Biological mechanism of sex difference in stroke manifestation and outcomes

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Abstract

Background and Objectives

Female patients tend to have greater disability and worse long-term outcomes after stroke than male patients. To date, the biological basis of sex difference in ischemic stroke remains unclear. We aimed to 1) assess sex differences in clinical manifestation and outcomes of acute ischemic stroke and 2) investigate whether the sex disparity is due to different infarct locations or different impacts of infarct in the same location.

Methods

This MRI-based multicenter study included 6,464 consecutive patients with acute ischemic
stroke (<7-days) from 11-centers in South-Korea (May-2011~January-2013). Multivariable statistical and brain mapping methods were used to analyze clinical and imaging data collected prospectively: admission National Institutes of Health Stroke Scale (NIHSS)-score, early neurological deterioration within 3-weeks, modified Rankin Scale (mRS)-score at 3-months, and culprit cerebrovascular lesion (symptomatic large artery steno-occlusion and cerebral infarction) locations.

Results

Mean (SD) age was 67.5 (12.6) years, and 2,641 (40.9%) were female patients. Percentage infarct volumes on diffusion-weighted MRI did not differ between female patients and male patients (median 0.14% vs. 0.14%, P=0.35). However, female patients showed higher stroke severity (NIHSS-score, median 4 vs. 3, P<0.001) and had more frequent early neurological deterioration (adjusted-difference 3.5%; P=0.002) than male patients. Female patients had more frequent striatocapsular lesions (43.6% vs. 39.8%, P=0.001) and less frequent cerebrocortical and cerebellar lesions than male patients, which aligned with angiographic findings: female patients had more prevalent symptomatic steno-occlusion of the middle cerebral artery (31.1% vs. 25.3%; P<0.001) compared to male patients, who had more frequent symptomatic steno-occlusion of the extracranial internal carotid artery (14.2% vs. 9.3%; P<0.001) and vertebral artery (6.5% vs. 4.7%; P=0.001). Cortical infarcts in female patients, specifically left-sided parieto-occipital regions, were associated with higher NIHSS-scores than expected for similar infarct volumes in male patients. Consequently, female patients had a higher likelihood of unfavorable functional outcome (mRS-score>2) than male patients (adjusted-absolute-difference 4.5%; 95%-CI 2.0–7.0; P<0.001).
Discussion

Female patients have more frequent middle cerebral artery disease and striatocapsular motor-pathway involvement with acute ischemic stroke, along with left parieto-occipital cortical infarcts showing greater severity for equivalent infarct volumes than in male patients. This leads to more severe initial neurological symptoms, higher susceptibility to neurological worsening, and less 3-month functional independence, when compared with male patients.

Glossary

CRCS-K = Clinical Research Collaboration for Stroke-Korea; FLAIR = fluid-attenuated inversion recovery; DWI = diffusion-weighted image; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; END = early neurological deterioration; WMH = white matter hyperintensity; LAA = large artery atherosclerosis; SVO = small vessel occlusion; CE = cardioembolism; MCA = middle cerebral artery; ICA = internal carotid artery; ROI = region of interest; AAL atlas = Automated Anatomical Labeling atlas; JHU atlas = Johns Hopkins University atlas; ACA = anterior cerebral artery; NNT = number needed to treat.

Introduction

The greater impact of stroke on female patients could be related to older age, more pre-stroke comorbidities, lower socioeconomic status, and more conservative treatment. However, previous studies showed that statistical adjustments for these factors did not abolish sex
differences in stroke manifestations and outcomes. The underlying mechanism of age- and comorbidity-adjusted sex differences needs to be unraveled, preferably in a large number of consecutive patients with acute ischemic stroke in order to minimize selection bias and better account for socioeconomic and cultural factors.

A recent study by Bonkhoff et al. (n=555 derivation-cohort patients vs. 503 validation-cohort patients) showed that higher stroke severity in female patients was associated with left hemisphere lesions in the vicinity of the posterior circulation, which was not the case in male patients. In the present MRI-based multicenter study of 6,464 consecutive patients with acute ischemic stroke, we investigated 1) the presence (vs. absence) and magnitude of sex difference (if present) in clinical manifestation and outcomes and 2) whether the biological basis of sex disparities is related to a) different lesion locations between female patients and male patients or b) different impact of a lesion in the same location.

Methods

Study Population

As a subproject of Clinical Research Collaboration for Stroke-Korea (CRCS-K, a nationwide stroke registry; http://crcs-k.strokedb.or.kr/), the Korean image-based stroke database project is a prospective multicenter study, in which 11 stroke centers in Korea participated (eMethods in the Supplement). From May-2011 to January-2013, we consecutively enrolled patients with acute ischemic stroke who were admitted to the 11 participating centers within seven days of symptom onset. Exclusion criteria were: not undergoing MRI, poor quality or unavailability of fluid-attenuated inversion recovery (FLAIR) or diffusion-weighted image
(DWI), MRI registration error, or patients lost to follow-up at 3 months following stroke onset.

**Clinical data and outcome measurement**

Under a standardized protocol,7,9,10,12 we collected demographic data, prior medication history, laboratory data, and information regarding risk factors. Stroke subtypes were determined by consensus among experienced vascular neurologists at each participating center, using a validated MRI-based algorithm for acute ischemic stroke subtype classification (eMethods in the Supplement).13 Pre-stroke modified Rankin Scale (mRS) score, National Institutes of Health Stroke Scale (NIHSS) score at admission, early neurological deterioration (END within 21 days; eMethods in the Supplement) information, and mRS score at 3 months following stroke were collected prospectively.

**MRI registration and analysis**

Brain MRI was performed on 1.5 Tesla (n=5,525) or 3.0 Tesla (n=939) MRI systems and stroke-related lesions were quantified as previously reported7-10,14,15 (eMethods in the Supplement). Acute infarct volume on DWI and white matter hyperintensity (WMH) volume on FLAIR MRI were converted to percentage lesion volumes: percentages of the total brain parenchymal volume.

Infarct locations and relevant arterial stenoses (>50% stenosis or occlusion) were determined by attending neurologists at each participating center based on neurological symptoms and signs as well as imaging findings (eMethods in the Supplement).
**Statistical analysis**

To compare groups stratified by inclusion vs. exclusion and female vs. male, we used the Student’s t-test or rank-sum test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables, as appropriate.

The association between percentage infarct volumes and admission NIHSS scores was evaluated using a mixed-effects quantile regression model due to the right-skewed distribution of the NIHSS scores. We used the mixed-effects model to account for hospital clustering. To examine an effect modification by sex, an interaction term ‘sex × percentage infarct volume’ was included in the model. The following predefined covariates, identified in the literature\textsuperscript{7-11,16} as potentially associated with stroke severity, END, and post-stroke functional outcomes, were entered in the models: age, pre-stroke mRS score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, history of prior stroke, percentage WMH volume, and onset to imaging time. At 10, 25, 50, 75, and 90\textsuperscript{th} percentiles of percentage infarct volumes, we estimated mean admission NIHSS scores with 95% CI for female patients and male patients and calculated adjusted differences of the NIHSS scores (95% CI) between female patients and male patients. We repeated these analyses after stratification with a cut-off age of 52 years, the median age of menopause.\textsuperscript{17} We also repeated the analyses in the patients without pre-stroke morbidity (those with pre-stroke mRS scores of 0) for sensitivity analyses. In all of the following multivariable analyses, except for ones to predict NIHSS scores, revascularization therapy was also included as a predefined covariate.

Adjusted sex differences in a) presenting symptoms and b) regional infarct probabilities with increasing percentage infarct volumes were assessed by mixed-effects logistic regression with adjustments for the aforementioned covariates. In the regression analyses for each of eight NIHSS subitems (consciousness, weakness, ataxia, aphasia, dysarthria, sensory abnormality,
and visual field defect), ‘score 0 vs. ≥1’ was a dependent variable. In the regression analyses for each of nine brain regions (cortex, striatocapsular region [corona radiata, basal ganglia, and internal capsule], thalamus, brainstem [midbrain, pons, or medulla], and cerebellum), ‘lesion presence/absence’ was a dependent variable. We repeated these infarct probability-related analyses after stratification with a cut-off age of 52 years.

Adjusted sex differences in a) symptomatic steno-occlusion of the middle cerebral artery [MCA], extracranial internal carotid artery [ICA], and vertebral arteries and b) regional infarct probabilities (in the striatocapsular region, cortex, and cerebellum) with increasing age were assessed by mixed-effects logistic regression with adjustments for the same covariates (without age).

The association between percentage infarct volume and either the incidence of END or unfavorable functional outcome (3-month mRS score>2) was also explored using a mixed-effects logistic regression model, adjusted for the same covariates. We dichotomized the 3-month outcomes due to violation of the proportional odds assumption. For 10, 25, 50, 75, and 90th percentiles of percentage infarct volume strata, we estimated the adjusted incidences of END and unfavorable functional outcome for female patients and male patients and calculated the adjusted risk differences between them. To examine an effect modification by sex, an interaction term ‘sex × percentage infarct volume’ was included in the model. As a surrogate to generate estimates of END- and outcome-related sex differences, the number needed to treat was calculated as the inverse of the adjusted absolute female-male difference for the incidences of END and unfavorable functional outcome, respectively. We repeated these analyses after stratification with a cut-off age of 52 years. We also repeated the analyses in the patients without pre-stroke morbidity for sensitivity analyses.

As additional pre-specified subgroup analyses according to stroke etiology, we focused on
three stroke subtypes (large artery atherosclerosis [LAA], small vessel occlusion [SVO], and cardioembolism [CE])\textsuperscript{13} and then re-explored sex differences in the neurological severity, END, unfavorable functional outcome with increasing percentage infarct volumes. Again, to examine effect modification by sex, an interaction term ‘sex × percentage infarct volume’ was included in the models.

We also conducted mediation analysis\textsuperscript{18} to evaluate the direct and indirect effects of sex on unfavorable functional outcome (eMethods in the Supplement).

Data were analyzed using STATA (STATA Corp., College Station, TX). A two-sided P less than 0.05 was considered statistically significant. We used P<0.10 as a threshold for the presence of a potential interaction, considering its low sensitivity.\textsuperscript{19} In addition, the following brain mapping-related multivariable analyses were performed using MATLAB R2021b (Mathworks, Natick, MA).

**Multivariable brain mapping to detect regions showing sex difference in lesion probability**

We compared lesion presence/absence in each of 164 distinct regions of interest (ROIs), drawn from a combined set of Automated Anatomical Labeling (AAL) atlas\textsuperscript{20} and Johns Hopkins University (JHU) white-matter atlas\textsuperscript{21} between female patients and male patients. Overlapping voxels for the AAL and JHU ROIs were allocated as the corresponding AAL ROIs (AAL was senior in tie-breaking). We defined infarct lesions to be present in each ROI without any thresholds. Thus, if there was one lesion-positive voxel in an ROI, the whole ROI would be considered lesion-positive. Next, a multivariable logistic regression was performed for lesion presence/absence in each ROI with sex (0 for female patients, 1 for male
patients) as an independent variable with adjustment for the same predefined covariates (See the Statistical analysis section above). The independent variable and all covariates were standardized by z-score normalization. We labeled ROIs showing significant (false-discovery-rate-corrected P<0.05) sex difference as either female-infarct-prone region or male-infarct-prone region, thereby defining ‘Anatomic ROIs’. We mapped ROI-wise ‘lesion probability differences’ between female patients and male patients in the significant ROIs along the axial plane. Additionally, a three-dimensional representation of the ROIs was generated using the BrainNet Viewer.

Multivariable brain mapping to identify regions showing sex-dependent interactions in the relationship of a regional lesion presence/absence with admission NIHSS score, END incidence, or the incidence of unfavorable functional outcome

To explore whether initial stroke severity-, stroke worsening-, or poor functional outcome-related sex differences are because infarct lesions in the same brain regions impact female patients and male patients differently, we performed ROI-wise brain mapping with the NIHSS score, END incidence, or the incidence of unfavorable functional outcome as a dependent variable while including sex, lesion presence/absence, sex × lesion presence/absence as well as the aforementioned predefined covariates (except for revascularization therapy in the NIHSS score-related mapping) as independent variables. The independent variables and all covariates were standardized by z-score normalization. Then, we identified ROIs showing a significant (false-discovery-rate-corrected P<0.05) interaction effect, thereby defining ‘Intrinsic ROIs’.
Multivariable regression analyses to investigate the relationship of sex-related regional lesion presence rate with admission NIHSS score, END incidence, or the incidence of unfavorable functional outcome

Multivariable regression analyses were conducted to explore the relationship of the lesion presence rate (= number of infarct-positive ROIs / number of all ROIs) in each of the sex-related brain regions (i.e., statistically significant female-infarct-prone and male-infarct-prone regions [Anatomic ROIs] and interaction regions [Intrinsic ROIs], if present) with the NIHSS score, END incidence, or the incidence of unfavorable functional outcome. For the NIHSS score, linear regression analysis was performed with the lesion presence rates in the female-infarct-prone and male-infarct-prone regions and an interaction term ‘sex × lesion presence rate’ in the interaction region as independent variables, adjusting for the same covariates (except revascularization therapy). For the END incidence and the incidence of unfavorable functional outcome, logistic regression analysis was conducted with the same variables used for the linear regression analysis (and revascularization therapy). In addition, we repeated the multivariable analyses after stratification with a cut-off age of 52 years. A significant difference between beta coefficients was identified by evaluating the overlap between 95% confidence intervals.24

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review boards of all participating centers approved the study (DUIH2010-01-083-020). All patients or their legally authorized representatives provided written informed consent for study participation.
Data availability

Unpublished anonymized data within this article can be made available on reasonable request, after seeking the approval of the CRCS-K steering committee.

RESULTS

Baseline characteristics

During the 21-month study period, a total of 8,472 patients with ischemic stroke were admitted to the 11 participating centers within seven days of symptom onset. Of 8,010 patients who gave research consent, 6,464 remained after excluding the following: contraindications or refusal to MRI (n=258), poor quality or unavailability of FLAIR or DWI (n=904), MRI registration error (n=31), and lost to follow-up (n=353) at 3 months following stroke onset. The mean (SD) age of the included patients was 67.5 (12.6) years and 2,641 (40.9%) patients were female patients. Female patients were older (71.1 vs. 65.1, P<0.001), had more risk factors, and had higher admission NIHSS scores (median 4 vs. 3, P<0.001) than male patients (Table 1). Median (interquartile range) onset to imaging time did not differ significantly between female patients and male patients: respectively, 15.4 (6.0-38.1) hours and 13.8 (5.7-37.9) hours (P=0.103). Percentage infarct volumes on DWIs did not differ between the two groups (median 0.14% vs. 0.14%, P=0.35, eFigure 1 in the Supplement). There was no significant sex difference in admission NIHSS score between the included and excluded (n=1,546) patients (eTable 1 in the Supplement), who were less likely to have received revascularization therapy (16.3% vs. 13.2%). Sex distributed comparably between the two groups (P=0.09).
Sex difference in admission NIHSS score

Female patients had higher NIHSS scores than male patients with similar total percentage infarct volumes, particularly older (>52 years) female patients (n=2,641 vs. 3,823 male patients; Figure 1A, Table 2, eFigure 2, eTables 2 and 3 in the Supplement) and those with low percentage infarct volume (up to 0.6% of brain parenchymal volume, encompassing about 70% of all cases). The sex-related modification of the association between percentage infarct volume and stroke severity held in the majority of large arterial infarctions due to LAA (with infarct volume up to 75th percentile, eTable 4 in the Supplement) or CE (with infarct volume up to 50th percentile, eTable 5 in the Supplement). However, in SVO strokes (eTable 6 in the Supplement), the NIHSS score was significantly higher in male patients than in female patients with similar infarct volumes only when the infarct volume was as low as ~0.005% of brain parenchymal volume; this comprised about 10% of all SVO cases.

In the analyses of NIHSS subitems with adjustment for covariates (Figure 1A), weakness was more often observed in female patients than in male patients in all infarct strata. In contrast, ataxia was more frequent in male patients than in female patients, regardless of percentage infarct volume. There were no significant inter-group differences in the other NIHSS subitems (eFigure 3A in the Supplement), except for aphasia in patients (n=1,216, 18.8%) with very large percentage infarct volume (higher than 2.7% of brain parenchymal volume).

Sex difference in infarct locations

Overall, female patients had more frequent striatocapsular lesions (43.3% vs. 39.3%, P=0.001; eTable 7 in the Supplement). Multivariable analyses (Figure 1B and eFigure 3B in the Supplement) also showed that compared with male patients, female patients were
significantly more likely to have striatocapsular lesions (regardless of percentage infarct volume). In contrast, male patients had a significantly higher likelihood of cortex lesions than female patients in all infarct strata. Moreover, cerebellar lesions were more frequently observed in male patients than female patients when the percentage infarct volumes were as low as ~0.9%, which encompassed about 80% of all cases. Taken together with the aforementioned sex difference in the NIHSS score, these findings suggest that more frequent striatocapsular involvement and thus more frequent weakness in female patients could explain why female patients had higher NIHSS scores than male patients.

**Sex differences in preferential locations of symptomatic large artery steno-occlusion and cerebral infarction**

Symptomatic steno-occlusion of the MCA and anterior cerebral artery (ACA) were more frequent in female patients vs. male patients (31.1% vs. 25.3% for the MCA and 3.5% vs. 1.8% for the ACA, all P<0.001), whereas symptomatic steno-occlusion of the extracranial ICA (14.2% vs. 9.3%, P<0.001) and the vertebral artery (6.5% vs. 4.7%, P=0.001) were more frequent in male patients than in female patients (eTable 8 in the Supplement). These sex differences were significant only in the older group. The probability of symptomatic MCA steno-occlusion increased with age, more steeply in female patients than male patients (Figure 2A). However, the aging-related increase in the probability of symptomatic extracranial ICA steno-occlusion was steeper in male patients than in female patients. The probability of symptomatic vertebral artery stenosis decreased with age, similarly in female patients and male patients.
The probability of striatocapsular involvement by infarction seemed to increase with age in female patients but decrease with age in male patients (Figure 2B). In line with the higher likelihood of symptomatic MCA steno-occlusion in older female patients (vs. older male patients), the probability of the striatocapsular involvement was significantly higher in female stroke than in male stroke at age 55 or higher. In contrast, cortical and cerebellar involvement by infarction was significantly higher in male patients than in female patients, respectively in older (≥65 years) and younger (≤65 years) patients (Figure 2B and eTable 7 in the Supplement), in line with the higher likelihood of symptomatic steno-occlusion of the extracranial ICA and vertebral artery in male patients (vs. female patients).

**Sex difference in the incidence of early neurological deterioration**

After adjusting for the covariates, the incidence of END was significantly higher in female patients than in male patients (adjusted difference 3.5%, 95% CI 1.2–5.7, P=0.002; number needed to treat [NNT] 28.6; Table 2), regardless of percentage infarct volume (Figure 3A), though only in the older group. In LAA strokes, female patients had significantly higher END incidence than male patients, regardless of percentage infarct volume (eTable 4 in the Supplement). CE strokes showed a similar trend (eTable 5 in the Supplement). However, there was no significant sex difference in the END incidence for SVO strokes, regardless of percentage infarct volume (eTable 6 in the Supplement).

**Sex difference in the likelihood of unfavorable functional outcome (mRS>2)**

In multivariable logistic regression analysis, female patients had a higher likelihood of
unfavorable functional outcome than male patients (adjusted risk difference=4.5%, 95% CI 2.0–7.0, P<0.001; NNT 22.2; Table 2), regardless of percentage infarct volume (Figure 3B). The sex difference in 3-month functional outcome held in the older group (n=5,570) but not in the younger group (n=894).

The mediation analysis was performed to reveal the mechanism underlying the association between sex and post-stroke functional outcome. As mentioned before, we pre-specified the hypothetical pathways from female (vs. male) to more frequent unfavorable functional outcome via older age, higher admission NIHSS score, less frequent revascularization therapy, and more frequent END, while adjusting for the covariates (See eMethods in the Supplement). We found that these four factors significantly mediated the association female patients have with unfavorable functional outcome (eFigure 4 in the Supplement; adjusted beta coefficient=0.058 [95% CI, 0.045–0.070]), accounting for 63.7% of total effect.

**Sensitivity analyses**

When the analyses were confined to 5,192 patients without pre-stroke morbidity, female patients again had higher NIHSS scores, higher END incidence, and elevated risk of unfavorable functional outcome at 3 months, compared with male patients (eTable 9 in the Supplement).
Multivariable brain mapping to explain sex differences in stroke manifestation and outcomes

Figure 4A shows significant (false-discovery-rate-corrected P<0.05) female-infarct-prone regions (total 6 ROIs) and male-infarct-prone regions (total 10 ROIs), defining in total 16 Anatomic ROIs. In line with the aforementioned multivariable analysis results (Figure 1B), female patients had higher lesion probability predominantly in the left striatocapsular region (red/orange in the figure), whereas in male patients, lesions more frequently occurred in cerebral cortical and posterior circulation regions (blue shades in the figure). This result demonstrates how the purely anatomic differences in stroke locations give rise to different outcomes between sexes. It is also notable that in the younger group no brain region showed significant sex difference in the regional lesion probability (eFigure 5 in the Supplement).

We found nine ROIs showing a sex-related interaction in the lesion presence-mediated increase in admission NIHSS score (Figure 4B, defining the Intrinsic ROIs, only one of which [left middle occipital gyrus] overlapped with the 10 male-infarct-prone Anatomic ROIs). The presence of infarct in each of these (mostly left parieto-occipital cortical) ROIs were significantly correlated with admission NIHSS score, more strongly in female patients than in male patients. There was no single ROI penalizing male infarction. This result shows that in some cases, even for similar infarct locations, female patients do worse than male patients, likely due to intrinsic biological differences. In terms of the incidence of END or unfavorable functional outcome, there were no Intrinsic ROIs showing sex-related interactions to penalize either female or male infarction for similar infarct volumes (eFigures 6 and 7 in the Supplement).

Multivariable regression models estimated the relative contributions of anatomic vs. intrinsic sex differences in explaining: 1) admission NIHSS score, 2) END incidence, and 3) the
incidence of unfavorable functional outcome (Figure 4C). First, significant predictors of the NIHSS score were: i) the lesion presence rate in the female-infarct-prone (i.e., anatomic) region ($\beta=1.24$), and ii) the lesion presence rate $\times$ sex (0 for female patients, 1 for male patients) in the interaction (i.e., intrinsic) region, but with a significantly lower $\beta$ coefficient ($\beta=-0.43, P<0.01$; a negative $\beta$ value corresponds to the direction of reducing the predicted NIHSS score in male patients). The effect on the initial stroke severity in the male-infarct-prone anatomic region was significant only in the older patients ($P<0.001$), and its $\beta$ coefficient (0.44) was significantly lower when compared with the corresponding value for the female-infarct-prone region ($\beta=1.76, P<0.01$; eFigure 8 in the Supplement). In summary, the higher NIHSS score in female patients was better explained by the anatomically different infarct distribution (i.e., more frequent striatocapsular involvement in female vs. male infarction), and less well by intrinsic differences in the cortical regions (where female infarction associated with a higher neurological severity for similar infarct volumes). Second, the lesion presence rate in the female-infarct-prone region significantly ($P=0.003$) and positively ($\beta=0.10$) correlated with the END incidence, which was not the case in the male-infarct-prone region, indicating that striatocapsular infarcts (more frequent in female patients) are more prone to complications leading to additional neurologic injury. Third, the lesion presence rate in the female-infarct-prone region and that in the male-infarct-prone region positively correlated with the incidence of unfavorable functional outcome (both $P<0.001$); however, the $\beta$ coefficient was again significantly lower for the male-infarct-prone region, when compared with the female-infarct-prone region ($\beta=0.21$ and 0.32, respectively; $P<0.05$). Thus, a higher incidence of unfavorable functional outcome in female patients (vs. male patients) also seemed to be attributed more to more frequent striatocapsular involvement in female (vs. male) infarction. These findings held true for the older group (eFigure 8 in the Supplement).
P-values for all multivariable models were less than $10^{-5}$.

**DISCUSSION**

In our MRI-based nationwide multicenter study of 6,464 consecutive patients with acute ischemic stroke, multivariable statistical analyses revealed that, compared with male patients, female patients have more severe neurological symptoms and poorer 3-month functional outcomes probably due to anatomic sex differences; i.e., more frequent symptomatic MCA steno-occlusion and striatocapsular lesions that more frequently produce motor weakness and END. Covariate-adjusted sex differences in the incidences of END and unfavorable functional outcome were 3.5% and 4.5% higher in female patients, respectively, corresponding to NNTs of 28.6 and 22.2. These values are similar to the magnitude of treatment effect by acute stroke unit care vs. general ward care in reducing unfavorable functional outcome. In addition, multivariable brain mapping showed that left parieto-occipital cortical brain regions associate with a significantly higher neurological severity in female patients, although this intrinsic difference had less impact when compared with the anatomic sex differences.

In line with previous research, our study showed that female patients with acute ischemic stroke presented with more severe neurological symptoms compared with male patients. Multivariable adjustment for age and other covariates did not change the result, and female patients had higher admission NIHSS scores than male patients with similar percentage infarct volumes. Earlier work showed that female patients had better collateral flow and
smaller infarct core volume in large vessel occlusion strokes. However, our study found that percentage infarct volumes did not differ significantly between female patients and male patients. Moreover, in female patients, stroke more frequently affected the basal ganglia, internal capsule, and corona radiata compared with male patients. That these motor-eloquent subcortical regions are more often involved in female patients (vs. ataxia-related cerebellar regions in male patients) align with higher NIHSS scores in female patients, since the motor elements have a maximum total of 11 points (facial palsy and unilateral limb weakness) in the scoring system. In contrast, the ataxia element has a maximum of only 2 points. Although cerebrocortical and cerebellar lesions were more common in male patients than in female patients, these lesions are less often associated with limb weakness.

More frequent striatocapsular lesions in female patients were in line with more frequent symptomatic MCA and ACA steno-occlusion (by about 6% and 2%, respectively, than in male patients). This is a novel finding that merits further future investigation. In contrast, more frequent cerebrocortical and cerebellar lesions in male patients aligned with more frequent symptomatic steno-occlusion of the extracranial ICA and the vertebral artery (by about 5% and 2%, respectively, than in female patients). In addition, the probability of symptomatic MCA steno-occlusion increased with aging, more steeply in female patients than in male patients. The sex difference in symptomatic intracranial arterial stenosis locations is supported by a Chinese prospective multicenter study of 2,864 consecutive patients with acute ischemic stroke that showed intracranial atherosclerosis occurred about 6% more in female than male patients aged>63 years.

In accordance with our recent study, covariate-adjusted END was higher in female patients (18.3%) than male patients (14.9%), particularly in patients aged>52 years and non-SVO strokes. The higher END incidence in female patients (vs. male patients) may be partly
because female patients’ infarctions, particularly in the elderly, are more likely to occur in the striatocapsular region, which is susceptible to END.\textsuperscript{32} Also, note that a) an increment in NIHSS score is a key element in defining END, b) greater amount of real estate afforded to motor/strength testing in the NIHSS scoring system,\textsuperscript{33} and c) motor deficit progression is frequently observed in patients with striatocapsular infarctions.\textsuperscript{34} Future studies should investigate if and how a) changes in sex hormone levels in the elderly strengthen the association between female (vs. male) stroke and END and b) more aggressive acute treatment should be considered for female patients (vs. male patients with similar percentage infarct volume), especially in elderly patients with MCA steno-occlusion-related infarction involving the striatocapsular region.

Many studies have reported that female patients were less likely than male patients to regain functional independence after ischemic stroke. A recent meta-analysis suggested that worse post-stroke outcomes in female patients could be explained mainly by age, stroke severity, and pre-stroke dependency.\textsuperscript{3} Several other studies,\textsuperscript{3,4} however, showed that these factors do not fully explain sex differences in post-stroke outcomes. Our study demonstrated that older age, more severe presenting symptoms, and more frequent END accounted for about 64\% of female patients’ higher risk of unfavorable functional outcome (eDiscussion in the Supplement). Other biological,\textsuperscript{35-37} socioeconomic,\textsuperscript{38,39} cultural,\textsuperscript{40} and psychological\textsuperscript{41} factors are likely also relevant. Sociocultural and psychological features are outside the scope of the present work, as these data were not collected. Follow-up investigations should identify important but still unknown factors that contribute (about 36\%) to the sex difference in functional outcomes after ischemic stroke.

The study by Bonkhoff et al.,\textsuperscript{6} which was based on a low-dimensional representation of anatomical stroke lesions and a Bayesian hierarchical modeling framework, found more
widespread eloquent lesion patterns in female patients than in male patients, indicating that
more regions (predominantly left hemisphere lesions in the posterior circulation territory such
as thalamus, hippocampus, and occipital cortical brain regions) contributed to stroke severity
in female patients. Our study is based on conventionally-used multivariable statistical and
mapping methods applied to a larger dataset of consecutive stroke patients, but reports similar
sex disparities in ischemic stroke: for example, both studies showed pronounced female-
specific effects with advanced age, and our study also found left posterior circulation
territories to be associated with a significantly higher admission NIHSS score in female
patients than in male patients. However, we further demonstrate that compared with the
intrinsic difference, more frequent involvement of motor-eloquent subcortical regions in
female (vs. male) infarction (i.e., anatomic difference) may have a stronger relationship with
stroke severity. In addition, our study provides a more comprehensive view of biological
mechanism underlying sex difference in stroke, including END and 3-month functional
outcome as well as the initial neurological severity (Figure 5).

Our study has several strengths and weaknesses (See eDiscussion in the Supplement).

In conclusion, our study demonstrates that the biological basis of sex differences in stroke,
including more severe stroke manifestation, more frequent END, and poorer functional
outcome in female patients, is probably due to more frequent symptomatic steno-occlusion in
the MCA and accordingly more frequent infarction in the motor-eloquent striatocapsular
region in female patients, particularly in the elderly. In addition, there is likely a minor
contribution from the left parieto-occipital cortical brain regions, where female patients have
a higher stroke severity than male patients with similar infarct volumes. More aggressive
acute stroke therapy and more prolonged rehabilitation therapy should be considered for
female patients, clinical changes that should be based on the sex difference in culprit
cerebrovascular and infarct locations.

References


37. Luders E, Gaser C, Narr KL, Toga AW. Why sex matters: brain size independent


## Table 1. Baseline characteristics: female vs. male.

<table>
<thead>
<tr>
<th></th>
<th>Female (n=2,641)</th>
<th>Male (n=3,823)</th>
<th>P</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), year</td>
<td>71.1±12.0</td>
<td>65.1±12.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LKW time to admission, median (IQR), hour</td>
<td>13.0 (3.6–36.0)</td>
<td>11.4 (3.3–35.8)</td>
<td>0.09c</td>
<td>0.87</td>
</tr>
<tr>
<td>Onset to imaging time, median (IQR), hour</td>
<td>15.4 (6.0–38.1)</td>
<td>13.8 (5.7–37.9)</td>
<td>0.10c</td>
<td>0.62</td>
</tr>
<tr>
<td>Pre-stroke mRS score &gt; 2, No. (%)</td>
<td>404 (15.3%)</td>
<td>390 (10.2%)</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Admission NIHSS score, median (IQR)</td>
<td>4 (2–9)</td>
<td>3 (2–7)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Subtype, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAA</td>
<td>966 (36.6%)</td>
<td>1591 (41.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVO</td>
<td>431 (16.3%)</td>
<td>673 (17.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>636 (24.1%)</td>
<td>713 (18.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>541 (20.5%)</td>
<td>767 (20.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other determined</td>
<td>67 (2.5%)</td>
<td>79 (2.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke, No. (%)</td>
<td>499 (18.9%)</td>
<td>775 (20.3%)</td>
<td>0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary artery disease, No. (%)</td>
<td>226 (8.6%)</td>
<td>324 (8.5%)</td>
<td>0.91</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>1931 (73.1%)</td>
<td>2529 (66.2%)</td>
<td>&lt;0.001</td>
<td>0.036</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>862 (32.6%)</td>
<td>1309 (34.2%)</td>
<td>0.18</td>
<td>0.056</td>
</tr>
<tr>
<td>Hyperlipidemia, No. (%)</td>
<td>915 (34.7%)</td>
<td>1354 (35.4%)</td>
<td>0.52</td>
<td>0.97</td>
</tr>
<tr>
<td>Smoking, current or quit ≤ 5 years, No. (%)</td>
<td>187 (7.1%)</td>
<td>2430 (63.6%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, No. (%)</td>
<td>646 (24.5%)</td>
<td>688 (18.0%)</td>
<td>&lt;0.001</td>
<td>0.042</td>
</tr>
<tr>
<td>Pre-stroke antiplatelet use, No. (%)</td>
<td>795 (30.1%)</td>
<td>1085 (28.4%)</td>
<td>0.13</td>
<td>0.20</td>
</tr>
<tr>
<td>Pre-stroke statin use, No. (%)</td>
<td>423 (16.4%)</td>
<td>607 (15.9%)</td>
<td>0.88</td>
<td>0.29</td>
</tr>
<tr>
<td>Revascularization therapy, No. (%)</td>
<td>429 (16.2%)</td>
<td>625 (16.4%)</td>
<td>0.91</td>
<td>0.70</td>
</tr>
<tr>
<td>Percentage infarct volume, median (IQR)</td>
<td>0.14 (0.03–0.81)</td>
<td>0.14 (0.03–0.86)</td>
<td>0.35c</td>
<td>0.09</td>
</tr>
<tr>
<td>in cm³</td>
<td>2.32 (0.61–12.7)</td>
<td>2.26 (0.51–13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage WMH volume, median (IQR)</td>
<td>0.96 (0.46–2.00)</td>
<td>0.74 (0.39–1.53)</td>
<td>&lt;0.001c</td>
<td>0.23</td>
</tr>
<tr>
<td>in cm³</td>
<td>15.7 (7.56–32.6)</td>
<td>12.0 (6.29–24.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age.

Data are presented as the percentage of total brain parenchymal volume; and, the calculation of the lesion volumes in cm³ was based on the reported mean brain volume of an elderly Korean population (1,170 cm³). For a reference map that displays lesion volumes in cm³, see the reference. A rank-sum test was used.

LKW = last known well; IQR, interquartile range; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; LAA = large artery atherosclerosis; SVO = small vessel occlusion; CE = cardioembolism; WMH = white matter hyperintensity.
Table 2. Association of sex with National Institutes of Health Stroke Scale (NIHSS) score, incidence of early neurological deterioration (END), and unfavorable functional outcome: overall and at 10, 25, 50, 75, and 90\textsuperscript{th} percentiles of percentage infarct volumes

<table>
<thead>
<tr>
<th>Percentage infarct volume</th>
<th>Overall</th>
<th>10\textsuperscript{th} percentile</th>
<th>25\textsuperscript{th} percentile</th>
<th>50\textsuperscript{th} percentile</th>
<th>75\textsuperscript{th} percentile</th>
<th>90\textsuperscript{th} percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct Volume (% of total brain parenchymal volume)</td>
<td>0.009</td>
<td>0.034</td>
<td>0.144</td>
<td>0.860</td>
<td>3.389</td>
<td></td>
</tr>
<tr>
<td>NIHSS score\textsuperscript{a}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female patients, adjusted mean (95% CI)</td>
<td>2.7 (2.1–3.4)</td>
<td>1.9 (1.3–2.5)</td>
<td>1.9 (1.3–2.6)</td>
<td>2.0 (1.3–2.6)</td>
<td>2.5 (1.8–3.1)</td>
<td>4.2 (3.5–4.8)</td>
</tr>
<tr>
<td>Male patients, adjusted mean (95% CI)</td>
<td>2.6 (1.9–3.3)</td>
<td>1.5 (0.8–2.2)</td>
<td>1.5 (0.8–2.2)</td>
<td>1.6 (0.9–2.3)</td>
<td>2.2 (1.6–2.9)</td>
<td>4.4 (3.7–5.1)</td>
</tr>
<tr>
<td>Adjusted mean difference (95% CI)</td>
<td>0.2 (-0.1–0.4)</td>
<td>0.4 (0.1–0.7)</td>
<td>0.4 (0.1–0.7)</td>
<td>0.4 (0.1–0.6)</td>
<td>0.2 (0.0–0.5)</td>
<td>-0.2 (-0.6–0.1)</td>
</tr>
<tr>
<td>P</td>
<td>0.23</td>
<td>0.004</td>
<td>0.004</td>
<td>0.006</td>
<td>0.07</td>
<td>0.22</td>
</tr>
<tr>
<td>END\textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female patients, adjusted incidence (95% CI)</td>
<td>18.3 (16.7–20.0)</td>
<td>16.8 (15.0–18.3)</td>
<td>16.7 (12.5–15.1)</td>
<td>16.8 (15.2–18.5)</td>
<td>17.6 (15.9–19.3)</td>
<td>20.6 (18.7–22.6)</td>
</tr>
<tr>
<td>Male patients, adjusted incidence (95% CI)</td>
<td>14.9 (13.7–16.1)</td>
<td>13.8 (12.5–15.1)</td>
<td>13.8 (12.6–15.1)</td>
<td>13.9 (12.6–15.1)</td>
<td>14.4 (13.2–15.6)</td>
<td>16.3 (14.8–17.8)</td>
</tr>
<tr>
<td>Adjusted risk difference, % (95% CI)</td>
<td>3.5 (1.2–5.7)</td>
<td>2.9 (0.6–5.1)</td>
<td>2.9 (0.6–5.1)</td>
<td>2.9 (0.7–5.2)</td>
<td>3.2 (1.0–5.5)</td>
<td>4.3 (1.7–6.9)</td>
</tr>
<tr>
<td>P</td>
<td>0.002</td>
<td>0.013</td>
<td>0.012</td>
<td>0.011</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>Unfavorable functional outcome\textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female patients, adjusted incidence (95% CI)</td>
<td>39.7 (37.9–41.5)</td>
<td>32.9 (30.9–34.9)</td>
<td>33.1 (31.1–35.1)</td>
<td>33.8 (31.9–35.8)</td>
<td>39.1 (37.1–41.1)</td>
<td>59.0 (54.8–63.2)</td>
</tr>
<tr>
<td>Male patients, adjusted incidence (95% CI)</td>
<td>35.2 (33.8–36.6)</td>
<td>28.4 (26.8–30.0)</td>
<td>28.6 (26.9–30.2)</td>
<td>29.3 (27.7–30.9)</td>
<td>34.1 (32.5–35.7)</td>
<td>53.2 (49.9–56.5)</td>
</tr>
<tr>
<td>Adjusted risk difference, % (95% CI)</td>
<td>4.5 (2.0–7.0)</td>
<td>4.5 (1.7–7.2)</td>
<td>4.5 (1.7–7.3)</td>
<td>4.6 (1.8–7.3)</td>
<td>5.0 (2.2–7.8)</td>
<td>5.8 (0.4–11.2)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.037</td>
</tr>
</tbody>
</table>

\textsuperscript{a}A mixed-effects quantile regression model was used. The estimates were adjusted for age, pre-stroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia,
atrial fibrillation, smoking, history of prior stroke, percentage white matter hyperintensity volume, and onset to imaging time.

Difference for female patients relative to male patients.

A mixed-effects logistic regression model was used. The estimates were adjusted for age, pre-stroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, history of prior stroke, percentage white matter hyperintensity volume, onset to imaging time, and revascularization therapy.
**Figure legends**

**Figure 1. Associations of percentage infarct volume with admission National Institutes of Health Stroke Scale (NIHSS) score, its subitems, and regional infarct probabilities: female vs. male.** (A) Admission NIHSS score and its subitems (weakness and ataxia). (B) Regional infarct probabilities in cortex, striatocapsular region [corona radiata, basal ganglia, and internal capsule], and cerebellum. Mixed-effects quantile regression analyses were performed to investigate the sex differences by adjusting for age, pre-stroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, history of prior stroke, percentage white matter hyperintensity volume, and onset to imaging time. Dots and error bars (red for female patients and blue for male patients) indicate the adjusted mean values and their 95% CIs, respectively. Green bars show the distribution of percentage infarct volumes in this study cohort. *P<0.05 for the adjusted difference between female patients and male patients. Please note that “P for interaction” does not reflect sex difference in infarct expansion-related increase of the values within individual patients.
Figure 2. Age-related sex differences in the probabilities of symptomatic large artery steno–occlusion vs. regional infarct probabilities. (A) Probabilities of symptomatic steno-occlusion of the middle cerebral artery (MCA), extracranial internal carotid artery (ICA), and vertebral artery with age: female vs. male. (B) Infarct probabilities in the striatocapsular region (basal ganglia / internal capsule and corona radiata), cortex, and cerebellum with age: female vs. male. Mixed-effects logistic regression analyses were performed with adjustment for pre-stroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, history of prior stroke, percentage white matter hyperintensity volume, and onset to imaging time. Each dot and error bars (red for female patients and blue for male patients) indicate the adjusted mean probability and its 95% CIs, respectively. Green bars show the age distribution in this study cohort. *P<0.05 for the adjusted difference between female patients and male patients.
Figure 3. Association of percentage infarct volume with the incidence of either early neurological deterioration (END) or unfavorable functional outcome, with stratification by sex and age. (A) Analyses of END for all patients, younger patients (≤52 years), and older patients (>52 years). (B) Analyses of unfavorable functional outcome (3-month modified Rankin Scale score>2) for all patients, younger patients (≤52 years), and older patients (>52 years). Mixed-effects logistic regression analysis shows age-specific and percentage infarct volume-dependent sex differences in the incidence of either END or unfavorable functional outcome, with adjustment for age, pre-stroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, history of prior stroke, percentage white matter hyperintensity volume, onset to imaging time, and revascularization therapy. Dots and error bars (red for female patients and blue for male patients) indicate adjusted mean incidences of either END or unfavorable functional outcome and their 95% CIs, respectively. Green bars show the distribution of percentage infarct volumes in this study cohort. *P<0.05 for the adjusted difference between female patients and male patients.
Figure 4. Multivariable brain mapping and regression analyses to investigate sex-dependent associations of the lesion presence rates in sex-related brain regions with admission National Institutes of Health Stroke Scale (NIHSS) score, the incidence of early neurological deterioration (END), or the incidence of unfavorable functional outcome. (A) Female- and Male-infarct-prone regions of interest (ROIs; Anatomic ROIs different between sexes) showing a significant sex difference in the regional lesion probability. Top left. ROI-wise t-scores for the sex difference in the lesion probabilities are displayed with color coding (red/orange for female patients and blue shades for male patients) on the axial images of Montreal Neurological Institute brain templates (z-axis coordinates = -40, -5 and 30). L and R denote left and right, respectively. Bottom left. A three-dimensional representation of the significant ROIs is displayed. C, A, and S denote coronal, axial, and sagittal views, respectively. Right. A complete list of the significant ROIs, with their labels from the Anatomical Labeling (AAL) and Johns Hopkins University (JHU) atlases. (B) Sex-NIHSS interaction ROIs showing similar anatomic areas with different sex-related impact on admission NIHSS score, suggesting intrinsic (as opposed to anatomic) sex differences. Unlike these Intrinsic ROIs that penalize female infarction, there is no ROI that penalizes male infarction. An Intrinsic ROI (left middle occipital cortex) that overlaps with the male-infarct-prone Anatomic ROIs is outlined in blue. Note that there was no significant sex-END_incidence interaction region or sex-unfavorable_outcome interaction region (eFigures 6 and 7 in the Supplement). (C) Multivariable regression analyses to show sex-related associations of the lesion presence rate (=number of infarct-positive ROIs / number of all ROIs) in each of the sex-related brain regions (female- and male-infarct-prone regions with or without sex-NIHSS interaction region) with the NIHSS score, the incidence of END and the incidence of unfavorable functional outcome (3-month modified Rankin scale score > 2). $\beta$s indicate beta coefficients, and Ts indicates t-statistics for independent variables in the
regression models.

PAL = pallidum; PUT = putamen; AIC = anterior limb of internal capsule; PIC = posterior limb of internal capsule; EC = external capsule; SFOF = superior fronto-occipital fasciulus; IOC = inferior occipital cortex; MOC = middle occipital cortex; CBL = cerebellum; CBV = cerebellar vermis; MTC = middle temporal cortex; SPC = superior parietal cortex; IPC = inferior parietal cortex; SMG = supramarginal gyrus; ANG = angular gyrus; SOC = superior occipital cortex; CUN = cuneus; CAL = calcarine.

<table>
<thead>
<tr>
<th>ROI list</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female-infarct-prone region</strong></td>
</tr>
<tr>
<td>AAL</td>
</tr>
<tr>
<td>JHU</td>
</tr>
<tr>
<td><strong>Male-infarct-prone region</strong></td>
</tr>
<tr>
<td>AAL</td>
</tr>
<tr>
<td>JHU</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Center</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ROI list</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex-NIHSS interaction region that penalizes female infarction</strong></td>
</tr>
<tr>
<td>AAL</td>
</tr>
<tr>
<td>JHU</td>
</tr>
<tr>
<td><strong>Sex-NIHSS interaction region that penalizes male infarction</strong></td>
</tr>
<tr>
<td>No significant region</td>
</tr>
</tbody>
</table>

| Model | Independent variables | \( \beta \) | 95% CI | T | P |
|-----------------------------------|
| **NIHSS = Intercept + \( \beta_{\text{IHSS}} \times \text{sex} \) + Covariates** | Sex-NIHSS interaction region | Message rate | Message rate | 1.53 | 1.32–1.74 | 14.44 | <0.001 |
| **END = Intercept + \( \beta_{\text{END}} \times \text{sex} \) + Covariates** | Male-infarct-prone region | Message rate | Message rate | 0.43 | 0.36–0.53 | 4.23 | <0.001 |
| **Unfavorable functional outcome = Intercept + \( \beta_{\text{outcome}} \times \text{sex} \) + Covariates** | Male-infarct-prone region | Message rate | Message rate | 0.08 | 0.05–0.22 | 2.13 | 0.047 |

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Figure 5. Graphical representation of proposed mechanisms of sex difference in stroke manifestation and outcomes. This diagram was generated based on our results from the multivariable statistical and brain mapping as well as the literature on other biological, socioeconomic, cultural, and psychological factors. The middle occipital cortex is outlined in II (yellow) and III (blue) to show the overlapping region.

>: comparison of the strength of the effect of two significant factors, based on the comparison of corresponding beta coefficients from the multivariable brain mapping-related regression analyses (Figure 4). *in older patients (>52 years).

MCA = middle cerebral artery; ICA = internal carotid artery; NIHSS = National Institutes of Health Stroke Scale; END = early neurological deterioration.