

Long-Term Recovery, Morbidity, and Mortality After Maternal Ischemic Stroke

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Abstract

Background and Objectives

The long-term prognosis after maternal ischemic stroke (IS) remains understudied. The objectives were to examine if mortality and long-term morbidity are more frequent in women with prior maternal IS compared with women without a pregnancy-related stroke and to assess recovery in maternal IS patients based on functional outcomes and vocational status.

Methods

In this retrospective nationwide cohort study, maternal IS patients in Finland during years 1987–2016 were identified from national healthcare registers and verified from patient records. Three pregnant controls without a pregnancy-related stroke were selected for each case and matched by delivery year, age, parity, and geographical area. Deaths were acquired from the Causes-Of-Death Register until 2022. Morbidities (cardiovascular diseases and depression) were collected from Hospital Discharge Register and vocational status from Statistics Finland until 2016 for those who survived ≥ 1 year after stroke. Functional outcomes by modified Rankin scale (mRS) were estimated from patient records.

Results

There were 97 women with maternal IS, of whom 92 survived ≥ 1 year after stroke, and 265 matched controls (median age 30.6 years at index delivery in both groups). The median follow-up time was 17.4 years for mortality and 11.6 years for morbidity and vocational status. The overall mortality was higher in maternal IS patients than controls (8.3% vs 1.8%, age-adjusted odds ratio [aOR] 4.96, 95% CI 1.58–15.60) but did not differ significantly after the first year. There were 5 (5.6%) recurrent strokes in maternal IS patients. Patients had more frequently major cardiovascular events (6.7% vs 0%, $p < 0.001$), cardiac diseases (aOR 8.57, 95% CI 2.22–33.08), and depression (aOR 3.92, 95% CI 1.86–8.24) than controls. Of the patients who survived until the end of follow-up, 92.1% had good functional outcomes (mRS 0–2). Still, employment was rarer (aOR 0.55, 95% CI 0.32–0.94) and retirement (aOR 4.55, 95% CI 2.03–10.17) more common in maternal IS patients than controls.

Discussion

Maternal IS patients had a significant cardiovascular burden and were retired more often than controls at the end of follow-up, although most patients had good functional outcomes. Optimizing long-term prognosis in these young patients necessitates comprehensive management of vascular risk factors and targeted rehabilitation strategies to address residual neurologic deficits.

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Glossary

aOR = adjusted odds ratio; HDR = Hospital Discharge Register; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, 10th Revision; IQR = interquartile range; IS = ischemic stroke; MACE = major cardiovascular event; MBR = Medical Birth Register; mRS = modified Rankin scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

Introduction

Maternal ischemic stroke (IS) is a rare event during pregnancy, which may cause maternal morbidity and mortality. It has an estimated incidence of 12.2 per 100,000 pregnancies,¹ and several studies have shown that the incidence is increasing.^{2–4} Regarding short-term outcomes, in-hospital mortality after maternal IS has recently varied from 2.1% to 3.6%.^{5–7} Functional outcome has been found good (modified Rankin Scale [mRS] 0–2) in 80%–84% of maternal IS patients at hospital discharge.^{8,9}

There are only a few studies on long-term mortality, morbidity, recovery, or recurrence of stroke after maternal IS.^{6–8,10,11} In a French study, the mortality was 3.0%, the occurrence of cardiovascular events was 13.0%, and the recurrence of stroke was 6.5% in a mean follow-up of 6 years after a maternal IS.⁶ In a Dutch study, a 20-year cumulative risk of IS recurrence was estimated as 15.6% after maternal IS or TIA.⁸ More data on long-term prognosis after maternal IS are needed for counselling patients and planning effective secondary prevention and rehabilitation.

We aimed to study long-term mortality, recovery, and morbidity after maternal IS in a nationwide cohort of maternal IS patients in Finland during years 1987–2016. The objectives were to examine if mortality and long-term morbidity, focusing on cardiovascular and cerebrovascular disease, are more frequent in women with prior maternal IS compared with women without a pregnancy-related stroke and to assess the recovery of maternal IS patients by functional outcomes and vocational status.

Methods

This article follows the STrengthening the Reporting of OBservational studies in Epidemiology reporting guidelines.¹²

Study Design

In this retrospective and population-based nationwide longitudinal cohort and nested case-control study, patients diagnosed with IS during pregnancy or postpartum during years 1987–2016 in Finland and 3 stroke-free matched controls for each patient were identified using national healthcare registers. Follow-up data were gathered from healthcare registers (for patients and controls) and medical records (patients) until 2016 (recovery and morbidity) or 2022 (mortality).

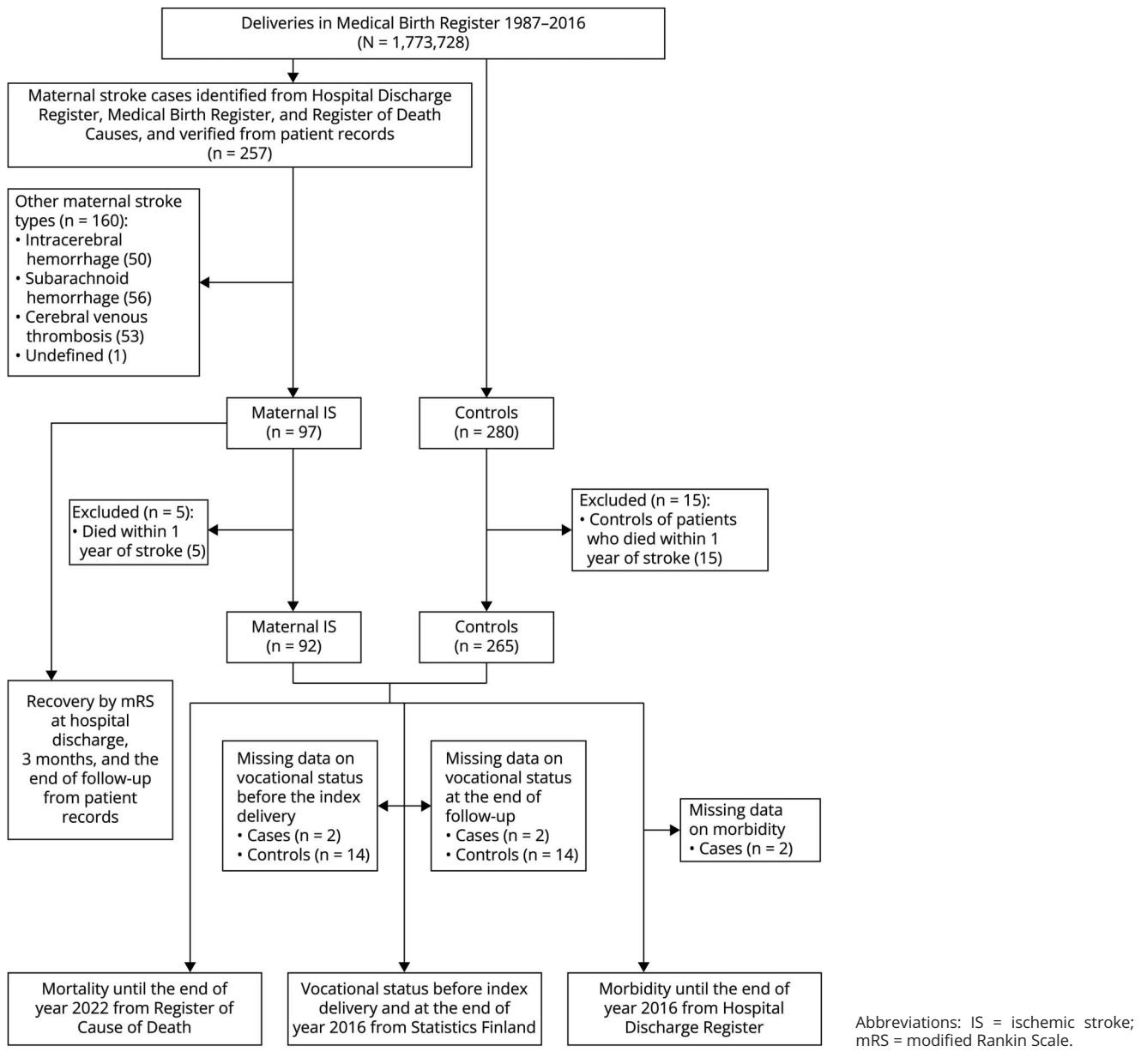
Cohort Identification

Maternal IS patients were identified using Medical Birth Register (MBR),¹³ Hospital Discharge Register (HDR),¹⁴ and the Causes-of-Death Register. Disease and procedure codes indicating stroke or its treatment in the HDR from 9 months (270 days) before and up to 3 months (90 days) after the delivery date in the MBR were used to identify the patients. The diagnostic codes used to identify patients with maternal IS have been described previously.¹⁵ The MBR includes all women in Finland with a pregnancy resulting in delivery (live births and stillbirths with gestational age $\geq 22 + 0$ weeks or with birthweight ≥ 500 g). All inpatient hospitalizations since 1967 and all outpatient clinic visits since 1998 in public hospitals in Finland are registered in the HDR. The Finnish version of International Classification of Diseases (ICD) codes accepted by World Health Organization (ICD-9 in years 1987–1995 and ICD-10 in years 1996–2016) were used in the MBR and HDR.

The medical records of patients identified from the registers were acquired from the healthcare facilities until the end of 2016. The diagnosis of IS, as recorded in ICD-9 and ICD-10, and its temporal connection to pregnancy was verified from the medical records by stroke neurologists. The diagnosis of IS was based on clinical findings and radiographic features. Only IS cases of arterial origin were included. We excluded the patients who had no IS during pregnancy or postpartum period and recorded the reasons for exclusion (Figure 1). The etiologies of IS were defined using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, which include large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology (including 2 or more causes identified (TOAST 5a), negative diagnostic evaluation (TOAST 5b), or incomplete evaluation (TOAST 5c)).¹⁶ Detailed pregnancy and disease definitions are presented in eMethods.

Three controls were identified from the MBR for each IS case and matched by delivery year, age, parity, and geographical area for a nested case-control analysis. Controls were delivered women without a pregnancy-related stroke. No controls for 1 case and only 1 control for another case were available because of the extreme age and sparsely inhabited geographical area. In addition, 2 cases had no follow-up register data available, and they had no controls. The demographics of index pregnancy were collected from the MBR and HDR with corresponding ICD-9 and ICD-10 codes (eTable 1).

Figure 1 Flowchart of the Maternal IS Cohort and Controls



Follow-Up Data on Mortality, Morbidity, Vocational Status, and Recovery

Data on mortality were collected from the Causes-of-Death Register until the end of year 2022 for all cases and controls. The register includes dates of deaths and ICD-codes for all causes of death. In addition, the death certificates were studied. Patients who died within 1 year after index stroke ($n = 5$) and their controls ($n = 15$) were excluded from analyses of long-term morbidity and vocational status. Morbidity and vocational status were collected until year 2016 and mortality until year 2022 due to different register data sources and their availability.

Data on morbidity (stroke, TIA, cardiac diseases, major cardiovascular events [MACEs], depression, and venous

thromboembolism) during the follow-up (from the beginning of the index pregnancy until the end of year 2016) were searched from the HDR for cases and controls with corresponding ICD-9 and ICD-10-codes (eTable 1). The diagnoses of strokes and TIAs in maternal IS patients were verified by stroke neurologists from patient records. All case-control analyses were performed based on register data, except for a sensitivity analysis comparing strokes and TIAs in cases and controls, for which diagnoses of stroke and TIA were verified for cases. Symptomatic epilepsy was collected for maternal IS patients from patient records solely. In addition, secondary preventive medication used was collected from patient records for those with cerebrovascular disease during follow-up.

Data on vocational status for cases and controls were acquired from Statistics Finland, in which vocational status has been coded every 5 years before 2004, and yearly since 2004. Data were collected 2 years before the index pregnancy (or the previously available time point) and until the end of year 2016. Categories of vocational status were being employed, being a student, pensioner, or unemployed. In addition, a comparison of socioeconomic groups in employed cases and controls before the index delivery and at the end of follow-up was performed. Socioeconomic groups were categorized as self-employed (self-employed farmers, employers, or own-account workers), upper-level employees (senior officials, management tasks of public administration, enterprises or organizations, planning and research, education), lower-level employees (management and employees in clerical, sales, care or other tasks), and manual workers (including mechanical work in agriculture, manufacturing, other production, distribution or service).¹⁷

Functional outcome was estimated by stroke neurologists for all maternal IS patients from patient records during follow-up based on mRS.¹⁸ The estimated mRS scores were based on description of patient's symptoms and functional capacity, and neurologic examination recorded by the treating neurologist during follow-up visits, and additionally on records from other specialties (neurosurgery, obstetrics, internal medicine). In Finland, rehabilitation and evaluation of working capacity after acute stroke belong to the neurologic specialty, so most patients were followed by neurologists for several months or years from acute care through rehabilitation. Detailed description on functional status during rehabilitation from the reports from physiotherapy, occupational therapy, speech therapy, and/or neuropsychology were often available. Functional outcome was reported at hospital discharge, 3 months after the index stroke, and at end of year 2016 or until the last available medical record. A good functional outcome was defined as mRS score 0–2.

Outcomes

The primary outcomes were (1) short-term and long-term mortality, (2) short-term and long-term functional outcome, and (3) long-term morbidity: cerebrovascular disease, cardiovascular disease, and MACE (including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). The secondary outcomes were (1) vocational status before the index delivery and at the end of follow-up and (2) other long-term morbidity: venous thromboembolism, depression, and symptomatic epilepsy.

Statistical Methods

Data were presented as numbers and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Binary logistic regression was used to analyze age-adjusted odds ratios (aORs) and their respective 95% CIs. Chi-square or Fisher exact tests were used to test differences between categorical variables, when logistic regression was not possible. *p* Value <0.05 was considered

statistically significant. Statistical analyses were performed with SPSS statistics version 29.

Standard Protocol Approvals, Registrations, and Patient Consents

The study has been approved by the Ethics committee of Helsinki University Central hospital (HUS/2228/2016 13.12.2016) and THL Finnish Institute of Health and Welfare (THL/750/5.05.00/2017) and Statistics Finland (TK-53-783-17, TK-53-591-20). Findata, the Finnish Social and Health Data Permit Authority, has granted a permit for the secondary use of these data until December 31, 2033 (THL/1784/14.06.00/2023). According to Findata's regulations, to ensure anonymity, a minimum frequency of 3 must be used when reporting frequencies so that is not possible to identify these patients. The EU and Finnish data protection legislation allows the use of register data in scientific research without a written patient consent.

Data Availability

Owing to the national Finnish and European Union data protection legislation, the data of this study cannot be shared in open data depositories.

Results

Maternal IS Cohort and Controls

There were 1,773,738 deliveries, 1,792,791 live births, and 6799 stillbirths in the MBR during the years 1987–2016. In total, 97 patients diagnosed with maternal IS and 280 controls were identified (Figure 1). Register data on the demographics of index pregnancy were available for 95 maternal IS patients and 280 controls (Table 1). The median age at index delivery was 30.9 years (IQR 26.9–35.0 years) in maternal IS patients and 30.7 years (IQR 26.7–35.1 years) in controls.

Mortality

Data on mortality were analyzed for 97 maternal IS patients and 280 controls (Table 2). The median follow-up time for mortality (from index delivery until the end of 2022) was 17.4 years (IQR 10.7–26.6 years). Overall, there were 8 (8.3%) deaths in maternal IS patients compared with 5 (1.8%) deaths in controls (aOR 4.96, 95% CI 1.58–15.60). Five (5.2%) maternal IS patients died in hospital, and primary causes for in-hospital deaths were IS, severe preeclampsia, acute infective endocarditis, other immediate postpartum hemorrhage (associated with disseminated intravascular coagulation), and postpartum coagulation defects (disseminated intravascular coagulation). After 1 year of the initial stroke, 3 (3.3%) maternal IS patients and 5 (1.9%) controls died, and the difference was statistically insignificant. Causes for these late deaths in maternal IS patients were a recurrent stroke, long-term consequences of initial stroke, and cancer. When considering IS etiology, the mortality was highest in patients with cardioembolism and stroke of other determined etiology (eFigure 1).

Table 1 Demographics, Risk Factors, and Pregnancy Complications of the Maternal IS Patients and Controls During the Index Pregnancy

	All (n = 375)	Maternal IS (n = 95) ^a	Controls (n = 280)	Age-adjusted OR (95% CI)	p Value
Age, y, median (IQR)	30.7 (26.8–35.0)	30.9 (26.9–35.0)	30.7 (26.7–35.1)		
Nulliparous	133 (35.5)	34 (35.8)	99 (35.4)	1.03 (0.63–1.71)	0.898
Primiparous	124 (33.1)	31 (32.6)	93 (33.2)	1.00 (0.96–1.05)	0.857
Multiparous	118 (31.5)	30 (31.6)	88 (31.4)	0.99 (0.58–1.68)	0.990
Cesarean section	82 (21.9)	36 (37.9)	46 (16.4)	3.10 (1.84–5.23) ^h	<0.001 ^h
Risk factors					
Obesity (BMI ≥30 kg/m²)^b	26 (12.9)	8 (15.7)	18 (11.9)	1.37 (0.56–3.37)	0.496
Smoking^c	55 (14.9)	15 (16.5)	40 (14.4)	1.18 (0.62–2.28)	0.612
Chronic hypertension	<5 (<1.3)	3 (3.2)	<3 (<1.1)	9.10 (0.93–89.30)	0.058
Hypercholesterolemia	<10 (<2.6)	3 (3.2)	<3 (<1.1)	4.57 (0.75–27.82)	0.099
Migraine	<15 (<4.0)	11 (11.6)	<3 (<1.1)	36.50 (4.65–286.86) ^h	<0.001 ^h
Diabetes mellitus	<3 (<0.3)	0	<3 (<1.1)	N/A	N/A
Complications of pregnancy					
Diabetes during pregnancy^d	41 (10.9)	15 (15.8)	26 (9.3)	1.83 (0.92–3.63)	0.085
Gestational or chronic hypertension^e	24 (6.4)	11 (11.6)	13 (4.6)	2.70 (1.16–6.28) ^h	0.021 ^h
Preeclampsia or eclampsia	23 (6.1)	14 (14.7)	9 (3.2)	5.28 (2.19–12.74) ^h	<0.001 ^h
Hypertensive disorders of pregnancy^f	41 (10.9)	15 (15.8)	26 (9.3)	3.81 (1.93–7.50) ^h	<0.001 ^h
Prior stroke or TIA	N/A	4 (4.2)	N/A		
Prior cardiac diseases^g	N/A	<3 (<3.2)	N/A		
Prior thrombophilia	N/A	3 (3.2)	N/A		

Abbreviations: BMI = body mass index; IQR = interquartile range; IS = ischemic stroke; N/A = not available; OR = odds ratio.

Data are presented as n (%) or median (IQR). Data were collected from the registers, except for prior stroke/TIA/cardiac disease/thrombophilia, which were collected from patient records. p Values, adjusted ORs and CIs were analyzed through binary logistic regression.

^a Table includes 95 maternal IS patients, since 2 patients had no register data available on index pregnancy demographics.

^b BMI before index pregnancy, 44 cases and 129 controls missing.

^c During index pregnancy, 4 cases and 3 controls missing.

^d ICD code O24.

^e ICD codes O10 and O13.

^f Preeclampsia, eclampsia, gestational hypertension, chronic hypertension and/or hemolysis, elevated liver enzymes, low platelets (HELLP).

^g Atrial fibrillation, ischemic heart disease, myocardial infarction, or congestive heart failure.

^h Indicates statistical significance.

Morbidity

Data on long-term morbidity were available for 90 maternal IS patients and 265 controls after excluding those who died within 1 year after index stroke and their controls (Table 2). The median follow-up time for morbidity (from index delivery until the end of 2016) was 11.6 years (IQR 4.7–20.6 years).

There were 5 (5.6%) recurrent strokes and 7 (7.8%) recurrent strokes or TIAs verified from patient records in women with prior maternal IS. Recurrent stroke subtypes included 3 ISs, 1 ICH, and 1 undefined stroke. The etiologies of recurrent ISs were undetermined with negative diagnostic evaluation in 2 cases and other determined etiology in 1 case. The patient with undefined stroke had multiple cerebral microbleeds and corresponding neurologic symptoms. During the follow-up,

stroke (5.6% vs 0%, $p < 0.001$) and IS (3.3% vs 0%, $p = 0.016$) were more common in maternal IS patients compared with controls. Maternal IS patients had more frequently stroke or TIA (aOR 24.35, 95% CI 5.41–109.58) than controls during the follow-up based on the register data. However, there were only 2 TIAs (2.2%) in maternal IS patients verified from the patient records compared with 9 TIAs (10.0%) identified from the registers. Therefore, we performed a sensitivity analysis by comparing verified strokes and TIAs in maternal IS patients to the register-identified strokes and TIAs in controls (no medical records were available for controls). In this analysis, having a stroke or TIA (aOR 11.1, 95% CI 2.26–54.39) was more common in maternal IS patients, but there was no statistically significant difference in having solely TIA (aOR 2.98, 95% CI 0.41–21.51).

Table 2 Long-Term Mortality, Morbidity, and Vocational Status of the Maternal IS Patients Who Survived ≥1 Year After Stroke and Controls

	All (n = 357)	Maternal IS (n = 92)	Controls (n = 265)	Age-adjusted OR (95% CI)	p Value ^a
Age at index delivery, y, median (IQR)	30.6 (26.8–34.8)	30.6 (26.8–34.7)	30.6 (26.7–34.8)		
Age at the end of 2016, y, median (IQR)	43.6 (36.3–50.8)	43.7 (35.8–50.6)	43.6 (36.7–50.8)		
Vocational status before index delivery^b					
Employed	254 (74.5)	64 (71.1)	190 (75.7)	0.78 (0.44–1.37)	0.387
Unemployed	22 (6.5)	9 (10.0)	13 (5.2)	2.03 (0.84–4.94)	0.117
Student	60 (17.6)	17 (18.9)	43 (17.1)	1.13 (0.59–2.18)	0.719
Pensioner	3 (0.9)	0	3 (1.2)	N/A	N/A
Vocational status at the end of follow-up^c					
Employed	254 (74.7)	58 (65.9)	196 (77.8)	0.55 (0.32–0.94) ^h	0.028 ^h
Unemployed	41 (12.2)	9 (10.2)	32 (12.7)	0.79 (0.36–1.72)	0.546
Student	17 (5.0)	5 (5.7)	12 (4.8)	1.23 (0.42–3.65)	0.707
Pensioner	28 (8.2)	16 (18.2)	12 (4.8)	4.55 (2.03–10.17) ^h	<0.001 ^h
Long-term outcomes					
Mortality	8 (2.3)	3 (3.3)	5 (1.9)	1.75 (0.41–7.48)	0.452
Morbidity^d					
Cerebrovascular event	<20 (<5.6)	14 (15.6)	<3 (<1.1)	24.35 (5.41–109.58) ^h	<0.001 ^h
Stroke^e	5 (1.4)	5 (5.6)	0	N/A	<0.001 ^h
IS^e	3 (0.8)	3 (3.3)	0	N/A	0.016 ^h
TIA	<15 (<4.2)	9 (10.0)	<3 (<1.1)	14.63 (3.10–69.08) ^h	<0.001 ^h
MACE	6 (1.7)	6 (6.7)	0	N/A	<0.001 ^h
Cardiac disease^f	11 (3.1)	8 (8.9)	3 (1.1)	8.57 (2.22–33.08) ^h	0.002 ^h
Atrial fibrillation	<10 (<2.8)	5 (5.6)	<3 (<1.1)	7.74 (1.48–40.64) ^h	0.016 ^h
IHD or MI	3 (0.8)	<3 (<3.3)	<3 (<1.1)	6.06 (0.54–67.82)	0.144
Congestive heart failure	<3 (<0.8)	<3 (<3.3)	0	N/A	0.064
Deep venous thromboembolism	<10 (<2.8)	<3 (<3.3)	4 (1.5)	1.48 (0.27–8.21)	0.657
Depression	32 (9.0)	17 (18.9)	15 (5.7)	3.92 (1.86–8.24) ^h	<0.001 ^h
Symptomatic epilepsy^g	N/A	10 (10.8)	N/A		

Abbreviations: BMI = body mass index; IHD = ischemic heart disease; IQR = interquartile range; IS = ischemic stroke; MACE = major cardiovascular events (includes cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); MI = myocardial infarction; N/A = not available; OR = odds ratio. Data are presented as n (%) or median (IQR). Adjusted ORs and CIs were analyzed through binary logistic regression. Data on vocational status and morbidity were collected from registers until the end of year 2016, and data on mortality were collected from registers until the end of year 2022.

^a p Values were calculated via logistic regression when possible and otherwise through the Fisher exact test.

^b Two cases and 14 controls missing. There were <3 stay-at-home mothers in controls, who are not included in table.

^c Four cases and 13 controls missing.

^d Two cases missing.

^e Stroke diagnoses were verified from patient records.

^f Atrial fibrillation, ischemic heart disease, myocardial infarction, and/or congestive heart failure.

^g Collected solely from patient records.

^h Indicates statistical significance.

Three of the verified recurrent strokes or TIAs (42.9%) in maternal IS patients occurred during the subsequent pregnancies, while 4 strokes or TIAs occurred outside of the subsequent pregnancies. Regarding secondary preventive medications, 4 patients with a recurrent stroke used warfarin,

acetylsalicylic acid, or low-molecular weight heparin during the recurrent stroke, and 1 patient had no antithrombotic medication. Two maternal IS patients with a TIA during follow-up used acetylsalicylic acid or low-molecular weight heparin as an antithrombotic medication.

MACEs were more common in maternal IS patients than controls (6.7% vs 0%, $p < 0.001$). In total, 8.9% of maternal IS patients had cardiac disease (atrial fibrillation, ischemic heart disease, myocardial infarction, and/or congestive heart failure) compared with 1.1% in controls (aOR 8.57, 95% CI 2.22–33.08). Of cardiac diseases, atrial fibrillation was significantly more common in maternal IS patients than controls (aOR 7.74, 95% CI 1.48–40.64). Depression was more frequent in maternal IS patients compared with controls (18.9% vs 5.7%, aOR 3.92, 95% CI 1.86–8.24). There were no statistically significant differences in the frequency of deep venous thromboembolisms, and no pulmonary embolisms were detected during the follow-up. Ten maternal IS patients (10.8%) had symptomatic epilepsy during the follow-up.

Vocational Status

After excluding those who died within 1 year after index stroke, data on vocational status were available for 90 maternal IS patients and 251 controls before index pregnancy, and for 88 maternal IS patients and 252 controls at the end of year 2016 (Table 2). The median follow-up time for vocational status (from index delivery until the end of 2016) was 11.6 years (IQR 4.7–20.6 years).

Vocational status was similar in maternal IS patients and controls before the index delivery. At the end of follow-up, maternal IS patients were less often employed (65.9% vs 77.8%, aOR 0.55, 95% CI 0.32–0.94) than controls. Being retired at the end of follow-up was more common in maternal IS patients compared with controls (18.2% vs 4.8%, aOR 4.55, 95% CI 2.03–10.17). In total, 81.2% of maternal IS patients on pension at the end of follow-up were younger than 60 years, reflecting a retirement due to a disease or disability.

The comparison of socioeconomic groups (self-employed, upper-level employees, lower-level employees, and manual workers) in employed maternal IS patients and controls before the index delivery and at the end of follow-up is presented in eTable 2. Before the index delivery, there were no statistically significant differences in socioeconomic groups of the employed maternal IS patients and controls. At the end of follow-up, maternal IS patients were less frequently upper-level employees than controls (12.5% vs 23.4%, aOR 0.45, 95% CI 0.23–0.92).

Recovery

The functional outcomes at hospital discharge, at 3 months after the index stroke and at the end of follow-up, were estimated for all maternal IS patients based on mRS scores (Figure 2). The median follow-up time in patient records was 5.3 years (IQR 1.4–14.9 years). In total, 83.4% of maternal IS patients had good functional outcomes (mRS scores of 0–2) at 3 months, indicating being independent in daily activities. At the end of follow-up, 86.8% of maternal IS patients had good functional outcomes. After excluding deaths, 88.0% of maternal IS patients had good functional outcomes at 3 months and 92.1% at the end of follow-up. mRS scores by

TOAST etiologies are presented in eFigure 1. At hospital discharge, having a good functional outcome was more common in TOAST 5b (undetermined etiology with negative diagnostic evaluation) etiology compared with other etiologies (85.4% vs 68.5%, $p = 0.022$). At the end of follow-up, patients with TOAST 5b etiology had less frequently mRS scores 4–6 compared with patients with other etiologies (0% vs 14.8%, $p = 0.019$).

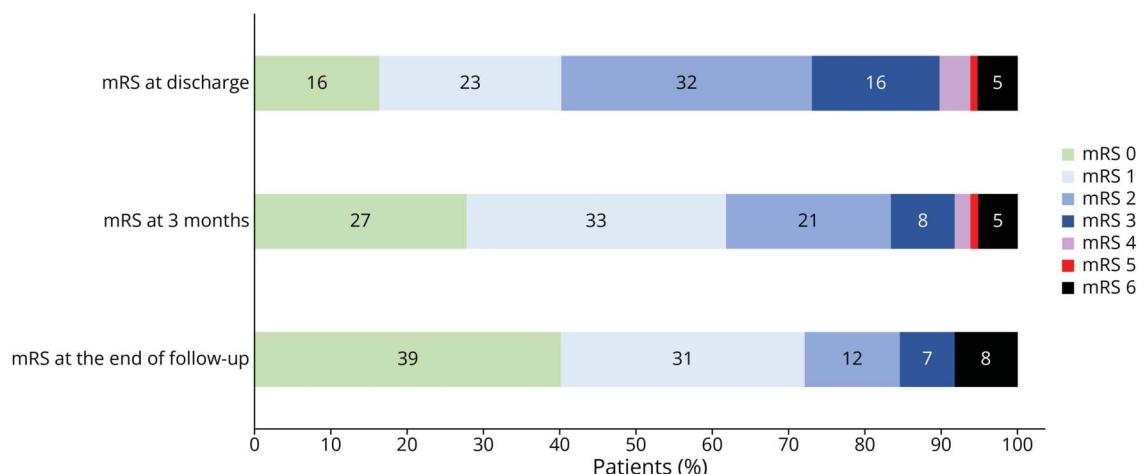
Discussion

In this nationwide retrospective cohort study, we examined long-term mortality, morbidity, functional, and vocational status after maternal IS with a median follow-up of 12 years (morbidity and vocational status) and 17 years (mortality). The mortality did not differ in patients and controls after 1 year of stroke. The long-term morbidity regarding cerebrovascular and cardiovascular diseases, as well as depression, was higher in maternal IS patients than controls. A total of 5.6% of women with prior maternal IS had recurrent strokes. Most maternal IS patients had good functional outcomes in short-term and long-term follow-up but being employed was rarer and being on pension was more frequent than in controls.

Maternal IS patients had 8.3% overall mortality—accumulating in patients with cardioembolism or other determined IS etiology—with 5-fold odds in overall mortality compared with controls, but there were no statistically significant differences in mortality after 1 year of the initial stroke. In-hospital mortality was 5.2% in maternal IS patients, which has been lower or similar (0%–5.4%) in other studies.^{6,7,19,20} Bejot et al.⁶ found 3.0% mortality in maternal IS patients in a median follow-up of 6 years. In another study, there were no deaths in a 5-year follow-up, but the patient group was small.¹⁰ Our finding of higher overall mortality might be partly explained by longer follow-up time than in these studies. In-hospital mortality after a maternal stroke has decreased in the United States between 2007 and 2015 from 5.5% to 2.7%;² therefore, in-hospital and overall mortality might be lower nowadays.

In total, 7.8% of maternal IS patients had a recurrent stroke or TIA during follow-up and nearly half of them occurred during the subsequent pregnancies. The recurrence of stroke after maternal IS has varied in previous studies. Similarly to our findings, Bejot et al.⁶ reported stroke recurrence of 6.5% in maternal IS patients, with most of recurrent strokes being ISs. In a Dutch study, there was a 15.6% cumulative risk of IS recurrence in maternal IS or TIA patients in 20 years.⁸ Garg et al.⁷ found that 2.3% of maternal stroke patients readmitted to hospital due to acute stroke in 1 year, with 400-fold hazard ratio if initial stroke was IS compared with pregnant women with no stroke. These accumulating data indicate that the risk of stroke recurrence after maternal IS is notable both during pregnancy and puerperium and in nonpregnant state.

Figure 2 Functional Outcome of Maternal IS Patients by mRS at Hospital Discharge, 3 Months, and the End of Follow-Up



mRS = modified Rankin Scale.

Women with prior maternal IS had a higher cardiovascular disease burden than controls, with 6.7% suffering MACE, 8.9% any cardiac disease, and 5.6% atrial fibrillation during follow-up. There are not many studies on long-term morbidity after maternal IS. Bejot et al.⁶ found that 13.0% of maternal IS patients were hospitalized due to cardiovascular events during follow-up. The risk of acute coronary syndrome was higher, but risk of overall cardiovascular events was lower than in non–pregnancy-related IS.⁶ In our study, the frequency of atrial fibrillation was almost 6% in maternal IS patients during follow-up, although generally in young adults the prevalence has been estimated as low as 0.1%,²¹ being significantly more frequent in this patient population. Atrial fibrillation is a high-risk cardiogenic source for embolism and can also predispose to recurrent strokes.²²

Functional outcomes by mRS scores were good in most maternal IS patients at the end of follow-up, and most favorable in the TOAST etiology undetermined with negative diagnostic evaluation. However, only two-thirds of maternal IS patients were employed and one-fifth were on pension at the end of year 2016. No patients were on pension before the initial stroke and most patients on pension were younger than 60 years. At the end of follow-up, maternal IS patients were less frequently upper-level employees than controls—a finding that may reflect poststroke symptoms in higher-order cognitive functions, such as attention, executive functions, and language, that are often required in tasks of upper-level employees. In a study of young IS patients, almost half had not returned to work at 5 years from IS, with a higher proportion in cases of severe aphasia, limb paresis, or visual deficit.²³ In addition to residual deficits, a higher frequency of depression and cardiovascular diseases in maternal IS patients compared with controls also might affect the ability to work. In addition, cognitive impairment occurs in up to half of young stroke patients, and there might be other residual symptoms, like

often underestimated fatigue and poststroke pain.²⁴ The obstacles that young stroke patients face in returning to work and how they could be influenced by rehabilitation should be the focus of further research.

There are limitations in this study. The cohort size is rather small due to rareness of maternal IS and the size of Finnish population, which might lead to both Types I and II statistical error, that is, false positive and negative results, and limit statistical power, especially in subgroup analyses. The case-control analyses were based on register data to ensure comparability, except for the sensitivity analysis comparing cerebrovascular diseases in cases and controls. In the sensitivity analysis, recurrent strokes and TIAs could be verified from patient records only for maternal IS patients, so the data on strokes and TIAs are only register-based for controls, which may bias the comparison. In the register-based analyses, there may be detection bias since maternal IS patients were likely followed up more frequently in the public healthcare than controls. The symptoms of stroke or TIA during the follow-up may have been examined with a lower threshold in patients than controls. In Finland, cerebrovascular diseases and significant cardiac diseases are usually diagnosed and treated in the public healthcare system, so it is unlikely that these diagnoses would have been missed. Depression and deep venous thromboses can be diagnosed and treated in primary outpatient health care or private sector especially in mild cases, so some of these diagnoses could have been unrecorded. However, these factors in the Finnish healthcare system apply to both cases and controls and therefore do not make results more prone to bias between cases and controls. The Finnish population is homogenous and the healthcare system is public with heavily subsided costs, which might lead to results not being applicable to all populations. The functional outcomes were estimated from patient records retrospectively rather than systematically assessed, which might lead to underestimation of

cognitive and other nonmotor stroke symptoms. The follow-up time was long in our study but is still rather short to estimate cardiovascular burden and mortality later in life.

To conclude, there are considerable long-term consequences after maternal IS, with higher morbidity particularly regarding cardiovascular diseases and depression. Mortality among maternal IS patients did not differ from that of controls after the first year poststroke. The recurrence of cerebrovascular diseases was notable, both outside pregnancy and puerperium and in association to subsequent pregnancies. Recovery by functional outcome was mostly good after maternal IS in short-term and long-term follow-up, but still more than one-third of patients were out of work at the end of follow-up. The findings in this study highlight the need for adequate secondary prevention, surveillance, and rehabilitation after maternal IS to improve long-term prognosis.

Author Contributions

A. Richardt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. L. Verho: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K.K. Rantanen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. A. Korhonen: major role in the acquisition of data. H. Laivuori: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Tikkainen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Gissler: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. K. Aarnio: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. P.H. Ijäs: drafting/revision of the manuscript 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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