

1. Sharper and Fairer Comparisons: effect of sexual activity on the longevity of male fruitflies

[Limit analysis to fruitflies with 1 partner .. the effect is obvious in those with 8]

When we first analyzed these data, PE, now on McGill faculty, argued that thorax size cannot be used as a predictor/explanatory variable since fruitflies who die young may not be fully grown, i.e., it is also an "intermediate" variable. Later, NK (now on faculty elsewhere) had studied entomology & assured us that fruitflies do not grow longer after birth; i.e., thorax length is not time- (age)-dependent!

Refer again to the comparison of the mortality (hazard) rates for sexually active (index category) vs. inactive (reference category) fruitflies. Restrict attention to ones supplied with 1 partner every two days.

- i Multiply the 50 thorax sizes into Z-scores, so that you are dealing with a more familiar scale . Fit a p h model that contains 2 terms: an indicator for active (1) vs. inactive (0), and the z score for thorax size (used as a 'continuous' variate).

Estimate the S curve for active=0, thorax.z = 0, using built in routines (survfit in R, or basesurv in Stata, or the covariate statement in proc phreg in SAS)

Use the R code provided on the website (under Resources - Cox) to create the "effective numbers at risk" in each riskset if we used a weight of $HR.hat = \exp[\beta.hat.active \times active + \beta.hat.thorax.z \times thorax.z]$ to convert each fly into a number of "zero-equivalents" i.e. a HR.hat of 2 means that having one such fly in one's 'insurance portfolio' is the same as having 2 others of average size, who are inactive (i.e., active=0, thorax.z=0).

Use the R code provided to then compute a single Nelson-Aalen survival curve from the risksets with these "effective numbers at risk". {see JH note re Breslow estimator of Baseline survival curve }
 Compare this curve with the baseline survival curve (the one corresponding to active=0, thorax.z=0) obtained above using the inbuilt routines.

Obtain -- using built in routines -- the fitted Survival curves for 3 other types of flies: (a) average thorax, active (b) thorax 1 SD larger than average, not active (c) thorax 1 SD larger than average, active.

Verify that if you had the S value for a particular timepoint on the curve for active = 0, thorax.z=0, you then get the corresponding point for any value of active, and any value of thorax.z by taking

$$S_{active,thorax.z}[t] = \{ S_{active=0,thorax.z=0}[t] \}^{\exp[score]}$$

where

$$score = \beta.hat.active \times active + \beta.hat.thorax.z \times thorax.z.$$

- ii Divide the range of thorax size into 4 roughly equal strata (using cut points at say $Z = -0.67, 0, \text{ and } 0.67^*$), and fit a p h model that contains just 1 term: an indicator for active (index category) vs. inactive flies (reference category), but that stratifies (matches) on the stratum of thorax size. Compare the $\beta.hat.active$ with that obtained in (i).

Write out (in words) the 'hazard' assumptions for this approach vs. that in (i).

Which approach to dealing with thorax size you prefer? Why?

** In a Gaussian distribution with mean 0, SD=1, one half of the probability mass is between -0.674 and +0.674. Indeed, to use a now-seldom-used term, 0.674.. is the "probable error" of the distribution, in that an observation is equally probable to be more than or less than this distance from the mean.*

- iii Use graphical methods to assess the fit of the model used in (i).

2 Refer to the article "Weekend versus Weekday Admission and Mortality from Myocardial Infarction". Restrict attention to the data for 1999-2002.

- i Given Table 1, how different will any crude and adjusted hazard ratios be? Can you anticipate (without consulting Table 4) whether adjustment by these factors will move hazard ratios away from, the null?
- ii Convert the *cumulative* mortality data [the two "percent (mortality)" columns in Table 3] into day-specific hazards (or incidence density) for each of the first seven days, and into period-specific incidence density values for the periods 7-14, 14-21, 21-30, 30-180, and 180-365 (R code available in Resources-Cox .. could also do by Excel, or (a bit tedious!) on a hand-calculator).

In the R code, the %s for the 1st seven days are given to 2 decimal places (these, courtesy of the authors) are

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Weekdays: 1.10, 2.72, 3.83, 4.70, 5.40, 5.97, 6.57
Weekends: 1.27, 3.31, 4.67, 5.77, 6.37, 6.95, 7.54.
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Then examine the day-by-day and period by period (crude) hazard ratios (a plot helps). Comment.

- iii The authors reported one hazard ratio for mortality in days 1&2, another for days 1-7, another for 1-30, etc. From your examination of the day- and period-specific hazard ratios, which days / periods would you keep together so that the hazard ratios within each grouping are reasonably homogeneous?
- iv One news source [<http://www.cbc.ca/health/story/2007/03/14/heart-attacks-weekend.html>] that reported on this study told us

People admitted on weekends to hospital for heart attack show higher death rates compared to those entering on weekdays (..), U.S. researchers say. The risk of death was about five per cent higher in the month after the attack.

Where did they get this "about five per cent higher"? Is it the most relevant number to report? Which one would you use? Why?

- v The news report also tells us that "In the U.S., the rate translates into several thousand people each year". How many avoidable* deaths does it translate to for New Jersey for each of the 4 years 1999-2002 (base your calculations on the mortality data in Table 3)? {New Jersey has approx 1/35th of the US population}
 - {* "in an ideal world" and assuming no residual confounding, How they might be avoided, and the cost of doing so, are discussed in the Editorial by Redelmeier and Bell, and in the Audio interview with Dr. Lee, network president at Partners Healthcare System in Boston. <http://content.nejm.org/>}
- vi The Editorial tries to link the lower intervention rates on weekends to the higher mortality:

"Kostis et al. report that patients with myocardial infarction arriving at the hospital on weekends are one third less likely to receive percutaneous coronary intervention (PCI) on admission than patients who arrive on weekdays."

It then goes on to say

" If PCI yields a 15% increase in survival, then the reduced use of PCI on weekends might explain the observed 5% increase in mortality associated with weekend admission."

Can you explain the 'math' being used here? Use concrete numbers.

JH Note / "Rant": Survival is increased by *decreasing mortality*: that's why we should study mortality rather than survival. *We should study mortality rates over time, and then translate them into cumulative mortality*. If 7-day survival is already 90%, it is difficult to increase it by 15% (in absolute or in relative terms). I suspect that this "15% increase in survival" came from a hazard (*mortality*) ratio of 0.85. If this is so, then yes we can start to work on bringing down the 10% 7-day risk of death*. That is why JH prefers and strongly recommends -- for situations where the cumulative incidence never gets above 25% say (survival curve never drops below 75%), showing the results as CI (risk) functions, where the work cumulative' [increasing] makes sense (as in Fig 1 of article) . Semantically, "cumulative" survival does not. * Also, I expect that by focusing on mortality rates that than the (vague) "survival", you will have some chance of mathematically linking a specific increase in mortality with a decrease in PCI rate.

- vii Table 4 shows several ph models, including the very interesting one in the last columns, showing the 'mediation'. For this analysis, they censored all records at 30 days. This is easy to do. But how should the last 3 (lack of intervention) variables be included in the model? Explain.
- viii Suppose the authors were willing to send us a data file so we could perform analyses that address the key topics in Tables 3 & 4. Say that, either because of limitations in R or Stata (they are memory based; SAS is disk based and so can accommodate larger datasets) or in the size of the file that they could email, we were limited to say 20,000 data-records. *Which* records from the almost 60,000 for the period 1999-2002 would you ask the authors to send us (we would like to get the greatest amount of "information per record") ?