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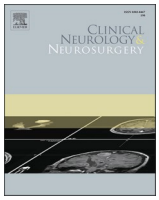

Review Article

Gender differences in mortality of hospitalised stroke patients. Systematic review and meta-analysis

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ABSTRACT

Objective: Gender differences in mortality after stroke remains unclear in the current literature. We therefore aimed to systematically review the gender differences in mortality up to five years after ischaemic (IS) or haemorrhagic stroke (HS) to address this evidence gap.

Methods: The literature was systematically searched using Ovid EMBASE, Ovid Medline, and Web of Science databases, from inception-November 2021. The quality of evidence was appraised using the CASP Cohort-study checklist. Unadjusted and adjusted odds and hazard ratios were meta-analysed, separately for IS and HS and a subgroup analysis of age-stratified mortality data was conducted.

Results: Forty-one studies were included (n = 8,128,700; mean-age 68.5 yrs; 47.1% female). 37 studies were included in meta-analysis (n = 8, 8008, 110). Compared to men, women who had an IS had lower mortality risk in-hospital (0.94; 95%CI 0.91–0.97), at one-month (0.87; 95%CI 0.77–0.98), 12-months (0.94; 95%CI 0.91–0.98) and five-years (0.93 95%CI 0.90–0.96). The subgroup analysis showed that this gender difference in mortality was present in women $\geq$ 70 years up to one-month post-IS (in-hospital: 0.94; 95%CI 0.91–0.97; one-month: 0.87; 95% CI 0.77–0.98), however, in women < 70 years this difference was no longer present.

Nevertheless, analysis of crude data showed women were at higher risk of mortality in-hospital, at 12-months and five-years (in-hospital: 1.05; 95%CI 1.03–1.07, 12-months: 1.10; 95%CI 1.06–1.14, five-years: 1.06; 95% CI 1.02–1.10). After HS, women had higher mortality risk in-hospital (1.03; 95%CI 1.01–1.04) however, no gender differences were found post-discharge.

Conclusion: The gender differences in post-stroke mortality differ by stroke type, age group and follow-up. Crude stroke mortality in women is higher than in men and this appears to be driven by pre-existing comorbidities. In adjusted models, women have a lower mortality risk following IS, independent of duration of follow-up. After HS, women had higher mortality in hospital however, no gender differences after hospital discharge were found.

1. Introduction

There is a growing emphasis on understanding the epidemiology of gender differences in outcomes following a stroke. Stroke remains a worldwide public health concern and is now recognised as the leading cause of long-term disability [1]. Women have higher incidence of stroke than men as well as worse stroke outcomes, which may be attributed to poorer pre-stroke function, older age, and higher prevalence of atrial fibrillation (AF) [2]. More recent literature has emphasised the major influence of confounders such as age, prevalence of AF and poorer premorbid status suggesting that women are less likely to die after a stroke compared to men after adjusting for confounders [3,4]. This is not uniformly observed across the geographical regions or ethnicities, with two large observational studies form North America suggesting that no gender differences exist in stroke mortality regardless of follow-up time-period [4,50,51]. In contrast, some studies from

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Southeast Asia and the Indian subcontinent reported higher stroke mortality in women compared to men [3,52,53].

Understanding the gender differences in stroke mortality is of paramount importance to epidemiologists, clinicians and healthcare industries as this understanding may form the basis for the development of gender-specific stroke prevention and management. As a result, this would improve outcomes of stroke in women and reduce its dominant burden on disability-adjusted-life-years (DALYs) worldwide.

We aimed to undertake a systematic review and meta-analysis to assess the gender differences in stroke-type specific mortality at multiple time points from admission through hospital discharge to five-years follow up. We also carried out an exploratory subgroup analysis stratified by age group (mean age <70 years and ≥70 years) to investigate whether age influences gender differences in stroke mortality.

2. Methods

A systematic review and meta-analysis of RCTs was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidance [5].

2.1. Search strategy

Two authors selected studies reporting gender differences in mortality of hospitalised stroke patients by independently carrying out a literature search of the following databases: Ovid MEDLINE, Ovid EMBASE and Web of Science, from inception to November 2021. Detailed search strategy is shown in Supplementary File 1. The articles searched were confined to English-language only. A manual search of reference lists of relevant reviews and their included studies was also performed.

2.2. Eligibility and study selection

The inclusion criteria for the studies included observational studies in English with adult participants > 18 years hospitalised due to stroke. Studies which stratified their data by stroke type (IS or HS) were analysed. Strokes of unspecified type (SUT) were also pooled for meta-analysis where appropriate. No limitations on geographical location were applied. Studies which analysed animal subjects or were conference abstracts or poster presentations were excluded. Similarly, studies reporting patients with non-stroke diagnoses such as those with transient ischaemic attacks (TIAs) were also excluded.

2.3. Data extraction

Two authors independently screened titles and abstracts [anonymous]. Potentially relevant studies were reviewed together to ascertain their eligibility. The final study selection and data extraction of the included studies were performed by the same two authors, then reviewed and verified by a third author. The extracted data included basic study characteristics including: mean age, proportion of females, country of origin, follow-up time frame and co-morbidities. Primary authors of all eligible studies were contacted to request any missing data.

2.4. Bias assessment

Bias assessment of the included studies was performed by two authors independently using the CASP Cohort tool (Table 2).

2.5. Data synthesis and outcome measure

Unadjusted and adjusted odds, hazard and risk ratios for in-hospital, one-month, 12-months and five-years mortality were pooled using the generic inverse variance method using fixed-effects model in RevMan 5.4 software. Study heterogeneity was assessed by evaluating the population characteristics and observed value of I^2, to determine which studies were appropriate to pool. Data with sufficient homogeneity were included in the meta-analysis. The primary outcome was risk of mortality in women compared to men as the baseline after IS, HS or SUT. The outcome of interest was assessed at the following follow-up time periods: in-hospital, up to one month, up to 12-months and up to five-years. Due to heterogeneity in risk reporting; odds ratio (OR), hazard ratio (HR) and risk ratios (RR) were all meta-analysed together and results expressed as 'risk', since mortality is a rare event. Descriptive and analytical epidemiological findings were synthesised from separate analyses of unadjusted (crude) and adjusted data, respectively. Whenever studies reported more than one result within an individual time bracket (e.g. three months and six months data) priority was given to the longer-term follow up (e.g. six months).

Mortality data for women and men stratified by age were collated where available to facilitate for an exploratory subgroup analysis stratified by age group. Mean age of study cohort was used where age-stratified data was not available. The age brackets: < 70 years and ≥ 70 years, were chosen based on literature suggesting that elderly patients over 70 years have a different aetiology and epidemiology of stroke mortality [53].

3. Results

3.1. Search results

Forty-one studies were included in the systematic review (n = 8,128,700; mean age 68.5 years; 47.1% female) and 36 studies were deemed appropriate for meta-analysis (n = 8,008,110). The PRISMA flowchart can be found in Supplementary Fig. 1. Justification for exclusion of papers (n = 4) is detailed in Supplementary Table 2.

3.2. Characteristics of included studies

The characteristics of the included studies are presented in Table 1.

Table 1
Characteristics of included studies.

Papers (N = 41)	Population (N = 8 128,700)	% female (Mean %= 47.1)	Mean female age (years) (Mean= 68.7 yrs)	Mean male age (yrs) (Mean= 68.2 yrs)	Region	Time points for mortality	Co-morbidities
Bonkhoff, 2021	761,106	48.0	75.3	69.4	Germany	In-hospital mortality	Age, diabetes mellitus (DM), hypertension (HTN), atrial fibrillation (AF), ischaemic heart disease (IHD), previous stroke, hypercholesterolaemia (HL), stroke severity using NIHSS scale and pre-stroke functional status
Eriksson, 2021	335,183	48.3	78.1	73.3	Sweden	7, 28 and 90 days	Age, DM, smoking, HTN, AF, previous stroke
Irie, 2021	17,956	41.3	n/a	n/a	Japan	30 days	Age and stroke severity

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Table 1 (*continued*)

Papers (N = 41)	Population (N = 8 128,700)	% female (Mean %= 47.1)	Mean female age (years) (Mean= 68.7 yrs)	Mean male age (yrs) (Mean= 68.2 yrs)	Region	Time points for mortality	Co-morbidities
Phan, 2021	9441	46.0	78.8	72.0	Australasia	1 year	Age, stroke severity. Comorbidities: dementia, HTN, smoking, HL, AF, HF, renal disease, liver disease, COPD, DM and cancer
Uchida, 2019	2399	45.3	79.7	72.8	Japan	90 days	Age, past and current smoker, HTN, DM, AF, history of stroke, pre-modified Rankin scale (mRS), baseline NIHSS score, baseline blood glucose, baseline LDL cholesterol and baseline creatinine
Weber, 2019	1,112,570	48.9	74.0	74.0	Germany	In-hospital mortality	Not stated
James, 2017	192,826	48.9	75	67	USA and Canada	In-hospital mortality	Race, AF, transient ischaemic attack (TIA) or stroke, coronary artery disease (CAD), myocardial infarction (MI), carotid stenosis, DM, HTN, peripheral vascular disease (PVD), dyslipidemia, smoking, international normalised ratio (INR), glucose, systolic blood pressure (SBP), creatinine, prior anti-platelet and/or anti-coagulant use, region, number of beds and hospital type, annual intracerebral haemorrhage (ICH) volume, rural location, The Joint Commission Primary Stroke Center Status
Mapoure, 2017	818	44.4	62.3	58.4	Cameroon	In-hospital mortality	AF, DM, stroke history
Ong, 2017	4278	41.1	72.2	69.9	Taiwan	In-hospital mortality	AF, DM, stroke history
Renoux, 2017	2553	50.6	76.5	71.4	United Kingdom	1 year	Age, HTN, DM, angina, MI, PVD, CHF, prior TIA/stroke, HL, VHD, cancer, VTE, dementia, current and past smokers and migraine
Xing, 2017	1325	32.3	63.1	59.1	China	3, 12 and 36 months	HTN, AF, DM, stroke history
Hsieh, 2016	1196	42.5	66.3	62.2	Singapore	30 days	HTN, DM, HL
Dehlendorff, 2015	79,617	47.2	74.4	69.5	Denmark	7 and 30 days	HTN, AF, DM, stroke and alcohol history and intermittent arterial claudication
Li, 2015	810	44	> 75	> 75	China	12 and 36 months	Age, stroke type, HTN, AF, DM, dyslipidemia, stroke history, anaemia, HF, rehabilitation, chronic kidney disease (CKD)
Talebi, 2014	341	56.0	69.9	67.7	Iran	7 days	HTN, DM, HL, IHD
Zhou, 2014	615	35.8	63.5	62.7	China	3, 6 and 12 months	HTN, AF, HL
Denti, 2013	1993	49.5	76.9	71.4	Italy	1 month	Age, stroke severity and premorbid disability
Ganti, 2013	245	51	77	69	Worldwide	7 days	HTN, AF, DM, stroke and alcohol history
Koton, 2013	5034	45.4	73.3	68.7	Israel	In hospital mortality and 3 months	Age, prior disability, modified Rankin Scale, NIHSS score, prior stroke, CHD, previous acute coronary syndrome (ACS) or HF, HTN, DM, HL, AF, Dyslipidemia, IHD, cancer, PAD and smoking
Santalucia, 2013	367	48.2	77.2	72.3	Italy	In-hospital mortality	AF, HTN, dyslipidemia, DM, obesity, TIA, AF The results were adjusted for age alone.
Lewsey, 2012	157,639	55	74	69	Scotland	30 days	Admission and socioeconomic deprivation. Comorbidities: DM, cancer, respiratory disease, HF, PVD, AF, HTN, renal failure, CAD, rheumatic/ valvular heart disease, venous thromboembolism (VTE), depression, parkinsonism, dementia, falls and fractures and alcohol misuse.
Park, 2012	6635	42.7	70	64	Korea	In-hospital mortality	HTN, previous IHD and previous stroke
Olsen, 2012	26,818	48.5	73.9	68.9	Denmark	3 months	HTN, AF, DM, stroke and alcohol history and intermittent arterial claudication
Watila, 2012	91	33.0	55.6	56.2	Nigeria	30 days	HTN, AF, DM and Human immunodeficiency virus (HIV) infection
Wu, 2012	103,689	46.7	73.4	68.8	Hong Kong	30 days	Age, year of hospitalisation
DeVries, 2011	15,806	51.6	75	75	USA	30 days	AF, HF, CKD and anaemia
Ovbiagele, 2011	2,553,742	> 84	80.3	77.6	USA		Age, race, ethnicity, hospital region and location, stroke type and number of major procedures. Comorbidities: HF,

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Table 1 (*continued*)

Papers (N = 41)	Population (N = 8 128,700)	% female (Mean %= 47.1)	Mean female age (years) (Mean= 68.7 yrs)	Mean male age (yrs) (Mean= 68.2 yrs)	Region	Time points for mortality	Co-morbidities
						In-hospital mortality (2005–2006)	MI, chronic pulmonary disease, cerebrovascular disease, hemiplegia, paraplegia, dementia, DM, malignancy, metastatic solid tumour, liver disease, peptic ulcer disease, PVD, renal disease and acquired immune deficiency syndrome (AIDS)
Towfighi, 2011	2,537,097	47.5	35–64 (no mean stated)	35–64 (no mean stated)	USA	In-hospital mortality	HF, MI, PVD, AIDS, DM, chronic pulmonary disease, cerebrovascular disease, hemiplegia/paraplegia, dementia, malignancy, metastatic solid tumour, liver disease, peptic ulcer disease, connective tissue disease and renal disease
Martinez-Sanchez, 2010	310	41.3	41.1	42.1	Spain	In-hospital mortality	Migraine, HTN, HL
Olsen, 2010	40,155	48.1	74.5	69.7	Denmark	1 week, 1 and 3 months, 1 year	HTN and cardiovascular risk factors
Wiszniewska, 2010	2534	54.4	74.3	68.8	Poland	30 days	HTN, HF, AF, TIA, CAD, DM and alcohol abuse
Oh, 2009	18,634	43.4	68.4	63.4	Korea	25 months	HTN, HL, AF
Palnum, 2009	29,549	63.1	> 80	> 80	Denmark	30 and 90 days	Age, civil status, type of residence, stroke severity, AF, HTN, DM, intermittent claudication, Charlson comorbidity index score, smoking, and alcohol intake and hospital department.
Olsen, 2009	25,607	45.3	72.6	68.5	Denmark	1 week	HTN, AF, DM, stroke and alcohol history, smoking, intermittent claudication, and previous stroke
Sweileh, 2009	186	51.1	68.7	69.5	Palestine	In-hospital mortality	Hypertension, diabetes, congestive heart failure, atrial fibrillation, ischaemic heart disease, smoking, recurrent stroke attack, chronic kidney disease, obesity
Vaartjes, 2009	30,675	51.9	72.9	69.3	Netherlands	1 and 5 years	AF, DM, and stroke history
Olsen, 2007	39,484	48.0	75.3	70.3	Denmark	7, 30, 90, 150 days	Alcohol, smoking, diabetes, HTN, AF, Intermittent arterial claudication
Andersen, 2005	999	56.0	77.0	70.9	Denmark	1, 5 and 10 years	HTN, IHD, AF, other disabling disease
Kapral, 2004	3323	46.0	73	69	Canada	In-hospital and 6 months	Age, Charlson comorbidity index score (of comorbidities), level of consciousness, stroke type, CNS score, hospital consent rate, marital status and living situation. Comorbidities: previous stroke, DM, HT, smoking, HL, AF, MI, Dementia
Di Carlo, 2003	4499	50.2	74.5	69.2	Europe	48 h and 3 months	HTN, AF, DM
Vemmos, 2000	555	44.4	76.1	75.1	Greece	1 year	Age, smoker, HT, HL, alcohol, DM, TIA, AF, MI, angina, CHF and VHD

The mean age in women was 75.3 years and 69.4 years in men. Sample populations of the included studies were from various regions worldwide including Germany [3,6], Sweden [7], Denmark [8–14], Japan [4, 15], Australia [16], North America [17], United States [18–20], Canada [21], Cameroon [22], Taiwan [23], China [24–26], Hong Kong [27], Singapore [28], Iran [29], Italy [30,31], Israel [32], Scotland [33], United Kingdom [34], Korea [35,36], Nigeria [37], Spain [38], Poland [39], Palestine [40], Netherlands [41], Greece [42], Di Carlo Europe [43] and worldwide [44].

3.3. Quality appraisal

Forty studies were analysed using the CASP cohort study tool (Table 2). One study had no full-text available therefore quality appraisal was not feasible [4]. All studies clearly addressed a research question (100%). Thirty-seven studies recruited the study cohort appropriately (92.5%), although only 34 studies measured mortality accurately (85%). Confounding was a major limitation as 30 studies identified confounders poorly (75%). One study did not have any access to information on confounding [6]. Data reported were overall precise in 34 studies (85%), however attrition bias may have been introduced due to incomplete follow-up data in 13 studies (32.5%).

3.4. Results of meta-analysis

3.4.1. Ischaemic stroke (IS)

Fifteen studies reported data on IS-specific mortality between women and men. Compared to men, analysis of adjusted data (Table 3) showed that women had lower mortality risk after IS at all time points, from in-hospital (Risk 0.94; 95% CI 0.91–0.97, n = 793,976) to one month (Risk 0.87; 95% CI 0.77–0.98, n = 20,040), 12 months (Risk 0.94; 95% CI 0.91–0.98, n = 63,255) and five years (Risk 0.93 95% CI 0.90–0.96, n = 31, 485) (Fig. 1).

When analysing crude data, women were at a higher risk of in-hospital mortality (Risk 1.05; 95% CI 1.03–1.07, n = 903,223), up to 12 months (Risk 1.10; 95% CI 1.06–1.14, n = 81,889) and up to five years (Risk 1.06; 95% CI 1.02–1.10, n-50 119). In the immediate period after discharge and up to one-month post-IS, there was no gender difference in risk of mortality (Risk 1.12; 95% CI 0.98–1.27, n = 23,161).

Data from the subgroup analysis (Table 3) showed no gender difference in mortality in of women < 70 years after IS up to one-month from onset of stroke (in hospital, Risk 1.05; 0.69–1.60, n = 25,269; one month, Risk 1.41; 0.07–26.85, n = 91), however, women ≥ 70 years had lower mortality risk compared to men (in hospital, Risk 0.94; 0.91–0.97, n = 768,707; one month, Risk 0.87; 0.77–0.98, n = 19,949).

Table 2
CASP quality assessment tool.

Question assessed (Success rate)	Di Carlo, 2003	Olsen, 2010	Denti, 2013	Santalucia, 2013	Andersen, 2005	DeVries 2013	Olsen 2012	Wiszniewska, 2011	Yang, 2004	Watila, 2012	Olsen, 2008	Oh, 2009	Vaartjes, 2009	Martinez-Sanchez, 2010	Wu, 2011	Renoux, 2017	Lewsey, 2012	Palnum, 2009	Vemmos, [illegible]	Eriksson, 2021
1. Did the study address a clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the cohort recruited in an acceptable way? (92.5%)	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the exposure accurately measured to minimise bias? (85%)	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y
4. Was the outcome accurately measured to minimise bias? (100%)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5a. Have the authors identified all important confounding factors? (25%)	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	Y	N	Y
b. Have they taken account of the confounding factors in the design and/or analysis? (47.5%)	Y	Y	Y	N	N	N	Y	N	N	Y	Y	N	N	N	N	Y	N	Y	N	Y
6a. Was the follow up of subjects complete enough? (67.5%)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	N
b. Was the follow up of subjects long enough? (70%)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	N
7.Are the results clearly presented? (97.5%) (clearly presented – Y/N)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Are the results precise? (85%)	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
9. Can the results be applied to the general population? (80%)	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total (/11):	9	10	10	4	8	8	10	9	9	8	10	9	8	10	8	9	8	9	7	9

	Barker-Collo, 2015	Mapoure, 2017	Kapral, 2005	Ovbiagele, 2011	Hsieh, 2016	James, 2017	Koton, 2013	Park, 2013	Li, 2015	Towfighi, 2011	Sharma, 2002	Zhou, 2014	Talebi, 2014	Sweileh, 2009	Xing, 2017	Dehlendorff, 2015	Weber, 2019	Bonkhoff, 2021	Irie, 2021	Uchida, 2019	Phan, 2021
1. Did the study address a clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y
2. Was the cohort recruited in an acceptable way?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y
3. Was the exposure accurately measured to minimise bias?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	-	Y	Y
4. Was the outcome accurately measured to minimise bias?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y
5a. Have the authors identified all important confounding factors?	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	N	Y	-	N	Y
b. Have they taken account of the confounding factors in the design and/or analysis?	Y	N	Y	Y	N	Y	Y	N	N	N	N	N	N	N	Y	Y	N	Y	-	Y	Y
6a. Was the follow up of subjects complete enough?	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	N	-	N	N
b. Was the follow up of subjects long enough?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	N	N	-	N	N
7.Are the results clearly presented? (clearly presented – Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y
8. Are the results precise?	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	-	Y	Y
9. Can the results be applied to the general population?	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	Y	-	Y	Y
Total (/11):	9	8	11	11	5	10	10	6	8	9	6	9	7	6	11	11	5	9	-	8	9

*Y=1 and N=0

*Y= 1 and N = 0

Table 3
Summary table of meta-analysis and subgroup analysis results illustrating risk of mortality in women, compared to men, up to one-month, 12-months and five-years after ischaemic (IS) and haemorrhagic stroke (HS) and stroke of unspecified type (SUT); Risk and corresponding 95% confidence intervals (CI) reported.

Summary results from meta-analysis								
	Unadjusted mortality (Risk, 95% CI, sample size)				Adjusted mortality (Risk, 95% CI, sample size)			
	In hospital	1-month	12-months	5-years	In hospital	1-month	12-months	5-years
IS	1.05 (1.03, 1.07) N = 1,903,223	1.12 (0.98, 1.27) N = 23,161	1.10 (1.06, 1.14) N = 81,889	1.06 (1.02, 1.10) N = 50,119	0.94 (0.91, 0.97) N = 793,976	0.87 (0.77, 0.98) N = 20,040	0.94 (0.91, 0.98) N = 63,255	0.93 (0.90, 0.96) N = 31,485
HS	1.04 (1.03, 1.05)[σ] N = 192,826	1.09 (0.81, 1.47) N = 1441	95. (0.93, 1.07) N = 32,615	95. (0.94, 1.07) N = 32,000	1.03 (1.01, 1.04)[σ] N = 192,826	1.09 (0.70, 1.72) N = 1441	0.97 (0.90, 1.04) N = 31,290	0.96 (0.90, 1.02)[∫] N = 30,675
SUT	0.98 (0.95, 1.01) N = 5,120,945	1.11 (1.08, 1.15) N = 282,445	1.11 (1.06, 1.15) N = 114,647	1.02 (0.79, 1.32) ϕ N = 999	1.02 (1.00, 1.04) N = 5,254,065	0.98 (0.94, 1.04) N = 202,994	0.95 (0.90, 0.99) N = 120,145	N/A
Subgroup analysis by age group								
	Unadjusted mortality (Risk, 95% CI, sample size)				Adjusted mortality (Risk, 95% CI, sample size)			
	Mean Age	In hospital	1-month	12-months	5-years	In hospital	1-month	12-months	5-years
IS	**< 70**	1.22 (1.03, 1.45) N = 25,269	1.14 (0.98, 1.32) N = 18,634	1.11 (1.01, 1.21) N = 49,309	1.07 (1.00, 1.15) N = 49,309	1.05 (0.69, 1.60) N = 25,269	1.41 (0.07, 26.85) N = 91	N/A	N/A
	≥ 70	1.05 (1.03, 1.07) N = 1,907,954	1.07 (0.83, 1.38) N = 4527	1.03 (0.99, 1.06) N = 63,255	0.98 (0.96, 1.01) N = 31,485	0.94 (0.91, 0.97) N = 768,707	0.87 (0.77, 0.98) N = 19,949	N/A	N/A
HS	**< 70**	N/A	1.08 (0.79, 1.46) N = 1196	1.06 (0.83, 1.36) N = 49,309	1.63 (1.20, 2.22) N = 32,000	N/A	1.09 (0.69, 1.71) N = 1196	1.15 (0.56, 2.37) N = 615	N/A
	≥ 70	N/A	1.30 (0.41, 4.14) N = 245	0.96 (0.88, 1.05) N = 63,255	0.98 (0.93, 1.03) N = 30,675	N/A	1.62 (0.06, 42.79) N = 245	0.96 (0.90, 1.03) N = 30,675	N/A
SUT	**< 70**	0.99 (0.96, 1.02) N = 133,238	0.95 (0.82, 1.09) N = 5,090,839	1.03 (0.85, 1.23) N = 29,549	N/A	0.98 (0.96, 1.01) N = 187,188	1.03 (0.94, 1.13) N = 5,248,664	0.96 (0.79, 1.16) N = 29,549	N/A
	≥ 70	0.96 (0.92, 1.00) N = 197,188	1.11 (1.08, 1.15) N = 2,583,848	1.11 (1.06, 1.15) N = 84,527	N/A	1.03 (1.01, 1.05) N = 202,994	0.98 (0.94, 1.04) N = 2,716,782	0.95 (0.90, 0.99) N = 79,029	N/A

*IS= Ischaemic stroke, HS= Haemorrhagic stroke, SUT= Stroke of unspecified type, CI= confidence intervals.
[σ]Results available from one study only, James et al. [17].
[ϕ]Results from one study only, Andersen et al. [14].
[∫]Results from one study only, Vaartjes et al. [41].

No adjusted data were available beyond one-month post-IS. Crude data showed that women < 70 years were at higher risk of mortality post-IS up to five years after stroke (in hospital, Risk 1.22; 1.03–1.45, n = 25,269; 12 months Risk 1.11; 1.01–1.21, n = 49, 309; five years, Risk 1.07; 1.00–1.15, n = 49,309). However, apart from the in-hospital period, there was no difference in women ≥ 70 years, compared to men, in mortality up to five years after IS.

3.5. Haemorrhagic stroke (HS)

Six studies reported data on HS-specific mortality between women and men. The analysis of data adjusted for confounding variables (detailed in Supplementary Table 1) showed that women had higher risk of mortality in hospital (Risk 1.03; 95% CI 1.01–1.04, n = 192,826) yet no difference was found after discharge and up to five years following discharge. Data from meta-analysis of unadjusted estimates yielded a similar result (in-hospital: Risk 1.04; 95% CI 1.03–1.05, n = 192,826) (Fig. 2).

Data from the subgroup analysis were consistent with adjusted and crude results from the primary analyses. The data show that there was no gender difference in mortality after HS in both the < 70 years and ≥ 70 years groups. No in-hospital data were available for HS patients to compare with the primary analysis findings.

3.6. Stroke of unspecified type (SUT)

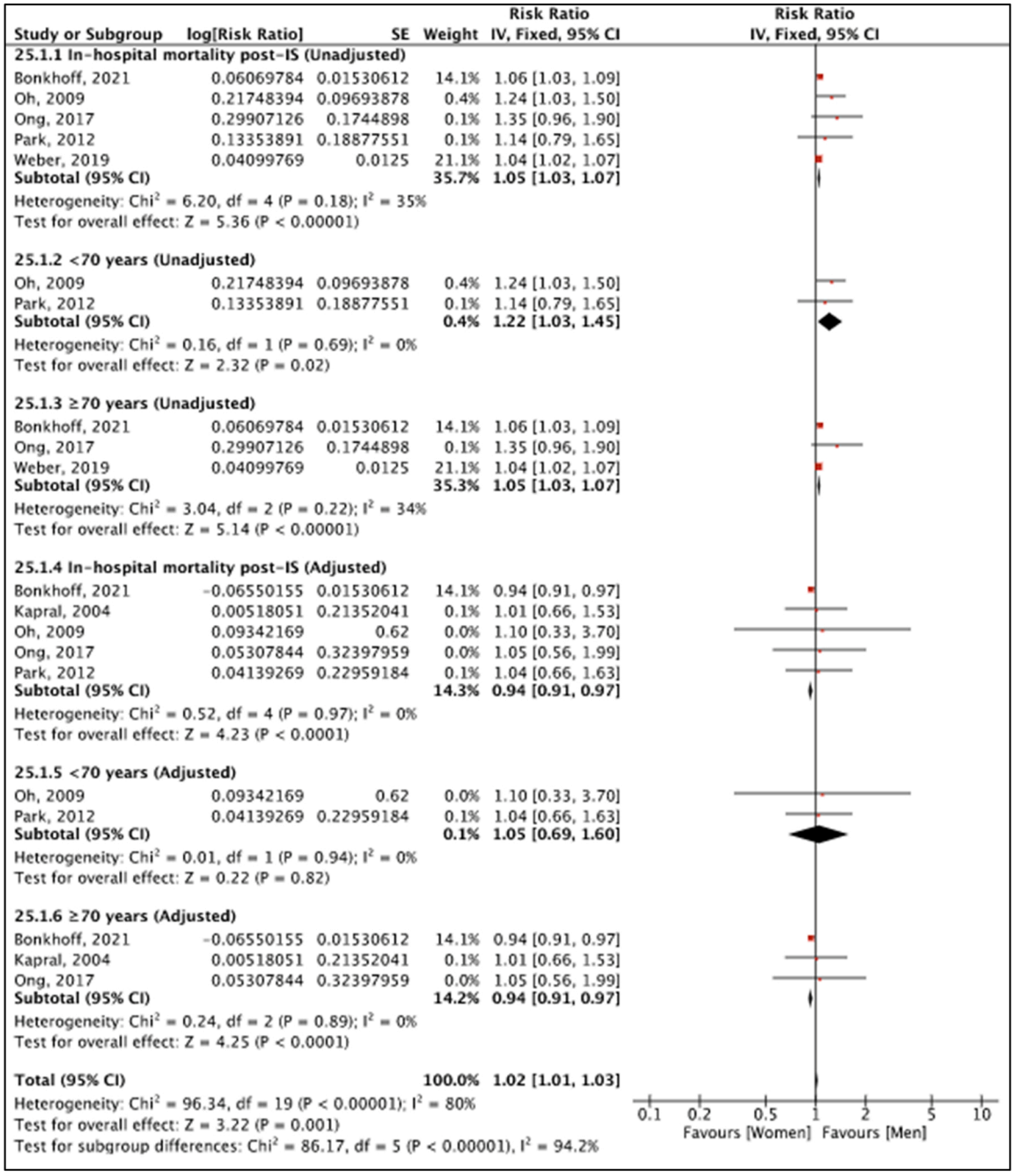
Seventeen studies reported on mortality after stroke without specifying stroke type. Analysis of adjusted data (Table 3) showed higher mortality risk in women during the in-hospital period (Risk 1.02; 95% CI 1.00–1.04, n = 5,254,065), however, lower risk after one-month (up to 12-months) (Risk 0.95; 95% CI 0.90–0.99, n = 120,145) post-SUT (Fig. 3). No gender difference was found in the first month after discharge (Risk 0.98; 95% CI: 0.94–1.04, n = 202,99).

On the other hand, meta-analysis of crude data showed no gender difference in risk of mortality was found in-hospital (Risk 0.98; 95% CI 0.95–1.01, n = 5,120,945), however higher mortality risk up-to one-month (Risk 1.11; 95% CI 1.06–1.15, n = 114,647) and 12-months post-SUT (Risk 1.11; 95% CI 1.06–1.15, n = 114,64).

Results from the subgroup analysis of patients after SUT were consistent with the primary analysis for subjects ≥ 70 years. Compared to men, women in this group had higher mortality in-hospital (Risk 1.03; 1.01–1.05, n = 202,994) however, lower mortality after one-month post-SUT (Risk 0.95; 0.90–0.99, n = 79,029). In women < 70 years, there was no difference in mortality from stroke onset through to 12-months. No adjusted data were available beyond 12-months follow-up post-SUT.

Crude data showed no gender difference after SUT in the < 70 years age group. On the other hand, consistent with the primary analysis,

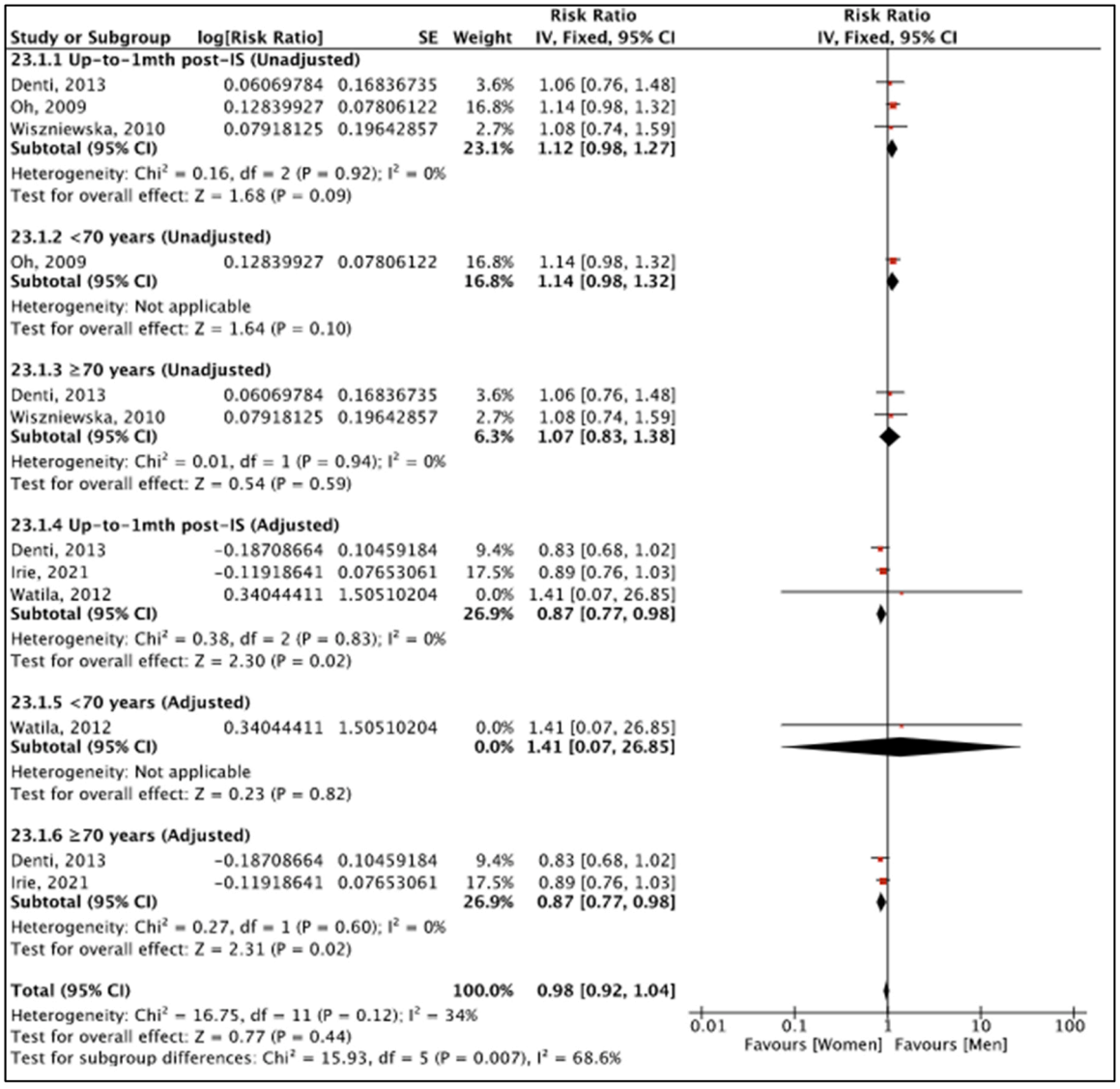
A) In-hospital mortality



*IS= Ischaemic stroke

Fig. 1. Forest plots of meta-analysis and subgroup analysis results for mortality in women, compared to men, after ischaemic stroke (IS); Risk and corresponding 95% confidence intervals (CI) reported.

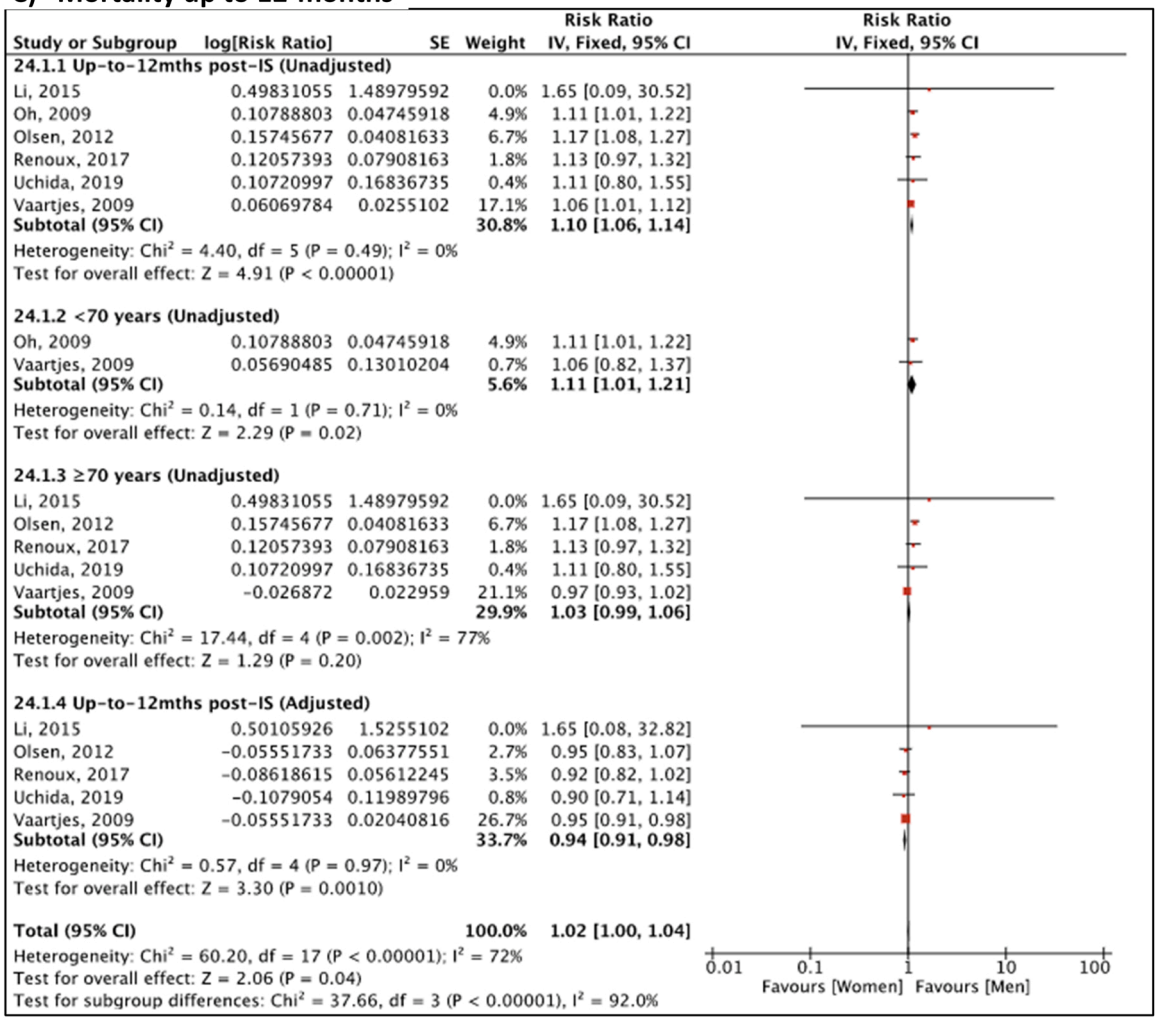
B) Mortality up to one-month



*IS= Ischaemic stroke

Fig. 1. (*continued*).

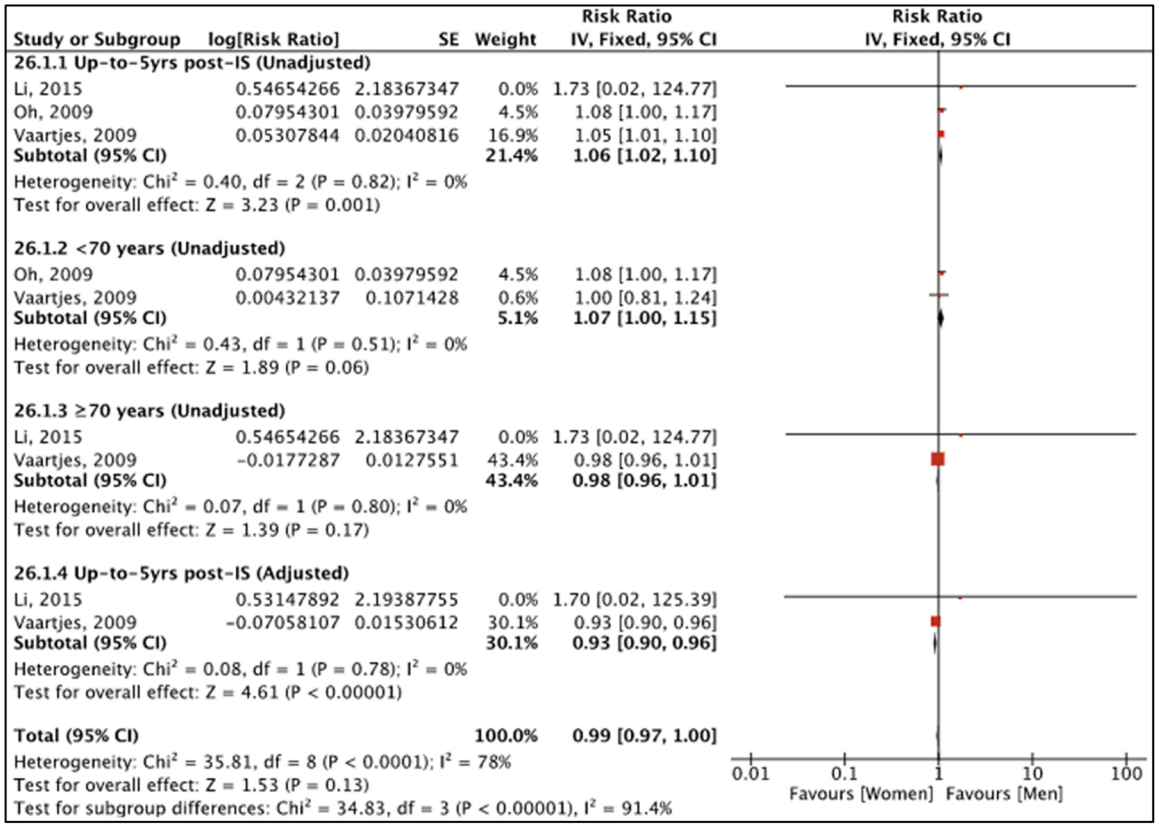
C) Mortality up to 12-months



*IS= Ischaemic stroke

Fig. 1. (*continued*).

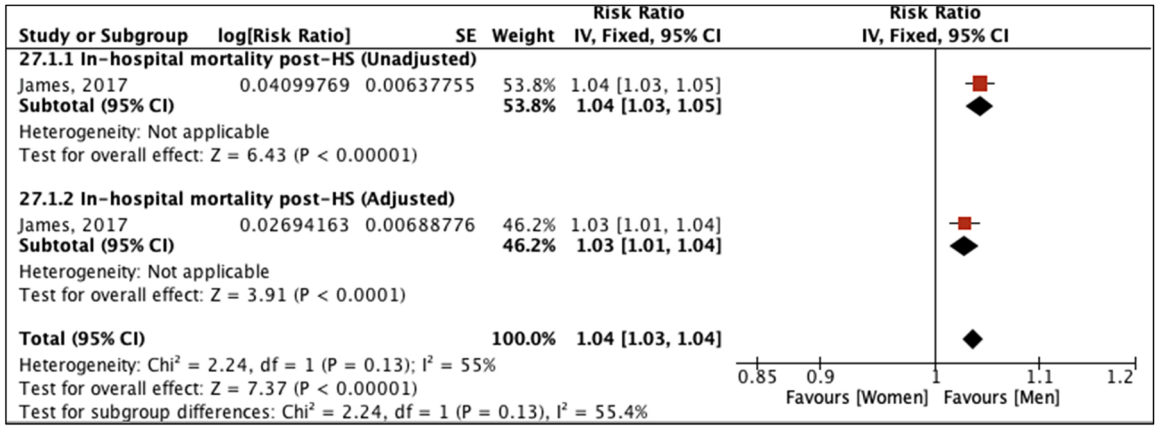
D) Mortality up to five-years



*IS= Ischaemic stroke

Fig. 1. (*continued*).

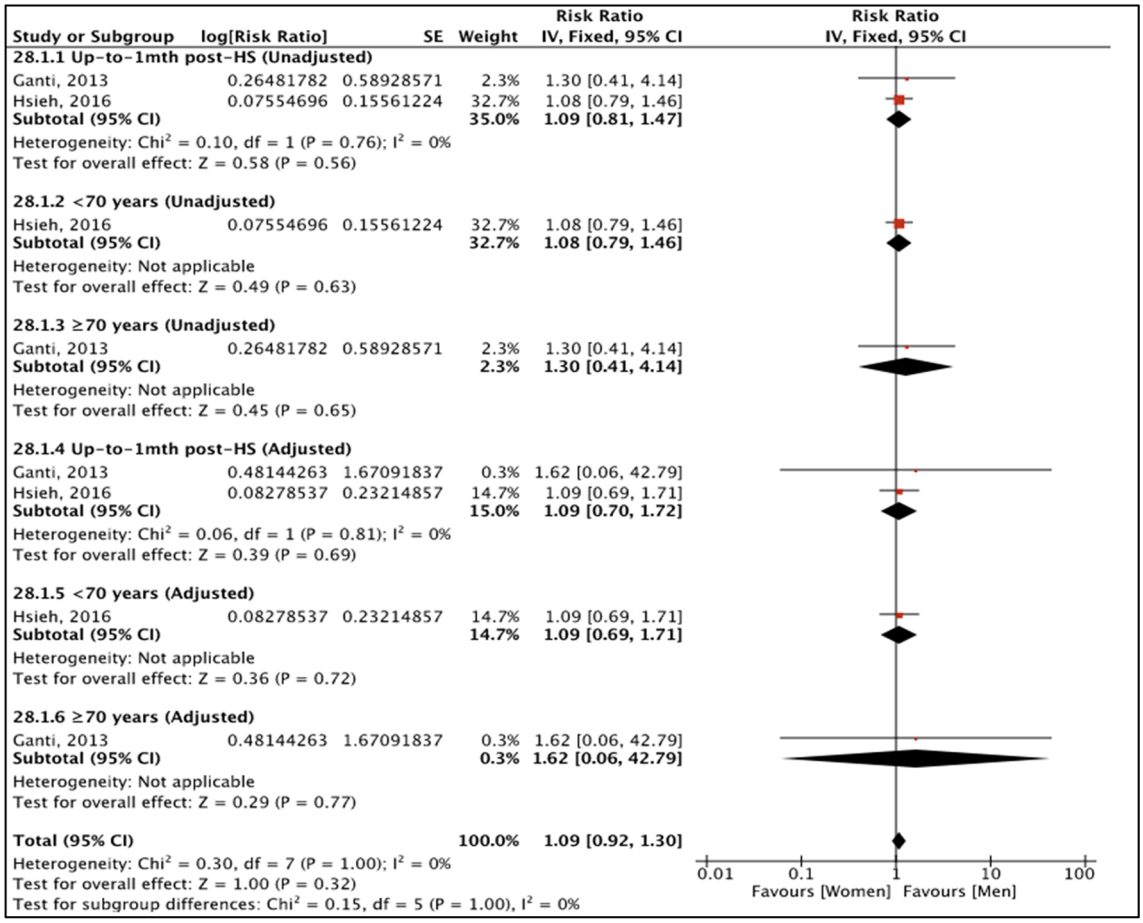
A) In-hospital mortality



*HS= Haemorrhagic stroke

**Results available from one study only; James et al., 2017.

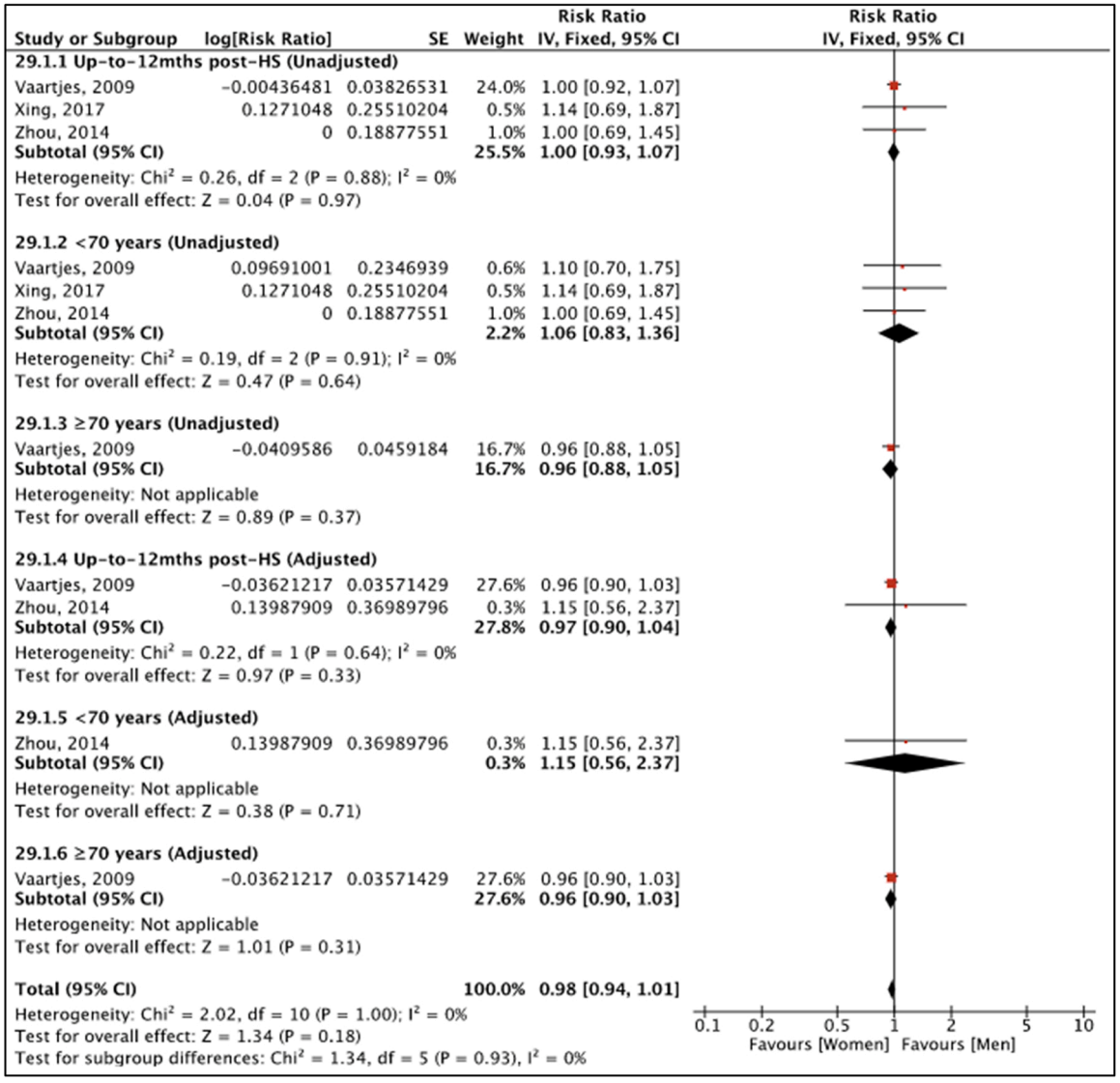
B) Mortality up to one-month



*HS= Haemorrhagic stroke

Fig. 2. Forest plots of meta-analysis and subgroup analysis results for mortality in women, compared to men, after haemorrhagic stroke (HS); Risk and corresponding 95% confidence intervals (CI) reported.

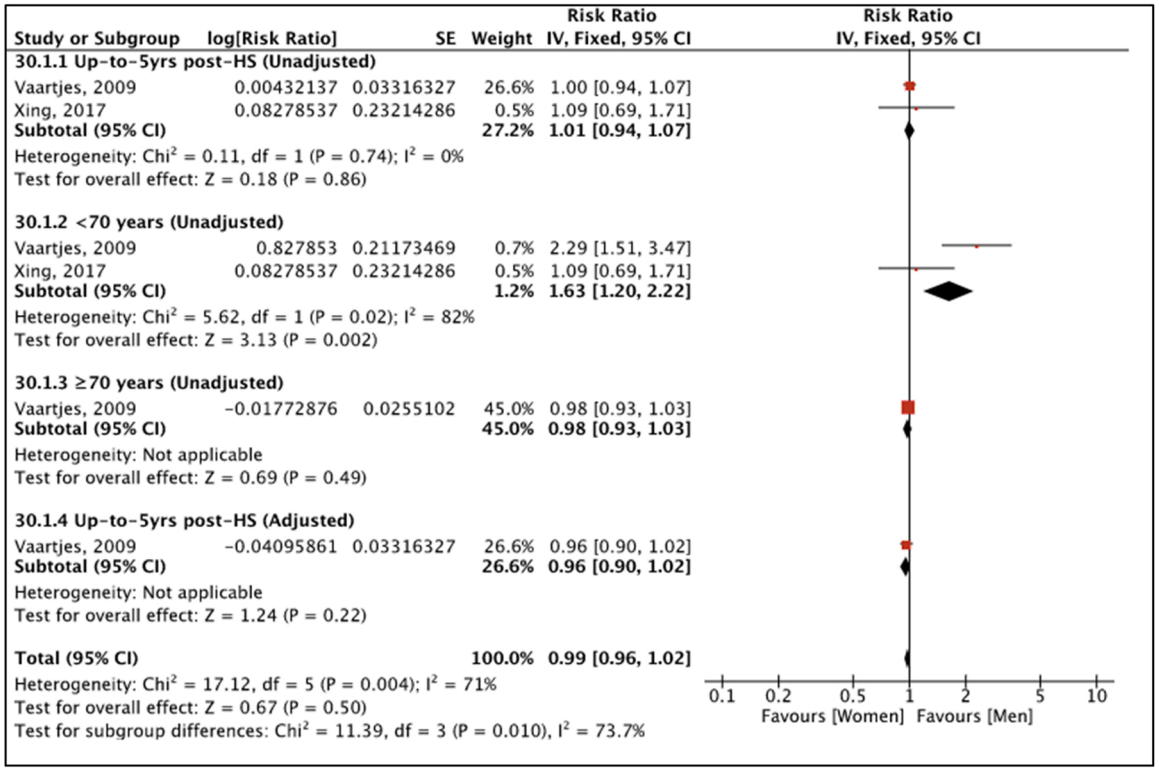
C) Mortality up to 12-months



*HS= Haemorrhagic stroke

Fig. 2. (*continued*).

D) Mortality up to five-years

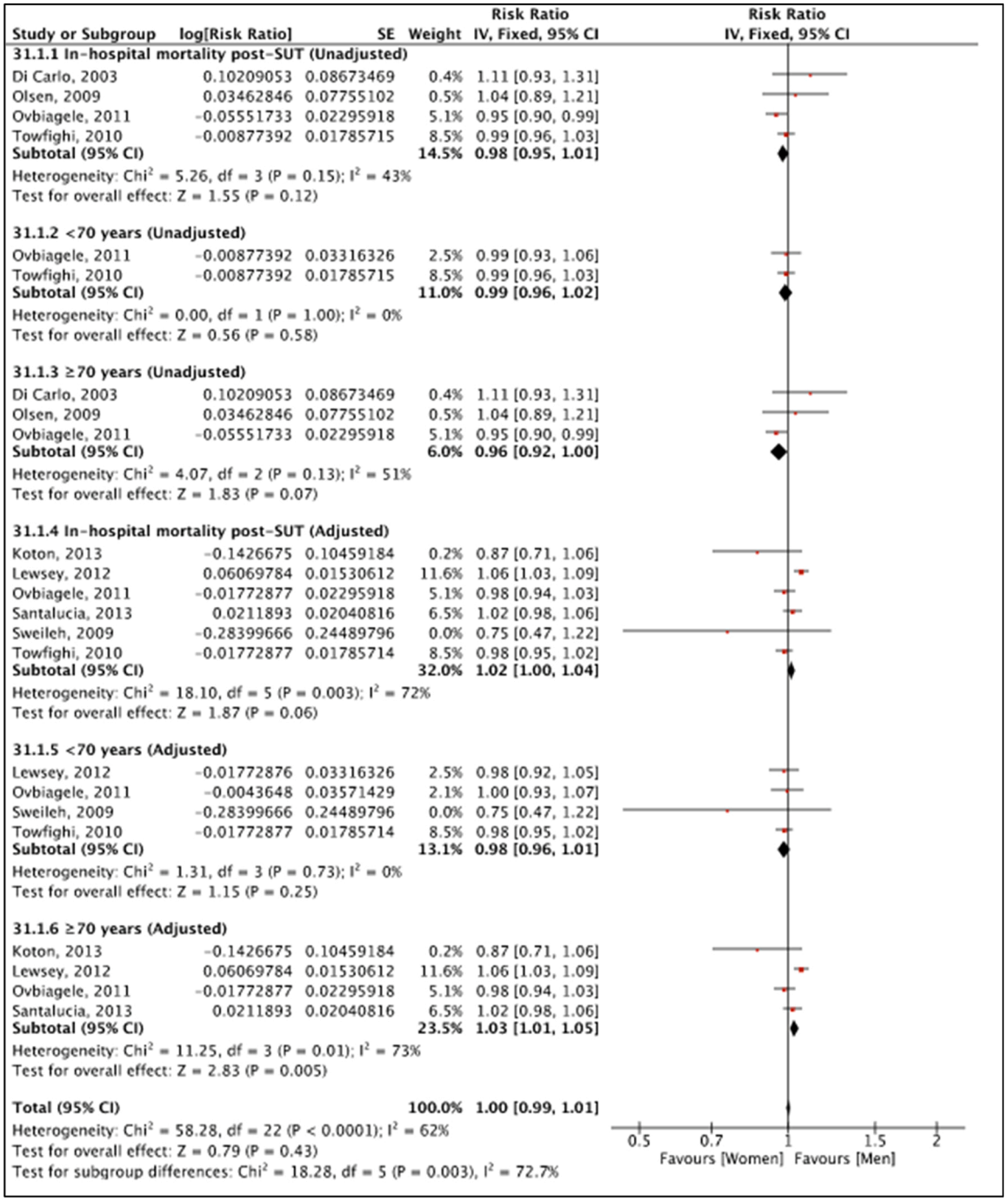


*HS= Haemorrhagic stroke

**Adjusted results available from one study only; Vaartjes et al., 2009

Fig. 2. (*continued*).

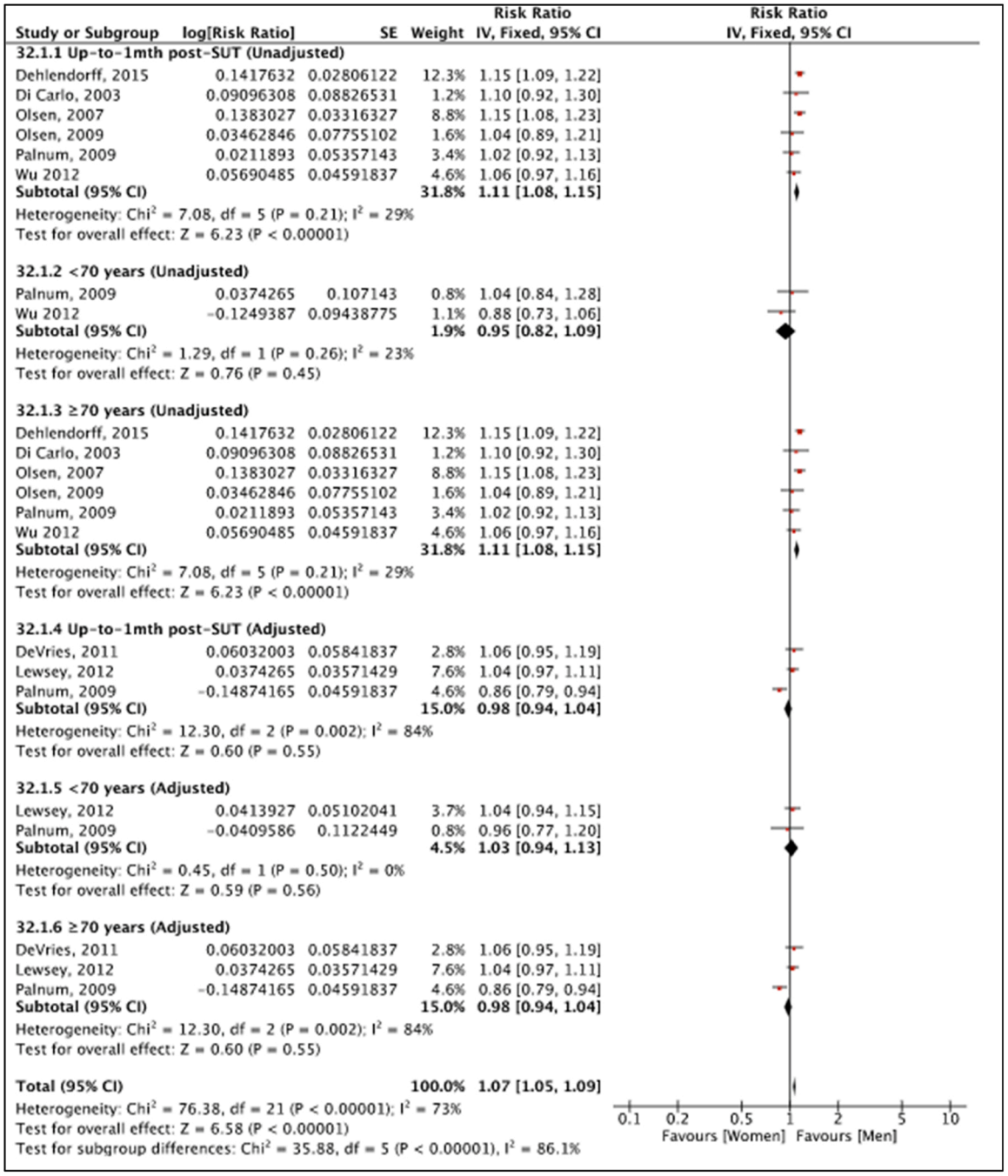
A) In-hospital mortality



*SUT= Stroke of unspecified type

Fig. 3. Forest plots of meta-analysis and subgroup analysis results for mortality in women, compared to men, after stroke of unspecified type (SUT); Risk and corresponding 95% confidence intervals (CI) reported.

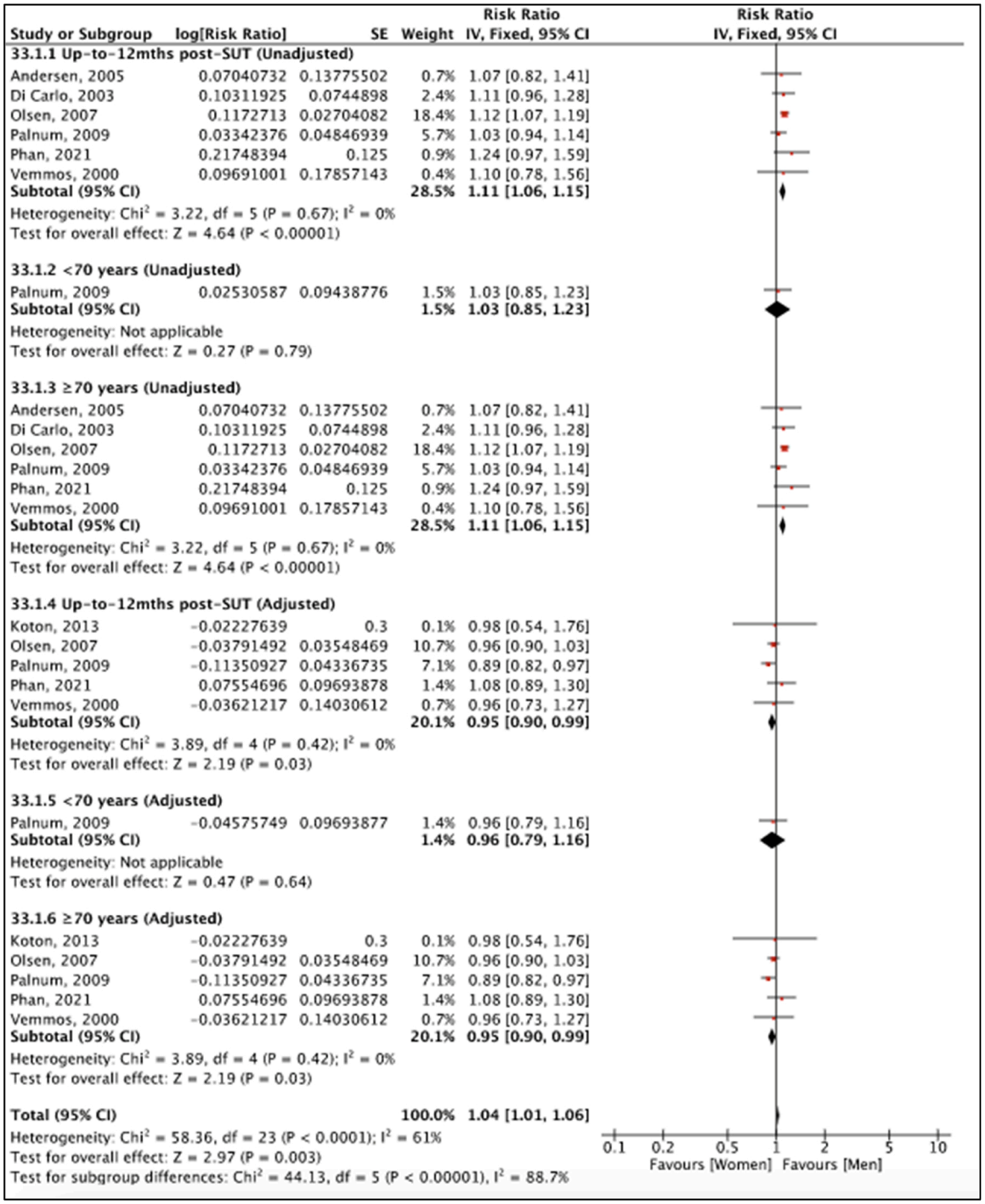
B) Mortality up to one-month



*SUT= Stroke of unspecified type

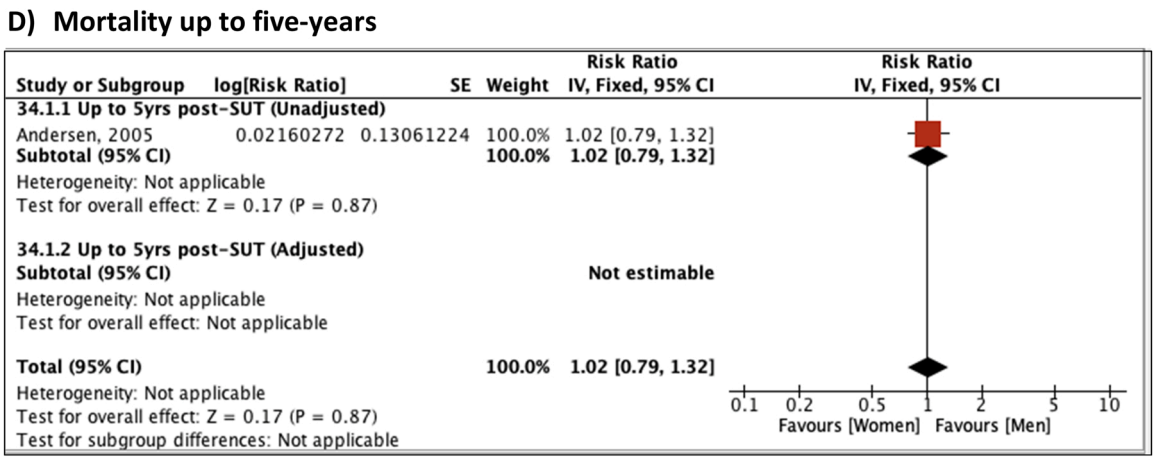
Fig. 3. (*continued*).

C) Mortality up to 12-months



*SUT= Stroke of unspecified type

Fig. 3. (*continued*).



*SUT= Stroke of unspecified type

**Results available from one study only; Andersen et al., 2005. No data available for adjusted data on up to five-years mortality after stroke of unspecified type (SUT).

Fig. 3. (*continued*).

women ≥ 70 years had higher mortality after one and 12-months post-SUT (one-month: Risk 0.96; 0.92–1.00, n = 2,583,848; 12 months: Risk 1.11; 1.06, 1.15, n = 84,527).

4. Discussion

The results of our systematic review provide robust evidence that there are important gender differences in medium- and long-term mortality after stroke, which are dependent on stroke type and length of follow-up. After ischaemic stroke, women consistently had lower risk of mortality than men, ranging from 6% in-hospital to 13% lower risk by one-month and 7% by five years, after adjusting for important confounders, such as: age, history of previous strokes, hypertension, hyperlipidaemia, atrial fibrillation, ischaemic heart disease. Nevertheless, meta-analysis of unadjusted estimates showed up to 10% higher mortality post-IS in women at all follow-up points, suggesting that this higher raw mortality is mostly explained by gender-based characteristics of female stroke patients, such as higher age at stroke onset and prevalence of comorbidities.

The results of our age-stratified subgroup analysis show that older women (≥70 years) had a lower mortality after IS compared to men, however this gender difference was not apparent in younger women (<70 years). Unadjusted data appears to unmask the higher mortality in women compared to men regardless of age group. These findings support current literature which suggests that age-adjusted data may obscure the complex relationship of sex differences at specific ages [2].

A retrospective analysis of participants from the International Stroke Trial (IST) showed a higher raw mortality 24.5% in women (24.5%) compared to in men (19.3%) at six-months [45]. However, when they adjusted for age, stroke severity, atrial fibrillation, and blood pressure, women had lower mortality at six months (OR 0.90; 95% CI 0.83–0.98). Other previous studies also yielded similar findings of higher post-stroke raw mortality in women, but lower mortality after adjustment for relevant confounders [2,3].

Two important conclusions pertaining to gender equity in stroke care can be drawn from this study. Firstly, the higher stroke mortality in women is unlikely to be driven independently by intrinsic biological differences in stroke pathophysiology, but largely by age as well as co-morbid disease burden. Thereby, it is essential to recognise that the differences in raw mortality seen in routine clinical practice can be reduced by changes in clinical practice, namely; better primary prevention of comorbidities including cardiovascular disease and smoking cessation as well as more tailored clinical management of these comorbidities in women.

In terms of HS, it can be concluded that beyond discharge, no gender difference appears between the risks of mortality of women and men after a HS, irrespective of confounders or age group. Our data is concordant with that of one study which concluded no gender differences in unadjusted or adjusted risk of mortality risk irrespective of confounding (OR 1.19; 95% CI 0.92–1.53 and OR 0.188; 95% CI 0.84–1.75), respectively [28]. Nevertheless, more studies assessing risk of mortality in women compared to men post-HS are crucial for more robust evidence.

Cellular-level investigations into the role of cell-death pathways and inflammatory signalling cascades, influenced by the effects of oestrogen in women, appear to provide some basis to the gender-specific biology of ischaemia in IS. One study highlighted that the neuroprotection offered by higher levels of oestrogen in women as well as slowing large artery atherosclerosis build-up [46]. Although these studies suggest women have less severe strokes, it is important to highlight that lack of adjustment for stroke subtype, severity and comorbidities is an important notable limitation of these studies.

Geographical, racial and socio-economic factors are also important to highlight as potential confounders to differences in stroke mortality between women and men. Excess stroke mortality in women is of particular concern in Asian populations, where there are clear differences in patient biology and epidemiology documented in the literature compared to Western populations [19,47,48]. The prevalence of intracranial plaques causing IS has been reported as 38.5% in Caucasians compared to 69.1% in Chinese populations (p = 0.02) [19]. Large racial-ethnic disparities in Black and Hispanic individuals compared to white individuals have also been highlighted in the literature [51]. In these populations, the higher rates of stroke mortality, particularly in women, were due to key geopolitical and economic factors including: poorer health literacy, a large

Table 4
Studies included in meta-analysis of gender differences in stroke mortality; by geographical region.

Region	No. of studies	Name of study	No. of participants (%) Total= 8, 008, 110
USA and Canada	5	James, 2017 DeVries, 2011 Ovbiagele, 2011 Towfighi, 2011 Kapral, 2004	5, 302, 794 (66.2%)
Europe	16	Bonkhoff, 2021 Eriksson, 2021 Weber, 2019 Renoux, 2017 Denti, 2013 Santalucia, 2013 Lewsey, 2012 Olsen, 2012 Wiszniewska, 2010 Palnum, 2009 Olsen, 2009 Vaartjes, 2009 Olsen, 2007 Andersen, 2005 Di Carlo, 2003 Vemmos, 2000	2, 532, 686 (31.6%)
East Asia	10	Irie, 2021 Uchida, 2021 Ong, 2017 Xing, 2017 Hsieh, 2016 Li, 2015 Zhou, 2014 Park, 2012 Wu, 2012 Oh, 2009	157, 537 (1.97%)
Australia	1	Phan, 2021	9441 (0.12%)
Africa	1	Watila, 2012	91 (0.0011%)
Middle East	2	Sweileh, 2009 Talebi, 2014	527 (0.0066%)
Near East	1	Koton, 2013	5034 (0.063%)
Worldwide	1	Ganti, 2013	245 (0.0031%)

gender pay gap resulting in lower income and poorer healthcare affordability in women, differences in socio-economic status and differing beliefs [49,53] in African countries, unique barriers to the provision of quality stroke care include a shortage of medical transport, specialist staff and well-equipped stroke units, economic recessions resulting in inability to support the cost of brain imaging, thrombolysis or out-patient rehabilitation. These reasons are responsible for inter-continental disparities in stroke care and outcomes [51].

Due to the wide distribution of the included studies across the globe, analysing data from specific regions by time period or stroke type was not possible due to insufficient data for pooling (Table 5). In addition, as shown in Table 4, the Western hemisphere represents 98% (n = 7, 835,

Table 5
Names and population of studies for age-stratified subgroup analysis of gender differences in stroke mortality: mean age < 70 years and >or= 70 years.

Follow-up time period	**Ischaemic stroke**			
	< 70 years		**≥ 70 years**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
In-hospital mortality	Oh, 2009 Park, 2012	Oh, 2009 Park, 2012	Bonkhoff, 2021 Weber, 2019 Ong, 2017	Bonkhoff, 2021 Kapral, 2004 Ong, 2017
No. of participants (N =)	N = 25,269	N = 25,269	N = 1,907,954	N = 768,707
Up to 1 month	Oh, 2009	Watila, 2012	Denti, 2013 Wiszniewskwa, 2010	Denti, 2013 Irie, 2021
No. of participants (N =)	N = 18,634	N = 91	N = 4527	N = 19,949
Up to 12 months	Oh, 2009 Vaartjes, 2009 *	–	Li, 2015 Olsen, 2012 Renoux, 2017 Uchida, 2019 Vaartjes, 2009 *	–
No. of participants (N =)	N = 49,309	–	N = 63,255	–
Up to 5 years	Oh, 2009 Vaartjes, 2009 *	–	Li, 2015 Vaartjes, 2009 *	–
No. of participants (N =)	N = 49,309	–	N = 31,485	–
Haemorrhagic stroke				
	< 70 years		**≥ 70 years**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**

(*continued on next page*)

Table 5 (*continued*)

In-hospital mortality	–	–	–	–
Up to 1 month	Hsieh, 2016	Hsieh, 2016	Ganti, 2013	Ganti, 2013
No. of participants (N =)	N = 1196	N = 1196	N = 245	N-245
Up to 12 months	Vaartjes, 2009 * Xing, 2017 Zhou, 2014	Zhou, 2014	Vaartjes, 2009 *	Vaartjes, 2009 *
No. of participants (N =)	N = 49,309	N = 615	N = 63,255	N = 30,675
Up to 5 years	Vaartjes, 2009 * Xing, 2017	–	Vaartjes, 2009 *	–
No. of participants (N =)	N = 32,000	–	N = 30,675	–
Stroke of unspecified type (SUT)				
	< 70 years		**≥ 70 years**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
In-hospital mortality	Palnum, 2009 * Wu, 2012 *	Lewsey, 2012 * Palnum, 2009 *	Lewsey, 2012 * Palnum, 2012 *	DeVries, 2011 Lewsey, 2012 * Palnum, 2009 *
No. of participants (N =)	N = 133,238	N = 187,188	N = 197,188	N = 202,994
Up to 1 month	Ovbiagele, 2011 * Towfighi, 2010	Lewsey, 2012 * Ovbiagele, 2011 * Sweileh, 2009 Towfighi, 2010	Di Carlo, 2003 Olsen, 2009 Ovbiagele, 2011 *	Koton, 2013 Lewsey, 2012 * Ovbiagele, 2011 * Santalucia, 2013
No. of participants (N =)	N = 5,090,839	N = 5,248,664	N = 2,583,848	N = 2,716,782
Up to 12 months	Palnum, 2009 *	Palnum, 2009 *	Andersen, 2015 Di Carlo, 2003 Olsen, 2007 Palnum, 2009 * Phan, 2021 Vemmos, 2000	Koton, 2013 Olsen, 2007 Palnum, 2009 * Phan, 2021 Vemmos, 2000
No. of participants (N =)	N = 29,549	N = 29,549	N = 84,527	N = 79,029
Up to 5 years	–	–	–	–

*Age-stratified data was available in the paper and extracted for subgroup analysis (see Supplementary Tables 3–6 for age-stratified data).

480/ 8, 008, 110) of the participants in the meta-analysis, whist Eastern Asia, Africa and Middle/Near East combined represent 2% (n = 172, 630) of the participants. Therefore, an analysis by geographical region would be statistically underpowered and therefore add little value to our findings.

This comprehensive systematic review and meta-analysis has a number of strengths. It presents the most up-to-date evidence from observational studies comparing risk of mortality between women and men after IS and HS, from diagnosis to five-years follow up. The participants of the studies represented a large demographic spread from various different healthcare systems which increases the generalisability and global applicability of our findings. All literature searches, data extraction, meta-analysis and quality appraisal were put through a rigorous cross-check by at least two independent researchers at every stage. There are also some limitations worth highlighting. There was a high degree of heterogeneity in the variables that were adjusted for as well as a lack of adjustment of stroke severity. Further, the majority of studies in the current literature are those with Western study cohorts. Therefore, it is important to note that East Asia and Africa are underrepresented in the existing analysis and would be statistically underpowered if analysis was stratified by region. In addition, there was an inadequate number of studies available to meta-analyse results at individual post-operative follow-up time points therefore, time brackets were utilised.

Clinicians treating stroke patients must be cognisant of the important risk factors including age, HTN and AF which put women at higher risk of mortality than men. Equally however, they should understand that this relationship is an interplay of various confounding factors that when adjusted for, women have a lower risk of mortality than men post-IS. Finally, it is important to recognise the lack of evidence surrounding the gender differences in risk of mortality following HS and the necessity of further research for haemorrhagic aetiology of stroke.

5. Conclusion

The gender differences in mortality risk after stroke is dependent on stroke type, age group and duration since stroke onset. Crude stroke mortality in women was found to be higher than in men however this appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period where women are at higher risk of mortality, there is no gender difference in mortality risk. Further research pertaining to gender differences specifically after HS is warranted to better understand this relationship. Appropriate prevention and management of IS in women is paramount to ensuring gender equity in the provision of stroke care.

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Conflict of interest

None declared.

CRediT authorship contribution statement

Abdel-Rahman Abdel-Fattah: Primary reviewer, Literature review, Data-analysis and Drafting manuscript. **Tiberiu A. Pana:** Statistical analysis and Supervision, Drafting manuscript. **Toby O. Smith:** Senior reviewer for systematic review, Supervision of systematic review, drafting manuscript**. Zahra Pasdar:** Second data extraction, Drafting manuscript. **Maha Aslam:** Second reviewer, Drafting manuscript.

Mamas A. Mamas: Supervision, Critical revision. **Phyo K. Myint:** Supervision, Senior reviewer, Critical revision, Guarantor.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2022.107359.

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