ARTICLE

Generalizability of Results from Randomized Controlled Trials in Post-Stroke Physiotherapy

Matteo Paci, MSc, PT; Claudia Prestera, BA, PT;† Francesco Ferrarello, MSc, PT**

ABSTRACT

Purpose: The randomized controlled trial (RCT) is considered a reliable experimental design, able to detect the effect of an intervention. However, a criticism frequently levelled at RCTs by clinicians is their lack of generalizability. This study aimed to evaluate the generalizability of findings from RCTs of physiotherapy interventions for individuals with stroke. ***Method:*** A sample of RCTs of physiotherapy interventions after stroke indexed in the PEDro database was selected, and the reported inclusion and exclusion criteria were analyzed. ***Results:*** We reviewed 100 articles, which included 7,366 participants (41.6% women, with a mean weighted age of 65.5 years). The most frequent criteria for exclusion were comorbidity (83%), cognitive impairments (69%), communication skills (55%), recurrent stroke (53%), low functional level (47%) and being elderly (25%). ***Conclusions:*** A variety of cohorts of individuals who have had a stroke are excluded from RCTs published in the field of physiotherapy. Because they represent a substantial proportion of the real-world population with stroke, and consequently treated in clinical practice, more vulnerable cohorts of participants should be included in RCTs.

Key Words: rehabilitation; reproducibility of results; stroke.

RÉSUMÉ

Objectif : l'essai aléatoire et contrôlé (EAC) est considéré comme une méthodologie expérimentale fiable, en mesure de déterminer l'effet d'une intervention. Cependant, les cliniciens en critiquent souvent l'absence de généralisabilité. La présente étude visait à évaluer la généralisabilité des résultats des EAC sur des interventions de recherche en physiothérapie auprès de personnes ayant subi un accident vasculaire cérébral (AVC). ***Méthodologie :*** les auteurs ont sélectionné un échantillon d'EAC sur des interventions de physiothérapie après un AVC indexées dans la base de données PEDro. Ils ont analysé les critères d'inclusion et d'exclusion déclarés. ***Résultats :*** les auteurs ont examiné 100 articles, qui incluaient 7 366 participants (41,6 % de femmes, d'un âge moyen pondéré de 65,5 ans). Les critères d'exclusion les plus fréquents étaient la comorbidité (83 %), les déficiences cognitives (69 %), les aptitudes à la communication (55 %), les AVC récurrents (53 %), un faible niveau fonctionnel (47 %) et le fait d'être âgé (25 %). ***Conclusion :*** diverses cohortes de personnes qui ont subi un AVC sont exclues des EAC publiés en physiothérapie. Puisqu'elles représentent une forte proportion de la population de personnes qui subissent un AVC en situation réelle et qui sont ensuite traitées en pratique clinique, il faudrait inclure plus de cohortes de participants vulnérables dans les EAC.

Mots-clés : accident vasculaire cérébral; réadaptation; reproductibilité des résultats

Randomized controlled trials (RCTs) and systematic reviews are considered to be the most reliable research methods for determining the effects of an experimental intervention. Health care providers use the evidence from RCTs to guide their clinical decisions, and payers and policy-makers use it to support their recommendations for therapies to adopt in clinical practice.[1] RCTs must be internally valid, and to be clinically useful, findings must have external validity, also called *applicability* or *generalizability*. Jüni and colleagues[2] defined internal validity as the extent to which bias is minimized in RCTs. High internal validity suggests that any differences observed among groups of participants can be attributed to the intervention tested in a trial rather than to systematic or random errors. External validity is the extent to which the results of an RCT can be generalized into clinical practice and applied to the general population.[3] Internal validity is usually considered a prerequisite for external validity.[2]

The relationship between internal validity and external validity could be described as a trade-off relationship.[4] To protect an experiment from potential confounders and thereby reduce the risk of bias (and maintain internal validity), researchers investigate a strongly controlled group of participants in a highly artificial setting. Therefore, the experimental results are unlikely to represent the effects of these treatments in the real world (external validity). Suggestions for pragmatic features of a trial have been proposed (e.g., recruiting investigators and participants, setting, intervention and its delivery modalities, outcome measures, and analysis),[5] but the relationship between

From the: *Unit of Functional Recovery, Azienda USL Toscana Centro, Florence; †Rehabilitation Center, Fondazione Filippo Turati Onlus, Gavinana, Pistoia, Italy.

Correspondence to: Matteo Paci, Unit of Functional Rehabilitation, Azienda USL Toscana Centro, Presidio ospedaliero Piero Palagi, Viale Michelangiolo, 41, 50122, Firenze, Italy; matteo.paci@applicazione.it.

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internal and external validity in RCTs is a complex and debated issue, especially in the physiotherapy field.

A criticism frequently directed by clinicians at RCTs, systematic reviews, and guidelines is their lack of generalizability. Limited external validity can partially explain the underuse in routine practice of the recommendations reported in guidelines,[6] and it is a major barrier to developing clinical practice guidelines that are relevant to the general population.[7] Developing a clinical trial programme usually requires four phases: Phase 1 studies assess safety, Phase 2 studies assess efficacy, Phase 3 studies confirm the intervention's safety and efficacy, and Phase 4 studies investigate generalizability of the results.[8,9] Phase 4 studies are not common in the physiotherapy literature; systematic reviews of, or clinical guidelines for, physiotherapy interventions are mainly based on Phase 2 or Phase 3 RCTs.

The generalizability of an RCT can be affected by differences among trial protocols and routine practice, such as setting, outcome measures, follow-up length, access policy, and individuals' characteristics.[3] Inclusion and exclusion criteria are important issues in assessing the external validity and relevance of an RCT in clinical practice.[10]

Globally, stroke is the second most common cause of death[11] and a leading cause of adult physical disability.[12] Stroke survivors can experience a wide range of long-lasting outcomes, such as mobility restriction, vision and speech impairment, and fatigue.[13] Many motor, sensory, cognitive, and affective impairments, as well as demographic and clinical variables, may influence patients' functional status and rehabilitation outcomes after a stroke.[14] Moreover, individuals with stroke are much more likely to have associated conditions than those without stroke.[15]

Despite the fact that a large proportion of stroke survivors experience lasting sequelae of stroke and associated conditions, practice guidelines are often based on studies with strict inclusion criteria that may not be generalizable to this population. Van Peppen and colleagues[16] acknowledged that almost 90% of the recommendations in their guidelines were based on the results of intervention studies involving participants with a less severe or uncomplicated stroke; their guidelines were therefore aimed at a sub-group of patients.

Gaynor and colleagues[17] showed that, in stroke rehabilitation studies, participants' mean age was significantly lower than that observed in daily practice. A secondary finding was that the trials had excluded participants with cognitive impairment, dysphasia, and multiple strokes. Kafri and Dickstein[10] found that recurrent stroke, comorbidities, cognitive status, walking ability, and place of residence were major reasons for excluding potential participants in intervention studies aimed at improving gait in individuals with stroke. Recently, Nelson and colleagues[18] confirmed that RCTs of stroke rehabilitation had often excluded individuals with comorbidities. Previous investigations of the generalizability of RCTs have included a variety of subdisciplines[17,18] focused on a primary exclusion criterion such as age[17] or comorbidity,[18] or a specific area of intervention, such as gait rehabilitation.[10]

With the aim of evaluating the generalizability of results from RCTs investigating physiotherapy interventions after stroke, we reviewed a random sample of RCTs. In particular, we wanted to identify the characteristics that led to the exclusion of potential participants and to investigate whether included participants were representative of the general population with stroke.

METHODS

We conducted a literature search of RCTs in the Physiotherapy Evidence Database (PEDro). We selected and randomized the sample of eligible studies on May 22, 2017.

PEDro is a free database, updated every month, that indexes RCTs, systematic reviews, and practice guidelines in the field of physiotherapy. It assesses the reported methodological quality of each RCT using the PEDro scale,[19,20] which consists of 10 criteria. Studies are rated on the randomness and concealment of allocation; baseline comparability between groups; blinding of participants, therapists, and assessors; adequacy of follow-up assessments; intention-to-treat analysis; between-groups comparisons; reporting of point estimates; and variability. Because the first item (eligibility criteria) is not scored, the total score can range from 10 (*all criteria are satisfied*) to 0 (*none of the criteria are satisfied*); a score of 6 is considered the threshold for identifying high-quality studies.[21]

Within the subdiscipline neurology we searched the database using the key words *stroke, cerebrovascular accident,* and *cerebrovascular disorders*. The following therapy categories, representing the field of therapeutic exercise, were used as filters: *neurodevelopmental therapy, neurofacilitation, behaviour modification, fitness training, skill training, strength training,* and *stretching-mobilisation-manipulation-massage*.

To be included, articles had to assess an experimental physiotherapy intervention administered to individuals with stroke; have a PEDro score of 6 or higher; be written in English, French, Italian, German, or Spanish; and provide a clear description of the eligibility criteria for participants. We did not perform a formal sample size calculation because of the lack of preliminary data; indeed, previous studies differed from this one in eligibility criteria, sources, and methods of study selection.

We selected a random convenience sample of 100 studies. We performed the random selection by entering the sequence numbers of all the titles acquired from the search into Research Randomizer, a free online randomization tool (https://www.randomizer.org). Following the randomized sequence, we then assessed the studies for eligibility until the desired sample size was reached. Full texts were retrieved and assessed for inclusion by one investigator (CP), who provided the reasons for exclusion

for each study that was eventually excluded. For each selected study, two independent researchers (CP and MP) extracted the mean age and gender of participants, sample size, year of publication, PEDro score, and inclusion or exclusion criteria. Disagreements were resolved by consensus. Data analysis included descriptive statistics; the eligibility criteria reported were described as percentage frequency and 95% CI.

RESULTS

The literature search identified 1,005 studies, with 243 duplicates, resulting in 762 unique trials. After randomization, we assessed 109 articles for eligibility. The selection process led to the exclusion of 9 articles; 6 were in languages other than the pre-established ones (1 was in Turkish, and 5 were in Chinese), 1 focused on individuals with Parkinson's disease, 1 did not explicitly state the eligibility criteria, and we could not retrieve the full text of 1 article. The articles included in the analysis represented 13% of the identified trials (see Figure 1). A total of 7,366 participants were included in the selected studies, with a mean weighted age of 65.5 (SD 6.7) years (range 52–71 y). Women made up 41.6% of the sample. The sample size ranged from 10 to 2.104 participants (mean 73.6), and the subacute and chronic phases of the disease were equally represented (about one-third of the studies, whereas residual studies did not discriminate between phases). The year of publication of the reviewed RCTs ranged from 1999 to 2016 (see Figure 2). The PEDro scores of the selected RCTs ranged from 6 to 9, with a median of 7; data are absolute frequency (see Figure 3).

The most frequent exclusion criteria we observed were comorbidity (83%), cognitive impairments (69%), recurrent stroke (53%) and low functional level (47%; determined from the inclusion criteria), and being elderly (aged >75 y; 25%). The presence of spasticity was an exclusion criterion in more than 20% of the studies. If the exclusion criteria presence of aphasia or dysphasia and

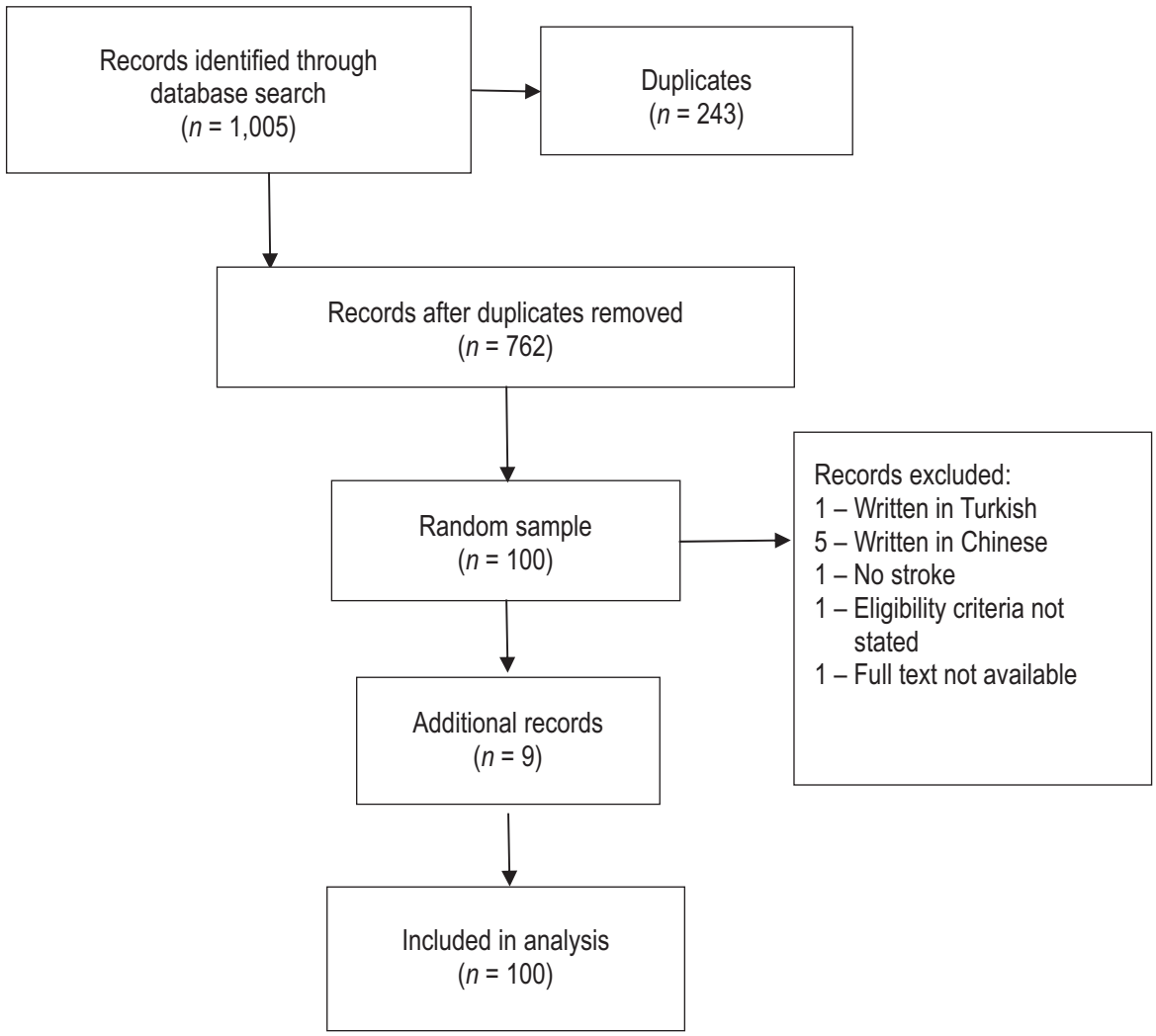

Figure 1 Flow chart of study selection.

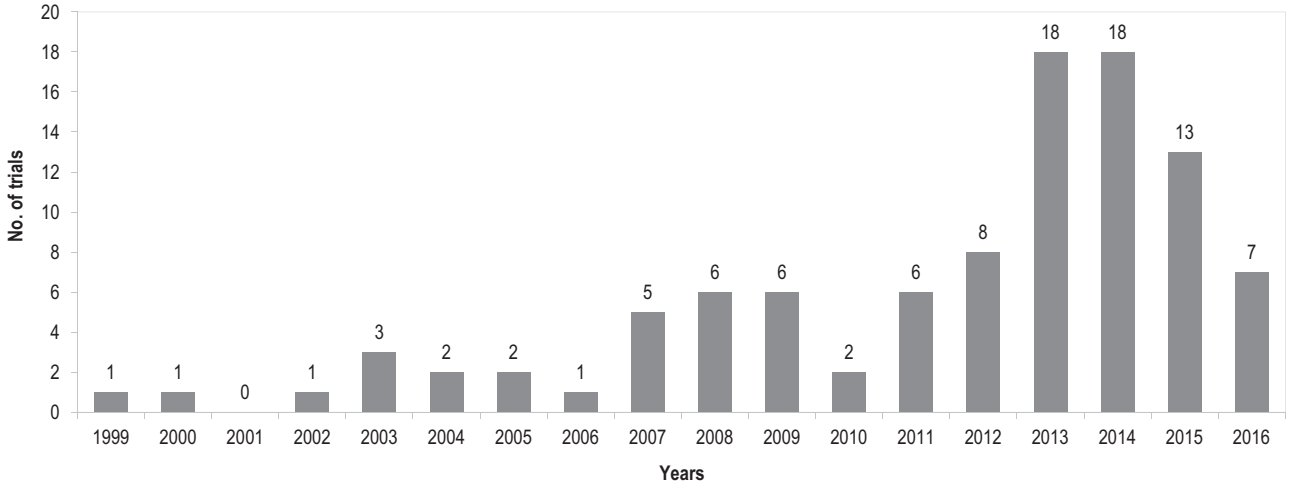

Figure 2 Number of included trials by year of publication.

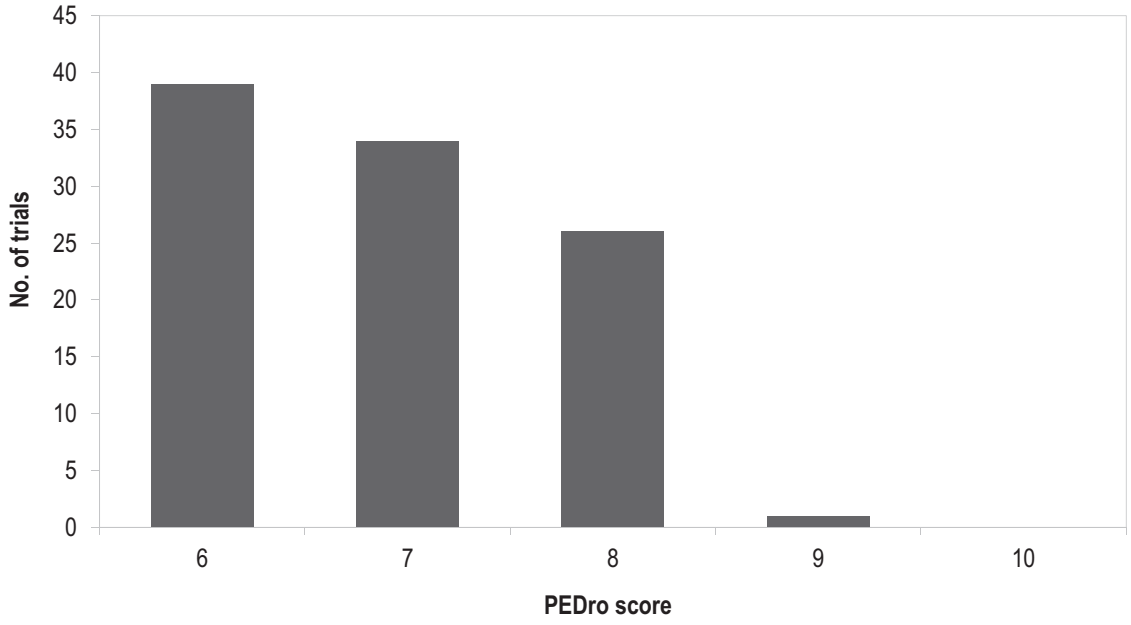

Figure 3 PEDro scores of included trials.

PEDro = Physiotherapy Evidence Database.

absence of good communication skills were grouped with the inclusion criterion able to understand simple instructions, the global criterion communication skills was used to exclude individuals in 55% of the studies. Being able to walk independently and having good balance were criteria for inclusion in 27% and 24% of the studies, respectively (see Tables 1 and 2).

DISCUSSION

A variety of criteria led to patients being included or excluded from participating in RCTs of physiotherapy interventions after stroke. Communication skills and comorbidity seemed to be the most influential criteria. Our findings regarding the criteria used to select the participants showed that large cohorts of individuals treated in clinical practice are excluded from participating in RCTs in the field of physiotherapy after stroke.

Age was an explicit exclusion criterion in 25% of the studies. The participants in our sample of studies had a mean age of 65.5 years and were therefore quite like those reported by Gaynor and colleagues[17] and Nelson and colleagues.[18] The average age of individuals post-stroke is approximately 75 years,[17] so the age range of the samples in the reviewed articles implies that the studies' participants do not fully represent the real population with stroke. Gender is rarely adopted as an eligibility criterion in RCTs that investigate

Table 1 Reported Inclusion Criteria for Included Studies

Criterion	Relative frequency (95% CI)	References*
High functional level	53 (43, 63)	1–3, 6, 8, 10, 12, 13, 15, 16, 18, 20, 23, 24, 29, 32, 35, 38, 42, 44–47, 49, 52–55, 58, 62, 63, 66, 67, 69–74, 77, 79–82, 85, 87, 89–91, 97–100
First stroke	47 (37, 57)	5, 10, 11, 13, 14, 17–19, 21, 23, 24, 26, 29, 30, 32, 35–37, 40–42, 45, 47, 49, 51, 52, 56–59, 61, 62, 67, 69, 71, 73, 76, 82, 83, 85, 88, 90, 93–95, 97, 100
Aged > 18 y	40 (30, 50)	1, 2, 5, 6, 9, 10, 12, 14, 17, 18, 22–27, 30, 31, 36, 40, 47–50, 56, 61, 63–66, 74, 76, 82–84, 88, 90, 91, 94, 95
< 6 mo post-stroke	34 (25, 43)	1–3, 7, 9, 10, 17, 24, 29, 32, 33, 35, 38, 40, 41, 43, 44, 48, 50–52, 55, 61, 79, 80, 81, 83, 89, 90, 92, 96–98, 100
Good communication skills	39 (29, 49)	2–4, 7, 11–14, 17, 19, 22–25, 28, 29, 40, 47, 48, 58–61, 65, 66, 72, 75–79, 82, 86, 88, 91, 94, 97, 99, 100
> 6 mo post-stroke	32 (23, 41)	5, 8, 11–13, 15, 16, 23, 25, 28, 42, 46, 47, 49, 53, 54, 57, 58, 62, 64–69, 71, 75, 76, 78, 84, 91, 95
Ability to walk independently	27 (18, 36)	3, 5, 6, 10, 14, 27, 28, 36, 42, 47, 50, 57, 64, 65, 71, 72, 74, 75, 78, 80, 82, 84, 86, 87, 91, 95, 98
Good balance	24 (16, 32)	3, 7, 12, 15, 18, 25, 33, 35, 37, 41, 51, 60, 69, 70, 73–75, 77, 83–85, 93, 99, 100
Able to understand simple instructions	29 (20, 38)	7–9, 11–13, 23, 27, 29, 37, 38, 40, 43, 48, 51, 55, 56, 58, 64, 67, 72, 73, 76, 81, 90, 91, 96–98
Low functional level	9 (3, 15)	9, 17, 32, 41, 56, 61, 78, 83, 94
Autonomy in basic activities of daily living	4 (0, 8)	23, 32, 77, 82

* The numbers shown in this column refer to references listed in Appendix.

Table 2 Reported Exclusion Criteria of Included Studies

Criterion	Relative frequency (95% CI)	References*
Comorbidities	83 (76, 90)	2, 4–10, 12–14, 16, 17, 20–24, 26, 28, 29, 31–42, 44, 47–64, 66–69, 71, 72, 74–87, 89, 90, 92–100
Cognitive impairments (Mini-Mental State Exam with different or unidentified cutoff)	69 (60, 78)	2–4, 7–13, 15–17, 19, 20, 22–24, 27–30, 33, 35, 36, 40–42, 44–48, 51–55, 57–61, 63–66, 68–73, 75, 77–80, 82, 83, 85, 89–92, 94, 95, 99, 100
Aged > 75 y	25 (17, 33)	7, 9–11, 18, 25–27, 36, 49, 54, 55, 59, 63, 65–68, 78, 79, 84, 85, 89, 91, 99
Neglect or visual impairments (e.g., hemianopsia)	29 (20, 38)	9, 11–13, 17, 23, 25, 35–40, 44, 47–49, 53, 55, 57–59, 61, 62, 68, 72, 75, 76, 83, 86
Spasticity	21 (13, 29)	8, 10, 15, 17, 18, 21, 23, 26, 32, 42, 45, 46, 58, 59, 61, 68–70, 76, 77, 83
Aphasia	26 (17, 35)	2–4, 7, 11, 13, 17, 19, 23–25, 28, 29, 40, 47, 48, 58, 61, 72, 75–77, 79, 82, 86, 97
Previous rehabilitation treatments	17 (10, 24)	2, 15, 19, 22, 38, 42, 43, 45–47, 61, 64, 66, 68, 92, 99, 100
Physical pain	17 (10, 24)	3, 16, 18, 29, 38, 40, 41, 47, 51, 66, 71, 74, 76, 77, 80, 83, 92
Sensory deficits	12 (6, 18)	10, 29, 35, 37, 41, 48, 51, 59, 63, 68, 73, 85
Hospitalization	12 (6, 18)	1, 2, 4, 5, 12, 18, 28, 34, 50, 58, 62, 65
Apraxia	12 (6, 18)	2, 11, 13, 19, 23, 40, 41, 48–51, 58
Hearing deficits	6 (1, 11)	39, 53, 55, 57, 72, 75
Depression	4 (0, 8)	16, 65, 76, 89
Attention deficits	4 (0, 8)	17, 48, 49, 76
Risk of falling	1 (0, 3)	3

* The numbers shown in this column refer to the references listed in the Appendix.

physiotherapy interventions after stroke. The proportion of women in our sample (41.6%) was comparable to that reported by Gaynor and colleagues;[17] however, as Nelson and colleagues[18] underscored, women aged older than 64 years have a greater rate of stroke rehabilitation admissions than men.[22]

Although evidence has suggested that in less than 6% of cases, stroke occurs in people with no comorbidity,[15,23]

a large number of the trials analyzed in this study excluded people with associated medical conditions (83%). Comorbidity has a negative correlation with the functional outcomes achieved by individuals during post-stroke rehabilitation;[24] including participants with this characteristic should be one of the key determinants of the external validity of RCTs in the physiotherapy literature. However, we must acknowledge that the lack of consensus about the definition of comorbidity makes it a complex issue.[25] In our study, we defined *comorbidity* as the presence of one or more conditions other than stroke and any stroke-related comorbidity reported as an exclusion criterion. The conditions frequently described as comorbidities were heart disease, hypertension, and orthopedic or neurological disabling deficits. In some cases, associated pathologies were generically reported as comorbidity.

Of the articles in our sample, 69% excluded people with cognitive impairments. As reported by Kafri and Dickstein,[10] the prevalence of cognitive decline among individuals post-stroke varies from 20% to 80%, with differences across countries, races, and diagnostic criteria.[26] In Europe, Douri and colleagues found, using the Mini-Mental State Exam, that the prevalence of cognitive impairments 3 months after an event is about 35% and deficits persist in 20% of people after 6 months,[26] whereas, using complete neuropsychological tests, the prevalence rises to 96%. Kafri and Dickstein[10] also reported that more than half the studies had excluded patients with recurrent stroke (53%), although recurrent stroke accounts for almost 25% of all ischemic or hemorrhagic events.[27]

Communication skills play an important role in patients' positive participation in rehabilitation and restoration of independent life.[28] A German study showed that 30% of stroke survivors had chronic aphasia and an inability to understand or speak correctly; 1 year after the event, about half these individuals still showed aphasia-related deficits.[29] A lack of communication skills was observed as an exclusion criterion in 55% of the articles reviewed; this is probably due to the difficulty of obtaining informed consent and reaching informed decisions about the research process.[30]

Our findings are similar to those reported in previous literature,[10,17,18] although the percentages for exclusion criteria reported in other studies are generally lower (see Table 3). These differences could be due to the dissimilarity in the fields examined (general rehabilitation or gait rehabilitation vs. physiotherapy) and the ambiguity in reporting the criteria[1] as well as the fact that previous studies did not consider all the exclusion criteria.

As a post hoc analysis, we pooled the mean relative frequencies weighted by number of trials in each stroke rehabilitation study (this one and previous studies) that had reported on eligibility criteria; we performed this calculation, using StatsDirect statistical analysis software (StatsDirect Ltd, Birkenhead, United Kingdom), whenever at least three studies had reported on the same criterion (see Table 3). According to the pooled frequencies, comorbidity and cognitive impairment are likely to be exclusion criteria in a considerable number of RCTs. As a result of the broad 95% CIs, an estimate of the frequency with which recurrent stroke and age are used as exclusion criteria is uncertain. According to our findings, age and gender are used relatively little and almost never, respectively, as exclusion criteria; it is possible that there may be other barriers to the participation of older individuals and women with stroke in rehabilitation clinical trials.

Our study reports on several additional criteria not previously investigated (e.g., sensory deficits, pain, and spasticity), which only 10%–21% of the included studies had taken into consideration. Individuals with a lower functional level were excluded in about half the studies in our sample, but this finding was never reported. The prevalence of somatosensory deficits after stroke varies from 25% to 85%, depending on the parts of the body assessed and the outcome measures used.[31] The reported prevalence of post-stroke pain also varied among the studies (between 11% and 55%), depending on the amount of time from stroke onset, the definition and subtype of pain examined, and the sampled cohorts.[32] However, because it is not adequately recognized and treated, the prevalence of post-stroke pain has probably been underestimated.[32]

Table 3 Mean Relative Frequencies Weighted by Number of Trials in Each Stroke Rehabilitation Study that Reported on Eligibility Criteria

		Exclusion criteria, %*				
Study	No. of trials	Cognitive impairment	Dysphasia or aphasia	Recurrent stroke	Age	Comorbidity
Ours	100	69	55	53	25	83
Gaynor (2014)	182	46	23	13	13	n/a
Kafri (2016)	52	52	n/a	44	15	73
Nelson (2017)	428	55	n/a	36	n/a	83
No. of trials, pooled	n/a	762	282	762	334	580
Pooled mean frequency,* % (95% CI)	n/a	54 (42, 67)	n/a	33 (10, 57)	17 (1, 33)	82 (73, 90)

Note: n/a = not applicable.
* Weighted by the number of trials in each study.

The prevalence of spasticity varied as well, depending on the amount of time from stroke onset and the severity of the impairment; a recent systematic review reported a prevalence ranging from 17% to 43% of the population.[33] Both somatosensory deficits and pain have negative effects on motor and functional performance,[31,32] whereas spasticity is correlated with limitations on activity.[28]

The results of this study are limited to English language articles indexed in PEDro and of high methodological quality. We are aware that using a single database may be a source of inclusion bias; however, PEDro has virtually complete coverage of RCTs in physiotherapy.[34,35] RCTs with high internal validity are more likely to be selected as primary studies for systematic reviews or clinical guidelines.[36] Nevertheless, we do not know whether the same eligibility criteria could be observed in publications reporting RCTs of physiotherapy interventions after stroke with lower methodological quality or in a language other than English. These factors limit the generalizability of the findings.

We recognize that the sample size of 100 was arbitrary, and whether the included studies represent the eligible sample is uncertain. However, using random sampling across a population minimizes selection bias;[37] moreover, we did not screen the eligible sample for inclusion. If we consider only the articles that eventually met the criteria for inclusion in our review, they may represent a larger percentage of the eligible sample.

The frequencies of eligibility criteria observed here should be interpreted with caution, because we often observed large CIs. The variability is probably due to the heterogeneity of the aims, methods, and interventions across the studies. In future RCTs, it would be desirable to consider for analysis specific aspects of the studies such as phase of the disease, type of stroke, and intervention administered. Moreover, considering the pooled frequencies, one consideration should be that some RCTs may have been analyzed in more than one stroke rehabilitation study that reported on eligibility criteria, thereby inflating the size of pooled samples.

CONCLUSIONS

Our results suggest that eligible individuals with conditions frequently observed in daily clinical practice are systematically excluded from participating in trials. This issue might represent a bias for systematic reviews and clinical guidelines, with the result that individuals who have had a stroke receive ineffective treatments and inadequate clinical pathways. The ageing of the general population, with the increasing prevalence of cognitive and communication disorders and comorbidity, requires that this frailer cohort of participants be adequately represented in trials.

Including these individuals could require revisiting and developing suitable outcome measures and reorganizing study designs to reflect real-world health care situations in a general clinical setting. Further barriers to the participation of older individuals and women in RCTs of physiotherapy interventions after stroke should also be researched.

KEY MESSAGES

What is already known on this topic

The generalizability of the results of a randomized controlled trial (RCT) can be affected by dissimilarities between the trial protocols and routine practice, such as setting, outcome measures, and individuals' characteristics. Inclusion and exclusion criteria are important issues in assessing the external validity and relevance of an RCT in clinical practice.

What this study adds

The most frequent criteria for exclusion from RCTs published in the field of physiotherapy after stroke are comorbidity, communication skills, and cognitive impairments. Individuals with these characteristics represent a substantial proportion of the population with stroke in the real world and consequently of those treated in clinical practice.

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