A Story of Confounding in a Randomized Design

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Motivation

The issue of confounding comes up over and over, and sometimes in very subtle ways. Papers which show the problem clearly are very valuable.

This talk is about a classical case of confounding which was exposed by a careful look at the data from a randomized, controlled clinical trial. The confounding was discovered by the investigators themselves.

Acknowledgment This talk is taken mainly from Chapter 2 of Freedman, Pisani, and Purves, *Statistics*.

My contributions:

► Obtained and read the original article on this study, in *New England Journal of Medicine*

► Made connections with STA 4211 course material

► Added an explanation of the statistical test for comparing two independent proportions

Setting: The Coronary Drug Project

The Coronary Drug Project was a randomized, controlled double-blind experiment, with the goal of evaluating five drugs for the prevention of heart attacks.

► Subjects: 8,341 middle-aged men with heart trouble
► Treatment: `Drug`, with five active drugs and a placebo (lactose)
► Randomization: 5,552 assigned at random to the five drug groups, and 2,789 to the control group
► Patients were followed for five years.
► Response variable: In this talk, we consider mortality (dead or alive, a binary variable)

This was a completely randomized design with one factor at six levels.

Response variable is not quantitative, and we need a method for comparing two binomial proportions.

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Clofibrate

One of the drugs on study was clofibrate, which reduces the level of cholesterol in the blood.

Results:

20% of the clofibrate group died during followup, compared to 21% of the placebo group.

Thus, clofibrate did not save any lives.

We have enough information to check statistical significance of the difference between 20% and 21%.

Hypothesis test comparing two proportions

Define parameters:

- ▶ Let p_P be the population proportion who would die in five years if given the placebo.
- ▶ Let p_T be the population proportion who would die in five years if given the drug clofibrate.

Hypotheses:

$H_0 : p_P - p_T = 0$ vs. $H_a : p_P - p_T \neq 0$

Test statistic:

$$z_{\text{obs}} = \frac{\hat{p}_P - \hat{p}_T}{\text{SE}(\hat{p}_P - \hat{p}_T)} = \frac{.209 - .20}{.0144} = .625$$

SE(*observed difference*) is found using the "pooled" estimate of the proportion, which is valid under H_0. (Details of the standard error calculation may be found in the paper.)

Null distribution is $\mathcal{N}(0, 1)$, $P = P(|Z| > .625) = .53$

Conclusion: The five-year mortality risk is equal in the Placebo and Treatment groups.

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Possible reason for ineffectiveness of clofibrate

In the clofibrate group of 1,103 men, only 708 or 64% adhered to protocol.

Adherence: Took at least 80% of the prescribed medicine

Table 1. The clofibrate trial. Numbers of subjects, and percentages who died during 5 years of followup. Adherers take 80% or more of prescription.

	Number	Deaths
Adherers	708	15%
Non-adherers	357	25%
Total group	1,103	20%

This looks like strong evidence that clofibrate is effective.

However, caution is in order.

Criticism of concluding that use of clofibrate decreases mortality

The comparison between adherers and non-adherers is observational, not experimental.

Consider the same comparison in the Placebo group.

Table 2.

| | Clofibrate | | Placebo | |
	Number	Deaths	Number	Deaths
Adherers	708	15%	1,813	15%
Non-adherers	357	25%	882	28%
Total group	1,103	20%	2,789	21%

Note: Data on adherence missing for 38 subjects in the clofibrate group and 94 in the placebo group. Deaths from all causes.

Source: The Coronary Drug Project Research Group, "Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project," *New England Journal of Medicine* vol. 303 (1980) pp.] 1038-41.

Conclusions (from Freedman, Pisani, and Purves)

(i) Clofibrate does not have an effect.

(ii) Adherers are different from non-adherers.

Probably, adherers are more concerned with their health and take better care of themselves in general. That would explain why they took their capsules and why they lived longer.

Important point

Observational comparisons can be quite misleading. The investigators in the clofibrate trial were unusually careful, and they found out what was wrong with comparing adherers to non-adherers.