Sex Differences in Severity of Stroke in the INSTRUCT Study: a Meta-Analysis of Individual Participant Data

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***Background*—**Women have worse outcomes after stroke than men, and this may be partly explained by stroke severity. We examined factors contributing to sex differences in severity of acute stroke assessed by the National Institutes of Health Stroke Scale.

***Methods and Results*—**We pooled individual participant data with National Institutes of Health Stroke Scale assessment (N=6343) from 8 population-based stroke incidence studies (1996–2014), forming part of INSTRUCT (International Stroke Outcomes Study). Information on sociodemographics, stroke-related clinical factors, comorbidities, and pre-stroke function were obtained. Within each study, relative risk regression using log-binominal modeling was used to estimate the female:male relative risk (RR) of more severe stroke (National Institutes of Health Stroke Scale>7) stratified by stroke type (ischemic stroke and intracerebral hemorrhage). Study-specific unadjusted and adjusted RRs, controlling for confounding variables, were pooled using random-effects meta-analysis. National Institutes of Health Stroke Scale data were recorded in 5326 (96%) of 5570 cases with ischemic stroke and 773 (90%) of 855 participants with intracerebral hemorrhage. The pooled unadjusted female:male RR for severe ischemic stroke was 1.35 (95% CI 1.24–1.46). The sex difference in severity was attenuated after adjustment for age, pre-stroke dependency, and atrial fibrillation but remained statistically significant (pooled $RR_{adjusted}$ 1.20, 95% CI 1.10–1.30). There was no sex difference in severity for intracerebral hemorrhage (RR_{crude} 1.08, 95% CI 0.97–1.21; $RR_{adjusted}$ 1.08, 95% CI 0.96–1.20).

***Conclusions*—**Although women presented with more severe ischemic stroke than men, much although not all of the difference was explained by pre-stroke factors. Sex differences could potentially be ameliorated by strategies to improve pre-stroke health in the elderly, the majority of whom are women. Further research on the potential biological origin of sex differences in stroke severity may also be warranted. **(*J Am Heart Assoc*. 2019;8:e010235. DOI: 10.1161/JAHA.118.010235.)**

Key Words: epidemiology • sex difference • stroke

Women are less likely to survive following stroke because of a higher case fatality rate in the acute phase, but long-term sex differences in mortality persist up to 5 years after stroke.[1] Women also often have poorer functional outcome, increased participation restriction, and lower health-related quality of life after stroke than men.[1,2] One explanation for these sex differences in outcome is that women have more severe strokes than men.[1–3] While several

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Accompanying Data S1 and S2, Tables S1 through S9 and Figures S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010235

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Clinical Perspective

What Is New?

- Our article shows that women present with more severe ischemic stroke than men and the difference is partly explained by their older age, greater pre-stroke dependency, and higher prevalence of atrial fibrillation compared with men.

What are the clinical implications?

- Better preventative health care for women may potentially reduce their incidence of stroke but also minimize the severity of strokes if they occur.
- Given the greater severity of these events in women ensuring that there is equal access to treatments including thrombolysis and thrombectomy may reduce severity.

studies have reported on sex differences in the severity of stroke, most often these studies use severity as a covariate rather than as a primary outcome.[4,5] Another challenge is that the measurement of severity can differ between studies.[6–8] Thus the importance and causes of the association between sex and stroke severity, remain uncertain.[3] Although there are reports on factors that contribute to severity of stroke (eg, hypertension,[9] cardiovascular diseases,[10] dementia,[11] embolic stroke mechanism[12]), the relative importance of these factors to differences in severity between women and men has not been investigated thoroughly.

Among the few studies designed to examine the etiology of sex differences in stroke severity,[13,14] there are important differences in the data sources, methods of analysis, and adjustment for confounding factors. Renoux et al[14] reported 49% (unadjusted odds ratio 1.49, 95% CI 1.23–1.80) increased odds of having a severe stroke (National Institutes of Health Stroke Scale [NIHSS] ≥5) for women compared with men, which was partly explained by age and pre-stroke modified Rankin Scale (adjusted odds ratio 1.19, 95% CI 0.94–1.52 following adjustment for these 2 variables). In contrast, Gall and colleagues reported a 23% (unadjusted relative risk [RR] 1.23, 95% CI 1.05–1.45) greater risk of severe stroke (NIHSS>7) in women; but the difference was almost completely explained by women's older age, presence of dementia, atrial fibrillation, and pre-stroke Barthel index (adjusted RR 1.05 95% CI 0.91–1.22).[13] Other than age, pre-stroke functional limitations, and comorbidities, there has been limited consideration on the influence of other potential confounding factors such as pre-stroke medication,[15] delay in presenting to the hospital,[16] and mechanism of ischemic stroke (ie, cardioembolic strokes)[17] on the sex difference in severity.

Examination of a wider range of potential contributors to any observed sex difference in stroke severity is important to help address the gaps in our understanding of factors affecting sex-specific difference in stroke outcomes. Using information from an individual participant data (IPD) meta-analysis we aimed to 1) quantify the sex difference in stroke severity assessed by initial the National Institutes of Health Stroke Scale (NIHSS) score among patients with first-ever acute stroke (both ischemic and hemorrhagic); and 2) investigate the factors (ie, sociodemographics, pre-stroke health, comorbidities, and clinical factors) that contribute to any observed difference.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Qualified investigators can request access to patient-level data, analytic methods, and study materials after ethics clearance and approval by all authors.

The INSTRUCT (International stroke outcomes study)—an IPD meta-analysis of long-term outcomes after stroke—is a collaboration of investigators from 13 "gold standard" population-based stroke incidence studies (limited to first-ever acute strokes) from Australasia, Europe, South America, and the Caribbean.[1] The INSTRUCT study was registered in the International prospective register of systematic reviews (PROSPERO; CRD 42016036723)[18] and performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines.[19] Further details about the INSTRUCT study are provided in Data S1 and Table S1.

Outcome Measurement

Of the 13 studies forming the INSTRUCT, 8 studies had data on National Institutes of Health Stroke Scale (NIHSS) scores recorded at the acute stage and so were included in this analysis. The NIHSS assessment was recorded directly in 7 studies and responses were mapped from Scandinavian Stroke Scale) data available in 1 other study (Tartu) using the formula: Scandinavian Stroke Scale $=50-2\times$NIHSS.[20]

Predictors of Outcome (Covariates)

We obtained data on a range of covariates in each cohort that might explain differences in stroke severity between men and women. These factors included: sociodemographics, pre-stroke health (functional dependence, comorbidities, health behaviors, pre-stroke medications), stroke type; acute management (hospital admission, time delay to hospital presentation), and the year of stroke occurrence (1996–2014). Details on how these data were collected and the definitions

used for each variable in each specific study are provided in Data S2 and Table S2.

Available sociodemographic data included race/ethnicity (2 studies), marital status (4 studies), education (4 studies), and socioeconomic status (3 studies). Data on pre-stroke health status included dependence before stroke (4 studies, modified Rankin Scale >2; 3 studies, Barthel Index ≤20; 4 studies, institutional residence); comorbidities/medical history (all studies—atrial fibrillation, hypertension, ischemic heart disease, transient ischemic attack; 5 studies, peripheral vascular disease; 4 studies, diabetes mellitus; 3 studies, dementia); medications before stroke (4 studies, antihypertensives; 4 studies, antiplatelets; 1 study, anticoagulants); body mass index (5 studies), and health behaviors (7 studies, smoking status; 6 studies, alcohol use status). Type of stroke was categorized into 4 groups: ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage, and undetermined stroke. Ischemic stroke subtypes, available in 4 studies, were categorized by TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification[21] including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and other determined etiology.

Statistical Analysis

All analyses were conducted in Stata 12.1. A 2-tailed $P \leq 0.05$ was considered statistically significant.

Study-specific analyses of the characteristics of participants (eg, mean age, percentage of pre-stroke functional limitation) were compared between men and women and then pooled using random-effects meta-analysis. We only undertook analyses for IS and ICH because NIHSS was not routinely collected for subarachnoid hemorrhage and undetermined stroke. Stroke severity was dichotomized into severe (NIHSS>7) or not-severe (NIHSS ≤7).[13]

Since covariates were not measured uniformly between studies, we used the 2-stage method of analysis proposed for IPD meta-analyses.[22] The first stage involved building study-specific unadjusted and adjusted relative risk regression using log-binomial models to estimate the relative risk of severe stroke (NIHSS>7 versus ≤7) for women compared with men. Assuming the confounding role[23] of covariates in the association between sex and severity are similar across studies, the equivalent covariates were adjusted across studies. They included age, pre-stroke function, and history of atrial fibrillation (AF) that were well-established to influence sex differences in stroke outcomes[1,2] among IS, and age only for ICH. Adjustment was first done for age, and then further for pre-stroke function, when possible, and AF in multivariable model. Within each study, we assessed whether these 3 variables and other covariates met the following criteria of being a confounder (associated with sex, associated with stroke severity, and the inclusion of the covariate changed the magnitude of the sex coefficient by ≥10%).[24] We tested whether continuous covariates (ie, age, pre-stroke Rankin, or pre-stroke Barthel) require a transformation using fractional polynomials in multivariable modeling,[25] to get the best model fit. Within each study, statistical interactions were assessed by a test of statistical significance of a sex×covariate or covariate×covariate product term.

For the second stage of the analysis, both unadjusted and adjusted study-specific estimates were pooled in separate random-effects meta-analyses, because of inconsistent study designs, settings, covariates and outcome measures across different populations. We also presented estimates from fixed-effects meta-analyses to compare with the random-effects approach. Heterogeneity was evaluated using Q statistics and I^2 statistics. Meta-regression was used to identify the sources of statistically significant heterogeneity among study-level characteristics including the presence of pre-stroke function data, geographic regions, and proportion of women.

Sensitivity Analyses

We also reported the subgroup analyses of the difference in severity of IS by TOAST subtype. Given the uncertainty over the particular cut point to use to define a severe stroke, we also undertook a sensitivity analysis by analyzing NIHSS as a continuous variable to compare with the main results of dichotomous analyses. Where necessary, transformations of NIHSS outcome data were performed to remove skewness.

To further test the robustness of our findings, we used a single-stage meta-analysis pooling all IPD data sets (8 studies).[26] Adjustment for common covariates that are important confounders or contributing factors to the association between sex and stroke severity was performed. Similar to the analyses using a 2-stage modeling approach, we included age, the presence of atrial fibrillation, and pre-stroke function when possible, in multivariable models for IS and age for ICH.

We tried to harmonize the data to conduct a multivariable analysis of the pooled IPD. Because of inconsistent measures of (or closely related to) pre-stroke function among 6 studies, a binary variable of pre-stroke functional limitation was generated whereby the existing of functional limitation before stroke was defined as the modified Rankin Scale >2 (Oxford, Perth, Tartu), Barthel Index <20 (Melbourne), or being in an institution (Orebro, Dijon). For those 2 studies without data on pre-stroke function (Joinville, Mãtao), multiple imputation using chained equations[27] (m=50 imputations) was performed to account for these missing values based on the available data on NIHSS and covariates in the pooled data set. To compare with our main findings using 2-stage approach, we reported pooled estimates of all 8 studies and a subset of 6 studies with data on pre-stroke function.

Statistical interactions in multivariable models were also assessed within the single pooled data set. Year of stroke occurrence and age that were measured consistently in all studies were further examined whether they modified the relationship between sex and stroke severity.

Results

Sex Difference in Patient Characteristics

Data on initial NIHSS recorded after acute stroke onset were available among 5326/5570 (95.6%) IS and 773/855 (92.6%) ICH participants of the 8 studies[28–35] (Tables S3 and S4). Among those with IS, compared with men, women were on average 4.5 years (95% CI 3.8–5.3) older (statistically significant difference in 6/8 studies; Table 1) and were less likely to be living with a spouse (summary estimate 39.4% versus 71.2%, $P<0.001$; significant difference in 3/4 studies). Women also had higher prevalence of functional limitation (modified Rankin Scale >2 or Barthel≤20) before stroke (summary estimate 22.6% versus 14.0%, $P<0.001$; significant difference in 2/5 studies) and institutional residence than men (summary estimate 12.0% versus 4.6%, $P<0.001$; significant difference in 3/4 studies). In IS, more women were prescribed anti-hypertensive agents (3/5 studies) before stroke than men. Men with IS were more often ever-smokers (significant difference in 7/7 studies) and consumers of alcohol (significant difference in 4/6 studies; Tables S3 and S4; "IS"). Among ICH participants, women were on average 4.7 years (95% CI 2.6–6.7) older than men (significant difference in only 3/8 studies), and there was few difference in other baseline characteristics between women and men (Tables S3 and S4; "ICH").

Distribution of the NIHSS by sex among those with either IS or ICH was illustrated in Figure 1 (n=6099; 8 studies) and Figure S1 (for each study).

Analyses of initial NIHSS scores among 8 studies included 5200/5326 participants with IS (Table 2; 2% of cases were excluded because of missing data on covariates). In unadjusted analyses, women with IS were 35% (pooled RR 1.35, 95% CI 1.24–1.46) more likely to suffer more severe strokes than men; study-specific crude RRs varied from 1.20 (Perth) to 1.71 (Mãtao; Figure 2, top). We found no statistical evidence of heterogeneity in unadjusted RR estimates (I^2=0%; Q=4.4, P=0.732) across the studies. In multivariable analysis, adjustment for age alone reduced the sex difference in severity by 36% (pooled $RR_{age\text{-}adjusted}$ 1.21, 95% CI 1.11–1.31) with non-statistically significant heterogeneity (I^2=0%; Q=4.9, P=0.670). After further accounting for AF and pre-stroke dependency, the pooled estimate was substantially attenuated but remained statistically significant (pooled $RR_{fully\text{-}adjusted}$ 1.20, 95% CI 1.10–1.30). Although study-specific adjusted RRs of the association between sex and severity of IS varied from 1.09 (Dijon) to 1.70 (Mãtao), there was no statistically significant heterogeneity between studies (I^2=0%; Q=4.5, P=0.719; Figure 2, bottom). Factors that met all criteria for being a confounder were inconsistent between studies (Table 2). Among IS, these confounding factors were age (6/8 studies, pre-stroke dependency (5/6 studies), atrial fibrillation (2/8 studies). Transformation of continuous covariates using fractional polynomials in multivariable modeling was not required. None of these factors modified the effect of sex on stroke severity (ie, all sex×covariate or covariate×covariate interactions were non-significant). There was also no evidence that IS subtype (TOAST; Table S5), or any of the other covariates (eg, socioeconomic position, education, pre-stroke medications, alcohol use, and other comorbidities such as diabetes mellitus and hypertension) contributed to the sex difference in NIHSS (Table S6).

Analyses of 855/773 participants with ICH (Table 2; 10% of cases were excluded because of missing data on confounding factors) found no sex difference in the severity of stroke (pooled $RR_{unadjusted}$ 1.08, 95% CI 0.97–1.21; Figure 3, top) without a statistical heterogeneity (I^2=0%; Q=2.1, P=0.957). There was no effect of adjusting for age with the age-adjusted pooled RR being 1.08, 95% CI 0.96–1.20 (Figure 3, bottom; I^2=0%; Q=1.4, P=0.985) or any other covariates.

We found no evidence of differences in the pooled unadjusted or adjusted estimates between random-effects and fixed-effects meta-analyses, suggesting our results were robust. Meta-regression did not identify any sources of the heterogeneity between studies. Neither study-level factors including geographic region, the availability of pre-stroke function (Table S7), nor the proportion of women modified the sex differences in either unadjusted (IS: $P_{meta\text{-}regression}$=0.559; ICH: $P_{meta\text{-}regression}$=0.726) or adjusted analyses ($P_{meta\text{-}regression}$=0.403; ICH: $P_{meta\text{-}regression}$=0.723). Removing 2 studies without data on pre-stroke function (Figures S2 and S3) did not greatly influence the pooled estimates compared with the main results (8 studies; Figures 2 and 3) in either unadjusted (IS: pooled $RR_{unadjusted}$ 1.30 versus 8 studies 1.35; ICH 1.12 versus 8 studies 1.08) or adjusted analyses (IS: $RR_{adjusted}$ 1.15 versus 8 studies 1.20; ICH: $RR_{unadjusted}$ 1.12 versus 8 studies 1.08).

Sensitivity Analyses

Sensitivity analyses using NIHSS as a continuous variable showed consistent results to dichotomous analyses (Table S8).

Our pooled estimates using the single-stage method of meta-analysis were generally similar (8 studies; IS: $RR_{unadjusted}$

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Table 1. Details of 8 Included Cohorts: Baseline Data on First-Ever Ischemic Stroke and Intracerebral Hemorrhage Stroke

Study	Study, y	Baseline, n	Among Participants With NIHSS Data							
			n	Women (%)	Mean Age, y (SD)		Median NIHSS (IQR)		NIHSS>7, n (%)	
					Men	Women	Men	Women	Men	Women
Ischemic stroke									(n=2603)	(n=2723)
Oxford, UK[28]	2002–2013	1103	1087	49.4%	72.4 (12.0)*	77.7 (12.1)*	3 (1–6)*	3 (1–9)*	112 (20.4)*	157 (29.2)*
Joinville, Brazil[29]	2009–2014	1494	1494	47.8%	63.5 (12.5)*	66.8 (15.7)*	3 (2–8)*	4 (2–11)*	198 (25.4)*	253 (35.4)*
Melbourne, Australia[30]	1996–1999	921	744	52.0%	72.4 (12.7)*	76.3 (14.3)*	4 (2–10)	5 (2–12)	112 (31.4)*	150 (38.8)*
Perth, Australia[31]	2000–2001	140	123	50.4%	74.0 (12.5)	78.0 (10.1)	5 (3–11)	6 (3–13)	21 (34.4)	26 (41.9)
Orebro, Sweden[32]	1999–2000	274	274	54.4%	73.1 (10.5)*	77.1 (10.7)*	4 (2–6)*	5 (3–10)*	28 (22.4)*	50 (33.6)*
Dijon, France[33]	2006–2012	1238	1238	54.1%	71.7 (15.3)*	77.2 (15.8)*	4 (2–9)*	4 (2–12)*	170 (29.9)*	248 (37.0)*
Mãtao, Brazil[34]	2003–2004	68	67	38.8%	65.1 (12.3)	64.5 (12.6)	5 (2–11)*	8 (5–10)*	12 (29.3)	13 (50.0)
Tartu, Estonia†35	2002–2003	332	299	59.5%	68.1 (10.9)*	75.6 (10.9)*	5 (0–14)*	9 (2–16)*	44 (36.4)*	97 (54.5)*
Summary estimate (95% CI)		5570	5326	51.6%	70.0 (67.4–72.6)*	74.5 (72.0–77.2)*	4 (2–8)	4 (2–11)	27.9% (24.1–31.9%)*	38.6% (33.8–43.6%)*
Intracerebral hemorrhage									(n=400)	(n=333)
Oxford, UK[28]	2002–2013	112	94	48.9%	69.5 (14.3)	73.5 (16.2)	7 (3–15)	7 (3–16)	22 (45.8)	22 (47.8)
Joinville, Brazil[29]	2009–2014	223	223	42.2%	58.2 (15.4)*	62.5 (15.5)*	17 (5–27)	17 (5–27)	86 (66.7)	66 (70.2)
Melbourne, Australia[30]	1996–1999	191	136	49.3%	70.3 (13.5)*	75.2 (15.2)*	8 (3–20)*	14 (5–27)*	39 (53.4)	47 (66.2)
Perth, Australia[31]	2000–2001	19	13	46.7%	68.0 (18.5)	73.5 (12.3)	9 (3–23)	15 (1–21)	4 (50.0)	5 (71.4)
Orebro, Sweden[32]	1999–2000	44	44	43.2%	71.9 (11.5)	75.6 (9.9)	9 (4–12)	10 (4–23)	15 (60.0)	12 (63.2)
Dijon, France[33]	2006–2012	197	197	53.3%	71.0 (15.8)*	76.6 (18.3)*	9 (4–22)	10 (4–22)	54 (58.7)	67 (63.8)
Mãtao, Brazil[34]	2003–2004	12	11	27.3%	62.9 (7.0)	68.7 (7.5)	18 (8–25)	32 (7–32)	6 (75.0)	2 (66.7)
Tartu, Estonia*[35]	2002–2003	57	55	50.9%	63.6 (15.9)	68.1 (12.6)	20 (5–25)	14 (7–25)	19 (70.4)	19 (67.9)
Summary estimate (95% CI)		855	773	48.3%	67.0 (63.7, 70.3)	71.7 (68.5, 75.1)	10 (4–23)	12 (5–24)	60.9% (55.6%, 66.2%)	64.2% (59.3%, 68.9%)

*denotes statistically significant results. IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale.
†Stroke severity in Tartu study was mapped from Scandinavian Stroke Scale to NIHSS (see Methods, page 7).

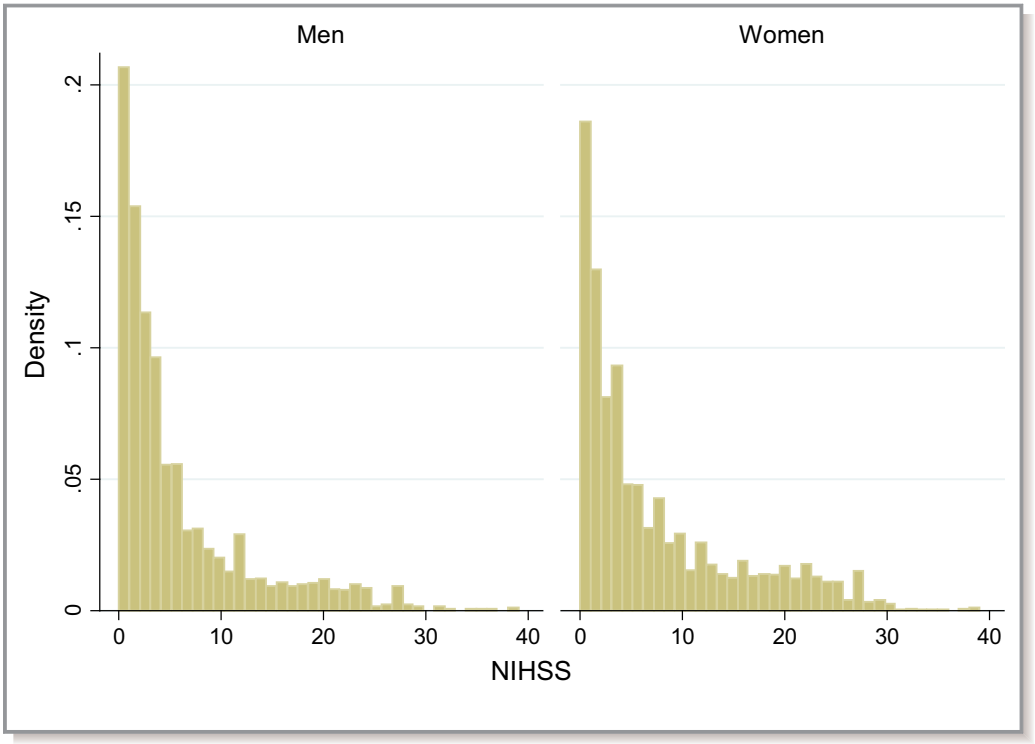

Figure 1. Distribution of the National Institutes of Health Stroke Scale scores by sex among those with stroke (both ischemic and intracerebral hemorrhagic stroke; n=6099). NIHSS indicates National Institutes of Health Stroke Scale.

1.35, 95% CI 1.23–1.49; $RR_{fully\text{-}adjusted}$ 1.19, 95% CI 1.08–1.32; ICH: $RR_{unadjusted}$ 1.08, 95% CI 0.90–1.29; $RR_{age\text{-}adjusted}$ 1.08, 95% CI 0.90–1.29) to our main findings using the 2-stage method (IS: Figure 2; ICH: Figure 3). Analyses of IS among a subset of 6 studies with pre-stroke function data reassured that our effect estimates did not greatly differ between these 2 approaches (1-stage $RR_{unadjusted}$ 1.33, 95% CI 1.18–1.49; $RR_{fully\text{-}adjusted}$ 1.15, 95% CI 1.03–1.30 versus 2-stage $RR_{unadjusted}$ 1.30, 95% CI 1.18–1.44; $RR_{fully\text{-}adjusted}$ 1.15, 95% CI 1.04–1.27; Table S7).

In the single pooled data set, we found no statistically significant interactions either between sex and each covariate,

Table 2. List of Factors Contributing to the Difference in Stroke Severity Between Women and Men in Multivariable Models by Stroke Type (more severe stroke was defined as National Institutes of Health Stroke Scale >7)

	Ischemic Stroke		Intracerebral Hemorrhage	
Study	n*	Covariates in the Fully Adjusted Model	n*	Covariate in the Fully Adjusted Model
Oxford[28]	1077	Age (y), pre-stroke mRS, AF	94	Age†
Joinville‡[29]	1494	Age, AF†	223	Age†
Melbourne[30]	647	Age, pre-stroke Barthel, AF†	136	Age†
Perth[31]	123	Age, pre-stroke mRS†, AF†	13	Age†
Orebro[32]	274	Age†, pre-stroke institutional residence, AF	44	Age†
Dijon[33]	1238	Age, pre-stroke institutional residence, AF†	197	Age†
Mãtao[34]‡	67	Age†, AF†	11	Age†
Tartu[35]	280	Age, pre-stroke mRS, AF†	55	Age†
Pooled	5200		773	

AF indicates atrial fibrillation; mRS, modified Rankin Scale.

*The sample size were the same among the unadjusted model and fully-adjusted model.

†Age, the presence of AF, and pre-stroke function (mRS, Barthel, or institutional residence when possible) were selected to be forced into all the final fully adjusted models regardless of meeting our criteria of being a confounder (associated with NIHSS; associated with sex, and changed the magnitude of the sex coefficient by ≥10%; see Methods, page 8).

‡Data on pre-stroke dependency were unavailable.

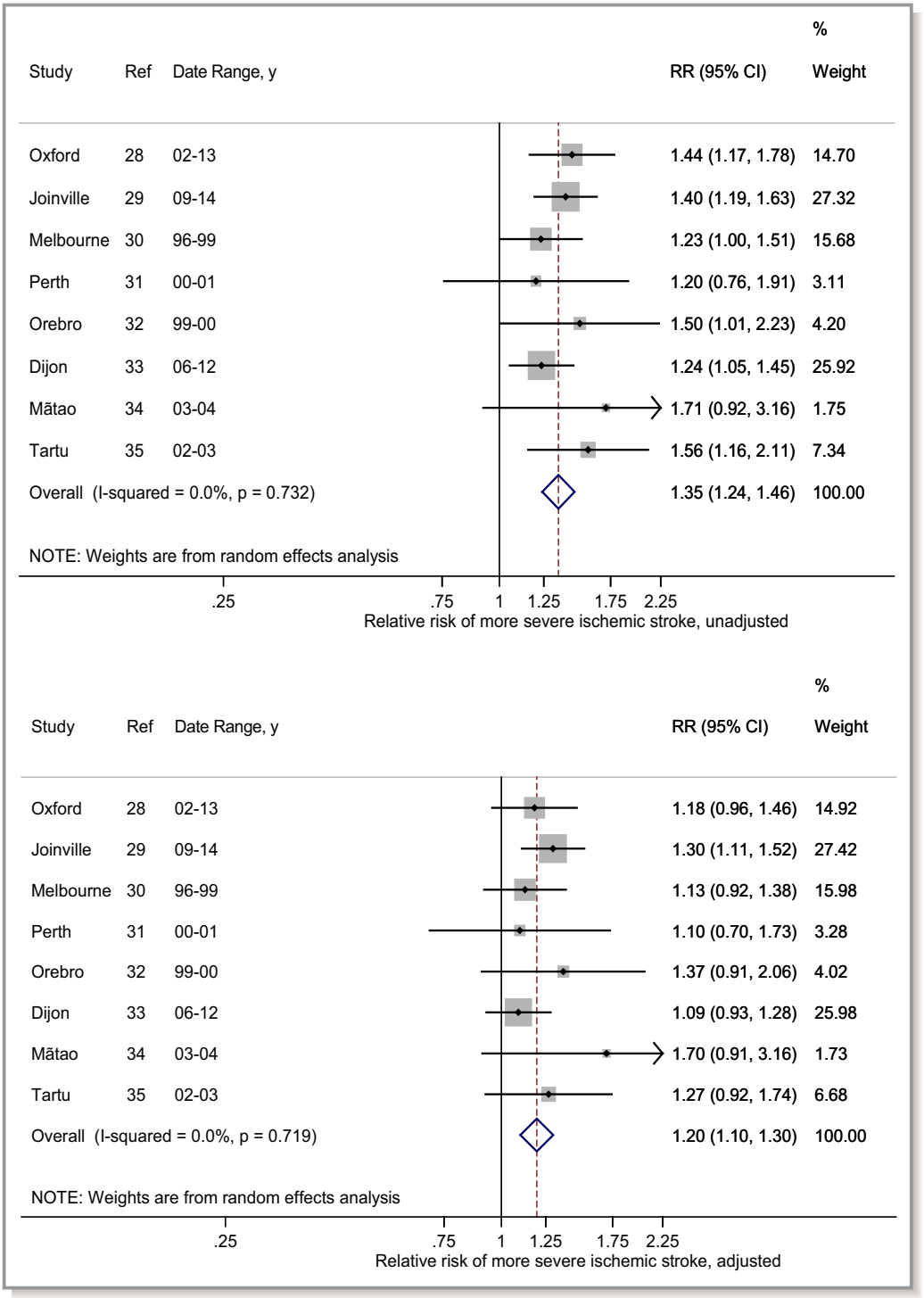

Figure 2. Difference in stroke severity between women and men with ischemic stroke: unadjusted (top) and adjusted (bottom) random-effects meta-analyses. More severe stroke was defined as National Institutes of Health Stroke Scale >7. Both unadjusted and adjusted effect estimates using fixed-effects meta-analysis were the same compared with those with random-effects approach. RR indicates relative risk.

or between covariates in multivariable models. The effect of age as a confounding factor was similar (IS: pooled $RR_{unadjusted}$ 1.34, 95% CI 1.22–1.49; $RR_{age\text{-}adjusted}$ 1.21, 95% CI 1.10–1.34; ICH: pooled $RR_{unadjusted}$ 1.08, 95% CI 0.90–1.29; $RR_{age\text{-}adjusted}$ 1.08, 95% CI 0.90–1.29; Table S9) to the one using the aforementioned 2-stage approach. There were no evidence of statistical interactions assessed by a test of statistical significance of a sex×age (continuous) product term (IS:

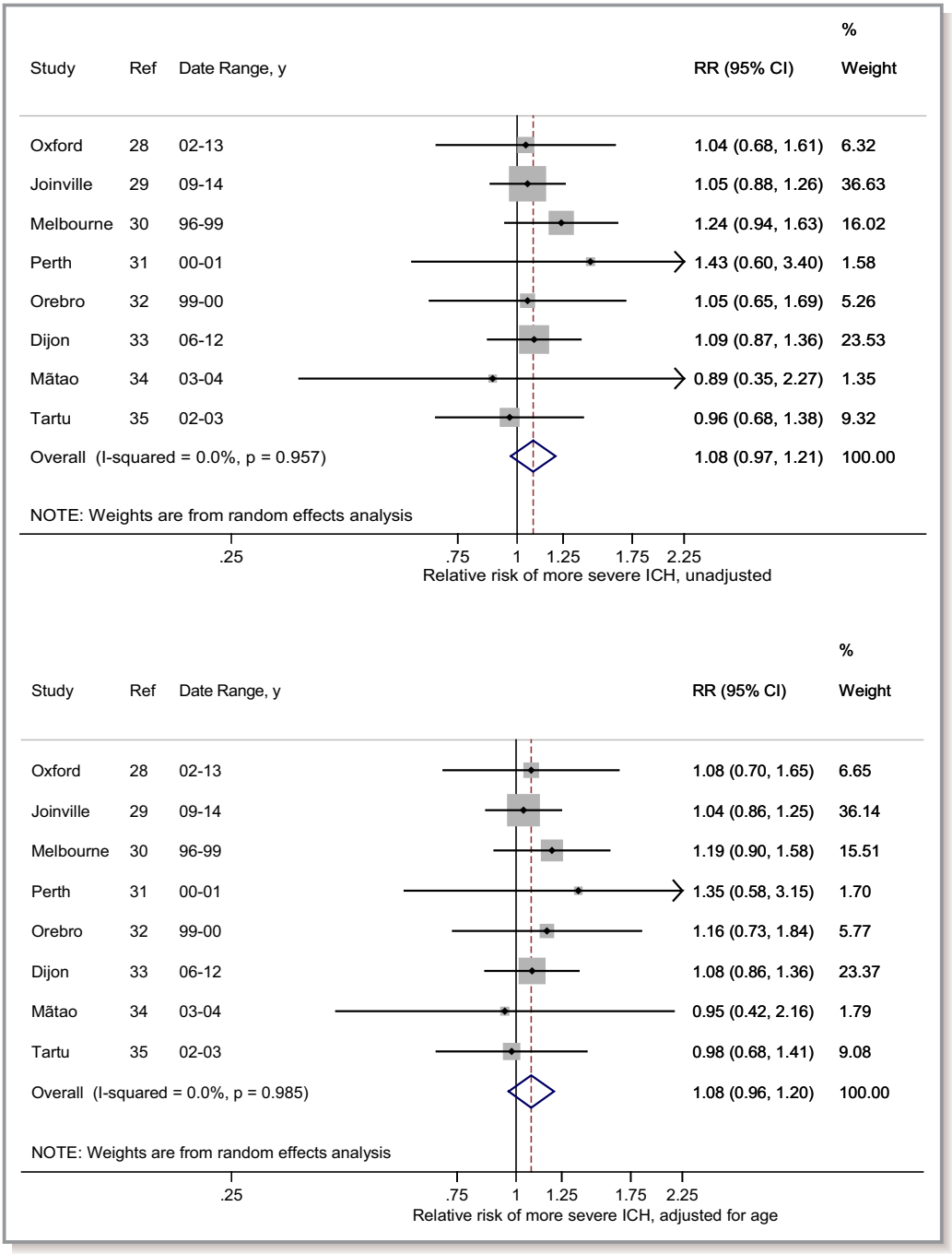

Figure 3. Difference in stroke severity between women and men with intracerebral hemorrhage (ICH) in unadjusted (top) and adjusted (bottom) random-effect meta-analyses. More severe stroke was defined as National Institutes of Health Stroke Scale >7. Both unadjusted and adjusted effect estimates using fixed-effects meta-analysis were the same compared with those with random-effects approach. ICH indicates intracerebral hemorrhage; RR, relative risk.

$P_{interaction}$=0.793; ICH: $P_{interaction}$=0.324). The magnitude of the sex differences in severity among those with IS and ICH was neither modified by age group (Table S9) and other covariates. Neither did the year of stroke occurrence modify the sex differences in stroke severity in both unadjusted (IS: $P_{interaction}$=0.067; ICH: $P_{interaction}$=0.128) and age-adjusted analyses (IS: $P_{interaction}$=0.264; ICH: $P_{interaction}$=0.281).

Discussion

We found that women with IS faced a 35% greater risk of severe stroke than men, and that much of this difference was explained by pre-stroke factors including: women's older age, the presence of functional limitations before stroke and atrial fibrillation. However, adjustment for these factors did not fully explain the sex difference and their effects were often

inconsistent between studies. We also found that there was no sex difference in severity of ICH.

Because of the more advanced age at stroke onset in women than men, age was the most important confounding factor of the association between sex and severity of IS, accounting for 36% of the sex difference. Older age may be associated with more severe strokes because of reduced functional capacity of supporting brain cells, ie, endothelial cells, and astrocytes after neurological insults.[36] The physiological decrease of cerebral blood flow and its regulation that occurs with increasing age[37] potentially influence neuronal damage after stroke in the elderly. As a consequence, impaired brain circulation and subsequent neurological dysfunction might lead to more severe strokes and less recovery in older adults with stroke. A better understanding of the pathophysiology of both stroke and cognitive function in the elderly may have important implications for clinical management and preventative strategies. Strategies such as enhancing geriatric care may help to reduce the poor outcome of chronic diseases[38] including stroke among frail older community-dwelling adults.[39]

Pre-stroke function was an important confounding factor of the sex differences in stroke severity in several (5/6) studies. The association between more severe stroke in women and their poorer functional limitation before stroke has been shown to be correlated with age and several cardiovascular comorbidities (eg, AF, hypertension, diabetes mellitus) at baseline.[14,40] Poor physical function and interrelated conditions such as frailty, which is more common in women,[41] may reflect underlying biologic mechanisms, including chronic inflammation, that play an important role in the pathogenesis of IS and the severity of brain tissue damage.[42] Better management of comorbid diseases and prevention of frailty in the elderly[43] could help ameliorate the effects of more severe strokes when they occur in women.[13] It is also possible that poor pre-stroke function and the presence of frailty may affect the accurate measurement of items in the NIHSS, as reported by others.[44] Combining clinical, imaging, and biomarker data of the severity of stroke may provide a better assessment of severity than a single instrument like the NIHSS.[45]

Atrial fibrillation (AF) contributed to the sex difference in severity of IS although surprisingly this was only statistically significant in 2 out of 8 studies (Oxford and Orebro). The inconsistent findings may be attributable to the variations in the data collection and definition of AF between studies (Table S2). One reason for more severe strokes in women is that women with AF more often have cardioembolic strokes than men.[46] In addition, previous studies have found that the management of AF, specifically, treatment with anticoagulants[47] or catheter ablation[48] appear to be suboptimal for women compared with men. It is thus possible that our observed confounding effect of AF on stroke severity could reflect the widespread under-treatment of AF in older patients.[49] However, we cannot confirm this possibility as treatments for AF were missing from our data set. This highlights the need for the better detection and treatment of AF in both older men and women before stroke occurrence.[50]

Age, AF, and pre-stroke function combined only accounted for 39% of the sex difference in severity of IS (with RR reduced from 1.35 to 1.20). Other unmeasured or poorly measured confounding factors could explain the remaining difference. However, it is also possible that a true biological or pathophysiological sex difference does exist. Further research is needed to explore potential biological and clinical mechanisms that could lead to a greater stroke severity in women. Potential dimorphic differences between men and women in severity of stroke include biologic (eg, hormone-dependent) and intrinsic (non-hormonal) factors (eg, sex chromosomes).[51] Research on biologic mechanisms has established the neuroprotective effect of hormones in women on IS injury during premenopause.[51] Little is known about how the decline of sex steroid hormones in women after menopause and ovariectomy influences the sex disparities in post-stroke neurologic deficits. Further examination of the sex differences in neurologic function, specifically injury response and recovery after stroke with regard to different age groups, are needed. Infarct size and location of stroke appear to influence the level of neurologic deficits and eventual stroke outcomes eg, left-hemispheric ischemic strokes are more frequent and often have higher admission NIHSS scores as well as poorer survival than right-hemispheric counterparts.[52] However, few authors have attempted to unravel the relative role of these factors in the severity differences across the different patient groups including men and women, or young and older people. Recent advanced brain imaging undertaken to investigate neurological deficits among people with different stroke types may offer better opportunities to understand the sex and age differences in brain injury.[53] Also, female members are often excluded in the neuroscience experiments because of the hormonal fluctuations associated with the reproductive cycle.[54] A recent meta-analysis of neuroscience studies has shown that data from female rats are no more variable than data from males.[55] This suggests a need to include females in animal models to understand the sex difference in severity of stroke.[56]

The sex differences in stroke severity existed for IS but not ICH. In our analyses, age, pre-stroke function, and AF were contributing factors to more severe strokes in women. By contrast, there were no evidence of the confounding effects in the ICH group (the unadjusted and adjusted estimates were the same). The reasons for this difference is unclear. It may be related to the differences in the underlying mechanisms

between these 2 types of stroke.[57] Further research is warranted to examine the uncertainty over the sex differences in stroke severity among women and men with ICH. Our study has a number of strengths. To our knowledge, we have provided the first pooled estimates of sex differences in stroke severity, separately for IS and ICH. We compiled the IPD from 8 population-based studies from various regions of the world. The use of 2-stage method for meta-analysis of IPD allowed us to overcome some of the limitations that result from not all potential confounding factors being measured across all studies.[22] The data came from high-quality population-based studies free of the limitations of hospital-based or convenience samples and had a large sample, making this study adequately powered to test our hypotheses.

However, limitations need to be acknowledged. The population-based studies in our research networks are mostly from high-income countries (7/8 studies), potentially leading to less generalizable results. We were unable to include 5 studies because NIHSS data were not available (Table S1) thereby reducing the statistical power. The methods and sources of data collection differed across cohorts, and this may have contributed to the differing confounding variables identified between studies. In particular, our inability to detect whether IS subtypes confounded the association between sex and severity is likely attributable to the scarce data on IS subtypes (TOAST classification) which were only collected in 4 studies. Further research is needed to explore the role of the mechanism of IS on the sex difference in severity of stroke. There was a lack of data on subdomain scores of NIHSS, another potential contributor to the sex difference in severity of stroke. Although the rate of missing data on NIHSS and covariates (<10%) was low enough that imputation of missing data was not required, we could not eliminate the possibility of some selection bias. Finally, the number of studies forming our pooled estimates was less than required (≥10) for the exploration of heterogeneity between studies using meta-regression.[58]

Conclusion

In clinical practice, women are more likely to present with severe IS than men but the difference is partly explained by their advanced age, greater pre-stroke functional limitation and presence of AF. Given these findings, strategies to improve pre-stroke health and access to evidence-based care for the elderly could help reduce differences in stroke severity between men and women. In addition, understanding the origin of more severe strokes in women compared with men should be a priority area for further research, more studies that attempt to identify other potential explanatory factors such as IS stroke mechanism, treatment of AF, and other comorbidities are needed.

Author Contributions

All authors satisfying the 4 criteria for authorship recommended by International Committee of Medical Journal Editors, as specified: Substantial contributions to the conception or design of the work (Dr Phan, Dr Gall, Dr Reeves, Dr Blizzard, Dr Thrift, Dr Cadilhac, Dr Heeley, Dr Sturm, and Mr Otahal) and the acquisition, analysis, or interpretation of data for the work (all authors); drafting the work or revising it critically for important intellectual content (all authors); final approval of the version to be published (all authors); agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (all authors).

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Search strategy, search term, data collection and data management

Our study was a collaboration between investigators for 13 population-based incidence studies identified through a previous systematic review,[1] and our research networks. To understand how representative these studies were of all possible studies we undertook a systematic literature search of the literature published after the aforementioned systematic review, as detailed below.

Search strategy

We identified potential studies using previous systematic reviews of these 'ideal' stroke incidence studies[1,2] supplemented with an updated search for new studies published since May 2008, the end date for the systematic review by Feigin et al.[1] We systematically searched population-based studies from academic databases (PubMed, Scopus, Embase and ScienceDirect) aiming to identify all 'ideal' incidence studies conducted between May 2008 and May 2014 with terms "stroke", "isch(a)emic stroke", "intracerebral", "intraparenchymal", "subarachnoid", "h(a)emorrhage", "population-based", "community-based", "community", "epidemiology", "epidemiological", "incidence", "attack rates", "survey", "surveillance", "mortality", "morbidity", "fatality", "case fatality", or "trends".

Our inclusion criteria comprised any stroke incidence study which met criteria of 'gold standard',[2,3] restricted to human studies only and published in the English language. These studies have standardised methods to ensure high quality data, including standard definitions for first-ever-in-a-lifetime stroke; a prospective design, population-based case ascertainment from multiple overlapping sources from inside and outside hospital systems; subtyping of a large proportion of events using imaging; a large and preferably stable population base; and surveillance over at least one year to control for seasonal variation in stroke occurrence. Our exclusion criteria was any population-based study which was not an adequate design (e.g. age limitation, ischemic stroke only).

We then established whether investigators of all eligible studies identified by reviews and updated search had published on outcomes at 1 or more years after stroke. We then invited those who had published these outcomes to participate. Where repeat incidence studies with assessments were conducted over time, we requested access to the follow-up data from the most recent incidence study.

Two reviewers (HP, SG) performed an online database search separately to identify eligible studies based on title or abstract and, where necessary, review the full-text article. References list of studies were also searched for additional eligible articles, while unpublished data were identified from contact with authors. Each reviewer also performed an assessment to determine which studies met our inclusion criteria and all these activities were undertaken with each reviewer blinded to the results. Disagreements were resolved via consensus.

Our search strategy identified 28 new 'ideal' studies in addition to 56 population-based studies identified by the previous systematic review. Of these, 22 'ideal' population-based stroke incidence studies had published on follow-up of participants at 1 year or more after stroke. We approached investigators of 17 eligible studies with long term follow-up to participate, with 13 agreeing. The main reasons for exclusion of 9 studies occurred due to refusal to participate (4 studies) and late identification of the study (5 studies).

Search term

Pubmed (n=1851)

Search ((“stroke”[Title] OR “isch(a)emic stroke”[Title] OR “intracerebral”[Title] OR “intraparenchymal”[Title] OR “subarachnoid”[Title] OR “h(a)emorrhage”[Title])) AND (“population-based”[Title] OR “community-based”[Title] OR “community”[Title] OR “epidemiology”[Title] OR “epidemiological”[Title] OR “incidence”[Title] OR “attack rates”[Title] OR “survey”[Title] OR “surveillance”[Title] OR “mortality”[Title] OR “morbidity”[Title] OR “fatality”[Title] OR “case fatality”[Title] OR “trends”[Title]) Filters: Publication date from 2008/05/01 to 2014/05/01; English

Embase (n=721)

(1) 'population-based' OR 'community-based' OR 'community' OR 'epidemiology' OR 'epidemiological' OR 'incidence' OR 'attack rates' OR 'survey' OR 'surveillance' OR 'ideal study' OR 'mortality' OR 'morbidity' OR 'fatality' OR 'case fatality' OR 'trends' OR 'population-based' OR 'community-based' OR 'community' OR 'epidemiology' OR 'epidemiological' OR 'incidence' OR 'attack rates' OR 'survey' OR 'surveillance'
(2) 'stroke' OR 'ischaemic stroke' OR 'ischemic stroke' OR 'intracerebral' OR 'intraparenchymal' OR 'subarachnoid' OR 'haemorrhage' OR 'hemorrhage' OR 'ischemic stroke' AND .tw
(3) #1 AND #2 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py), human, English

Scopus (n=1966)

Search (TITLE ("population-based" OR "community-based" OR "community" OR "epidemiology" OR "epidemiological" OR "incidence" OR "attack rates" OR "survey" OR "surveillance" OR "mortality" OR "morbidity" OR "fatality" OR "case fatality" OR "trends")) AND (TITLE ("stroke" OR "ischaemic stroke" OR "ischemic stroke" OR "intracerebral" OR "intraparenchymal" OR "subarachnoid" OR "haemorrhage" OR hemorrhage)) AND (LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "ip")) AND (LIMIT-TO (LANGUAGE , "English"))

ScienceDirect (n=811)

Limitation: pub-date > 2007 and pub-date < 2015 and TITLE ("stroke" OR "ischaemic stroke" OR "ischemic stroke" OR "intracerebral" OR "intraparenchymal" OR "subarachnoid" OR "haemorrhage" OR hemorrhage OR "ischemic stroke") AND TITLE ("mortality" OR "morbidity" OR "fatality" OR "case fatality" OR "trends" OR "population-based" OR "community-based" OR "community" OR "epidemiology" OR "epidemiological" OR "incidence" OR "attack rates" OR "survey" OR "surveillance")

Data collection

Authors of each eligible study were contacted with a request for de-identified individual participant data (IPD) on stroke outcomes up to 5 years after stroke. Outcomes included mortality (date, time of stroke, date of death), functional outcomes and health-related quality of life. Data on participant characteristics were requested if available including socio-demographics (age, sex, marital status, education, occupation, socioeconomic position), pre-stroke health including body mass index, health behaviors (smoking, alcohol use), pre-stroke function (dependency, institutional residence), pre-stroke medication, history of comorbidities (atrial fibrillation, hypertension, ischemic heart disease, peripheral vascular disease, transient ischemic attack, diabetes, dementia), stroke-related factors (stroke severity, stroke type, the year of stroke occurrence), treatment and management (hospital admission, time to hospital, admission and discharge medication, neuroimaging, carotid investigation, echocardiography and surgical intervention) and post-stroke factors (depression and recurrence). Data provided were checked again with published data, where possible, and if discrepancies were identified, clarification was sought from authors. When no response was provided to data requests or no response from authors, we checked whether results of sex differences were reported in published papers.

Data management

Study-specific outcomes and variable definitions (i.e. covariates) were recorded and, where necessary, recoded to create common variables with consistent definitions (e.g. stroke severity). Following recoding, 13 datasets were then merged into one common database using study identification numbers.

Data S2.

Measurement of potential confounding factors of sex difference in NIHSS of stroke at acute stroke

Socio-demographics

Data on age at the index stroke were available in all studies without age restriction. Race data from studies in Melbourne and Matão were categorised as Caucasian/Non-Caucasian. Educational level (studies conducted in Oxford, Joinville, Melbourne and Matão) was divided into two groups with the cut-off point of completing secondary education (grade 12). Classification of socioeconomic position (SEP) includes three groups: professional / non-manual (skilled + unskilled) / manual (skilled + unskilled) in 4 studies (Oxford, Melbourne, and Perth). Data on marital status (Oxford, Perth, Orebro and Matão) were categorized into 2 group: married / unmarried (including single, divorced, and widowed).

Pre-stroke health

Co-morbidities

Analysis of binary data of self-reported history of diabetes (4 studies: Oxford, Melbourne, Perth and Orebro), dementia (3 studies Melbourne, Orebro and Matão), and cardiovascular diseases including ischaemic heart disease (all studies), atrial fibrillation (all studies), hypertension (all studies), transient ischaemic attack (all studies), and peripheral vascular disease (5 studies: Oxford, Melbourne, Orebro, Dijon and Matão) were performed.

Body mass index (BMI) was recorded in 5 studies including Oxford, Joinville, Perth, Martinique and Porto.

Pre-stroke medication

Data on pre-stroke use of antihypertensive and antiplatelet agents were available in 5 studies (Joinville, Melbourne, Perth, Auckland and Tartu) and information on use of anticoagulants before stroke was only available in 2 studies (Melbourne and Auckland).

Smoking and alcohol use

Smoking status, which was recorded in 7 studies (not including Tartu), was categorized into 3 levels: never / former / current. Data on alcohol consumption were available in 6 studies. Alcohol use was analysed as 3 groups – no / current drinkers / ex-drinkers in 3 studies (Perth, Dijon, Matão) or 4 groups – no / not heavy drinkers / heavy drinkers / ex-drinkers in 3 studies (Oxford, Melbourne and Auckland) which depend on available data within different studies.

Pre-stroke dependency

Pre-stroke functional status was assessed according to residing in an institution before stroke in 4 studies (Melbourne, Perth, Orebro and Dijon), the pre-stroke Barthel Index in 3 studies (Melbourne, Perth and Orebro) or pre-stroke modified Rankin Score (mRS) in 4 studies (Oxford, Perth and Tartu). Pre-stroke dependency was defined as pre-stroke Barthel <20 or pre-stroke mRS>2.

Management at acute stroke

Hospital admission

Data on whether the patient was admitted to hospital were available in all studies.

Delay to hospital

Analyses of these data were based on the time from stroke onset to admission time. Among 3 studies with these data (Oxford, Perth and Tartu), we calculated the time to hospital from time of stroke onset to time of admission and then categorized into them three groups (≤4.5 hours / 4.5 hours-24 hours / >24 hours). Delay to hospital was defined as a longer time for admission to hospital (i.e. > 24 hours).

Table S1. Eligible 'ideal' population-based studies of stroke with long-term outcome data available through systematic search.

Study	Year	Baseline (N)	Data on NIHSS	Notes
13 studies for which long-term IPD were provided (n=18,342)				
Oxford, UK[4]	'02-'13	1374	✓	
Joinville, Brazil[5]	'09-'14	2357	✓	
Melbourne, Australia[6]	'96-'99	1316	✓	
Arcadia, Greece[7]	'93-'95	555		
Perth, Australia[8]	'00-'01	183	✓	
Orebro, Sweden[9]	'99-'00	377	✓	
Dijon, France[10]	'87-'12	4621	✓ (only available during the year '06-'12; n=1505)	
Martinique, French West Indies[11]	'98-'99	580		Other severity instrument (Barthel Index)
Porto, Portugal[12]	'98-'00	688		Other severity instrument (Unified Neurological Stroke Scale)
Auckland, NZ[13]	'02-'03	1423		Other severity instrument (Glasgow Coma Scale)
L'Aquila, Italia[14]	'94-'98	4353		Other severity instrument (loss of consciousness)
Matão, Brazil[15]	'03-'04	81	✓	
Tartu, Estonia[16]	'02-'03	433	✓ (mapped from Scandinavian Stroke Scale)	
9 studies for which long-term IPD were not provided (n=9,985)				
Ludwigshafen, Germany [17]	'06-'07	725		No information of severity measurement
Warsaw, Poland [18,19]	'05	127	✓	No sex-specific findings in sex difference in NIHSS
South London, UK [20]	'95-'06	3373	✓	
Erlangen, Germany [21]	'98-'06	1631		Other severity instrument (Barthel Index)
Malmo, Sweden [22]	'89-'92	2290		Other severity instrument (Katx Index)
Aeolian Islands, Italia [23]	'99-'00	62		No information of severity measurement
Vibo Valentia, Italia [24]	'96	321		No information of severity measurement
Rural Tanzania, Africa[25]	'03-'06	130		Other severity instrument (Barthel index)
Valley of Aosta, Italy [26]	'04-'08	1326		No information of severity measurement

National Institute Health Stroke Scale=NIHSS
✓ denotes study with data

Table S2. Data collection methods of study factors across eight studies.

Study	Source of data
Oxford[4]	Pre-morbid medication and vascular risk factors were obtained from the patients or relative, hospital records, and general practice records. Atrial fibrillation (AF) was defined as either a known history with a confirmation from primary care or hospital records. Blood pressure (BP) was recorded from the general practice records. Premorbid modified Rankin score (mRS) was recorded from self-report questionnaire.
Joinville[5]	A self-reported history or current treatment for cardiovascular diseases and risk factors, smoking and alcohol was obtained from patients or their relatives by research nurses.
Melbourne[6]	Risk factors and management of risk factors were recorded by trained data collectors using a standardised questionnaire. Supporting data were collected from patients, relatives, medical records and treating doctor. Dementia, hypertension, peripheral vascular disease (PVD), prior transient ischemic attack (TIA), and prior myocardial infarction were defined as a known history. Diabetes was defined as either a known history or current presentation with fasting blood glucose ≥7.0 mmol/L. AF was defined as either a known history or current presentation confirmed on ECG. Smoking status was classified from self-report as current smoker, ex-smoker, or never smoked. Prestroke disability was recorded from self-report questionnaire using the Barthel Index.
Perth[8]	The presence of heart failure was based on clinical criteria that included 1 of the following: raised venous pressure, gallop cardiac rhythm, and crepitations at the lung bases. The presence of AF required confirmation by an ECG within 1 month of the onset of stroke. Premorbid levels of physical disability were based on self-report or proxy sources (caregivers or medical records for those patients who were deceased or disabled) with the modified Barthel Index and mRS.
Orebro[9]	A record of medical history was taken and logistic data regarding hospital treatment period and investigations were noted. Premorbid mRS was recorded from self-report questionnaire.
Dijon[10]	History of hypertension was defined as known hypertension in a patient's medical history (either self-reported or from medical notes) or when a patient was treated with anti-hypertensive agents. A history of AF, previous myocardial infarction, a history of TIA were recoded. Pre-stroke treatments by anticoagulants, antiplatelet agents and antihypertensive treatments were noted.
Matão[15]	Risk factors and management of risk factors were recorded by trained data collectors using a standardised questionnaire.
Tartu[16]	Stroke risk factors were recorded based on case history and clinical evaluations. History of disease was obtained from outpatients and hospital records, family and patients. BP was measured at admission. AF was confirmed by ECG. Myocardial infarction was confirmed by ECG or autopsy. Premorbid mRS was recorded from self-report questionnaire.

Table S3. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Oxford, Joinville, Melbourne and Perth.

Characteristic	Oxford[4]				Joinville[5]				Melbourne[6]				Perth[8]			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Number of cases	550	537	48	46	780	714	129	94	357	387	73	71	61	62	8	7
SOCIODEMOGRAPHIC																
Mean (SD) Age	**72.4 (12.0)**	**77.7 (12.1)**	69.5 (14.3)	73.5 (16.2)	**63.5 (12.5)**	**66.8 (15.7)**	**58.2 (15.4)**	**62.5 (15.5)**	**72.4 (12.7)**	**76.3 (14.3)**	**70.3 (13.5)**	**75.2 (15.2)**	74.0 (12.5)	78.0 (10.1)	68.0 (18.5)	73.5 (12.3)
Race (%)																
Caucasian	-	-	-	-	-	-	-	-	93.0	94.6	91.8	93.0	-	-	-	-
Non-Caucasian									3.4	2.8	4.1	5.6				
Unknown									3.6	2.6	4.1	1.4				
Marital status (%)																
Single/widowed	**23.6**	**54.0**	12.5	39.1	-	-	-	-	-	-	-	-	**64.0**	**37.1**	87.5	57.1
Married	**65.3**	**34.6**	62.5	54.4									**32.8**	**58.1**	12.5	42.9
Unknown	**11.1**	**11.4**	25.0	6.5									**3.3**	**4.8**	0.0	0.0
Education level (%)																
≤ Grade 12	**65.1**	**66.5**	47.9	60.9	93.9	93.7	93.8	95.7	**51.3**	**56.1**	**39.7**	**47.9**	-	-	-	-
> Grade 12	**15.6**	**9.1**	8.3	6.5	5.8	5.6	6.2	3.2	**43.4**	**42.4**	**53.4**	**52.1**				
Unknown	**19.3**	**24.4**	43.8	32.6	0.4	0.7	0.0	1.1	**5.3**	**1.6**	**6.9**	**0.0**				
Social class (%)																
Professional	**17.1**	**6.5**	**6.3**	**4.4**	-	-	-	-	**38.7**	**32.8**	**38.4**	**42.3**	**21.3**	**3.2**	12.5	0.0
Non-manual	**21.8**	**27.9**	**20.8**	**47.8**					**10.4**	**14.2**	**16.4**	**9.9**	**6.6**	**12.9**	0.0	0.0
Manual	**41.1**	**35.9**	**35.4**	**19.6**					**43.7**	**35.9**	**38.4**	**25.4**	**21.3**	**15.8**	50.0	14.3
Unknown	**20.0**	**29.6**	**37.5**	**28.3**					**7.3**	**17.1**	**6.9**	**22.5**	**50.8**	**58.1**	37.5	85.7
PRE-STROKE HEALTH																
Modified Rankin Score (%)																
0-2	**85.8**	**73.6**	79.2	69.6	-	-	-	-	-	-	-	-	82.0	67.7	12.5	14.3
3-5	**13.6**	**25.1**	10.4	26.1									16.4	24.2	75.0	71.4
Unknown	**0.6**	**1.3**	10.4	4.4									1.6	8.1	12.5	14.3
Institutional residence (%)																
Yes	-	-	-	-	-	-	-	-	**6.4**	**13.2**	6.9	15.5	4.9	9.7	62.5	14.3
No									**93.3**	**86.3**	91.8	84.5	95.1	90.3	12.5	42.9
Unknown									**0.3**	**0.5**	1.4	0.0	0.0	0.0	25.0	42.9
Barthel Index (%)																
20	-	-	-	-	-	-	-	-	**60.2**	**49.6**	54.8	36.6	-	-	-	-
<20									**13.5**	**19.6**	6.9	14.1				
Unknown									**26.3**	**30.8**	38.4	49.3				
MEDICAL HISTORY																
Atrial fibrillation (%)																
Yes	21.1	25.5	16.7	10.9	4.6	6.0	0.0	1.1	22.4	26.6	12.3	11.3	19.7	24.2	0.0	28.6
No	78.9	74.3	83.3	89.1	95.4	94.0	100.0	98.9	77.0	73.1	84.9	88.7	75.4	74.2	75.0	71.4
Unknown	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.9	1.6	0.0	0.0
Hypertension (%)																
Yes	61.3	66.7	54.2	47.8	**65.8**	**72.6**	69.0	77.7	53.2	58.9	53.4	64.8	54.1	61.3	37.5	42.9
No	38.7	33.3	41.7	52.2	**34.2**	**27.5**	31.0	22.3	45.9	40.6	45.2	35.2	41.0	38.7	37.5	57.1
Unknown	0.0	0.0	4.2	0.0	**0.0**	**0.0**	0.0	0.0	0.8	0.5	1.4	0.0	4.9	0.0	25.0	0.0
Ischemic heart disease (%)																
Yes	**16.2**	**9.3**	8.3	0.0	**7.6**	**3.5**	3.1	1.1	16.8	14.0	**15.8**	**2.8**	18.0	8.1	12.5	0.0
No	**83.5**	**90.7**	83.3	97.8	**92.4**	**96.5**	96.9	98.9	82.6	85.8	**83.6**	**97.2**	78.7	88.7	62.5	100.0
Unknown	**0.4**	**0.0**	8.3	2.2	**0.0**	**0.0**	0.0	0.0	0.6	0.3	**1.4**	**0.0**	3.3	3.2	25.0	0.0
Peripheral vascular disease (%)																

Table S3. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Oxford, Joinville, Melbourne and Perth.

Characteristic	Oxford[4]				Joinville[5]				Melbourne[6]				Perth[8]			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Yes	9.1	5.6	2.1	0.0	-	-	-	-	**12.6**	**5.7**	6.9	2.8	-	-	-	-
No	90.7	94.2	97.9	100.0					**86.8**	**94.1**	91.8	95.8				
Unknown	0.2	0.2	0.0	0.0					**0.6**	**0.3**	1.4	1.4				
Transient ischemic attack (%)																
Yes	14.4	11.9	10.4	10.9	2.6	2.4	3.9	0.0	9.8	9.8	8.2	5.6	21.3	11.3	12.5	14.3
No	85.6	87.9	89.6	89.1	97.4	97.6	96.1	100.0	89.6	89.7	89.0	94.4	67.2	80.7	50.0	85.7
Unknown	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.5	2.7	0.0	11.5	8.1	37.5	0.0
Diabetes (%)																
Yes	15.6	12.1	8.3	8.7	-	-	-	-	19.9	18.4	9.6	4.2	24.6	21.0	0.0	14.3
No	84.4	87.9	91.7	91.3					79.6	91.7	90.4	95.8	75.4	79.0	75.0	85.7
Unknown	0.0	0.0	0.0	0.0					0.6	0.0	0.0	0.0	0.0	0.0	25.0	0.0
Dementia (%)																
Yes	-	-	-	-	-	-	-	-	**4.5**	**9.3**	**4.1**	**15.5**	-	-	-	-
No									**81.8**	**78.3**	**84.9**	**81.7**				
Unknown									**13.7**	**124**	**11.0**	**2.8**				
Smoking (%)																
Current	**17.5**	**13.8**	**20.8**	**4.4**	**29.6**	**13.2**	**34.9**	**59.6**	**20.2**	**13.7**	**16.4**	**9.9**	**11.5**	**4.8**	25.0	0.0
Former	**53.5**	**28.3**	**39.6**	**28.3**	**41.3**	**18.6**	**34.1**	**25.5**	**46.2**	**22.5**	**53.4**	**19.7**	**52.5**	**14.5**	25.0	14.3
Never	**28.4**	**56.4**	**27.1**	**56.5**	**29.1**	**68.2**	**31.0**	**14.9**	**29.4**	**55.0**	**23.3**	**52.1**	**18.0**	**53.2**	25.0	42.9
Unknown	**0.7**	**1.5**	**12.5**	**10.9**	**0.0**	**0.0**	**0.0**	**0.0**	**4.2**	**8.8**	**6.9**	**18.3**	**18.0**	**27.4**	25.0	42.9
Alcohol use (%)																
Non-drinkers	**28.6**	**57.0**	**16.7**	**41.3**	**49.0**	**83.1**	**19.4**	**2.1**	**20.2**	**46.0**	**15.1**	**35.2**	27.9	30.7	25.0	28.6
Not heavy drinkers	**63.8**	**34.6**	**45.8**	**32.6**	**38.7**	**15.8**	**34.9**	**18.1**	**56.3**	**41.3**	**53.4**	**38.0**	9.8	14.5	0.0	0.0
Heavy drinkers	**3.3**	**1.7**	**8.3**	**2.2**	**13.3**	**1.1**	**45.7**	**79.8**	**8.2**	**1.3**	**12.3**	**1.4**	29.5	17.7	37.5	0.0
Ex-drinkers	**-**	**-**	**-**	**-**	**-**	**-**	-	-	**8.7**	**1.3**	**11.0**	**2.8**	6.6	1.6	0.0	0.0
Unknown	**4.4**	**6.7**	**29.2**	**23.9**	**0.0**	**0.0**	0.0	0.0	**6.7**	**10.1**	**8.2**	**22.5**	26.2	35.5	37.5	0.0
Mean (SD) Body mass index	26.4 (4.6)	26.2 (5.8)	25.3 (3.4)	23.2 (7.5)	26.7 (4.2)	26.9 (5.5)	27.0 (4.8)	25.8 (5.0)	-	-	-	-	25.9 (4.0)	25.0 (4.0)	-	-
Medication																
Antihypertensives (%)																
Yes	-	-	-	-	**61.2**	**69.5**	**55.0**	**69.2**	53.3	61.8	41.1	49.3	45.9	56.5	37.5	42.9
No					**38.9**	**30.5**	**45.0**	**30.9**	46.2	38.0	57.5	50.7	47.5	40.3	37.5	57.1
Unknown					**0.0**	**0.0**	**0.0**	**0.0**	0.3	0.3	1.4	0.0	6.6	3.2	25.0	0.0
Antiplatelet (%)																
Yes	-	-	-	-	30.1	33.6	20.9	24.5	30.5	30.5	20.6	28.2	**29.5**	**43.6**	25.0	42.9
No					69.9	66.4	79.1	75.5	69.2	69.5	78.1	71.9	**70.5**	**51.6**	62.5	57.1
Unknown					0.0	0.0	0.0	0.0	0.3	0.0	1.4	0.0	**0.0**	**4.8**	12.5	0.0
STROKE-RELATED FACTORS																
Hospital admission (%)	82.7	83.1	100.0	97.8	100.0	100.0	100.0	100.0	98.0	99.0	100.0	98.6	77.1	83.9	100.0	57.1
Ischemic stroke subtype																
Atherothrombotic	-	-	-	-	27.9	26.0	-	-	23.8	18.1	-	-	-	-	-	-
Cardioembolic					27.4	28.4			26.3	25.3						
Lacunar					22.4	18.3			19.1	13.2						
Other Causes					22.2	27.3			1.1	1.6						
Undetermined					0.0	0.0			29.7	41.9						
Time to hospital† (%)																
≤ 4.5 hours	-	-	-	-	41.4	45.1	57.4	64.9	-	-	-	-	14.9	19.2	25.0	0.0
> 4.5 – 24 hours					27.7	24.7	24.8	20.2					8.5	13.5	12.5	0.0

Table S3. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Oxford, Joinville, Melbourne and Perth.

Characteristic	Oxford[4]				Joinville[5]				Melbourne[6]				Perth[8]			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
> 24 hours					28.6	26.9	14.7	11.7					10.6	19.2	0.0	25.0
Unknown					2.3	3.4	3.1	3.2					66.0	18.1	62.5	75.0

Bold denotes statistically significant differences between men and women; IS, Ischemic stroke; ICH, intracerebral hemorrhage; † among hospitalized patients

Table S4. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Orebro, Dijon, Mãtao and Tartu.

Characteristic	Orebro[9]				Dijon[10]				Mãtao[15]				Tartu[16]			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Number of cases	125	149	25	19	568	670	92	105	41	26	8	3	121	178	27	28
SOCIODEMOGRAPHIC																
Mean (SD) Age	**73.1 (10.5)**	**77.1 (10.7)**	71.9 (11.5)	75.6 (9.9)	**71.7 (15.3)**	**77.2 (15.8)**	**71.0 (15.8)**	**76.6 (18.3)**	65.1 (12.3)	64.5 (12.6)	62.9 (7.0)	68.7 (7.5)	**68.1 (10.9)**	**75.6 (10.9)**	63.6 (15.9)	68.1 (12.6)
Marital status (%)																
Single/widowed	**32.8**	**36.9**	**32.0**	**63.2**	-	-	-	-	26.8	38.5	25.0	66.7	-	-	-	-
Married	**67.2**	**61.7**	**68.0**	**36.8**					68.3	61.5	75.0	0.0				
Unknown	**0.0**	**0.0**	**0.0**	**0.0**					4.8	0.0	0.0	33.3				
Education level (%)																
≤ Grade 12	-	-	-	-	-	-	-	-	80.5	96.2	75.0	33.3	-	-	-	-
> Grade 12									7.3	3.9	25.0	0.0				
Unknown									12.2	0.0	0.0	66.7				
PRE-STROKE HEALTH																
Modified Rankin Score (%)																
0-2	-	-	-	-	-	-	-	-	-	-	-	-	87.6	87.1	85.2	82.1
3-5													4.1	7.9	3.7	3.6
Unknown													8.3	5.1	11.1	14.3
Institutional residence (%)																
Yes	**2.4**	**9.4**	4.0	21.1	**3.5**	**10.8**	4.4	6.7	-	-	-	-	-	-	-	-
No	**97.6**	**90.6**	96.0	79.0	**96.5**	**89.3**	95.7	93.3								
Unknown	**0.0**	**0.0**	0.0	0.0	**0.0**	**0.0**	0.0	0.0								
Barthel Index (%)																
20	76.0	65.1	4.0	47.4	-	-	-	-	-	-	-	-	-	-	-	-
<20	6.4	7.4	68.0	5.3												
Unknown	17.6	27.5	28.0	47.4												
MEDICAL HISTORY																
Atrial fibrillation (%)																
Yes	20.8	26.2	24.0	5.3	14.6	19.0	11.9	20.2	2.4	0.0	0.0	0.0	30.6	41.6	7.4	7.1
No	79.2	73.8	76.0	94.7	85.3	80.4	88.1	79.8	90.2	100	100	66.7	69.4	58.4	92.6	92.9
Unknown	0.0	0.0	0.0	0.0	0.2	0.6	0.0	0.0	7.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Hypertension (%)																
Yes	31.2	42.3	32.0	31.6	66.2	70.6	68.3	64.9	63.4	69.2	87.5	66.7	55.4	71.4	63.0	71.4
No	67.2	55.7	68.0	68.4	33.6	28.8	31.7	35.1	31.7	30.8	12.5	0.0	44.6	28.7	37.0	28.6
Unknown	1.6	2.0	0.0	0.0	0.2	0.6	0.0	0.0	4.9	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Ischemic heart disease (%)																
Yes	19.2	14.8	8.0	0.0	16.3	12.7	8.9	7.0	2.4	11.5	12.5	0.0	38.0	43.8	22.2	32.1
No	80.8	85.2	92.0	100.0	93.5	86.7	91.1	93.0	90.2	88.5	87.5	66.7	62.0	56.2	77.8	67.9
Unknown	0.0	0.0	0.0	0.0	0.2	0.6	0.0	0.0	7.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Peripheral vascular disease (%)																
Yes	37.6	26.9	28.0	21.1	**7.7**	**4.5**	5.9	5.3	-	-	-	-	-	-	-	-
No	62.4	72.5	78.0	79.0	**92.1**	**94.9**	94.1	94.7								
Unknown	0.0	0.7	0.0	0.0	**0.2**	**0.6**	0.0	0.0								
Transient ischemic attack (%)																
Yes	20.0	13.4	4.0	10.5	6.6	8.8	5.9	3.5	9.8	3.9	0.0	0.0	7.4	8.4	0.0	0.0
No	80.0	86.6	96.0	89.5	93.3	91.2	94.1	96.5	82.9	93.2	100.0	33.3	92.6	91.6	100.0	100.0
Unknown	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Diabetes (%)																
Yes	20.8	16.1	8.0	10.5	-	-	-	-	-	-	-	-	-	-	-	-

Table S4. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Orebro, Dijon, Mãtao and Tartu.

Characteristic	Orebro[9]				Dijon[10]				Mãtao[15]				Tartu[16]			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
No	78.4	81.9	92.0	89.5												
Unknown	0.8	2.0	0.0	0.0												
Dementia (%)																
Yes	4.8	10.1	8.0	10.5	-	-	-	-	-	-	-	-	-	-	-	-
No	85.2	89.9	92.0	89.5												
Unknown	0.0	0.0	0.0	0.0												
Smoking (%)																
Current	**29.6**	**18.1**	24.0	10.5	**47.0**	**81.7**	**59.4**	**82.5**	**43.9**	**19.2**	50.0	33.3	-	-	-	-
Former	**-**	**-**	-	-	**23.2**	**2.5**	**15.8**	**2.6**	**-**	**-**	-	-				
Never	**63.2**	**79.2**	64.0	79.0	**27.3**	**12.3**	**21.8**	**9.7**	**51.2**	**80.8**	50.0	33.3				
Unknown	**7.2**	**2.7**	12.0	10.5	**2.6**	**3.5**	**3.0**	**2.3**	**4.9**	**0.0**	0.0	33.3				
Alcohol use (%)																
Non-drinkers	-	-	-	-	86.6	95.6	77.1	95.6	**70.7**	**100.0**	75.0	33.3	-	-	-	-
Current drinkers*					11.5	2.3	20.8	3.5	**22.0**	**0.0**	25.0	33.3				
Ex-drinkers					-	-	-	-	-	-	-	-				
Unknown					1.9	2.1	2.0	0.9	**7.3**	**0.0**	0.0	33.3				
STROKE-RELATED FACTORS																
Hospital admission (%)	95.2	96.0	92.0	94.7	99.7	100.0	100.0	99.1	100.0	100.0	100.0	100.0	98.4	99.4	100.0	100.0
Ischemic stroke subtype																
Atherothrombotic	54.4	55.7	-	-	-	-	-	-	-	-	-	-	28.9	25.8	-	-
Cardioembolic	12.8	14.1											28.1	39.3		
Lacunar	30.4	26.9											30.6	23.0		
Other Causes	1.6	1.3											12.4	10.7		
Undetermined	0.8	2.0											0.0	1.1		
Time to arrive hospital† (%)																
≤ 4.5 hours	-	-	-	-	-	-	-	-	-	-	-	-	30.3	32.2	59.3	57.1
> 4.5 – 24 hours													6.7	5.1	3.7	0.0
> 24 hours													2.5	2.8	0.0	0.0
Unknown													60.5	59.9	37.0	42.8

Bold denotes statistically significant differences between men and women; IS, Ischemic stroke; ICH, intracerebral hemorrhage; † among hospitalized patients

Table S5. Severity of ischemic stroke by subtype among women and men.

Study	Number of cases (%)		NIHSS, mean (IQR)		NIHSS>7, n (%)		More severe stroke
	Men	Women	Men	Women	Men	Women	RR (95% CI)
Large-artery atherosclerosis							
Joinville[5]	247 (56.0%)	194 (44.0%)	4.0 (2.0-9.0)	5.0 (2.0-12.0)	74/247 (30.0%)	73/194 (37.6%)	1.26 (0.97-1.63)
Melbourne[6]	85 (23.8%)	70 (45.2%)	4.0 (1.0-8.0)	4.0 (2.0-14.0)	22/85 (25.9%)	29/70 (41.4%)	**1.60 (1.01-2.53)**
Orebro[9]	68 (45.0%)	83 (55.0%)	3.0 (2.0-10.5)	6.0 (3.0-10.0)	20/68 (29.4%)	34/83 (41.0%)	1.39 (0.89-2.19)
Tartu[16]	35 (43.2%)	46 (56.8%)	12.0 (6.0-20.0)	13.0 (7.0-19.0)	22/35 (62.9%)	33/46 (71.7%)	1.14 (0.93-1.56)
Pooled	435 (52.5%)	393 (47.5%)	4.0 (2.0-10.0)	6.0 (3.0-13.0)	138/435 (31.7%)	169/393 (43.0%)	**1.32 (1.05-1.66)***
Cardioembolism							
Joinville[5]	259 (47.3%)	289 (52.7%)	5.0 (2.0-12.0)	8.0 (3.0-16.0)	100/259 (38.6%)	150/289 (51.9%)	**1.34 (1.11-1.63)**
Melbourne[6]	94 (49.0%)	98 (51.0%)	7.5 (4.0-14.0)	9.5 (5.0-17.0)	47/94 (50%)	58/98 (59.2%)	1.18 (0.91-1.54)
Orebro[9]	16 (43.2%)	21 (56.8%)	4.0 (2.0-7.0)	12.0 (4.0-20.0)	4/16 (25.0%)	13/21 (61.9%)	2.48 (0.98-6.25)
Tartu[16]	34 (32.7%)	70 (67.3%)	8.5 (4.0-20.0)	12.5 (4.0-20.0)	18/34 (52.9%)	43/70 (61.4%)	1.16 (0.80-1.68)
Pooled	403 (45.7%)	478 (54.3%)	6.0 (3.0-13.0)	9.0 (3.0-17.0)	169/403 (41.9%)	264/478 (55.2%)	**1.32 (1.08-1.60)***
Small-vessel occlusion							
Joinville[5]	247 (56.5%)	190 (43.5%)	3.0 (2.0-4.0)	2.0 (1.0-5.0)	17/247 (6.9%)	20/190 (10.5%)	1.53 (0.82-2.84)
Melbourne[6]	68 (57.1%)	51 (42.9%)	3.0 (2.0-4.0)	2.0 (1.0-5.0)	3/68 (4.4%)	6/51 (11.8%)	2.67 (0.70-10.2)
Orebro[9]	38 (48.7%)	40 (51.3%)	4.0 (3.0-5.0)	3.0 (2.0-4.0)	2/38 (5.3%)	2/40 (5.0%)	0.95 (0.14-6.49)
Tartu[16]	37 (47.4%)	41 (52.6%)	0.0 (0.0-3.0)	2.0 (0.0-8.0)	1/37 (2.7%)	11/41 (26.8%)	**9.93 (1.33-74.2)**
Pooled	390 (54.8%)	322 (45.2%)	3.0 (2.0-4.0)	3.0 (1.0-5.0)	23 (5.9%)	39 (12.1%)	**2.05 (1.23, 3.44)***
Other etiology							
Joinville[5]	27 (39.7%)	41 (60.3%)	2.0 (1.0-8.0)	2.0 (1.0-6.0)	7/27 (25.9%)	10/41 (24.4%)	0.94 (0.41-2.18)
Melbourne[6]	4 (40.0%)	6 (60.0%)	4.0 (1.5-8.5)	5.0 (1.0-10.0)	1/4 (25%)	2/6 (33.3%)	1.33 (0.16-11.5)
Orebro[9]	2 (50.0%)	2 (50.0%)	7.5 (6.0-9.0)	14.5 (5.0-24.0)	1/2 (50.0%)	1/2 (50.0%)	1.00 (0.10-9.61)
Tartu[16]	15 (44.1%)	19 (55.9%)	5.0 (0.0-7.0)	5.0 (1.0-15.0)	3/15 (20.0%)	9/19 (47.4%)	2.37 (0.76-7.36)
Pooled	48 (41.4%)	68 (58.6%)	3.0 (1.0-7.5)	3.0 (1.0-10.0)	12/48 (25.0%)	22/68 (32.4%)	1.29 (0.64-2.61)*
Undetermined							
Joinville[5]	-	-	-	-	-	-	-
Melbourne[6]	106 (39.6%)	162 (60.5%)	5.0 (2.0-11.0)	4.0 (2.0-10.0)	39/106 (36.8%)	55/162 (34.0%)	0.92 (0.66-1.28)
Orebro[9]	1 (25.0%)	3 (75.0%)	28.0 (NA)	3.0 (0.0-6.0)	1/1 (100%)	0/3 (0%)	NA
Tartu[16]	0 (0.0%)	1 (100%)	-	7.5 (3.0-12.0)	0/0 (0%)	1/2 (50.0%)	NA
Pooled	107 (39.1%)	167 (61.0%)	5.0 (2.0-11.0)	4.0 (2.0-10.0)	40/107 (37.4%)	56 (33.5%)	0.90 (0.60-1.35)*

National Institutes of Health Stroke Scale=NIHSS; Bold denotes statistically significant differences between men and women

*RR was pooled using log-binominal regression with random-effects

Table S6. **List of covariates not meeting the criteria for confounding factors of sex difference in severity (NIHSS) of ischemic stroke.**

Study	Covariates
Oxford[4]	SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, BMI, smoking, marital status, alcohol, hospital admission,
Joinville[5]	Stroke subtype, race, hypertension, AF, PVD, TIA, BMI, smoking, hospital admission (100%), pre-stroke medication (antihypertensives, antiplatelets, anticoagulants), delay to hospital, IHD, alcohol
Melbourne[6]	Stroke subtype, race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, smoking, alcohol, hospital admission, pre-stroke medication (antiplatelets, anticoagulants, antihypertensives), institutional residence
Perth[8]	SEP, hypertension, AF, IHD, TIA, diabetes, smoking, alcohol, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets), institutional residence, pre-stroke Barthel, hospital admission
Orebro[9]	Stroke subtype, age†, marital status, hypertension, AF, IHD, PVD, TIA, diabetes, dementia, pre-stroke Barthel, hospital admission, smoking
Dijon[10]	Hypertension, IHD, PVD, TIA, alcohol, hospital admission, institutional residence
Matão[15]	Race, marital status, education, age†, hypertension, AF, IHD, PVD, TIA, smoking, alcohol, hospital admission
Tartu[16]	Stroke subtype, hypertension, AF, IHD, TIA, hospital admission, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets)

AF, Atrial fibrillation; BMI, body mass index; IHD, ischaemic heart disease; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease, TIA, transient ischemic attack; SEP, socioeconomic position.

* Not meeting all 4 criteria (missing <20% of cases, associated with sex, associated with stroke severity, and the inclusion of the covariate changed the magnitude of the sex coefficient by ≥10%) but to be included in the final multivariable model

Table S7. Analyses of heterogeneity in the sex differences in stroke severity (NIHSS>7) among eight population-based studies.

	No of studies	Unadjusted				Adjusted for covariates*			
		I^2 (%)	P^H	RR(95% CI)	$P^{sub\text{-}group}$	I^2 (%)	P^H	RR(95% CI)	$P^{sub\text{-}group}$
Ischaemic stroke									
Geographic region									
Australasia	2	0.0	0.444	**1.23 (1.02-1.48)**	0.565	0.0	0.916	1.12 (0.93-1.35)	0.385
Europe	4	0.0	0.533	**1.36 (1.21-1.52)**		0.0	0.680	1.16 (1.03-1.30)	
South America	2	0.0	0.925	**1.41 (1.22-1.64)**		0.0	0.413	**1.32 (1.13-1.53)**	
Pre-stroke function									
Unavailable	2	0.0	0.515	**1.43 (1.24-1.64)**	0.334	0.0	0.901	**1.29 (1.12-1.49)**	0.232
Available	6	0.0	0.718	**1.30 (1.18-1.44)**		0.0	0.741	**1.15 (1.04-1.27)**	
Intracerebral hemorrhagic stroke									
Geographic region									
Australasia	2	0.0	0.958	1.26 (0.97-1.63)	0.515	0.0	0.948	1.21 (0.97-1.20)	0.503
Europe	4	0.0	0.728	1.05 (0.89-1.24)		0.0	0.832	1.07 (0.91-1.26)	
South America	2	0.0	0.759	1.05 (0.88-1.25)		0.0	0.778	1.03 (0.87-1.24)	
Pre-stroke function									
Unavailable	2	0.0	0.665	1.12 (0.97-1.30)	0.483	0.0	0.779	1.12 (0.97-1.30)	0.549
Available	6	0.0	0.935	1.04 (0.88-1.22)		0.0	0.983	1.03 (0.87-1.21)	

Bold denotes statistically significant differences between men and women; NIHSS, National Institutes of Health Stroke Scale; P^H, P-value of heterogeneity; RR (95% CI), relative risk (95% confidence interval) of having more severe stroke (NIHSS>7) for women compared to men

*List of covariates were demonstrated in main Table 2.

Table S8. Testing the interactions between sex and two covariates: age and time period using a single pooled individual participant dataset in stroke severity.

	Unadjusted			Adjusted for age		
Covariates	**RR***	**(95% CI)**	**$P_{interaction}$**	**RR**	**(95% CI)**	**$P_{interaction}$**
Ischaemic stroke						
Age (continuous)	1.35	(0.69-2.64)	0.793			
Age group						
≤65 years	1.19	(0.92-1.53)	Ref	-		
>65-75 years	**1.23**	**(1.00-1.52)**	0.855	-		
>75 years	**1.25**	**(1.11-1.41)**	0.705	-		
Year of stroke occurrence						
1996-2011 (continuous)	**1.26**	**(1.15-1.41)**	0.067	**1.15**	**(1.03- 1.29)**	0.128
Intracerebral hemorrhagic stroke						
Age (continuous)	0.85	(0.52-1.39)	0.324			
Age group						
≤65 years	1.00	(0.86-1.16)	Ref	-		
>65-75 years	**1.14**	**(0.97-1.33)**	0.360	-		
>75 years	**1.13**	**(1.03-1.24)**	0.136	-		
Year of stroke occurrence						
1996-2011 (continuous)	**1.16**	**(0.99, 1.36)**	**0.264**	**1.16**	**(1.09-1.22)**	0.281

Ref, Reference group

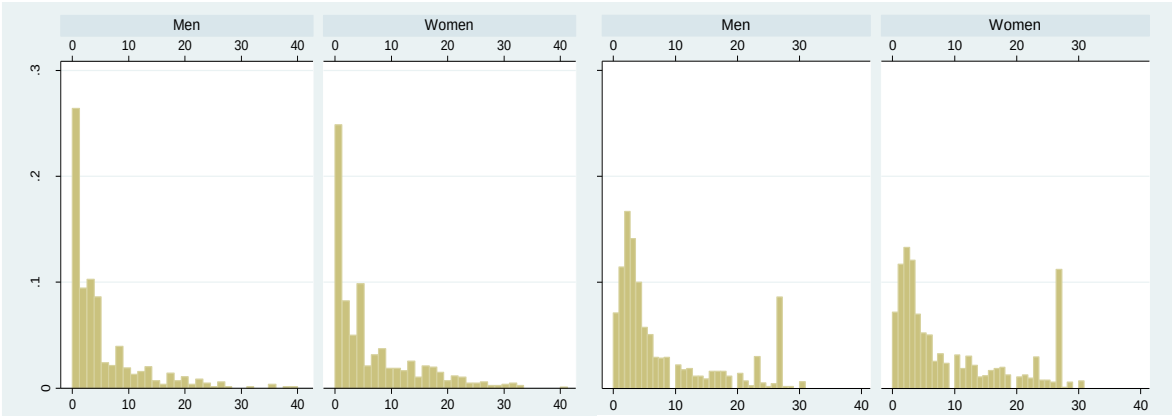
* RR (95% CI), relative risk (95% confidence interval) of more severe stroke (NIHSS>7)

Table S9. Sensitivity analyses of difference in National Institutes of Health Stroke Scale (NIHSS) continuous scores between women and men.

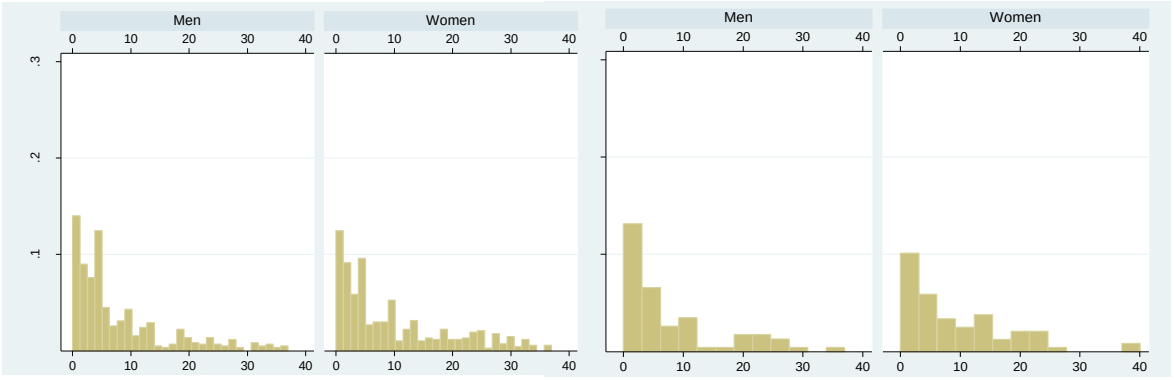
Study	N*	Unadjusted	Adjusted for		
			Age	Pre-stroke dependency	All confounding factors
		MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)
Ischemic stroke					
Oxford[4]	1077	**0.834 (0.265, 1.404)**	0.391 (-0.177, 0.959)	0.478 (-0.089, 1.045)	0.247 (-0.228, 0.722)
Joinville[5]	1494	**0.856 (0.278, 1.434)**	**0.607 (0.038, 1.176)**	---	**0.607 (0.038, 1.176)**
Melbourne[6]	647	**1.171 (0.190, 2.152)**	0.697 (-0.260, 1.654)	**1.141 (0.190, 2.091)**	0.645 (-0.334, 1.625)
Perth[8]	123	-0.466 (-2.893, 1.960)	-1.162 (-3.596, 1.215)	-0.681 (-3.240, 1.876)	-1.162 (-3.596, 1.215)
Orebro[9]	274	1.220 (-0.029, 2.469)	1.102 (-0.196, 2.373)	1.021 (-0.210, 2.252)	0.853 (-0.278, 1.984)
Dijon[10]	1238	**1.130 (0.467, 1.794)**	0.640 (-0.017, 1.297)	**0.086 (0.213, 1.500)**	0.018 (-0.703, 0.7381)
Matão[15]	67	**3.330 (0.095, 6.564)**	**3.337 (0.078, 6.595)**	---	**3.337 (0.078, 6.595)**
Tartu[16]	280	**2.477 (0.742, 4.213)**	1.182 (-0.619, 2.983)	**1.729 (0.078, 3.380)**	1.122 (-0.911, 2.900)
Pooled	5,200	**1.011 (0.700, 1.323)**	**0.601 (0.296, 0.905)**	**0.802 (0.440, 1.164)**	**0.426 (0.095, 0.757)**
Intracerebral haemorrhage					
Oxford[4]	223	1.996 (-1.661, 5.654)	1.96 (-1.748, 5.671)	---	---
Joinville[5]	94	0.207 (-2.380, 2.793)	-0.118 (-2.718, 2.482)	---	---
Melbourne[6]	114	**4.139 (0.598, 7.680)**	**3.572 (0.014, 7.129)**	---	---
Perth[8]	15	1.932 (-10.391, 14.257)	1.081 (-11.677, 13.840)	---	---
Orebro[9]	44	2.912 (-2.450, 8.276)	3.751 (-1.649, 9.150)	---	---
Dijon[10]	197	0.914 (-1.579, 3.406)	0.460 (-2.044, 2.964)	---	---
Matão[15]	11	6.046 (-9.800, 21.891)	0.627 (-10.243, 25.496)	---	---
Tartu[16]	55	-0.828 (-5.104, 3.449)	-0.706 (-5.074, 3.662)	---	---
Pooled	753	**1.654 (0.188, 3.120)**	1.452 (-0.027, 2.931)		

Bold denotes statistically significant results; MD=mean difference

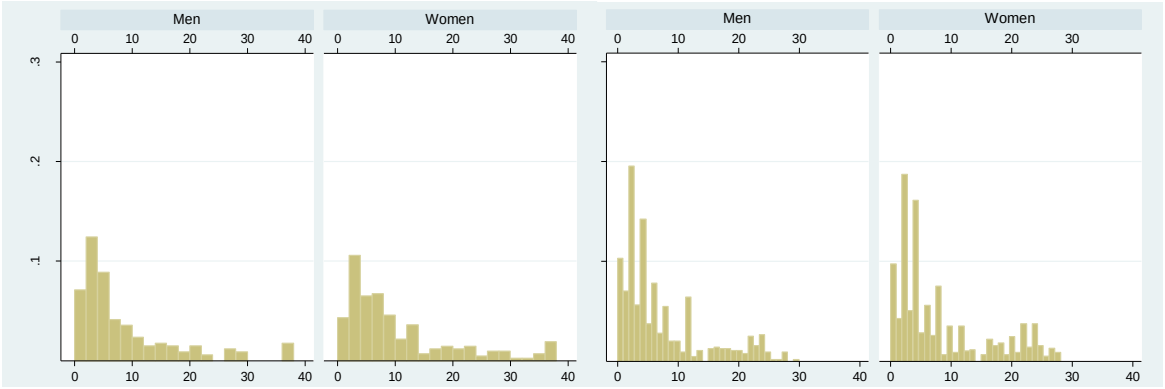
Figure S1. Distribution of the National Institutes of Health Stroke Scale (NIHSS) scores by sex among those with stroke (both ischemic and intracerebral hemorrhagic stroke) in each study.



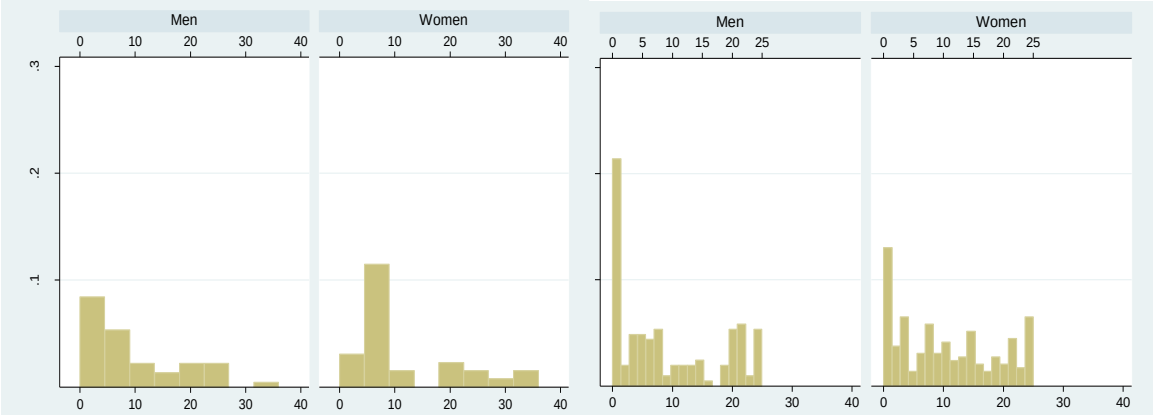
Oxford[4] Joinville[5]



Melbourne[6] Perth[8]

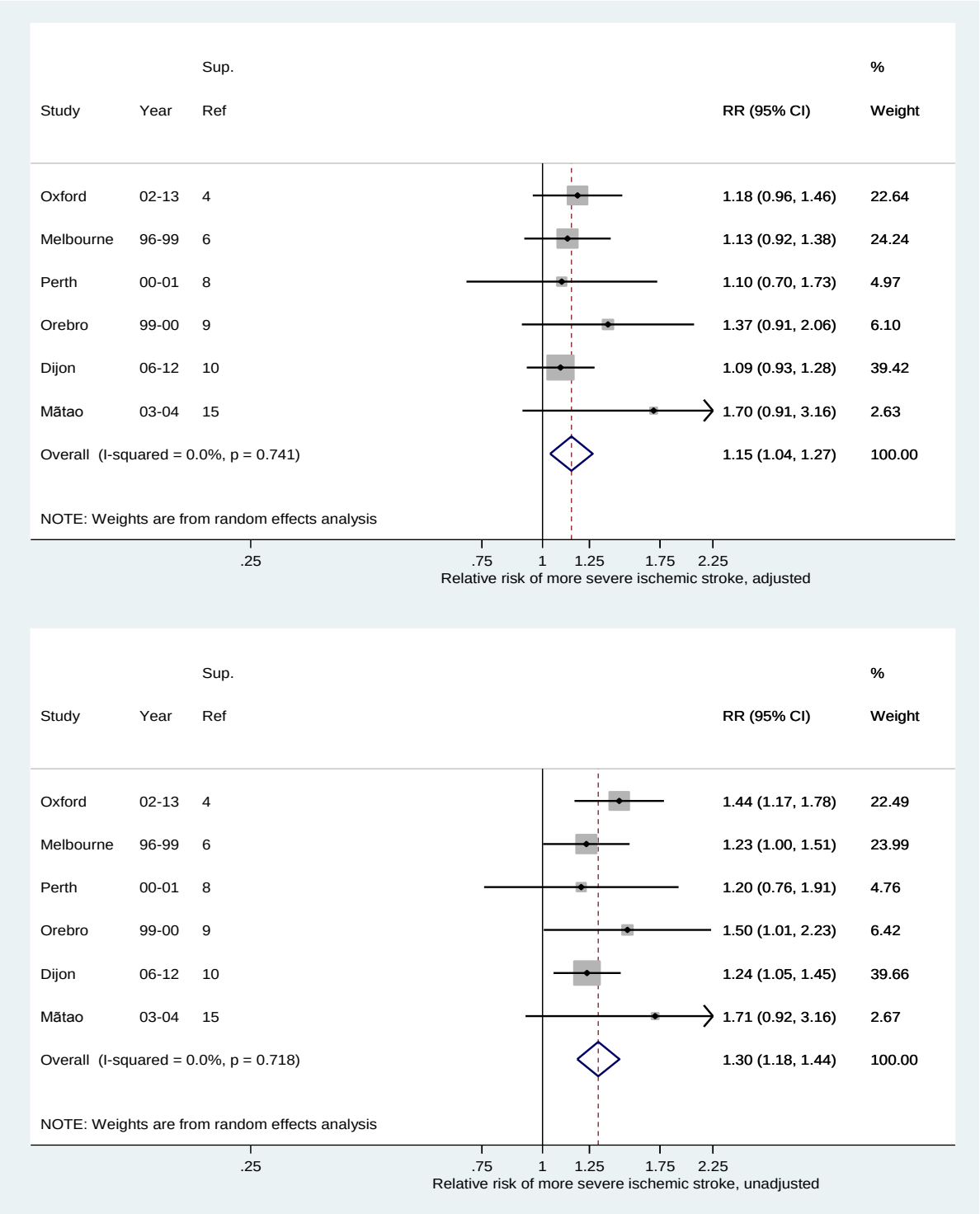


Orebro[9] Dijon[10]



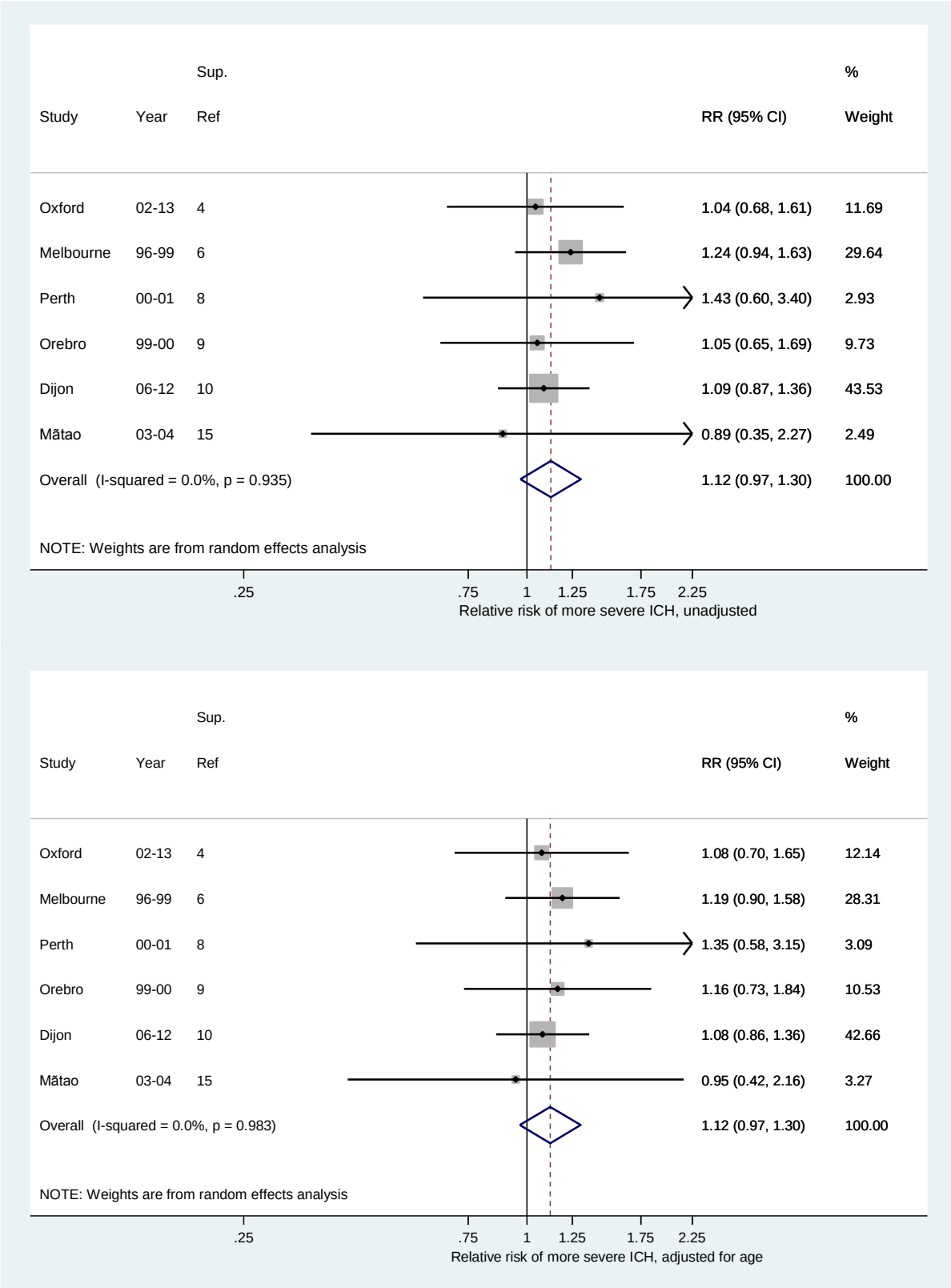
Mãtao[15] Tartu[16]

Figure S2. Difference in stroke severity between women and men with ischemic stroke: unadjusted (top) and adjusted (bottom) random-effects meta-analyses among 6 studies.



More severe stroke was defined as National Institutes of Health Stroke Scale >7.

Figure S3. Difference in stroke severity between women and men with intracerebral haemorrhage (ICH): unadjusted (top) and adjusted (bottom) random-effects meta-analyses among 6 studies.



More severe stroke was defined as National Institutes of Health Stroke Scale >7.

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