Measurement, Design, and Analytic Techniques in Mental Health and Behavioral Sciences

Lecture 10 (April 30, 2009): Causal Inferences using Rubin's model

XH Andrew Zhou

azhou@u.washington.edu

Professor, Department of Biostatistics, University of Washington

Notation

- For subject i, observed data - Z_i, $D_i = D_i(Z_i)$, and $Y_i = Y_i(Z_i, D_i)$.
- Missing-data - $D_i(1 - Z_i)$ and $Y_i(1 - Z_i, D_i(1 - Z_i))$.
- Let $S(z, d)$ be the subset of patients with $Z_i = z$ and $D_i = d$.
- Let N_{zd} be the number of elements in $S(z, d)$ and r_{zd} be # of $Y_i = 1$ in $S(z, d)$.
- That is, the observed data:

$$N_{zd} = \sum_{i=1}^{N} I_{[Z_i=z, D_i=d]}, r_{zd} = \sum_{i=1}^{N} Y_i I_{[Z_i=z, D_i=d]}.$$

- Parameters

$$\eta_{zt} = P(Y_i(z, D_i(z)) = 1 \mid Z_i = z, C_i = t), \omega_t = P(C_i = t), \xi_z = P(Z_i = z),$$

where $z = 0, 1$ and $t = n, a, c, d$.

Issues of identifiability

- Degree of freedom in the observed data (forming a contingency table ($D \times Z \times Y$): $8 - 1 = 7$.
- Without monotonicity and exclusion restriction, # of parameters: 8+3+1=12.
- There are 5 parameters are not estimable from the data

Role of assumptions

- Under the monotonicity assumption, we have $\omega_d = 0$.
- In addition,
  - for $S(0,0)$ ($D_i(0) = 0$), patients can have either never-takers or compliers ($C_i = n$ or c).
  - For $S(1,0)$ ($D_i(1) = 0$), patients are never-takers ($C_i = n$)
  - For $S(1,1)$ ($D_i(1) = 1$), patients are always-takers or compliers ($C_i = a$ or c).
  - For $S(0,1)$, patients are always-takers ($C_i = a$).

Role of assumptions, cont

- Under the exclusion restriction assumption on all t, we have $\eta_{zt} = \eta_t$, $t = n, a, c$.
- Hence under both the monotonicity and exclusion restriction assumptions, the number of parameters is 3 + 2 +1=6.
- We only need to make the exclusion restriction assumption for $t = n$ and $t = a$. That is, $\eta_{zn} = \eta_n$ and $\eta_{za} = \eta_a$. Then, the number of parameters is 4+2+1=7.

Moment methods

- We first derive moment estimators for η_n and η_a.
- Note that the set that $Z_i = 1$ and $C_i = n$ is equivalent to the set that $Z_i = 1$ and $D_i = 0$ because of monotonicity assumption.
- Hence, we have

$$\eta_n = P(Y_i = 1 \mid Z_i = 1, C_i = n) = \frac{P(Y_i = 1, Z_i = 1, C_i = n)}{P(Z_i = 1, C_i = n)} =$$

$$\frac{P(Y_i = 1, Z_i = 1, D_i = 0, C_i = n)}{P(Z_i = 1, D_i = 0, C_i = n)} = \frac{P(Y_i = 1, Z_i = 1, D_i = 0)}{P(Z_i = 1, D_i = 0)}.$$

- Therefore, the moment estimators for η_n is

$$\widehat{\eta_n} = \frac{\sum_{i=1}^{N} Y_i Z_i (1 - D_i)}{\sum_{i=1}^{N} Z_i (1 - D_i)} = \frac{r_{10}}{N_{10}}.$$

- Similarly, we have

$$\eta_a = \frac{P(Y_i = 1, Z_i = 0, D_i = 1)}{P(Z_i = 0, D_i = 1)}.$$

Moment Estimators, cont

- Hence, the moment estimator for η_a is given by

$$\widehat{\eta}_a = \frac{\sum_{i=1}^{N} Y_i(1-Z_i)D_i}{\sum_{i=1}^{N}(1-Z_i)D_i} = \frac{r_{01}}{N_{01}}.$$

Moment estimators for ω_t

- We next derive moment estimators for ω_t.
- Because of randomization, we have that

$$\omega_n = P(C_i = n \mid Z_i = 1) = \frac{P(C_i = n, Z_i = 1, D_i = 0)}{P(Z_i = 1)} = \frac{P(Z_i = 1, D_i = 0)}{P(Z_i = 1)}.$$

- Hence, the moment estimator for ω_n is given by

$$\widehat{\omega}_n = \frac{\sum_{i=1}^N Z_i(1 - D_i)}{\sum_{i=1}^N Z_i}.$$

- Similarly, we obtain the following moment estimator for ω_a:

$$\widehat{\omega}_a = \frac{\sum_{i=1}^N (1 - Z_i)D_i}{\sum_{i=1}^N (1 - Z_i)}.$$

- The moment estimator for ω_c is given by

$$\widehat{\omega}_c = 1 - \widehat{\omega}_n - \widehat{\omega}_a.$$

Moment estimation - cont

- Next we derive moment estimators for outcome parameters in complier-type, η_{0c} and η_{1c}.
- Since $(Z_i = 0, D_i = 0) \equiv (Z_i = 0, D_i = 0, C_i = c) \cup (Z_i = 0, D_i = 0, C_i = n)$, we have that

$$P(Y_i = 1 \mid Z_i = 0, D_i = 0) =$$

$$P(Y_i = 1 \mid Z_i = 0, D_i = 0, C_i = n)P(C_i = n \mid Z_i = 0, D_i = 0) +$$

$$P(Y_i = 1 \mid Z_i = 0, D_i = 0, C_i = c)P(C_i = c \mid Z_i = 0, D_i = 0).$$

Note that

$$P(C_i = c \mid Z_i = 0, D_i = 0) = \frac{P(C_i = c, Z_i = 0, D_i = 0)}{\sum_{t=n,c} P(Z_i = 0, D_i = 0, C_i = t)} =$$

$$\frac{P(D_i = 0 \mid C_i = c, Z_i = 0)P(C_i = c)P(Z_i = 0)}{\sum_{t=n,c} P(D_i = 0 \mid Z_i = 0, C_i = t)P(C_i = t)P(Z_i = 0)} = \frac{\omega_c}{\omega_c + \omega_n}.$$

Moment Estimator, Cont

- And,

$$P(C_i = n \mid Z_i = 0, D_i = 0) = \frac{\omega_n}{\omega_c + \omega_n}.$$

- Hence

$$P(Y_i = 1 | Z_i = 0, D_i = 0) = \eta_n \frac{\omega_n}{\omega_c + \omega_n} + \eta_{0c} \frac{\omega_c}{\omega_c + \omega_n}.$$

- Similarly, we can show that

$$P(Y_i = 1 | Z_i = 1, D_i = 1) = \eta_a \frac{\omega_a}{\omega_c + \omega_a} + \eta_{1c} \frac{\omega_c}{\omega_c + \omega_a}.$$

Moment estimation - cont

- Hence by solving the above two equations for η_{0c} and η_{1c}, we obtain the moment estimators for η_{oc} and η_{1c} as follows:

$$\widehat{\eta}_{0c} = [\frac{\sum_{i=1}^{N} Y_i(1-Z_i)(1-D_i)}{\sum_{i=1}^{N}(1-Z_i)(1-D_i)} - \widehat{\eta}_n \frac{\widehat{\omega}_n}{\widehat{\omega}_c + \widehat{\omega}_n}]\frac{\widehat{\omega}_c + \widehat{\omega}_n}{\widehat{\omega}_c},$$

and

$$\widehat{\eta}_{1c} = [\frac{\sum_{i=1}^{N} Y_i Z_i D_i}{\sum_{i=1}^{N} Z_i D_i} - \widehat{\eta}_a \frac{\widehat{\omega}_a}{\widehat{\omega}_c + \widehat{\omega}_a}]\frac{\widehat{\omega}_c + \widehat{\omega}_a}{\widehat{\omega}_c}.$$

Vitamin example

- A randomized community trial of the impact of vitamin A supplements on children's survival (Sommer and Zeger, 1991).
- In this trial, villages in Indonesia were randomized assigned to receive or not to receive vitamin supplements.
- Although no subjects from the control group receive the supplements, a number of subjects assigned to the intervention group did not receive them.
- In this example, $D_i(0) = 0$ but $D_i(1) = 0$ or 1; hence monotonicity holds, and $\omega_a = \omega_d = 0$.

Sommer-Zeger vitamin supplement data

Type	Assignment $Z_{obs,i}$	Vitamin supplements $D_{obs,i}$	Survival $Y_{obs,i}$	Number of units (Total 23,682)
Complier or never-taker	0	0	0	74
Complier or never-taker	0	0	1	11,541
Never-taker	1	0	0	34
Never-taker	1	0	1	2,385
Complier	1	1	0	12
Complier	1	1	1	9,663

Results

- The estimate under the exclusion for CACE is 0.0032 with the 90% confidence interval of $(0.0012, 0.0051)$.

Estimating Efficacy of the AN1792 Vaccine for Alzheimer's Disease

- The May 1, 2005 issue of *Neurology* included two reports from a randomized trial of an experimental vaccine (AN1792) intended to benefit patients with Alzheimer's disease (AD).
- The vaccine was designed to provoke an antibody response to Aβ, the main protein constituent of amyloid plaques.
- Because preliminary studies had suggested that only about one-fourth of recipients would mount an antibody response to AN1792, eligible patients with mild to moderate AD were randomized in a 4:1 ratio to vaccine or placebo.

Estimating Efficacy of the AN1792 Vaccine for Alzheimer's Disease

- During the trial, 59 (20%) of 300 vaccine recipients actually developed an anti-AN1792 IgG titer of $\geq$1:2,200 and were called *responders*. The other 241 vaccine recipients were called *non-responders*.
- Anti-AN1792 titers were not measured in the 72 placebo recipients.
- The trial was stopped early after 6% of vaccine recipients developed meningoencephalitis.

Estimates of vaccine causal efficacy

- As shown in Figure 1, the vaccine group consists of two subgroups: patients who mount an antibody response to the vaccine (responders) and those who do not (non-responders).
- In the AN1792 trial, about 20% of vaccine recipients were responders. Now consider an outcome variable Y, such as a cognition score.
- Algebraically, among vaccine recipients, the mean value of Y for the group as a whole ($\overline{y}_{1\bullet}$) can be shown to be a 20:80 weighted average of the mean in responders ($\overline{y}_{1R}$) and the mean in non-responders ($\overline{y}_{1N}$).
- Likewise, the placebo group consists of two subgroups: patients who *would have* mounted an antibody response if they had received the active vaccine instead of placebo (potential responders), and those who *would not have* done so (potential non-responders). Say that p is the percentage of potential responders among placebo recipients. The overall mean value of Y among all placebo recipients ($\overline{y}_{0\bullet}$) is a $p : (100 - p)$ weighted average of the mean in potential responders ($\overline{y}_{0R}$) and the mean in potential non-responders ($\overline{y}_{0N}$).

Three Approaches

In assessing the effect of the vaccine on Y, three approaches can now be contrasted.

- Method A, the classic intent-to-treat approach, compares $\overline{y}_{1\bullet}$ with $\overline{y}_{0\bullet}$. Method A remains faithful to the randomized design, but if only 20% of vaccine recipients mount an antibody response to the vaccine, this method may seriously underestimate the effect of the vaccine among responders (“efficacy”).
- Method B, the approach used by the AN1792 trial investigators in an attempt to circumvent this problem, compares $\overline{y}_{1R}$ with $\overline{y}_{0\bullet}$. However, this comparison is vulnerable to confounding, because a non-random subset of one treatment group is compared to the entire other treatment group. Biological host factors, not random chance, determine whether a vaccine recipient has an antibody response. For example, in the AN1792 trial, whether a patient had 0, 1, or 2 copies of the APOE $\epsilon 4$ allele differed significantly between responders and non-responders [**?**]. Some of the biological factors associated with antibody response may also affect Y, leading to bias in the comparison.

Three Approaches

- Method C, the proposed approach, compares $\overline{y}_{1R}$ with $\overline{y}_{0R}$. Outcomes among responders in the vaccine group are compared with outcomes among patients in the placebo group *who would have responded to the vaccine if they had received it*. No test results are available to identify which specific patients in the placebo group are potential responders. However, because assignment to the vaccine and placebo groups is at random, it is safe to assume that the *percentage* of potential responders is approximately the same as the percentage of actual responders in the vaccine group. Moreover, if the underlying theory of vaccine action is correct, then for a patient who has (or would have) no antibody response to the vaccine, it does not matter whether he/she receives active vaccine or placebo. This motivates an assumption that $\overline{y}_{1N} \approx \overline{y}_{0N}$. With those assumptions, one can solve for $\overline{y}_{1R} - \overline{y}_{0R}$, a measure of efficacy, indirectly.

Formal arguments

- Let $R(D) = k$ designate the antibody response status ($k = 1$ if an antibody response, 0 if not) of a particular patient if he/she were to receive treatment D ($D = 1$ for vaccine, 0 for placebo). Each person has both an $R(1)$ value and an $R(0)$ value, although only one of them is observed during the trial.
- Each patient thus falls into one of four possible types, as follows:

Type	$R(0)$	$R(1)$
A	0	0
B	0	1
C	1	0
D	1	1

Four types

- Patients in type A would not respond to either vaccine or placebo.
- Patients in type B would respond only to vaccine.
- Patients in type C would respond (perversely) only to placebo.
- Patients in type D would respond indiscriminately to both placebo and vaccine.
- Note that types C and D consist of persons who, upon receiving placebo, nonetheless spontaneously develop antibody to a vaccine to which they have not been exposed. On biological grounds, types C and D should be very rare, if they exist at all.

Formal arguments, cont

- Now let π_j be the prevalence of type j, such that $\pi_A + \pi_B + \pi_C + \pi_D = 1$.
- By the above argument, we assume *a priori* that $\pi_C = \pi_D = 0$.
- Also let μ_{ij} be the expected value of a continuous outcome variable Y among patients who receive treatment i and who belong to type j.
- The expected values of Y in the two randomized groups, $\mu_{1\bullet}$ and $\mu_{0\bullet}$, can thus be written as:

$$\mu_{1\bullet} = \pi_A \mu_{1A} + \pi_B \mu_{1B} \quad (1)$$

$$\mu_{0\bullet} = \pi_A \mu_{0A} + \pi_B \mu_{0B} \quad (2)$$

- We now make the further simplifying assumption that $\mu_{1A} = \mu_{0A}$. If an antibody response is necessary for the vaccine to influence Y, then among persons who mount no such response regardless of what they receive, Y should be unaffected by whether they receive vaccine or placebo.

Formal arguments, cont

- Under this assumption, the first terms of (1) and (2) are equal.
- Subtracting (2) from (1) and solving for $\mu_{1B} - \mu_{0B}$ yields:

$$\mu_{1B} - \mu_{0B} = (\mu_{1\bullet} - \mu_{0\bullet})/\pi_B \tag{3}$$

- The left side of (3) is the proposed measure of efficacy. From study data, using the notation in Figure 1, it can be estimated as $(\overline{y}_{1\bullet} - \overline{y}_{0\bullet})/p_r$, where p_r is the observed proportion of responders in the vaccine group.

Relations to other approaches

- This approach is closely related to estimators of efficacy proposed for clinical trials with non-compliance, or for trials involving switching of patients between intended treatment regimens.
- The same result can be obtained by regarding treatment-group assignment as an instrumental variable in assessing the effect of antibody response on outcome.

An example

- All three methods were applied to results published from the AN1792 trial concerning the ventricular volume boundary shift integral (BSI), a measure of cerebral atrophy.
  item BSI represents the increase in ventricular volume between baseline and follow-up MRI examinations, expressed as a percentage of whole brain volume.
- Higher BSI values thus imply more rapid cerebral atrophy.
- Contrary to the hypothesis of the AN1792 trial, mean BSI was found to be *greater* in all vaccine recipients (0.64 ± 0.55 [mean $\pm$ SD], $n = 228$), and in the vaccine responder subgroup ($1.10 \pm 0.75, n = 45$), than in placebo recipients ($0.48 \pm 0.40, n = 56$).
- (Sample sizes differ slightly from those stated earlier due to missing MRI data.)
- However, the investigators speculated that some of the reduction in cerebral volume may have been due to removal of amyloid itself from brain parenchyma.