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Author/s:

Phan, HT;Reeves, MJ;Blizzard, CL;Thrift, AG;Cadilhac, DA;Sturm, J;Otahal, P;Rothwell, P;Bejot, Y;Cabral, NL;Appelros, P;Körv, J;Vibo, R;Minelli, C;Gall, SL

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

Hoang T. Phan, MD; Mathew J. Reeves, PhD; Christopher L. Blizzard, PhD; Amanda G. Thrift, PhD; Dominique A. Cadilhac, PhD; Jonathan Sturm, PhD; Petr Otahal, GDipSc; Peter Rothwell, PhD; Yannick Bejot, MD; Norberto L. Cabral, PhD; Peter Appelros, PhD; Janika Kõrv, PhD; Riina Vibo, PhD; Cesar Minelli, MD; Seana L. Gall, PhD

**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<sub>adjusted</sub> 1.20, 95% CI 1.10–1.30). There was no sex difference in severity for intracerebral hemorrhage (RR<sub>crude</sub> 1.08, 95% CI 0.97–1.21; RR<sub>adjusted</sub> 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.<sup>1</sup> Women also often have poorer

functional outcome, increased participation restriction, and lower health-related quality of life after stroke than men.<sup>1,2</sup> One explanation for these sex differences in outcome is that women have more severe strokes than men.<sup>1–3</sup> While several

From the Menzies Institute for Medical Research Tasmania, University of Tasmania, Hobart, Australia (H.T.P., C.L.B., P.O., S.L.G.); Department of Health Management and Health Economics, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam (H.T.P.); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI (M.J.R.); Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Vic., Australia (A.G.T., D.A.C.); Florey Institute Neuroscience and Mental Health, Heidelberg, University of Melbourne, Vic., Australia (D.A.C.); Faculty of Health and Medicine, University of Newcastle, NSW, Australia (J.S.); Stroke Prevention Research Unit, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, United Kingdom (P.R.); Department of Neurology, University of Burgundy, University Hospital of Dijon, France (Y.B.); Clinica Neurológica de Joinville, Joinville Stroke Registry, University of Joinville Region-Joinville, Joinville, Brazil (N.L.C.); Department of Neurology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden (P.A.); Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia (J.K., R.V.); Department of Neurology, Hospital Carlos Fernando Malzoni and Neurologic Center of Research and Rehabilitation, Matão, SP, Brazil (C.M.).

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>

**Correspondence to:** Seana Gall, PhD, University of Tasmania, Menzies Institute for Medical Research, MS2, Medical Science Precinct, 17 Liverpool Street, Hobart, TAS, Australia 7000. E-mail: Seana.Gall@utas.edu.au

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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.<sup>4,5</sup> Another challenge is that the measurement of severity can differ between studies.<sup>6–8</sup> Thus the importance and causes of the association between sex and stroke severity, remain uncertain.<sup>3</sup> Although there are reports on factors that contribute to severity of stroke (eg, hypertension,<sup>9</sup> cardiovascular diseases,<sup>10</sup> dementia,<sup>11</sup> embolic stroke mechanism<sup>12</sup>), 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,<sup>13,14</sup> there are important differences in the data sources, methods of analysis, and adjustment for confounding factors. Renoux et al<sup>14</sup> 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]  $\geq 5$ ) 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).<sup>13</sup> 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,<sup>15</sup> delay in presenting to the hospital,<sup>16</sup> and mechanism of ischemic stroke (ie, cardioembolic strokes)<sup>17</sup> 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.<sup>1</sup> The INSTRUCT study was registered in the International prospective register of systematic reviews (PROSPERO; CRD 42016036723)<sup>18</sup> and performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines.<sup>19</sup> 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 =  $50 - 2 \times \text{NIHSS}$ .<sup>20</sup>

## 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<sup>21</sup> 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).<sup>13</sup>

Since covariates were not measured uniformly between studies, we used the 2-stage method of analysis proposed for IPD meta-analyses.<sup>22</sup> 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<sup>23</sup> 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<sup>1,2</sup> 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  $\geq 10\%$ ).<sup>24</sup> We tested whether continuous covariates (ie, age, pre-stroke Rankin, or pre-stroke Barthel) require a transformation using fractional polynomials in multivariable modeling,<sup>25</sup> 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).<sup>26</sup> 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, Mātao), multiple imputation using chained equations<sup>27</sup> ( $m=50$  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<sup>28–35</sup> (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 $\leq 20$ ) 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 (Mātao; 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<sub>age-adjusted</sub> 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<sub>fully-adjusted</sub> 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 (Mātao), 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 $\times$ covariate or covariate $\times$ 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<sub>unadjusted</sub> 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:  $P_{\text{meta-regression}}=0.559$ ; ICH:  $P_{\text{meta-regression}}=0.726$ ) or adjusted analyses ( $P_{\text{meta-regression}}=0.403$ ; ICH:  $P_{\text{meta-regression}}=0.723$ ). 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<sub>unadjusted</sub> 1.30 versus 8 studies 1.35; ICH 1.12 versus 8 studies 1.08) or adjusted analyses (IS: RR<sub>adjusted</sub> 1.15 versus 8 studies 1.20; ICH: RR<sub>unadjusted</sub> 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).

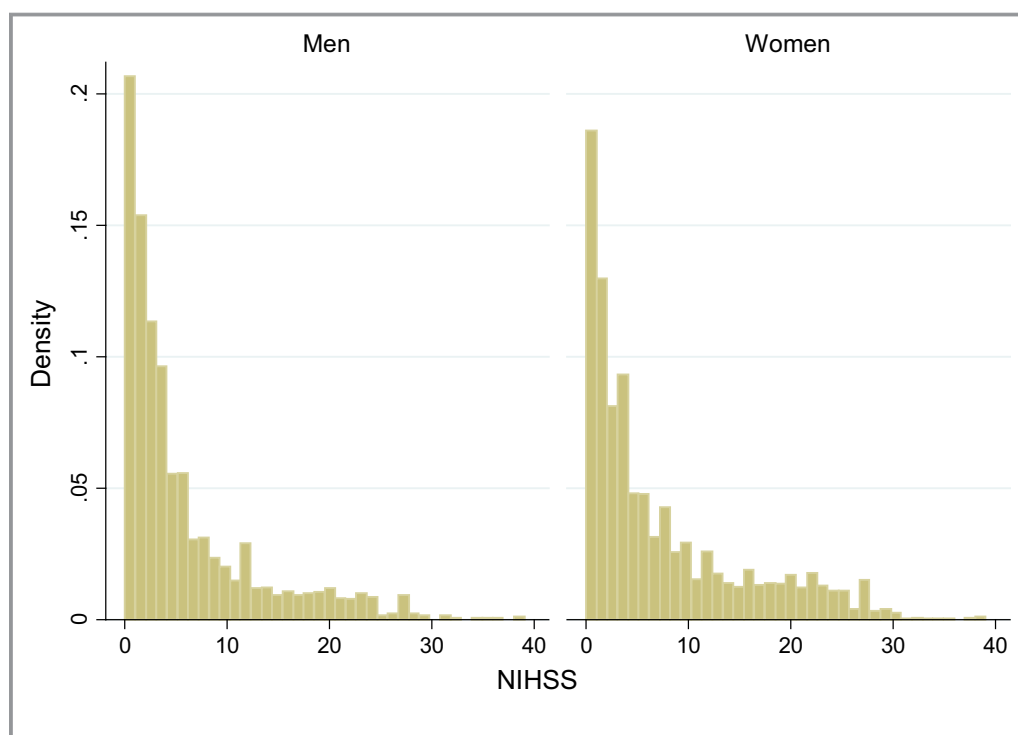
Our pooled estimates using the single-stage method of meta-analysis were generally similar (8 studies; IS: RR<sub>unadjusted</sub>

**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 |                  |                   |                   |           |            | Median NIHSS (IQR)   |                      | NIHSS>7, n (%) |  |
|------------------------------------|-----------|-------------|------------------------------------|------------------|-------------------|-------------------|-----------|------------|----------------------|----------------------|----------------|--|
|                                    |           |             | n                                  | Mean Age, y (SD) |                   | Women (%)         |           | Men        | Women                | Men                  | Women          |  |
|                                    |           |             |                                    | Women (%)        | Men               | Women             | Men       | Men        | Women                |                      |                |  |
| Ischemic stroke                    |           |             |                                    |                  |                   |                   |           |            |                      |                      |                |  |
| Oxford, UK <sup>28</sup>           | 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 <sup>29</sup>    | 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 <sup>30</sup> | 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 <sup>31</sup>     | 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 <sup>32</sup>       | 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 <sup>33</sup>        | 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 <sup>34</sup>        | 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 <sup>35</sup>       | 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           |           |             |                                    |                  |                   |                   |           |            |                      |                      |                |  |
| Oxford, UK <sup>28</sup>           | 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 <sup>29</sup>    | 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 <sup>30</sup> | 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 <sup>31</sup>     | 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 <sup>32</sup>       | 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 <sup>33</sup>        | 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 <sup>34</sup>        | 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 <sup>35</sup>       | 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.

<sup>†</sup>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;  $RR_{\text{fully-adjusted}}$  1.19, 95% CI 1.08–1.32; ICH:  $RR_{\text{unadjusted}}$  1.08, 95% CI 0.90–1.29;  $RR_{\text{age-adjusted}}$  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  $RR_{\text{unadjusted}}$  1.33, 95% CI 1.18–1.49;  $RR_{\text{fully-adjusted}}$  1.15, 95% CI 1.03–1.30 versus 2-stage  $RR_{\text{unadjusted}}$  1.30, 95% CI 1.18–1.44;  $RR_{\text{fully-adjusted}}$  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  $>7$ )

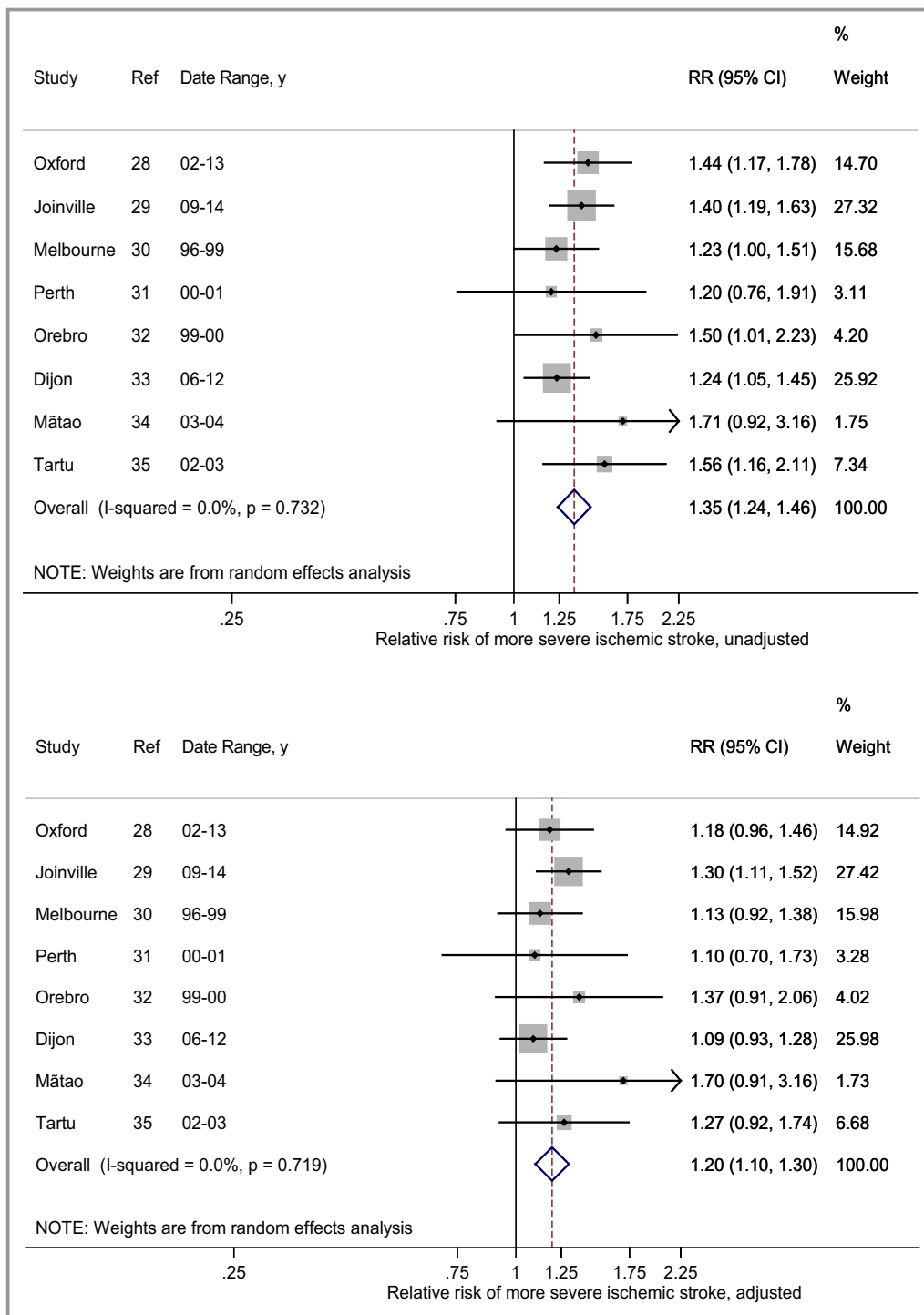
| Study                    | Ischemic Stroke |   | Intracerebral Hemorrhage |                                       |
|--------------------------|-----------------|---|--------------------------|---------------------------------------|
|                          | n*              | Covariates in the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

<sup>†</sup>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  $\geq 10\%$ ; see Methods, page 8).

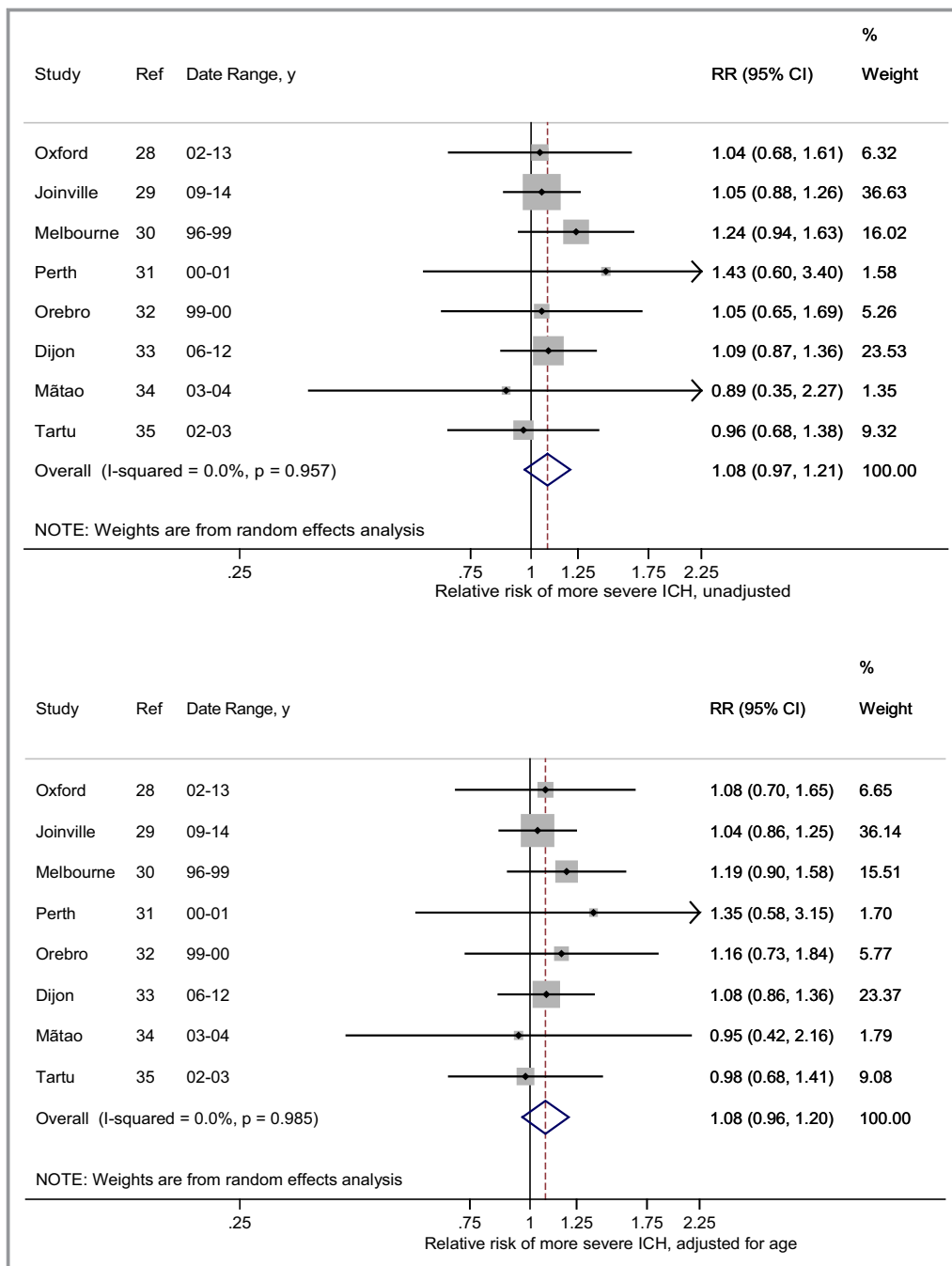
<sup>‡</sup>Data on pre-stroke dependency were unavailable.



**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;  $RR_{age-adjusted}$  1.21, 95% CI 1.10–1.34; ICH: pooled  $RR_{unadjusted}$  1.08, 95% CI 0.90–1.29;  $RR_{age-adjusted}$  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.

$P_{\text{interaction}}=0.793$ ; ICH:  $P_{\text{interaction}}=0.324$ ). 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:  $P_{\text{interaction}}=0.067$ ; ICH:  $P_{\text{interaction}}=0.128$ ) and age-adjusted analyses (IS:  $P_{\text{interaction}}=0.264$ ; ICH:  $P_{\text{interaction}}=0.281$ ).

## 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.<sup>36</sup> The physiological decrease of cerebral blood flow and its regulation that occurs with increasing age<sup>37</sup> 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<sup>38</sup> including stroke among frail older community-dwelling adults.<sup>39</sup>

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.<sup>14,40</sup> Poor physical function and interrelated conditions such as frailty, which is more common in women,<sup>41</sup> 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.<sup>42</sup> Better management of comorbid diseases and prevention of frailty in the elderly<sup>43</sup> could help ameliorate the effects of more severe strokes when they occur in women.<sup>13</sup> 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.<sup>44</sup> 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.<sup>45</sup>

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.<sup>46</sup> In addition, previous studies have found that the management of AF, specifically, treatment with anti-coagulants<sup>47</sup> or catheter ablation<sup>48</sup> 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.<sup>49</sup> 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.<sup>50</sup>

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).<sup>51</sup> Research on biologic mechanisms has established the neuroprotective effect of hormones in women on IS injury during premenopause.<sup>51</sup> 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.<sup>52</sup> 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.<sup>53</sup> Also, female members are often excluded in the neuroscience experiments because of the hormonal fluctuations associated with the reproductive cycle.<sup>54</sup> A recent meta-analysis of neuroscience studies has shown that data from female rats are no more variable than data from males.<sup>55</sup> This suggests a need to include females in animal models to understand the sex difference in severity of stroke.<sup>56</sup>

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.<sup>57</sup> 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.<sup>22</sup> 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 ( $\geq 10$ ) for the exploration of heterogeneity between studies using meta-regression.<sup>58</sup>

## 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.

## References

- Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, Heeley E, Otahal P, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Bejot Y, Cabral NL, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Gall S. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STROKE oUtcomes sTudy): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003436.
- Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Heeley E, Otahal P, Vemmos K, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Bejot Y, Cabral NL, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Gall SL. Factors contributing to sex differences in functional outcomes and participation after stroke. *Neurology*. 2018;90:e1945–e1953.
- Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7:915–926.

4. Bushnell CD, Reeves MJ, Zhao X, Pan W, Prvu-Bettger J, Zimmer L, Olson D, Peterson E. Sex differences in quality of life after ischemic stroke. *Neurology*. 2014;82:922–931.
5. Wang Z, Li J, Wang C, Yao X, Zhao X, Wang Y, Li H, Liu G, Wang A, Wang Y. Gender differences in 1-year clinical characteristics and outcomes after stroke: results from the China National Stroke Registry. *PLoS One*. 2013;8:e56459.
6. Dehlerdorff C, Andersen KK, Olsen TS. Sex disparities in stroke: women have more severe strokes but better survival than men. *J Am Heart Assoc*. 2015;4:e001967. DOI: 10.1161/JAHA.115.001967.
7. Zhou J, Zhang Y, Arima H, Zhao Y, Zhao H, Zheng D, Tian Y, Liu Y, Huang Q, Yang J; for the Nanjing First Hospital Stroke Registry I. Sex differences in clinical characteristics and outcomes after intracerebral haemorrhage: results from a 12-month prospective stroke registry in Nanjing, China. *BMC Neurol*. 2014;14:172.
8. Salihovic D, Smajlovic D, Sinanovic O, Kojic B. Sex differences in patients with acute ischemic stroke in Tuzla region, Bosnia and Herzegovina. *Bosn J Basic Med Sci*. 2010;10:116–120.
9. Faraji F, Ghasami K, Talaie-Zanjani A, Mohammadbeigi A. Prognostic factors in acute stroke, regarding to stroke severity by Canadian Neurological Stroke Scale: a hospital-based study. *Asian J Neurosurg*. 2013;8:78–82.
10. Kakar P, Boos CJ, Lip GYH. Management of atrial fibrillation. *Vasc Health Risk Manag*. 2007;3:109–116.
11. Appelros P, Nydevik I, Seiger A, Terent A. Predictors of severe stroke: influence of preexisting dementia and cardiac disorders. *Stroke*. 2002;33:2357–2362.
12. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev*. 2010;6:150–161.
13. Gall SL, Donnan G, Dewey HM, Macdonell R, Sturm J, Gilligan A, Srikanth V, Thrift AG. Sex differences in presentation, severity, and management of stroke in a population-based study. *Neurology*. 2010;74:975–981.
14. Renoux C, Coulombe J, Li L, Ganesh A, Silver L, Rothwell PM. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke*. 2017;48:2731–2738.
15. Park JM, Kang K, Cho YJ, Hong KS, Lee KB, Park TH, Lee SJ, Ko Y, Han MK, Lee J, Cha JK, Kim DH, Kim DE, Kim JT, Choi JC, Yu KH, Lee BC, Lee JS, Lee J, Gorelick PB, Bae HJ. Comparative effectiveness of prestroke aspirin on stroke severity and outcome. *Ann Neurol*. 2016;79:560–568.
16. Oh MS, Yu KH, Roh JK, Lee BC. Gender differences in the mortality and outcome of stroke patients in Korea. *Cerebrovasc Dis*. 2009;28:427–434.
17. Bill O, Zufferey P, Faouzi M, Michel P. Severe stroke: patient profile and predictors of favorable outcome. *J Thromb Haemost*. 2013;11:92–99.
18. Phan H, Blizzard L, Thrift A, Cadilhac D, Reeves M, Sturm J, Gall S. Sex difference in long-term outcomes of stroke in the International Stroke Outcome Study (INSTRUCT): a meta-analysis of individual patient data. PROSPERO 2016:CRD42016036723. York, United Kingdom: Centre for Reviews and Dissemination, University of York; 2016. Available at: [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42016036723](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036723). Accessed September 12, 2016.
19. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA*. 2015;313:1657–1665.
20. Ali K, Cheek E, Sills S, Crome P, Roffe C. Development of a conversion factor to facilitate comparison of National Institute of Health Stroke Scale scores with Scandinavian Stroke Scale scores. *Cerebrovasc Dis*. 2007;24:509–515.
21. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41.
22. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. *Stat Med*. 2001;20:2115–2130.
23. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health*. 1989;79:340–349.
24. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. *Stroke*. 2012;43:1982–1987.
25. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol*. 1999;28:964–974.
26. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. *PLoS One*. 2012;7:e46042.
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30:377–399.
28. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PA, Dennis MS, Warlow CP, Bamford JM, Anslow P. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363:1925–1933.
29. Cabral NL, Goncalves AR, Longo AL, Moro CH, Costa G, Amaral CH, Fonseca LA, Efluf-Neto J. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. *J Neurol Neurosurg Psychiatry*. 2009;80:755–761.
30. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Thrift AG. Determinants of handicap after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke*. 2004;35:715–720.
31. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. *Stroke*. 1994;25:1935–1944.
32. Appelros P, Nydevik I, Seiger A, Terent A. High incidence rates of stroke in Orebro, Sweden: further support for regional incidence differences within Scandinavia. *Cerebrovasc Dis*. 2002;14:161–168.
33. Bejot Y, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, Di Carlo A, Osseby GV, Moreau T, Giroud M. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. *Stroke*. 2008;39:1945–1951.
34. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matao, Brazil: a population-based prospective study. *Stroke*. 2007;38:2906–2911.
35. Korv J, Roose M, Kaasik A-E. Stroke registry of Tartu, Estonia, from 1991 through 1993. *Cerebrovasc Dis*. 1997;7:154–162.
36. Sohrabji F, Bake S, Lewis DK. Age-related changes in brain support cells: implications for stroke severity. *Neurochem Int*. 2013;63:291–301.
37. Strandgaard S. Cerebral blood flow in the elderly: impact of hypertension and antihypertensive treatment. *Cardiovasc Drugs Ther*. 1991;4(Suppl 6):1217–1221.
38. Gur AY, Tanne D, Bornstein NM, Milo R, Auriel E, Shopin L, Koton S. Stroke in the very elderly: characteristics and outcome in patients aged  $\geq 85$  years with a first-ever ischemic stroke. *Neuroepidemiology*. 2012;39:57–62.
39. Golden AG, Tewary S, Dang S, Roos BA. Care management's challenges and opportunities to reduce the rapid rehospitalization of frail community-dwelling older adults. *Gerontologist*. 2010;50:451–458.
40. Di Legge S, Koch G, Diomedei M, Stanzione P, Sallustio F. Stroke prevention: managing modifiable risk factors. *Stroke Res Treat*. 2012;2012:391538.
41. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156.
42. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. *J Leukoc Biol*. 2010;87:779–789.
43. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, Cesari M, Chumlea WC, Doehner W, Evans J, Fried LP, Guralnik JM, Katz PR, Malmstrom TK, McCarter RJ, Gutierrez Robledo LM, Rockwood K, von Haehling S, Vandewoude MF, Walston J. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14:392–397.
44. Abdul-Rahim AH, Fulton RL, Sucharew H, Kleindorfer D, Khatri P, Broderick JP, Lees KR. National Institutes of Health Stroke Scale item profiles as predictor of patient outcome. *Stroke*. 2015;46:395.
45. Barbieri A, Giuliani E, Carone C, Pederzoli F, Mascheroni G, Greco G, Stucchi C, Genedani S. Clinical severity of ischemic stroke and neural damage biomarkers in the acute setting: the STROke MARKers (STROMA) study. *Minerva Anestesiologica*. 2013;79:750–757.
46. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *QJM*. 2014;107:955–967.
47. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke*. 2000;31:822–827.
48. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, Bassouni M, Cummings J, Wang Y, Lewis WR, Diaz A, Horton RP, Beheiry S, Hongo R, Galligorsky GJ, Zagrodzky JD, Bailey SM, Al-Ahmad A, Wang P, Schweikert RA, Natale A. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm*. 2010;7:167–172.
49. Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R, Bull LM, Welch SJ, Gutnikov SA, Mehta Z, Rothwell PM. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. *Circulation*. 2014;130:1236–1244.

50. Desai Y, El-Chami MF, Leon AR, Merchant FM. Management of atrial fibrillation in elderly adults. *J Am Geriatr Soc.* 2017;65:185–193.
51. Gibson CL. Cerebral ischemic stroke: is gender important? *J Cereb Blood Flow Metab.* 2013;33:1355–1361.
52. Hedna VS, Bodhit AN, Ansari S, Falchook AD, Stead L, Heilman KM, Waters MF. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? *J Clin Neurol.* 2013;9:97–102.
53. Etherton MR, Wu O, Cougo P, Giese AK, Cloonan L, Fitzpatrick KM, Kanakis AS, Boulouis G, Karadeli HH, Lauer A, Rosand J, Furie KL, Rost NS. Structural integrity of normal appearing white matter and sex-specific outcomes after acute ischemic stroke. *Stroke.* 2017;48:3387–3389.
54. Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev.* 2011;35:565–572.
55. Becker JB, Prendergast BJ, Liang JW. Female rats are not more variable than male rats: a meta-analysis of neuroscience studies. *Biol Sex Differ.* 2016;7:34.
56. McCullough LD, de Vries GJ, Miller VM, Becker JB, Sandberg K, McCarthy MM. NIH initiative to balance sex of animals in preclinical studies: generative questions to guide policy, implementation, and metrics. *Biol Sex Differ.* 2014;5:15.
57. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. *J Stroke.* 2017;19:3–10.
58. Green S, Higgins J. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration; 2011.

# **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,<sup>1</sup> 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<sup>1,2</sup> supplemented with an updated search for new studies published since May 2008, the end date for the systematic review by Feigin et al.<sup>1</sup> 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’,<sup>2,3</sup> 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   |
|--|---------|--------------|--|---|
| <b>13 studies for which long-term IPD were provided (n=18,342)</b>   |         |              |  |   |
| Oxford, UK <sup>4</sup>  | '02-'13 | 1374         | ✓  |   |
| Joinville, Brazil <sup>5</sup>                                       | '09-'14 | 2357         | ✓  |   |
| Melbourne, Australia <sup>6</sup>                                    | '96-'99 | 1316         | ✓  |   |
| Arcadia, Greece <sup>7</sup>   | '93-'95 | 555          |  |   |
| Perth, Australia <sup>8</sup>  | '00-'01 | 183          | ✓  |   |
| Orebro, Sweden <sup>9</sup>  | '99-'00 | 377          | ✓  |   |
| Dijon, France <sup>10</sup>  | '87-'12 | 4621         | ✓ (only available during the year '06-'12; n=1505) |   |
| Martinique, French West Indies <sup>11</sup>                         | '98-'99 | 580          |  | Other severity instrument (Barthel Index)                     |
| Porto, Portugal <sup>12</sup>  | '98-'00 | 688          |  | Other severity instrument (Unified Neurological Stroke Scale) |
| Auckland, NZ <sup>13</sup>   | '02-'03 | 1423         |  | Other severity instrument (Glasgow Coma Scale)                |
| L'Aquila, Italia <sup>14</sup>                                       | '94-'98 | 4353         |  | Other severity instrument (loss of consciousness)             |
| Matão, Brazil <sup>15</sup>  | '03-'04 | 81           | ✓  |   |
| Tartu, Estonia <sup>16</sup>   | '02-'03 | 433          | ✓ (mapped from Scandinavian Stroke Scale)          |   |
| <b>9 studies for which long-term IPD were not provided (n=9,985)</b> |         |              |  |   |
| Ludwigshafen, Germany <sup>17</sup>                                  | '06-'07 | 725          |  | No information of severity measurement                        |
| Warsaw, Poland <sup>18,19</sup>                                      | '05     | 127          | ✓  | No sex-specific findings in sex difference in NIHSS           |
| South London, UK <sup>20</sup>                                       | '95-'06 | 3373         | ✓  |   |
| Erlangen, Germany <sup>21</sup>                                      | '98-'06 | 1631         |  | Other severity instrument (Barthel Index)                     |
| Malmo, Sweden <sup>22</sup>  | '89-'92 | 2290         |  | Other severity instrument (Katx Index)                        |
| Aeolian Islands, Italia <sup>23</sup>                                | '99-'00 | 62           |  | No information of severity measurement                        |
| Vibo Valentia, Italia <sup>24</sup>                                  | '96     | 321          |  | No information of severity measurement                        |
| Rural Tanzania, Africa <sup>25</sup>                                 | '03-'06 | 130          |  | Other severity instrument (Barthel index)                     |
| Valley of Aosta, Italy <sup>26</sup>                                 | '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.**

| <b>Study</b>           | <b>Source of data</b>   |
|------------------------|---|
| Oxford <sup>4</sup>    | Pre-morbid medication and vascular risk factors were obtained from the patients or relative, hospital records, and general practice records.<br>Atrial fibrillation (AF) was defined as either a known history with a confirmation from primary care or hospital records.<br>Blood pressure (BP) was recorded from the general practice records.<br>Premorbid modified Rankin score (mRS) was recorded from self-report questionnaire.  |
| Joinville <sup>5</sup> | 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 <sup>6</sup> | 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.<br>Dementia, hypertension, peripheral vascular disease (PVD), prior transient ischemic attack (TIA), and prior myocardial infarction were defined as a known history.<br>Diabetes was defined as either a known history or current presentation with fasting blood glucose $\geq 7.0$ mmol/L.<br>AF was defined as either a known history or current presentation confirmed on ECG.<br>Smoking status was classified from self-report as current smoker, ex-smoker, or never smoked.<br>Pre-stroke disability was recorded from self-report questionnaire using the Barthel Index. |
| Perth <sup>8</sup>     | 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.<br>The presence of AF required confirmation by an ECG within 1 month of the onset of stroke.<br>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 <sup>9</sup>    | A record of medical history was taken and logistic data regarding hospital treatment period and investigations were noted.<br>Premorbid mRS was recorded from self-report questionnaire.  |
| Dijon <sup>10</sup>    | 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.<br>A history of AF, previous myocardial infarction, a history of TIA were recorded.<br>Pre-stroke treatments by anticoagulants, antiplatelet agents and antihypertensive treatments were noted.  |
| Matão <sup>15</sup>    | Risk factors and management of risk factors were recorded by trained data collectors using a standardised questionnaire.  |
| Tartu <sup>16</sup>    | 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.<br>BP was measured at admission.<br>AF was confirmed by ECG.<br>Myocardial infarction was confirmed by ECG or autopsy.<br>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 <sup>d</sup> |             |             |             | Joinville <sup>e</sup> |             |             |             | Melbourne <sup>f</sup> |             |             |             | Perth <sup>g</sup> |             |       |       |
|-------------------------------|---------------------|-------------|-------------|-------------|------------------------|-------------|-------------|-------------|------------------------|-------------|-------------|-------------|--------------------|-------------|-------|-------|
|                               | 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         | -                      | -           | -           | -           | <b>12.6</b>            | <b>5.7</b>  | 6.9         | 2.8         | -                  | -           | -     | -     |
| No                            | 90.7                | 94.2        | 97.9        | 100.0       | -                      | -           | -           | -           | <b>86.8</b>            | <b>94.1</b> | 91.8        | 95.8        | -                  | -           | -     | -     |
| Unknown                       | 0.2                 | 0.2         | 0.0         | 0.0         | -                      | -           | -           | -           | <b>0.6</b>             | <b>0.3</b>  | 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                           | -                   | -           | -           | -           | -                      | -           | -           | -           | <b>4.5</b>             | <b>9.3</b>  | <b>4.1</b>  | <b>15.5</b> | -                  | -           | -     | -     |
| No                            | -                   | -           | -           | -           | -                      | -           | -           | -           | <b>81.8</b>            | <b>78.3</b> | <b>84.9</b> | <b>81.7</b> | -                  | -           | -     | -     |
| Unknown                       | -                   | -           | -           | -           | -                      | -           | -           | -           | <b>13.7</b>            | <b>12.4</b> | <b>11.0</b> | <b>2.8</b>  | -                  | -           | -     | -     |
| Smoking (%)                   |                     |             |             |             |                        |             |             |             |                        |             |             |             |                    |             |       |       |
| Current                       | <b>17.5</b>         | <b>13.8</b> | <b>20.8</b> | <b>4.4</b>  | <b>29.6</b>            | <b>13.2</b> | <b>34.9</b> | <b>59.6</b> | <b>20.2</b>            | <b>13.7</b> | <b>16.4</b> | <b>9.9</b>  | <b>11.5</b>        | <b>4.8</b>  | 25.0  | 0.0   |
| Former                        | <b>53.5</b>         | <b>28.3</b> | <b>39.6</b> | <b>28.3</b> | <b>41.3</b>            | <b>18.6</b> | <b>34.1</b> | <b>25.5</b> | <b>46.2</b>            | <b>22.5</b> | <b>53.4</b> | <b>19.7</b> | <b>52.5</b>        | <b>14.5</b> | 25.0  | 14.3  |
| Never                         | <b>28.4</b>         | <b>56.4</b> | <b>27.1</b> | <b>56.5</b> | <b>29.1</b>            | <b>68.2</b> | <b>31.0</b> | <b>14.9</b> | <b>29.4</b>            | <b>55.0</b> | <b>23.3</b> | <b>52.1</b> | <b>18.0</b>        | <b>53.2</b> | 25.0  | 42.9  |
| Unknown                       | <b>0.7</b>          | <b>1.5</b>  | <b>12.5</b> | <b>10.9</b> | <b>0.0</b>             | <b>0.0</b>  | <b>0.0</b>  | <b>0.0</b>  | <b>4.2</b>             | <b>8.8</b>  | <b>6.9</b>  | <b>18.3</b> | <b>18.0</b>        | <b>27.4</b> | 25.0  | 42.9  |
| Alcohol use (%)               |                     |             |             |             |                        |             |             |             |                        |             |             |             |                    |             |       |       |
| Non-drinkers                  | <b>28.6</b>         | <b>57.0</b> | <b>16.7</b> | <b>41.3</b> | <b>49.0</b>            | <b>83.1</b> | <b>19.4</b> | <b>2.1</b>  | <b>20.2</b>            | <b>46.0</b> | <b>15.1</b> | <b>35.2</b> | 27.9               | 30.7        | 25.0  | 28.6  |
| Not heavy drinkers            | <b>63.8</b>         | <b>34.6</b> | <b>45.8</b> | <b>32.6</b> | <b>38.7</b>            | <b>15.8</b> | <b>34.9</b> | <b>18.1</b> | <b>56.3</b>            | <b>41.3</b> | <b>53.4</b> | <b>38.0</b> | 9.8                | 14.5        | 0.0   | 0.0   |
| Heavy drinkers                | <b>3.3</b>          | <b>1.7</b>  | <b>8.3</b>  | <b>2.2</b>  | <b>13.3</b>            | <b>1.1</b>  | <b>45.7</b> | <b>79.8</b> | <b>8.2</b>             | <b>1.3</b>  | <b>12.3</b> | <b>1.4</b>  | 29.5               | 17.7        | 37.5  | 0.0   |
| Ex-drinkers                   | -                   | -           | -           | -           | -                      | -           | -           | -           | <b>8.7</b>             | <b>1.3</b>  | <b>11.0</b> | <b>2.8</b>  | 6.6                | 1.6         | 0.0   | 0.0   |
| Unknown                       | <b>4.4</b>          | <b>6.7</b>  | <b>29.2</b> | <b>23.9</b> | <b>0.0</b>             | <b>0.0</b>  | 0.0         | 0.0         | <b>6.7</b>             | <b>10.1</b> | <b>8.2</b>  | <b>22.5</b> | 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)  | -     | -     |
| <b>Medication</b>             |                     |             |             |             |                        |             |             |             |                        |             |             |             |                    |             |       |       |
| Antihypertensives (%)         |                     |             |             |             |                        |             |             |             |                        |             |             |             |                    |             |       |       |
| Yes                           | -                   | -           | -           | -           | <b>61.2</b>            | <b>69.5</b> | <b>55.0</b> | <b>69.2</b> | 53.3                   | 61.8        | 41.1        | 49.3        | 45.9               | 56.5        | 37.5  | 42.9  |
| No                            | -                   | -           | -           | -           | <b>38.9</b>            | <b>30.5</b> | <b>45.0</b> | <b>30.9</b> | 46.2                   | 38.0        | 57.5        | 50.7        | 47.5               | 40.3        | 37.5  | 57.1  |
| Unknown                       | -                   | -           | -           | -           | <b>0.0</b>             | <b>0.0</b>  | <b>0.0</b>  | <b>0.0</b>  | 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        | <b>29.5</b>        | <b>43.6</b> | 25.0  | 42.9  |
| No                            | -                   | -           | -           | -           | 69.9                   | 66.4        | 79.1        | 75.5        | 69.2                   | 69.5        | 78.1        | 71.9        | <b>70.5</b>        | <b>51.6</b> | 62.5  | 57.1  |
| Unknown                       | -                   | -           | -           | -           | 0.0                    | 0.0         | 0.0         | 0.0         | 0.3                    | 0.0         | 1.4         | 0.0         | <b>0.0</b>         | <b>4.8</b>  | 12.5  | 0.0   |
| <b>STROKE-RELATED FACTORS</b> |                     |             |             |             |                        |             |             |             |                        |             |             |             |                    |             |       |       |
| 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 <sup>†</sup> |       |     |       | Joinville <sup>5</sup> |       |      |       | Melbourne <sup>6</sup> |       |     |       | Perth <sup>8</sup> |       |      |       |
|----------------|---------------------|-------|-----|-------|------------------------|-------|------|-------|------------------------|-------|-----|-------|--------------------|-------|------|-------|
|                | 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, Mātao and Tartu.**

| Characteristic                | Orebro <sup>9</sup> |             |      |      | Dijon <sup>10</sup> |             |             |             | Mātao <sup>15</sup> |              |       |       | Tartu <sup>16</sup> |      |       |       |
|-------------------------------|---------------------|-------------|------|------|---------------------|-------------|-------------|-------------|---------------------|--------------|-------|-------|---------------------|------|-------|-------|
|                               | 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                       | <b>29.6</b>         | <b>18.1</b> | 24.0 | 10.5 | <b>47.0</b>         | <b>81.7</b> | <b>59.4</b> | <b>82.5</b> | <b>43.9</b>         | <b>19.2</b>  | 50.0  | 33.3  | -                   | -    | -     | -     |
| Former                        | -                   | -           | -    | -    | <b>23.2</b>         | <b>2.5</b>  | <b>15.8</b> | <b>2.6</b>  | -                   | -            | -     | -     | -                   | -    | -     | -     |
| Never                         | <b>63.2</b>         | <b>79.2</b> | 64.0 | 79.0 | <b>27.3</b>         | <b>12.3</b> | <b>21.8</b> | <b>9.7</b>  | <b>51.2</b>         | <b>80.8</b>  | 50.0  | 33.3  | -                   | -    | -     | -     |
| Unknown                       | <b>7.2</b>          | <b>2.7</b>  | 12.0 | 10.5 | <b>2.6</b>          | <b>3.5</b>  | <b>3.0</b>  | <b>2.3</b>  | <b>4.9</b>          | <b>0.0</b>   | 0.0   | 33.3  | -                   | -    | -     | -     |
| Alcohol use (%)               |                     |             |      |      |                     |             |             |             |                     |              |       |       |                     |      |       |       |
| Non-drinkers                  | -                   | -           | -    | -    | 86.6                | 95.6        | 77.1        | 95.6        | <b>70.7</b>         | <b>100.0</b> | 75.0  | 33.3  | -                   | -    | -     | -     |
| Current drinkers*             |                     |             |      |      | 11.5                | 2.3         | 20.8        | 3.5         | <b>22.0</b>         | <b>0.0</b>   | 25.0  | 33.3  |                     |      |       |       |
| Ex-drinkers                   |                     |             |      |      | -                   | -           | -           | -           | -                   | -            | -     | -     |                     |      |       |       |
| Unknown                       |                     |             |      |      | 1.9                 | 2.1         | 2.0         | 0.9         | <b>7.3</b>          | <b>0.0</b>   | 0.0   | 33.3  |                     |      |       |       |
| <b>STROKE-RELATED FACTORS</b> |                     |             |      |      |                     |             |             |             |                     |              |       |       |                     |      |       |       |
| 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<br>RR (95% CI) |
|-------------------------------------|---------------------|-------------|-------------------|-----------------|-----------------|-----------------|-----------------------------------|
|                                     | Men                 | Women       | Men               | Women           | Men             | Women           |                                   |
| <b>Large-artery atherosclerosis</b> |                     |             |                   |                 |                 |                 |                                   |
| Joinville <sup>5</sup>              | 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 <sup>6</sup>              | 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%)   | <b>1.60 (1.01-2.53)</b>           |
| Orebro <sup>9</sup>                 | 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 <sup>16</sup>                 | 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%) | <b>1.32 (1.05-1.66)*</b>          |
| <b>Cardioembolism</b>               |                     |             |                   |                 |                 |                 |                                   |
| Joinville <sup>5</sup>              | 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%) | <b>1.34 (1.11-1.63)</b>           |
| Melbourne <sup>6</sup>              | 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 <sup>9</sup>                 | 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 <sup>16</sup>                 | 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%) | <b>1.32 (1.08-1.60)*</b>          |
| <b>Small-vessel occlusion</b>       |                     |             |                   |                 |                 |                 |                                   |
| Joinville <sup>5</sup>              | 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 <sup>6</sup>              | 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 <sup>9</sup>                 | 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 <sup>16</sup>                 | 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%)   | <b>9.93 (1.33-74.2)</b>           |
| 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%)      | <b>2.05 (1.23, 3.44)*</b>         |
| <b>Other etiology</b>               |                     |             |                   |                 |                 |                 |                                   |
| Joinville <sup>5</sup>              | 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 <sup>6</sup>              | 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 <sup>9</sup>                 | 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 <sup>16</sup>                 | 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)*                 |
| <b>Undetermined</b>                 |                     |             |                   |                 |                 |                 |                                   |
| Joinville <sup>5</sup>              | -                   | -           | -                 | -               | -               | -               | -                                 |
| Melbourne <sup>6</sup>              | 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 <sup>9</sup>                 | 1 (25.0%)           | 3 (75.0%)   | 28.0 (NA)         | 3.0 (0.0-6.0)   | 1/1 (100%)      | 0/3 (0%)        | NA                                |
| Tartu <sup>16</sup>                 | 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 <sup>4</sup>    | SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, BMI, smoking, marital status, alcohol, hospital admission,  |
| Joinville <sup>5</sup> | Stroke subtype, race, hypertension, AF, PVD, TIA, BMI, smoking, hospital admission (100%), pre-stroke medication (antihypertensives, antiplatelets, anticoagulants), delay to hospital, IHD, alcohol                 |
| Melbourne <sup>6</sup> | Stroke subtype, race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, smoking, alcohol, hospital admission, pre-stroke medication (antiplatelets, anticoagulants, antihypertensives), institutional residence |
| Perth <sup>8</sup>     | SEP, hypertension, AF, IHD, TIA, diabetes, smoking, alcohol, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets), institutional residence, pre-stroke Barthel, hospital admission            |
| Orebro <sup>9</sup>    | Stroke subtype, age†, marital status, hypertension, AF, IHD, PVD, TIA, diabetes, dementia, pre-stroke Barthel, hospital admission, smoking   |
| Dijon <sup>10</sup>    | Hypertension, IHD, PVD, TIA, alcohol, hospital admission, institutional residence  |
| Matão <sup>15</sup>    | Race, marital status, education, age†, hypertension, AF, IHD, PVD, TIA, smoking, alcohol, hospital admission   |
| Tartu <sup>16</sup>    | 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  $\geq 10\%$ ) 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 <sup>2</sup> (%) | P <sup>H</sup> | RR(95% CI)              | P <sup>sub-group</sup> | I <sup>2</sup> (%)       | P <sup>H</sup> | RR(95% CI)              | P <sup>sub-group</sup> |
| <b>Ischaemic stroke</b>                 |               |                    |                |                         |                        |                          |                |                         |                        |
| Geographic region                       |               |                    |                |                         |                        |                          |                |                         |                        |
| Australasia                             | 2             | 0.0                | 0.444          | <b>1.23 (1.02-1.48)</b> | 0.565                  | 0.0                      | 0.916          | 1.12 (0.93-1.35)        | 0.385                  |
| Europe                                  | 4             | 0.0                | 0.533          | <b>1.36 (1.21-1.52)</b> |                        | 0.0                      | 0.680          | 1.16 (1.03-1.30)        |                        |
| South America                           | 2             | 0.0                | 0.925          | <b>1.41 (1.22-1.64)</b> |                        | 0.0                      | 0.413          | <b>1.32 (1.13-1.53)</b> |                        |
| Pre-stroke function                     |               |                    |                |                         |                        |                          |                |                         |                        |
| Unavailable                             | 2             | 0.0                | 0.515          | <b>1.43 (1.24-1.64)</b> | 0.334                  | 0.0                      | 0.901          | <b>1.29 (1.12-1.49)</b> | 0.232                  |
| Available                               | 6             | 0.0                | 0.718          | <b>1.30 (1.18-1.44)</b> |                        | 0.0                      | 0.741          | <b>1.15 (1.04-1.27)</b> |                        |
| <b>Intracerebral hemorrhagic stroke</b> |               |                    |                |                         |                        |                          |                |                         |                        |
| 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<sup>H</sup>, 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.**

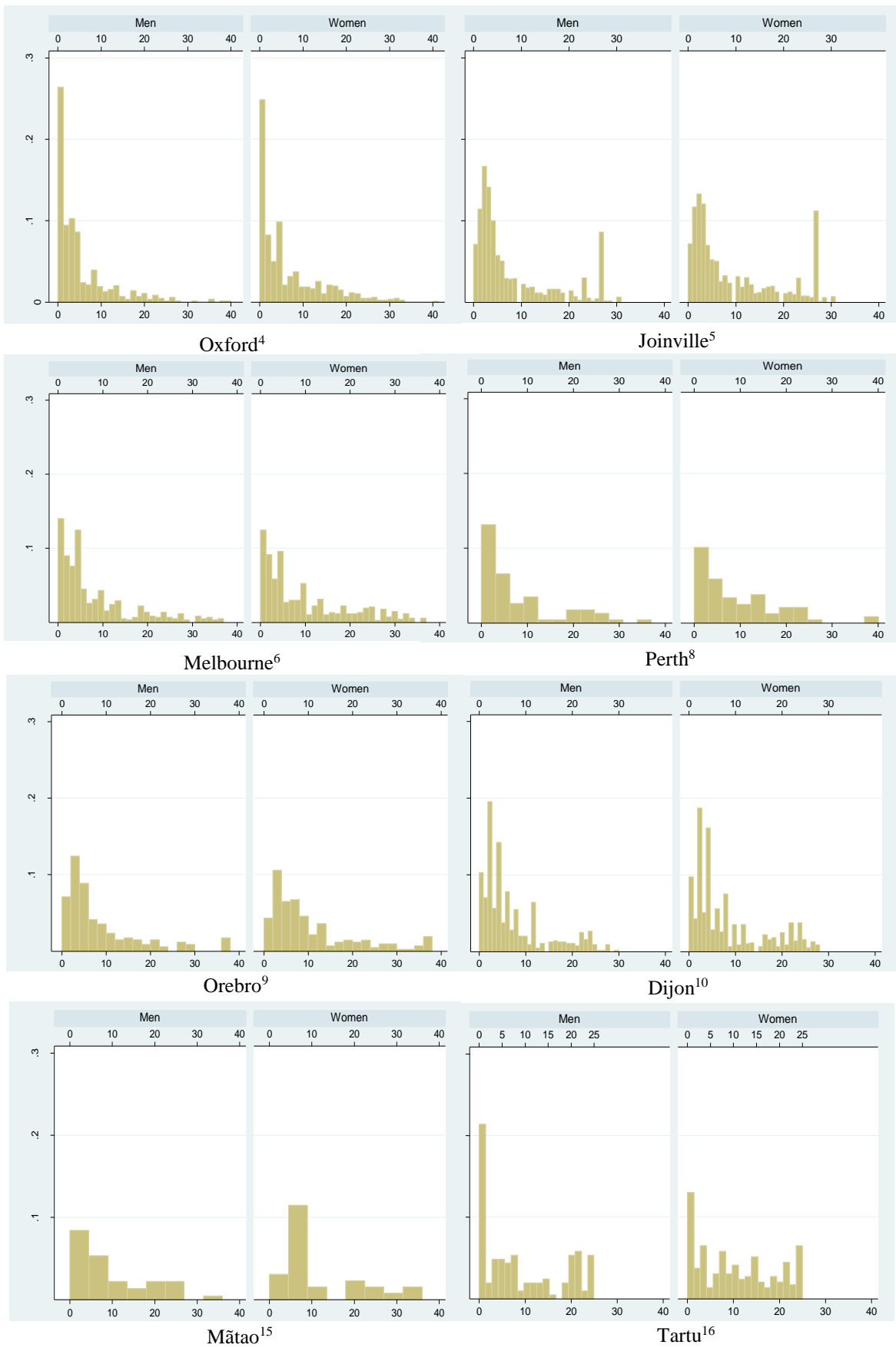
| Covariates   | Unadjusted               |                          | Adjusted for age         |                          |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
|  | RR* (95% CI)             | P <sub>interaction</sub> | RR (95%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

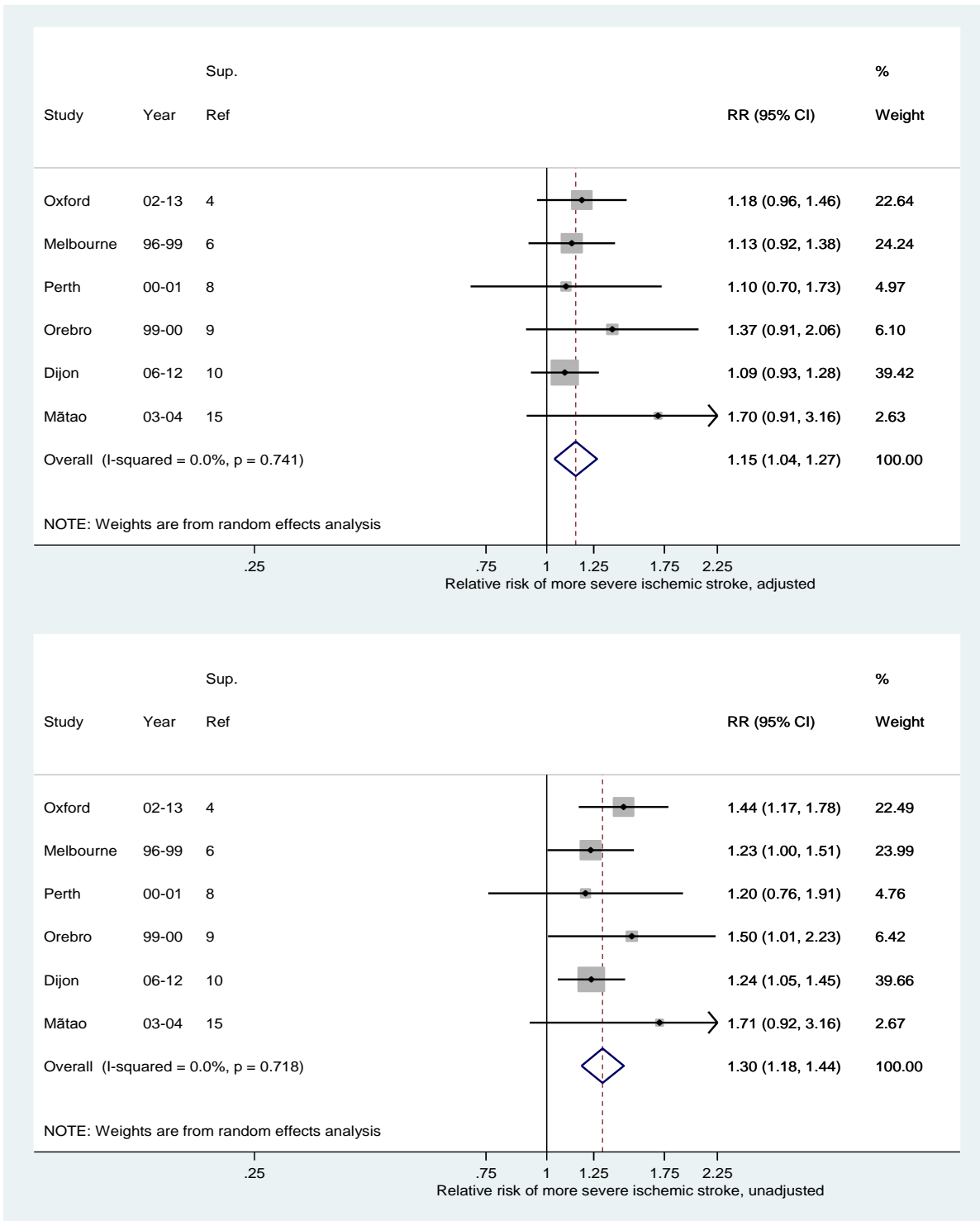
| Study                            | N*    | Adjusted for                |                             |                             |                             |
|----------------------------------|-------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|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

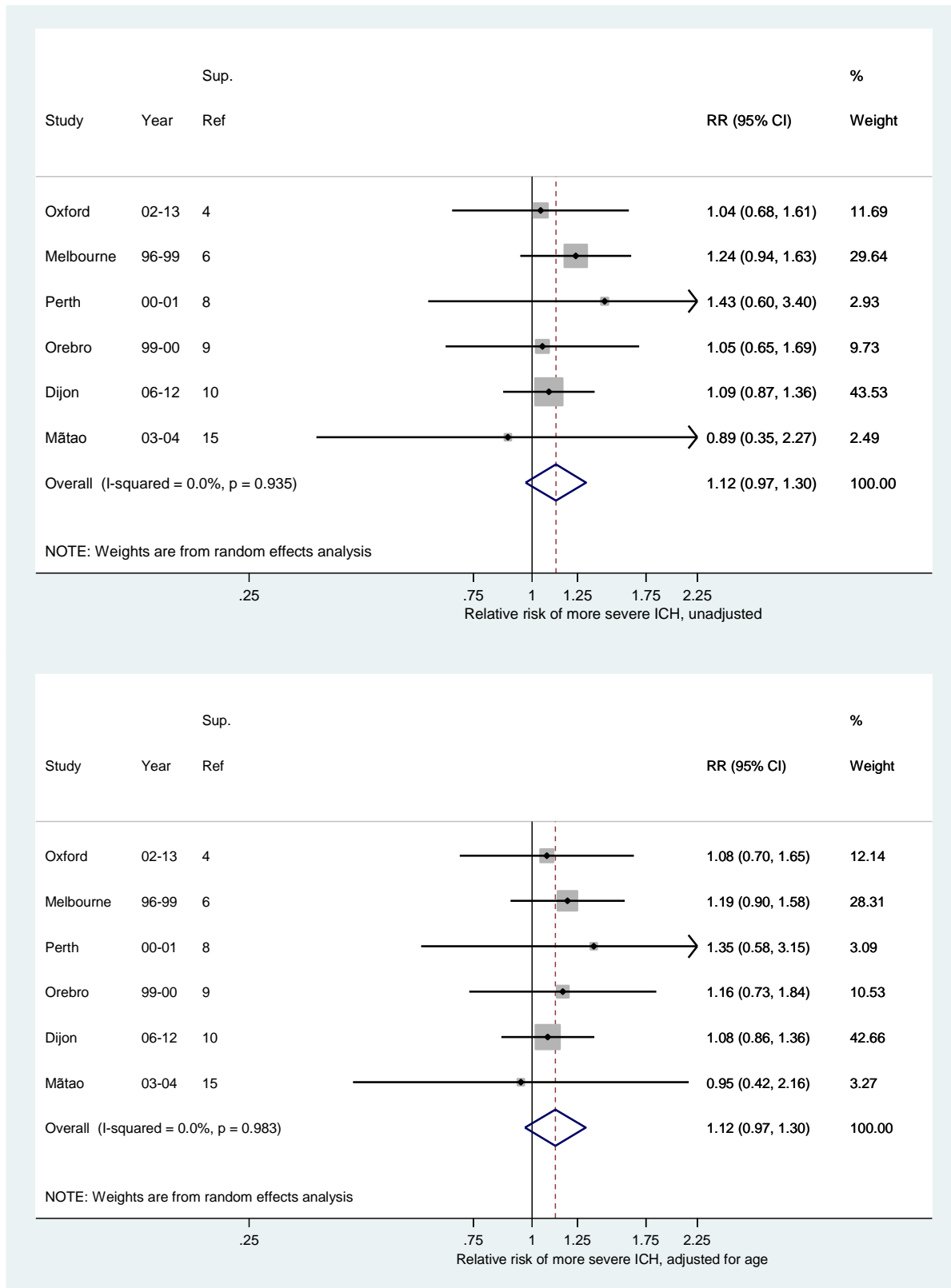


**Figure S2. Difference in stroke severity between women and men with ischemic stroke: unadjusted (top) and adjusted (bottom) random-effects meta-analyses among 6 studies.**



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.

## Supplemental References:

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 2009;8:355-69.
2. Sudlow C, Warlow C. Comparing Stroke Incidence Worldwide: What Makes Studies Comparable? *Stroke.* 1996;27:550-558.
3. Feigin VL, Carter K. Editorial comment—Stroke incidence studies one step closer to the elusive gold standard? *Stroke.* 2004;35:2045-7.
4. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PA, Dennis MS, Warlow CP, Bamford JM, Anslow P. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet.* 2004;363:1925-33.
5. Cabral NL, Goncalves AR, Longo AL, Moro CH, Costa G, Amaral CH, Fonseca LA, Eluf-Neto J. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. *J Neurol Neurosurg Psychiatry.* 2009;80:755-61.
6. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Thrift AG. Determinants of handicap after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke.* 2004;35:715-20.
7. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, Stamatielopoulos S. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. *Stroke.* 1999;30:363-70.
8. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. *Stroke.* 1994;25:1935-44.
9. Appelros P, Nydevik I, Seiger A, Terent A. High incidence rates of stroke in Orebro, Sweden: Further support for regional incidence differences within Scandinavia. *Cerebrovasc Dis.* 2002;14:161-8.
10. Bejot Y, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, Di Carlo A, Osseby GV, Moreau T, Giroud M. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. *Stroke.* 2008;39:1945-51.
11. Smadja D, Cabre P, May F, Fanon JL, Rene-Corail P, Riocreux C, Charpentier JC, Fournier P, Saint-Vil M, Ketterle J. ERMANCIA: Epidemiology of Stroke in Martinique, French West Indies: Part I: methodology, incidence, and 30-day case fatality rate. *Stroke.* 2001;32:2741-7.
12. Correia M, Silva MR, Matos I, Magalhaes R, Lopes JC, Ferro JM, Silva MC. Prospective community-based study of stroke in Northern Portugal: incidence and case fatality in rural and urban populations. *Stroke.* 2004;35:2048-53.
13. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, Chen MH, Anderson C. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002-2003. *Lancet Neurol.* 2006;5:130-9.
14. Carolei A, Marini C, Di Napoli M, Di Gianfilippo G, Santalucia P, Baldassarre M, De Matteis G, di Orio F. High stroke incidence in the prospective community-based L'Aquila registry (1994-1998). First year's results. *Stroke.* 1997;28:2500-6.
15. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matao, Brazil: a population-based prospective study. *Stroke.* 2007;38:2906-11.
16. Korv J, Roose M, Kaasik A-E. Stroke registry of Tartu, Estonia, from 1991 through 1993. *Cerebrovascular Diseases.* 1997;7:154-162.
17. Palm F, Urbanek C, Rose S, Buggle F, Bode B, Hennerici MG, Schmieder K, Inselmann G, Reiter R, Fleischer R, Piplack KO, Safer A, Becher H, Grau AJ. Stroke Incidence and Survival in Ludwigshafen am Rhein, Germany: the Ludwigshafen Stroke Study (LuSSt). *Stroke.* 2010;41:1865-70.
18. Heuschmann PU, Di Carlo A, Bejot Y, Rastenyte D, Ryglewicz D, Sarti C, Torrent M, Wolfe CD. Incidence of stroke in Europe at the beginning of the 21st century. *Stroke.* 2009;40:1557-63.
19. Sienkiewicz-Jarosz H, Gluszkiewicz M, Pniewski J, Niewada M, Czlonkowska A, Wolfe C, Ryglewicz D. Incidence and case fatality rates of first-ever stroke - comparison of data from two prospective population-based studies conducted in Warsaw. *Neurol Neurochir Pol.* 2011;45:207-12.
20. Wolfe CDA, Crichton SL, Heuschmann PU, McKevitt CJ, Toschke AM, Grieve AP, Rudd AG. Estimates of outcomes up to ten years after stroke: analysis from the prospective South London Stroke Register. *PLoS Med.* 2011;8:e1001033.
21. Liman TG, Heuschmann PU, Endres M, Floel A, Schwab S, Kolominsky-Rabas PL. Changes in cognitive function over 3 years after first-ever stroke and predictors of cognitive impairment and long-term cognitive stability: the Erlangen Stroke Project. *Dement Geriatr Cogn Disord.* 2011;31:291-9.
22. Elneihoum AM, Göransson M, Falke P, Janson L. Three-year survival and recurrence after stroke in Malmö, Sweden: an analysis of stroke registry data. *Stroke.* 1998;29:2114-2117.

23. La Spina P, Savica R, Serra S, Calabro RS, Postorino P, Morgante L, Savettieri G, Musolino R. Long-term survival and outcome after first stroke in the Sicilian Aeolian Island Archipelago population. *Neurol Sci.* 2008;29:153-6.
24. Di Carlo A, Inzitari D, Galati F, Baldereschi M, Giunta V, Grillo G, Furchi A, Manno V, Naso F, Vecchio A, Consoli D. A prospective community-based study of stroke in Southern Italy: the Vibo Valentia incidence of stroke study (VISS). Methodology, incidence and case fatality at 28 days, 3 and 12 months. *Cerebrovasc Dis.* 2003;16:410-7.
25. Walker RW, Wakefield K, Gray WK, Jusabani A, Swai M, Mugusi F. Case-fatality and disability in the Tanzanian Stroke Incidence Project cohort. *Acta Neurol Scand.* 2016;133:49-54.
26. Corso G, Bottacchi E, Giardini G, Di Giovanni M, Meloni T, Pesenti Campagnoni M, Veronese Morosini M. Epidemiology of stroke in northern Italy: the Cerebrovascular Aosta Registry, 2004-2008. *Neurol Sci.* 2013;34:1071-81.