Coursework for

Advanced Statistical Methods in Epidemiology 2015

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The coursework has a total value of **100 Marks** and has to be handed in **26 May 2015** (3pm).

A meta-analysis (Gupta *et al.* 2002) has been performed to evaluate the diagnostic accuracy of endometrial thickness measurement by pelvic ultrasonography predicting endometrial carcinoma and disease (hyperplasia and/or carcinoma). The meta-analysis includes 56 studies and are available at http://www.personal.soton.ac.uk/dab1f10/AdvancedStatsEpi/tabledata.htm.

The data contain the following variables:

Study: study identifier

Author: some details on the study

Disease: describes the groups with (1) and without (0) the condition (hyperplasia and/or carcinoma).

Diagnostic test: describes the outcome of the diagnostic test based on the endometrial thickness: positive (1) or negative (0)

Frequency: frequency of women with a specific diagnostic test – disease combination: true positive, false-positive, true negative, false negative

Cutoff: thickness value used to decide when a test value is defined positive or negative

Layer: number of investigated layers of the endometrium (1 or 2)

In diagnostic study analysis the risk for the diagnostic test being positive in the diseased group is called *sensitivity* and the risk for the diagnostic test being positive in the healthy groups the *false positive rate.* Also, the relative risk, namely the ratio of sensitivity to false positive rate is called the *positive likelihood ratio.* The higher the likelihood ratio the better diseased and healthy patients are separated, in other words, the higher is the diagnostic accuracy as measured by the likelihood ratio. In the following we focus in the analysis on the likelihood ratio as a relative risk measure. Note that *diseased* becomes *exposed* and a *positive diagnostic test* value will become a *case*. Use for all calculations the software STATA.

1. Produce an easy to read table of true positive, false-positive, true negative, false negative test results by study. Compute a crude likelihood ratio for the diagnostic test with 95% confidence interval and give an interpretation of the result. **[10 Marks]**

2. An important explanatory variable is the cutoff value used to define if the test value is positive or negative. Provide a stratified Mantel-Haenszel analysis where the stratifying variable is cutoff. Collapse studies with cutoff equal or larger than 7.

    a. Interpret your findings!
    b. Is there a difference between the crude and the Mantel-Haenszel likelihood ratio?
    c. Is there effect heterogeneity in the sense of the likelihood ratio over the cutoff?
    d. Which cutoff-values give the best diagnostic accuracy results in terms of the likelihood ratio? **[25 Marks]**

3. Use a Poisson regression model approach to analyse the diagnostic accuracy of the diagnostic test based on the endometrial thickness. Note that this question needs a reorganization of the data and that the log-size of the diseased and non-diseased group has to be used as an *offset.* Analyse the effect of the cutoff value. Are the results different from what was found in question 2? Note that effect heterogeneity with respect to cutoff can be tested via a likelihood ratio test which is testing for interaction of cutoff and disease status. **[30 Marks]**

4. Using a Mantel-Haenszel and well as Poisson regression model analysis, investigate whether there is an effect of *layer* on the diagnostic accuracy. **[10 Marks]**

An independent role for the exercise-induced heart rate (HR) response—and specifically the chronotropic incompetence (CI)—in the prognosis of heart failure (HF) is still debated. The multicentre study reported here (see Magrì et al., 2014) sought to investigate the prognostic values of HR and CI variables on cardiovascular mortality in a large cohort of systolic HF patients. The data are available at
http://www.personal.soton.ac.uk/-dab1f10/AdvancedStatsEpi-/tabledata.htm.

List of variables:

- **age** (in years)**,**
- **gender** (1 = male**, 0** otherwise),
- **fu_total** (follow-up time in days),
- **bmi** (body mass index weight/height^2),
- **bb** (beta-blocker therapy 1 = treatment 0 = otherwise), phrabs_65_CI (absence of chronotropic incompetence 1 = absent 0 = otherwise),
- **cardiac_cause** (status at the end of survival time: 1 = event occurrence, 0 otherwise).

Note that the observation time is censored if no event has occurred and the follow-up time is below the maximum follow-up time.

5. Produce an easy to read graph of the survival function (by using the Kaplan-Meier estimator) showing that considering CI is crucial in stratifying cardiovascular mortality. Can you quantify the difference between the Kaplan-Meier curves? **[10 Marks]**

6. By adopting the Cox proportional hazards regression model, check for the effectiveness of the beta-blocker therapy once CI, Age, Gender and BMI effects are accounted for. Interpret your findings **[10 Marks]**

7. Produce a test and graphical diagnostic for the proportional hazard assumption **[5 marks]**

References

Gupta, J.K., Chien, P.F. W., Voit, D., Clark, T.J., Khan, K.S. (2002). Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstetricia et Gynecoliga Scandinavica* 81: 799-816.

Magrì, D. et al. (2014) Cardiovascular mortality and chronotropic incompetence in systolic heart failure: the importance of a reappraisal of current cut-off criteria. European Journal of Heart Failure 16: 201-209