RESEARCH ARTICLE

# Representation of Women in Stroke Clinical Trials

## A Review of 281 Trials Involving More Than 500,000 Participants

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## Abstract

### Background and Objectives

Women have been underrepresented in cardiovascular disease clinical trials but there is less certainty over the level of disparity specifically in stroke. We examined the participation of women in trials according to stroke prevalence in the population.

### Methods

Published randomized controlled trials with ≥100 participants enrolled between 1990 and 2020 were identified from ClinicalTrials.gov. To quantify sex disparities in enrollment, we calculated the participation to prevalence ratio (PPR), defined as the percentage of women participating in a trial vs the prevalence of women in the disease population.

### Results

There were 281 stroke trials eligible for analyses with a total of 588,887 participants, of whom 37.4% were women. Overall, women were represented at a lower proportion relative to their prevalence in the underlying population (mean PPR 0.84; 95% confidence interval [CI] 0.81–0.87). The greatest differences were observed in trials of intracerebral hemorrhage (PPR 0.73; 95% CI 0.71–0.74), trials with a mean age of participants <70 years (PPR 0.81; 95% CI 0.78–0.84), nonacute interventions (PPR 0.80; 95% CI 0.76–0.84), and rehabilitation trials (PPR 0.77; 95% CI 0.71–0.83). These findings did not significantly change over the period from 1990 to 2020 ($p$ for trend = 0.201).

### Discussion

Women are disproportionately underrepresented in stroke trials relative to the burden of disease in the population. Clear guidance and effective implementation strategies are required to improve the inclusion of women and thus broader knowledge of the impact of interventions in clinical trials.

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## Glossary

**CI** = confidence interval; **GBD** = Global Burden of Disease; **ICH** = intracerebral hemorrhage; **PPR** = participation to prevalence ratio; **SSWM** = sample size weighted mean.

Globally, women and men (age >25 years) have an equal, 1 in 4, risk of experiencing a stroke in their lifetime.[1] Of the nearly 14 million people who have a stroke worldwide each year,[2] there are differential consequences between the sexes, with women experiencing worse functional outcomes and requiring more supportive care.[3-5] In an analysis of more than 19,000 patients with individual participant data from randomized controlled trials in acute stroke, men had greater case fatality whereas women had greater loss of health-related quality of life.[5] Another systematic review of patient-reported outcomes indicates that women experience greater participation restriction or handicap than men.[6]

Improved understanding of sex disparities in stroke risk and care are critical to the design, analysis, and interpretation of the effects of interventions for the prevention, treatment, and recovery of stroke. Central to this effort is sufficient representation of both sexes in randomized controlled trials, considered the gold standard for testing the effectiveness of interventions to inform clinical practice. Rather than targeting an exact sex parity, where there is 50% enrollment of each sex, participation in stroke trials should ideally reflect the sex-specific prevalence of stroke in the underlying target population. Enrolling patients who reflect the source population likely to benefit from the trial findings increases the likelihood that the results are generalizable beyond the trial participants. Although studies have shown varying degrees of representation of women in cardiovascular trials,[7-9] only recently has this issue been examined among published stroke trials.[10]

Herein, using a large database, we aim to investigate the participation of women in stroke trials according to the stroke prevalence in the population being investigated. We explored whether participation differed by age, pathologic subtype, intervention group, and region.

## Methods

### Data Source and Selection

This study builds upon a prior review of recruitment of women in stroke trials, which identified 277 published trials up to December 31, 2018, the details of which are described elsewhere.[11] For this study, we searched ClinicalTrials.gov for data on randomized controlled trials listed as completed or terminated from January 1, 2019, to January 31, 2020, with the following criteria: randomized, interventional, stroke and cerebrovascular accident trials including both women and men, with ages ≥18 years and ≥100 participants enrolled. ClinicalTrials.gov is a web-based registry, supported by the US National Library of Medicine, of human clinical studies conducted around the world.[12]

Identified trials were included if data of study characteristics and final results were published in a journal. The publication status of the trials was verified systematically.[11,13,14] The Clinicaltrials.gov webpage was initially searched for relevant publications; then the PubMed database was searched using the national clinical trial identifier assigned to the trial. If no matching publication was found, Google Scholar and the Scopus database were explored using the national clinical trial identifier, trial name, and primary investigator name.

Data were extracted on (1) year of publication; (2) mean age of patient population; (3) total number of patients enrolled; (4) the proportion of included female and male participants; (5) type of stroke; (6) type of intervention; (7) number of study sites; and (8) location by country. The type of interventions was divided into acute (intervention within 24 hours of symptom onset), nonacute, and rehabilitation. Type of stroke was subdivided into ischemic, hemorrhagic (intracerebral hemorrhage [ICH] only), or mixed. Subarachnoid hemorrhage trials were not included in our analysis.

Stroke prevalence data were obtained from the Global Burden of Disease (GBD) study.[15] Data on each country were extracted and split by sex, age (<70 or ≥70 years), and type of stroke. Where trials were conducted in a single country location, country-specific prevalence estimates were used. Where trials were conducted across multiple countries, regional (Asia–Pacific, North America, or Europe) or across more than one region (worldwide) prevalence estimates were assigned to the respective trials.

### Statistical Analysis

The primary study outcome was female participation to prevalence ratio (PPR), which is a relative measure that weights the percentage of women participating in a trial against the prevalence of women in the disease population.[7,8]

The percentage of women among the disease population was estimated as follows: percentage of women among disease population = (prevalence of disease among women/total prevalence of disease among women and men) × 100.

PPR was estimated overall and by age group (<70, ≥70 years), type of stroke (ischemic, ICH, mixed), intervention (acute, nonacute, rehabilitation), and region (Asia-Pacific, North America, Europe, worldwide).

To assess whether PPR varied by study sample size, we plotted this figure together with mean PPR and a sample size weighted mean (SSWM) of the PPR across all trials. SSWM was calculated by multiplying the trial PPR by the trial sample

size and dividing by the sum of participants in all trials included in this study. The sum of this quantity is the SSWM. Bootstrap methods were used to obtain 95% confidence intervals (CIs) for the mean PPR and SSWM, using the percentile method with 100,000 iterations. As a sensitivity analysis, we calculated the mean PPR with bootstrapped 95% CIs by number of participants in a trial (<1,000 participants, 1,000–4,999 participants, ≥5,000 participants).

Trends over time were displayed overall by number of trials and mean PPR.

All data analysis was performed in R version 4.0.2 (R Core Team, 2020).

### Standard Protocol Approvals, Registrations, and Patient Consents

Research involving the use of existing collections of data or records that contain nonidentifiable data are exempt from ethics review in Australia.

### Data Availability

Access to de-identified data is available upon reasonable request through the corresponding author.

## Results

Over the previously identified 277 trials, we found 18 more stroke clinical trials on clinicaltrials.gov listed as completed or terminated from January 1, 2019, to January 31, 2020 (eTable 1, doi.org/10.5061/dryad.02v6wwq37). Of the 18 trials, only 4 were published, and therefore a total of 281 eligible stroke trials were identified from January 1, 1990, to January 31, 2020. These trials included 588,887 participants, of whom 37.4% were women. The number of participants in the trials ranged from 100 to 26,449, with a mean of 2,096 (SD 4,583) and median of 362 (interquartile interval 163,1193). There were 182 trials conducted in a single country (64.8%), with approximately equal representation across regions (Table 1). The participation of women varied widely across individual trials, from 3% to 78%, with a mean of 40% (eFigure 1 and eTable 1, doi.org/10.5061/dryad.02v6wwq37). Based on GBD data, the mean prevalence of stroke in women across countries was 48% (range 40%–56%) (eFigure 2 and eTable 2). The overall mean age of the participants in the trials was 65 years. There were 214 trials (76%) that had a mean age <70 years, and 67 had a mean age ≥70 years. According to pathologic subtype, there were 143 ischemic trials, 3 ICH trials, and 135 with mixed stroke types. There were 71 acute, 168 nonacute, and 41 rehabilitation trials.

Overall, across all stroke types, women were represented at a lower proportion relative to the proportion in the underlying stroke population (mean PPR 0.84; 95% CI 0.81–0.87). The disparity was greatest for ICH trials (PPR 0.73; 95% CI 0.71–0.74), trials with a mean age of participants <70 years (PPR 0.81; 95% CI 0.78–0.84), nonacute intervention (PPR 0.80; 95% CI 0.76–0.84), and rehabilitation trials (PPR 0.77; 95% CI 0.71–0.83) (Figure 1, Table 2). For regions, Europe (PPR 0.90; 95% CI 0.85–0.95) had the highest representation; Asia–Pacific (PPR 0.79; 95% CI 0.74–0.83) had the lowest. A total of 77% of trials had a PPR <1 (eFigure 3, doi.org/10.5061/dryad.02v6wwq37), and the mean PPR did not significantly change over the 1990 to 2020 period ($p$ for trend = 0.201) (Figure 2).

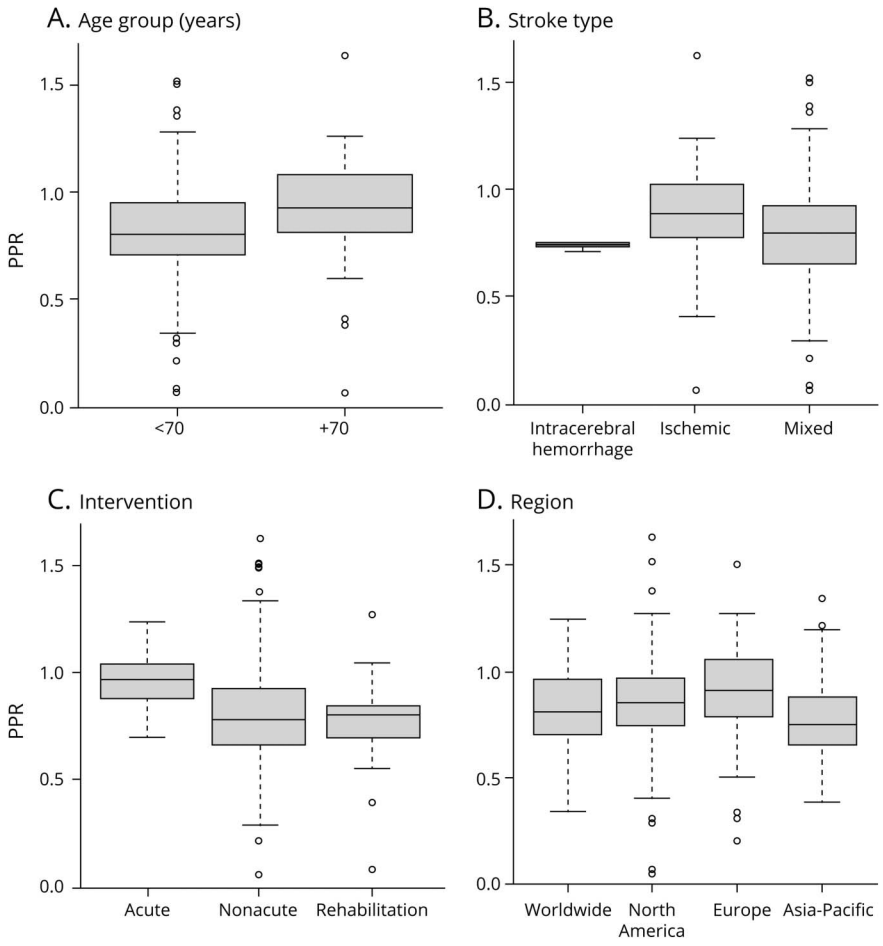
Figure 3 compares the PPR with the number of participants per trial. Although trials with fewer than 21,000 participants showed a broad spectrum of PPR values, the 4 trials with more than 21,000 had low values of PPR of 0.51, 0.35, 0.51, and 0.79. Hence, the SSWM (0.78 [95% CI 0.59–0.98]), which gives more weight to larger trials, was found to be lower than

**Table 1** Baseline Trial Characteristics

| Characteristics | Trial (%)[a] | Participants (%)[a] | Female participants (%)[b] |
|---|---|---|---|
| **Trials** | 281 | 588,887 | 220,344 (37.4) |
| **Age group, y** | | | |
| **<70** | 214 (76.2) | 453,826 (77.1) | 165,109 (36.4) |
| **70+** | 67 (23.8) | 135,061 (22.9) | 55,235 (40.9) |
| **Stroke type** | | | |
| **Ischemic** | 143 (50.9) | 288,140 (48.9) | 110,757 (38.4) |
| **Intracerebral hemorrhage** | 3 (1.1) | 3,840 (0.7) | 1,402 (36.5) |
| **Mixed** | 135 (48.0) | 296,907 (50.4) | 108,185 (36.4) |
| **Intervention[c]** | | | |
| **Acute** | 71 (25.4) | 71,087 (12.1) | 30,555 (43.0) |
| **Nonacute** | 168 (60.0) | 507,339 (86.2) | 185,790 (36.6) |
| **Rehabilitation** | 41 (14.6) | 10,328 (1.8) | 3,938 (38.1) |
| **Region** | | | |
| **Worldwide** | 76 (27.0) | 391,187 (66.4) | 132,801 (33.9) |
| **North America** | 65 (23.1) | 49,995 (8.5) | 20,163 (40.3) |
| **Europe** | 70 (24.9) | 51,276 (8.7) | 19,591 (38.2) |
| **Asia–Pacific** | 70 (24.9) | 96,429 (16.4) | 47,789 (49.6) |
| **Distribution of participants** | | | |
| **Conducted in a single country** | 182 (64.8) | 178,883 (30.4) | 79,882 (44.7) |
| **Conducted in multiple countries** | 99 (35.2) | 410,004 (69.6) | 140,462 (34.3) |

[a] Trial and participants % calculated out of the total number of trials and total number of participants, respectively.
[b] The female participants % was calculated out of total number of participants.
[c] One trial did not have intervention status recorded; thus % was calculated out of known totals.

**Figure 1** Distribution of Participation to Prevalence Ratio (PPR) Across Stroke Trials




Distribution by age group (A), stroke type (B), intervention (C), and region (D). Box and whisker plots represent the distribution of PPR within each category. The thick black horizontal bar represents the median PPR within the category, with the gray box representing the interquartile interval between the first quarter and upper quarter of the dataset. The thin black lines represent whiskers that extend to one and a half times the interquartile interval; values beyond are extreme values represented as white dots with black outline. Note that that the box and whisker plot for intracerebral hemorrhage trials is calculated using data from 3 trials, thus the plot represents the median and interquartile interval 0.74 (0.72–0.74).

the simple mean PPR (0.84; 95% CI 0.81–0.87). In a sensitivity analysis of trials by number of participants, the mean PPR was 0.85 (95% CI 0.82–0.89) for trials with <1,000 participants, 0.82 (95% CI 0.77–0.89) for trials with 1,000–4,999 participants, and 0.76 (95% CI 0.67–0.86) for trials with ≥5,000 participants.

## Discussion

Adequate representation of women in clinical stroke trials that reflects the burden of stroke in the underlying population can provide a more reliable assessment of the treatment benefits and harms and inform treatment guideline recommendations for women with this serious condition. When one sex is underrepresented in clinical trials, it limits the generalizability of the study findings and possibly limits access to new therapies. In our study, where the overall PPR was 0.84, more than 3/4 of clinical trials had a PPR of <1.0, indicating that they enrolled fewer women than the expected proportion of stroke in the background population. While the participation of women approached the disease prevalence in those trials investigating acute interventions, the underrepresentation of women was greater in nonacute interventions and especially in rehabilitation trials. These findings provide important insights into the proportion of women enrolled in different types of clinical stroke trials. Implications for the future of stroke and neurology research include involving more women in clinical trials, which can be accomplished through the efforts of several stakeholders such as study investigators who actively recruit more women and research funders who require more reliable and sex-balanced evidence.

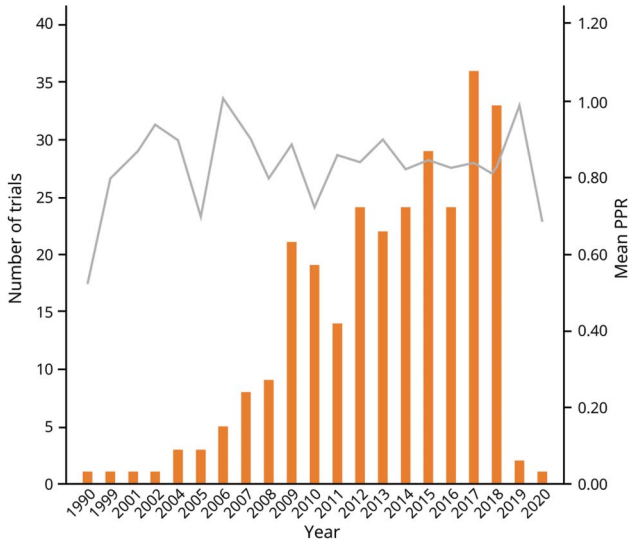
Our findings are consistent with prior studies examining the participation of women in cardiovascular trials. In a review of 156 randomized clinical trials, the proportion of women enrolled in the areas of coronary artery disease, heart failure, diabetes mellitus, hypercholesterolemia, and hypertension trials was lower relative to the proportion of women estimated to have the underlying disease in the target population.[16] Another more recent review of women's participation in cardiovascular clinical trials registered in ClinicalTrials.gov that took account of underlying disease prevalence using the PPR found that women were underrepresented in the areas of stroke (PPR 0.73), cardiac arrhythmia (PPR 0.78), coronary heart disease (PPR 0.67), acute coronary syndrome (PPR

**Table 2** Summary Statistics of Participation to Prevalence Ratio (PPR) Overall and by Age Group, Stroke Type, Intervention, and Region

| Category | Median (IQI) | Mean (SD) | 95% CI |
|---|---|---|---|
| **Overall** | 0.84 (0.72–0.97) | 0.84 (0.23) | 0.81–0.87 |
| **Age group, y** | | | |
| **<70** | 0.80 (0.70–0.95) | 0.81 (0.23) | 0.78–0.84 |
| **70+** | 0.93 (0.82–1.08) | 0.92 (0.23) | 0.87–0.98 |
| **Stroke type** | | | |
| **Ischemic** | 0.89 (0.77–1.02) | 0.89 (0.19) | 0.85–0.92 |
| **Intracerebral hemorrhage** | 0.74 (0.72–0.74) | 0.73 (0.02) | 0.71–0.74 |
| **Mixed** | 0.80 (0.66–0.92) | 0.79 (0.26) | 0.75–0.84 |
| **Intervention** | | | |
| **Acute** | 0.98 (0.89–1.05) | 0.97 (0.12) | 0.94–0.99 |
| **Nonacute** | 0.78 (0.67–0.94) | 0.80 (0.26) | 0.76–0.84 |
| **Rehabilitation** | 0.81 (0.71–0.86) | 0.77 (0.19) | 0.71–0.83 |
| **Region** | | | |
| **Worldwide** | 0.82 (0.71–0.96) | 0.83 (0.19) | 0.78–0.87 |
| **North America** | 0.86 (0.74–0.98) | 0.85 (0.30) | 0.77–0.92 |
| **Europe** | 0.91 (0.78–1.06) | 0.90 (0.22) | 0.85–0.95 |
| **Asia–Pacific** | 0.76 (0.66–0.88) | 0.79 (0.19) | 0.74–0.83 |

Abbreviations: CI = confidence interval; IQI = interquartile interval.
95% CI calculated using bootstrap methods. Median (IQI) and mean (SD) for the percentage of women in trials, 40.0 (34.5–46.1) and 40.1 (11.0); corresponding summary statistics for percentage of women in disease population are 47.9 (46.7–49.9) and 47.9 (2.4).

**Figure 2** Mean Participation to Prevalence Ratio (PPR) by Year of Trial Publication




Orange bars represent the number of trials undertaken in a specific year indicated on the left axis. Gray line represents the linear trend of mean PPR over time indicated on the right axis.

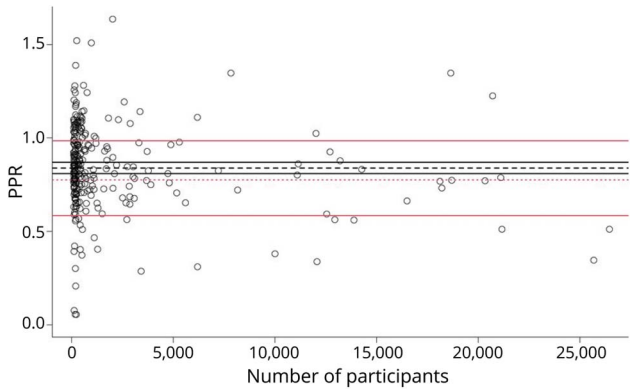
0.66), and heart failure (PPR 0.48), but overrepresented for pulmonary hypertension (PPR 1.33).[8]

Several studies have found that the enrollment of women in cardiovascular trials varied by type of intervention; those investigating drug and lifestyle factors were better represented than device or procedural trials.[8,17] There are several plausible explanations for our findings wherein acute intervention trials had greater participation. First, women (or their proxy) may be more likely to consent to participate in acute stroke trials. There is greater impetus for potential benefits to improve recovery: the symptoms of stroke are abrupt, frightening, and immediate, especially for women with more severe neurologic deficits than men.[5,18] A Cochrane systematic review of qualitative and mixed-methods studies provided important insights into the complex factors that influence a person's decision whether to participate in a trial.[19] One of the key findings was the level of perceived benefits, including for treatments that were often new or alternatives to standard of care. People are also more likely to agree to participate when they were able to anticipate a positive effect on their care. Second, in acute stroke trials, which are particularly vulnerable to slow recruitment due to the narrow therapeutic window for an intervention, there may be less restriction on inclusion criteria,[20] which has been shown to improve recruitment.[21] Moreover, an analysis of the most-cited randomized controlled trials of cardiology from 1996 to 2015 showed that a protocol limiting maximum age for participation negatively affects enrollment of women in the trials.[17] While these trials did not specifically investigate stroke, the findings are relevant given that women are older than men at the time of stroke,[18] and underline our finding of a higher PPR in those over, compared to under, 70 years of age. There may be other social and medical reasons that influence enrollment and participation of women in acute intervention trials.

Although more research is required to better understand why acute stroke trials have greater participation of women, our findings strengthen the need for further efforts to optimize all trials, and especially nonacute and rehabilitation interventions. While the mechanisms for underrepresentation of women in cardiology trials are available, more data are required for stroke, where there are likely to be different trial, patient, and social barriers and levers influencing the effects of disability on people's lives.[22]

There was no change from 1990 to 2020 in the representation of women in stroke trials relative to the burden of stroke in the population. Over this 30-year period, several countries and regions, most notably the United States, Canada, and Europe, have adopted policies that emphasize the importance of inclusion of women in clinical trials[23,24]; our findings suggest these efforts have not clearly translated in action.

**Figure 3** Participation to Prevalence Ratio (PPR) by Number of Participants for Each Trial, With Sample Size Weighted Mean PPR With 95% Bootstrap Confidence Intervals




For each trial, we calculated (PPR × number of participants)/total number of participants in all trials and plotted this against the number of participants (plotted as white dots with black outline). The sum of this value (0.776) is considered the sample size weighted mean PPR, plotted as the red dotted line, compared with the mean PPR (0.840), plotted as the black dashed line. Using bootstrap methods with replacement and 100,000 replicates, we calculated 95% confidence intervals (using the percentile method) around the mean (0.81–0.87), plotted as black solid lines, and around the sample size weighted mean (0.586–0.985), plotted as the red solid lines.

Other studies have used the PPR range 0.8 and 1.2 limits as indicators of acceptable sex parity,[7,8] but these are arbitrary limits and do not capture the realistic representation of women in stroke trials, where we found that the mean PPR of 0.84 was towards the lower ideal limit and beyond the lower limit when considering the SSWM (0.78) that gives more weight to the larger trials. Thus, when considering a large number of trials, as our study does, more appropriate measures should consider the actual numbers to derive an estimate rather than utilize arbitrary limits that accept disparities of up to 20%. One must be cautious not to over-rely on the SSWM as some trials may naturally be smaller because the intervention is only relevant for a subpopulation. Thus, it may be unfair to consider these trials as less important by giving them less weight.

Our study has several limitations. By including only studies registered on ClinicalTrials.gov, rather than the more international World Health Organization–International Clinical Trials Registry platform, we may not have captured all stroke trials conducted during the study period, and similarly for restricting our search of PubMed, Google Scholar, and Scopus for those published, despite them being the 3 largest databases where publications are indexed. Another limitation is that the background population to derive the PPR calculation may not have been representative of the true at-risk population. Finally, our search for hemorrhagic trials only captured ICH trials; this limits generalization of other types of hemorrhagic trials, such as those of subarachnoid hemorrhage.

Our study has shown that a lower participation of women in stroke trials cannot be explained by their lower prevalence in the underlying population. Our prevalence-corrected estimates of women's participation in stroke trials suggests other factors are responsible for the lower enrollment of women in stroke trials. Further research is required to untangle the barriers to enrolling women in stroke trials in order to address knowledge gaps in the understanding and treatment of women with stroke.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| **Katie Harris, PhD** | The George Institute for Global Health, New South Wales, Australia | Study concept and design, statistical analysis and interpretation of data |
| **Sanne A.E. Peters, PhD** | The George Institute for Global Health, Imperial College London, UK | Study concept and design, interpretation of data |
| **Else Charlotte Sandset, MD** | Oslo University Hospital, Norway | Study concept and design, critical revision of manuscript for intellectual content |
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Continued

## Appendix *(continued)*

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| **Mark Woodward, PhD** | The George Institute for Global Health, New South Wales, Australia | Study concept and design, statistical analysis and interpretation, critical revision of manuscript for intellectual content |

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