to increases in both π and τ. More rapid development of tumours will be reflected in decreased values for τ, since the disease will move through the PCDP more quickly. Finally, τ will also be affected by factors which determine rapidity of diagnosis in the absence of screening, so that populations with better access to medical services will usually have smaller values for τ.

We shall now show how these parameters may be estimated from studies of *interval tumours* — incident cases detected by normal clinical means in the intervals between screening appointments. Let us consider the expected variation of incidence following a negative screening test under our simple model, assuming first that the test is 100% sensitive (i.e. $\pi = 1.0$). In this case, there would be zero incidence of interval tumours for a period of length τ following the negative screen, since all the tumours which would have arisen in this period will have been detected at screening. Conversely, after a time τ has elapsed since screening, the rate of diagnosis of interval tumours will return to the normal incidence rate in an unscreened population, since no tumour detected in this period could possibly have been found at the screening appointment. Thus, the rate ratio

$$\frac{\text{Incidence rate of interval tumours following negative screening test}}{\text{Incidence rate in the unscreened population}}$$

will be 0 until time τ following screening, and then jump to 1. Making allowance for less than 100% sensitivity leads to the relationship shown in Fig. 32.5; the proportion of the normal incidence seen in the period after screening is contributed by those cases missed by the screening test.

This model is clearly oversimplified, and we would not expect to observe anything so clearly defined in practice. A more realistic model may be obtained either by allowing for sojourn times to vary or, alternatively, allowing the sensitivity of the test to vary smoothly throughout the PCDP from zero up to π. These models are indistinguishable and lead to a predicted incidence pattern such as is shown in Fig. 32.6. The curve shown is a simple exponential function of time elapsed since negative screen,

$$\text{Rate ratio} = 1 - \pi \exp\left(-\frac{\text{Time since screen}}{\tau}\right).$$

The parameters of this curve, π and τ, may be thought of as the sensitivity and mean sojourn time respectively.

Fig. 32.7 illustrates observation of four subjects in a follow-up study. Three of these enter the study prior to having been screened but are

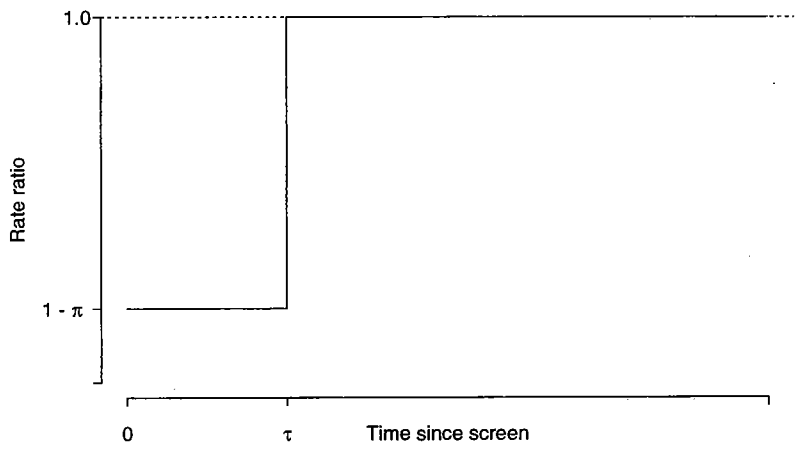

Fig. 32.5. Incidence following a negative screen.

screened during follow-up, while the fourth enters the study some time after a negative screening test. Two of the subjects subsequently develop interval tumours. In an analysis with calendar time as the major time scale,

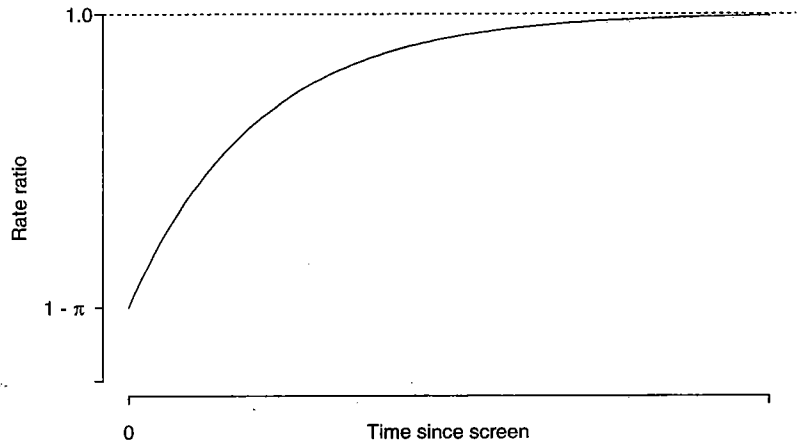

Fig. 32.6. A more realistic evolution of incidence.

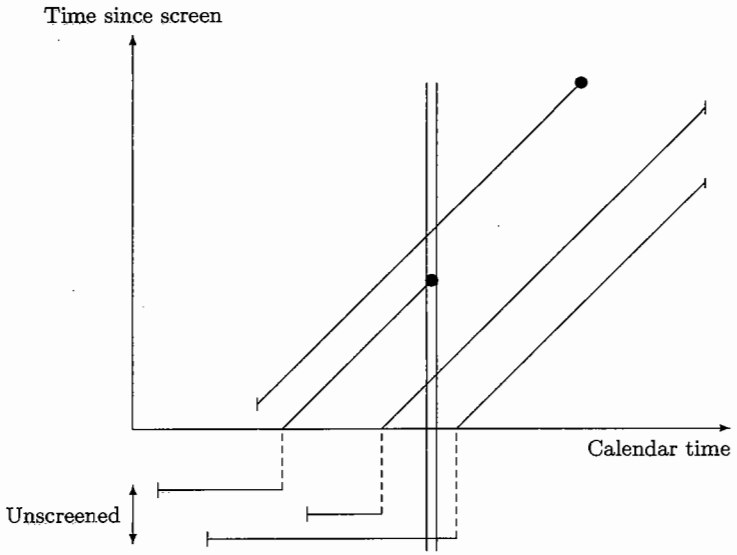

Fig. 32.7. A follow-up study of incidence following a negative screen.

these cases will be compared with risk sets comprising all individuals under study at the date of diagnosis. In the diagram this is illustrated for the first case by the vertical band. It can be seen that all four of the indicated subjects fall into this risk set; one is still unscreened and is assigned $\theta = 1$ by the model, while the other three have different times since their negative screening test and, for any values of τ and π, a model such as that illustrated by Fig. 32.6 assigns three different values of θ to the others. Each interval tumour contributes similarly to the log likelihood, and computer programs may be used to maximize this with respect to τ and π to obtain best estimates of these quantities. Approximate confidence intervals may be found in the usual way from the curvature of the profile log- likelihoods.

Exercise 32.3. What assumption concerning selection of subjects for screening must hold for this analysis to yield unbiased results?

The above discussion slightly over-simplifies the analysis. In particular, it will be necessary to allow for age in the model. As in our previous example, sampling risk sets to create a nested case-control study will avoid some computation, and also suggests a true case-control design.

Exercise 32.4. Describe a case-control study to investigate sensitivity and sojourn time of a screening test for breast cancer. Would you expect to obtain approximately the same results as in a cohort study?

Solutions to the exercises

32.1 The Transplant main effect measures the log rate ratio immediately following transplantation. We might expect this to be positive immediately after surgery, corresponding to an elevated mortality rate, but then to decrease with time, giving way eventually to a beneficial effect. In this case the interaction parameter would be negative.
The predictions of the model in terms of the log rate ratio are shown in Fig. 32.8. The parameter α is the Transplant initial effect and is shown here as positive, indicating an adverse effect. The slope of the line is the Transplant·Time interaction parameter and is shown as negative. This model predicts that transplantation will have an increasingly beneficial effect with increased time from transplantation. The horizontal dotted line represents the level of mortality in untransplanted controls. On the original scale, the rate ratio initially jumps to $\exp(\alpha)$ immediately after transplant but then falls exponentially towards zero.

32.2 The events of interest are deaths in elderly people, let us say those over 70 years of age. A geographically based case-control study would include as cases all such deaths amongst residents of a town or county. Each time such a death occurs, a set of controls would be drawn from the study base. Matching of controls to cases for age and sex would improve the efficiency of the study. Information concerning vital status of spouse and, where appropriate, date of death of spouse, would be obtained retrospectively for all cases and controls. This study would run little risk of information bias, since the relevant data are on public record. However, selection bias could be a problem. These are some of the problems:

- A suitable, accurate, sampling frame may not be available.
- Refusal to participate by potential controls could lead to 'volunteer' bias in the control group finally obtained.
- Migration away from the sampling frame as a result of bereavement is a very real possibility. A bereaved old person may not be able to care for him or herself and might be forced to go into residential care or to live with relatives.

These problems do not exist when a cohort of identified subjects is followed prospectively.

32.3 It must be assumed that individuals selected for screening would have the same subsequent incidence rates as those not selected. This assumption would not be violated by a screening policy which varies with age, providing confounding by age is dealt with in the analysis. However, if patients are referred to screening as a result of early non-specific symptoms, there would be some bias.

32.4 A population based screening programme requires a computer register to generate screening invitations, so this register can form the study base. The study would be of newly diagnosed cases who were not diagnosed as a result of routine screening and whose names could be found on the computer register. Controls for each case would then be drawn from this register. If carried out carefully, it is difficult to see any reason why such a study should give different answers from a cohort study. Indeed, the existence of the computer register means that the study is really nested within a cohort study (see Chapter 33).

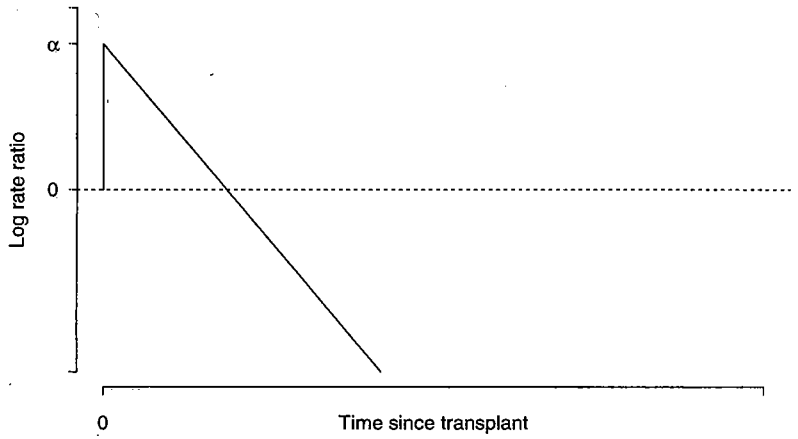

Fig. 32.8. Log rate ratio against time since transplant.