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RESEARCH LETTER

Female Sex–Related Stroke Risk in Atrial Fibrillation: A Thing From the Past?

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Women with atrial fibrillation (AF) have traditionally been considered to have a higher risk of ischemic stroke compared with men.[1,2] More in-depth analyses have suggested that female sex acts as a risk modifier, increasing the risk of stroke only in older patients.[1,3] Moreover, the stroke risk associated with female sex has decreased over the past decades.[2,4] As with the mechanisms underlying the elevated risk, the reasons for its decline remain poorly understood.

We hypothesized that the observed decline in stroke risk associated with female sex and its age-dependency may reflect 2 sides of the same coin, potentially stemming from a cohort effect. Cohort effects refer to health outcomes from exposures experienced by individuals born in the same period. In the case of women with AF, the elevated stroke risk could be linked to earlier birth cohorts, and the apparent age-dependency might reflect generational differences. This could also explain the observed attenuation of the sex differences in stroke risk in patients with newly diagnosed AF. Therefore, we conducted an age-period-cohort analysis in a nationwide cohort to investigate whether sex differences in stroke risk are associated with the birth year of patients with AF.

The registry-based FinACAF study (Finnish Anticoagulation in Atrial Fibrillation Study) covers all patients diagnosed with AF at all levels of care in Finland.[5] The present study was conducted within a cohort of incident AF patients from 2007 to 2018, established in a previous study assessing sex differences in stroke risk.[2] The definitions for baseline variables, follow-up, and stroke outcome were consistent with those in the previous publication.[2] The University of Helsinki Ethics Committee approved the study, with informed consent waived due to its retrospective registry design. Because of the sensitive nature of the data collected for this study, requests to access the data set may be sent to the Finnish national register holders through Findata (https://findata.fi/en/). All analysis code used in this study is publicly available in the Zenodo repository: https://zenodo.org/records/15243403.

We used a standard age-period-cohort approach and applied Poisson regression with natural splines for age, observation calendar year, and birth year, along with an interaction term between sex and birth year. The model accounted for increasing age during follow-up. Incidence rate ratios of stroke comparing women to men were computed across the range of birth years. Further adjusted regression included baseline variables for diabetes, hypertension, heart failure, dyslipidemia, vascular disease, prior stroke or transient ischemic attack, and income tertiles at the time of AF diagnosis, as well as oral anticoagulant exposure, which was considered to begin from the first anticoagulant purchase.

The cohort included 229 565 patients with new-onset AF (50.0% women; mean birth year 1942; SD, 13.5; range, 1902–1998; mean age at diagnosis, 72.7 years; SD, 13.2, range, 20–107; and median follow-up time, 3.2 years; interquartile range, 1.2–6.2 years), of whom 7.1% experienced stroke. The association between female sex and stroke decreased across the range of birth years (Figure). In those born before 1940, women had significantly higher stroke rates than men, but this association diminished and became nonsignificant around the 1940 to 1960 birth years.

Key Words: atrial fibrillation ■ cohort effect ■ Finland ■ ischemic stroke ■ women

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
FinACAF	Finnish Anticoagulation in Atrial Fibrillation Study

The excess stroke risk in women with AF is mainly evident among cohorts born before 1940 in Finland, but not among later-born cohorts. The factors underlying this cohort effect are likely multifactorial. World War II and the subsequent reconstruction era undoubtedly shaped the early life environment of individuals born before 1940, but other broader societal and lifestyle shifts, such as changes in living conditions, nutrition, and healthcare, may also underlie the observed cohort effects.

By disentangling the effects of age, observation period, and birth cohort, the current analytical approach demonstrates that the excess stroke risk traditionally attributed to female sex in AF is linked to earlier birth cohorts rather than higher age alone. The observed generational trends may thus partly explain the previously reported age-dependency and the decrease in female sex–related stroke risk, as recent decades may reflect the increasing proportion of later-born patients with newly diagnosed AF.[1,2,4] This phenomenon may have implications for stroke risk stratification in contemporary patients with AF, and potentially even more so in future cohorts, such as using the nonsex CHA_2DS_2-VASc score (ie, CHA_2DS_2-VA), as currently recommended by the European Society of Cardiology guidelines.

Key strengths of this study include its unique nationwide coverage of AF patients across all levels of care and the use of a well-validated hospital register with high diagnostic accuracy for cardiovascular outcomes. However, our analysis has some important limitations inherent to register-based retrospective cohort studies. Although the underlying causes and primary drivers of the observed phenomenon warrant further investigation, our findings indicate that the elevated stroke risk associated with female sex is no longer evident in more recent generations. Whether similar generational differences exist in other countries warrants additional research.

In conclusion, the findings from this nationwide cohort study indicate that the higher stroke rate traditionally associated with female sex in AF may be related to a cohort effect and is mainly evident in those born before 1940. Female sex may not be needed for stroke risk stratification and decision-making for oral anticoagulant therapy in contemporary—and potentially future—patients with AF.

ARTICLE INFORMATION

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REFERENCES

1. Buhari H, Fang J, Han L, Austin PC, Dorian P, Jackevicius CA, Yu AYX, Kapral MK, Singh SM, Tu K, et al. Stroke risk in women with atrial fibrillation. *Eur Heart J*. 2024;45:104–113. doi: 10.1093/eurheartj/ehad508
2. Teppo K, Airaksinen KEJ, Jaakkola J, Halminen O, Salmela B, Kouki E, Haukka J, Putaala J, Linna M, Aro AL, et al. Ischaemic stroke in women with atrial fibrillation: temporal trends and clinical implications. *Eur Heart J*. 2024;45:1819–1827. doi: 10.1093/eurheartj/ehae198
3. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? *Circulation*. 2018;137:832–840. doi: 10.1161/CIRCULATIONAHA.117.029081
4. Nielsen PB, Brøndum RF, Nøhr AK, Overvad TF, Lip GYH. Risk of stroke in male and female patients with atrial fibrillation in a nationwide cohort. *Nat Commun*. 2024;15:6728. doi: 10.1038/s41467-024-51193-0
5. Lehto M, Halminen O, Mustonen P, Putaala J, Linna M, Kinnunen J, Kouki E, Niiranen J, Hartikainen J, Haukka J, et al. The nationwide Finnish Anticoagulation in Atrial Fibrillation (FinACAF): study rationale, design, and patient characteristics. *Eur J Epidemiol*. 2022;37:95–102. doi: 10.1007/s10654-021-00812-x

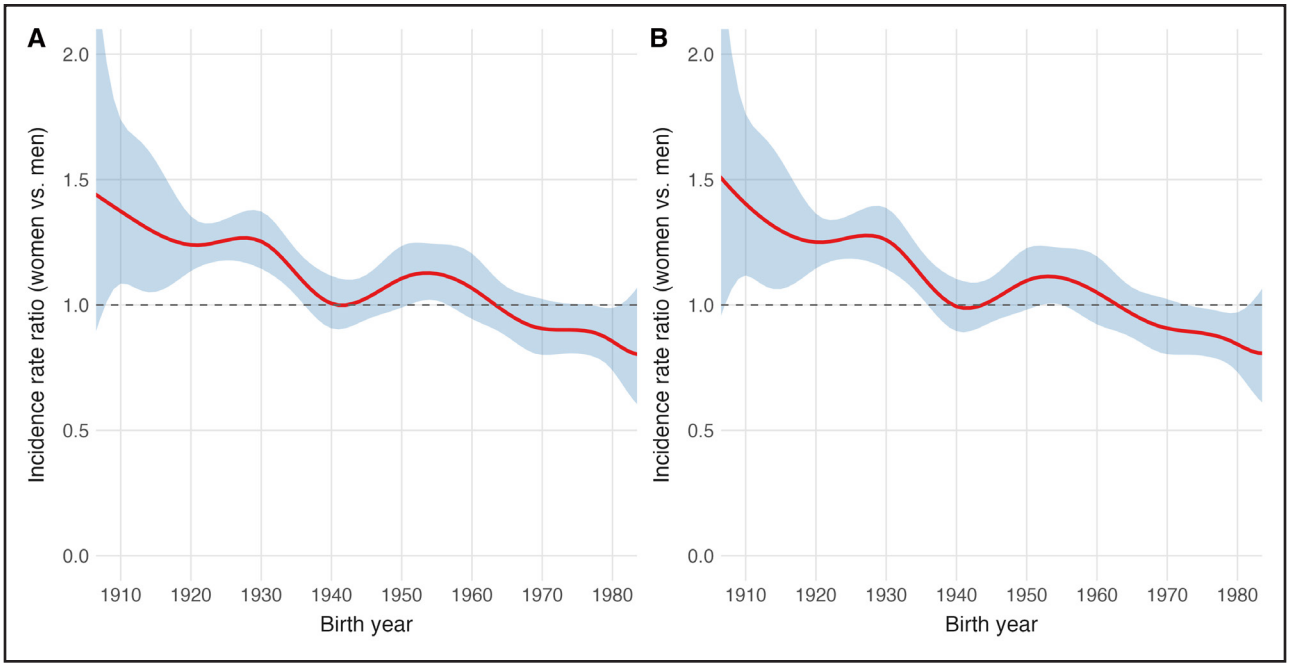

Figure. Incidence rate ratio of ischemic stroke comparing women to men by birth year.
A, The model including for age, observation year, birth year, and sex. **B**, Additional adjustment for comorbidities, income, and anticoagulant use.