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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 sprovedenim u osnovnim i srednjim školama

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Abstract

Background/Aim. Randomization allows for study groups to be formed so that they are similar in all characteristics except outcomes. The aim of this study was to examine the frequency of randomization methods and their effect on achieving baseline balance in cluster randomized studies conducted in schools. **Methods.** A literature search of the Medline bibliographic database showed that the total number of collected articles in the full text was 343, out of which 81 were eligible for inclusion. Each publication was reviewed by two independent reviewers, and data were 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 groups in studies in which simple randomization was applied. However, there was a statistically significant difference in the 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 a larger sample in order to establish the effect of randomization methods on baseline balance, when the size of clusters is in question.

Key words:
random allocation; research; research design; sample size; schools.

Apstrakt

Uvod/Cilj. Formiranje grupa u istraživanjima tako da budu slične u svim karakteristikama izuzev ishoda, obezbeđuje se postupkom slučajne raspodele. Cilj ove studije bio je da ispita učestalost tehnika slučajne raspodele i njihov uticaj na postizanje ravnoteže na početku istraživanja u studijama sa grupama formiranim pomenutom metodom, koje su sprovedene u školama. **Metode.** Pretraživanjem bibliografske baze podataka *Medline* ukupan broj prikupljenih radova je bio 343, od kojih je 81 ispunilo kriterijume za uključenje u studiju. Svaku publikaciju su pregledala dva nezavisna istraživača, podaci su ekstrahovani i analizirani. **Rezultati.** Najčešće primenjena tehnika slučajne raspodele bila je stratifikacija koja je opisana u 28 (34,6%) studija. U studijama u kojima je primenjena prosta metoda slučajne raspodele nije bilo statistički značajne razlike u broju ispitanika i klastera kao i veličini klastera između ispitivanih grupa. U studijama u kojima su primenjene tehnike restriktivne slučajne raspodele 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 slučajne raspodele, trebalo bi sprovesti dodatna istraživanja na većem uzorku kako bi se utvrdio uticaj primenjenih tehnika slučajne raspodele na prisustvo ravnoteže na početku istraživanja kada je u pitanju veličina klastera.

Ključne reči:
slučajni izbor, metod; istraživanje; istraživanje, dizajn; uzorak, veličina; škole.

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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 (CRTs) [1]. Clusters may be groups of subjects, hospitals, schools, geographic regions, etc.

Compared with individually randomized studies, cluster randomized studies are of a more complex design and require more subjects to achieve adequate statistical power and the application of a 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 a 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].

The 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 the trial are attributed to the effect of study treatment, not 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 [7]. Regarding the use of the randomization method in CRTs, some authors believe that adequate balance cannot be achieved by the application of simple randomization, especially if the number of randomized clusters is small [8]. That is the main reason why a matched or stratified design of the study is used [6], although certain authors [2, 6, 9] favor stratification when studies of such design are in question.

In a systematic review of CRTs in the field of primary health care, published 1997–2000, Eldridge et al. [10] quote that in 54% of studies, matching and stratification were applied during randomization. In a systematic review of group randomized trials in the field of cancer prevention, published 2002–2006, Murray et al. [11] 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. In a systematic review of Rutterford et al. [12] that included 300 CRTs published 2000–2008, the 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.

The aim of this study was to investigate the frequency of randomization methods and their relation with the size of the cluster in terms of achieving baseline balance in CRTs conducted in schools.

Methods

A literature search of the Medline bibliographic database was conducted until March 31, 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”, “prevention randomised trial”, “prevention randomized trial”, “randomised prevention trial”, “randomized prevention trial”, “randomised prevention trial”. Study inclusion criteria were: prospective CRTs that include two study groups, with schools as randomization units and students as observation units. Exclusion criteria were: studies in which randomization is not performed at the level of clusters, cluster randomized studies in which randomization units are not schools, and pilot trials. After reading through the published titles and abstracts, all the ones which met the inclusion criteria were downloaded *in extenso*. The total number of collected articles in the full text was 343, out of which 81 (Appendix 1) were eligible for inclusion [13-93]. Each publication was reviewed by two independent reviewers and data about randomization methods, the 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 by the number of randomized clusters (Figure 1).

Data analysis

For primary data analysis, descriptive methods and methods for testing statistical hypotheses were used. The measure of central tendency (median), a measure of variability [interquartile range (IQR)], and relative numbers were used from descriptive statistical methods. 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 $p < 0.05$.

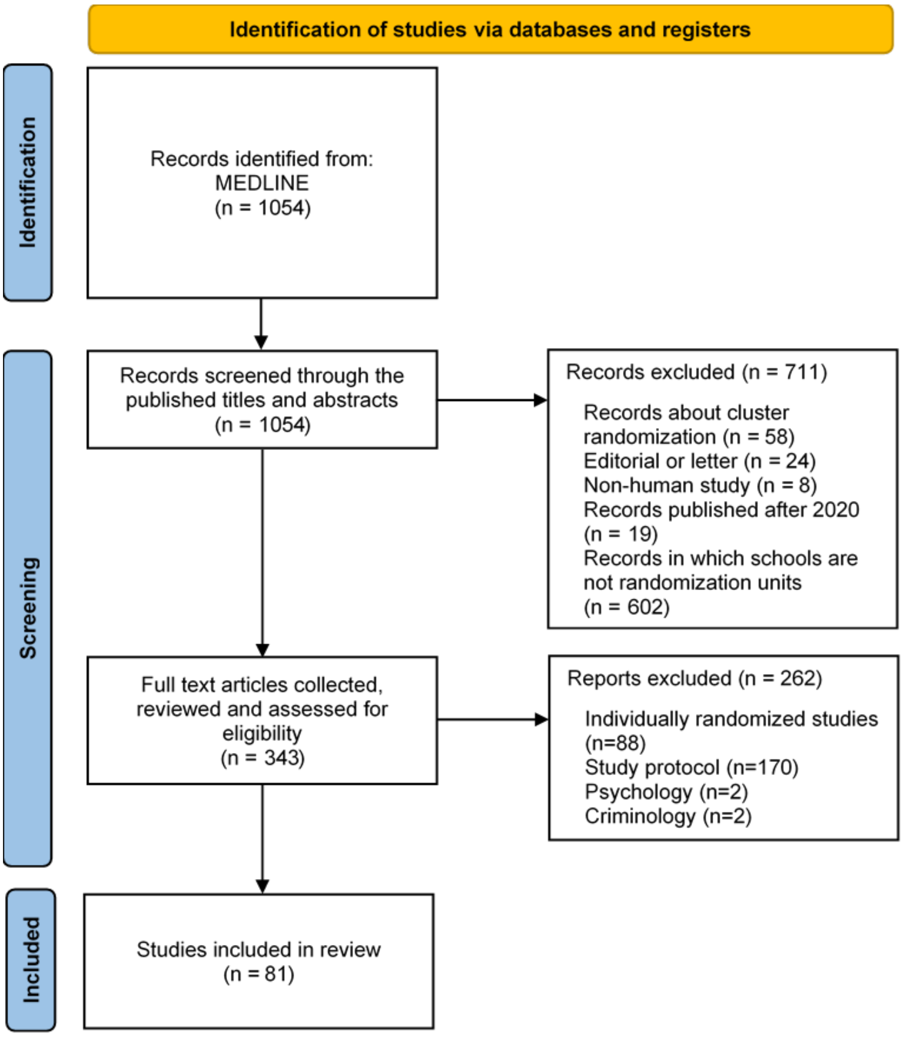

Fig. 1 − Identification of cluster randomized trials from PubMed citations indexed in March 2020.

Results

The most often applied randomization method was the method of stratification 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 was not reported which randomization methods were used. The frequency of other randomization methods was less than 5% (Table 1).

When the entire sample was considered, there was a statistically significant difference in the number of subjects and clusters between the intervention and control group, while there was no statistically significant difference in the size of clusters between groups. Studies where a simple randomization method was applied demonstrated the absence of a 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 a statistically significant difference between study groups in the number of subjects and clusters but not in the size of clusters (Table 2).

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)

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 (394–2.710)	823 (380–2.864)	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
Baseline simple randomization studies (n = 18)			
Number of participants	314 (113–691)	314 (108–718)	0.088
Number of clusters	10 (6–13)	10 (7–12)	0.953
Cluster size	45 (28.9–62.8)	42.6 (24.9–65)	0.365
Baseline restricted randomization studies (n = 54)			
Number of participants	1,115 (669.5–4.253)	1,093 (628.5–4.299)	0.012
Number of clusters	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 arms; **Wilcoxon test**
Note: Values are given as median and IQR (interquartile range 25–75 percentiles).

Discussion

The results of this trial show the possible presence of bias during randomization. The difference in the number of subjects and clusters between study groups during randomization is slight but statistically significant. According to the literature, there is a much greater probability of not achieving the balance between trial arms, especially if the number of clusters is small [94] like in the studies from this research. Without withstanding the aforementioned, there was no statistically significant difference in the number of subjects and clusters between study groups in studies where simple randomization was applied, which leads to the conclusion that the baseline balance was achieved although the randomization method, otherwise not recommended in CRTs, was applied.

In the bibliography, restrictive randomization methods are recommended for CRTs because they may improve the chances of achieving balanced study groups [95]. Author Lewsey [96] quotes that, when CRTs 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 the cluster, cluster-level socio-economic status, geographic location, and categorized levels of individual-level prognostic factors. On the other hand, this trial showed 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 was significantly higher in intervention groups.

Although CRTs are of complex design, in certain cases, they are the only choice, for instance, if the nature of the intervention requires it to be performed in the entire community or to prevent contamination if subjects from both study groups come from the same population. The application of adequate randomization methods in these studies has a great impact on the quality of the trial. Several authors [6, 2, 9] recommend stratification, which is the most frequently applied method in one-third of all studies in this research. We can find a similar result in the research of Varnell et al. [97], while in the systematic review of CRTs in the field of oral health, stratification was reported to be the most frequently used randomization method in 48% of studies [98].

Although certain authors [6, 12] believe that balance in CRTs cannot be achieved by application of simple randomization, its frequency of 22.2% in this trial is rather high. In the bibliography, there is a trial where simple randomization was applied in more than half of the studies covered by systematic review [99], but there are also trials where the frequency of this method is similar to our results [98].

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 [100]. In the case of CRTs, the most efficient design is achieved when the sizes of clusters are equal [101]. The results of this trial showed that there were no differences in the size of clusters between study groups. However, the possible presence of bias can be seen through the presence of differences 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 the study. For this reason, we believe that additional investigation is necessary.

The limitation of this study is that it included only studies conducted in schools as randomization units. There is a heterogenicity between trials that has not been investigated, which also represents a limitation of this trial. Moreover, the only balance measuring factor we took into consideration was the size of the cluster that represents a number of subjects and clusters in trial arms, without the 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 a simple randomization method was applied, there was no difference in the number of subjects and clusters between study groups, unlike in studies where some restrictive randomization methods were applied. Even though there was no difference in the size of clusters between study groups, either with respect to the entire sample or the randomization method applied, additional research should be conducted on a larger sample in order to determine the effects of the randomization method on achieving baseline balance, when cluster size is in question.

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Appendix 1

Trials included in the analysis

Study	Publication year	Study power	Randomization methods	Intervention group	Control group	Intervention group	Control group
				number of participants randomized	number of participants randomized	number of clusters randomized	number of clusters randomized
Pereira et al. [13]	2012	Described	Stratification	176,843	171,240	388	375
Barreto et al. [14]	2011	Described in previous report	Stratification	176,843	171,240	388	375
Stephenson et al. [15]	2008	Described	Stratification	4,516	4,250	14	13
Cunha et al. [16]	2008	Described	Stratification	72,980	79,458		
Henderson et al. [17]	2007	Described	Balanced	2,080	2,135	13	12
Cooper et al. [18]	2006	Described	Block randomization	1,164	1,209	34	34
Rodrigues et al. [19]	2005	Described in previous report	Stratification	176,843	171,240	386	375
Madsen et al. [20]	2013	Described	Not reported	82	74	4	3
Sancho-Garnier et al. [21]	2012	Described	Stratification	798	567	39	31
Tol et al. [22]	2012	Described	Simple randomization	199	200	12	12
James-Burdumy et al. [23]	2012	Not reported	Block randomization	6,400	4,590	20	16
Ezendam et al. [24]	2012	Described in previous report	Stratification	485	398	11	9
Hartmann et al. [25]	2010	Not reported	Simple randomization			16	11
Walsh et al. [26]	2010	Described	Stratification	2,270	2,461		
Hunter et al. [27]	2010	Described	Block randomization	1,115	1,376	11	11
Wen et al. [28]	2010	Described	Matching	1,339	1,004	2	2
Berg et al. [29]	2009	Described	Stratification	375	378	17	17
Wolfe et al. [30]	2009	Not reported	Stratification	968	754	10	10
Ringwalt et al. [31]	2009	Described	Matching	3,990	4,348	20	10
Tol et al. [32]	2008	Described	Simple randomization	237	258	7	7
Martínez Vizcaíno et al. [33]	2008	Described	Simple randomization	691	718	10	10
Naldi et al. [34]	2007	Described in previous report	Stratification	5,676	5,554	62	60
Martiniuk et al. [35]	2007	Described	Block and stratification	403	380	12	12
Rapp et al. [36]	2006	Described	Simple randomization	605	629	16	16
Martiniuk et al. [37]	2003	Described	Simple randomization	197	271	8	11
Aveyard et al. [38]	2001	Described in previous report	Balanced	4,660	4,641	27	26
Priest et al. [39]	2014	Described	Stratification	8,859	7,386	34	34
Halliday et al. [40]	2014	Described	Stratification	2,710	2,523	51	50
Isensee et al. [41]	2014	Described	Stratification	2,437	2,335	26	22
Ebenezer et al. [42]	2013	Described	Block randomization	813	808	49	49
Martínez-Vizcaíno et al. [43]	2014	Described in previous report	Simple randomization	769	823	10	10
Bere et al. [44]	2014	Described	Not reported	585	1,365		
Primack et al. [45]	2014	Described	Stratification	554	578	31	33
Barreto et al. [46]	2014	Described in previous report	Stratification	176,843	172,240	388	375
Muhumuza et al. [47]	2014	Described	Stratification	2,523	3,036	6	6
Tol et al. [48]	2014	Described	Stratification	153	176	7	7
Santos et al. [49]	2014	Described	Block randomization	340	347	10	10
Freeman et al. [50]	2013	Described	Stratification			20	20
O'Leary-Barrett et al. [51]	2013	Not reported	Not reported	1,529	1,114	11	8
Lewis et al. [52]	2013	Not reported	Matching			7	7
Peskin et al. [53]	2014	Described	Balanced	598	847	5	5

Coleman et al. [54]	2012	Described	Matching	647	626	4	4
Peterson et al. [55]	2009	Described	Matching	1,058	1,093	25	25
Telford et al. [56]	2013	Not reported	Not reported	394	314	13	16
Telford-2013 et al. [57]	2013	Not reported	Simple randomization	394	314	13	16
LaBrie et al. [58]	2008	Not reported	Not reported	603	559	12	8
Sloboda et al. [59]	2009	Described	Not reported	10,028	7,292	41	42
Gmel et al. [60]	2012	Described	Matching and stratification	973	885	57	56
Waters et al. [61]	2018	Described	Simple randomization	3,433	3,601	12	11
Mallick et al. [62]	2018	Described	Stratification	223	231	5	5
Kittayapong et al. [63]	2017	Described	Not reported	1,297	1,017	5	5
Marcano-Olivier et al. [64]	2019	Described	Simple randomization	86	90		
Nawi et al. [65]	2015	Described	Simple randomization	47	50	4	2
Rathleff et al. [66]	2015	Described	Simple randomization	62	59	2	2
Sutherland et al. [67]	2016	Described	Block randomization	837	631	5	5
Baker-Henningham et al. [68]	2019	Described	Not reported	108	112	7	7
Halliday et al. [69]	2020	Described	Stratification	4,850	4,721	29	29
Nsangi et al. [70]	2020	Described	Stratification	6,383	6,256	60	60
Chang Wu et al. [71]	2018	Described	Simple randomization	365	565	7	9
Morgan et al. [72]	2018	Not reported	Matching	118	79	34	26
Bundy et al. [73]	2017	Described in previous report	Simple randomization	113	108	6	6
Rozi et al. [74]	2019	Described	Stratification	738	589	10	8
Andersen et al. [75]	2015	Described	Stratification	2,381	1,786	53	44
Gerald et al. [76]	2019	Described	Matching	224	169	10	10
Penalvo et al. [77]	2015	Described	Stratification			12	12
Schonfeld et al. [78]	2015	Not reported	Block randomization	692	702	12	12
Sutherland et al. [79]	2016	Described	Block randomization	696	537	5	5
Kaufman et al. [80]	2016	Described	Stratification	565	661	13	13
Sanchez et al. [81]	2019	Described	Not reported	3,243	3,148	38	34
Dalma et al. [82]	2019	Described	Stratification	6,831	5,587	36	30
Valente et al. [83]	2020	Described	Simple randomization	3,340	3,318	38	34
Andrade et al. [84]	2016	Described	Matching	700	740	10	10
Vik et al. [85]	2015	Described	Matching	1,713	1,681	31	31
Chard et al. [86]	2019	Not reported	Stratification	2,021	1,972	50	50
D ziaugyt_e et al. [87]	2017	Described	Simple randomization	112	94	2	2
Okely et al. [88]	2017	Described	Matching	771	747	12	12
Asdigian et al. [89]	2017	Not reported	Simple randomization	314	321	6	7
Peterson et al. [90]	2016	Described	Matching	1,058	1,093	25	25
Bauer et al. [91]	2020	Described	Matching	639	723	8	8
Potter et al. [92]	2016	Not reported	Restricted	1,775	1,469		
Praena-Crespo et al. [93]	2016	Described	Simple randomization	2,856	2,864	47	50