

Sex differences in stroke subtype and risk factors in SiGN

Kathryn M. Rexrode, Braxton D. Mitchell, Kathleen A. Ryan,
Steven J. Kittner, Hakan Ay,
Sylvia Wassertheil-Smoller, and Tatjana Rundek,
on behalf of the NINDS SiGN Investigators

Background

- There is growing recognition of the clinical and public health importance of stroke disparities between women and men.
(AHA guideline: Prevention of stroke in women. *Stroke*. [February 6, 2014])
- The reasons for sex-related disparities in stroke prevalence, types and outcomes are not well understood.
- Whether there are substantial differences in the prevalence of risk factors and subtypes in women compared with men is unclear.
- Sex differences in the prevalence of risk factors and subtypes may have implications for GWAS analyses.

Hypothesis

- The distribution of ischemic stroke risk factors, comorbidities, and subtypes will differ by sex, with a later onset in women.

Methods: The Stroke Genetics Network (SiGN)

- The NINDS Stroke Genetics Network (SiGN) consortium was established to evaluate genetic risk factors for ischemic stroke.
- A total of 23 separate studies (12 from US, 11 from Europe/UK) classified subtypes of stroke using the Causative Classification of Stroke (CCS) computer algorithm, with standardized criteria.
- Data on a total of 16,228 cases of ischemic stroke (N=8005 women and N= 8223 men) were available.
- Each participating cohort also contributed data on risk factors and comorbidities. (SiGN Design and Rationale Paper: *Stroke*. 2013 Oct;44(10):2694-702.)
- Among cases we compared the prevalence of ischemic stroke risk factors and CCS phenotypes between men and women with ischemic stroke.

SiGN Case Characteristics

- Women comprise 49.3% of the 16,228 ischemic stroke cases in SiGN.
- The median age among women stroke cases was 73 years, compared with 66 years in men.
- Of ischemic stroke cases in SiGN, 58.7% of women were over 70 years of age, compared with 40% of men ($p < 0.0001$).

Prevalence of ischemic stroke risk factors by sex in SiGN

Stroke Risk Factor	Women	Men	P value
Age; mean (SD) years	69.5 (15.2)	64.7 (14.2)	<0.0001
Current smoking (%)	18.2	28.1	<0.0001
Race (%)			
Black	11.0	9.7	0.04
White	83.2	84.0	0.02
Other	5.8	6.3	0.28
Hypertension (%)	68.7	64.4	<0.0001
Diabetes (%)	23.5	25.3	0.003
Atrial Fibrillation (%)	23.2	17.7	<0.0001
Coronary artery disease (%)	19.4	24.5	<0.0001
P-values by t-test or chi-square test			

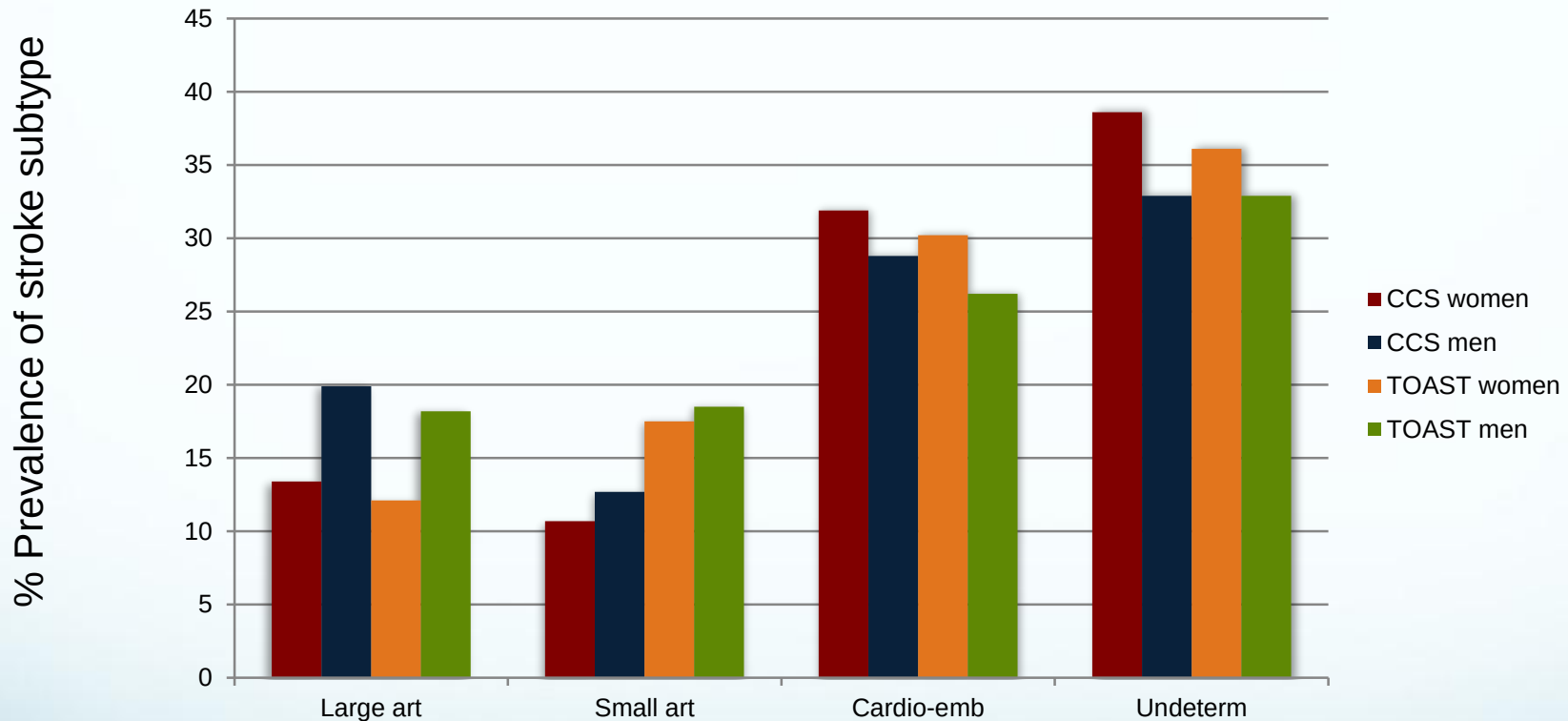
Distribution of CCS ischemic stroke subtypes, by sex

CCS classification	Total N= 16228	Women N= 8005	Men N= 8223	P value*
Large artery atherosclerosis	16.7%	13.4%	19.9%	<0.0001
Cardio-embolism	30.3%	31.9%	28.8%	<0.0001
Small artery Occlusion	11.7%	10.7%	12.7%	0.0001
Other	5.6%	5.4%	5.8%	0.31
Undetermined	35.7%	38.6%	32.9%	<0.0001
Cryptogenic	1.3%	1.3%	1.4%	0.72
Incomplete work-up	24.1%	27.2%	21.0%	<0.0001
Other/unclassified	10.3%	10.1%	10.6%	0.25

*P value comparing women and men.

- ♦ An omnibus test comparing distribution of types by gender was significant ($p < 0.001$).
- ♦ Relationships were similar for the 3 types using TOAST classifications.
- ♦ Statistical significance remained for each after adjustment for age (continuous).

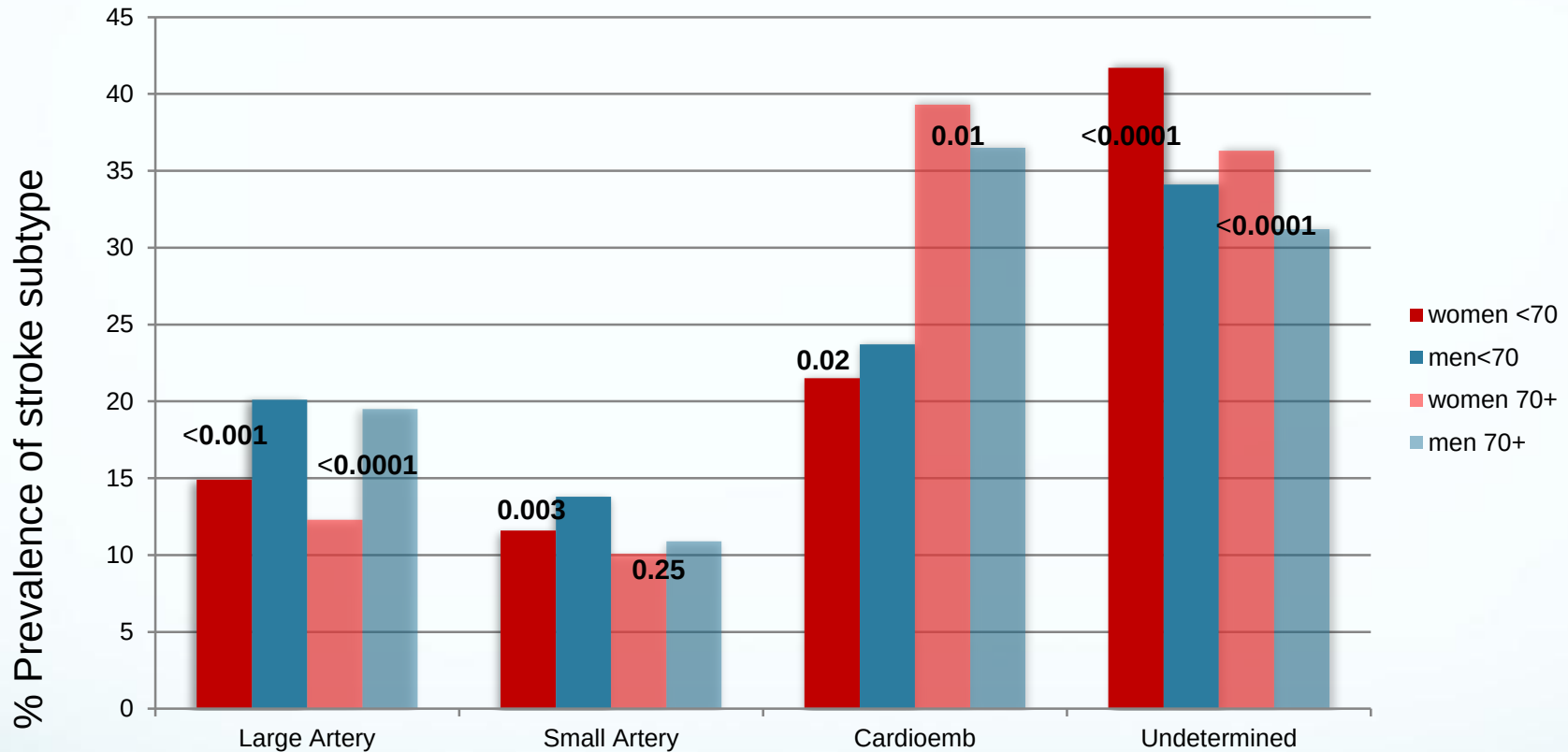
Comparison of subtypes: CCS versus TOAST*



Sex differences for large artery and cardioembolism were similar and significant in TOAST, while the difference was nonsignificant for small artery occlusion in TOAST.

* Based on the 6779 women and 7298 men with both TOAST and CCS available.

Comparison of strata and sex (age <70 and 70+)



Among those <70, all of the differences by sex were significant, but cardioembolism was more prevalent in men than women.

Among those ≥ 70 , small artery occlusion did not differ by sex, and cardioembolic was more common in women.

* Based on the 8237 case <70 years (3306 W/ 4931 M) and 7978 cases ≥ 70 ears (4691W/ 3287 M).

Demographic factors by CCS stroke subtype and sex

	Large artery			Small Artery			Cardio embolic		
	W	M	p	W	M	p	W	M	p
Age group ≥ 70	54.0	39.2	<0.0001	55.3	34.5	<0.0001	72.2	50.6	<0.0001
Race									
Black	10.2	8.3	0.09	15.1	12.2	0.06	7.8	9.4	0.04
White	82.1	84.1	0.17	77.2	78.0	0.66	86.7	84.3	0.02
Other	7.6	7.5	0.93	7.7	9.8	0.11	5.6	6.3	0.28
Smoking	26.7	34.6	<0.0001	19.2	34.7	<0.0001	11.2	20.8	<0.0001

- ♦ For each subtype, a larger percentage of women than men were aged ≥ 70 .
- ♦ For cardioembolic stroke only, a greater percentage of whites were female, while blacks were more likely to be male than female.
- ♦ For each subtype, women were less likely to be current smokers than men.

Stroke risk factors by CCS Stroke subtype and sex

	Large artery			Small Artery			Cardio embolic		
	W	M	P	W	M	P	W	M	P
Hypertension	74.3	69.4	0.02	71.5	64.1	0.002	71.1	65.5	<0.0001
Diabetes	27.3	28.9	0.26	24.1	29.1	0.008	23.8	24.2	0.67
Atrial Fibrillation	9.4	5.4	<0.0001	3.7	2.6	0.15	57.4	47.6	<0.0001
CAD	18.3	25.1	<0.0001	11.3	15.4	0.007	27.7	33.5	<0.0001

- ♦ For each subtype, women had a higher prevalence of hypertension.
- ♦ Diabetes prevalence was higher in men with small artery infarction, while similar for the other subtypes.
- ♦ Atrial fibrillation prevalence was substantially higher in women than men with large artery infarction and cardioembolic stroke.
- ♦ For each subtype, women had a lower prevalence of coronary artery disease than men.

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Additional analyses

- Exclusion of female only cohorts (NHS and WHI) resulted in similar associations (N=6695).
- Restriction of results to European ancestry only yielded similar results (N=6655 women, 6906 men).

Strengths and Limitations

- Strengths

This study includes a very large collection of ischemic stroke cases, from different countries, uniformly adjudicated, with central quality control.

- Limitations

Male and female stroke cases enrolled in SiGN may not be representative of ischemic strokes in the general population.

Conclusions

- In SiGN, women with ischemic stroke were more likely to be older, hypertensive, and have atrial fibrillation and less likely to smoke, have diabetes or coronary artery disease than men.
- Female ischemic stroke cases were more likely to have cardioembolic subtype, and less likely to have large artery arteriosclerotic or small artery occlusion subtypes, than male stroke cases.
- Women were significantly more likely to have incomplete workup and undetermined subtype than men.
- Evaluation of the causes of these differences may highlight areas for improved prevention and risk reduction in both genders.
- These sex-specific differences in the distribution of ischemic stroke subtypes need to be considered in SiGN genomic analyses.

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Diagnostic evaluation by sex

Completeness of the workup	Overall N= 16228 (%)	Women N= 8005 (%)	Men N= 8223 (%)
CCS classification incomplete – either 2a, 3a or 4a is checked	7874 (48.5)	4228 (52.8)	3646 (44.3)
MRI performed	8571 (52.8)	3995 (49.9)	4576 (55.7)
Intracranial MRA/CTA /TCD performed	8405 (51.8)	3740 (46.7)	4665 (56.7)
Extracranial MRA/CTA/ Duplex performed	13509 (83.3)	6454 (80.6)	7055 (85.8)
TTE/TEE performed	10450 (64.4)	4964 (62.0)	5486 (66.7)