An introduction to covariate adjustment in trials

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Preliminaries

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References to papers / web pages are given as red hyperlinks.

These slides are available at https://thestatsgeek.com.

Outline

Randomised trials - marginal estimands and unadjusted analyses

Before talking about covariate adjustment, let's first briefly consider trial analyses that do not adjust for any baseline covariates.

For simplicity, let Y for now be a continuous outcome variable.

Let *trt* denote binary randomised treatment variable, taking values 0 (control) and 1 (active).

A standard unadjusted analysis would be a two-sample t-test, comparing randomised groups. This estimates

$$E(Y|trt = 1) - E(Y|trt = 0)$$

Unadjusted analyses - what's the estimand?

Because of randomisation $E(Y|trt = 0) = E(Y^0)$ and $E(Y|trt = 1) = E(Y^1)$, where Y^0 and Y^1 are the *potential outcomes* for a given patient under control and active treatment respectively.

$E(Y^0)$ and $E(Y^1)$ are the mean outcomes were we to assign everyone to control / active treatment respectively.

So the two-sample t-test is estimating the **marginal effect**

$$E(Y^1) - E(Y^0)$$

This is also equal to the average of the **individual level effects**

$$E(Y^1 - Y^0)$$

but this is not generally true...

Binary outcome case

Now suppose Y is binary, and we choose to use the risk ratio to measure the treatment effect.

To estimate the risk ratio we calculate the risk/proportion with $Y = 1$ in each group and take their ratio. This estimates

$$\frac{E(Y^1)}{E(Y^0)}$$

This is a **marginal effect**.

It is **not** an average of individual level risk ratio effects...

Individual treatment effects

Suppose for a given individual, $Y^0 = 0$ and $Y^1 = 0$, so treatment has no effect for this individual.

The risk difference is zero (this is fine).

The risk/probability of the event is then 0 under both treatments.

The **risk ratio is undefined**, since it is $\frac{0}{0}$.

The **odds ratio is similarly undefined**, since the odds of the event under each treatment is $0/1 = 0$, and so the odds ratio is $0/0$.

I am assuming deterministic potential outcomes / counterfactuals. You might consider them to be inherently stochastic - see Technical Point 1.2 of Hernán and Robins' book.

Outline

Why adjust for covariates?

For marginal effects/estimands, there is no need to adjust for covariates for validity of effect estimates.

Why might we adjust for covariates:

- to obtain more precise effect estimates / more statistical power to reject null
- to realise (in the SE and p-value) the gain afforded by use of stratified randomisation
- to estimate an estimand/effect measure that is deemed more useful/relevant
- to make missing data assumptions (e.g. MAR) more plausible

Improved precision / power gain

Randomisation balances distribution of baseline variables (measured and unmeasured) which may influence outcome **on average**.

But by chance, covariates will have some imbalance between randomised groups.

In imaginary repeated trials, such chance imbalances contribute to variability in effect estimates.

Covariate adjustment adjusts the effect estimate to account for whatever chance imbalance does occur (in those variables adjusted for), reducing uncertainty in effect estimate (and thereby **increasing power**).

Methods for covariate adjustment

Let X be a binary baseline covariate (e.g. sex) we want to adjust for.

There are various methods of covariate adjustment, including:

- outcome regression (direct adjustment), adjusting for *trt* and X as covariates
- standardisation / G-formula
- inverse probability of treatment weighting (Tim Morris will talk about this)

Outline

Outcome regression / direct adjustment

We fit a suitable regression model for Y, with *trt* and X as covariates.

We report the coefficient of *trt* as our treatment effect estimate.

This coefficient generally represents **the conditional effect** of treatment, within strata defined by X.

Linear models

Let's start with the case of continuous Y, modelled by linear regression:

$$Y_i = \beta_0 + \beta_1 trt_i + \beta_2 X_i + \epsilon_i$$

$\hat{\beta}_1$ estimates the effect of *trt* conditional on X.

Here this is $E(Y^1|X = x) - E(Y^0|X = x)$, for $x = 0$, or for $x = 1$.

But this can hold only if effect of treatment on mean outcome is the same for $X = 0$ as for $X = 1$ patients.

For example, if treatment is a blood pressure reducing treatment, there is no reason why treatment will reduce blood pressure on average by the same amount in males and as in females.

Linear models - special properties to the rescue!

Fortunately, it turns out that $\hat{\beta}_1$ estimates $E(Y^1) - E(Y^0)$, the marginal estimand defined earlier.

This holds even if our model assumptions are not 100% correct.

E.g. even if
$E(Y^1|X = 1) - E(Y^0|X = 1) \neq E(Y^1|X = 0) - E(Y^0|X = 0)$.

$\hat{\beta}_1$ is a more precise estimator compared to the mean difference in outcomes unadjusted for X.

And rather amazingly, the model based SEs are valid even under model misspecification, unless the randomisation is not 1:1.

Binary outcomes

Suppose now that Y is binary. The default model choice is logistic regression:

$$\text{logit}P(Y_i = 1|trt_i, X_i) = \beta_0 + \beta_1 trt_i + \beta_2 X_i$$

so that

$$P(Y_i = 1|trt_i, X_i) = \text{expit}(\beta_0 + \beta_1 trt_i + \beta_2 X_i)$$

e^{β_1} is the odds ratio for treatment effect. It is a **conditional effect/estimand**, conditional on X.

But what does this mean?

Example table from FDA guidance

Success proportions by sex and treatment:

	% of pop.	New trt.	Placebo	Odds ratio
Males	50%	80%	33.3%	8.0
Females	50%	25%	4%	8.0
Combined	100%	52.5%	18.7%	4.8

Here $e^{\beta_1} = 8$.

It is the odds ratio considering just the sub-population of males, or here, equivalently, the odds ratio considering only females.

Effect modification

Suppose instead:

	% of pop.	New trt.	Placebo	Odds ratio
Males	50%	80%	33.3%	8.0
Females	50%	25%	**8%**	**3.8**
Combined	100%	52.5%	20.7 %	4.2

We have **effect modification** on the odds ratio scale.

Our logistic regression will estimate an average of the two sex specific conditional odds ratios.

We will (wrongly) interpret this average as the common effect of treatment on males and females.

Outline

Standardisation / G-formula / G-computation

The FDA covariate adjustment guidance described a standardisation method for binary outcomes:

1. fit logistic regression model for $P(Y = 1|trt, X)$:

$$\text{logit}P(Y_i = 1|trt_i, X_i) = \beta_0 + \beta_1 trt_i + \beta_2 X_i$$

2. estimate $E(Y^0)$ by $\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\hat{\beta}_0 + \hat{\beta}_2 X_i)$
3. estimate $E(Y^1)$ by $\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 X_i)$
4. these can then be used to estimate marginal effects, e.g. risk difference, risk ratio, odds ratio

See slide in Appendix for justification of this procedure.

Standardisation - robustness

For normal linear regression, logistic regression, Poisson regression (canonical link GLMs), this standardisation estimator is (in large trials) unbiased even if the model is not correctly specified.

This is a rather remarkable property.

It also confers a robustness property for testing the null hypothesis.

For other types of models, estimators of marginal effects can be constructed which are guaranteed unbiased even if outcome model is misspecified.

Outline

Stratified randomisation

Stratified randomisation avoids chance imbalance between treatment groups in respect of selected baseline covariates.

It is well known that if you use stratified randomisation, you must adjust for stratification variables in the analysis to realise power gains in p-values and CIs.

Recent results have shown that with large sample sizes, if analysis adjusts for randomisation strata via indicator variables, stratified randomisation does not increase power, if either

- randomisation is 1:1, **or**
- covariate adjusted model is correctly specified

Outline

Conclusions

- There is (rightfully) an ongoing debate about whether trials should target marginal or conditional effects/estimands
- Considerations include which effect(s) is most relevant to patients/clinicians/payers, and which can be robustly estimated using pre-specified statistical analysis?
- Covariates can be used to improve power when estimating marginal, as well as conditional effects (e.g. via standardisation method)
- In large trials with 1:1 randomisation, stratified randomisation may not be worth the effort

Outline

Standardisation - why does it work?

$$
\begin{aligned}
E(Y^0) &= E(Y^0|trt = 0) \text{ since } trt \perp\!\!\!\perp Y^0 \\
&= E(Y|trt = 0) \text{ since } Y = Y^0 \text{ when } trt = 0 \\
&= E(E(Y|trt = 0, X)|trt = 0) \text{ by law of total expectation} \\
&= E(E(Y|trt = 0, X)) \text{ since } X \perp\!\!\!\perp trt
\end{aligned}
$$

and similarly for $E(Y^1)$.

In the last line, we are averaging the expected value of Y under treatment level 0 at covariate value X across the distribution of X across all patients (not just those with $trt = 0$) in the trial.