Pregnancy related risk factors as predictors of early onset cerebrovascular disease in offspring - the Northern Finland Birth Cohort Study 1966

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Abstract

Background and purpose

For prevention of cerebrovascular diseases, it is important to understand the risk factors occurring early in life. The aim was to investigate the relationship of maternal and offspring anthropometrics, and pregnancy complications with offspring's risk of ischemic and hemorrhagic stroke and TIA in adulthood.

Methods

Within the population-based prospective Northern Finland Birth Cohort 1966, 11,991 persons were followed from early pregnancy to 52 years of age. Information on pregnancy and birth complications were collected starting from between 24th and 28th gestational week and at birth. Ischemic and hemorrhagic strokes of the offspring were identified from national registers in Finland. Cox proportional hazard models were used to estimate the association of pregnancy and birth complications with incidence of cerebrovascular disease in the offspring, with adjustments for sex, family socioeconomic status, mother's age and smoking during pregnancy.

Results

During 568,821 person-years of follow-up, 453 (3.8%) of the offspring had a stroke or TIA. Small and large gestational weight gain among normal weight mothers were associated with increased ischemic stroke risk in offspring (adjusted hazard ratio (aHR) 1.93; 95% confidence interval (CI) 1.28-2.90 and aHR 1.54; CI 1.02-2.31, respectively). Small birth weight for gestational age and small ponderal index were associated with increased risk for

ischemic stroke (aHR 1.95; CI 1.21-3.13 and aHR 1.36; CI 1.04-1.77, respectively). Threatening miscarriage was also associated with increased risk of any stroke (aHR 1.64; CI 1.14-2.37). Maternal smoking, hypertension, or birth complications were not associated with increased risk of cerebrovascular disease in the offspring.

Conclusions

The results of this study suggest that disturbances in maternal and fetal growth during pregnancy may predispose offspring to developing cerebrovascular diseases in adulthood.

Non-standard Abbreviations and Acronyms: Body Mass Index (BMI), Northern Finland Birth Cohort (NFBC), Transient Ischemic Attack (TIA), standard deviation (SD), hazard ratio (HR), confidence interval (CI).

1 Introduction

The burden of stroke is tremendously high across the globe(1). Nearly a quarter of all strokes and up to a half of hemorrhagic strokes occur in people younger than 50 years(2). Strokes occurring early in life lead to significant economical burdens due to losses in working years and health care costs.

There is consistent reportage of rising stroke incidence within the young adult group(3,4) and it is notable that in cohorts of young stroke patients up to 30% of strokes remain cryptogenic(5-7). The larger proportions of undetermined etiologies in younger age-groups may be explained by unrecognized predisposing genetic factors(8,9) and knowledge on any previously unidentified risk factors is therefore of crucial importance.

In a Finnish previous birth cohort study, individuals born after pregnancies complicated by pre-eclampsia or gestational hypertension were at increased risk of stroke in later life(10). There is a lack of knowledge on other pregnancy related complications, such as maternal weight gain or threatening miscarriage, in relation to the newborn's stroke risk at adulthood.

A few studies on early life attributes have linked childhood height, weight and growth factors to increased stroke risk later in life, in which small birth weight, thinness during infancy and short stature in childhood are known to increase risk of high blood pressure, cardiovascular disease and stroke(11,12). Accelerated growth in height, above-average BMI and increases in BMI during childhood have also been associated with increased risk of stroke(13,14). Still, early life factors potentially predisposing to later cerebrovascular disease have not been sufficiently studied.

In this large, unselected, and population-based birth cohort study we set up to investigate pregnancy complications, maternal and fetal anthropometrics, and sociodemographic factors in relation to the individuals' cerebrovascular disease risk later in life. The aim was to identify previously unknown risk factors for the incidence of cerebrovascular disease among adults until age of 52 years.

2 Materials and methods

2.1. Data availability statement

Data is available from the Northern Finland Birth Cohort (NFBC) for researchers who meet the criteria for accessing confidential data. Please, contact NFBC project center (NFBCprojectcenter@oulu.fi) and visit the cohort website (www.oulu.fi/nfbc) for more information.

2.2. Design of Study and Sample

The Northern Finland 1966 Birth Cohort (NFBC1966) is an unselected, population-based birth cohort containing data on 12,068 pregnant women and their 12,058 live-born children in the provinces of Oulu and Lapland with an expected date of birth in 1966(15). Excluded from the study were the subjects who declined use of their data (n=59) and persons who had suffered stroke or TIA under the age of 15 years (n=8). The sample for this study included 11,991 subjects who were followed from birth date to their first stroke, death, moving abroad, or until the end of year 2018. The 84 persons who had moved abroad but whose moving date was unknown were censored on their birthday. The mean follow-up time per participant was 47.4

years (standard deviation (SD) 13.5 years). Data collection on the parents and individuals born into the NFBC1966 started between the 24th and 28th week of gestation.

The questionnaire and clinical examination data collected of mothers were linked to existing nationwide registers of offspring, *i.e*. Care Register for Health Care, Causes of Death Register, and register of medication reimbursement, with personal, pseudonymized identification numbers.

Permission to gather data was obtained from the Ministry of Social Affairs and Health, and the study was approved by the Ethical Committee of Northern Ostrobothnia Hospital District in Oulu, Finland. Data protection was scrutinized by the Office of Data Protection Ombudsman of Finland. Informed consent was inquired from all the participants.

2.3. Risk factors related to pregnancy

Variables measuring pregnancy-related factors were obtained from the questionnaires during pregnancy, from the maternity clinic cards requested from the antenatal clinics, and from delivery reports requested from the maternity hospitals. The prespecified variables measuring risk factors related to pregnancy and birth included pre-eclampsia and hypertension, threatening miscarriage, smoking during pregnancy, pre- and post-term birth, multiple delivery, placenta previa or placental abruption, prolonged second stage of labor, abnormal fetal position/presentation or deviant fetal heart frequency. Antenatal clinic nurses interviewed the mothers between gestational weeks 24-28 using a questionnaire form. Information on deliveries was obtained from delivery records.

Mother's blood pressure was measured at the antenatal visits. Hypertension was defined as systolic blood pressure ≥145mmHg or diastolic blood pressure ≥95mmHg any time during the pregnancy or a diagnosis of essential hypertension in questionnaire or maternity clinic cards. Pre-eclampsia was defined as blood pressure ≥145/95mmHg or more after 20th gestational week and proteinuria at least in one sample during pregnancy. Information on bleeding during pregnancy was filled in questionnaire by maternity hospital nurses at time of birth and did not include data on the timing of bleeding during pregnancy. Threatening miscarriage was defined as bleeding occurring during first or second trimester of pregnancy and for analyses, these two variables were combined. Mother's smoking status was asked in questionnaire. Mothers who did not smoke before the pregnancy and mothers who quit smoking during the first gestational month were defined as non-smokers, and mothers who smoked after the first month were considered smokers.

Gestational week at birth was obtained from delivery reports and classified as number of weeks from last menstrual period. Twin births were defined as multiple delivery. The variable of operative management during birth included cesarean delivery and vacuum or forceps assisted delivery. For the analysis of 'any birth complication' the variables of prolonged second stage, placenta previa, placental abruption, deviant fetal heart rate and fetal position were combined.

2.4. Gestational weight gain and newborn anthropometrics

Maternal body mass index (BMI) was calculated from pre-pregnancy weight and height, self-reported at first antenatal clinic visit and was classified according to the World Health

Organization (WHO) classification: underweight, <18.50; normal weight, 18.50–24.99; overweight ≥25.00. Maternal weight was also measured during the second trimester and before delivery. Gestational weight gain was classified into three categories: small (-11.3–7.9kg), average (8.0–14.4kg) and large (14.5–50.0kg) based on quartiles from data of this study population. Gestational weight gain was further analyzed for normal weight and overweight mothers specifically.

Birth height and birth weight were obtained from delivery reports. Small and large birth weight were defined as ≤ -2SD and ≥ +2SD from the mean for sex and each gestation week, based on Finnish birth weight standards (16,17). Accordingly, these standard values were used to define small and large birth height as ≤ -2SD and ≥ +2SD from the mean. Ponderal index was used to evaluate the infant's body proportionality without taking gestational age into consideration. Ponderal index can be calculated with the following formula: PI= birth weight x 100 / length^3. These values were classified using quartile cut-offs based on this study population.

Birth weight to placental weight ratio was used to estimate placental efficiency and groups classified using quartile cut-offs based on this study population.

2.5. Sociodemographic factors

Sociodemographic factors were obtained from the questionnaires during the pregnancy, maternity clinic cards requested from the antenatal clinics, and delivery reports requested from the maternity hospitals. This data included information on place of residence according to population density, desirability of current pregnancy, and marital status. Place of residence was divided in two categories in which 'Urban' was defined as any living in a town or village and

‘Rural’ as living in an out of the way village. Desirability of pregnancy was classified as ‘No’ if mothers reported in questionnaire to have wished for the pregnancy to come later or not at all as opposed to pregnancy being desired. In 1966, terminations of pregnancy were rare and largely limited to medical conditions. Marital status was classified as married or either single, widowed or divorced.

2.6. Cerebrovascular disease

Cerebrovascular disease was the outcome variable of this study. The offspring’s strokes and TIAs were identified from the Care Register for Health Care and Causes of Death Register based on medical records. The diagnostic coding has been based on the WHO international classification of diseases (ICD) in Finland since 1967. Cerebrovascular diseases were classified by first primary diagnosis: subarachnoid hemorrhages (SAH; ICD-8 430; ICD-9 430; ICD-10 I60 and I69.0), intracerebral hemorrhages (ICH; ICD-8 431; ICD-9 431; ICD-10 I61 and I69.1), ischemic strokes (ICD-8 432-434; ICD-9 433-434; ICD-10 I63 and I69.3), transient ischemic attack (TIA; ICD-8 435; ICD-9 435; ICD-10 G45), and other cerebrovascular diseases (ICD-8 436-438; ICD-9 436-437; ICD-10 I64-I68, I69.4 and I69.8). Other cerebrovascular diseases included e.g. central venous sinus thromboses and non-ruptured cerebral aneurysms. Stroke syndromes (ICD-9 438; ICD-10 G46) were classified according to etiological sub-code (ICD-9 430-437; ICD-10 I60-I67) or as other cerebrovascular diseases if sub-codes were not present. The linkage to other data with pseudonymization was fully complete for stroke diagnoses.

Ischemic strokes and transient ischemic attacks were defined as ischemic strokes and subarachnoid hemorrhages and intracerebral hemorrhages as hemorrhagic strokes. For analyses of ‘any cerebrovascular disease’ ischemic strokes, hemorrhagic strokes, and other

cerebrovascular diseases were combined. Traumatic SAH, traumatic ICH, epidural hematoma or subdural hematoma were not considered as strokes. Subjects with two or more cerebrovascular disease diagnoses were classified by primary diagnosis.

As sensitivity analyses, we repeated the models excluding the offspring who suffered a TIA, and the results were similar to original analyses (results not shown).

2.7. Covariates

Covariates were sex, socioeconomic status of family, and mother's age. Sex was obtained from delivery reports. Socioeconomic status of family was asked in the questionnaires and was defined as the highest occupational status of the mother or father during the pregnancy, and categorized as unemployed or unskilled worker, skilled worker, and professional. Maternal age was obtained from population registers.

2.8. Statistical analyses

Cox proportional hazards model was used to estimate the associations of pregnancy complications, maternal and infant anthropometrics, and sociodemographic factors with incidence of cerebrovascular disease, ischemic stroke and hemorrhagic stroke in the offspring during follow-up. All models included adjustment for sex of the child, maternal age, socioeconomic status of the family and maternal smoking during pregnancy. Additional analyses with time dependent covariates were done to assure that cox proportional hazard assumption was met.

Results are presented with adjusted hazard ratios (aHR) with 95% confidence intervals (CI).

Because weight gain is dependent on pre-pregnancy BMI, we performed an additional analysis among mothers with normal pre-pregnancy BMI only. To further investigate the independent association of maternal and infant weight gain during pregnancy with stroke we did an additional analysis in which maternal weight gain was adjusted for fetal birth weight.

All the statistical analyses were carried out using IBM SPSS Statistics 25.0 for Windows (IBM Corp., Armonk, NY, USA).

3 Results

The amount of person years the cohort members were followed up starting from their birth date until end of follow-up period was 568,821 in total. During the follow-up period, 453 (3.8%) individuals had a cerebrovascular disease. Characteristics of stroke sample and controls are shown in Table 1. Of all cerebrovascular diseases, 144 (31.8%) were ischemic strokes, 164 (36.2%) TIAs, 59 (13.0%) were SAHs, 36 (7.9%) ICHs, and 50 (11.0%) were other cerebrovascular events. The median age at cerebrovascular disease onset was 46.4 (standard deviation (SD) 7.2) years for ischemic stroke, 47.3 (SD 5.0) years for TIA, 45.7 (SD 8.7) years for ICH and 43.6 (SD 9.7) years for SAH.

The incidences and adjusted HRs for cerebrovascular disease, ischemic stroke, or hemorrhagic stroke in relation to pregnancy complications are shown in Table 2. Threatening miscarriage associated with offspring's increased risk for cerebrovascular disease with a HR of 1.64 (95%CI 1.14-2.37) (Figure 1 Panel A), but not specifically for ischemic or hemorrhagic strokes.

Small gestational weight gain showed an association with an increased risk for offspring of cerebrovascular disease with a HR of 1.45 (95%CI 1.07-1.97) and ischemic stroke (HR 1.77; 95%CI 1.24-2.54) (Table 3). Among the offspring of normal weighted mothers, small gestational weight gain had a HR of 1.79 (95%CI 1.28-2.53) for cerebrovascular disease and a HR of 1.93 (95%CI 1.28-2.90) for ischemic stroke (Figure 1 Panel B). Large gestational weight gain among normal weighted mothers was also associated with increased risk of cerebrovascular disease (HR 1.45; 95%CI 1.03-2.04) and ischemic stroke (HR 1.54; 95%CI 1.02-2.31) for the offspring. The results did not change when adjusted for offspring birth weight (data not shown).

Offspring born with small birth weight for gestational age had an increased risk for cerebrovascular disease (HR 1.66; 95%CI 1.09-2.53) (Figure 1 Panel C) and especially for ischemic stroke (HR 1.95; 95%CI 1.21-3.14). Offspring with short height for gestational age had an increased HR of 1.45 (95%CI 1.09-1.94) for ischemic stroke. Small ponderal index was associated with increased risk of cerebrovascular disease with a HR of 1.33 (95%CI 1.07-1.66) and ischemic stroke (HR 1.36; 95%CI 1.04-1.77).

The incidences and adjusted HRs for cerebrovascular disease, ischemic stroke, or hemorrhagic stroke in relation to sociodemographic factors are shown in Table 4. Place of residence, desirability of pregnancy or parent's marital status were not associated with the offspring's increased risk of cerebrovascular disease later in life.

4 Discussion

In this study we found small and large maternal weight gain during pregnancy among normal weight mothers to be associated with the offspring's increased risk for ischemic stroke later in life. We also found that small birth weight, height and ponderal index at birth were associated with an increased risk of later ischemic stroke. In addition, our data showed an association between threatening miscarriage and risk of cerebrovascular disease in the offspring. We did not find associations between hypertension or pre-eclampsia, maternal smoking during pregnancy, birth complications, or sociodemographic factors and the offspring's stroke risk.

To our knowledge, the current study is the first to report small gestational weight gain to be associated with increased offspring cerebrovascular disease risk. One study reported large gestational weight gain to increase the risk of cerebrovascular disease in the adult offspring(18) and previous studies have found large gestational weight gain to increase the risk of cardiovascular disease in the offspring(19,20). One study found both excessive and inadequate gestational weight gain to be associated with offspring childhood adiposity, hypertension and insulin resistance(21). In line with our findings, earlier studies have also supported the notion that malnutrition in utero and intrauterine growth restriction contribute to increased cardiometabolic and cerebrovascular disease risk of the offspring(22,23). Maternal weight gain during pregnancy correlates with offspring birth weight(24). However, adjustment for birth weight did not alter the observed associations for maternal weight gain in our study, which suggests them to be independent risk factors for cerebrovascular disease. Small gestational weight gain may be a sign of maternal malnutrition or placental dysfunction and our findings support the idea that an unfavorable gestational environment predisposes offspring to chronic diseases in adulthood.

In this study we found thinness at birth, i.e. small ponderal index and small birth weight, to be associated with a higher risk of cerebrovascular disease, particularly ischemic stroke, later in life. Our findings are in accordance with previous studies that have revealed a relation between small birth weight and later risk of cardiovascular disease and stroke(25,26). A previous Finnish cohort study also found thinness during infancy to be associated with increased stroke risk later in life(27). Some studies have examined possible underlying mechanisms between cardiovascular disease and birth weight, and it has been reported that small birth weight is associated with functional and structural changes in the individuals vascular tree development and altered hemodynamics in young adulthood(28,29). Shared genetic and environmental characteristics between mother and offspring may account for these relationships. This study did not assess the contribution of genetic factors to the observed associations, but we have attempted to account for shared environmental characteristics by adjusting for family socioeconomic status and maternal smoking. This study did not examine stroke causes in the individual stroke cases identified.

Furthermore, our data showed an association between threatening miscarriage and the offspring's later risk of cerebrovascular disease. To our knowledge, there are no previous studies examining the relationship between threatening miscarriage and the offspring's later cerebrovascular disease risk. Previous studies have linked early pregnancy bleeding with adverse infant outcomes, such as small birth weight(30,31). Threatening miscarriage is a sign of placental dysfunction and it is known that placental problems can reduce the transition of nutrients from mother to child. This may lead to intrauterine growth restriction, small birth weight and possibly through epigenetic regulation to an increased risk of adverse events in the

offspring's later life. Increasing evidence suggests that epigenetic regulation plays an important role in development of adult disease(32), therefore knowledge on any novel risk factors is important for allowing earlier and more aggressive prevention strategies for individuals at higher risk.

Maternal hypertension in pregnancy was not associated with offspring stroke, the HR with its 95%CI being 1.09 (0.88-1.33). In a study of people born in Helsinki, Finland, 1934-1944, the HR for stroke was 1.4 (95%CI 1.0-1.8) for those exposed to maternal gestational hypertension. Taken together, our results argue against a moderate or large association between maternal hypertension and stroke, but a weak association is possible. Our study had limited power to assess specific associations with pre-eclampsia.

It should be noted that the present study had some limitations. The main limitation was the sample size of stroke groups. Cerebrovascular disease at young age is rare(33) and even in this large-scale cohort with comprehensive follow-up only 453 persons had a cerebrovascular event. Sample sizes in some exposure groups might have been too small to detect existing differences, e.g., the number of underweight mothers was too small for reliable analyses for their weight gain during pregnancy. Some variables were added together to allow for bigger sample sizes and e.g. the heterogeneity of the variable "Any birth complication" could contribute to the lack of association. Also, although the cohort was designed to examine pregnancy risk factors in relation to later diseases, for our study we were restricted to the risk factors that were collected in 1960s. Data on gestational diabetes, for example, was not available for analysis since it was not systematically screened in the era. Timing of bleeding during pregnancy was not documented in questionnaire. Finally, we did several analyses, and

the findings should be interpreted with caution. Further studies that examine the causality and underlying mechanisms that account for the observed associations are warranted.

This study also had several strengths, one being the use of a large, unselected, population-based birth cohort containing almost 12,000 mothers and their children with nearly 570 000 person years of follow-up. The data collection started from the second trimester of cohort members' antenatal period and follow-up lasted up to 52 years of age. Also, data collection was prospective reducing the potential for recall bias, and questionnaire and clinical examination data were combined with comprehensive nationwide registers based on medical records. Furthermore, information on cerebrovascular disease diagnoses from nationwide registers was complete for the entire cohort. The validity of Finnish hospital discharge registers and causes of death registers are proven to be good(34). The small number of missing data for detailed measures collected throughout the follow-up period permitted meaningful adjustments for potential confounders.

5 Conclusions

The results of this study show that both maternal and fetal growth during pregnancy play an important role in development of ischemic stroke risk for the offspring. This supports the notion that individual cerebrovascular disease risk may start accumulating long before onset age, as early as prenatal stage.

6. Tables

Table 1. Population characteristics

All (N=11,991)	**Any cerebrovascular disease N (%) / Mean (SD)**	**No cerebrovascular disease N (%) / Mean (SD)**
Sex (n=11991)	453	11538
Female (n=5855)	228 (50.3%)	5630 (48.8%)
Male (n=6136)	225 (49.7%)	5908 (51.2%)
Person years in follow-up	19964	548857
Mean age at end of follow up	44.0 (7.7)	47.6 (13.6)
Mean age of mother at birth (n=11923)	27.5 (6.6)	27.8 (6.6)
Mean age of father at birth (n=11246)	30.5 (7.2)	30.8 (7.2)
Highest occupational status in family (n=11863)	448	11415
Professional (n=4428)	159 (35.1%)	4269 (37.4%)
Skilled worker (n=4075)	176 (38.9%)	3899 (34.2%)
Unskilled worker (n=3261)	110 (24.3%)	3151 (27.6%)
No occupation (n=99)	3 (0.7%)	96 (0,8%)
Residence (n=11963)	459	11504

Urban (n=7083)	256 (56.5%)	6827 (59.2%)
Rural (n=4872)	195 (43.0%)	4677 (40.5%)

Table 2. Adjusted hazard ratios (95% Confidence Intervals) for offspring's cerebrovascular disease in relation to pregnancy complications.

	Any cerebrovascular disease		Ischemic stroke or TIA		Hemorrhagic stroke	
	N (%)	HR (95% CI)	N (%)	HR (95% CI)	N (%)	HR (95% CI)
All (N=11,991)	453 (3.8%)	n.a.	308 (2.6%)	n.a.	95 (0.8%)	n.a.
Pre-eclampsia or hypertension (all=10468)						
No (n=6627)	240 (3.6%)	ref.	172 (2.6%)	ref.	49 (0.8%)	ref.
Yes (n=3841)	151 (3.9%)	1.09 (0.88-1.33)	93 (2.5%)	0.93 (0.72-1.20)	35 (0.9%)	1.20 (0.78-1.86)
Threatening miscarriage (all=10802)						
No (n=10524)	376 (3.7 %)	ref.	255 (2.5%)	ref.	78 (0.8%)	ref.
Yes (n=548)	31 (5.7 %)	**1.64 (1.14-2.37)**	19 (3.5%)	1.49 (0.93-2.37)	8 (1.5%)	2.00 (0.97-4.16)
Mother smoking during pregnancy (all=11991)						
No (n=9395)	352 (3.7 %)	ref.	245 (2.6%)	ref.	71 (0.8%)	ref.
Yes (n=2597)	101 (3.9 %)	1.07 (0.86-1.35)	63 (2.5%)	0.98 (0.74-1.30)	24 (1.0%)	1.28 (0.79-2.07)
Gestational week at delivery(n=11523)						
Preterm (weeks 25-36) (n=688)	27 (3.9%)	1.20 (0.81-1.78)	20 (2.9%)	1.35 (0.85-2.13)	4 (0.6%)	0.83 (0.30-2.28)
Average (weeks 37-41) (n=8646)	341 (3.9%)	ref.	229 (2.7%)	ref.	72 (0.9%)	ref.

Post-term (weeks 42 or above) (n=2189)	69 (3.2%)	0.80 (0.62-1.04)	48 (2.2%)	0.83 (0.61-1.13)	160.7%)	0.87 (0.51-1.50)
Preterm birth (n=11531)						
No (n=10841)	410 (3.8%)	ref.	277 (2.6%)	ref.	88 (0.8%)	ref.
Yes (n=690)	27 (3.9%)	1.25 (0.85-1.85)	20 (2.9%)	1.39 (0.89-2.20)	4 (0.6%)	0.86 (0.31-2.33)
Single/multiple delivery (all=11955)						
Single (n=11646)	440 (3.8%)	ref.	297 (2.6%)	ref.	94 (0.8%)	ref.
Multiple (n=309)	11 (3.6%)	1.07 (0.59-1.94)	10 (3.2%)	1.43 (0.76-2.69)	0	n.a
Operative management during delivery (all=4438)						
No (n=3716)	146 (3.9%)	ref.	95 (2.6%)	ref.	33 (0.9%)	ref.
Yes (n=722)	21 (2.9%)	0.73 (0.46-1.15)	16 (2.2%)	0.85 (0.50-1.45)	4 (0.6%)	0.61 (0.22-1.73)
Any birth complication (n=5725)						
0 (n=4474	165 (3.7%)	ref.	111 (2.5%)	ref.	33 (0.8%)	ref.
1 or more (n=1251)	50 (4.0%)	1.15 (0.84-1.58)	36 (2.9%)	1.24 (0.85-1.80)	10 (0.8%)	1.15 (0.57-2.34)

Cox regression adjusted for sex, socioeconomic status, mother's age and mother's smoking during pregnancy. Any birth complication = placenta previa or placental abruption, lengthy second stage, abnormal fetal position/presentation or deviant fetal heart frequency. N=number; HR=hazard ratio; CI=confidence interval; n.a.=not applicable; Ref=reference group. Boldface indicates statistical significance.

Table 3. Adjusted hazard ratios (95% Confidence Intervals) for offspring's cerebrovascular disease in relation to anthropometrics and maternal weight gain during pregnancy.

	Any cerebrovascular disease		Ischemic stroke or TIA		Hemorrhagic stroke	
	N (%)	HR (95% CI)	N (%)	HR (95% CI)	N (%)	HR (95% CI)
All (N=11,991)	453 (3.8%)	n.a.	308 (2.6%)	n.a.	95 (0.8%)	n.a.
Gestational weight gain (n=7070)						
Small (-11.3 – 7.9 kg) n=1530	67 (4.4 %)	**1.45 (1.07-1.97)**	51 (3.4%)	**1.77 (1.24-2.54)**	7 (0.5%)	0.53 (0.23-1.22)
Average (8.0 – 14.4 kg) n=3834	126 (3.3 %)	ref.	81 (2.1%)	ref.	33 (0.9%)	ref.
Large (14.5 – 50.0 kg) n=1706	69 (4.0 %)	1.18 (0.88-1.59)	48 (2.8%)	1.28 (0.89-1.84)	15 (0.9%)	1.02 (0.55-1.90)
Gestational weight gain (normal weight mother) (n=5148)						
Small (-11.0 – 8.9 kg) n=1227	59 (4.8%)	**1.79 (1.28-2.53)**	43 (3.6%)	**1.93 (1.28-2.90)**	7 (0.6%)	0.88 (0.37-2.10)
Average (9.0 – 15.4 kg) n=2606	79 (3.0%)	ref.	53 (2.1%)	ref.	20 (0.8%)	ref.
Large (15.5 – 35.0 g) n=1315	60 (4.6%)	**1.45 (1.03-2.04)**	42 (3.2%)	**1.54 (1.02-2.31)**	12 (0.9%)	1.12 (0.55-2.30)
Gestational weight gain (overweight mother) (n=1194)						

Small (-7.0 – 8.2 kg) n=224	8 (3.6%)	1.06 (0.47-2.40)	7 (3.1%)	1.70 (0.67-4.34)	1 (0.5%)	0.40 (0.05-3.36)
Average (8.3 – 13.9 kg) n=641	22 (3.4%)	ref.	13 (2.1%)	ref.	6 (1.0%)	ref.
Large (14.0 – 31.0 kg) n=329	7 (2.1%)	0.64 (0.27-1.52)	4 (1.2%)	0.58 (0.19-1.79)	3 (0.9%)	1.39 (0.34-5.66)
Birth height for gestational age (n=11829)						
Small (30 – 48 cm) n=2181	88 (4.0%)	1.26 (0.98-1.61)	68 (3.1%)	**1.45 (1.09-1.94)**	10 (0.5%)	0.66 (0.33-1.30)
Average (49-51 cm) n=6475	226 (3.5%)	ref.	152 (2.4%)	ref.	49 (0.8%)	ref.
Large (52 – 59 cm) n=3173	133 (4.2%)	1.22 (0.98-1.52)	85 (2.7%)	1.14 (0.87-1.49)	34 (1.1%)	1.48 (0.95-2.32)
Birth weight for gestational age (n=11522)						
Small (390 – 3130 g) n=431	23 (5.3%)	**1.66 (1.09-2.53)**	18 (4.2%)	**1.95 (1.21-3.14)**	2 (0.5%)	0.66 (0.16-2.67)
Average (3140 – 3790 g) n=10703	393 (3.7%)	ref.	268 (2.5%)	ref.	85 (0.8%)	ref.
Large (3800 – 6080 g) n=388	20 (5.2%)	1.45 (0.93-2.28)	11 (2.9%)	1.18 (0.64-2.15)	5 (1.3%)	1.64 (0.67-4.06)
Ponderal index (1000 x g/cm^3) (n=11747)						

Small (n=2900)	130 (4.5%)	**1.33 (1.07-1.66)**	90 (3.1%)	**1.36 (1.04-1.77)**	28 (1.0%)	1.36 (0.84-2.20)
Average (n=5830)	207 (3.6%)	ref.	142 (2.5%)	ref.	42 (0.7%)	ref.
Large (n=3017)	103 (3.4%)	0.95 (0.75-1.20)	71 (2.4%)	0.93 (0.70-1.25)	22 (0.7%)	1.00 (0.60-1.68)
Placental weight to birth weight ratio (n=10285)						
Small (n=2059)	67 (3.3%)	0.88 (0.67-1.16)	47 (2.3%)	0.93 (0.67-1.29)	16 (0.8%)	1.03 (0.59-1.82)
Average (n=6159)	239 (3.9%)	ref.	161 (2.6%)	ref.	52 (0.9%)	ref.
Large (n=2067)	77 (3.7%)	0.97 (0.75-1.26)	58 (2.8%)	1.10 (0.81-1.49)	14 (0.7%)	0.80 (0.43-1.47)

Cox regression adjusted for sex, family socioeconomic status, mother's age and maternal smoking during pregnancy. N=number; HR=hazard ratio; CI=confidence interval; n.a.=not applicable; Ref=reference group. Boldface indicates statistical significance.

Table 4. Adjusted hazard ratios (95% Confidence Intervals) for cerebrovascular disease in relation to socioeconomic factors.

	Any cerebrovascular disease		Ischemic stroke or TIA		Hemorrhagic stroke	
	N (%)	HR (95% CI)	N (%)	HR (95% CI)	N (%)	HR (95% CI)
All (N=11,991)	453 (3.8%)	n.a.	308 (2.6%)	n.a.	95 (0.8%)	n.a.
Residence (all=11955)						
Urban (n=7083)	256 (3.6%)	ref.	179 (2.6%)	ref.	50 (0.7%)	ref.
Rural (n=4872)	195 (4.0%)	1.13 (0.92-1.39)	128 (2.7%)	1.05 (0.84-1.31)	44 (0.9%)	1.23 (0.78- 1.94)
Desired pregnancy (all=11681)						
Yes (n=7327)	279 (3.8%)	ref	194 (2.7%)	ref	55 (0.8%)	ref
No (n=4354)	165 (3.8%)	1.05 (0.86-1.27)	109 (2.5%)	1.00 (0.79-1.27)	37 (0.9%)	1.15 (0.75-1.76)
Marital status of parent/s at birth (all=11939)						
Marriage (n=11422)	426 (3.7%)	ref.	292 (2.6%)	ref.	90 (0.8%)	ref.

Single, widowed or divorced (n=517)	24 (4.6%)	1.25 (0.80-2.00)	14 (2.8%)	1.07 (0.59-1.93)	4 (0.8%)	0.84 (0.26-2.71)
Highest occupational status of parents (n=11863)						
Unskilled worker or unemployed (n=3360)	113 (3.4%)	ref.	80 (2.4%)	ref.	21 (0.6%)	ref.
Professional or skilled worker (n=8503)	335 (3.9%)	1.22 (0.99 – 1.51)	226 (2.7%)	1.17 (0.90 – 1.51)	72 (0.9%)	1.42 (0.88 – 2.32)

Cox regression adjusted for sex, socioeconomic status of family and mother's age. Highest occupational status in family adjusted for sex, mother's smoking during pregnancy and mother's age. N=number; HR=hazard ratio; CI=confidence interval; n.a.=not applicable; Ref=reference group.

7 Figure legends

Figure 1. Cumulative incidences of cerebrovascular disease

8 Graphic Abstract legend

Gestational weight gain and birth weight predict increased cerebrovascular disease risk of the offspring.

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