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crtrest: A command for ratio estimators of intervention effects on event rates in cluster randomized trials

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Abstract. We describe five asymptotically unbiased estimators of intervention effects on event rates in nonmatched and matched-pair cluster randomized trials, and we present a bias-corrected version of the estimators for use when the number of clusters is small. The estimators are the ratio of mean counts (r_1), ratio of mean cluster-level event rates (r_2), ratio of event rates (r_3), double ratio of counts (r_4), and double ratio of event rates (r_5). r_1, r_2, and r_3 estimate the total effect, which comprises the direct and indirect effects; r_4 and r_5 estimate the direct effect. We describe a new command, `crtrest`, that provides these ratio estimators and their standard errors in nonmatched and matched-pair cluster randomized trials.

Keywords: st0695, crtrest, ratio estimator, intervention effects, event rate, cluster randomized trial

1 Introduction

The cluster randomized trial (CRT) is an important study design in health and social science as well as in program evaluation (Hayes and Moulton 2017; Donner and Klar 2000; Imai, King, and Nall 2009). A CRT randomizes clusters of individuals to receive different interventions. The clusters may be residential communities, schools, families, and so on, depending on context. All individuals in the same cluster are assigned to receive the same intervention. The simple form of CRTs, which we refer to as nonmatched CRTs, randomizes each cluster independently. In contrast, the matched-pair CRT design

begins with identifying pairs of clusters similar in features, such as disease incidence in previous years and socioeconomic characteristics. Then, within each pair of clusters, one cluster is randomized to receive the intervention, and the other receives the alternative. There are various situations when a CRT is preferred. One example is when a trial that randomizes individuals carries a significant risk of "contamination", meaning individuals assigned not to receive an intervention may actually adopt the intervention as they are influenced by individuals in their proximity who are allocated to receive it, or vice versa.

Data on outcome events may be collected by passive or active surveillance systems. The advantage of passive surveillance is that the monetary and opportunity cost of data collection tends to be lower, making it a popular choice for research in low-to-middle-income countries (Dron et al. 2021). Passive surveillance methods often determine only the number of events in a cluster without identifying which individuals in the cluster experienced the events (Dufault and Jewell 2020). Thus, data analysis is at the cluster level (Hayes and Moulton 2017). That is, clusters are the units of analysis.

The denominator for calculating event rates is the amount of person-time, which is sometimes approximated by the population size at midpoint of the trial duration. The collection of person-time data requires extra operations and resources, such as a demographic surveillance system or rounds of community surveys. These data may or may not be available in CRTs that use passive surveillance to enumerate the outcome events (Dufault and Jewell 2020). The analytic methods have to adapt accordingly.

An intervention may offer a direct effect and an indirect effect on event rates. The latter may be via, for example, reducing disease transmission in the community (Dron et al. 2021; Halloran, Longini, and Struchiner 2010). In CRTs, it is common that only a specific group of the cluster members is eligible to receive the intervention or its control comparator. For example, in trials of vaccines for prevention of pediatric infectious diseases, usually only young children in a specific age range are eligible; older children or adults are not eligible. We refer to them as the target and nontarget groups, respectively. While only the target group can benefit from the intervention's direct effect, both groups may benefit from the indirect effect, if any. The total effect that benefits the target group comprises the direct and indirect effects. Popular estimators of intervention effects on event rates in the CRT literature mainly concern the estimation of the total effect (Ma et al. 2022).

We recently reviewed and evaluated two conventional estimators of incidence-rate ratio (IRR) for cluster-level analysis of CRTs (Ma et al. 2022). We proposed and evaluated three new estimators, two of which are estimators of the direct effect and are more powerful than the conventional estimators in the absence of indirect effect if there is a high level of heterogeneity between clusters. All five estimators are asymptotically unbiased. Because CRTs often involve only a handful of clusters per trial arm, we derived a bias-corrected version of each of the five estimators that we called approximately unbiased estimators.

In this article, we introduce the command `crtrest`, which stands for CRT ratio estimators. It implements all the aforementioned ratio estimators in Stata. Section 2 describes the estimators. Section 3 presents the `crtrest` syntax. Section 4 provides two examples, one for nonmatched CRT and the other for matched-pair CRT, to illustrate the command.

2 Ratio estimators

Suppose there is a sample dataset of $\{y_{ijk}, p_{ijk} : j = 1, 2, \ldots, n_i;\ i = 0, 1;\ k = 0, 1\}$ from a nonmatched CRT, where y_{ijk} and p_{ijk} are the number of events and person-time, respectively, in the kth group of the jth cluster in the ith trial arm in the population; $k = 1$ and 0 represent the target and nontarget groups, respectively; and $i = 1$ and 0 represent intervention and control trial arms, respectively. For matched-pair CRTs, suppose there are n pairs of clusters ($n_1 = n_0 = n$). Within the jth pair of clusters, one cluster is randomized to receive intervention ($i = 1$) and the other is the control cluster ($i = 0$). The sample dataset additionally contains a matched-pair identifier.

For nonmatched or matched-pair CRTs, define $\overline{y}_i = (\sum_{j=1}^{n_i} y_{ij1})/n_i$, $c_{ij} = y_{ij1}/p_{ij1}$, $\overline{c}_i = (\sum_{j=1}^{n_i} c_{ij})/n_i$, $R_i = (\sum_{j=1}^{n_i} y_{ij1})/(\sum_{j=1}^{n_i} p_{ij1})$, $R_i^* = (\sum_{j=1}^{n_i} y_{ij1})/(\sum_{j=1}^{n_i} y_{ij0})$, $R'_{ik} = (\sum_{j=1}^{n_i} y_{ijk})/(\sum_{j=1}^{n_i} p_{ijk})$, and $R_i^\dagger = (R'_{i1})/(R'_{i0})$ for $i = 0, 1;\ k, = 0, 1$, where $\overline{y}_i$ is the arithmetic mean of the number of outcome events in the target group in the ith trial arm; c_{ij} is the cluster-level event rate in the target group of the jth cluster in the ith trial arm and $\overline{c}_i$ is the arithmetic mean of c_{ij}; R_i^* is the ratio of event counts in the target and nontarget groups in the ith trial arm; R'_{ik} is a ratio estimate of the event rate for the kth group in the ith trial arm; and $R_i^\dagger$ is the ratio of event-rate estimates in the target and nontarget groups in the ith trial arm. Note that $R_i = R'_{i1}$.

For brevity, in section 2 we focus on nonmatched CRTs and only briefly mention matched-pair CRTs. Details on the estimators for matched-pair CRTs and on the derivations and analytic and simulation evaluation of all the estimators can be found in Ma et al. (2022).

2.1 Asymptotically unbiased estimators

In this section, we describe the asymptotically unbiased estimators and their key features. The estimators for nonmatched CRTs, r_l ($l = 1, 2, 3, 4, 5$), are shown in statistical notation in table 1. r_1, r_2, and r_3 estimate the total effect of the intervention, while r_4 and r_5 estimate the direct effect.

Table 1. Estimators of IRR for nonmatched CRTs

Estimators	Definition
Ratio of mean counts	$r_1 = \dfrac{\overline{y}_1}{\overline{y}_0} = \dfrac{\sum_{j=1}^{n_1} y_{1j1}/n_1}{\sum_{j=1}^{n_0} y_{0j1}/n_0}$
Ratio of mean cluster-level event rate	$r_2 = \dfrac{\overline{c}_1}{\overline{c}_0} = \dfrac{\sum_{j=1}^{n_1} c_{1j}/n_1}{\sum_{j=1}^{n_0} c_{0j}/n_0}$
Ratio of event rates	$r_3 = \dfrac{R_1}{R_0} = \dfrac{\sum_{j=1}^{n_1} y_{1j1}/\sum_{j=1}^{n_1} p_{1j1}}{\sum_{j=1}^{n_0} y_{0j1}/\sum_{j=1}^{n_0} p_{0j1}}$
Double ratio of counts	$r_4 = \dfrac{R_1^*}{R_0^*} = \dfrac{\sum_{j=1}^{n_1} y_{1j1}/\sum_{j=1}^{n_1} y_{1j0}}{\sum_{j=1}^{n_0} y_{0j1}/\sum_{j=1}^{n_0} y_{0j0}}$
Double ratio of event rates	$r_5 = \dfrac{R_1^\dagger}{R_0^\dagger} = \dfrac{\left(\frac{\sum_{j=1}^{n_1} y_{1j1}}{\sum_{j=1}^{n_1} p_{1j1}}\right) / \left(\frac{\sum_{j=1}^{n_1} y_{1j0}}{\sum_{j=1}^{n_1} p_{1j0}}\right)}{\left(\frac{\sum_{j=1}^{n_0} y_{0j1}}{\sum_{j=1}^{n_0} p_{0j1}}\right) / \left(\frac{\sum_{j=1}^{n_0} y_{0j0}}{\sum_{j=1}^{n_0} p_{0j0}}\right)}$

An estimator of the intervention effect in terms of IRR that uses only event data is the "ratio of mean counts" (Dufault and Jewell 2020), denoted by r_1. It is the ratio of the arithmetic mean of the number of outcome events per cluster in the intervention arm to that in the control arm. Despite its simplicity, simulation experiments have shown that r_1 performs and compares well with the two estimators that follow (r_2 and r_3) in terms of relative bias, coverage probability, and power, provided that the number of clusters per trial arm is approximately 30 or higher.

The amount of person-time is usually variable across clusters in CRTs. Typical statistical practice compares event rates instead of mean number of events between trial arms. If both the number of events and the person-time are collected for each cluster, one may calculate c_{ij}, an estimate of cluster-level event rate, for each cluster. A popular estimator of the IRR in the CRT literature is the ratio of the arithmetic mean of the cluster-level event-rate estimates for the intervention arm to that for the control arm, r_2, as defined in table 1 (Hayes and Moulton 2017; Bennett et al. 2002; Pacheco et al. 2009).

In contrast to the CRT literature, the survey sampling literature does not recommend using $\overline{c}_i$ to estimate a ratio, because it is known to be biased (Cochran 1977). The survey sampling literature leads to the estimation of the event rate (in each trial arm) as the sum of the number of events divided by the sum of person-time over the clusters (in that trial arm), which is asymptotically unbiased (Cochran 1977). Then an alternative estimator of IRR is the ratio of these event-rate estimates between the trial arms. We call this the "ratio of event rates", denoted by r_3 (table 1).

In passive surveillance, the event data may be enumerated for the nontarget group in addition to the target group at a small additional cost because the capital cost is already invested for the target group. We proposed an estimator called the "double ratio of counts", denoted by r_4, by replacing the sums of person-time in r_3 with the sums of the numbers of events in the nontarget groups (table 1). This estimator is defined even if the number of events in the nontarget group is zero in some clusters, which is a realistic situation because the reason that the group is not targeted by the intervention is usually that it has a relatively low-disease incidence rate. Because both the target and the nontarget groups may be affected by the indirect effect of an intervention, the estimator cancels this out and estimates only the direct effect. The contrast of the target and nontarget groups within each cluster reduces the noise arising from heterogeneity between clusters. If there is no indirect effect or only a trivial indirect effect, r_4 is more precise (smaller standard error) and more powerful than r_2 and r_3 when the heterogeneity between clusters is large (Ma et al. 2022). If a nontrivial indirect effect is present, the point estimates are not comparable, but the absolute values of the test statistics, $|t(r_l)|$, for $l = 2$, 3, or 4 are still comparable in that they all indicate the probability of rejecting the null hypothesis of the target ratio being 1. In general, the larger the correlation between the number of events in the target and nontarget group, $\text{corr}(y_{ij1}, y_{ij0})$, compared with the correlation between the number of events and person-time in the target group, $\text{corr}(y_{ij1}, p_{ij1})$, the more powerful r_4 is compared with r_2 and r_3. This condition may occur in, for example, diseases like malaria that are highly influenced by environmental factors.

We also proposed a new estimator called the "double ratio of event rates", denoted by r_5. It has the ratio of event rates between the target and nontarget groups in the intervention arm as the numerator and its counterpart in the control arm as the denominator (table 1). This tends to be more precise and powerful than r_4, at the cost of demanding more data inputs.

Asymptotically unbiased estimators for matched-pair CRTs, $r_l^{\text{paired}} (l = 1, 2, 3, 4, 5)$, are defined similarly (Ma et al. 2022).

2.2 Approximately unbiased estimators

The survey sampling literature about bias in ratio estimators and the mitigation methods was very much focused on paired observations and on estimators in the form of r_1^{paired}, r_3^{paired}, and r_4^{paired} (Cochran 1977; Durbin 1959; Rao and Pereira 1968). These previous works showed that the estimators have a bias of order n^{-1}. The CRT literature has mainly focused on r_2. Its degree of bias appeared to depend on not only the number of clusters but also the coefficient of variation of the cluster-level event rate, $\text{CV}(c_{ij})$ (Bennett et al. 2002; Pacheco et al. 2009). Previous simulation studies appeared to have limited the degree of heterogeneity between clusters to a range that is too small to be realistic (Ma et al. 2022). The number of clusters per trial arm is highly variable in CRTs, ranging from a few to hundreds. We therefore proposed a bias-corrected version for each of the aforementioned estimators so that they can be applied widely. The general approach is to determine the expectation and therefore bias of a ratio estimator

and then subtract the bias from the estimator to provide a bias-corrected version of the estimator (Rao and Pereira 1968; van Kempen and van Vliet 2000). We refer to this version as an "approximately unbiased estimator". The approximately unbiased estimators r_1^* to r_5^* that correspond to the asymptotically unbiased estimators r_1 to r_5, respectively, are

$$
\begin{aligned}
r_1^* &= r_1 \left\{ 1 - \frac{1}{n_0} \mathrm{CV}^2(y_{0j1}) \right\} \\
r_2^* &= r_2 \left\{ 1 - \frac{1}{n_0} \mathrm{CV}^2(c_{0j}) \right\} \\
r_3^* &= r_3 \left\{ 1 + \frac{1}{n_1} \mathrm{CV}(y_{1j1}) \mathrm{CV}(p_{1j1}) \mathrm{corr}(y_{1j1}, p_{1j1}) \right. \\
&\quad \left. + \frac{1}{n_0} \mathrm{CV}(y_{0j1}) \mathrm{CV}(p_{0j1}) \mathrm{corr}(y_{0j1}, p_{0j1}) - \frac{1}{n_0} \mathrm{CV}^2(y_{0j1}) - \frac{1}{n_1} \mathrm{CV}^2(p_{1j1}) \right\} \\
r_4^* &= r_4 \left\{ 1 + \frac{1}{n_1} \mathrm{CV}(y_{1j1}) \mathrm{CV}(y_{1j0}) \mathrm{corr}(y_{1j1}, y_{1j0}) \right. \\
&\quad \left. + \frac{1}{n_0} \mathrm{CV}(y_{0j1}) \mathrm{CV}(y_{0j0}) \mathrm{corr}(y_{0j1}, y_{0j0}) - \frac{1}{n_0} \mathrm{CV}^2(y_{0j1}) - \frac{1}{n_1} \mathrm{CV}^2(y_{1j0}) \right\} \\
r_5^* &= r_5 \left(1 + \sum_{i=0}^{1} \left[\frac{1}{n_i} \left\{ \mathrm{CV}(y_{ij1}) \mathrm{CV}(y_{ij0}) \mathrm{corr}(y_{ij1}, y_{ij0}) \right. \right. \right. \\
&\quad \left. + \mathrm{CV}(p_{ij1}) \mathrm{CV}(p_{ij0}) \mathrm{corr}(p_{ij1}, p_{ij0}) \right\} \\
&\quad \left. + \sum_{k=0}^{1} \sum_{k'=0}^{1} \frac{(-1)^{k+k'}}{n_i} \mathrm{CV}(y_{ijk}) \mathrm{CV}(p_{ijk'}) \mathrm{corr}(y_{ijk}, p_{ijk'}) \right] - \frac{1}{n_0} \mathrm{CV}^2(y_{0j1}) \\
&\quad \left. - \frac{1}{n_0} \mathrm{CV}^2(p_{0j0}) - \frac{1}{n_1} \mathrm{CV}^2(y_{1j0}) - \frac{1}{n_1} \mathrm{CV}^2(p_{1j1}) \right)
\end{aligned}
$$

Their counterparts for matched-pair CRTs can be found in Ma et al. (2022).

2.3 Variances and confidence intervals

In Ma et al. (2022), we showed that $\mathrm{Var}(r_l^*) = \mathrm{Var}(r_l)$ for $l = 1, 2, 3, 4$, and 5. This equality between the variances of the approximately unbiased estimators and asymptotically unbiased estimators also holds for the estimators for matched-pair CRTs. In nonmatched CRTs, the variances of r_1 to r_5 are, respectively,

$$\mathrm{Var}(r_1) = \left(\frac{\overline{y}_1}{\overline{y}_0}\right)^2 \left\{\frac{\mathrm{CV}^2(y_{1j1})}{n_1} + \frac{\mathrm{CV}^2(y_{0j1})}{n_0}\right\}$$
$$\mathrm{Var}(r_2) = \left(\frac{\overline{c}_1}{\overline{c}_0}\right)^2 \left\{\frac{\mathrm{Var}(c_{1j})}{n_1\overline{c}_1^2} + \frac{\mathrm{Var}(c_{0j})}{n_0\overline{c}_0^2}\right\}$$
$$\mathrm{Var}(r_3) = \left(\frac{R_1}{R_0}\right)^2 \left\{\frac{\mathrm{Var}(R_1)}{R_1^2} + \frac{\mathrm{Var}(R_0)}{R_0^2}\right\}$$
$$\mathrm{Var}(r_4) = \left(\frac{R_1^*}{R_0^*}\right)^2 \left\{\frac{\mathrm{Var}(R_1^*)}{R_1^{*2}} + \frac{\mathrm{Var}(R_0^*)}{R_0^{*2}}\right\}$$
$$\mathrm{Var}(r_5) = \left(\frac{R_1^\dagger}{R_0^\dagger}\right)^2 \left\{\frac{\mathrm{Var}(R_1^\dagger)}{R_1^{\dagger 2}} + \frac{\mathrm{Var}(R_0^\dagger)}{R_0^{\dagger 2}}\right\}$$

where $\mathrm{Var}(R_i^*) = (R_i^{*2}/n_i)\{\mathrm{CV}^2(y_{ij1}) + \mathrm{CV}^2(y_{ij0}) - 2\mathrm{CV}(y_{ij1})\mathrm{CV}(y_{ij0})\mathrm{corr}(y_{ij1}, y_{ij0})\}$,

$$\mathrm{Var}(R_i) = \mathrm{Var}(R'_{i1})$$
$$\mathrm{Var}(R'_{ik}) = \frac{R'^2_{ik}}{n_i}\{\mathrm{CV}^2(y_{ijk}) + \mathrm{CV}^2(p_{ijk}) - 2\mathrm{CV}(y_{ijk})\mathrm{CV}(p_{ijk})\mathrm{corr}(y_{ijk}, p_{ijk})\}$$
$$\mathrm{Var}(R_i^\dagger) = R_i^{\dagger 2}\left\{\frac{\mathrm{Var}(R'_{i1})}{R'^2_{i1}} + \frac{\mathrm{Var}(R'_{i0})}{R'^2_{i0}} - \frac{2\mathrm{cov}(R'_{i1}, R'_{i0})}{R'_{i1}R'_{i0}}\right\}$$
$$\mathrm{cov}(R'_{i1}, R'_{i0}) = \frac{1}{n_i\overline{p}_{i\cdot 1}\overline{p}_{i\cdot 0}}\{\mathrm{cov}(y_{ij1}, y_{ij0}) + R'_{i1}R'_{i0}\mathrm{cov}(p_{ij1}, p_{ij0}) - R'_{i0}\mathrm{cov}(y_{ij1}, p_{ij0}) - R'_{i1}\mathrm{cov}(y_{ij0}, p_{ij1})\}$$
$$\overline{p}_{i\cdot k} = \sum_{j=1}^{n_i} p_{ijk}/n_i, \quad i = 0, 1; \quad k = 0, 1$$

For matched-pair CRTs, the formulas for each $\mathrm{Var}(r_l^{\mathrm{paired}})$, l = 1, 2, 3, 4, and 5, involves subtraction of a (scaled) covariance term; see Ma et al. (2022). Because the matched-pair design tends to generate positive covariances of the relevant quantities, it tends to provide smaller variances.

Because the distribution of sample ratios is not normal, for construction of confidence intervals (CIs), we calculate $\ln(r_l)$ and $\ln(r_l^*)$ $\forall$ l. With the delta method, $\mathrm{Var}\{\ln(r_l)\} = \mathrm{Var}(r_l)/r_l^2$ and $\mathrm{Var}\{\ln(r_l^*)\} = \mathrm{Var}(r_l)/r_l^{*2}$ $\forall$ l. CIs are calculated using the t distribution with $n_1 + n_0 - 2$ and $n - 1$ degrees of freedom for nonmatched and matched-pair CRTs, respectively (Hayes and Bennett 1999). The CIs are then exponentiated back to the original scale.

The asymptotic variance estimator of $\mathrm{Var}(R_i) = \mathrm{Var}(\sum_{j=1}^{n_i} y_{ij1})/(\sum_{j=1}^{n_i} p_{ij1})$ is a component of the formula for $\mathrm{Var}(r_3)$. This variance estimator is also involved in the calculation of $\mathrm{Var}(R_i^*)$ and $\mathrm{Var}(R_i^\dagger)$, which are then plugged into the estimators of $\mathrm{Var}(r_4)$ and $\mathrm{Var}(r_5)$, respectively. On the one hand, Cochran (1977) demonstrated that

this variance estimator gave a substantial underestimation when the number of observations is small. On the other hand, he showed that the jackknife method only slightly overestimated the variance and the overestimation was much reduced with respect to increase in the number of observations. We proposed an option to use the jackknife method to estimate $\text{Var}(R_i)$, $\text{Var}(R_i^*)$, and $\text{Var}(R_i^\dagger)$ and then plug these values into the calculation of $\text{Var}\{\ln(r_l^*)\}$, $l = 3$, 4, and 5, and their respective CIs. We used $r^*_{l(J)}$, $l = 3$, 4, and 5, to denote the estimators when used together with this jackknife-based variance estimation. The same applies to matched-pair CRTs as well. Simulation showed that this jackknife-based method gave more accurate coverage probability of CIs when the number of clusters was small (Ma et al. 2022).

3 The crtrest command

3.1 Syntax

`crtrest` has the following syntax:

`crtrest` *varlist* [*if*] [*in*], `by(`*groupvar*`)` [`match(`*pairvar*`)` `r(#)` `jack` `level(#)`]

varlist is a list of variables required for the different estimators. If there is only one variable specified in *varlist*, `crtrest` assumes that the variable is the number of events in the target group, and it uses the estimator r_1. If there are two variables specified in *varlist*, by default `crtrest` assumes that the variables are the number of events and person-time in the target group, respectively, and uses the estimator r_2. If there are four variables specified in *varlist*, `crtrest` assumes that the variables are the number of events and person-time in the target group and in the nontarget group, respectively, and it uses the estimator r_5. See option `r()` in section 3.2 for further details.

3.2 Options

`by(`*groupvar*`)` specifies a variable defining the groups. It must be dummy coded `1` for intervention or exposed and `0` for control or unexposed. `by()` is required.

`match(`*pairvar*`)` specifies a variable defining pairs of clusters in matched-pair CRTs.

`r(#)` indicates the estimator; it can be `r(1)` to `r(5)`, including the asymptotically unbiased version and the bias-corrected, approximately unbiased version (starred). `r(1)` requires only one variable in *varlist*, representing the number of events in the target group (`y1`). `r(2)` and `r(3)` require only two variables in *varlist*, representing `y1` and the person-time in the target group (`p1`), respectively. `r(4)` requires only two variables in *varlist*, representing the number of events in the target group (`y1`) and in the nontarget group (`y0`), respectively. `r(3)` and `r(4)` perform the same calculation, but the results are labeled differently to reflect the different choices of denominators and estimands. `r(5)` requires four variables in *varlist*, representing `y1`, `p1`, `y0`, and `p0`, respectively, where `p0` is the person-time in the nontarget group.

`jack` is valid only for the approximately unbiased estimators for `r(3)`, `r(4)`, and `r(5)`. It uses a jackknife plugin for the estimation of the standard error.

`level(#)` specifies the confidence level for estimating the CI. The default is `level(95)`.

3.3 Stored results

`crtrest` stores the following in `e()`:

Scalars

`e(N)`	total number of clusters
`e(N_1)`	number of clusters in the intervention or exposed arm
`e(N_0)`	number of clusters in the control or unexposed arm
`e(N_Pairs)`	number of pairs of clusters
`e(CIlevel)`	confidence level (%)
`e(df_t)`	degree of freedom for t distribution

Macros

`e(cmd)`	`crtrest`
`e(type)`	type of CRTs
`e(estimator)`	name of estimator
`e(rname)`	asymptotically unbiased estimator
`e(rnameC)`	approximately unbiased estimator
`e(rnameJ)`	approximately unbiased estimator with jackknife-based variance
`e(matched)`	name of the variable defining pairs of clusters in matched-pair trials

Matrices

`e(r)`	estimate vector
`e(se)`	standard error vector of ln(estimate)

4 Examples

We illustrate the use of `crtrest` with two simulated datasets: `parallel.dta` and `matched.dta`. The first dataset, `parallel.dta`, which was generated to resemble the nonmatched CRT of seasonal malaria chemoprevention reported in Ma et al. (2022), contains the variables `y1`, `p1`, `y0`, `p0`, and `group`, where the variables `y1` and `p1` represent the number of events and person-time in the target group, respectively, and the variables `y0` and `p0` represent the number of events and person-time in the nontarget group, respectively. The group variable defines the intervention groups: `1` for intervention group and `0` for control group. The second dataset, `matched.dta`, which was generated to represent a matched-pair CRT, contains the variables `y1`, `p1`, `y0`, `p0`, `group`, and `pair`. The variable `pair` defines pairs of clusters in a matched-pair trial.

We begin with loading the nonmatched CRT dataset and inspecting the data format:

```
. use parallel
. describe
Contains data from parallel.dta
 Observations:            20
    Variables:             6                  15 Jun 2022 14:03
-------------------------------------------------------------------------------
Variable      Storage   Display    Value
    name         type    format    label      Variable label
-------------------------------------------------------------------------------
cid             float   %9.0g                 cluster id
group           byte    %10.0g                group
y1              float   %9.0g                 counts in target group
y0              float   %9.0g                 counts in non-target group
p1              float   %9.0g                 person-time in target group
p0              float   %9.0g                 person-time in non-target group
-------------------------------------------------------------------------------
Sorted by: cid  group
. list in 1/5, noobs
```

cid	group	y1	y0	p1	p0
1	0	6	10	1837	1199
2	0	17	22	649	448
3	0	4	8	1283	965
4	0	6	4	1622	1117
5	0	5	12	4594	2897

To implement the ratio of the mean counts estimator, `r(1)`, we use the following command:

```
. crtrest y1, by(group)
Non-matched Cluster Randomized Trials
No. of clusters                                 =    20
No. of clusters in the intervention group       =    10
No. of clusters in the control group            =    10
Ratio of mean counts: r(1)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.
r(1)	.8791209	.4477817	2.233	0.019	.3431501
r*(1)	.8313602	.4735062	2.112	0.024	.3074349

Estimators	Interval]
r(1)	2.252231
r*(1)	2.24815

This is equivalent to

```
crtrest y1, by(group) r(1)
```

The asymptotically unbiased estimator and approximately unbiased estimator are labeled as `r(1)` and `r*(1)` in the output table, respectively. Because the hypothesis testing and CIs are first calculated on the log scale, the output table shows the standard errors of ln(estimate).

To implement the ratio of the mean cluster-level event-rates estimator, `r(2)`, we use the following command:

```
. crtrest y1 p1, by(group)
Non-matched Cluster Randomized Trials
No. of clusters                                =    20
No. of clusters in the intervention group      =    10
No. of clusters in the control group           =    10
Ratio of mean cluster-level event rates: r(2)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.	Interval]
r(2)	.4828219	.4523924	2.210	0.020	.1866447	1.248988
r*(2)	.4290171	.5091287	1.964	0.033	.1472095	1.250297

This is equivalent to

```
crtrest y1 p1, by(group) r(2)
```

For the ratio of event rates, `r(3)`, we use the following command:

```
. crtrest y1 p1, by(group) r(3)
Non-matched Cluster Randomized Trials
No. of clusters                                =    20
No. of clusters in the intervention group      =    10
No. of clusters in the control group           =    10
Ratio of event rates: r(3)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.	Interval]
r(3)	.7077515	.5265257	1.899	0.037	.2341363	2.139404
r*(3)	.6504768	.5728865	1.746	0.049	.1952178	2.167426

Specifying the `jack` option provides the jackknife-based standard error for the approximately unbiased estimator:

```
. crtrest y1 p1, by(group) r(3) jack
Non-matched Cluster Randomized Trials
No. of clusters                                 =    20
No. of clusters in the intervention group       =    10
No. of clusters in the control group            =    10
Ratio of event rates: r(3)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.
r(3)	.7077515	.5265257	1.899	0.037	.2341363
r*(3)	.6504768	.5728865	1.746	0.049	.1952178
r*(3)(J)	.6504768	.5999041	1.667	0.056	.1844455

Estimators	Interval]
r(3)	2.139404
r*(3)	2.167426
r*(3)(J)	2.294012

As expected, according to Cochran (1977), the jackknife-based standard error is larger than its asymptotic counterpart.

For the double ratio of event rates, `r(5)`, with a jackknife-based standard error, we use the following command:

```
. crtrest y1 p1 y0 p0, by(group) jack
Non-matched Cluster Randomized Trials
No. of clusters                                 =    20
No. of clusters in the intervention group       =    10
No. of clusters in the control group            =    10
Double ratio of event rates: r(5)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.
r(5)	.7784809	.3075215	3.252	0.002	.4079995
r*(5)	.7436442	.3219276	3.106	0.003	.3781224
r*(5)(J)	.7436442	.3490901	2.865	0.005	.3571485

Estimators	Interval]
r(5)	1.485376
r*(5)	1.462507
r*(5)(J)	1.548394

This is equivalent to

```
crtrest y1 p1 y0 p0, by(group) r(5) jack
```

Now we load the matched-pair dataset and inspect the format of the data:

```
. use matched
. describe
Contains data from matched.dta
 Observations:            14
    Variables:             6                  15 Jun 2022 14:04
```

Variable name	Storage type	Display format	Value label	Variable label
pair	float	%9.0g		paired cluster id
group	byte	%10.0g		group
y1	float	%9.0g		counts in target group
y0	float	%9.0g		counts in non-target group
p1	float	%9.0g		person-time in target group
p0	float	%9.0g		person-time in non-target group

```
Sorted by: pair  group
. list in 1/6, noobs separator(6)
```

pair	group	y1	y0	p1	p0
1	0	17	22	649	448
1	1	1	1	576	536
2	0	5	2	704	568
2	1	3	0	581	527
3	0	5	12	4594	2897
3	1	4	6	3718	3674

The following command provides the ratio of mean counts estimator for matched-pair CRTs, `r(1)`:

```
. crtrest y1, by(group) match(pair)
Matched-pair Cluster Randomized Trials
No. of clusters                                 =    14
No. of pairs of clusters                        =     7
Ratio of mean counts: r(1)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.
r(1)	.3888889	.5840712	1.712	0.069	.0931418
r*(1)	.357504	.6353463	1.574	0.083	.0755285

Estimators	Interval]
r(1)	1.623703
r*(1)	1.692197

For simplicity, in the output table, the asymptotically unbiased estimator and approximately unbiased estimator are labeled as `r(1)` and `r*(1)` without explicitly indicating that they are paired analysis estimators. But the description above the output table and the stored macro `e(type)` do indicate that this is an analysis of matched-pair CRTs.

For the double ratio of counts in matched-pair CRTs, `r(4)`, with a jackknife-based standard error, we use the following command:

```
. crtrest y1 y0, by(group) match(pair) r(4) jack
Matched-pair Cluster Randomized Trials
No. of clusters                                 =    14
No. of pairs of clusters                        =     7
Double ratio of counts: r(4)
```

Estimators	Estimate	SE(ln[Est.])	t	P>|t|	[95% Conf.
r(4)	.6416667	.3204982	3.120	0.010	.292902
r*(4)	.6604752	.3113713	3.212	0.009	.3082964
r*(4)(J)	.6604752	.3436941	2.910	0.013	.2848522

Estimators	Interval]
r(4)	1.405713
r*(4)	1.414961
r*(4)(J)	1.531417

5 Conclusion

In this article, we briefly reviewed recent developments in ratio estimators of intervention effects on event rates in CRTs and described a new command, `crtrest`. The command implements the asymptotically unbiased estimators of IRR in cluster-level analysis and their approximately unbiased counterparts proposed in Ma et al. (2022). Two versions of the estimators are available for nonmatched and matched-pair CRTs. We illustrated the use of `crtrest` through two examples, one for nonmatched CRTs and the other for matched-pair CRTs.

The strengths of our work are twofold. First, we provide bias-corrected versions of the five estimators for use when the number of clusters is small. This issue had not received much attention in the literature of ratio estimators in CRTs. Second, we propose the use of data from the nontarget group as an alternative to person-time in the target group in the estimation of (direct) intervention effects, giving estimators r_4 and r_5. This improves precision and power substantially when the event rate is highly heterogeneous across clusters. A limitation of the work is that it does not handle covariate adjustment. In nonmatched CRTs, one approach for controlling covariate unbalance is stratified analysis and pooling of stratum-specific estimates using weights inversely proportional to stratum-specific variances. But it is not practical to stratify for multiple covariates, and it may involve categorization of continuous covariates. However, good

use of study designs such as matched-pair CRT and restricted randomization may reduce the need for covariate adjustment in the analysis stage (Hayes and Moulton 2017; Imai, King, and Nall 2009).

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7 Disclaimer

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not reflect the views of the Ministry of Health or the National Medical Research Council, Singapore.

8 Programs and supplemental materials

To install a snapshot of the corresponding software files as they existed at the time of publication of this article, type

```
. net sj 22-4
. net install st0695     (to install program files, if available)
. net get st0695         (to install ancillary files, if available)
```

9 References

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