Summative Quiz Solutions

1. Consider studies designed to compare the occurrence of a binary outcome between two populations: population A and population B. In general, which of the following statements best describes the relationship between the relative risk estimate ($\hat{RR}$)and the odds ratio estimate ($\hat{OR}$), both based on the same two samples from populations A and B?

   a. $\hat{RR}$ and $\hat{OR}$ will always be exactly the same in value.
   b. If $\hat{RR}$>1 then $\hat{OR}$ will be less than 1.
   c. $\hat{RR}$ and $\hat{OR}$ may differ in value, but will show the same direction of association.
   d. $\hat{RR} = \frac{\hat{OR}}{\sqrt{n_1 + n_2}}$, where n_1 and n_2 are the sizes of the samples from population A and population B, respectively

2. How does the Kaplan-Meier approach to estimating the survival function utilize information from censored observations?

   a. It does not. All censored observations are dropped from the data sample before the curve is estimated.
   b. The Kaplan-Meier approach uses the censored observations when considering who is "at risk" of an event at a given time in the follow-up period. All censored observations are considered "at risk" of an event until the time of censoring.
   c. The Kaplan-Meier approach treats the censoring times as event times. (i.e., it ignores the fact that these observations are censored)
   d. The Kaplan-Meier approach treats the event times as censoring times

3. A randomized prospective study is conducted to estimate the association between taking a drug and remission for patients with a specific type of cancer. The estimated incidence rate ratio of remission for the treatment group relative to the placebo is 1.35. What is the proper interpretation of this value?

   a. In a random sample of 1,000 persons from the same cancer population, there would be 350 more remissions if these 1,000 persons took the drug as compared to if they did not take the drug.
   b. In a random sample of 1,000 persons from the same cancer population, there would be 650 less remissions if these 1,000 persons took the drug as compared to if they did not take the drug.
   c. An individual (from the same cancer population) who does not take the drug is 35% less likely to go into remission as compared to an individual who has taken the drug.
   d. An individual (from the same cancer population) who takes the drug is 35% more likely to go into remission as compared to an individual who has not taken the drug.

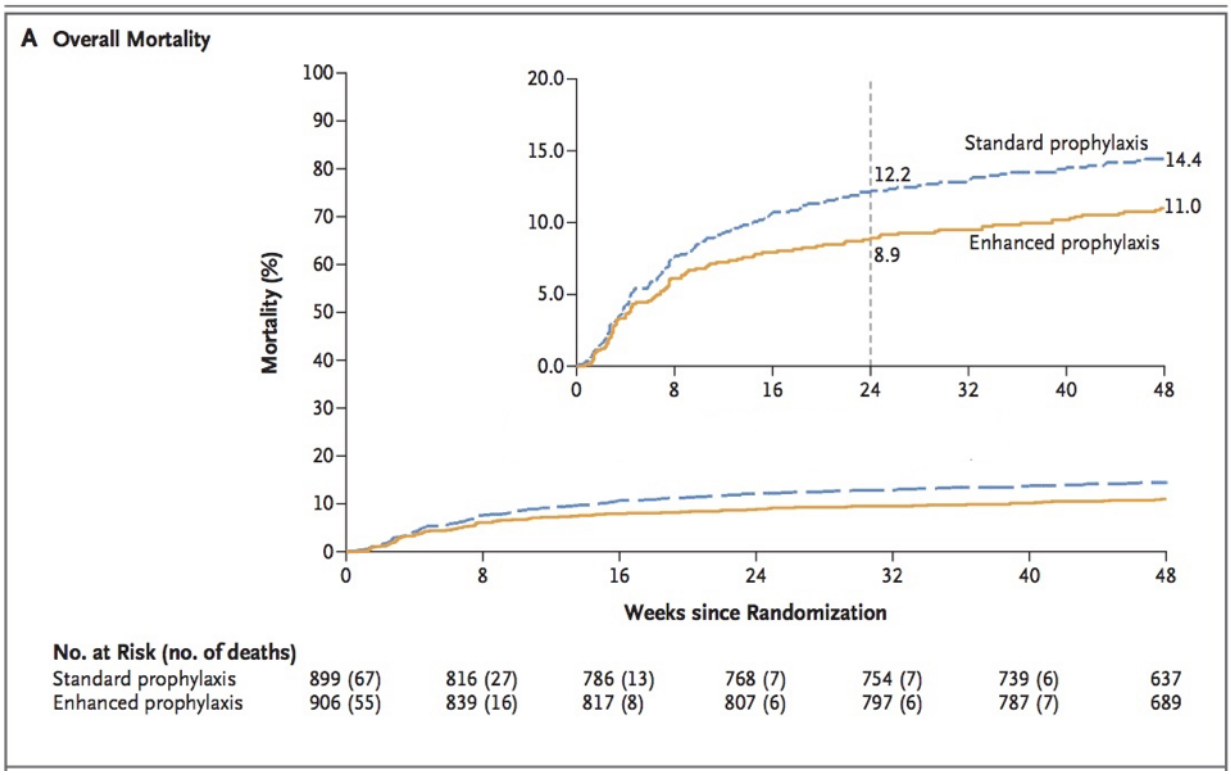
If $\widehat{IRR} = \frac{\widehat{IR}_{drug}}{\widehat{IR}_{placebo}} = 1.35$ then the drug group has a 35% higher risk (incidence) of reemission relative to the placebo. (Just FYI: Notice that if this ratio was computed in the oppositre direction of comparison, ie: $\frac{\widehat{IR}_{placebo}}{\widehat{IR}_{drug}}$, the resulting incidence rat ratio estimate would equal $\frac{1}{1.35} \approx 0.74$, and the placebo group has a 26% lesser risk of relapse compared to the drug group: remember, that with ratios, the percent change in the numerator compared to the denominator is not consistent if the two values are switched, This is why we will ultimately need to deal with ratios on the ln(scale) for certain computations. (more to come!!)

Choices 1 and 2 cannot be answered with the given information: we can't the absolute impact on a population with a fixed size from only a relative comparison, and would need some sort of absolute measure to do so, such as the proportions remaining remission-free over time in each group, from Kaplan-Meier curves.

An article in the *New England Journal of Medicine* reports the results from a randomized study designed to evaluate the efficacy of enhanced prophylaxis treatment for affecting mortality in patients with advanced AIDS living in sub-Saharan Africa.

As per the researchers, "A total of 1805 patients (1733 adults and 72 children or adolescents) underwent randomization to receive either enhanced prophylaxis (906 patients) or standard prophylaxis (899 patients) and were followed for 48 weeks (after start of treatment)". The primary outcome of interest was mortality (death) in the 48-week follow-up period after receiving the treatment.

The following Kaplan-Meier curves shows the estimated mortality (percentage of deaths) over the follow-up period separately for the treatment (enhanced prophylaxis) and control (standard prophylaxis) samples:



Data from the year 2012 National Health and Nutrition Examination Survey (NHANES) survey includes laboratory measurements on a random sample of more than four-thousand 18-65 year old persons in the United States. The following boxplots display the distribution of blood lead levels(mg/dL) for this sample, separately for males and females. The accompanying tables display summary statistics of the sample values.

4. (Approximately) what percentage of patients in the intervention (enhanced prophylaxis) group survived (lived) beyond 48 weeks after being randomized to this group?

a. 14.4%
b. 85.6%
c. 11%
d. 89%

5. Which of the following statements is true about the incidence rate ratio of death (IRR_hat) in the 48 week follow-up period for the enhanced prophylaxis group compared to the standard prophylaxis group (based on the results in the Kaplan-Meier curve)?

a. IRR_hat > 1
b. IRR_hat < 1
c. IRR_hat=1
d. IRR_hat should be "close" to 1, but there is no way to tell exactly how it will compare to 1.

The following information is used for questions 6-8:

An article in the November 20, 2008 edition of the *New England Journal of Medicine* reports the results from a large, randomized study designed to assess the relationship between statin treatment and cardiovascular disease (as indicated by having at least one of several clinical endpoints).

The researchers randomized 17,800 healthy (without a history of cardiovascular disease) men and women with non-elevated LDL cholesterol levels to either 20 mg of statins daily, or placebo. Subjects were followed for up to 5 years. At the end of the follow-up period the study results included the following:

Of the 8900 subjects randomized to the statins group, 142 developed cardiovascular disease. Of the 8900 subjects randomized to the placebo group, 251 developed cardiovascular disease.*(Reference:* Ridker P, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *New England Journal of Medicine*. (2008). 359;21)

6. In the article, the authors report an incidence rate of 2.3 deaths/1,000 person-weeks for patients randomized to the enhanced prohylaxis group. This incidence rate (IR1) was calculated using data on all patients in the enhanced prohylaxis group, including those who were censored. Suppose, instead, the authors computed this incidence rate, but only used the data on patients in the enhanced prohylaxis group who died while in the study (IR2). How would IR2 compare in value to this reported incidence rate, IR1, of 2.3 deaths/1,000 person-weeks?

   a. IR2 will be similar in value to IR1, but there is no way to predict exactly how the two estimates will compare.
   b. IR2 < IR1
   c. IR2 > IR1
   d. IR2 = IR1

$\widehat{IR}_1 = \frac{total\ relapsse\ in\ the\ follow-up\ period}{total\ follow-up\ time\ for\ all\ patients}$ for patients in enhanced prophylaxis cohort

and the denominator includes follow-up time for those who were censored. If the authors only used the data on those who relapse, the numerator of the new incidence rate estimate , $\widehat{IR}_2$, would be the same as the numerator for $\widehat{IR}_1$. However the denominator for $\widehat{IR}_2$would be smaller as it would only be based on times persons who relapsed in the follow-up period (and not include the times for those who were censored).

7. What is the estimated relative risk developing cardiovascular disease for subjects in the statins group compared to subjects on placebo over the 5-year follow-up?

e. The estimated relative risk is approximately 0.57.
f. The estimated relative risk is approximately - 0.012.
g. The estimated relative risk is approximately 1.77
h. The estimated relative risk is approximately 0.012.

This relative risk approximates the incidence rate ratio for the two-group comparison over the 5-year follow-up period. The actual incidence rate ratio is likely very similar to this relative risk estimate, but may differ slightly because of differences in the individual follow-up time distributions in the two groups.

The relative risk estimate is: $\widehat{RR} = \frac{\hat{p}_{statistics}}{\hat{p}_{placebo}} = \frac{149/8900}{251/8900} = \frac{0.0167}{0.0282} \approx 0.57.$

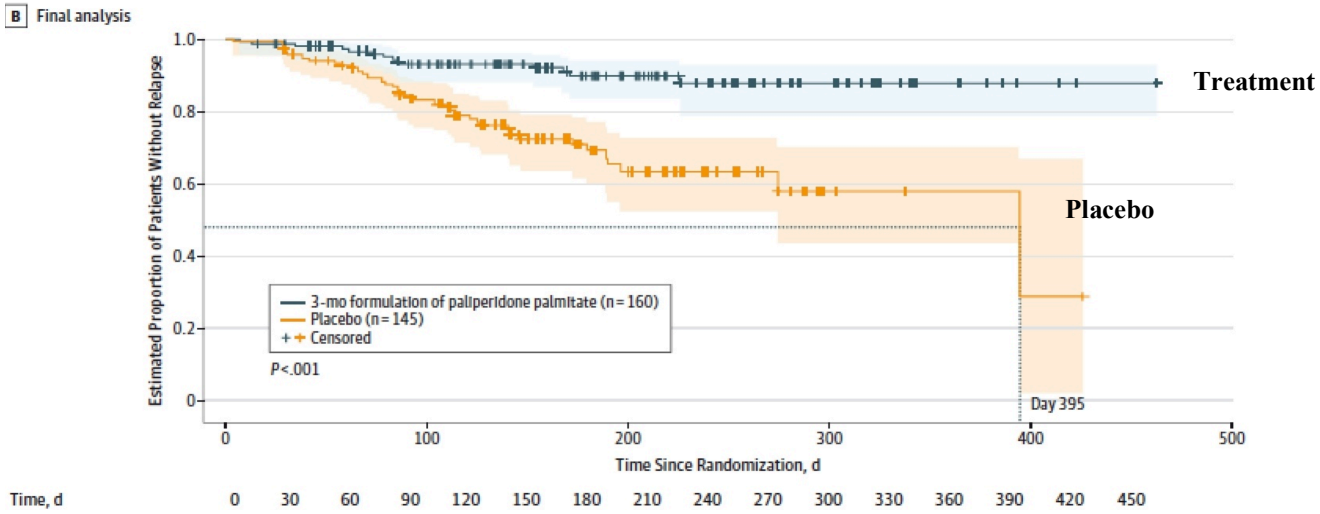
8. Suppose a group of 200,000 healthy persons from the same population as the study sample were given 20 mg of statins daily. Approximately how many CVD cases would be prevented in the 5 years following the start of statin usage, as compared to had the 200,000 healthy persons not been given statins?

The estimated risk difference (difference in proportions) of persons getting tested in the statins group compared to the control group is $\widehat{RD} = \hat{p}_{statins} - \hat{p}_{control} = 0.0167 - 0.0282 = -0.0115$ i.e., on the absolute scale 1.15% fewer persons developed CVD in the intervention group. This estimated can be applied to a community of a specific size to get an estimate of the (in this case) decreased number of outcomes (CVD) that would be expected if all were given statins: 0.0115*200,000 = 2300.

The following information is referenced in questions 9-10:

An article in *JAMA: Psychiatry*[1] presents the results of a randomized controlled trial of Paliperidone Palmitate (Treatment) compared to Placebo for preventing relapse in patients diagnosed with schizophrenia. Patients were followed for up to 500 days after randomization, until relapse or censoring.

The risk of relapse in the follow-up period is summarized by randomization group in the following Kaplan-Meier curve. The vertical dashes on each curve represent censoring times.



9. Based on the Kaplan-Meier curve, what is the approximate 20th percentile of the time-to-relapse distribution for subjects randomized to the placebo group?

    a. 20 days
    b. 400 days
    c. 110 days
    d. Percentiles cannot be estimated from a Kaplan-Meier curve

The proportion of patients remaining relapse free beyond 110 days in the placebo group is approximately 80%. As such approximately 20% of the sample relapsed within <= 110 days: as such, 110 days approximately corresponds to the 20th %ile of the time to relapse distribution.

1 Berwaerts J, et al. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia. JAMA Psychiatry. (2015) 72 (8).

10. In the Kaplan-Meier graph, why are the estimated curves for both groups (Treatment and Placebo) at 1 (100%) when time since randomization (the follow-up period) is 0 months?

    a. Because 100% of the subjects relapsed at 0 months of follow-up.
    b. Because 100% of the subjects were censored by the end of the study.
    c. Because the follow-up period is less than 2 years.
    d. Because all subjects followed in this study were event free (had not yet relapsed) at the beginning of the study