Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy) A Meta-Analysis of Individual Participant Data

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Background—Women are reported to have greater mortality after stroke than men, but the reasons are uncertain. We examined sex differences in mortality at 1 and 5 years after stroke and identified factors contributing to these differences.

Methods and Results—Individual participant data for incident strokes were obtained from 13 population-based incidence studies conducted in Europe, Australasia, South America, and the Caribbean between 1987 and 2013. Data on sociodemographics, stroke-related factors, prestroke health, and 1- and 5-year survival were obtained. Poisson modeling was used to estimate the mortality rate ratio (MRR) for women compared with men at 1 year (13 studies) and 5 years (8 studies) after stroke. Study-specific adjusted MRRs were pooled to create a summary estimate using random-effects meta-analysis. Overall, 16 957 participants with first-ever stroke followed up at 1 year and 13 216 followed up to 5 years were included. Crude pooled mortality was greater for women than men at 1 year (MRR 1.35; 95% confidence interval, 1.24–1.47) and 5 years (MRR 1.24; 95% confidence interval, 1.12–1.38). However, these pooled sex differences were reversed after adjustment for confounding factors (1 year MRR, 0.81; 95% confidence interval, 0.72–0.92 and 5-year MRR, 0.76; 95% confidence interval, 0.65–0.89). Confounding factors included age, prestroke functional limitations, stroke severity, and history of atrial fibrillation.

Conclusions—Greater mortality in women is mostly because of age but also stroke severity, atrial fibrillation, and prestroke functional limitations. Lower survival after stroke among the elderly is inevitable, but there may be opportunities for intervention, including better access to evidence-based care for cardiovascular and general health.

Key Words: incidence • mortality • risk factors • stroke • women

WHAT IS KNOWN

- The greater mortality for women compared with men after stroke has been reported by many investigators.
- We have a limited understanding of the factors that explain the disparity between men and women in survival after stroke.

WHAT THE STUDY ADDS

- This is the first meta-analysis of individual participant data from high-quality stroke incidence studies to confirm that women consistently have greater long-term mortality than men after stroke regardless of study location and time period.
- Women's advanced age, more severe strokes, worse prestroke function, and the presence of AF contributed to their greater mortality after stroke compared with men.

Women are reported to have greater mortality in the short term after stroke than men. In a review of 31 population-based studies of short-term mortality after stroke, Appelros et al[1] reported that women had a 25% greater risk of 1-month crude mortality than men. It remains unclear what accounts for this disparity and whether these differences persist into the longer term. There have been no studies specifically designed to examine sex differences in long-term mortality after stroke.

Identifying factors that explain the sex differences in mortality is important because better understanding could lead to interventions to reduce the disparities.[2] In an Australian study, the 36% greater risk of death at 28 days for women compared with men was explained by age, prestroke health, stroke severity, and use of anticoagulants at discharge.[3] After adjustment in that study, women had a 17% lower short-term mortality than men. It is unknown whether these same factors account for the relative sex differences in other geographical regions or in long-term mortality.

Our aims were to quantify the relative sex difference in long-term mortality and to identify factors that contribute to the greater mortality of women after stroke using a meta-analysis of pooled individual participant data (IPD) from 13 ideal incidence stroke studies conducted worldwide.

Methods

This study—the INSTRUCT (INternational STRoke oUtComes sTudy)—was registered in PROSPERO (CRD42016036723)[4] and adhered to the PRISMA-IPD (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data).[5] This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). All of the participating studies had signed informed consent and approval from their respective local ethics committees. INSTRUCT is an IPD meta-analysis of long-term outcomes after first-ever stroke. It included 13 ideal[6,7] population-based stroke incidence studies. These studies have greater internal validity and less selection bias than hospital-based studies.[8] The included studies represented 59% of the 22 potentially eligible studies later identified by systematic search. We requested deidentified IPD on mortality (≤5 years after stroke) and participant characteristics from the study investigators. The main reasons for exclusion of 9 studies occurred because of refusal to participate (4 studies) and late identification of the study (5 studies; see Supplement I, Figure I, and Table I in the Data Supplement for full details of study selection).

Outcome Measurement

The outcome was all-cause mortality at 1 year and 5 years after stroke. In 7 studies, mortality was obtained from national death registries (Table IIA in the Data Supplement). In the remaining 6 cohorts, a combination of hospital records, death certificates, or direct participant follow-up was used. In 4 studies (Martinique, L'Aquila, Matão, and Tartu) at 1 year and 2 studies at 5 years (Martinique and L'Aquila), vital status was recorded, but the exact date of death was not recorded (see the section on Statistical Analysis for further details).

Study Factors

The study factors assessed were those that might explain sex differences in mortality after stroke.[3] They included (1) sociodemo-graphics, (2) prestroke health (dependence, comorbidities, and health behaviors), (3) stroke-related factors (stroke type, severity of stroke, and year of stroke occurrence), (4) treatment and management, and (5) poststroke factors (depression and recurrence). Details on how these data were collected and the definitions used for each variable in each specific study are provided in brief below and in full in the Data Supplement (Table IIB and Supplement II in the Data Supplement). In general, the patient or a proxy was interviewed within a few days of their event with clinical information supplemented from medical records and physician consultation, where possible.

Sociodemographic factors included age, sex, race/ethnicity, marital status, education, and socioeconomic status. Data on prestroke health status included dependence (retrospective modified Rankin scale, 4 studies; retrospective Barthel Index, 3 studies; institutional residence, 4 studies; and whether or not the patient was living independently before stroke, 1 study); comorbidities (atrial fibrillation [AF], hypertension, ischemic heart disease, peripheral vascular disease, transient ischemic attack, diabetes mellitus, and dementia); medications

before stroke (antihypertensives, antiplatelets, and anticoagulants); body mass index; and health behaviors (smoking and alcohol use).

Stroke-related factors included the type of stroke categorized into 4 groups: ischemic stroke, intracerebral hemorrhage, subarach-noid hemorrhage, and undetermined stroke. Measurement of stroke severity included the National Institutes of Health Stroke Scale score (7 studies); Glasgow Coma Scale score (3 studies); Unified Neurological Stroke Scale score (1 study); Scandinavian Stroke Scale score (1 study); Barthel index at onset (1 study); or loss of consciousness (6 studies); hemiparesis (6 studies); and incontinence at onset (2 studies).

Treatment and management included whether the patient was admitted to hospital; time delay to hospital presentation; thrombolytic therapy (rtPA [recombinant tissue-type plasminogen activator]); admission and discharge medications (antihypertensives, antiplatelets, and anticoagulants); in-hospital investigations including neuroimag-ing (computed tomography scan or magnetic resonance imaging), carotid or transcranial Doppler, or echocardiography; and surgical interventions including carotid endarterectomy and aneurysm clip ping or coiling.

Poststroke depression was measured in 3 studies: the Irritability, Depression and Anxiety Scale[9] was used in Melbourne (scores ≥8 defining depression),[10] the General Health Questionnaire (subscore of depression)[11] in Auckland, and the Montgomery-Åsberg Depression Rating Scale[12] (scores ≥8 defining depression)[13] in Martinique. Stroke recurrence was gathered by self-report of stroke-like events during follow-up in 8 studies. In 6 out of 8 studies (not including Arcadia and Matão), these events were verified by physician review of medical records.

Statistical Analysis

Harmonizing covariates across studies was not possible because of lack of uniform definitions. We, therefore, used the 2-stage method of analysis proposed for IPD meta-analyses.[14] The first stage involved building study-specific crude and adjusted models to estimate the relative mortality rate ratio (MRR) for women compared with men. We used Poisson regression at 1 year (13 studies) and 5 years (8 studies) after stroke with the logarithm of the number of person-years at risk of dying within that period entered as an offset.[15] To undertake Poisson modeling in studies without exact date of death, multiple imputation by chained equations[16] (m=50 imputations) was used to impute person-years for men and women separately (see Supplement III in the Data Supplement for details). The role of covariates in the association between sex and mortality was determined using purposeful model building[17] to identify the significant confounders of sex difference in mortality. The following rules were applied to determine the covariates in the study-specific multivariable models: (1) the covariate was missing in <20% of cases; (2) the covariate was associated with mortality ($P<0.1$); (3) the covariate was associated with sex ($P<0.1$); and (4) the inclusion of the covariate in a model with only sex changed the magnitude of the sex coefficient by ≥10%.[17] Age and stroke severity were forced into the final multivariable models because they are well-established predictors of mortality and are associated with sex.[18] Covariates were transformed, as necessary using fractional polynomials in multivariable modeling,[19] to get the best model fit. We report fully adjusted models but also examine the effect of individual covariates on the sex difference in mortality. Within each study, statistical interactions were assessed by a test of statistical significance of a sex×covariate product term.

The second stage of the analysis involved combining the crude and adjusted study-specific effect estimates using random-effects meta-analysis. Statistical heterogeneity was evaluated using Q statistics and I^2 statistics. Potential sources of heterogeneity were assessed among variables of study-level characteristics (eg, geographic region, income group, and severity instrument; Supplement III in the Data Supplement). Between-study interactions between sex and these study-level characteristics were assessed by meta-regression.

To further examine the robustness of our findings, we also tested interaction effects using the single pooled IPD data set.[20] In this data, we assessed the interaction between sex and participant-level covari-ates (stroke type, age at stroke onset, and the year of stroke occurrence) by again testing the statistical significance of the sex×covariate product terms using multivariate random-effects meta-analysis.[21]

To describe the sex differences in crude mortality, Kaplan–Meier survival curves by sex, accounting for study-specific curves, were estimated among the pooled IPD of studies with exact date of death to 1 year (9 studies) and 5 years (5 studies) after stroke.

Sensitivity analyses were used to examine the effect of the multiple imputation to account for unknown date of death or missing data, early deaths after stroke (eg, 6 months) and, in a subset of studies, clinical treatment on the results (Supplement III in the Data Supplement).

Analyses were conducted in Stata 12.1. A 2-tailed P value ≤0.05 was considered statistically significant.

Results

There were 16 957 participants (13 studies; Figure II in the Data Supplement) with data on 1-year mortality and 13 216 with data on 5-year mortality (8 studies). Table 1 shows the baseline characteristics of each study population, further stratified by sex as shown in Table IIIa–IIIc in the Data Supplement. Women were older (statistically significant differences found in 10/13 studies) and more often unmarried (statistically significant difference 4/5 studies), living in institutions (statistically significant difference 3/4 studies) and functionally dependent before stroke (statistically significant difference 5/8 studies) than men (Table IIIa–IIIc in the Data Supplement). Women were more likely to be prescribed antihypertensive agents (statistically significant difference 3/5 studies) before stroke. In about half of the studies, women more often had an undetermined stroke type (statistically significant difference 6/12 studies) and had suffered more severe stroke than men (statistically significant difference 6/13 studies). In all studies, men were more often smokers (12/12 studies) or drinkers (10/10 studies) and more often had peripheral vascular disease (statistically significant difference 7/9 studies).

The crude survival rate using pooled IPD was 79.6% (men) and 68.5% (women) at 1 year (9 studies) and 58.7% (men) and 51.5% (women) at 5 years (6 studies; Figure 1). Data were available from 13 studies on 1-year mortality after stroke. The sample for complete-case analysis was n=14 972 cases (88% of available cases) because of missing data on some confounding factors. Women were 35% more likely than men to be deceased at 1 year in crude analyses (Figure 2, top) without evidence of heterogeneity (I^2=26.5; Q=16.3; P=0.177).

The direction of the pooled MRR was reversed in fully adjusted analyses, with women having lower 1-year mortality than men (adjusted MRR, 0.81; 95% confidence interval [CI], 0.72–0.92]), albeit with some evidence of statistical heterogeneity (I^2=36.4; Q=18.9; P=0.092; Figure 2, bottom). The following covariates met our conditions for inclusion in the study-specific multivariable models (Table 2): age, stroke severity, stroke type, AF, prestroke dependency, smoking, and history of peripheral vascular disease. There was limited evidence that other factors including socioeconomic status, cardiovascular risk factors, and other comorbidities were responsible for the greater 1-year mortality in women (Table IV in the Data Supplement). Partial adjustment by inclusion of individual covariates changed the coefficient for sex difference substantially with age alone, reducing the effect by 77%. Adjustment separately for stroke severity, AF, and pre-stroke dependency reduced the MRR by 42%, 5%, and 45%, respectively (Table V in the Data Supplement). There was no evidence that any of these covariates modified the effect of sex on mortality. In study-level analyses using meta-regression, estimated person-years was the only identifiable source of heterogeneity in the sex difference in 1-year mortality (Table 3, study-level characteristics). The sex difference in the adjusted MRR was less among studies with actual person-years than in studies with estimated person-years (adjusted MRR=0.74 versus 0.97; P=0.023; heterogeneity explained R^2=99.9%).

Data were available from 8 studies on 5-year mortality after stroke. The sample for complete-case analysis was n=11 368 (86% of available cases). In crude analyses of 5-year mortality, women were 24% more likely than men to have died after stroke (Figure 3, top), but heterogeneity was significant (I^2=57.2; Q=16.4; P=0.022).

The direction of the 5-year pooled MRR (Figure 3, bottom) was again reversed on adjustment for covariates (adjusted MRR, 0.76; 95% CI, 0.65–0.89). However, there was significant heterogeneity in the study-specific multivari-able estimates (I^2=69.1; Q=22.7; P=0.002). The factors most commonly adjusted for in the study-specific analyses were age, stroke severity, stroke type, and AF (Table 2). There was limited evidence that other factors including socioeconomic status, cardiovascular risk factors, and other comorbidities were responsible for the greater 5-year mortality in women (Table VI in the Data Supplement). Partial adjustment by inclusion of

individual covariates changed the coefficient for sex difference substantially; age alone reversed the relative sex difference in 5-year mortality (pooled age-adjusted MRR, 0.96; 95% CI, 0.86–1.08; I^2=59.7; P=0.015). The effect was also reduced with separate adjustment for stroke severity (51%), AF (11%), and prestroke dependency (55%; Table VII in the Data Supplement). There was no evidence that any of these covariates modified the effect of sex on mortality. Meta-regression did not identify any sources of the heterogeneity observed in 5-year crude or adjusted models (Table VIII, study-level characteristics, in the Data Supplement).

In participant-level analyses of the single pooled IPD data set using multivariate random-effects meta-analysis, estimations of the sex difference in unadjusted and adjusted mortality at either 1 or 5 years after stroke were independent of stroke type (Table 3; Table VIII, participant-level characteristics, in the Data Supplement) and the year that the stroke occurred (Figure III in the Data Supplement). As illustrated in Figure 4, the magnitude of the sex differences in mortality at 1 or 5 years after stroke was not modified by age group.

Sensitivity analysis to account for missing data in one study with ≥20% missing data (Melbourne) using multiple imputation showed no difference in the estimated pooled effects for 1-year and 5-year mortality analyses when compared with complete-case analyses (Table IXA–IXB in the Data Supplement).

There was some evidence that the relative sex differences in 1-year and 5-year mortality were greatest in the first 6 months after stroke. The unadjusted female:male MRRs were reduced markedly by excluding deaths before 6 months with pooled MRR changing from 1.35 (95% CI, 1.24–1.47) to 1.14 (95% CI, 0.92–1.40) at 1 year and from 1.24 (95% CI, 1.12– 1.38) to 1.07 (95% CI, 0.92–1.25) at 5 years (Table X in the Data Supplement).

There was a variety of measures of treatment and management of stroke and its risk factors across studies. Significant differences existed in the prevalence of some of these between men and women, but results were inconsistent across studies (Table XI in the Data Supplement). For example, women received less carotid investigations than men in 4 out of 9 studies and underwent fewer echocardiography procedures in 3 out of 7 studies, but there were no differences in neuroimaging, thrombolysis, discharge medication, and surgical intervention. However, there was very little evidence that these differences influenced the pooled female:male MRR at 1 or 5 years. With the exception of carotid investigations in Joinville, none of these factors confounded the association between sex and mortality among hospitalized patients (Table XII in the Data Supplement). In Joinville, adjustment for carotid investigations reduced the 1-year MRR by 59% among hospitalized cases. Nevertheless, the pooled estimates of the MRR for women compared with men were virtually unchanged by the revised estimate for Joinville (Table XIII in the Data Supplement).

Table 1. Baseline Characteristics of Participants With First-Ever Stroke Cases From 13 Population-Based Stroke Incidence Studies

Study	Study Year	Region	Baseline (N)	Women, %	Ischemic, %	Age, Median	1-y Mortality	5-y Mortality
Oxford, UK	2002–2013	Europe	1374	50.7	80.3	76.8	✓	✓(n=760)*
Joinville, Brazil	2011–2013	South	980	48.3	80.5	64.0	✓	
Melbourne,	1996–1999	Australasia	1316	55.6	70.0	77.2	✓	✓
Arcadia, Greece	1993–1995	Europe	555	44.3	67.6	77.0	✓†	
Perth, Australia	2000–2001	Australasia	183	52.5	76.5	77.4	✓	
Orebro, Sweden	1999–2000	Europe	377$	55.2	72.7	78.0	✓	✓
Dijon, France	1987–2012	Europe	4621	53.1	82.7	77.7	✓	✓(n=3719)*
Martinique, FWI	1998–1999	Caribbean	580	50.9	76.6	73.0	✓	✓
Porto, Portugal	1998–2000	Europe	688	58.7	76.2	73.0	✓	✓
Auckland, NZ	2002–2003	Australasia	1423	53.1	72.5	74.0	✓	✓
L'Aquila, Italia	1994–1998	Europe	4353	52.9	82.6	75.9	✓	✓
Matão, Brazil	2003–2004	South	81	37.0	84.0	65.0	✓	
Tartu, Estonia	2002–2003	Europe	433$	59.1	76.7	73.0	✓	
Total cases			16 964§				16 957	13 216

Check mark denotes studies with data. FWI indicates French West Indies.

*Follow-up data were available only among cases with year of stroke from 2002 to 2008 for Oxford and 1987 to 2008 for Dijon.

†There were 7 cases who were lost-to-follow-up when comparing to baseline.

$Baseline data without including cases of subarachnoid hemorrhage (Orebro: 11 cases, Tartu: 18 cases).

§Total cases including those with subarachnoid hemorrhage: 16 993.

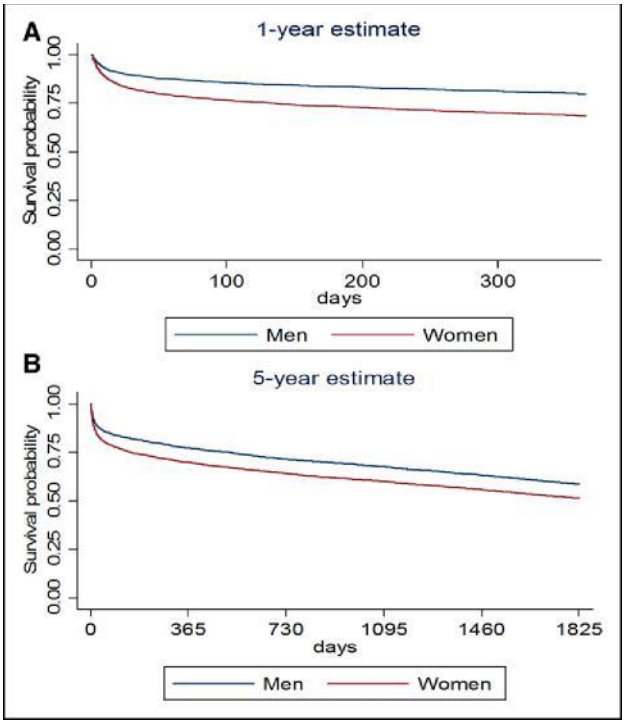

Figure 1. Kaplan–Meier survival curves showing survival for men and women after stroke using pooled data among 9 cohorts with 1-y follow-up (**top**) and among 6 cohorts with 5-y follow-up (**bottom**) accounting for study-specific curves.

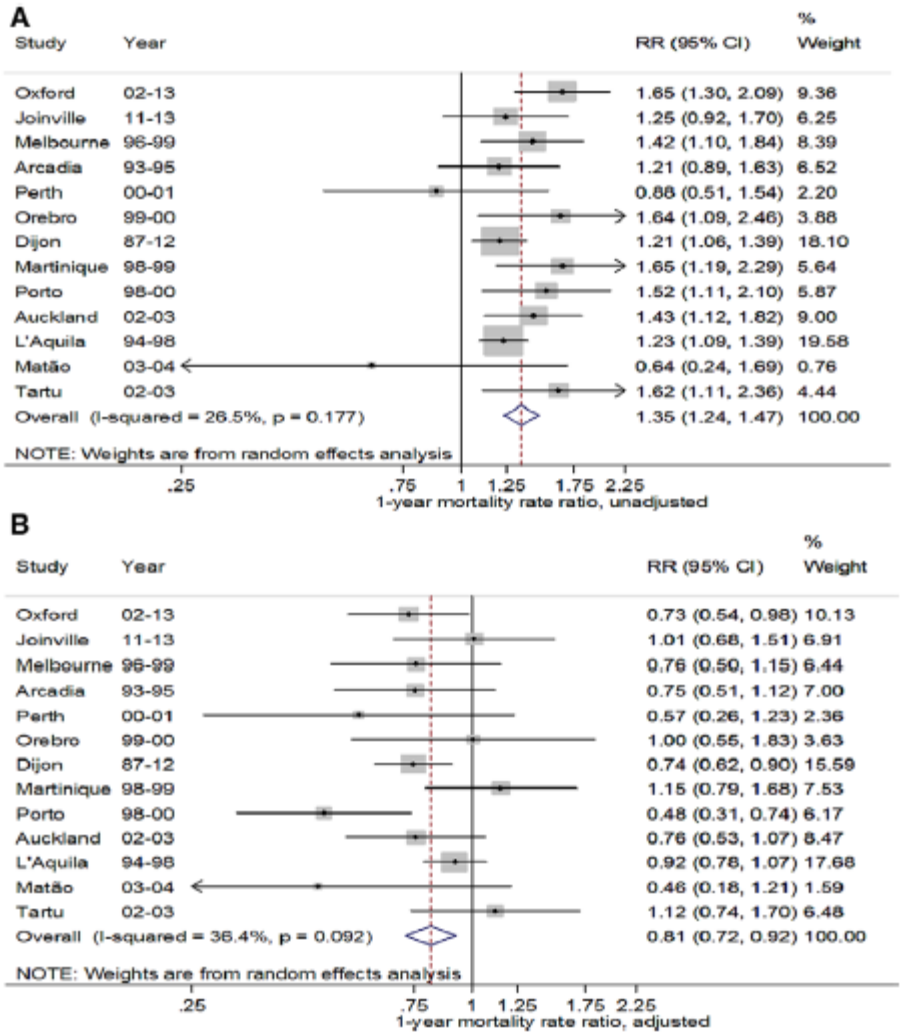

Figure 2. Mortality rate ratio (MRR) for women compared with men at 1 y after stroke in unadjusted (top) and adjusted (bottom) models from 13 studies combined using random-effects metaanalysis (n=14 972). Of note, each study was adjusted for different confounding factors as highlighted in Table 2. CI indicates confidence interval.

Table 2. Factors Contributing to Sex Difference in Long-Term Mortality Between Women and Men After Stroke Based on the Best-Fit Sex-Specific Model Within Studies

Study		1 y		5 y
	N*	Actual Confounding Factors Included in the Fully Adjusted Model	N*	Actual Confounding Factors Included in the Fully Adjusted Model
Oxford	1290	Age^3†, NIHSS (2-term)†, prestroke mRS, and stroke type	732	Age^3†, NIHSS (2-term)†, and prestroke mRS
Joinville	979	Age^3†, NIHSS, and stroke type	...	
Melbourne	975	Age, log NIHSS†, prestroke Barthel (2-term)†, AF, and stroke type	975	Age, log NIHSS†, prestroke Barthel (2-term)†, AF, and stroke type
Arcadia	547	Age, GCS, and AF	...	
Perth	183	Age, NIHSS, prestroke mRS, and stroke type	...	
Orebro	377	Age, log NIHSS†, institutional residence, and stroke type	377	Age^3†, log NIHSS†, institutional residence, and stroke type
Dijon	3994	Age^3†, LOC, AF, and smoking	3094	Age^3†, LOC, AF, smoking, and stroke type
Martinique	569	Age^3†, Barthel at onset (2-term)†, and history of PVD	569	Age^3† and Barthel at onset (2-term)†
Porto	650	Age, LOC, smoking, and prestroke mRS	650	Age, LOC, and prestroke mRS^3†
Auckland	1177	Age^3†, log GCS†, prestroke dependence‡, AF, and stroke type	1177	Age^3†, log GCS†, prestroke dependence‡, and AF
L'Aquila	3794	Age, LOC§, AF, hospital admission, stroke type, and smoking	3794	Age, LOC§, AF, hospital admission, and stroke type
Matão	79	Age§ and NIHSS	...	
Tartu	358	Age and log NIHSS†	...	
Total cases	14 972		11 368	

Of note, covariates were transformed, as necessary to get the best model fit. AF indicates atrial fibrillation; GCS, Glasgow Coma Scale; LOC, loss of consciousness; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; and PVD, peripheral vascular disease.
*The sample size was the same among the unadjusted model and fully adjusted model.
†Transformations were based on the powers (eg, 3rd power and 2 power terms) suggested by fractional polynomials that produced the best-fitting multivariable model.
‡Self-reported data about whether the patient lived independently before stroke.
§Not meeting criteria of being a confounder but remain in the fully-adjusted multivariable model.

Discussion

We found that the crude sex differences in long-term mortality after stroke were consistent across time periods and various regions of the world. Compared with men, women were 35% more likely to die by 1 year and 24% more likely to die by 5 years after stroke, consistent with the 25% greater case fatality for women at 1 month reported in a previous review.[1] Our meta-analysis of this large IPD data set demonstrated that the greater mortality after stroke in women was mostly attributable to their advanced age but that greater stroke severity,

greater prestroke functional limitations, and the presence of AF also explained the difference. The substantial sex difference in crude mortality rates was reversed after accounting for these confounding factors. This finding suggests that the sexdifference in mortality is largely because of biological and clinical differences between men and women present before or at the time of stroke while there was little evidence that differences in clinical management influenced the sex difference in mortality.

Age was the most important contributor to the sex difference in long-term mortality after stroke, but there was no statistical evidence of effect modification by age. This is potentially because of reduced functional capacity of brain cells to recover after neurological insults,[22] but it may also reflect other age-related factors such as comorbid disease, functional limitations, or social isolation.[23] Older age may also contribute to the worse stroke outcomes through reduced access to evidence-based stroke care,[24] particularly underinvestigation and undertreatment of carotid disease in the elderly with stroke.[25] Limited treatment of elderly people, who are predominantly women, may be appropriate given their health profile, potential contraindications to some treatments,[26] and preferences for end-of-life care. However, it is also possible that by building the evidence base for stroke prevention and clinical management in the elderly[27] and ensuring access to currently available evidence-based care for them, we could improve outcomes for men and women after stroke.

Women's greater mortality after stroke was attributable to their prestroke function, which is also closely related to their advanced age. There are sex differences in the specific causes of healthy life lost by age.[28] In men, they are mostly respiratory and cardiovascular conditions, whereas in women, they are most often musculoskeletal and mental disorders. It is possible that better chronic disease management targeting these conditions could improve function[29] and prevent frailty,[30] thereby improving the capacity to recover from stroke if it were to occur. Although we did not find evidence that social or economic factors influenced the sex differences in mortality, others have highlighted the influence of these factors across the life course on women's health.[31]

AF also contributed to the sex difference in long-term mortality after stroke. Women with AF have a greater risk of stroke than men, and AF-related stroke is more severe.[32] Management of AF in respect of proportions treated with anticoagulants[33] or catheter ablation[34] seems suboptimal for women compared with men. This observation is mostly biased by age with the widespread undertreatment of older patients with AF.[35] This highlights the need of better detection and treatment of AF in both elderly men and women before stroke.

We found that stroke severity was an important confounder. Although there were statistically significant sex differences in stroke severity in 6 out of 13 studies, the magnitude of differences between men and women were small. The differences in stroke severity between men and women are not well understood but may include sex differences in the localization of brain function[36] and women's greater susceptibility to subarachnoid hemorrhagic or cardioembolic strokes than men.[36] Stroke severity could be modified through better management of risk factors associated with stroke severity such as hypertension, AF, diabetes mellitus,[37] and better acute stroke management.[38]

Our meta-analysis revealed that the sex differences in mortality were greatest in the first 6 months after stroke, supporting previous research.[39] Evidence has shown that women with stroke suffer a disproportionately higher risk for death from cerebrovascular diseases, whereas men are more likely to die from cardiac disorders and other diseases.[40] The causes of death differed by the time intervals from the stroke,[41] but little is known about differences by sex and age group. Examination of causes of death by sex and age group could identify ways to reduce disparities between men and women in mortality, but such analyses were beyond the scope of our study. Further research is warranted to explore these differences after stroke and whether they are modifiable.

Table 3. Analyses of Heterogeneity in Sex Difference in Mortality at 1 y After Stroke Among 13 Population-Based Studies

		No. of Death (n/N)		Unadjusted				Adjusted*			
Variables of Interest	No. of Studies	Men	Women	I^2, %	P_H	MRR (95% CI)	$P_{subgroup}$	I^2, %	P_H	MRR (95% CI)	$P_{subgroup}$
Study-level characteristics†											
Geographic region											
Australasia	3	380/1339	584/1583	22.6	0.275	1.35 (1.10–1.65)	0.618	0.0	0.794	0.73 (0.57–0.94)	0.479
Europe	7	1684/5830	2297/6564	36.2	0.152	1.35 (1.21–1.50)		50.7	0.058	0.80 (0.68–0.94)	
South America	2	103/558	105/503	39.1	0.200	1.06 (0.60–1.86)		53.7	0.142	0.78 (0.38–1.59)	
Caribbean	1	76/285	113/295	NA	1.000	1.65 (1.19–2.29)		NA	1.000	1.15 (0.79–1.68)	
Income group											
HIC	10	2064/7169	2881/8147	26.4	0.201	1.34 (1.23–1.47)	0.948	32.0	0.152	0.79 (0.69–0.89)	0.186
LMIC‡	3	179/843	218/798	49.8	0.137	1.31 (0.92–1.86)		33.3	0.223	0.98 (0.69–1.39)	
Person-years											
Actual	9	1394/5450	1940/6060	20.1	0.264	1.35 (1.22–1.49)	0.904	0.0	0.471	0.74 (0.66–0.84)	0.023
Estimated	4	849/2562	1159/2885	50.8	0.107	1.37 (1.08–1.73)		24.2	0.266	0.97 (0.80–1.18)	
Death registries											
Yes	7	1042/3912	1482/4473	48.4	0.071	1.37 (1.16–1.62)	0.831	0.0	0.452	0.77 (0.68–0.88)	0.594
No	6	1201/4100	1617/4472	0.0	0.466	1.31 (1.20–1.43)		56.5	0.043	0.83 (0.68–1.02)	
Age difference§											
≤4.5 yr	5	934/3002	1149/3143	0.0	0.556	1.21 (1.09–1.34)	0.057	5.8	0.374	0.87 (0.75–1.01)	0.673
>4.5 yr	8	1309/5010	1950/5802	20.1	0.270	1.44 (1.30–1.59)		46.0	0.073	0.80 (0.67–0.95)	
Severity instrument											
NIHSS	7	687/2561	959/2731	15.5	0.311	1.41 (1.24–1.61)	0.198	0.0	0.639	0.78 (0.66–0.93)	0.345
Barthel Index	1	76/285	113/295	NA	1.000	1.65 (1.19–2.29)		NA	1.000	1.15 (0.79–1.68)	
Others‖	5	1480/5166	2027/5919	14.9	0.319	1.27 (1.15–1.39)		64.3	0.024	0.79 (0.64–0.97)	
SAH data											
Yes	11	2132/7666	2898/8481	28.5	0.174	1.32 (1.32–1.45)	0.210	38.5	0.093	0.79 (0.69–0.90)	0.166
No	2	111/346	201/464	0.0	0.971	1.63 (1.23–2.15)		0.0	0.766	1.08 (0.77–1.52)	
Sample size											
≤250	2	49/138	39/126	0.0	0.574	0.82 (0.50–1.32)	0.134	0.0	0.745	0.53 (0.29–0.96)	0.321
>250−1000	6	451/1730	643/1876	0.0	0.589	1.44 (1.26–1.65)		58.3	0.035	0.88 (0.67–1.16)	
>1000	5	1743/6144	2417/6943	40.9	0.149	1.33 (1.20–1.48)		0.0	0.422	0.82 (0.74–0.90)	
Participant-level characteristics#											
Stroke type	13	1551/6419	2076/6993	39.0	0.073	1.33 (1.20–1.49)	Ref	35.5	0.098	1.01 (0.91–1.12)	Ref
IS	13	443/1001	552/1035	26.2	0.179	1.35 (1.09–1.66)	0.894	51.2	0.017	1.22 (0.96–1.55)	0.940
ICH	10	87/241	137/358	8.3	0.365	1.11 (0.77–1.60)	0.318	78.0	<0.001	0.85 (0.40–1.80)	0.390
SAH	12	172/351	364/559	0.0	0.633	1.53 (1.19–1.98)	0.370	80.9	<0.001	0.91 (0.56–1.47)	0.449
Age group											
≤65	13	334/2295	243/1620	0.0	0.504	1.06 (0.89–1.27)	Ref	...			
>65–75	13	537/2350	446/1935	0.0	0.489	1.08 (1.00–1.17)	0.337	...			
>75	13	1372/3367	2410/5390	0.0	0.603	1.12 (0.99–1.28)	0.404	...			

Bold denotes statistically significant results. CI indicates confidence interval; HIC, high-income country; ICH, intracerebral hemorrhage; IS, ischemic stroke; LMIC, Low- and middle-income country; MRR, mortality rate ratio between women and men; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; P_H, P value of heterogeneity; $P_{subgroup}$, P value for subgroup analysis; Ref, reference group; SAH, subarachnoid hemorrhage.

*MRR adjusted for actual confounders, but estimates for stroke type adjusted for age only. †Estimates were performed using 2-stage method analysis. ‡Low- and middle-income country (LMIC) group included studies conducted in Martinique, Joinville, and Mãtao. §Indicates difference in median age at onset between women and men. ‖Other instruments including Glasgow Coma Scale and loss of consciousness. #Estimates were performed using multivariate random-effect meta-analyses from a pooled data set.

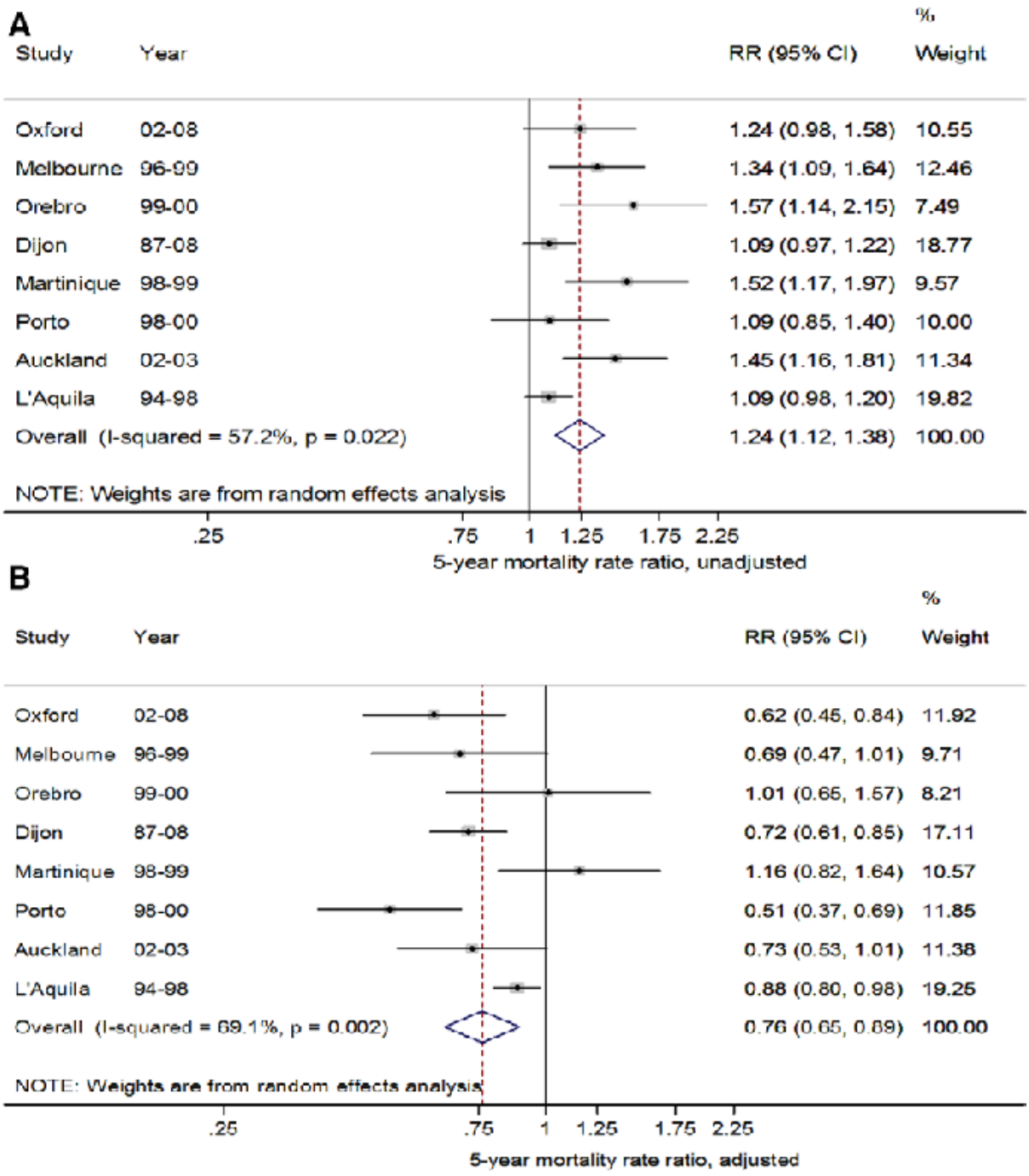

Figure 3. Mortality rate ratio (MRR) for women compared with men at 5 years after stroke in unadjusted (**top**) and adjusted (**bottom**) models from 8 studies combined using random-effects metaanalysis (n=11 368). Of note, each study was adjusted for different confounding factors as highlighted in Table 2. CI indicates confidence interval.

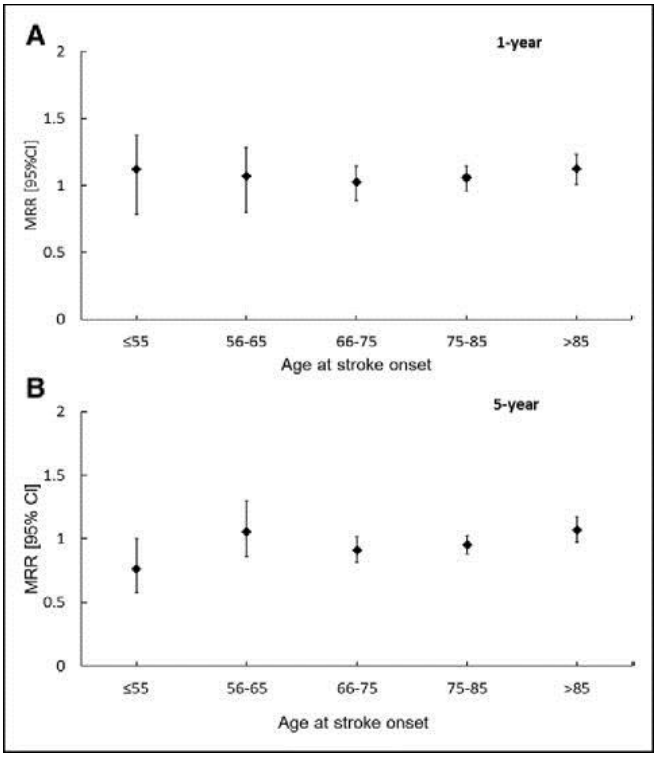

Figure 4. Unadjusted mortality rate ratio (MRR) with 95% confidence interval (CI) at 1 y (**top**) and 5 y (**bottom**) after stroke for women and men by age at stroke onset.

Limitations and Strengths

Several limitations need to be noted. Some potential confounding factors were not measured including hormonal, social, and some demographic factors, particularly race or ethnicity (only available in Joinville, Melbourne, and Matao). Missing data on confounding factors for some participants decreased the number of cases in fully adjusted analyses. Although we cannot discount the possibility of bias, sensitivity analyses that replaced missing data using multiple imputation did not markedly change the estimates, suggesting that the missing data did not greatly influence our results. The studies were mostly from high-income countries, so the results might not be generalizable to low- and middle-income countries. However, the magnitude of the sex differences and the contributing factors were the same for the studies in low- and middle-income countries as in high-income countries (Table 3). Among 9 ideal stroke cohorts for which long-term IPD were not provided, sex-specific findings from 3 studies showed similar differences in long-term crude mortality between women and men (Table I in the Data Supplement), suggesting that the results would not be greatly different had they been included. There were also limited data on management of stroke, poststroke recurrence, and depression. However, among studies with comprehensive data on these 3 factors, the sex difference in mortality was not attributable to any of these factors. The single exception was the Joinville study, for which carotid investigation explained part of the sex difference. In summary, we think that the absence of this data is unlikely to have greatly affected our results. The 5-year pooled estimates may have lower statistical power because few studies had follow-up into the long term, resulting in less than the recommended 10 studies for a meta-analysis.[42] There is also likely to be heterogeneity in the measurement of confounders across studies, particularly vascular risk factors. This may have resulted in measurement error in some studies and affected the adjusted estimates.

Despite these limitations, our study has several strengths. This is the first IPD meta-analysis to explore the magnitude and causes of sex difference in both short- and long-term mortality after stroke. The data came from high-quality and generalizable studies free of the limitations of hospital-based or convenience samples. We had a large number of participants, making this study adequately powered to test our hypotheses.

Conclusions

Our results indicate that women consistently have greater unadjusted long-term mortality after stroke than men. These differences were reversed after adjustment for confounders, indicating that greater mortality in women is explained by their greater age, greater stroke severity, worse prestroke function, and the presence of AF. The overwhelming importance of age in explaining the sex difference suggests that better stroke prevention and clinical management in the elderly is paramount to reduce the overall burden of stroke in men and women.

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Disclosures

None.

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