Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Variable Definitions

Number of enrolled women: The number of women enrolled and randomized in the trial. Participants with missing information on sex were excluded.

Number of enrolled men: The number of men enrolled and randomized in the trial. Participants with missing information on sex were excluded.

Number of enrolling clinical sites: The number of sites at which enrollment occurred. Centers that did not enroll any subjects were excluded from the total if sufficient information was provided to ascertain this.

Time period of enrollment: The year when enrollment began and the year when enrollment stopped.

Geographic location of patient enrollment/clinical sites: For each country in which enrollment took place we abstracted the number of patients enrolled from that country. If patient-level data was not available, we abstracted the number of enrolling clinical sites in that country. In order for a study to be classified into one specific region (e.g., Americas), >80% of the patients had to be enrolled in that region (or >80% of clinical sites had to be located in that region if patient-level data was not available). If a study could not be categorized into one specific region it was listed as multi-region.

Intervention type: Trials were classified into one of 5 types based on the primary intervention tested.

1. Endovascular therapy: trials testing endovascular interventions (e.g., mechanical thrombectomy or intra-arterial administration of alteplase) to achieve recanalization.
2. IV thrombolysis: trials testing a systemic drug (e.g., alteplase and tenecteplase) meant to achieve recanalization. Therapies intended to assist with recanalization after alteplase administration (e.g., sonothrombolysis) were also included in this category.
3. Secondary Prevention: trials testing an intervention (usually a pharmacological agent) to prevent recurrent stroke or other cardiovascular events after an index stroke or transient ischemic attack.
4. Surgery: Trials testing an intervention that involves the invasive and manual manipulation of the body by a surgeon. Examples include hemicraniectomy and surgical hematoma evacuation. Note that endovascular therapy (and other any endovascular procedure) was considered separately.
5. Other: Trials testing any other therapeutic intervention implemented in the acute stage. Examples include neuroprotection, blood pressure management, and early rehabilitation.

Pre-planned sample size: The number of participants the investigators planned to enroll before the study began (*a priori* sample size).

Final sample size: The number of participants actually randomized into the trial. Note that the recorded sample size reflects the total number of patients for whom sex was reported which may be slightly different than the total study sample size.

Representation of women in trial leadership: We considered a woman to be represented in trial leadership if a woman was listed as the first author or corresponding author.[1] If there were multiple first authors (e.g., multiple authors made contributions equal to the first author) or multiple corresponding authors, we considered a trial to have a woman in leadership as long as one of them was a woman. Determination of the sex of the first and corresponding author was first done through an internet search. If definitive information about the sex of the authors could not be obtained, sex was inferred from the given name.

Involvement of industry: Trials were considered to have industry involvement if a for-profit entity (i.e., company) provided either financial support for the trial (i.e., funding) and/or provided a drug or device for study purposes.

Eligibility criterion for age: Any limits on the age of participants that defined eligibility. This included limits on the youngest age of a participant (e.g., ≥18 years) or the oldest age of a participant (e.g., ≤80 years). Because many trials

did not specify an upper age limit, we analyzed eligibility criteria for age using a categorical variable with the following categories in the meta-regression analysis: upper age limit ≤ 80 years, age limit >80 years but <90 years, no upper age limit or age limit ≥90 years.

Eligibility criterion for stroke severity: Any limits on the severity of stroke that defined eligibility. Eligibility criteria for stroke severity were analyzed as a three-level categorical variable. Trials were considered to enroll 1) both mild and severe strokes, 2) only mild strokes, or 3) only severe strokes. An NIHSS score > 7[2] and/or a GCS score < 13[3] were considered to represent a severe stroke, while an NIHSS score ≤ 7 or GCS scores ≥ 13 were considered to represent a mild stroke. As an example, if a trial limited eligible participants to those with NIHSS scores of 6 to 19, then the trial would be considered to have enrolled both mild and severe strokes because an NIHSS score of 6 is considered mild according to our definition. If the trial enrolled patients with an NIHSS score of 10 or higher or a GCS score of 12 or lower, it would be considered to have only enrolled severe strokes.

Eligibility criterion for pre-stroke disability: Any limits on the physical function of eligible patients prior to the stroke occurring that defined eligibility. The preferred measure for pre-stroke function was the modified Rankin Scale (mRS). Some trials placed limits on pre-stroke disability through a verbal description of the highest level of permitted disability. These descriptions were converted to the mRS by matching it to the mRS level that most closely aligned with the description. For trials that limited the eligibility of patients based on their pre-stroke Barthel Index score, we converted it to the mRS scale using the equivalencies defined by Kwon et al.[4]

Eligibility criterion for time from stroke onset: Any limits on the time from stroke onset that determined eligibility. These limits were usually defined by the time between when the patient was last known to be well and a clinically important trial event such as enrollment/randomization or start of treatment.

Eligibility criterion related to qualification for endovascular therapy: Any requirement that patients had to be eligible to receive endovascular therapy. In practice, this could take two forms. Either the experimental intervention was endovascular therapy itself (and all patients had to qualify for it) or receipt of endovascular therapy was a pre-requisite for entering the trial in the first place.

Eligibility criterion related to qualification for intravenous thrombolysis: Any requirement that patients had to be eligible to receive intravenous thrombolysis. In practice, this could take two forms. Either the experimental intervention was intravenous thrombolysis itself (and all patients had to qualify for it) or receipt of intravenous thrombolysis was a pre-requisite for entering the trial in the first place.

Eligibility criterion related to the presence of comorbidities: Any requirement that eligible patients had to have a specific comorbidity. Examples include atrial fibrillation, hypertension, or diabetes mellitus.

Sensitivity Analyses

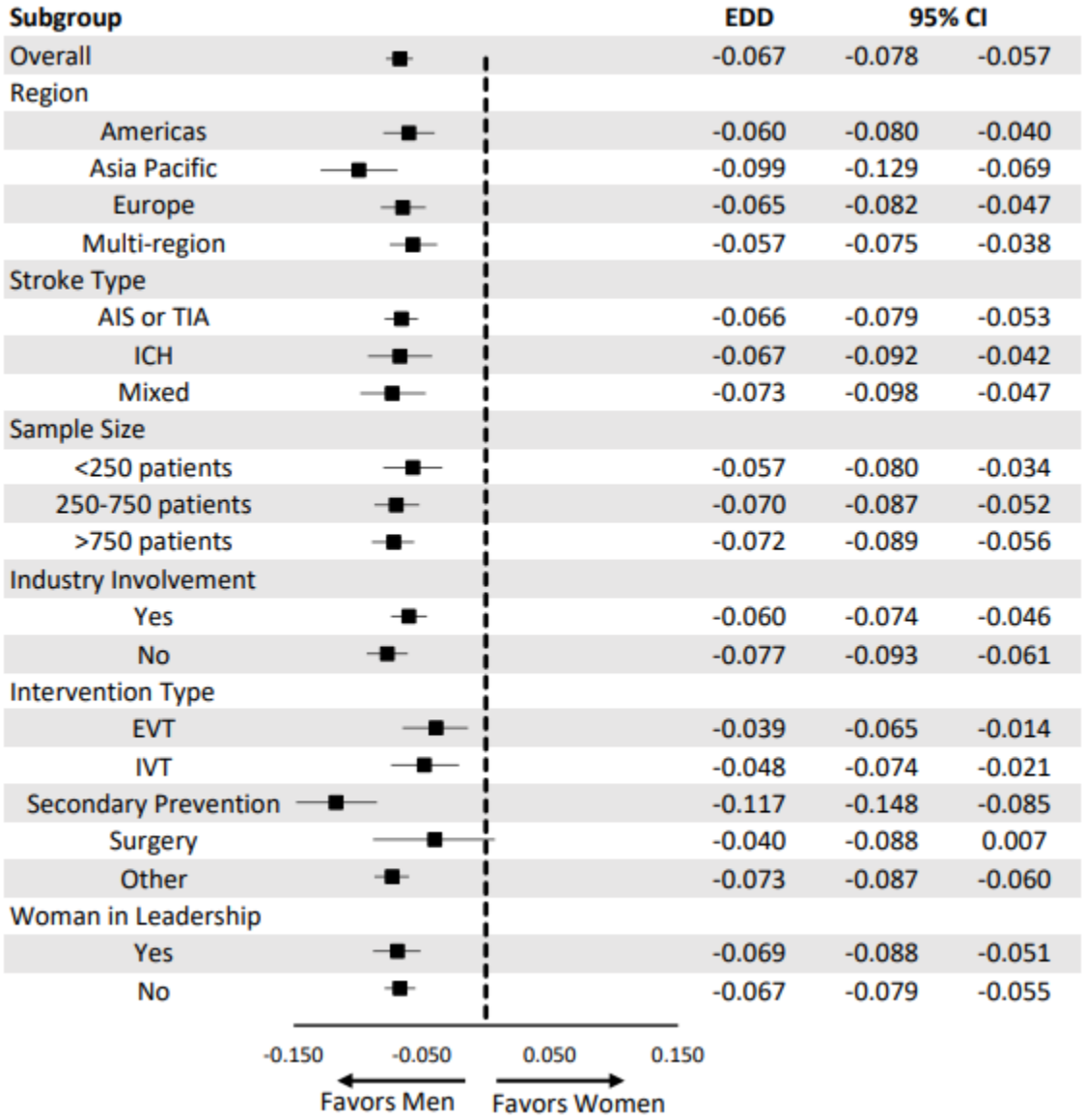
Sensitivity Analysis Using Published Incidence Data

The methods for this sensitivity analysis are described in the manuscript. An enrollment disparity difference (EDD) < 0 indicates that women were under-enrolled.

Sensitivity Analysis Using the Participation to Prevalence Ratio

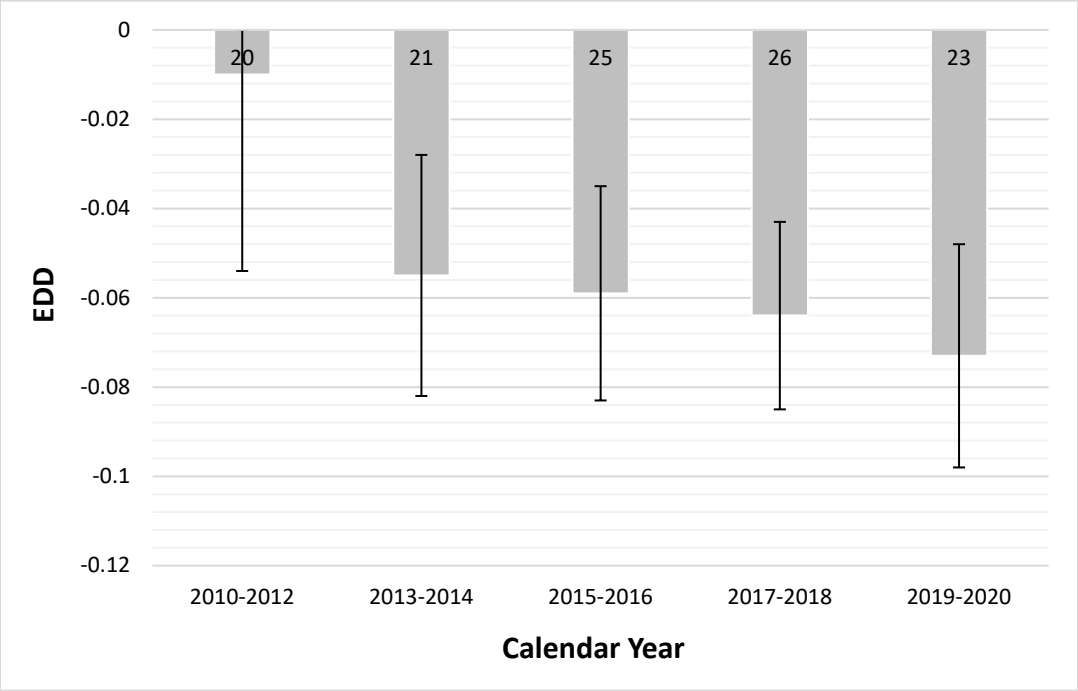
The participation to prevalence ratio (PPR)[5,6] was calculated as the proportion of trial participants who were women (PPW) divided by the proportion of strokes occurring in women in the underlying stroke populations (PSW), estimated with data from the Global Burden of Disease 2017 study.[7] In order to quantify the imprecision of the PPR estimates, we first used the number of men and women with stroke and the associated 95% uncertainty intervals reported in the GBD database to fit gamma distributions for each region-, stroke-, and time-specific estimate of the PSW. We then fit beta distributions to the PPW for each trial with shape1 (equal to the number of women in the trial) and shape2 (equal to the number of men in the trial) parameters. Each fitted distribution was independently sampled 100,000 times and PPWs, PSWs, and logarithm transformed PPRs were generated. The standard error was estimated by calculating the standard deviation of the samples of the log[PPR]. Summary measures from the meta-analysis of the log[PPR] were exponentiated for reporting purposes.

eFigure 1. Forest plot with the random effects, pooled enrolled enrollment disparity difference (EDD) for all trials (n=106) and for trial subgroups when subarachnoid hemorrhage trials were excluded. An EDD < 0 indicates that women were under-enrolled.



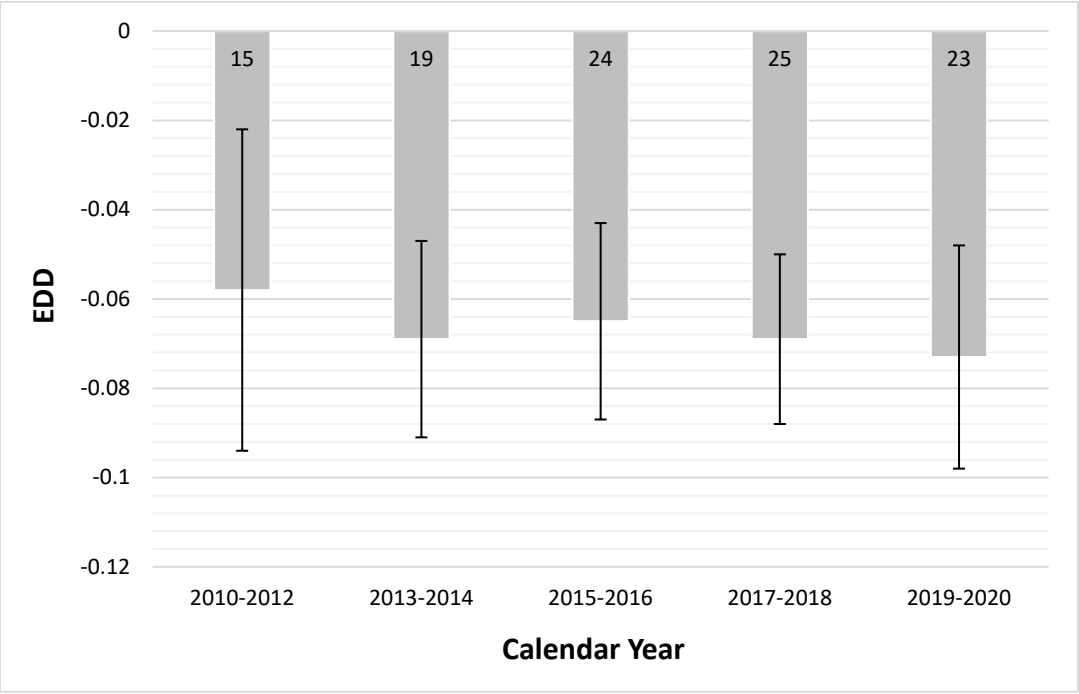
Abbreviations: EDD, enrollment disparity difference; CI, confidence interval; AIS, acute ischemic stroke; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; IVT, intravenous thrombolysis; EVT, endovascular therapy.

eFigure 2. Temporal trend by publication date in the representation of women in randomized controlled trials of acute stroke with subarachnoid hemorrhage trials included (n=115). A random effects model was used to pool enrollment disparity differences (EDD) for each 2-year period. The number of trials in each period as well as 95% confidence intervals for the pooled EDDs are depicted in the chart. Note that the interval for the 2010-2012 period is truncated at 0 for readability purposes.



Abbreviations: EDD, enrollment disparity difference. P-value for trend = 0.05.

eFigure 3. Temporal trend by publication date in the representation of women in randomized controlled trials of acute stroke with subarachnoid hemorrhage trials dropped (n=106). A random effects model was used to pool enrollment disparity differences (EDD) for each 2-year period. The number of trials in each period as well as 95% confidence intervals for the pooled EDDs are depicted in the chart.



Abbreviations: EDD, enrollment disparity difference. P-value for trend = 0.77.

eAppendix. Sensitivity Analyses

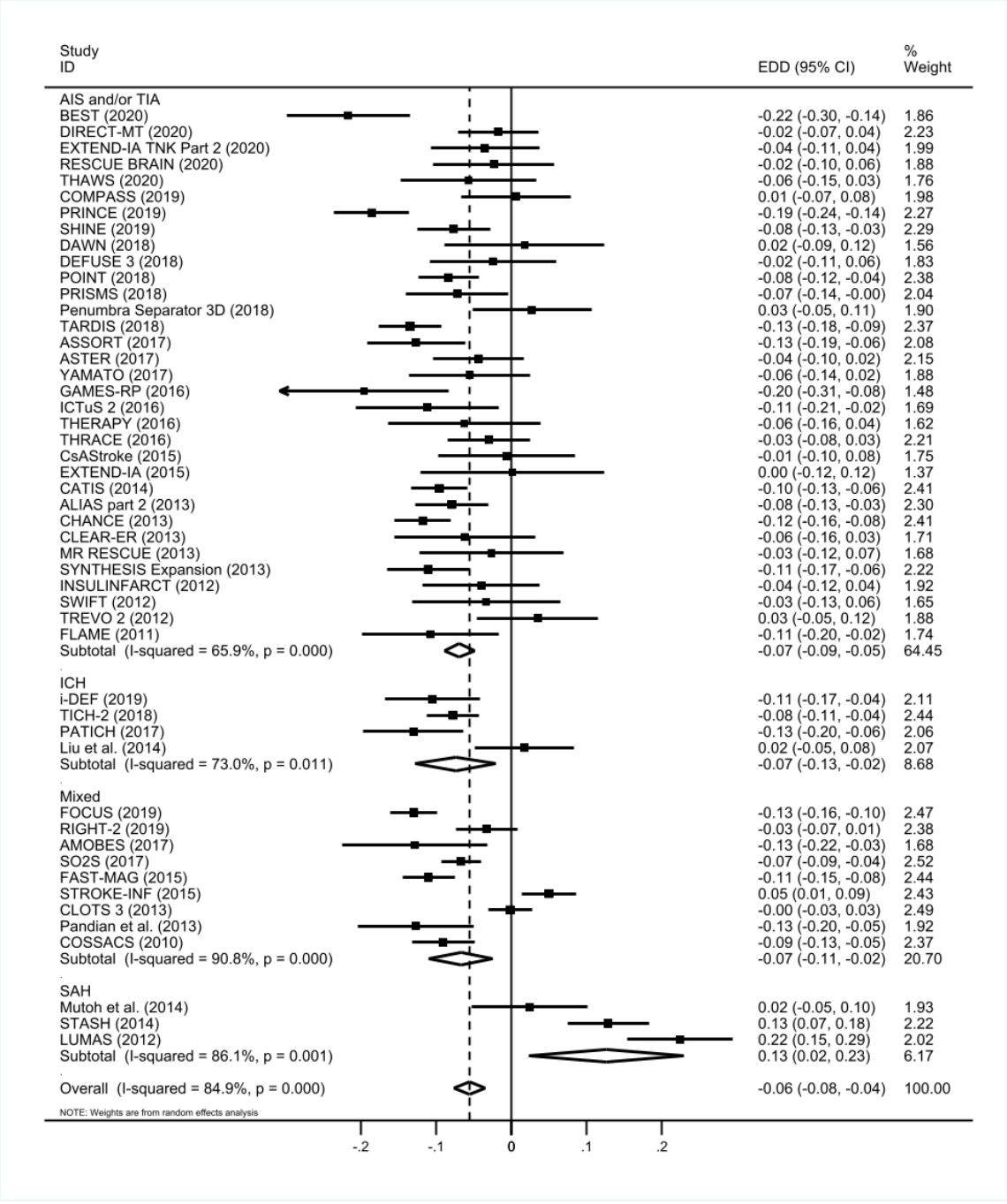
Sensitivity Analysis Using Published Incidence Data

In the sensitivity analysis comparing the use of Global Burden of Disease (GBD) data to published incidence studies to account for the representation of women in the underlying stroke populations, the findings were broadly similar with the exception of the summary estimate of the enrollment disparity difference (EDD) for trials enrolling subarachnoid hemorrhages (SAH) (eFigures 1 and 2). For the three trials with which an incidence study could be matched, the summary EDD was 0.127 (95% CI = 0.024, 0.229) using GBD data but was -0.026 (95% CI = -0.097, 0.046) when published incidence studies were used. We believe that this discrepancy is a consequence of the relative rarity of SAH compared to the other stroke types. Two of the three SAH trials in the analysis were conducted in the UK[8,9] and were matched to a stroke incidence study conducted in Oxfordshire, UK.[10] This incidence study registered 20 incident SAHs over 3 years of follow-up, of which only 4 occurred in men. The uncertainty of this estimate due to the rarity of SAH during the follow-up period is likely the cause of the discrepancy between the summary EDD using GBD data and the summary EDD using incidence data. Thus, data on the enrollment of women in SAH trials should be approached with caution. Note that when the three SAH trials were dropped, the summary EDD was very similar when using GBD data (-0.068 [95% CI = -0.086, -0.051]) and published incidence studies (-0.073 [95% CI = -0.090, -0.056]).

Sensitivity Analysis Using the Participation to Prevalence Ratio

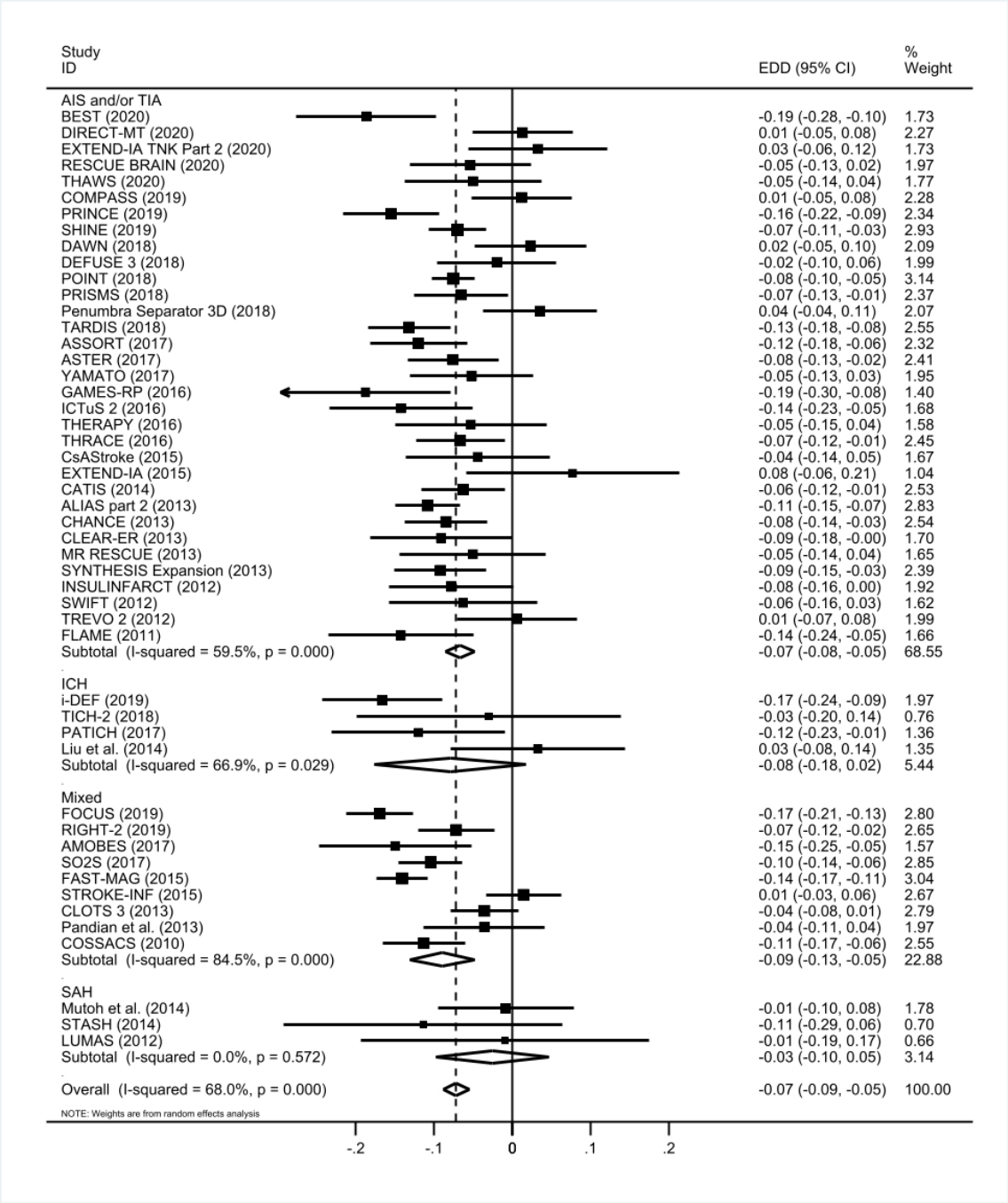
The results of this sensitivity analysis are depicted in eFigure 3. The overall, pooled participation to prevalence ratio (PPR) was 0.89 (95% CI = 0.87, 0.92), indicating that the representation of women in recent randomized controlled trials of acute stroke was 11% lower on a relative basis than their representation in underlying disease populations.

eFigure 4. Sensitivity analysis using Global Burden of Disease data to account for the representation of women in the underlying stroke populations. Random effects meta-analysis stratified by stroke type of the trials with which an incidence study could be matched (n=49). An enrollment disparity difference (EDD) < 0 indicates that women were under-represented.



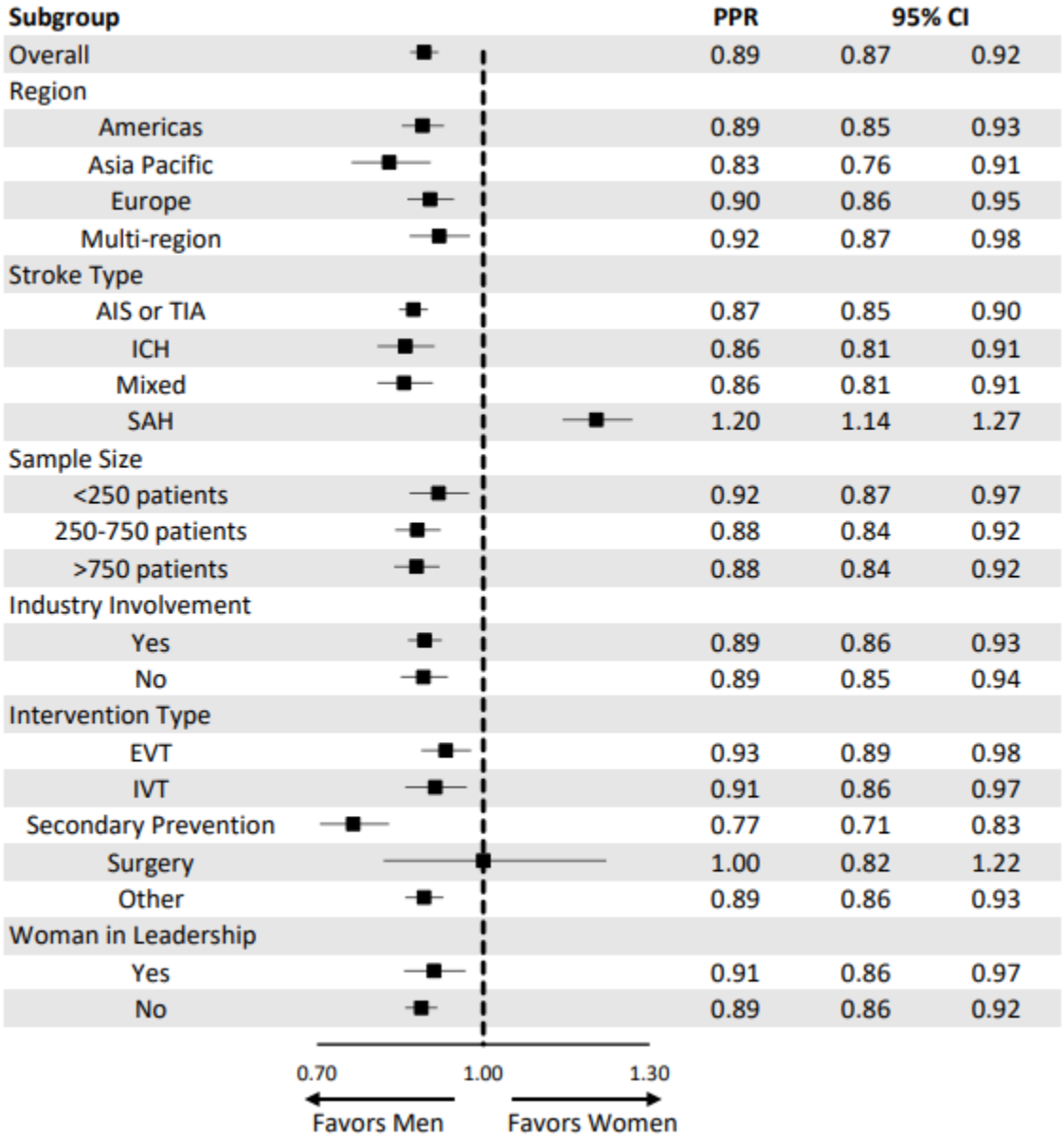
Abbreviations: EDD, enrollment disparity difference; AIS, acute ischemic stroke; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

eFigure 5. Sensitivity analysis using published incidence data to account for the representation of women in the underlying stroke populations. Random effects meta-analysis stratified by stroke type of the trials with which an incidence study could be matched (n=49). An enrollment disparity difference (EDD) < 0 indicates that women were under-represented.



Abbreviations: EDD, enrollment disparity difference; AIS, acute ischemic stroke; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage

eFigure 6. Forest plot with the random effects, pooled participation to prevalence ratio (PPR) for all trials and for trial subgroups, estimated as part of a sensitivity analysis (n=115 trials). A PPR < 1 indicates that women were under-enrolled.



Abbreviations: PPR, participation to prevalence ratio; CI, confidence interval; AIS, acute ischemic stroke; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVT, intravenous thrombolysis; EVT, endovascular therapy.

eReferences.

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