RESEARCH ARTICLE OPEN ACCESS

Biological Mechanism of Sex Difference in Stroke Manifestation and Outcomes

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Neurology® 2023;100:e2490-e2503. doi:10.1212/WNL.0000000000207346

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 NIH Stroke Scale (NIHSS) score, early neurologic deterioration (END) 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

The 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 END (adjusted difference 3.5%; $p = 0.002$) than male patients. Female patients had more frequent striato-capsular lesions (43.6% vs 39.8%, $p = 0.001$) and less frequent cerebrocortical (48.2% vs. 50.7% in patients older than 52 years, $p = 0.06$) and cerebellar (9.1% vs. 11.1%, $p = 0.009$) lesions than male patients, which aligned with angiographic findings: female patients had more prevalent symptomatic steno-occlusion of the middle cerebral artery (MCA) (31.1% vs 25.3%; $p < 0.001$) compared with 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

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

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

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 MCA 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 neurologic symptoms, higher susceptibility to neurologic worsening, and less 3-month functional independence, when compared with male patients.

The greater impact of stroke on female patients could be related to older age, more prestroke comorbidities, lower socioeconomic status, and more conservative treatment.[1,2] However, previous studies showed that statistical adjustments for these factors did not abolish sex differences in stroke manifestations and outcomes.[3-5] The underlying mechanism of age-adjusted and comorbidity-adjusted sex differences needs to be unraveled, preferably in a large number of consecutive patients with acute ischemic stroke to minimize selection bias and better account for socioeconomic and cultural factors.

A recent study (n = 555 derivation cohort patients vs 503 validation cohort patients)[6] 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[7]), the Korean image–based stroke database project is a prospective multicenter study, in which 11 stroke centers in Korea participated (eMethods, links.lww.com/WNL/C780).[8-13] From May 2011 to January 2013, we consecutively enrolled patients with acute ischemic stroke who were admitted to the 11 participating centers within 7 days of symptom onset. Exclusion criteria were as follows: 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 after stroke onset.

Clinical Data and Outcome Measurement

Under a standardized protocol,[8,10,11,13] we collected demographic data, 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, links.lww.com/WNL/C780).[14] Prestroke modified Rankin Scale (mRS) score, NIH Stroke Scale (NIHSS) score at admission, early neurologic deterioration ([END] within 21 days; eMethods) information, and mRS score at 3 months after stroke were prospectively collected.

MRI Registration and Analysis

Brain MRI was performed on 1.5T (n = 5,525) or 3.0T (n = 939) MRI systems, and stroke-related lesions were quantified as previously reported[8-11,15,16] (eMethods, links.lww.com/WNL/C780). 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 neurologic symptoms and signs and imaging findings (eMethods, links.lww.com/WNL/C780).

Statistical Analysis

To compare groups stratified by inclusion vs exclusion and female vs male, we used the Student *t* test or rank sum test for continuous variables and the χ^2 test or Fisher 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[8-12,17] as potentially associated with stroke severity, END, and poststroke functional outcomes, were entered in the models: age, prestroke mRS score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, a history of prior stroke, percentage WMH volume, and onset to MR imaging time. At 10th, 25th, 50th, 75th, and 90th 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 cutoff age of 52 years, the median age of menopause.[18] We also repeated the analyses in patients without prestroke morbidity (those with prestroke mRS scores of 0) for sensitivity analyses. In all the following multivariable analyses, except for ones to predict NIHSS scores, revascularization therapy was also included as a predefined covariate.

Adjusted sex differences in (1) presenting symptoms and (2) 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 8 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 9 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 cutoff age of 52 years.

Adjusted sex differences in (1) symptomatic steno-occlusion of the middle cerebral artery (MCA), extracranial internal carotid artery (ICA), and vertebral arteries and (2) 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 10th, 25th, 50th, 75th, 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-related 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 cutoff age of 52 years. We also repeated the analyses in the patients without prestroke morbidity for sensitivity analyses.

As additional prespecified subgroup analyses according to stroke etiology, we focused on 3 stroke subtypes (large artery atherosclerosis [LAA], small vessel occlusion [SVO], and cardioembolism [CE])[14] and then reexplored sex differences in the neurologic 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[19] to evaluate the direct and indirect effects of sex on unfavorable functional outcome (eMethods, links.lww.com/WNL/C780).

Data were analyzed using STATA (STATA Corp., College Station, TX). A 2-sided p value < 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.[20] 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[21] and Johns Hopkins University (JHU) white matter atlas[22] 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 tiebreaking). We defined infarct lesions to be present in each ROI without any thresholds. Thus, if there was 1 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[23] $p <$ 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. In addition, a 3-dimensional representation of the ROIs was generated using the BrainNet Viewer.[24]

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 an Unfavorable Functional Outcome

To explore whether initial stroke severity–related, stroke worsening–related, or poor functional outcome–related sex differences are because infarct lesions in the same brain regions affect female patients and male patients differently, we performed ROI-wise brain mapping with the NIHSS score, END incidence, or the incidence of an unfavorable functional outcome as a dependent variable while including sex, lesion presence/absence, sex × lesion presence/absence and 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 an (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 and 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 cutoff age of 52 years. A significant difference between β coefficients was identified by evaluating the overlap between 95% CIs.[25]

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 7 days of symptom onset. Of 8,010 patients who gave research consent, 6,464 remained after excluding based on the following criteria: 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 after 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). The median (interquartile range) onset to MR imaging time did not differ significantly between female patients and male patients: 15.4 (6.0–38.1) hours and 13.8 (5.7–37.9) hours ($p = 0.10$). Percentage infarct volumes on DWIs did not differ between the 2 groups (median 0.14% vs 0.14%, $p = 0.35$, eFigure 1, links.lww.com/WNL/C780). There was no significant sex difference in admission NIHSS score between the included and excluded (n = 1,546) patients (eTable 1), who were less likely to have received revascularization therapy (16.3% vs 13.2%). Sex distributed comparably between the 2 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 (older than 52 years) female patients (n = 2,641 vs 3,823 male patients; Figure 1A, Table 2, eFigure 2, eTables 2 and 3, links.lww.com/WNL/C780) and those with low percentage infarct volume (up to 0.6% of brain parenchymal volume, encompassing approximately 70% of all cases). The sex-related modification of the association between percentage infarct volume and stroke severity held in most large arterial infarctions due to LAA (with infarct volume up to 75th percentile, eTable 4) or CE (with infarct volume up to 50th percentile, eTable 5). However, in SVO strokes (eTable 6), 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 approximately 0.005% of brain parenchymal volume; this comprised about 10% of all cases with SVO.

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 intergroup differences in the other NIHSS subitems (eFigure 3A, links.lww.com/WNL/C780), except for aphasia in patients (n = 1,216, 18.8%) with very large percentage infarct volume (higher than 2.7% of brain parenchymal volume).

Table 1 Baseline Characteristics: Female vs Male

	Female (n = 2,641)	Male (n = 3,823)	*p* Value	*p* Value[a]
Age, y, mean ± SD	71.1 ± 12.0	65.1 ± 12.4	<0.001	
LKW time to admission, h, median (IQR)	13.0 (3.6–36.0)	11.4 (3.3–35.8)	0.09[b]	0.87
Onset to MR imaging time, h, median (IQR)	15.4 (6.0–38.1)	13.8 (5.7–37.9)	0.10[b]	0.62
Prestroke mRS score >2, n (%)	404 (15.3)	390 (10.2)	<0.001	0.003
Admission NIHSS score, median (IQR)	4 (2–9)	3 (2–7)	<0.001	0.001
Subtype, n (%)			<0.001	<0.001
LAA	966 (36.6)	1,591 (41.6)		
SVO	431 (16.3)	673 (17.6)		
CE	636 (24.1)	713 (18.7)		
Undetermined	541 (20.5)	767 (20.1)		
Other determined	67 (2.5)	79 (2.1)		
Previous stroke, n (%)	499 (18.9)	775 (20.3)	0.17	0.001
Coronary artery disease, n (%)	226 (8.6)	324 (8.5)	0.91	0.06
Hypertension, n (%)	1,931 (73.1)	2,529 (66.2)	<0.001	0.036
Diabetes, n (%)	862 (32.6)	1,309 (34.2)	0.18	0.056
Hyperlipidemia, n (%)	915 (34.7)	1,354 (35.4)	0.52	0.97
Smoking, current or quit ≤5 y, n (%)	187 (7.1)	2,430 (63.6)	<0.001	<0.001
Atrial fibrillation, n (%)	646 (24.5)	688 (18.0)	<0.001	0.042
Prestroke antiplatelet use, n (%)	795 (30.1)	1,085 (28.4)	0.13	0.20
Prestroke statin use, n (%)	423 (16.4)	607 (15.9)	0.88	0.29
Revascularization therapy, n (%)	429 (16.2)	625 (16.4)	0.91	0.70
Percentage infarct volume,[c] median (IQR)	0.14 (0.03–0.81)	0.14 (0.03–0.86)	0.35[b]	0.09
in cm^3	2.32 (0.61–12.7)	2.26 (0.51–13.8)		
Percentage WMH volume,[c] median (IQR)	0.96 (0.46–2.00)	0.74 (0.39–1.53)	<0.001[b]	0.23
in cm^3	15.7 (7.56–32.6)	12.0 (6.29–24.9)		

Abbreviations: CE = cardioembolism; IQR = interquartile range; LAA = large artery atherosclerosis; LKW = last known well; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; SVO = small vessel occlusion; WMH = white matter hyperintensity.
[a] Adjusted for age.
[b] A rank sum test was used.
[c] Data are presented as the percentage of total brain parenchymal volume; and the calculation of the lesion volumes in cm^3 was based on the reported mean brain volume of an elderly Korean population (1,170 cm^3).[26] For a reference map that displays lesion volumes in cm^3, see the reference.[15]

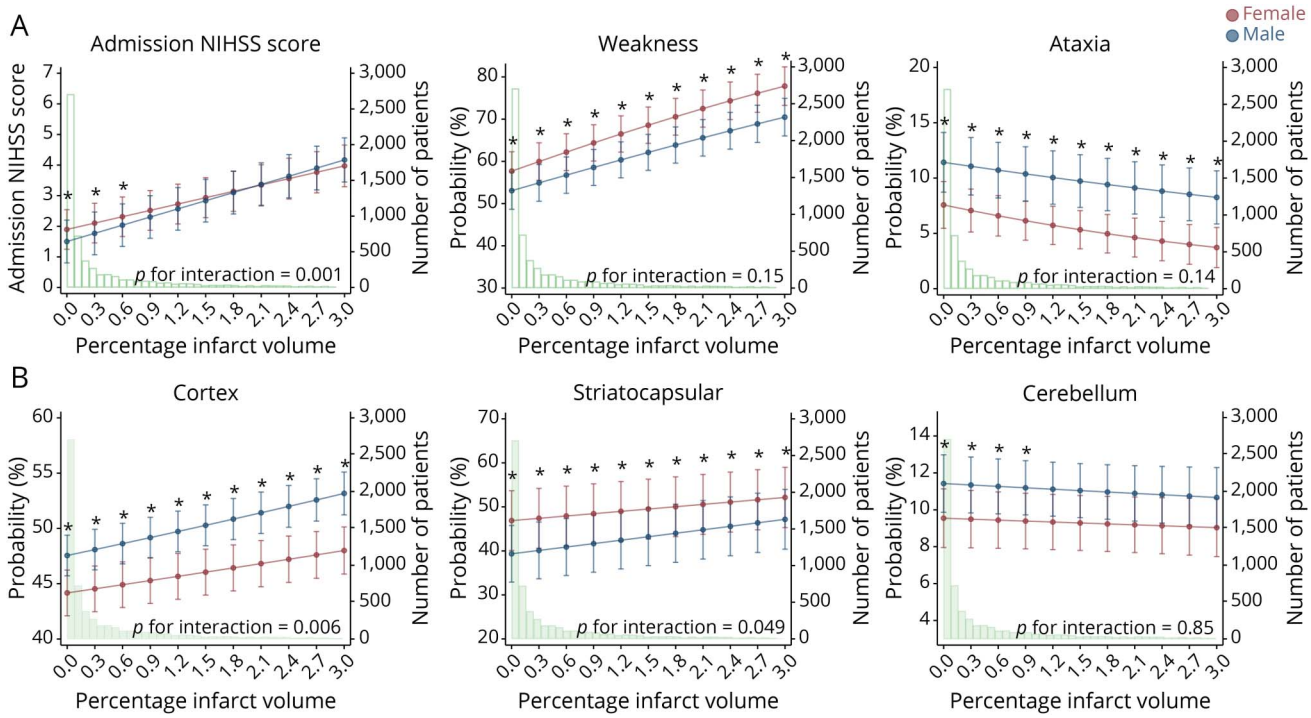
Sex Difference in Infarct Locations

Overall, female patients had more frequent striatocapsular lesions (43.3% vs 39.3%, $p = 0.001$; eTable 7, links.lww.com/WNL/C780). Multivariable analyses (Figure 1B and eFigure 3B) also showed that compared with male patients, female patients were significantly more likely to have striatocapsular lesions (regardless of percentage infarct volume). By 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 in female patients when the percentage infarct volumes were as low as approximately 0.9%, which encompassed approximately 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

Figure 1 Association of Percentage Infarct Volume With Admission NIHSS Score, Its Subitems, or 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 with adjustment for age, prestroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, a history of prior stroke, percentage white matter hyperintensity volume, and onset to MR 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. NIHSS = NIH Stroke Scale.

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, links.lww.com/WNL/C780). These sex differences held significance only in the older group. The probability of symptomatic MCA steno-occlusion increased with age, more steeply in female patients than in 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 years or higher. By contrast, cortical and cerebellar involvement by infarction was significantly higher in male patients than in female patients, in older (65 years or older) and younger (65 years or younger) patients, respectively (Figure 2B and eTable 7, links.lww.com/WNL/C780), 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 END

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), and the difference held significance 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, links.lww.com/WNL/C780). CE strokes showed a similar trend (eTable 5). However, there was no significant sex difference in the END incidence for SVO strokes, regardless of percentage infarct volume (eTable 6).

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

Table 2 Association of Sex With NIHSS Score, Incidence of END, or Unfavorable Functional Outcome: Overall and at 10th, 25th, 50th, 75th, and 90th Percentiles of Percentage Infarct Volumes

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

Abbreviations: END = early neurologic deterioration; NIHSS = NIH Stroke Scale.
[a] A mixed-effects quantile regression model was used. The estimates were adjusted for age, prestroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, a history of prior stroke, percentage white matter hyperintensity volume, and onset to MR imaging time.
[b] Difference for female patients relative to male patients.
[c] A mixed-effects logistic regression model was used. The estimates were adjusted for age, prestroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, a history of prior stroke, percentage white matter hyperintensity volume, onset to MR imaging time, and revascularization therapy.

2.0–7.0, $p < 0.001$; NNT 22.2; Table 2), regardless of percentage infarct volume (Figure 3B). The sex difference in the 3-month functional outcome held in the older group (n = 5,570) but not in the younger group (n = 894).

Mediation analysis was performed to reveal the mechanism underlying the association between sex and poststroke functional outcome. As mentioned earlier, we prespecified the hypothetical pathways from female (vs male) to more frequent unfavorable functional outcome through older age, higher admission NIHSS score, less frequent revascularization therapy, and more frequent END, while adjusting for the covariates (See eMethods, links.lww.com/WNL/C780). We found that these 4 factors significantly mediated the association female patients have with unfavorable functional outcome (eFigure 4; adjusted β coefficient = 0.058, 95% CI 0.045–0.070), accounting for 63.7% of total effect.

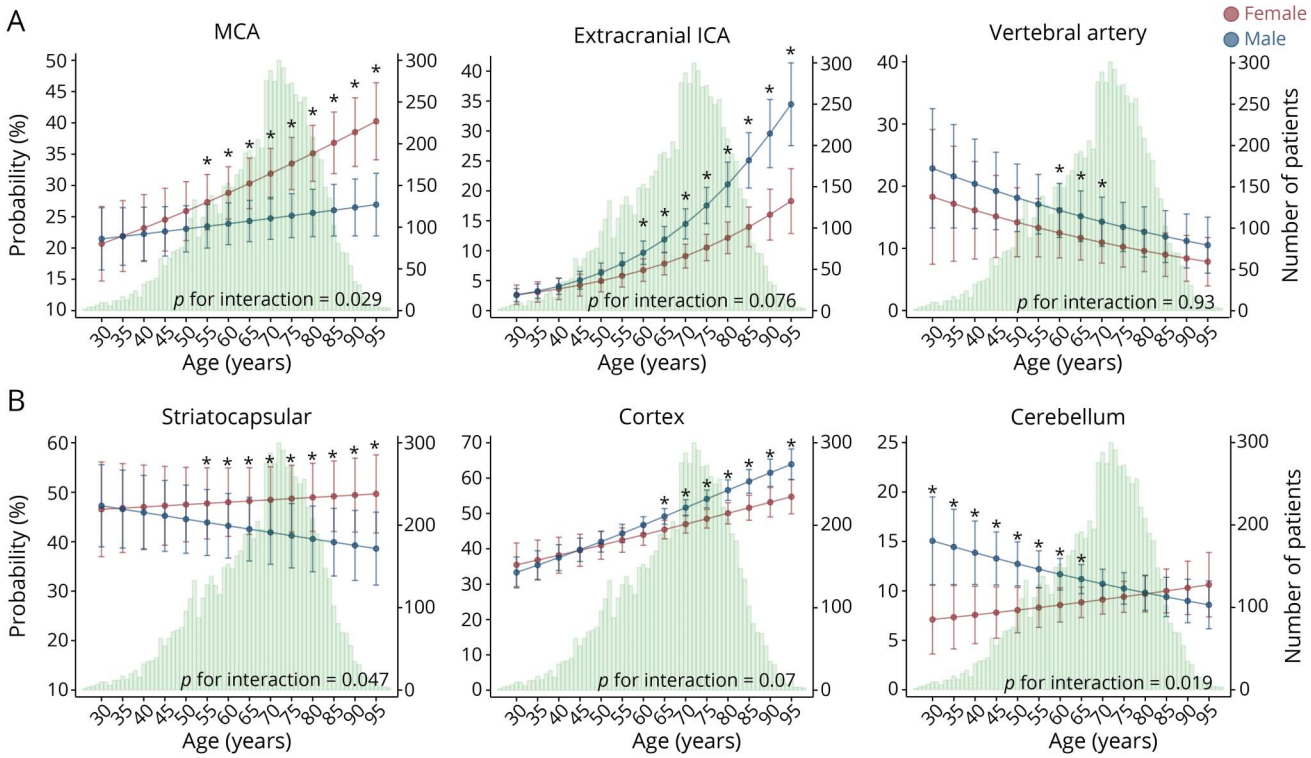
Sensitivity Analyses

When the analyses were confined to 5,192 patients without prestroke morbidity, female patients again had higher NIHSS scores, higher END incidence, and an elevated risk of unfavorable functional outcome at 3 months, compared with male patients (eTable 9, links.lww.com/WNL/C780).

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

Figure 2 Age-Related Sex Differences in the Probabilities of Symptomatic Large Artery Steno-Occlusion vs Regional Infarct Probabilities



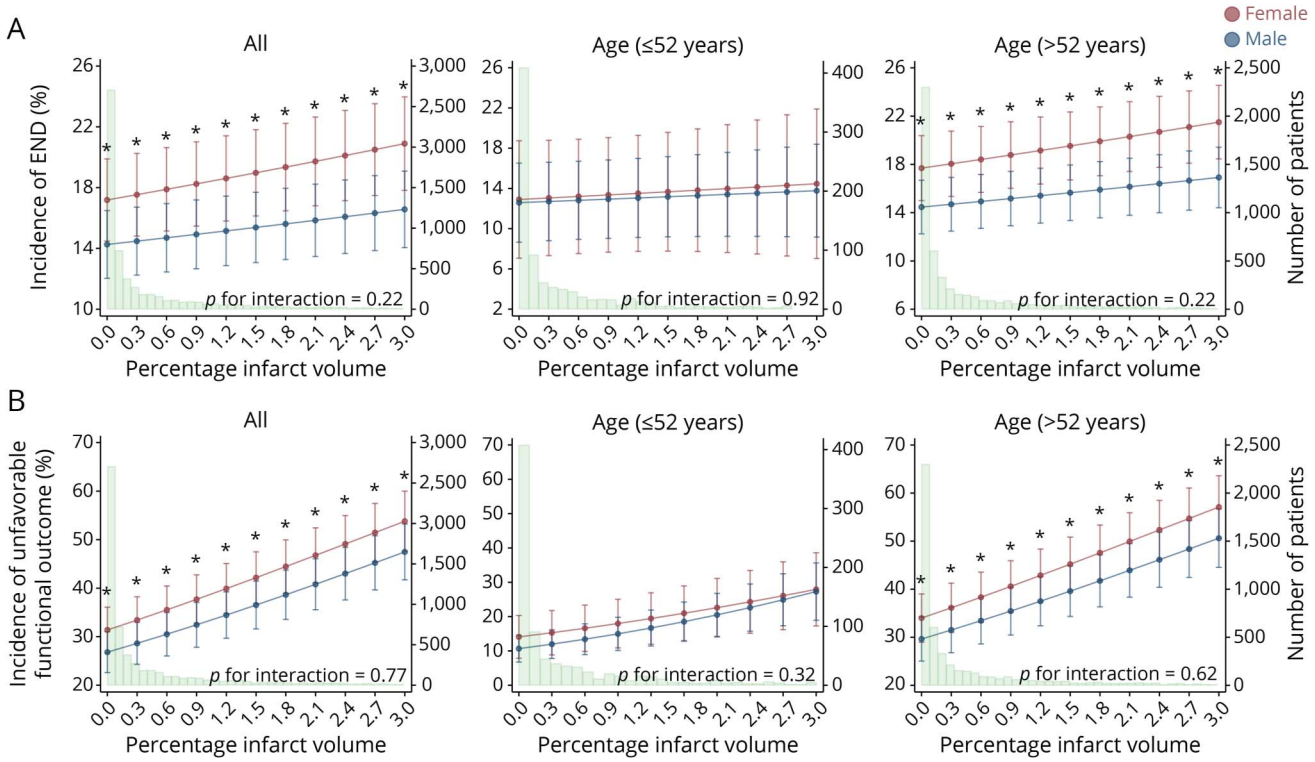
(A) Probabilities of symptomatic steno-occlusion of the MCA, extracranial ICA, and vertebral artery with age: female vs male. (B) Infarct probabilities in the striatocapsular region (basal ganglia/internal capsule and corona radiata), cortex, and cerebellum with age: female vs male. Mixed-effects logistic regression analyses were performed with adjustment for prestroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, a history of prior stroke, percentage white matter hyperintensity volume, and onset to MR 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. ICA = internal carotid artery; MCA = middle cerebral artery.

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, links.lww.com/WNL/C780).

We found 9 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. Regarding 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, links.lww.com/WNL/C780).

Multivariable regression models estimated the relative contributions of anatomic vs intrinsic sex differences in explaining the following: (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 as follows: (1) the lesion presence rate in the female infarct-prone (i.e., anatomic) region ($\beta = 1.24$) and (2) the lesion presence rate × sex (0 for female patients, 1 for male patients) in the interaction (i.e., intrinsic) region, but with a significantly lower β coefficient ($\beta = -0.43$, $p < 0.01$; a negative β 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 β 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, links.lww.com/WNL/C780). 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 neurologic severity for similar infarct volumes). Second, the lesion presence rate in the female infarct-prone region

Figure 3 Association of Percentage Infarct Volume With the Incidence of Either END or Unfavorable Functional Outcome, With Stratification by Sex and Age



(A) Analyses of END for all patients, younger patients (52 years or younger), and older patients (older than 52 years). (B) Analyses of unfavorable functional outcome (3-month modified Rankin Scale score >2) for all patients, younger patients (52 years or younger), and older patients (older than 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, prestroke modified Rankin Scale score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, a history of prior stroke, percentage white matter hyperintensity volume, onset to MR 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. END = early neurologic deterioration.

associated with the END incidence ($\beta = 0.10$, $p = 0.003$), 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 associated with the incidence of unfavorable functional outcome (both $p < 0.001$); however, the β 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). p Values for all multivariable models were less than 10^{-5}.

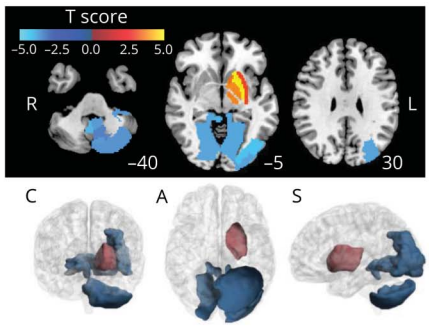
Discussion

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 neurologic symptoms and poorer 3-month functional outcomes probably due to anatomic sex differences: that is, 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.[27] In addition, multivariable brain mapping showed that left parieto-occipital cortical brain regions associate with a significantly higher neurologic severity in female patients, although this intrinsic difference had less impact when compared with the anatomic sex differences.

In line with previous research,[28,29] our study showed that female patients with acute ischemic stroke presented with more severe neurologic symptoms compared with male patients. Multivariable adjustment for age and other covariates

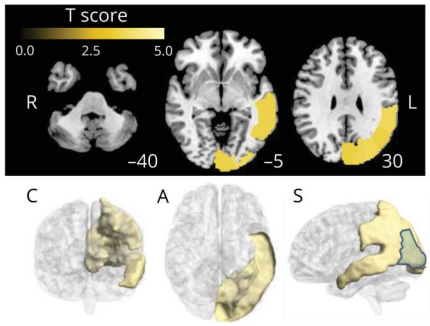
Figure 4 Multivariable Brain Mapping and Regression Analyses to Investigate Sex-Dependent Associations of the Lesion Presence Rates in Sex-Related Brain Regions With Admission NIHSS Score, the Incidence of END, or the Incidence of Unfavorable Functional Outcome

A



ROI list					
Female-infarct-prone region					
AAL	Left	PAL	PUT		
JHU	Left	AIC	PIC	EC	SFOF
Male-infarct-prone region					
AAL	Left	Lingual	IOC	MOC	CBL 7b
		CBL 8	CBL 9	CBL Crus2	
	Right	Lingual			
	Center	CBV 3	CBV 9		

B



ROI list					
Sex-NIHSS interaction region that penalizes female infarction					
AAL	Left	MTC			
		SPC	IPC	SMG	ANG
		SOC	MOC	CUN	CAL
Sex-NIHSS interaction region that penalizes male infarction					
No significant region					

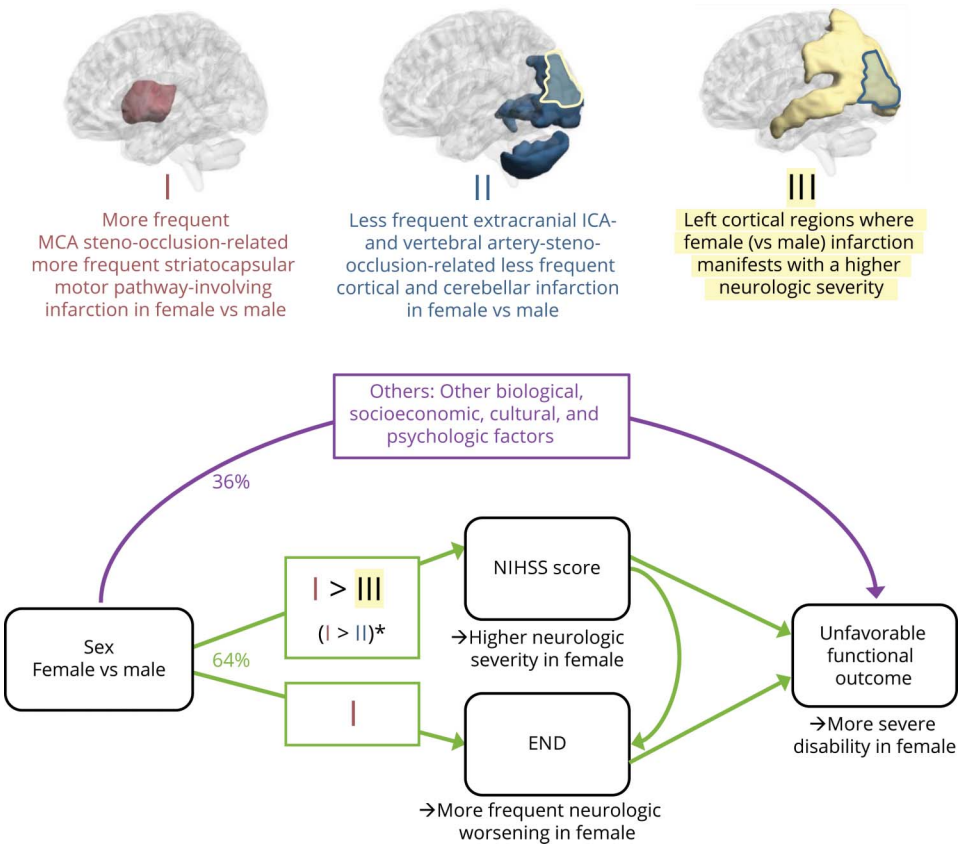
C

Model	Independent variables		β	95% CI	T	P
NIHSS = Intercept + β_{1-11} x Covariates[a] + β_{12-14} x lesion presence rate in regions + β_{15} x (lesion presence rate x sex) in the sex-NIHSS interaction region	Sex-NIHSS interaction region	Lesion presence rate	1.53	1.32–1.74	14.44	<0.001
		Lesion presence rate × sex	−0.43	−0.64–−0.23	−4.23	<0.001
	Female-infarct -prone region	Lesion presence rate	1.24	1.11–1.37	18.66	<0.001
	Male-infarct -prone region	Lesion presence rate	0.08	−0.05–0.22	1.23	0.219
END = Intercept + β_{1-12} x Covariates[b] + β_{13-14} x lesion presence rate in regions	Female-infarct -prone region	Lesion presence rate	0.10	0.03–0.16	2.96	0.003
	Male-infarct -prone region	Lesion presence rate	0.05	−0.02–0.12	1.49	0.137
Unfavorable functional outcome = Intercept + β_{1-12} x Covariates[b] + β_{13-14} x lesion presence rate in regions	Female-infarct -prone region	Lesion presence rate	0.32	0.26–0.37	10.79	<0.001
	Male-infarct -prone region	Lesion presence rate	0.21	0.16–0.27	7.34	<0.001

(A) Female infarct-prone and male infarct-prone 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 3-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 AAL and 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, links.lww.com/WNL/C780). (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 infarct-prone and male infarct-prone regions with or without sex-NIHSS interaction region) with the NIHSS score, the incidence of END, or the incidence of unfavorable functional outcome (3-month modified Rankin Scale score >2). βs indicate β coefficients, and Ts indicates *t* statistics for independent variables in the regression models. AIC = anterior limb of internal capsule; AAL = Automated Anatomical Labeling; ANG = angular gyrus; CAL = calcarine; CBL = cerebellum; CBV = cerebellar vermis; CUN = cuneus; EC = external capsule; END = early neurologic deterioration; IOC = inferior occipital cortex; IPC = inferior parietal cortex; JHU = Johns Hopkins University; MOC = middle occipital cortex; MTC = middle temporal cortex; NIHSS = NIH Stroke Scale; PAL = pallidum; PIC = posterior limb of internal capsule; PUT = putamen; ROI = region of interest; SFOF = superior fronto-occipital fasciculus; SMG = supramarginal gyrus; SOC = superior occipital cortex; SPC = superior parietal cortex.

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.[30] 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

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 and the literature on other biological,[36-38] socioeconomic,[39,40] cultural,[41] and psychological[42] 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 2 significant factors, based on the comparison of corresponding β coefficients from the multivariable brain mapping–related regression analyses (Figure 4). *In older patients (older than 52 years). END = early neurologic deterioration; ICA = internal carotid artery; MCA = middle cerebral artery; NIHSS = NIH Stroke Scale.

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 because the motor elements have a maximum total of 11 points (facial palsy and unilateral limb weakness) in the scoring system. By 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 approximately 6% and 2%, respectively, than in male patients). This is a novel finding that merits further future investigation. By 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 approximately 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[31] that showed intracranial atherosclerosis occurred approximately 6% more in female than male patients aged 63 years or older.

In accordance with our recent study,[32] covariate-adjusted END was higher in female patients (18.3%) than male patients (14.9%), particularly in patients older than 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 older individuals, are more likely to occur in the striatocapsular region, which is susceptible to END.[33] In addition, note that (1) an increment in the NIHSS score is a key element in defining END, (2) greater amount of real estate affords to motor/strength testing in the NIHSS scoring system,[34] and (3) motor deficit progression is frequently observed in patients with striatocapsular infarctions.[35] Future studies should investigate whether and how (1) changes in sex hormone levels in older individuals strengthen the association between female (vs male) stroke and END and (2) more aggressive acute treatment should be considered for female patients (vs male patients with similar percentage infarct volume), especially in older individuals 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 poststroke outcomes in female patients could be explained mainly by age, stroke severity, and prestroke

dependency.[1] Several other studies,[3,4] however, showed that these factors do not fully explain sex differences in poststroke outcomes. Our study demonstrated that older age, more severe presenting symptoms, and more frequent END accounted for approximately 64% of female patients' higher risk of unfavorable functional outcome (eDiscussion, links.lww.com/WNL/C780). Other biological,[36-38] socioeconomic,[39,40] cultural,[41] and psychological[42] factors are likely also relevant. Sociocultural and psychological features are outside the scope of this work because these data were not collected. Follow-up investigations should identify important but still unknown factors that contribute (approximately 36%) to the sex difference in functional outcomes after ischemic stroke.

A recent study,[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 neurologic severity (Figure 5).

Our study has several strengths and weaknesses (see eDiscussion, links.lww.com/WNL/C780). 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 older individuals. 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.

Acknowledgment

The authors appreciate the contributions of all members of the Clinical Research Collaboration for Stroke-Korea to this study.

Study Funding

This study was supported by the National Priority Research Center Program Grant (NRF- 2021R1A6A1A03038865), the Basic Science Research Program Grant (NRF-2020R1A2C3008295), and the Multiministry Grant for Medical Device Development (KMDF_PR_20200901_0098) of National Research Foundation, funded by the Korean government.

Disclosure

The authors report no potential conflicts of interests. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* September 7, 2022. Accepted in final form March 10, 2023.

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Jinyong Chung, PhD	Medical Science Research Center, Dongguk University Medical Center, Goyang, South Korea	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Dawid Schellingerhout, MD	Departments of Neuroradiology and Imaging Physics, University of Texas MD Anderson Cancer Center, Houston	Drafting/revision of the article for content, including medical writing for content
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Hang-Rai Kim, MD, PhD	Department of Neurology, Dongguk University Ilsan Hospital, Goyang, South Korea	Drafting/revision of the article for content, including medical writing for content
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Continued

Appendix *(continued)*

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Appendix *(continued)*

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Juneyoung Lee, PhD	Department of Biostatistics, Korea University, Seoul	Analysis or interpretation of data
Hee-Joon Bae, MD, PhD	Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea	Major role in the acquisition of data
Dong-Eog Kim, MD, PhD	Department of Neurology, Dongguk University Ilsan Hospital, Goyang; National Priority Research Center for Stroke, Goyang, South Korea	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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