STA 723 HW03 **Zach White**

Executive Summary

We seek to understand whether or not chlorinated water is a risk factor for bladder cancer. We do this by performing a meta-analysis on the results from seven studies spanning from 1978-1988. Of the different ways to perform a meta-analysis, we compare fixed and random effects model. We use the inverse variance weight in our final model. We can conclude that the heterogeneity between the studies isn't significant, but the overall estimate is significant.

Introduction

We use seven different studies to analyze whether or not chlorinated water is a risk factor for bladder cancer. The studies of interest span from 1978-1988 from different principal investigators. Although the studies are adjusted for similar factors, the populations are from different parts of the United States. We are given an adjusted odds-ratio with their accompanying 95% confidence interval. We are also given the method used to obtain odds-ratio and an overall quality score. The following table shows most of the relevant information on our data.

Author	Year	Adj. OR	LCL	UCL	Method	Quality
Cantor	1987	1.19	1.07	1.32	Logistic	78
Zierler	1988	1.60	1.20	2.10	M-H	71
Wilkins	1986	2.20	.71	6.82	Logistic	61
Gottlieb	1982	1.18	0.95	1.45	Adj	49
Brenniman	1980	0.98	0.77	1.25	Adj	46
Young	1981	1.15	0.70	1.89	Logistic	45
Alvanja	1978	1.69	1.07	2.67	Adj	43

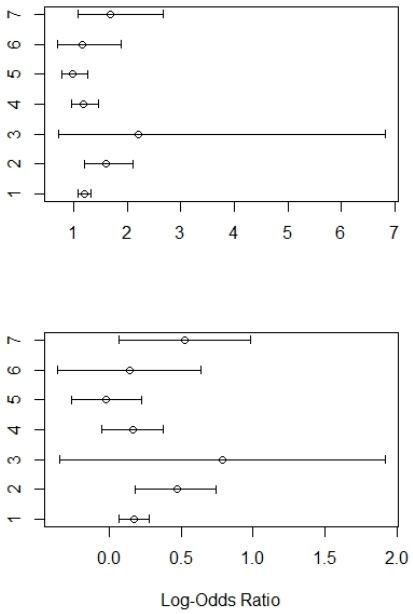
Another aspect of this analysis is to understand if these studies represent the same population or different populations. These studies might have been drawn from similar enough populations that they might be considered homogeneous, but they might also represent different populations. This will help us understand whether or not chlorinated water is a risk factor for the broader population or just certain some populations that are represented in this study. Also, our understanding of the data and our goals largely influence the type of meta-analysis we perform.

Analysis

Model Choice

The first thing to notice with these data is that the confidence intervals are asymmetric. We can suppose that this is because the data are in the odds scale. We propose a log transformation, and it is shown in the plots on the next page that the intervals become much more symmetric. We will continue in the log scale because although it is possible to meta-analysis in the odds-scale, it can be much more complex. Another important feature of the intervals is the varying lengths of the intervals, especially at the extremes. For example, Cantor's study has an 95% CI length of .21, while Wilkins has a length of 2.26. Also, although the intervals are estimating the same thing, the actual intervals seem to be different to some degree, which leads us to conclude that the studies may be estimating different populations.

We will discuss two possible models for this meta-analysis. The fist of which is fixed effect model which is characterized by $Y_i = \mu + \epsilon_i$ where $\epsilon_i \sim N(0, \sigma_i^2)$. In this case σ_i^2 represents variation within the studies, and we can calculate this based on the given confidence interval length. A common weighting technique under this model is the inverse weighting method, which means that $w_i = \frac{1}{\hat{\sigma}_i^2}$. Using this weighting method, studies with lower variance get the highest weight, while those with higher variance are down-weighted. The estimator used for μ is a weighted average of the given effects sizes and the inverse variance weights.



$$\mu_F = \frac{\sum_{i=1}^{N} w_i Y_i}{\sum_{i=1}^{N} w_i}$$

This variance of this estimator can be estimated as the inverse of the sum of the weights: $\text{Var}(\mu_F) = \frac{1}{\sum_{i=1}^{N} w_i}$. An assumption required for this model is that these studies come from a single homogeneous population or that these represent the population entirely. This assumption can be strong at times, and a way to counteract such a strong assumption is the random effects model.

The random effects model adds another level of variability into the model. So we can relax the assumption that all the studies come from a homogeneous population or that they represent the entire population. Under the random effects model, our model formulation is the following:

$$Y_i = \theta_i + \epsilon_i = \mu + \delta_i + \epsilon_i \qquad \theta_i = \mu + \delta_i$$
$$\delta_i \sim N(0, \tau^2) \qquad \epsilon_i \sim N(0, \sigma_i^2)$$

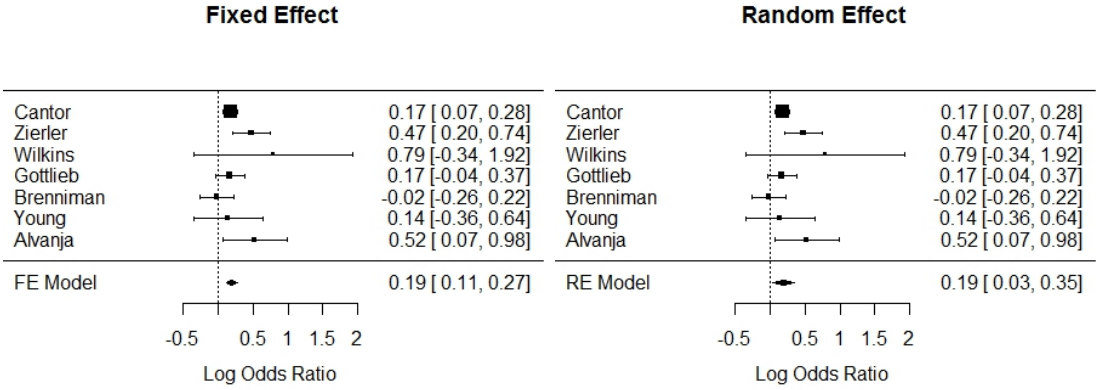
The connection to fixed effects is clear. The value σ_i^2 represents the variation within studies, and τ_2 represents the variation between studies. Thus, τ_2 is some measure heterogeneity of the studies. We use DerSimonian and Laird method test estimate the parameters.

$$\hat{\tau}^2 = \frac{Q - (N-1)}{S} \qquad Q = \sum_{i=1}^{N} w_i (Y_i - \hat{\mu}_F)^2$$
$$S = \sum_{i=1}^{N} w_i - \frac{\sum_{i=1}^{N} w_i^2}{\sum_{i=1}^{N} w_i}$$

If $Q < (N-1)$, then it is zero, and the random effects estimate is the fixed effect estimate. Using this methodology, the random effects model is building upon the fixed effect model, and we are adding another layer of variation, the variation between groups, which we need to estimate. This variation refers to the heterogeneity of the groups, and we can test to see if our estimate $\hat{\tau}^2$ is significant, which would indicate that populations of interest are different for the studies. Because the random effects model adds variation onto the fixed effect model, there will be more variation in the overall effect size estimate. This leads to wider confidence intervals, which will be seen in the results.

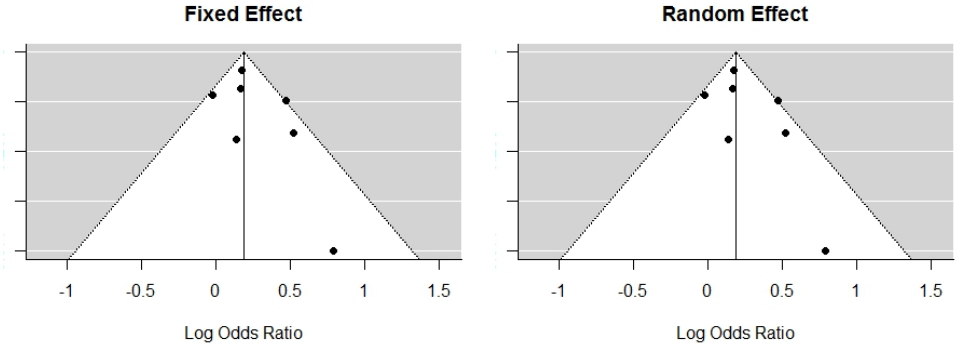
Results

We now discuss the estimates produced by both of the models. In the following plot, we can see the point estimate and confidence interval for all 7 of the studies. We can also see a visual representation of the weights for each of the studies. There is also the point estimate and interval for the overall estimate of the population log odds. It is



clear all the individual intervals and weights for the studies are the same. The highest weighted study is Cantor, and the lowest weighted study is Wilkins. Those should not change between random and fixed effect models. However, as expected, the lengths of the overall estimates are different. The confidence interval for fixed effect is (0.11,0.27), and for random effects, the confidence interval is (0.03,0.35). The random effects is clearly wider, but they are both above zero, which indicates that under both models, chlorinated water is a risk factor for bladder cancer. Under neither the fixed effect nor random effect is any measure of heterogeneity significant.

A bias that can occur in meta-analysis is publication, which is the idea that certain results are more likely to be published. We check this using a funnel plot, which is shown below. This plot shows the standard error by the log odds ratio, and it should look



symmetric. For the most part, it does. There is one point, which represents the Wilkins study, that isn't near the group, but it is still within the reasonable limit. Thus, this study is not of concern.

Conclusion

Under the fixed effect model, we are 95% confident that chlorinated water is associated with a 11.6 to 31% increase in odds of bladder cancer. Under the random effect model, we are 95% confident that chlorinated water is associated with a 3 to 41.9% increase in odds of bladder cancer. We also used different weighting mechanisms, but these change did not produce extreme changes in the results. But using different things for weights did obviously change the relative importance of different studies.