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REVIEW ARTICLE

Female Enrollment in Rehabilitation Trials: A Systematic Review of Reporting Sex and Female Participation in Randomized Controlled Trials of Poststroke Upper Extremity Rehabilitation Over 50 Years

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Abstract

Objective: To systematically assess the reporting of sex and the percentage of female participants in randomized controlled trials (RCTs) examining interventions for the post-stroke rehabilitation of upper extremity (UE) motor disorders.

Data Sources: CINAHL, Embase, PubMed, Scopus and Web of Science were searched from 1960 to April 1, 2021. Additional articles were identified using the Evidence-Based Review of Stroke Rehabilitation.

Study Selection: Studies were eligible for inclusion if they (1) were RCTs or crossovers published in English, (2) ≥50% of participants were diagnosed and affected by stroke, (3) included adults ≥18 years old, and (4) applied an intervention to the hemiparetic UE as the primary objective of the study.

Data Extraction: Two investigators independently screened the title and abstracts, and duplicates were removed. A full-text review was done for studies that met all inclusion criteria. Data were extracted using a custom data extraction template in Covidence and were transferred to online Excel (V16) for data management. Study characteristics and extracted variables were summarized using standard descriptive statistics. Data analyses were performed using SPSS (V29.0).

Data Synthesis: A total of 1276 RCTs met inclusion criteria, and of these, 5.2% did not report results on sex, accounting for 5.6% of participants. Women have been underrepresented in stroke RCTs, accounting for 38.8% of participants. Female participation was greater in the acute poststroke phase than in the chronic and subacute phases. Over almost 5 decades, there has been a small decrease in the proportion of female participants in these trials.

Conclusions: Evidence-based medicine for the treatment and prevention of stroke is guided by results from RCTs. Generalizability depends on sufficient representation in clinical trials. Stakeholders, such as funders and journal editors, play a key role in encouraging researchers to enroll enough of both sexes and to report the presence or absence of sex differences in RCTs.

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Historically, female participants have not been included in randomized controlled trials (RCTs) as frequently as male participants across many areas of medical research, specifically as they age.[1] This trend holds true in acute stroke research,[2] despite the fact that more women are living with the effects of stroke than men[3] and that women have a higher mortality rate post stroke.[4]

Stroke rehabilitation is an essential part of stroke care,[5] especially for those with moderate to severe strokes. Differences in functional outcomes after stroke rehabilitation have been described based on sex, though the findings are occasionally conflicting[6-8] and the overall information in this area is limited. Previous studies showed underrepresentation of female participants in trials of various medical conditions.[2,9-12] It is not currently known whether women are enrolled in stroke rehabilitation RCTs at a comparable rate to men. Because of disparities in sex for acute stroke and other medical conditions, stroke rehabilitation RCTs may not be generalizable to as much as half of the affected population.

The current systematic review investigates the rate of female subjects enrolled in RCTs assessing upper extremity (UE) motor disorders and function post stroke while exploring differences in other study characteristics, including time post stroke, methodological quality, and sample size. We examined UE motor rehabilitation trials because this topic is one of the most-studied research topics in stroke recovery, is important to people with stroke, and is likely representative of other stroke rehabilitation trials. Identifying if notable differences exist in the ratio of women to men enrolled in published stroke rehabilitation RCTs is an important first step in rectifying potential barriers and, ultimately, leading to more generalizable outcomes across sexes.

The main objective of this study is to examine RCTs assessing interventions for post stroke rehabilitation of UE motor disorders to investigate (1) the proportion of female participants enrolled over years; (2) whether the sex ratio is reported; and 3) whether female enrollment differed across RCTs with different levels of study quality and time poststroke phase.

Methods

The present systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses.[13] A protocol was not pre-registered for this review.

Definitions

In the context of this paper, sex refers to a set of biological attributes associated with chromosomes, genes, hormones, and reproductive systems.[14] On the other hand, gender refers to the roles, behaviors, and identities that are socially constructed to define male, female, and gender-diverse individuals.[14] Neither of these attributes are necessarily binary; however, the distinction between sex and gender can be challenging to identify by abstracting information from publications. Only 2 sexes (male and female) were reported in the literature that we analyzed. Therefore, we will only discuss biological sex throughout this paper, for simplicity and without prejudice.

List of abbreviations:

PEDro	**Physiotherapy Evidence Database**
RCT	**randomized controlled trial**
UE	**upper extremity**

Search strategy

Articles from CINAHL, Embase, PubMed, Scopus, and Web of Science were reviewed from 1960 to April 1, 2021, using the following search query: (*Stroke* OR *Cerebrovascular Accident* OR *CVA*) AND (*upper extremity* OR *upper limb* OR *arm* OR *hand* OR *shoulder*) AND (*Remediation* OR *Therapy* OR *Rehabilitation* OR *Intervention* OR *Stimulation* OR *Exercise* OR *Pharmacotherapy* OR *Medications* OR *Drug* OR *Pharmaceutical*). Where applicable, filters for "randomized controlled trial," "English," and "Human" were applied. Additional articles were identified through hand searching reference lists of the Evidence-Based Review of Stroke Rehabilitation.

Inclusion criteria

Inclusion criteria were determined *a priori.* Articles were included if they (1) had RCT or RCT crossover designs; (2) included adults ≥18 years old; (3) included participants diagnosed and affected by stroke (at least 50% poststroke participants in mixed-etiology study populations); (4) applied an intervention to the hemiparetic UE as the primary objective of the study; and (5) were written in English. Studies were excluded if they were not an RCT design; were not in English; or were a secondary analysis of RCTs; follow-up papers; interim or incomplete studies; narrative reviews; or dissertations.

Study selection and data extraction

Results from the initial search were imported into Covidence[a] (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). After duplicates were automatically removed, 2 investigators independently screened the title and abstracts using the inclusion criteria specified above. The remaining studies were then read in full and assessed for final eligibility. Once articles were identified for inclusion, data were extracted from the articles using a custom data extraction template in Covidence. Data extracted from the articles relevant to this article included year of publication, authors' names, sample size, absolute numbers, and proportion of male and female participants. If data were missing for any of these variables, it was recorded as not reported. At each step, disagreements were discussed between assessors before a final decision was made. If disagreements could not be resolved between assessors, a third reviewer was used for consensus.

Quality evaluation

Risk of bias and methodological quality of the RCTs was assessed using the Physiotherapy Evidence Database (PEDro) scale (table 1).[15] The scale consists of 11 yes/no items that examine randomization procedures, baseline comparability, blinding, study attrition, between-group comparisons, and presentation of point estimates and measures of variability.[16] Articles were assessed based on each item and were then given a total score between 1 and 10 (the first item was excluded). One reviewer scored each RCT, unless the article was already scored in the PEDro database

Table 1 PEDro scoring items

Item	Criteria
*1	Eligibility criteria were specified.
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated in the order in which treatments were received).
3	Allocation was concealed.
4	The groups were similar at baseline regarding the most important prognostic indicators.
5	There was blinding of all subjects.
6	There was blinding of all therapists who administered the therapy.
7	There was blinding of all assessors who measured at least 1 key outcome.
8	Measures of at least 1 key outcome were obtained from >85% of the subjects initially allocated to groups.
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, when this was not the case, data for at least 1 key outcome was analyzed by "intention to treat."
10	The results of between-group statistical comparisons are reported for at least 1 key outcome.
11	The study provides both point measures and measures of variability for at least 1 key outcome.

NOTE.
* Item one is not included in the total score.

(available at www.pedro.org.au). Four of the PEDro items have been empirically validated (ie, randomization, concealed allocation, blinding, and adequacy of follow-up), while the remainder have face validity.[16] The quality of RCTs were classified as excellent (PEDro 9-10), good (PEDro 6-8), fair (PEDro 4-5), and poor (PEDro≤3).[17]

Statistical analysis

Extracted data were transferred from Covidence to online Excel (V16.0) for data management. Study characteristics and extracted variables were summarized using standard descriptive statistics. Data analyses were performed using SPSS[b] (V29.0). The female enrollment percentages and study characteristics including study quality, year of publication, and time post stroke were described and analyzed. Data were assessed for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests alongside histograms and Q-Q plots. The binominal test was used to compare the total proportion of male and female participants. The linear regression analysis was performed for the percentage of female participants and time. The regression model was done for the RCTs from 2000 because data from former years were limited and affected the homoscedasticity of data. The Kruskal-Wallis test followed by Dunn-Bonferroni posthoc analysis were used to compare female percentages in groups of RCTs with different time poststroke phase and study quality. A P value of .05 was considered significant.

Ethics

There were no human participants involved in this systematic review; therefore, this study did not require informed consent or ethics approval.

Results

Study selection

The search identified 5408 studies for screening; 2288 studies underwent full-text review, and 1276 RCTs met the eligibility criteria for inclusion in this review, accounting for 59,032 participants (fig 1). Overall, 76 different interventions for the hemiparetic UE rehabilitation were used in the 1276 RCTs. The most-frequent control comparators—which were not one of the UE interventions—were conventional therapy, sham or placebo treatment, and no treatment waiting list, respectively. The number of RCTs in which individual UE motor stroke rehabilitation interventions were studied are shown in supplemental table A (available online only at http://www.archives-pmr.org/). Of the RCTs analyzed, 5.2% did not report on sex, accounting for 5.6% of participants.

Sex differences overall

For the 1209 RCTs that reported on sex, the average percentage of female participants was 38.8%±13%. Comparing the total proportions of male and female in all RCTs, the binominal test showed that the number of male participants was significantly greater than female participants (P<.001).

Sex differences over time

Table 2 shows the number of RCTs where sex is reported or not reported and the percentage of female participants in the clinical trials for each year since 1972. Overall, the average of female participation seems to be higher in the years before 2000, when the number of RCTs was very limited compared to the time after 1999, with 46.1% female participants in 50 RCTs (fig 2). From 1972 to 1999, RCTs without sex reporting accounted for 14% of all RCTs, while this rate was 4.8% for RCTs after 1999. The linear regression of female participant percentages and time shows a small but significant decreasing trend of female percentages since 2000 (β=−0.64, t=−2.17, P=.03).

Sex differences and study quality

Table 3 shows the quality of RCTs based on PEDro scores and the subsequent proportion of female participants across each category. The percentage of female participants for RCTs with each specific PEDro score is also shown in figure 3. The mean percentage of female participants was relatively similar between the groups of studies with different qualities. The only statistically significant

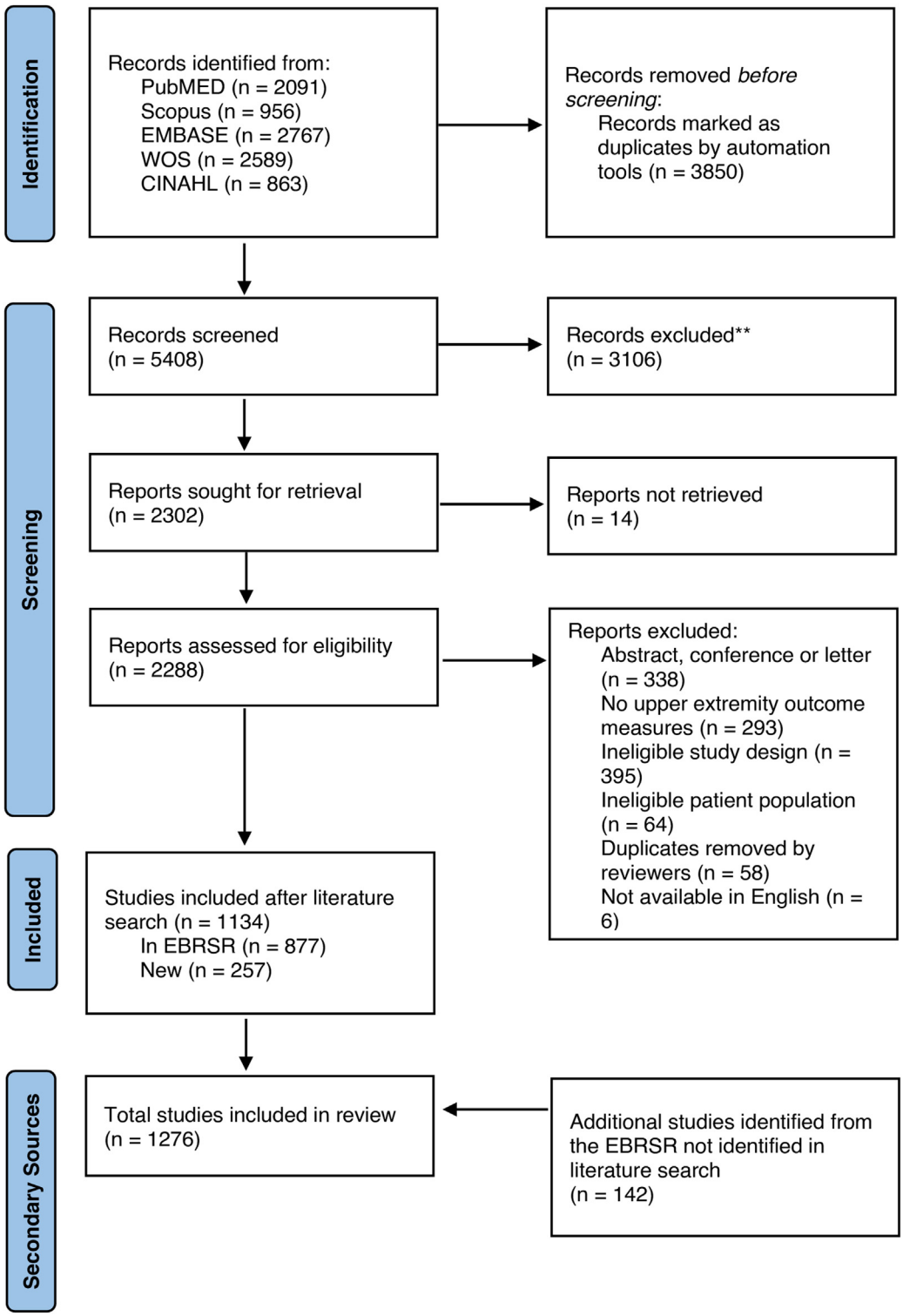

Fig 1 PRISMA flow diagram.

difference was between fair-quality RCTs with a higher percentage of female enrollment than RCTs with good quality (P=.02).

Sex differences and time post stroke

We examined whether there were significant differences associated with time post stroke and the percentage of female subjects enrolled in RCTs of UE motor disorder interventions. The proportion of female subjects decreased with longer time post stroke in participants (table 4). Comparing female ratios between the 3 time-poststroke groups, the percentage of female participants in RCTs of acute poststroke phase was significantly higher than those in subacute (P=.012) and chronic phases (P<.001).

Table 2 Total number RCTs, number of RCTs without sex reporting, and proportion of female participants by publication year

Year	Total RCTs	RCTs—Not Reported Sex (Count, %)	Female Participants (%)
1972	1	0 (0%)	54.5%
1973	0	0 (0%)	*N/A
1974	0	0 (0%)	N/A
1975	0	0 (0%)	N/A
1976	0	0 (0%)	N/A
1977	0	0 (0%)	N/A
1978	0	0 (0%)	N/A
1979	1	1 (100%)	N/A
1980	2	1 (50.0%)	35.0%
1981	0	0 (0%)	N/A
1982	1	1 (100%)	N/A
1983	1	0 (0%)	42.9%
1984	1	0 (0%)	33.3%
1985	0	0 (0%)	N/A
1986	1	0 (0%)	50.8%
1987	2	0 (0%)	49.2%
1988	1	0 (0%)	44.4%
1989	2	0 (0%)	49.2%
1990	5	1 (20%)	56.0%±14.5%
1991	1	0 (0%)	66.7%
1992	3	2 (66.7%)	54.5%
1993	1	0 (0%)	77.8%
1994	4	0 (0%)	40.5%±7.1%
1995	1	0 (0%)	51.9%
1996	5	0 (0%)	41.5%±13.7%
1997	2	0 (0%)	40.7%
1998	7	1 (14.3%)	42.3%±12.7%
1999	8	0 (0%)	47.6%±10.4%
2000	16	0 (0%)	44.0%±18.1%
2001	8	0 (0%)	41.8%±12.7%
2002	13	1 (7.7%)	44.0%±14.0%
2003	16	1 (6.3%)	41.3%±18.5%
2004	26	3 (11.5%)	42.9%±11.8%
2005	30	0 (0%)	46.5%±16.0%
2006	23	3 (13.0%)	40.5%±14.7%
2007	41	1 (2.4%)	40.2%±11.2%
2008	39	4 (10.3%)	40.5%±11.5%
2009	54	2 (3.7%)	39.4%±12.6%
2010	33	0 (0%)	36.2%±15.6%
2011	49	3 (6.1%)	38.7%±11.6%
2012	71	4 (5.6%)	36.8%±11.6%
2013	74	4 (5.4%)	37.5%±11.5%
2014	93	5 (5.4%)	38.6%±11.6%
2015	87	7 (8.0%)	36.3%±13.1%
2016	115	4 (3.5%)	38.2%±11.8%
2017	107	5 (4.7%)	38.5%±15.1%
2018	91	3 (3.3%)	36.5%±12.5%
2019	99	6 (6.1%)	37.7%±12.5%
2020	110	3 (2.7%)	38.9%±13.3%
2021 (Apr)	31	1 (3.2%)	40.5%±12.3%
Total	1276	67 (5.2%)	38.8%±13.0%

* N/A: Not applicable due to no RCT or recorded female number in that year.

Discussion

The primary finding from this systematic review is that women are underrepresented in poststroke rehabilitation trials relative to the general population, accounting for 38.8% of all participants in 1209 RCTs assessing UE motor disorder post stroke. To discuss the optimal proportion of male and female participants in rehabilitation trials, the underlying population characteristics and burden of disease need to be considered,[10,11] including differences in incidence and severity of disease, disability, recovery, mortality, morbidity, and specific treatment and rehabilitation needs by sex.[10,11]

Sex-specific stroke incidence and rehabilitation needs may be different by region. Worldwide, a higher incidence of stroke is reported in men, while women experience more severe stroke and at an older age than men.[3,18,19] The Heart and Stroke Foundation of Canada reported the incidence of stroke was essentially the same for both sexes, with a higher prevalence in women.[20] In the United States, women experience about 55,000 more strokes than men annually and have a higher prevalence compared to men.[3] Several studies have shown that women have more severe strokes, poorer functional outcomes, lower health-related quality of life, more dependency and lower recovery of activities of daily living, and more-restricted participation than men after stroke.[3,18,19,21,22] The fact that women experience less favorable poststroke outcomes highlights the importance of rehabilitation needs in female stroke survivors and the need to ensure they are well represented in stroke rehabilitation trials.

Recent studies have shown lower percentages of female enrollment in stroke trials.[2,11,12] Similarly, this study showed the underrepresentation of women in UE motor disorder rehabilitation RCTs. Despite recommendations and requirements for inclusion of female participants in clinical trials,[14,23] there was a small but significant decrease in the percentage of female subjects enrolled in UE motor disorder rehabilitation trials from 2000 to 2020. Comparing female enrollment between studies with different levels of quality also demonstrated that underrepresentation of female subjects was a challenge, even in good-quality studies, which are the most influential in determining levels of evidence. Ensuring sufficient inclusion of both sexes in clinical trials evaluating stroke is essential to more accurately assess the efficacy and safety of interventions. Insufficient representation of either sex in clinical trials hinders the generalizability of research findings.

Historically, women of childbearing age have been underrepresented in clinical trials because of concerns regarding reproductive health, hormonal fluctuations, and potential fetal harm.[24] These concerns led to exclusion criteria that disproportionally affected women.[25] Since then, efforts have been made to address sex biases and improve the inclusion of women in clinical research. The National Institutes of Health, European Commission, and Canadian Institute of Health Research have implemented policies requiring the consideration of sex as a variable in preclinical and clinical research.[14] Considering the implementation of these policies, and greater global recognition of sex biases in clinical research, we expected to see an increase in female recruitment over time; however, this was not the case. The reason for this finding is unknown, although a number of potential reasons are discussed below. The traditional concerns related to reproductive health and fetal harm would not apply to most stroke trials, because women suffering strokes are typically past childbearing age.

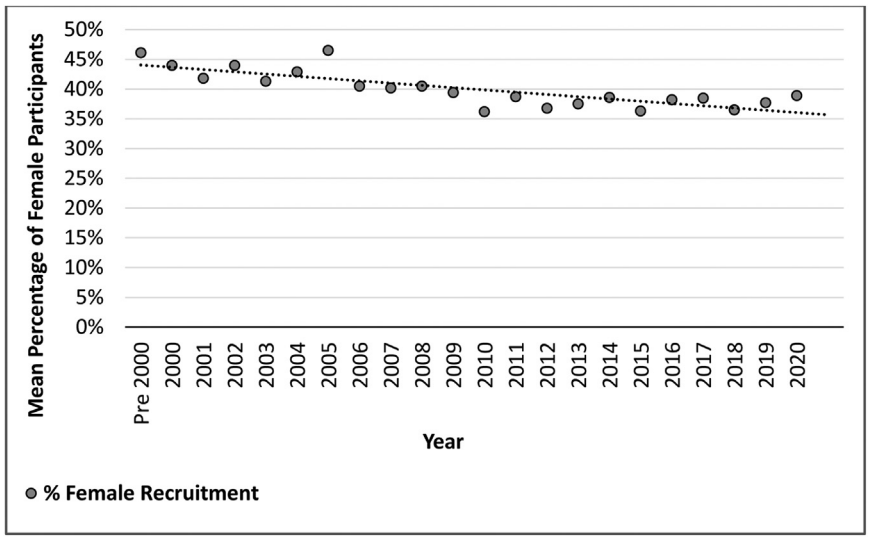

Fig 2 Percentage of female recruitment per annum.

Table 3 Study quality and mean percentage of female participants in each category

Study Quality	Total RCTs	RCTs—Not Reported Sex Count (%)	Female Participants (%)
Excellent (PEDro>8)	52	2 (3.8%)	37.1%
Good (PEDro 6-8)	794	29 (3.6%)	37.9%
Fair (PEDro 4-5)	363	24 (6.6%)	41.6%
Poor (PEDro≤3)	67	12 (17.9%)	37.8%

This study found that there was an improvement over time in the overall rate of poststroke UE rehabilitation RCTs that reported sex of participants, which is consistent with previously published literature.[25,26] This finding may reflect a growing recognition of the importance of considering sex as a biological variable in research. Although policies implemented by the National Institutes of Health, European Commission, and Canadian Institute of Health Research may not have led to greater inclusion of women in trials, they may have led to increased awareness of the influence of sex on health outcomes and a greater emphasis on sex-specific reporting. Although this trend is encouraging, an omission rate of 4.8% since 2000 should be improved on because sex is an essential component necessary for experimental replication.

A number of other factors not directly explored in this paper may influence the recruitment of women into clinical trials. Factors may include older age at stroke onset,[3,11] higher rates of post stroke depression and fatigue,[27,28] more dependency and limitations in activities of daily living in women,[11,21] all of which could hinder more women from participating in post stroke clinical trials. Given women suffer strokes at an older age on average and they have less favorable post stroke functional and recovery outcomes, they are more likely to live alone or rely on care givers and assisted living when compared to men,[29] which may further affect the willingness and ability of women to participate in trials.

This study showed that the proportion of female participants was significantly higher in RCTs conducted during the acute poststroke

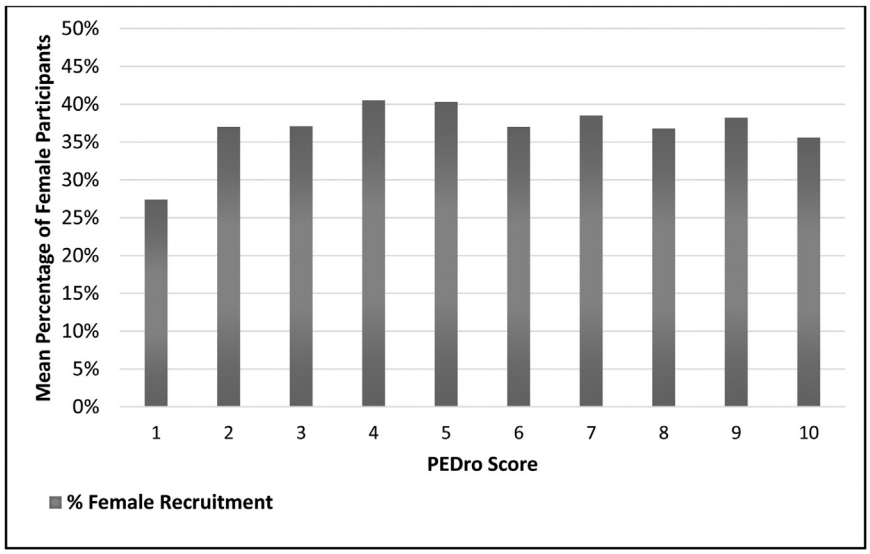

Fig 3 Percentage of female recruitment in studies with different PEDro scores.

Table 4 Mean percentage of female participants across RCTs with different time poststroke phases

Time Post Stroke	Total RCTs	RCTs—Not Reported Sex Count (%)	Female Participants (%)
Acute (<1 month)	246	13 (5.3%)	41.9%
Subacute (1-6 months)	317	23 (7.3%)	37.9%
Chronic (>6 months)	677	23 (3.4%)	37.3%
Not reported	36	8 (22.2%)	41.5%

phase when compared to the chronic and subacute phases. Other studies in Canada and USA indicated that female stroke survivors had longer lengths of stay in acute care and were more likely to be discharged to homecare facilities, while men were likely to be discharged home without care.[22,29] Female subjects may be more willing or able to participate in clinical trials when they are still admitted to hospital in the acute phase compared to the chronic phase where they are more likely to live alone or in long-term care.[22] However, the proportion of women recruited to RCTs is still lower than men (41.1%) even in the acute phase.

There are also barriers related to trial designs and criteria that may result in potential female participants being excluded. Women have identified transportation, cost, and time as difficulties in accessing trial sites and they were more reliant on their caregivers, which can be more challenging in studies with follow up visits.[30] As mentioned, older age at the time of stroke in women is related to higher rates of comorbidities, premorbid disability and worsening stroke severity, compared with men.[11,31] Accordingly, inclusion criteria such as upper age limits, meeting a certain score of stroke severity or motor function scale, and lack of mental/physical comorbidities may result in female stroke survivors being excluded more than male stroke survivors.[29]

These differences may contribute to an imbalance in sex recruitment and further research in this area is warranted.

Given the persistent underrepresentation of women in our extensive review of reported rehabilitation trials, it is recommended that researchers make extra attempts to recruit female subjects. One possible measure would be to modify the inclusion criteria to limit the exclusion of potential female participants. However, since participants in rehabilitation trials might need a minimum physical or cognitive capacity to perform exercises or follow instructions, inclusion criteria may not be expandable enough to include older poststroke women with more severe outcomes for all interventions. Reporting and comparing sex differences by intervention would reveal whether sex ratios differ by the nature of the intervention. As female participation declines with the chronicity of RCTs, it is recommended that trials conducted in the chronic poststroke phase better prioritize recruiting female participants from long-term care institutions, where women are more likely to live after stroke than men, or offer transportation to attend the trial. Because the population of interest in the poststroke rehabilitation trials are usually older adults who are experiencing some extent of disabilities, funding might be needed to provide transportation to research facilities or, when possible, conduct research in the community.

Study limitations

This study provides a very comprehensive overview on female enrollment is the UE motor disorder rehabilitation research field. However, this study has limitations. We did not analyze whether participation of women in stroke rehabilitation RCTs correlates with the overall incidence of stroke in women at the time the RCTs were performed. In this sense, future research should examine the overall incidence of stroke in women relative to their incidence in clinical trials. This study aimed to provide a broad overview of female enrollment in the poststroke UE rehabilitation trials worldwide; future studies are required to examine female recruitment in poststroke rehabilitation trials that take into account regional differences and epidemiologic characteristics of the populations under study. Additionally, few studies distinguished gender from sex, and there were no classification data beyond male/female reported in the studies. Further, the sex differences observed may reflect the eligibility criteria of trials, such as older age as an exclusion, and additional research is needed to determine the reasons women are excluded from clinical trials. Lastly, the findings of this study may not be generalizable to the rehabilitation of other important factors such as mobility or cognitive disorders, as we focused on UE motor disorder.

Conclusion

The data presented here highlight a need for education, awareness, and advocacy surrounding sex-based research recruitment, including the consideration of sex as a biological variable. Our analysis suggests there has been slight change in the inclusion of female participants in stroke rehabilitation research. If anything, there has been a small decline over time. There is a critical need for researchers to study the reasons for this imbalance and to develop recruitment strategies that reduce the effect of barriers to participation. Stakeholders, such as granting agencies and journal editors, play a key role in encouraging researchers to enroll enough of both sexes and to mandate the reporting of sex differences in RCTs.

Suppliers

a. Covidence, Veritas Health Innovation. b. SPSS; IBM.

Keywords

Differences; Female; Gender equity; Patient participation; Rehabilitation; Sex; Stroke; Upper extremity

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