Biostats VHM 811 Course
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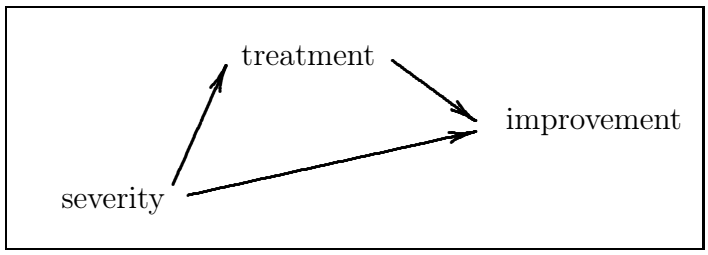
Brief solution to question on confounding/interaction on final exam

The data originate from a study in Denmark.

a) Study design and causal diagram

The study is a clinical trial, probably randomized although that it is not stated explicitly in the study description. The reaction of the patients to the treatment are monitored during a follow-up period, so the study may be considered of cohort type (but the follow-up period is very short). The causal diagram should be drawn as follows:



The arrow between severity and treatment might not exist if the trial was properly randomized. If necessary, we may assess the association between the two variables from the data at hand. From the diagram it is clear that if there is an association between severity and treatment, then severity may act as a confounder for the treatment effect. Treatment cannot be a confounder for the effect of severity because it is intermediate for the relation between severity and improvement.

b) Epidemiological analysis

The first Stata listing gives an analysis of the association between treatment and outcome stratified on severity. The second listing gives an analysis for severity stratified on treatment which is of less relevance and should be ignored. The (first) listing shows that there is hardly any difference between the crude and stratified risk ratios (1.33 and 1.29, respectively). This tells us that any confounding effect of severity on the treatment effect is negligible. More importantly, the risk ratios are clearly different in the two strata, and the test of homogeneity of the risks ratios is clearly significant. Therefore, the data show an *interaction* between severity and treatment (in which case the question about severity being a confounder cancels anyway). The role of severity for the treatment effect is that of a moderator or effect-modifying variable. The relevant measures of association to report are the stratum-specific risk ratios:

$$\begin{aligned} \text{less severe migraine}: &\quad \text{RR} = 2.29 \quad , \quad 95\%\ \text{CI: } (1.24, 4.22), \\ \text{severe migraine}: &\quad \text{RR} = 0.91 \quad , \quad 95\%\ \text{CI: } (0.66, 1.25). \end{aligned}$$

For patients with a less severe migraine, the treatment does better than placebo; it approximately multiplies the chance of improvement by a factor of 2.3, and this improvement seems statistically significant (because the CI does not contain 1). For patients with severe migraine, the treatment does no better than placebo; the risk ratio is less than 1 but that could very well be just random variation. It is seen directly from the data that for patients with severe migraine both placebo and the treatment have a good prognosis in terms an improvement for the patient, whereas for less severe

migraine this is only the case for the treatment. If desired, the actual risks could be computed. Also, although not of direct interest for the associations with improvement, one could assess the association between severity and treatment by a simple 2×2 table analysis; there is no evidence of an association ($X^2 = 0.65,\ P = 0.42$), so it seems the randomization worked well.

c) Treatment D

The improvement of treatment C relative to placebo was measured by the risk ratios in the two severity strata. For treatment D the corresponding risk ratios (odds-ratios could also be computed) are:

$$\begin{aligned} \text{less severe migraine}: \quad \text{RR} &= (7/20)\,/\,(8/24) = 1.05, \\ \text{severe migraine}: \quad \text{RR} &= (22/27)\,/\,(18/23) = 1.04. \end{aligned}$$

The two risk ratios are almost identical; it is an easy guess that there is going to be no evidence of heterogeneity across strata here. Also, 95% confidence intervals for the risk ratio should easily include 1 in both strata (note that the sample size is about the same as for the comparison between placebo and treatment C, where one of the confidence intervals extended well past 1). Therefore, our conclusion is that treatment D does no better than placebo, overall and in both groups of patients. A similar Stata analysis to the one shown for part **b)** restricted to the data for placebo and treatment D will confirm these findings, and may also allow a comparison between the crude and M-H adjusted effects of treatment D.