Stroke

CLINICAL AND POPULATION SCIENCES

Risk of Midlife Stroke After Adverse Pregnancy Outcomes: The FinnGen Study

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BACKGROUND: Adverse pregnancy outcomes (APO) contribute to higher risk of maternal cerebrovascular disease, but longitudinal data that include APO and stroke timing are lacking. We hypothesized that APO are associated with younger age at first stroke, with a stronger relationship in those with >1 pregnancy with APO.

METHODS: We analyzed longitudinal Finnish nationwide health registry data from the FinnGen Study. We included women who gave birth after 1969 when the hospital discharge registry was established. We defined APO as a pregnancy affected by gestational hypertension, preeclampsia, eclampsia, preterm birth, small for gestational age infant, or placental abruption. We defined stroke as first hospital admission for ischemic stroke or nontraumatic intracerebral or subarachnoid hemorrhage, excluding stroke during pregnancy or within 1 year postpartum. We used Kaplan-Meier survival curves and multivariable-adjusted Cox and generalized linear models to assess the relationship between APO and future stroke.

RESULTS: We included 144 306 women with a total of 316 789 births in the analysis sample, of whom 17.9% had at least 1 pregnancy with an APO and 2.9% experienced an APO in ≥2 pregnancies. Women with APO had more comorbidities including obesity, hypertension, heart disease, and migraine. Median age at first stroke was 58.3 years in those with no APO, 54.8 years in those with 1 APO, and 51.6 years in those with recurrent APO. In models adjusted for sociodemographic characteristics and stroke risk factors, risk of stroke was greater in women with 1 APO (adjusted hazard ratio, 1.3 [95% CI, 1.2–1.4]) and recurrent APO (adjusted hazard ratio, 1.4 [95% CI, 1.2–1.7]) compared with those with no APO. Women with recurrent APO had more than twice the stroke risk before age 45 (adjusted odds ratio, 2.1 [95% CI, 1.5–3.1]) compared with those without APO.

CONCLUSIONS: Women who experience APO have earlier onset of cerebrovascular disease, with the earliest onset in those with more than 1 affected pregnancy.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebrovascular disorders ■ hypertension, pregnancy-induced ■ pregnancy ■ stroke

See related article, p 1806

Stroke is a leading cause of death and disability in women.[1] While the incidence of stroke in older age groups is decreasing, stroke in younger and middle-aged adults, particularly women, have not demonstrated this improvement.[2–6] Stroke in midlife can have devastating effects on a woman's health and well-being. Midlife women are in their prime working years, often juggling multiple responsibilities including childcare and elder-care. A disabling stroke in midlife may therefore have ripple effects extending to multiple generations, as well as substantial economic impact.

Sex-specific risk factors, including adverse pregnancy outcomes (APO) such as preterm birth and hypertensive disorders of pregnancy, may contribute to early onset of

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Nonstandard Abbreviations and Acronyms

APO	adverse pregnancy outcome
ICH	intracerebral hemorrhage

cerebrovascular disease in women.[7] In a nationally representative US sample, self-reported history of any APO was associated with a 2.6-fold higher odds of stroke before age 60.[8] However, estimates of the impact of APO on future maternal cerebrovascular disease have been limited by the lack of granular, validated, longitudinal data regarding pregnancy history and future stroke risk. Furthermore, the impact of recurrent APO on future stroke risk has not been characterized.

We used national health registry data from Finland to investigate the relationship between APO and age at first stroke in parous women. We hypothesized that a history of APO is associated with younger age at first stroke and that the association between APO and earlier onset stroke is stronger in women with more than 1 pregnancy complicated by an APO.

METHODS

Data Availability and Transparency Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The complete prespecified analysis plan, ICD codes and specific registry sources, R code and results are publicly available in GitHub (https://github.com/akauko/stroke_preg).

Study Design and Sample Selection

FinnGen represents a public-private partnership that longitudinally collects and manages anonymous nationwide health information from across Finland. Our study sample drew from FinnGen Data Freeze 10 (December 31, 2021), consisting of randomly selected participants from Finnish cohort studies and biobanks.[9] We included all women who gave birth in Finland in 1969 or later, with at least 1 birth documented in the Medical Birth Register.[10] Out of a total of 430 885 FinnGen participants (both sexes), 184 012 women had data in the birth registry. We excluded individuals who gave birth before 1969 as hospital discharge data starts from this year. We excluded women with no recorded births, women who had a stroke before their first birth, and women with a pregnancy-associated stroke (stroke during any pregnancy or within 1 year postpartum) as these strokes may have unique pathophysiology.[11,12] We excluded women with missing data other than educational status, which was imputed. In total, 39 706 women were excluded, resulting in a final analysis sample of 144 306 women with total 316 789 births (Figure 1).

Standard Protocol Approvals and Informed Consent

All participants provided written informed consent. This study protocol was approved by The Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa, as described in the Supplemental Methods.

Primary Exposures of Interest

The primary exposure of interest was any pregnancy affected by an APO, defined as one or more of the following: gestational hypertension, preeclampsia/eclampsia, preterm birth (medically indicated or spontaneous birth before 37 weeks gestation), small for gestational age infant (birthweight more than 2 SDs below the sex- and gestational age-specific reference mean); or placental abruption. Due to incomplete data, stillbirth was not included. We categorized participants as having no APO, 1 pregnancy with APO, or 2 or more pregnancies with APO (recurrent APO). To ascertain exposures of interest we combined diagnoses from Hospital Discharge and Birth registers. Clinical diagnoses were identified from *International Classification of Diseases (ICD)* codes at the nationwide Hospital Discharge, Causes-of-Death and Birth registers and linked by personal nationwide identification codes. These ICD-code based diagnoses are made by the attending physician at the time of hospital discharge and are listed in Table S1. The accuracy of these codes is robust and has been described previously.[13] Diagnoses from the Hospital Discharge Register were linked to a given pregnancy if the event day was ±9 months from birth.

Primary and Secondary Outcomes

The primary end point was first hospital admission for any stroke after the first documented birth (excluding strokes occurring during pregnancy or within 1 year postpartum). These end points have been previously validated in this cohort.[14] We defined stroke as ischemic stroke, nontraumatic intracerebral hemorrhage, or nontraumatic subarachnoid hemorrhage. We excluded TIA from the outcome, as the definition of TIA has changed during the study period and was not validated in the cohort. Secondary outcomes included stroke subtypes (hemorrhagic or ischemic), and any stroke before predefined age cutoffs (≤45 years, ≤55 years, or ≤65 years).

Covariates of Interest

Covariates of interest included maternal age at first birth, year of first birth, total number of births, educational level, and stroke risk factors diagnosed before stroke, including hypertension, obesity, diabetes (including gestational diabetes), hyperlipidemia, ischemic heart disease, atrial fibrillation, heart failure, chronic kidney disease, lupus, and migraine. Hypertension was handled as a time-varying covariate. Due to incomplete data, smoking was included as an exposure only in sensitivity analysis. Year of the first birth, maternal age at first birth, and total number of births were obtained from the Birth Register and the Population Register Center. Educational and employment status were obtained from Statistics Finland. Educational data were imputed for 15 774 women, by using the most frequent educational category in each combination of birth decade and employment status (Table S2).

Statistical Analyses

We compared baseline characteristics between exposure groups using ANOVA or χ^2 as appropriate. We generated

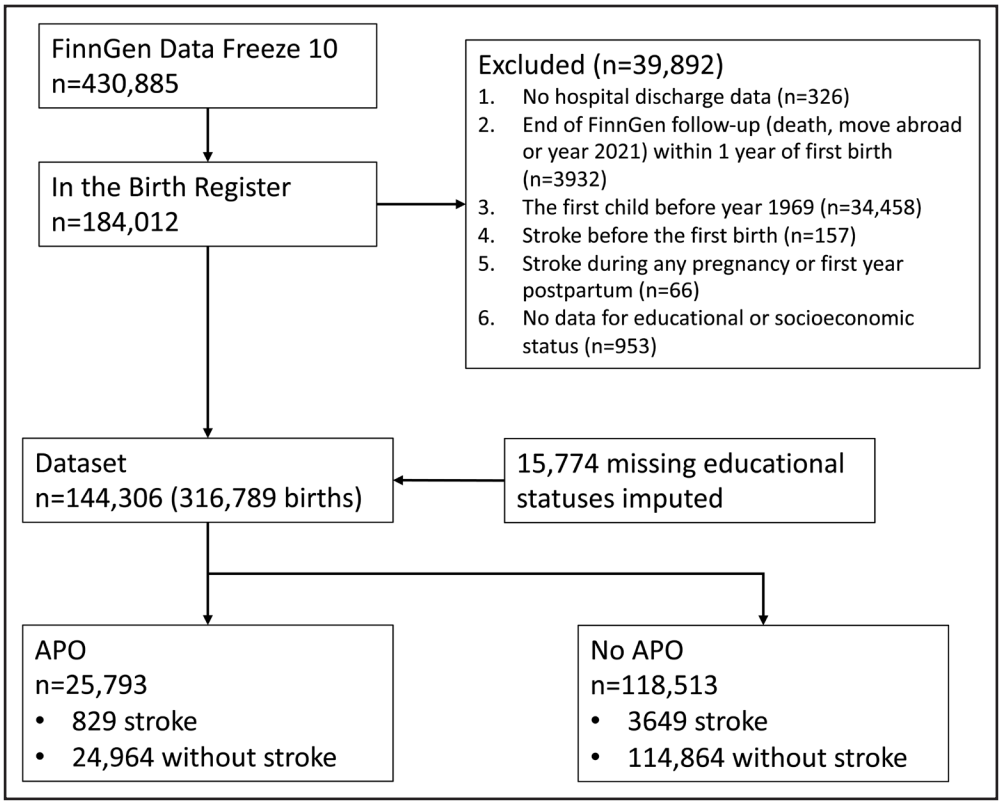

Figure 1. Flow diagram of analysis sample selection.
FinnGen Data Freeze 10 consists of participants from Finnish cohort studies and patients from Finland's national hospital biobanks. We included all people who gave birth in Finland in 1969 or later, with at least 1 birth documented in the Medical Birth Register. Out of a total of 430 885 FinnGen participants (male and female), 184 012 women had data as mothers in the birth registries. We excluded those who first gave birth before 1969; those with no recorded births; those who had a stroke before their first birth; those with pregnancy-associated stroke; and those with missing data other than educational status, which was imputed. APO indicates adverse pregnancy outcome.

Kaplan-Meier curves with age as the time axis, and created Cox proportional hazards models to assess the association between APO and stroke. Survival model follow-up spanned from first birth to December 31, 2021, with participants censored at end of follow-up, death, or time of the outcome event. The proportional hazards assumption was validated by visual inspection of log-minus-log plots due to the large sample size. We also studied associations between APO and stroke risk before defined age cutoffs (≤45, ≤55, ≤65 years) using generalized linear models, using the same covariates. Covariates were chosen a priori, using nested models as follows: Model 1 adjusted for age implicitly due to use of age as the time axis; Model 2 added education, number of births, age at first birth, year of first birth; Model 3a adjusted for model 2+hypertension as time-varying covariate; Model 3b: adjusted for model 2+stroke risk factors (covariates) but not hypertension; Model 4 adjusted for all of the above. We used R v.4.1.2 for all analyses. A 2-sided *P* value <0.05 was considered the threshold for statistical significance.

Secondary and Sensitivity Analyses

In secondary analyses, we created Cox models for subtypes of pregnancy complications, including any hypertensive disorder of pregnancy, gestational hypertension, preeclampsia/eclampsia, preterm birth and fetal growth restriction. We performed sensitivity analyses as follows: (1) excluding participants with multifetal gestations; (2) including Fine and Gray sub-distribution models to account for death and cardiovascular death as competing risks; (3) adjusting for baseline body mass index instead of obesity; (4) including smoking as a covariate in those with available data; and (5) excluding subarachnoid hemorrhage as an outcome, since subarachnoid hemorrhage pathophysiology differs substantially from that of ischemic stroke and intracerebral hemorrhage.

Results are reported in adherence to the STROBE guidelines (Supplemental Material).

RESULTS

Of 144 306 parous women included in the analysis with a total of 4 241 243 person-years of follow-up and median follow-up time of 30.7 years, 25,793 (17.9%) had at least 1 pregnancy with APO, and 4119 (2.9%) had more than 1 pregnancy with APO (recurrent APO). Participant characteristics are shown in Table 1. Compared with those who had zero or 1 APO, those with recurrent APO were younger at the time of their first birth, had higher parity, and lower educational status. Participants with any APO had higher proportion of stroke risk factors including obesity, hypertension, diabetes, smoking, heart disease, and migraine, with the highest proportions seen in those who had recurrent APO.

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Table 1. Characteristics of Women in the FinnGen Study Who Gave Birth at Least Once

Characteristic*	Overall N=144 306	No APO N=118 513	1 APO N=21 674	Recurrent APO N=4119	*P* value	% missing data
Age, y at first birth (mean, SD)	26.8 (5.1)	26.8 (5.0)	27.0 (5.3)	25.8 (4.9)	<0.001	0
Median follow-up time, y	30.7	31.5	27.5	25.0		
Education level† (n, %)					<0.001	0
High school or less	68 688 (47.6)	56 260 (47.5)	10 351 (47.8)	2077 (50.4)		
Post-secondary	27 400 (19.0)	22 802 (19.2)	3934 (18.2)	664 (16.1)		
Bachelor's or higher	48 218 (33.4)	39 541 (33.3)	7389 (34.1)	1378 (33.5)		
No. births recorded in MBR (mean, SD)	2.2 (1.1)	2.1 (1.0)	2.3 (1.3)	3.1 (1.7)	<0.001	0
Smoking during first pregnancy	17 845 (17.9)	13 723 (17.4)	3359 (19.5)	763 (21.1)	<0.001	31.0%
Smoking, ever	41 086 (48.5)	33 491 (48.1)	6337 (50.0)	1258 (51.0)	<0.001	41.3%
BMI, kg/m^2 at time of first birth (mean, SD)	26.6 (5.6)	26.4 (5.5)	27.1 (6.0)	27.4 (6.4)	<0.001	21.9%
Obesity (n, %)	10 462 (7.2)	7534 (6.4)	2313 (10.7)	615 (14.9)	<0.001	0
Hypertension at time of first birth (n, %)	867 (0.6)	474 (0.4)	292 (1.3)	101 (2.5)	<0.001	0
Hypertension, any time before stroke (n, %)	28 127 (19.5)	21 620 (18.2)	5222 (24.1)	1285 (31.2)	<0.001	0
Diabetes, including gestational (n, %)	18 375 (12.7)	13 963 (11.8)	3543 (16.3)	869 (21.1)	<0.001	0
Hyperlipidemia (n, %)	35 386 (24.5)	29 039 (24.5)	5340 (24.6)	1007 (24.4)	0.91	0
Ischemic heart disease (n, %)	4451 (3.1)	3537 (3.0)	763 (3.5)	151 (3.7)	<0.001	0
Atrial fibrillation (n, %)	6168 (4.3)	5091 (4.3)	895 (4.1)	182 (4.4)	0.48	0
Heart failure (n, %)	2521 (1.7)	2020 (1.7)	415 (1.9)	86 (2.1)	0.02	0
CKD (n, %)	1133 (0.8)	834 (0.7)	243 (1.1)	56 (1.4)	<0.001	0
SLE	559 (0.4)	434 (0.4)	100 (0.5)	25 (0.6)	0.008	0
Migraine	11 658 (8.1)	9081 (7.7)	2081 (9.6)	496 (12.0)	<0.001	0

APO indicates adverse pregnancy outcome; BMI, body mass index; CKD, chronic kidney disease; MBR, Medical Birth Registry; and SLE, systemic lupus erythematosus.

*Comorbid conditions are diagnosed any time up to time of stroke, unless otherwise specified.

†Highest-attained education level was used (even if attained after first birth)

A total of 4478 (3.1%) of study participants met the primary end point of any stroke during the follow-up period. The cumulative incidence of stroke over the life course did not differ between exposure groups (Table S3). However, median age at first stroke was 58.3 years in those with no APO; 54.8 years in those with 1 pregnancy with APO; and 51.6 years in those with recurrent APO ($P<0.001$; Figure 2). Kaplan-Meier curves for age at first stroke in each exposure group are shown in Figure 3, together with hazard ratios. In Cox survival models, after adjusting for demographic factors and comorbid conditions, those with recurrent APO had the highest stroke risk (adjusted hazard ratio, 1.4 [95% CI, 1.2–1.7]) compared with those with no APO. Hazard ratios for specific subtypes of APO are shown in Table 2; the effect sizes were largest for recurrent preterm birth, which was statistically significant (adjusted hazard ratio, 1.5 [95% CI, 1.03–2.1]) and small for gestational age infant, which was not statistically significant (adjusted hazard ratio, 1.7 [95% CI, 0.7–4.2]). In generalized linear models, those with recurrent APO had more than double the odds of stroke before the age of 45 (adjusted odds ratio, 2.1 [95% CI, 1.5–3.1]), compared with those with no APO (Table 3).

Sensitivity Analyses

In sensitivity analyses (1) excluding those with multiple gestation, (2) including only participants with baseline body mass index data, and (3) including only participants with smoking data, results were similar. When all-cause mortality and cardiovascular death were considered as competing risks, the results did not change. Excluding subarachnoid hemorrhage as an outcome also did not change the direction of the effect. Results of all sensitivity analyses are included in the Supplemental Material (Tables S4 through S9).

DISCUSSION

In our analysis of comprehensive longitudinal health registry data from Finland, we found that having at least 1 pregnancy with an APO was associated with younger age at first stroke. Those who experienced recurrent APO were the youngest at the time of their first stroke. This association remained significant after adjusting for demographics and known stroke risk factors. While the overall incidence of stroke at any age did not differ between exposure groups, stroke occurred earlier in

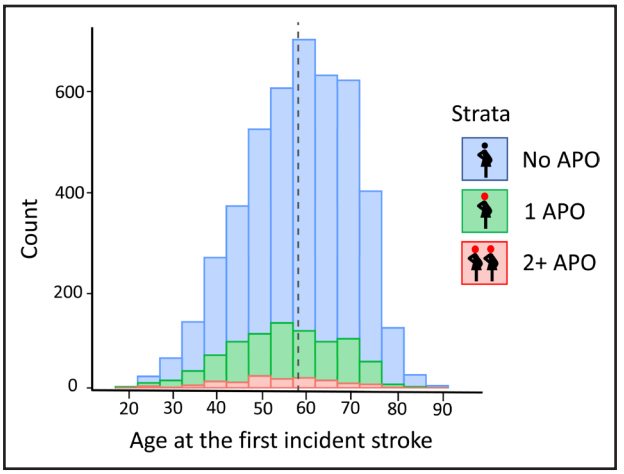

Figure 2. Median age at first stroke in parous women in the FinnGen study.
Stacked histogram plot shows age at the first incident stroke, among people with zero (blue), 1 (green) or 2 or more (red) pregnancies affected by adverse pregnancy outcome (APO). Overall, median age at first stroke was 57.5 y (dashed line). Median age was 58.3 y (interquartile range [IQR], 46.6–67.6) in those with no APO; 54.8 y (IQR, 43.3–64.2) in those with 1 pregnancy with APO; and 51.6 (IQR, 41.6–60.9) years in those with recurrent APO (P<0.001).

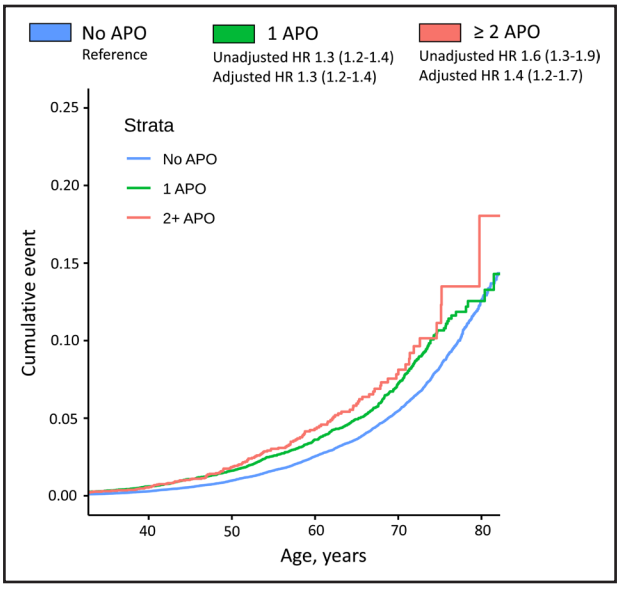

Figure 3. Age at first stroke in women with 0, 1, or ≥2 pregnancies complicated by adverse pregnancy outcome (APO).
Kaplan-Meier survival curves show age at time of first hospital admission for stroke, among women with 0 (blue), 1 (green), or 2 or more (red) pregnancies affected by an adverse pregnancy outcome. Follow-up time spanned from first birth until December 31, 2021. Unadjusted model is adjusted for baseline age implicitly, since age is the time axis. Fully adjusted model included education, number of births, age at first birth, year of first birth (cohort effects), hypertension as time-varying covariate, and additional stroke risk factors (obesity, diabetes, hyperlipidemia, ischemic heart disease, atrial fibrillation, heart failure, chronic kidney disease, lupus, and migraine). Numbers in parentheses indicate 95% CIs. APO defined as any pregnancy complicated by gestational hypertension, preeclampsia/eclampsia, preterm birth, small for gestational age infant, or placental abruption. HR indicates hazard ratio.

those with more pregnancies with an APO. In fact, nearly 75% of first strokes in women with recurrent APO in our cohort occurred before the age of 60.

There is currently no established cut-point for early onset with regards to stroke diagnosis. Studies of stroke in the young have variously defined young as anywhere from under 40 to under 70 years of age.[1,15–17] Regardless of arbitrary age cutoffs, the occurrence of stroke during midlife has profound implications on the individual, family, and societal level. Most strokes result in disability rather than death; thus, the economic costs of stroke at earlier ages can mount rapidly as stroke survivors may be unable to work and require full-time care for many years.[18–20] In addition, as many women during midlife care for children and older adults,[21,22] a disabling stroke at that time in the lifecourse may have disastrous consequences for family members of the stroke survivor, who previously depended on this care. Furthermore, even nondisabling strokes are associated with significantly higher risk for cognitive decline and dementia.[23–25]

Table 2. HRs for Stroke Risk After Specific Adverse Pregnancy Outcomes

Condition*	1 pregnancy complicated by condition		≥2 pregnancies complicated by condition	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Any APO	1.3 (1.2–1.5)	1.3 (1.2–1.4)	1.6 (1.3–1.9)	1.4 (1.2–1.7)
Hypertensive disorder of pregnancy (any)	1.4 (1.3–1.5)	1.3 (1.2–1.4)	1.6 (1.3–2.0)	1.4 (1.1–1.7)
Gestational HTN	1.4 (1.3–1.6)	1.3 (1.1–1.5)	1.6 (1.1–2.2)	1.3 (0.9–1.9)
Preeclampsia-eclampsia	1.4 (1.2–1.6)	1.3 (1.2–1.5)	1.5 (1.1–2.3)	1.4 (0.95–2.1)
Preterm birth (medically indicated or spontaneous)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.5 (1.03–2.1)	1.5 (1.03–2.1)
Small for gestational age	1.5 (1.2–2.0)	1.3 (1.0–1.7)	2.1 (0.9–5.1)	1.7 (0.6–4.2)

Unadjusted model: adjusted for baseline age implicitly, since age is the time axis. Adjusted model: adjusted for age, education, number of births, age at first birth, year of first birth, hypertension as time-varying covariate, obesity, diabetes, hyperlipidemia, ischemic heart disease, atrial fibrillation, heart failure, chronic kidney disease, lupus, and migraine. Smoking status was excluded due to missing data; a sensitivity analysis including only those participants with smoking data is included in the Supplemental Material. APO indicates adverse pregnancy outcome; and HR, hazard ratio.
*Placental abruption was not included in this table due to small numbers.

Table 3. Odds of Stroke in Midlife in Women With APO

	1 pregnancy with APO		≥2 pregnancies with APO	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Any stroke by age 45	1.7 (1.5–2.1)	2.0 (1.6–2.3)	1.7 (1.2–2.5)	2.1 (1.5–3.1)
Any stroke by age 55	1.4 (1.3–1.6)	1.7 (1.5–1.9)	1.5 (1.2–1.9)	2.0 (1.6–2.5)
Any stroke by age 65	1.2 (1.1–1.3)	1.5 (1.4–1.7)	1.2 (1.02–1.5)	1.8 (1.5–2.2)

Adjusted generalized linear model includes age, education, number of births, age at first birth, year of first birth, hypertension, obesity, diabetes, hyperlipidemia, ischemic heart disease, atrial fibrillation, heart failure, chronic kidney disease, lupus, and migraine. APO indicates adverse pregnancy outcome; and OR, odds ratio.

There is a strong relationship between stroke and aging.[26] Stroke represents an end-stage cardiovascular disease, with age being the single most important predictor of stroke risk.[18] Stroke affects more women than men, a fact that has often been attributed to women's longer lifespans.[27–29] However, recent studies demonstrate a higher incidence of stroke in young women, compared with young men.[6,30] In addition, stroke is more often the first acute presentation of cardiovascular disease in women, compared to men.[31] Our data suggest that sex-specific risk factors such as APO may lead to an accelerated onset of cerebrovascular disease in those who have given birth, similar to prior data demonstrating early onset of cardiovascular disease after APO.[32]

The pathophysiological basis for the connection between APO and early onset stroke is unknown. APO have robust associations with age-related cardiovascular diseases but also share many common risk factors.[7,33,34] It is possible that APO result from an underlying atherogenic profile present before pregnancy, which also predisposes to accelerated development of cardiovascular disease.[35] However, our models demonstrate APO is an independent risk factor for early stroke even after adjustment for comorbidities. Moreover, we observed a dose-response relationship: those with recurrent APO had earliest onset of stroke. APO such as hypertensive disorders of pregnancy and other placental disorders are associated with systemic inflammation, endothelial dysfunction, oxidative stress, rapid placental aging, and vascular damage.[36–39] Emerging evidence demonstrates that these disorders may cause lasting endothelial and cardiac dysfunction, which may contribute to vascular aging and premature development of overt cerebrovascular disease.[40–42] Our data suggest that these effects may be cumulative in those with recurrent APO.

Clinical Implications

The average age at first birth in our cohort was 27 years. Among those who went on to have a stroke, 1 in 4 of those with recurrent APO history had their stroke by the age of 42. This suggests an immediate need for aggressive primary stroke prevention after any APO, particularly for those with recurrent APO. In addition, it is plausible that prevention of recurrent APO could reduce stroke risk in those who have experienced 1 pregnancy with an adverse outcome. Thus, evidence-based interventions for prevention of recurrent APO, such as low-dose aspirin[43] and close blood pressure monitoring,[44] have potential downstream benefits for long-term cerebrovascular health. All clinicians who care for individuals who have been pregnancy capable, regardless of specialty, should screen for history of APO and consider these episodes as red flags for early onset cerebrovascular disease. In addition, younger women with acute neurological symptoms are at higher risk of having their symptoms misdiagnosed as migraine or functional neurological disorder, compared with men.[45,46] Clinicians evaluating patients in the emergency setting should be aware of sex-specific stroke risk factors such as recurrent APO, and take these into account when making treatment decisions.

Strengths and Limitations

Strengths of our study include its large sample size, as well as the granularity of longitudinal data available from the FinnGen study, which included validated pregnancy data and stroke outcomes. This allowed us to characterize the timing of exposures in relation to stroke. The 52-year length of follow-up is also an important strength, allowing us to investigate the effects of recurrent exposure to APO on stroke, a disease that typically manifests later in life.

Our study has limitations. We excluded pregnancy-associated stroke because it is well-established that pregnancy transiently increases stroke risk; by excluding these, we sought to isolate the long term rather than short-term effects of APO on stroke risk. However, this may have resulted in underestimating the impact of APO on maternal stroke risk. Incomplete capture of stroke or APO diagnoses from the Hospital Discharge, Causes-of-Death, and Birth registers may have affected our results, although validation studies in these registers have shown high agreement of register diagnoses with medical record review.[13,14,47,48] Due to our study's setting in a comprehensive lifelong health care system, our results may not be generalizable to contexts with more racial and ethnic diversity and differential access to health care. However, these study characteristics may also have reduced the confounding effects of structural racism and systemic inequities that have resulted in major disparities in both APO and stroke risk, for example in the United States. In addition, we lacked data regarding gender identity of study participants, precluding investigation of the relationship between

APO and stroke in gender-diverse birthing individuals. Although we adjusted for several potential confounding factors, such as age, educational level, and known stroke risk factors, there may still be unmeasured confounders that were not accounted for in the analysis. For example, lack of information on the severity of APO (eg, early versus late-onset preeclampsia) may have affected the strength of the association with stroke. Finally, our analysis did not assess other long-term effects of APO on cerebrovascular health beyond the first stroke, such as leukoaraiosis burden, asymptomatic carotid disease, evidence of subclinical small vessel disease or covert brain infarction, and vascular cognitive impairment. Future prospective studies should include neuroimaging and neurocognitive assessments, to better understand the full scope of the implications of APO on cerebrovascular health.

Conclusions and Future Directions

People who experience APO develop cerebrovascular disease at younger ages, with the earliest onset and the greatest risk in those with multiple pregnancies affected by APO. Mechanistic studies are needed to better understand the pathways by which APO may contribute to early onset cerebrovascular disease, for example, through endothelial dysfunction, inflammation, or microvascular damage. A meta-analysis of randomized trials of aspirin for primary prevention of stroke showed a 17% reduction in stroke risk in women, but not men.[49] Observational data suggested a possible role for aspirin in stroke risk reduction in those with a history of hypertensive disorders of pregnancy.[50] Our data suggest that those who experience 1 or more APO are at high risk for early onset of symptomatic cerebrovascular disease; thus, randomized clinical trials for primary stroke prevention in this high-risk population may be feasible and should be considered.

ARTICLE INFORMATION

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Disclosures

Dr Niiranen worked at AstraZeneca. Dr Bello provided end point adjudication for GSK (unrelated to the content of this work).

Supplemental Material

Supplemental Methods
Tables S1–S9
FinnGen Investigator Listing

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