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Acute Care, Secondary Prevention, and Outcomes after Ischaemic and Haemorrhagic Stroke in Men and Women: A Data-Linkage Study

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Sex factors · Stroke · Secondary prevention · Mortality · Registries

Abstract

Introduction: There is evidence that sex differences exist in stroke presentation, risk factors, severity, treatment, and outcomes. To further understand this, we explored how sex differences influence acute stroke management, secondary prevention prescribing, and mortality outcomes in a well-characterised cohort of first-ever stroke patients in Scotland. ***Methods:*** This is a retrospective, population-based, data-linkage study of stroke admissions to acute care hospitals in Scotland between January 1, 2011, and December 31, 2018. Data sources included the Scottish Stroke Care Audit (SSCA), the Prescribing Information System (PIS), the Scottish Morbidity Record 01 (SMR01), and the National Records of Scotland (NRS) death records. Multivariable logistic regression was used to explore the association between patient sex, acute stroke care, and secondary prevention prescribing, while Cox proportional hazards models were used to explore the association between patient sex and all-cause mortality up to 1 year after index event. ***Results:*** This study included 5,901 patients with a first-ever intracerebral haemorrhage (ICH) and 47,087 patients with a first-ever acute ischaemic stroke (AIS). After an ICH, women had significantly lower odds of receiving all components of the stroke care bundle (adjusted odds ratio [aOR], 0.78; 95% confidence interval [CI], 0.69–0.87) and were less likely to be prescribed antihypertensives within 90 days after discharge to the usual place of residence (aOR, 0.78; 95% CI, 0.63–0.97). There was no sex difference in stroke care bundle achievement for those admitted with AIS; however, women had significantly lower odds of receiving antihypertensives, lipid-lowering drugs, or oral anticoagulants after discharge. The risk of all-cause mortality was lower in women at 1 year after both ICH (adjusted hazard ratio [aHR], 0.90; 95% CI, 0.83–0.98) and AIS (aHR, 0.91; 95% CI, 0.87–0.95) after adjusting for potential confounders. ***Conclusion:*** The sex differences in stroke treatment and outcomes may be partly explained by the older age of women at the time of stroke, which influences stroke presentation, severity, and prognosis. However, following adjustment, women had a reduced risk of all-cause mortality after both ICH and AIS.

Introduction

Studies show that women are significantly older than men at the time of their first stroke and have higher stroke incidence at older ages [1, 2]. Women also present with

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poorer prestroke function, have poorer living circumstances, and experience more severe strokes [3]. After a stroke, women are more likely to report disability, have institutionalised care, or have poorer quality of life [4, 5]. Differences in stroke symptoms between men and women may lead to more delayed stroke recognition and treatment in women at baseline and in the long term [6]. There are currently limited data on the effect of sex on stroke stratified by stroke type, particularly with regards to a stroke care bundle and secondary prevention. In addition, few studies have explored sex differences in stroke care, secondary prevention, and outcome across an entire nation.

In Scotland, all health boards are held to national standards, and all patients are audited against a "stroke bundle of care" through the Scottish Stroke Care Audit (SSCA) [7]. Sex-disaggregated data on stroke bundle achievement and clinical outcomes in Scotland are sparse and do not always take into consideration how differences in comorbidity and other baseline characteristics might affect stroke care and outcomes between the two groups. This study aimed to explore the association between patient sex and acute stroke management including access to thrombolysis, secondary prevention prescribing, and mortality in a Scottish stroke cohort while accounting for important baseline characteristics.

Methods

Study Design and Data Sources

This is a retrospective, observational, data-linkage study of stroke patients in Scotland, using routinely collected data from national health and administrative datasets. Data sources included the SSCA, a national database which collects clinical audit data on all stroke patients presenting to publicly funded acute care hospitals from all fourteen geographical National Health Service (NHS) Health Boards in Scotland; the Prescribing Information System (PIS) which captures data on all medications prescribed, dispensed, and reimbursed in the community setting in NHS Scotland; the Scottish Morbidity Record 01 (SMR01) which records episode level data on hospital inpatient and day cases, and the National Records of Scotland (NRS) death records, which contains mortality data for all patients in Scotland. Further information on these datasets can be found in the online supplementary methods (for all online suppl. material, see https://doi.org/10.1159/000240371) and the Public Health Scotland website [8]. Patient data were linked using the Community Health Index (CHI) number, a unique health identifier, assigned at birth, or first contact with the healthcare system for all residents in Scotland. Data were anonymised, stored, and accessed through the Grampian Data Safe Haven (DaSH).

Study Population

The study population included adults (≥18 years) with a first-ever intracerebral haemorrhage (ICH) or first-ever acute ischaemic stroke (AIS) admitted to an acute care hospital between January 1, 2011, and December 31, 2018.

Variables

Patient sex was recorded in the dataset as either male or female, confirmed by the patient's CHI number. The Scottish Index of Multiple Deprivation (SIMD), version 2016, is an area-based measure of deprivation which assesses seven domains (income, employment, education/skills, health, access to services, crime, and housing) where residents may experience disadvantage [9]. SIMD quintile 1 represents the 20% most deprived areas and quintile 5 represents the 20% least deprived areas. Charlson comorbidities [10] were identified using the primary and secondary diagnoses fields of the SMR01. A modified Charlson Comorbidity Index (CCI) score (excluding cerebrovascular accident and paraplegia) was calculated for each patient representing the sum of the weighted score for each comorbid condition present. Any comorbidity recorded within 10 years prior to the index stroke event was included. Baseline stroke severity assessment scores were based on four variables recorded in the SSCA (able to walk unaided, able to lift both arms off the bed, able to talk, and poststroke orientation). The overall score was calculated from "0 to 4," where 0 indicates least severe (all yeses) and 4 indicates most severe (all nos). Prestroke medication use was defined as any prescription recorded in the PIS within 90 days before stroke admission.

Study Outcomes

a. Stroke care bundle achievement – admission to an acute stroke unit (ASU) within 1 day of admission, brain imaging within audit target, swallow screen assessment within 4 h of admission, and aspirin initiation (unless contraindicated) in AIS patients within 1 day of admission. Achievement of the complete bundle was defined as receiving three components for ICH and four components for AIS. Administration of thrombolysis was also assessed in patients with AIS.
b. Secondary prevention prescribing – at least one prescription for an antithrombotic, antihypertensive, or lipid-lowering drug within one to 90 days after discharge from the hospital to the usual place of residence. To account for immortal time bias, we used patients surviving to 6 months after hospital admission.
c. Cumulative all-cause mortality within 30, 90, 182, and 365 days – calculated from the date of stroke admission (or onset date for in-hospital cases) to date of death.

Statistical Analysis

Non-normally distributed continuous data variables were compared using Mann-Whitney U test and presented as medians and interquartile ranges. Categorical variables were compared using χ^2 tests and are presented as absolute numbers and percentages. Binary logistic regression was used to explore the association between patient sex (predictor variable) and treatment (dependent variable). Cox proportional hazards models explored the association between demographic and clinical characteristics and all-cause mortality up to 1 year after stroke. Missing variables were assessed as missing completely at random and multiple imputations done, with values imputed using the Markov chain Monte Carlo method. Sensitivity

Table 1. Baseline characteristics

Variables	ICH			AIS		
	men (n = 2,819)	women (n = 3,082)	p value	men (n = 23,626)	women (n = 23,461)	p value
Age, years, median (IQR)	73 (63–81)	79 (71–85)	<0.001	71 (62–80)	78 (68–85)	<0.001
SIMD quintiles[a], n (%)						
1 (most deprived areas)	527 (20.9)	552 (20.2)	0.417	5,324 (24.9)	5,349 (25.1)	0.038
2	534 (21.2)	600 (22.0)		4,758 (22.2)	5,023 (23.6)	
3	520 (20.7)	579 (21.2)		4,361 (20.4)	4,168 (19.6)	
4	518 (20.6)	512 (18.8)		3,666 (17.1)	3,506 (16.5)	
5 (least deprived areas)	419 (16.6)	483 (17.7)		3,298 (15.4)	3,250 (15.3)	
Prestroke functional status, n (%)						
Independent in ADL	2,462 (87.3)	2,341 (76.0)	<0.001	21,052 (89.1)	18,720 (79.8)	<0.001
Live alone before stroke	835 (29.6)	1,388 (45.0)	<0.001	7,187 (30.4)	11,007 (46.9)	<0.001
Baseline stroke severity measures, n (%)						
0 (least severe)	651 (23.1)	561 (18.2)	<0.001	10,410 (44.1)	8,211 (35.0)	<0.001
1	464 (16.5)	460 (4.9)		4,967 (21.0)	4,619 (19.7)	
2	649 (23.0)	658 (21.3)		4,214 (17.8)	4,789 (20.4)	
3	303 (10.7)	361 (11.7)		1,655 (7.0)	2,101 (9.0)	
4 (most severe)	752 (26.7)	1,042 (33.8)		2,380 (10.1)	3,741 (15.9)	
CCI scores, n (%)						
0	1,618 (57.4)	1,708 (55.4)	0.848	13,109 (55.5)	12,315 (52.5)	<0.001
1	416 (14.8)	524 (17.0)		3,722 (15.8)	4,062 (17.3)	
2	342 (12.1)	401 (13.0)		2,998 (12.7)	3,173 (13.5)	
≥3	443 (15.7)	449 (14.6)		3,797 (16.1)	3,911 (16.7)	
History of atrial fibrillation[b], n (%)	555 (19.8)	510 (16.6)	0.002	3,932 (16.7)	4,648 (19.9)	<0.001
Medication history[c], n (%)						
Antithrombotics	1,305 (46.3)	1,359 (44.1)	0.090	9,930 (42.0)	9,736 (41.5)	0.242
OACs	439 (15.6)	408 (13.2)	0.011	1,780 (7.5)	1,753 (7.5)	0.798
Antiplatelets	917 (32.5)	987 (32.0)	0.679	8,369 (35.4)	8,125 (34.6)	0.072
Antihypertensives	1,534 (54.4)	1,806 (58.6)	0.001	13,842 (58.6)	15,538 (66.2)	<0.001
Lipid-lowering drugs	1,194 (42.4)	1,187 (38.5)	0.003	10,045 (42.5)	9,006 (38.4)	<0.001
Glucose-lowering drugs	379 (13.4)	255 (8.3)	<0.001	3,990 (16.9)	3,138 (13.4)	<0.001
Antidepressants	445 (15.8)	837 (27.2)	<0.001	3,571 (15.1)	6,102 (26.0)	<0.001
Antiepileptic drugs	207 (7.3)	255 (8.3)	0.184	1,756 (7.4)	2,043 (8.7)	<0.001

ADL, activities of daily living; CCI, Charlson Comorbidity Index; IQR, interquartile range; SIMD, Scottish Index of Multiple Deprivation. [a]SIMD data available for 5,244 (88.9%) ICH patients (2,518 men and 2,726 women, respectively) and 42,703 (90.7%) AIS patients (21,407 men and 21,296 women, respectively). [b]Atrial fibrillation diagnosis data available for 5,878 (99.6%) ICH patients (2,808 men and 3,070 women, respectively) and 46,895 (99.6%) AIS patients (23,528 men and 23,367 women, respectively). [c]At least one prescription recorded in the PIS between 0 and 90 days prior to stroke admission.

analysis comparing the multiple imputation models and complete case analysis models was performed. Analyses were conducted using *Statistical Package for the Social Sciences (SPSS)* version 28.

Results

Baseline characteristics are shown in Table 1. At stroke admission, women were significantly older than men, were less likely to be independent in activities of daily living, and were more likely to live alone before stroke. Fewer women were able to talk, walk or lift arms at admission compared to men (see online suppl. Table 1), indicating more severe strokes at baseline assessment.

Table 2 shows women were less likely to receive an early brain scan, be admitted to an ASU within 1 day of admission or receive a timely swallow screen after an ICH. Overall, achieving the complete ICH stroke care

Table 2. Acute stroke care in women compared with men

Acute stroke care	ICH						AIS					
	men (*n* = 2,819)	women (*n* = 3,082)	model 1		model 2		men (*n* = 23,626)	women (*n* = 23,461)	model 1		model 2	
			aOR	95% CI	aOR	95% CI			aOR	95% CI	aOR	95% CI
Brain scan	2,669 (94.7)	2,851 (92.5)	0.78	0.63–0.97[a]	0.78	0.62–0.98[a]	21,738 (92.0)	21,422 (91.3)	0.97	0.91–1.04	0.99	0.92–1.06
Acute stroke unit	2,057 (73.0)	2,091 (67.8)	0.74	0.66–0.83[a]	0.79	0.70–0.89[a]	18,022 (76.3)	17,859 (76.1)	0.99	0.95–1.03	0.99	0.95–1.04
Swallow screen	2,537 (90.0)	2,705 (87.8)	0.79	0.67–0.94[a]	0.78	0.65–0.93[a]	21,428 (90.7)	21,245 (90.6)	0.95	0.90–1.02	0.94	0.88–1.00
Aspirin/ antiplatelet given	–	–	–	–	–	–	20,834 (88.2)	20,520 (87.5)	0.93	0.87–0.98[a]	0.94	0.88–0.99[a]
Achieved stroke care bundle	1,936 (68.7)	1,931 (62.7)	0.74	0.66–0.82[a]	0.78	0.69–0.87[a]	15,549 (65.8)	15,376 (65.5)	0.98	0.95–1.02	0.99	0.95–1.03
Intravenous thrombolysis[b]	–	–	–	–	–	–	2,710 (11.5)	2,436 (10.4)	0.93	0.87–0.98[a]	0.93	0.87–0.99[a]

Stroke care bundle for ICH patients includes brain scan in target time, admission to acute stroke unit, and swallow screen, while stroke care bundle for AIS patients includes brain scan in target time, admission to acute stroke unit, swallow screen, and aspirin/antiplatelet given. aOR, adjusted odds ratio; CI, confidence interval; ADL, activities of daily living. [a]Statistically significant at $p < 0.05$. [b]Missing data for intravenous thrombolysis, 82 (0.2%) patients. Model 1 adjusted for age at admission. Model 2 adjusted for age at admission, year of admission, independent in ADL before stroke, live alone before stroke, SIMD quintile, Charlson Comorbidity Index scores, baseline stroke severity scores. Analysis is based on multiple imputed data for SIMD quintiles. Univariable and complete case analysis are shown in online supplementary Table 2.

bundle was significantly lower in women compared with men (adjusted odds ratio [aOR], 0.78; 95% confidence interval [CI], 0.69–0.87). However, after an AIS, stroke care bundle achievement was similar in both men and women (aOR, 0.99; 95% CI, 0.95–1.03), though women were less likely to receive intravenous thrombolysis (aOR, 0.93; 95% CI, 0.87–0.99).

Secondary prevention prescribing is shown in Table 3. In patients surviving to 6 months after an ICH, women had significantly lower odds of being prescribed an antihypertensive compared to men (aOR, 0.78; 95% CI, 0.63–0.97). In AIS patients surviving to 6 months, women had lower odds of receiving a prescription for an antihypertensive (aOR, 0.91; 95% CI, 0.86–0.97), lipid-lowering drug (aOR, 0.80; 95% CI, 0.75–0.86), or oral anticoagulant (OAC) (aOR, 0.87; 95% CI, 0.82–0.93) within one to 90 days after discharge from hospital.

While the proportion of women dying after stroke was higher after both ICH and AIS, age-adjusted Cox proportional hazards models showed no difference in cumulative all-cause mortality between men and women after ICH, and no difference in all-cause mortality at 6 months (182 days) and 1-year (365 days) after AIS (shown in Fig. 1). However, multivariable-adjusted models showed a lower risk of mortality in women at 1 year after ICH, and between 30 days and 1 year after AIS. Unadjusted and complete case analysis models are shown in online supplementary Tables 2, 3, and 4. Sensitivity analysis showed findings from complete case and multiple imputed models agreed closely in both regression and survival analyses.

Discussion

This study found differences in the baseline characteristics of men and women at stroke presentation. After adjusting for these characteristics, sex differences in acute care, secondary prevention prescribing, and all-cause mortality remained. Stroke type also influenced the level of care and outcomes in women compared with men. We found differences in achievement of complete stroke bundle care after ICH, but not after AIS, suboptimal poststroke antihypertensive prescribing, yet a reduced risk of 1-year all-cause mortality in women after both ICH and AIS once important factors such as age, comorbidities, and stroke severity were taken into consideration.

Similar to our findings, other studies report significant sex differences in the baseline functional status [11] and risk factor profile at the time of stroke event [12, 13]. These differences can have a large

Table 3. Secondary prevention prescribing in women compared with men

Medication class	ICH						AIS					
	men (*n* = 1,284)	women (*n* = 1,159)	model 1		model 2		men (*n* = 16,595)	women (*n* = 14,379)	model 1		model 2	
			aOR	95% CI	aOR	95% CI			aOR	95% CI	aOR	95% CI
Antiplatelet	188 (14.6)	164 (14.2)	0.83	0.66–1.05	0.97	0.75–1.26	13,432 (80.9)	11,518 (80.1)	1.03	0.97–1.09	1.05	0.98–1.11
Antihypertensive	1,024 (79.8)	879 (75.8)	0.78	0.64–0.95[a]	0.78	0.63–0.97[a]	12,032 (72.5)	10,641 (74.0)	0.97	0.92–1.02	0.91	0.86–0.97[a]
Lipid-lowering drug	496 (38.6)	410 (35.4)	0.76	0.64–0.90[a]	0.86	0.68–1.07	14,822 (89.3)	12,286 (85.4)	0.72	0.68–0.77[a]	0.80	0.75–0.86[a]
Oral anticoagulant	99 (7.7)	71 (6.1)	0.71	0.51–0.98[a]	0.81	0.58–1.14	3,405 (20.5)	2,830 (19.7)	0.84	0.79–0.89[a]	0.87	0.82–0.93[a]

Analysis includes 2,443 ICH patients and 30,974 AIS patients who were discharged to usual place of residence within 90 days and survived to 6 months after stroke event. aOR, adjusted odds ratio; CI, confidence interval; ADL, activities of daily living. [a]Statistically significant at $p < 0.05$. Model 1 adjusted for age at admission. Model 2 adjusted for age at admission, year of admission, independent in ADL before stroke, live alone before stroke, SIMD quintile, Charlson scores, baseline stroke severity scores, prior antithrombotic, antihypertensive, or lipid-lowering drug use. Analysis is based on multiple imputation data. Univariable and complete case analysis are shown in online supplementary Table 3.

impact on treatment options, poststroke mortality and functional outcomes. Achieving the complete stroke care bundle is associated with improved patient outcomes including reduced risk of mortality and an increase in the rate of discharge to home [14, 15]. Women may be less likely to achieve this due to greater frailty at the time of stroke, less clear presentation, or more severe strokes. In this study, having an ICH was a predictor of lower rates of early brain scan, early swallow screen or early ASU admission in women. Administration of intravenous thrombolysis was also significantly lower in women than in men, consistent with previous research presented in a meta-analysis of twenty-four studies conducted between 2008 and 2018 [16].

Evidence-based secondary prevention prescribing after stroke addresses important risk factors and reduces the risk of another stroke or vascular event [17, 18]. Previous Scottish studies have also found poorer cardiovascular prescribing poststroke in women [19, 20]. This study found lower prescribing of antihypertensives after both ICH and AIS and lower prescribing of lipid-lowering drugs and OACs after AIS. As women are more likely to present with hypertension and atrial fibrillation [13], suboptimal prescribing in this group warrants further investigation. While antiplatelets, OACs (in patients with AF), and statins are recommended after AIS, the use of antithrombotics to prevent an ischaemic event after ICH must be weighed against the risk of haemorrhage [18]. However, national stroke guidelines do not specifically address the differences in stroke presentation, management and outcome in women compared to men [21].

Even though a higher proportion of women died within 1 year after both ICH and AIS, multivariable adjustments for age, prestroke function, stroke severity, CCI score and stroke bundle achievement, found women had a lower risk of all-cause mortality at 1 year after ICH, and between 30 days to 1 year after AIS. Lower all-cause mortality risk in women was also reported in two UK stroke cohort studies [22, 23] and the International Stroke Outcomes Study (INSTRUCT) [24]. However, observational studies suggest that even though women have better survival after stroke, they oftentimes present with worse stroke severity and prestroke functional status, leading to poorer poststroke functional outcomes [23, 25].

Our study has several strengths including the use of high-quality, validated clinical and administrative datasets, a large patient cohort and, stroke cases which are representative of an entire national health service. However, retrospective observational studies have limitations as they can be impacted by residual confounding and unmeasured factors (e.g., smoking status, frailty). Also, our analysis is limited to the data collected within these datasets, and PIS data may underestimate medication use as it does not capture over-the-counter dispensing (e.g., aspirin), private or in-hospital prescriptions.

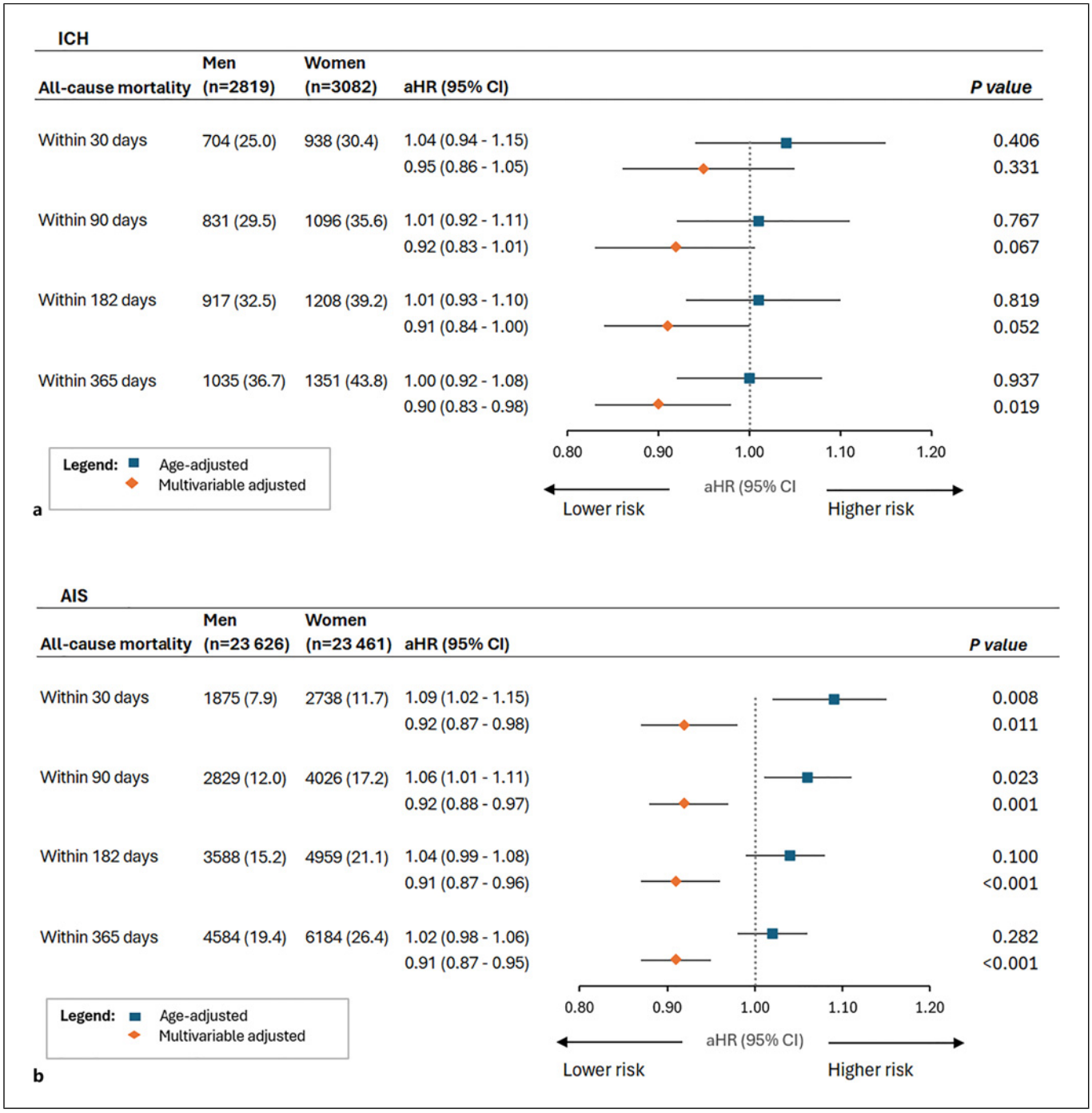

Fig. 1. All-cause mortality in women compared with men. Multivariable models adjusted for age at admission, year of admission, independent in ADL before stroke, live alone before stroke, SIMD quintile, Charlson Comorbidity Index scores, baseline stroke severity scores, achievement of stroke care bundle. Analysis is based on multiple imputation data. aHR, adjusted hazard ratio; CI, confidence interval. **a** ICH. **b** AIS.

Conclusion

We have shown that most of the variation in care and outcomes between men and women can be accounted for by age, stroke severity and comorbidities. However, we highlight the need to improve secondary prevention and management of ICH in females. Understanding and identifying inequities in care can help address these shortcomings, particularly in marginalised patients such as older, frailer women. Equitable access to procedures, medicines and delivery of healthcare services underpins fair clinical practice and government policies at the local and national levels. Interventions to understand and address these gaps in treatment may lead to more patients receiving beneficial treatment after stroke.

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Statement of Ethics

Informed patient consent is not required for data entered into the SSCA, where patient data are anonymised for audit purposes. Permission to access and use national health data for research purposes was requested through Public Health Scotland (PHS) electronic Data Research and Innovation Service (eDRIS). The information governance supervisory body, NHS Scotland (NHSS) Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP), assesses any request for access to national NHSS-controlled data by balancing the benefits against the potential risks to privacy. The PBPP approval reference number for this study is 1516-0411 and NHS Research Ethics Committee (REC) reference is 17/SS/0003.

Conflict of Interest Statement

The authors have no conflict of interest to report.

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Author Contributions

Melanie Turner and Mary Joan Macleod designed the study and applied for the ethical and data permissions. Melanie Turner carried out data preprocessing prior to data analysis. Kadie-Ann Sterling carried out the primary data analysis and drafted the manuscript. Melanie Turner, Mary Joan Macleod, and Mark Barber critically reviewed and edited the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available due to ethical and legal restrictions. Data are in controlled access data storage and are available on a PBPP application to eDRIS, Public Health Scotland, Edinburgh, Scotland. Further enquiries can be directed to the corresponding author.

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