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RANDOMIZATION METHODS AND CLUSTER SIZE IN CLUSTER RANDOMIZED TRIALS CONDUCTED IN ELEMENTARY AND HIGH SCHOOLS

TEHNIKE RANDOMIZACIJE I VELIČINA KLASTERA U KLASTER RANDOMIZOVANIM STUDIJAMA SPROVEĐENIM U OSNOVNIM I SREDNJIM ŠKOLAMA

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Abstract

**Background:** Randomization allows study groups to be formed so that they are similar in all characteristics except outcomes. **Aim:** The aim of this study is to examine the frequency of randomization methods and their effect on achieving baseline balance in cluster randomization studies conducted in schools. **Methods:** A literature search of MEDLINE bibliographic database shows that the total number of collected articles in full text was 343, out of which 81 were eligible for inclusion. Each publication was reviewed by two independent reviewers, and data was extracted and analyzed. **Results:** Stratification was the most commonly applied randomization method, reported in 28 trials (34.6%). There was no statistically significant difference in the number of subjects and clusters, as well as in cluster size between trial’s groups in studies in which simple randomization was used. However, there was a statistically significant difference in number of subjects and clusters between groups in trials in which restricted randomization methods were used. Yet, there was no difference in the cluster size. **Conclusion:** Although there is no difference in the size of clusters between trial arms, either at the level of the entire sample or in relation to randomization methods applied, additional research should be conducted on larger sample in order to establish the effect of randomization methods on baseline balance, when the size of clusters is in question.

**Key words:** randomization, balance, cluster size.

Apstrakt

**Uvod:** Formiranje studijskih grupa da budu slične prema svim karakteristikama izuzev ishoda obezbeduje se postupkom randomizacije. **Cilj:** Cilj ove studije je da ispita učestalost tehnika randomizacije i njihov uticaj na postizanje ravnoteže na početku istraživanja u klaster randomizovanim studijama koje su sprovedene u školama. **Metode:** Pretraživanjem bibliografske baze podataka MEDLINE ukupan broj prikupljenih radova je bio 343, od kojih je 81 ispunio kriterijume za uključenje. Svaka publikacija je pregledana od strane dva nezavisna istraživača, podaci su ekstrahovani i analizirani. **Rezultati:** Najčešće primenjena tehnika randomizacije bila je stratifikacija koja je saopštena u 28 (34.6 %) studija. U studijama u kojima je primenjena prosta randomizacija nije bilo statistički značajne razlike u broju ispitanika i klastera kao i veličini klastera.
između ispitivanih grupa, dok u studijama u kojima su primenjene tehnike restriktivne randomizacije postoji statistički značajna razlika u broju ispitanika i klastera između grupa, ali ne i u veličini klastera. **Zaključak:** Iako u veličini klastera ne postoji razlika između ispitivanih grupa kako na nivou celog uzorka tako i u odnosu na tehnike randomizacije, trebalo bi sprovesti dodatna istraživanja na većem uzorku kako bi se utvrdio uticaj primenjenih tehnika randomizacije na prisustvo ravnoteže na početku istraživanja kada je u pitanju veličina klastera.

**Ključne reči:** randomizacija, balans, veličina klastera.

**Introduction**

Randomized controlled studies in which randomization is conducted at the level of clusters, where all subjects within the same cluster, such as hospitals or general practitioners, are subjected to the same treatment, are called cluster randomized trials\(^1\). Clusters may be groups of subjects, hospitals, schools, geographic regions, etc.

As compared with individually randomized studies, cluster randomization studies are of more complex design and require more subjects to achieve adequate statistical power, and also the application of more complex method of analysis\(^2\). Compared with an individually randomized trial testing the same hypothesis, cluster randomization requires a significantly larger sample size\(^3\).

The main result of such design application is that the outcome for one patient cannot be considered independently from other patients (as in individual randomized studies). Patients in the same cluster will probably have similar outcomes\(^4\).

Formation of study groups so as to be similar in all characteristics except in the outcome is achieved through randomization. Baseline balance among groups shall ensure that all differences obtained at the end of trial are attributed to the effect of study treatment, and not to the existing differences.

In cluster randomized studies, it is necessary to achieve balance, both at the level of individual subjects and at the level of clusters\(^5\). Due to cluster size, a large number of clusters are often difficult to randomize into every study group, while a small number of clusters is not enough to provide adequate balance among study groups\(^6\). Furthermore, the necessary number of cases depends on the size of the clusters: 100 clusters each containing
10 probands lead to greater statistical power than 10 clusters of 100 probands each\textsuperscript{7}. As regards the use of randomization method in cluster randomized trials, some authors believe that the adequate balance cannot be achieved by application of simple randomization, especially if the number of randomized clusters is small \textsuperscript{8}. This is the main reason why a matched or stratified design of study is used\textsuperscript{6}, although certain authors \textsuperscript{6,9,10} favor stratification when studies of such design are in question.

In systematic review of cluster randomized trials in the field of primary health care, published 1997-2000, Eldridge et al. quote that in 54\% of studies, matching and stratification were applied during randomization \textsuperscript{11}, while in systematic review of group randomized trials in the field of cancer prevention, published 2002-2006, Murray et al. quote that simple randomization is applied in 40\% of studies, matching is applied in 20\% of studies, stratification in 35\% of studies, while a combination of matching and stratification is applied in 5.3\% of studies \textsuperscript{12}. In systematic review of Rutterford et al. that included 300 cluster randomized trials published 2000-2008, stratification method is applied in 39\% of studies, simple randomization in 37\% of studies, while matching is applied in 19\% of studies, and minimization in 5\% of studies \textsuperscript{13}.

The purpose of this study is to investigate frequency of randomization methods and their relation with the size of cluster in terms of achieving baseline balance in cluster randomized trials conducted in schools.

**Method**

A literature search of MEDLINE bibliographic database was conducted by 31.03.2020, using following key words in the title of the paper: “cluster randomised trial”, “cluster randomized trial”, “randomised cluster trial”, “randomized cluster trial”, “field randomised trial”, “field randomized trial”, “randomised field trial”, “randomized field trial”, “community based randomised trial”, “community based randomized trial”, “randomised community based trial”, “randomized community based trial”, “community randomised trial”, “community randomized trial”, “randomised community trial”, “randomized community trial”, “group randomised trial”, “group randomized trial”, “randomised group trial”, “randomized group trial”, “place based randomised trial”, “place based randomized trial”, “randomised place based trial”, “randomized place based trial”, “randomised place trial”, “randomized place trial”, “place randomised trial”, “place randomized trial”, “place
randomized trial”, “prevention randomised trial”, “prevention randomized trial”, “randomised prevention trial”, “randomized prevention trial”, “randomised prevention trial”. Study inclusion criteria: prospective cluster randomized trials that include two study groups, with schools as randomization units, and students as observation units. Exclusion criteria: studies in which randomization is not performed at the level of clusters, cluster randomized studies in which randomization units are not schools, pilot trials. After reading through the published titles and abstracts, all the ones which meet inclusion criteria were downloaded in extenso. The total number of collected articles in full text was 343, out of which 81 were eligible for inclusion. Each publication was reviewed by two independent reviewers and data about randomization methods, number of subjects and clusters at the beginning of the trial were extracted. The size of the cluster was obtained by dividing the total number of randomized subjects with the number of randomized clusters.
Fig 1 | Identification of cluster randomised trials from PubMed citations indexed in March 2020

Data analysis

For the analysis of primary data descriptive methods and methods for testing statistical hypotheses were used. From descriptive statistical methods, measure of central tendency (median), a measure of variability (IQR), and relative numbers were used. Statistical hypotheses were tested by the Wilcoxon test. Statistical data analysis was performed using IBM SPSS Statistics 21 (SPSS Inc., Chicago, IL, USA). The criterion for statistical significance was $p < 0.05$.

Results

The most often applied randomization method was the method of stratification which was reported in 28 (34.6 %) studies. The following were simple randomization reported in 18 (22.2 %) studies, matching in 12 (14.8%) studies and block randomization in 8 (9.9%) studies. In 9 (11.1%) studies, it wasn’t reported which randomization methods were used. Frequency of other randomization methods was less than 5% (Table 1).

Table 1. Randomization methods in cluster randomized trials conducted in schools as randomization units (n=81)

| Allocation techniques                  | n  | %   |
|----------------------------------------|----|-----|
| Stratification                         | 28 | 34.6|
| Simple randomization                   | 18 | 22.2|
| Matching                               | 12 | 14.8|
| Not reported                           | 9  | 11.1|
| Block randomization                    | 8  | 9.9 |
| Balanced randomization                 | 3  | 3.7 |
| Matching and stratification            | 1  | 1.2 |
| Block and stratification               | 1  | 1.2 |
| Restricted randomization               | 1  | 1.2 |


When the entire sample is considered, there is a statistically significant difference in the number of subjects and clusters between intervention and control group, while there is no statistically significant difference in the size of clusters between groups. Studies where simple randomization method is applied demonstrated the absence of statistically significant difference between study groups, in the number of subjects and clusters, as well as in the size of clusters, while studies with restrictive randomization methods demonstrated statistically significant difference between study groups, in the number of subjects and clusters, but not in the size of clusters (Table 2).
Table 2. The association of randomization methods and cluster size at baseline

| Cluster size at baseline (n=72) | Intervention group | Control group | p** |
|---------------------------------|--------------------|----------------|-----|
| Number of participants          | 813 (394-2710)     | 823 (380-2864) | 0.020 |
| Number of clusters              | 12.5 (7.75-34)     | 12 (8-31)      | 0.001 |
| Cluster size                    | 59.2 (33.8-160.4)  | 62.5 (33.9-158) | 0.736 |

Cluster size at baseline in studies which applied simple randomization (n=18)

|                                | Intervention group | Control group | p** |
|                                | 314 (113-691)      | 314 (108-718) | 0.088 |
| Number of participants          | 10 (6-13)          | 10 (7-12)     | 0.953 |
| Cluster size                    | 45 (28.9-62.8)     | 42.6 (24.9-65) | 0.365 |

Cluster size at baseline in studies which applied restricted randomization (n=54)

|                                | Intervention group | Control group | p** |
|                                | 1115 (669.5-4253)  | 1093 (628.5-4299) | 0.012 |
| Number of participants          | 20 (10-35)         | 16 (10-33.5)   | <0.001 |
| Cluster size                    | 76.8 (41.8-168.7)  | 74.7 (40.3-178) | 1.000 |

* number of subjects and clusters in trial’s arms

**Wilcoxon test

Note: Values are given as median and IQR (interquartile range 25-75 percentiles)

Discussion

Results of this trial show possible presence bias during randomization. The difference in the number of subjects and clusters between study groups during randomization is small, but it is statistically significant. According to the literature, there is a much greater probability of not achieving balance between trial arms, especially if the number of clusters is small like in the studies from this research. Notwithstanding the aforementioned, there is no statistically significant difference in the number of subjects and clusters between study groups in studies where simple randomization was applied, which leads to conclusion that the baseline balance was achieved although the randomization method otherwise not recommended in cluster randomized trials was applied.
In bibliography, restrictive randomization methods are recommended for cluster randomized trials because they may improve the chances of achieving balanced study groups. Author Lewsey quotes that when cluster randomized trials are in question matching and stratification are especially popular methods, and also quotes that the most commonly used factors of stratification are the size of cluster, cluster-level socio-economic status, geographic location and categorized levels of individual level prognostic factors. On the other hand, this trial shows that there is a significant difference in the number of subjects and clusters between trial arms in studies that applied certain restrictive randomization methods. The number of subjects and clusters is significantly higher in intervention groups.

Although cluster randomized trials are of complex design, in certain cases they are the only choice, for instance if the nature of the intervention requires that it must be performed in the entire community, or to prevent contamination if subjects from both study groups come from the same population. Application of adequate randomization methods in these studies has a great impact on quality of the trial. A number of authors recommend stratification, which is most frequently applied method in one third of all studies in this research. We can find the similar result in the research of Varnell et al., while in the systematic review of cluster randomized trial in the field of oral health, stratification was reported to be the most frequently used randomization method in 48% of studies.

Although certain authors believe that balance in cluster randomized trial cannot be achieved by application of simple randomization, its frequency of 22.2% in this trial is rather high. In bibliography, there is a trial where simple randomization was applied in more than a half number of studies covered by systematic review, but there are also trials where the frequency of this method is similar to our results.

As for individually randomized controlled trials, the goal of randomization in group randomized trials is to achieve a balance of baseline covariates. In contrast to individually randomized trials, another form of baseline balance applies to group randomized trials, namely, baseline balance of group sample size. In case of cluster randomized trials, the most efficient design is achieved when sizes of clusters are equal. Results of this trial show that there are no differences in the size of clusters between study groups. However, possible presence of bias can be seen through the presence of difference in the number of
subjects and clusters in the randomization process. The difference already existing between subjects and clusters at baseline may increase if a loss of subjects and/or clusters occurs during study, for which reason we believe that additional investigation is necessary.

The limitation of this study is the fact that it includes only studies that are conducted in schools as randomization units. There is a heterogeneity between trials that has not been investigated, which also represents a limitation of this trial. Also, the only balance measuring factor we took into consideration, was the size of cluster that represents a number of subjects and clusters in trial arms, without presence of balance in prognostic factors.

**Conclusion**

The most frequently applied randomization method is stratification, although the frequency of simple randomization is also high. In studies where simple randomization method was applied, there was no difference in the number of subjects and clusters between study groups, unlike in studies where some of restrictive randomization methods were applied. Even though there is no difference in the size of clusters between study groups, either with respect to entire sample or the randomization method applied, additional research should be conducted on larger sample in order to determine the effects of randomization method on achieving baseline balance, when cluster size is in question.

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### Appendix: trials included in the analysis

| Study | Publication year | Study power | Randomization methods | Intervention group No of participants randomized | Control group No of participants randomized | Intervention group No of clusters randomized | Control group No of clusters randomized |
|-------|------------------|-------------|-----------------------|-----------------------------------------------|-------------------------------------------|------------------------------------------|------------------------------------------|
| Pereira w^1 | 2012 | Described | Stratification | 176843 | 171240 | 388 | 375 |
| Barreto w^2 | 2011 | Described in previous report | Stratification | 176843 | 171240 | 388 | 375 |
| Stephenson w^3 | 2008 | Described | Stratification | 4516 | 4250 | 14 | 13 |
| Cunha w^4 | 2008 | Described | Stratification | 72980 | 79458 | 386 | 375 |
| Cooper w^5 | 2007 | Described | Balanced | 2080 | 2135 | 13 | 12 |
| Rodrigues w^6 | 2006 | Described | Block randomization | 1164 | 1209 | 34 | 34 |
| Madsen w^7 | 2013 | Described | Not reported | 82 | 74 | 4 | 3 |
| Sancho-Garnier w^8 | 2012 | Described | Stratification | 798 | 567 | 39 | 31 |
| Tol w^9 | 2012 | Described | Simple randomization | 199 | 200 | 12 | 12 |
| James-Burdumy w^10 | 2012 | Not reported | Block randomization | 6400 | 4590 | 20 | 16 |
| Ezendam w^11 | 2012 | Described in previous report | Stratification | 485 | 398 | 11 | 9 |
| Hartmann w^12 | 2010 | Not reported | Simple randomization | 375 | 378 | 17 | 17 |
| Walsh w^13 | 2010 | Described | Stratification | 2270 | 2461 | 16 | 11 |
| Hunter w^14 | 2010 | Described | Block randomization | 1115 | 1376 | 11 | 11 |
| Wen w^15 | 2010 | Described | Simple randomization | 1339 | 1004 | 2 | 2 |
| Berg w^16 | 2009 | Described | Simple randomization | 375 | 378 | 17 | 17 |
| Wolfe w^17 | 2009 | Not reported | Stratification | 968 | 754 | 10 | 10 |
| Ringwalt w^18 | 2009 | Described | Matching | 3990 | 4348 | 20 | 10 |
| Tol w^19 | 2008 | Described | Simple randomization | 237 | 258 | 7 | 7 |
| Martinez-Vizcaíno w^20 | 2008 | Described | Simple randomization | 691 | 718 | 10 | 10 |
| Naldi w^21 | 2007 | Described in previous report | Stratification | 5676 | 5554 | 62 | 60 |
| Martiniuk w^22 | 2007 | Described | Block and stratification | 403 | 380 | 12 | 12 |
| Rapp w^23 | 2006 | Described | Simple randomization | 605 | 629 | 16 | 16 |
| Martiniuk w^24 | 2003 | Described | Simple randomization | 197 | 271 | 8 | 11 |
| Aveyard w^25 | 2001 | Described in previous report | Balanced | 4660 | 4641 | 27 | 26 |
| Priest w^26 | 2014 | Described | Stratification | 8859 | 7386 | 34 | 34 |
| Halliday w^27 | 2014 | Described | Stratification | 2710 | 2523 | 51 | 50 |
| Isensee w^28 | 2014 | Described | Stratification | 2437 | 2335 | 26 | 22 |
| Ebenezer w^29 | 2013 | Described | Block randomization | 813 | 808 | 49 | 49 |
| Martinez-Vizcaíno w^30 | 2014 | Described in previous | Simple randomization | 769 | 823 | 10 | 10 |
| Study | Year | Description | Randomization | N1 | N2 |
|-------|------|-------------|---------------|----|----|
| Bere  | 2014 | Described   | Stratification | 585 | 1365 |
| Primack | 2014 | Described   | Stratification | 554 | 578 |
| Telford | 2014 | Described in previous report | Stratification | 176843 | 172240 |
| Kaufman | 2014 | Described   | Stratification | 2523 | 3036 |
| Sanchez | 2014 | Described   | Stratification | 153 | 176 |
| Santos | 2014 | Described   | Block randomization | 340 | 347 |
| Freeman | 2013 | Described   | Stratification | 388 | 375 |
| O'Leary-Barrett | 2013 | Not reported | Not reported | 1529 | 1114 |
| Lewis | 2013 | Not reported | Matching | 7 | 7 |
| Peskin | 2014 | Described   | Balanced | 598 | 847 |
| Coleman | 2012 | Described   | Matching | 647 | 626 |
| Peterson | 2009 | Described   | Matching | 1058 | 1093 |
| Telford | 2013 | Not reported | Not reported | 394 | 314 |
| Telford-2013 | 2013 | Not reported | Simple randomization | 394 | 314 |
| LaBrie | 2008 | Not reported | Not reported | 603 | 559 |
| Slobo da | 2009 | Described   | Not reported | 10028 | 7292 |
| Gmel | 2012 | Described   | Matching and stratification | 973 | 885 |
| Waters | 2018 | Described   | Simple randomization | 3433 | 3601 |
| Mallick | 2018 | Described   | Stratification | 223 | 231 |
| Kittayapong | 2017 | Described   | Not reported | 1297 | 1017 |
| Marciano-Olivier | 2019 | Described   | Simple randomization | 86 | 90 |
| Nawi | 2015 | Described   | Simple randomization | 47 | 50 |
| Rathleff | 2015 | Described   | Simple randomization | 62 | 59 |
| Sutherland | 2016 | Described   | Block randomization | 837 | 631 |
| Baker-Henningham | 2019 | Described   | Not reported | 108 | 112 |
| Halliday | 2020 | Described   | Stratification | 4850 | 4721 |
| Nsangi | 2020 | Described   | Stratification | 6383 | 6256 |
| Chang Wu | 2018 | Described   | Simple randomization | 365 | 565 |
| Morgan | 2018 | Not reported | Matching | 118 | 79 |
| Bundy | 2017 | Described in previous report | Simple randomization | 113 | 108 |
| Rozi | 2019 | Described   | Stratification | 738 | 589 |
| Andersen | 2015 | Described   | Stratification | 2381 | 1786 |
| Gerald | 2019 | Described   | Matching | 224 | 169 |
| Penalo | 2015 | Described   | Stratification | 12 | 12 |
| Schonfeld | 2015 | Not reported | Block randomization | 692 | 702 |
| Sutherland | 2016 | Described   | Block randomization | 696 | 537 |
| Kaufman | 2016 | Described   | Stratification | 565 | 661 |
| Sanchez | 2019 | Described   | Not reported | 3243 | 3148 |
| Dalma | 2019 | Described   | Stratification | 6831 | 5587 |
| Valente | 2020 | Described   | Simple randomization | 3340 | 3318 |
| Andrade | 2016 | Described   | Matching | 700 | 740 |
| Vik | 2015 | Described   | Matching | 1713 | 1681 |
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