Subarachnoid hemorrhage during pregnancy and puerperium – a population-based study

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Abstract

Background: Pregnancy-related subarachnoid hemorrhage (pSAH) is rare, but it causes high mortality and morbidity. Nevertheless, data on pSAH are limited. The objectives here were to examine the incidence trends, causes, risk factors, and outcomes of pSAH in a nationwide population-based cohort study in Finland covering 30 years.

Methods: We performed a retrospective population-based cohort study and nested case-control study in Finland for the period 1987-2016 (SIPP-FIN). The Medical Birth Register was linked to the Hospital Discharge Register to identify women with incident stroke during pregnancy or puerperium. A subcohort of women with SAH is included in this analysis. The temporal connection of SAH to pregnancy and clinical details were verified from patient records.

Results: The unadjusted incidence of pSAH was 3.21 (95%CI 2.46-4.13) per 100,000 deliveries. No significant increase occurred in the incidence throughout the study period. However, the age of the mother had a significant increasing effect on the incidence. In total, 77% of patients suffered an aneurysmal pSAH, resulting in death in 16.3% of women and with only 68.2% achieving good recovery (Modified Ranking Scale 0-2) at three months. Patients with non-aneurysmal pSAH recovered well. The significant risk factors for pSAH were smoking (OR 3.27 (1.56-6.86)), pre-pregnancy hypertension (OR 12.72 (1.39-116.46)), and pre-eclampsia/eclampsia (OR 3.88 (1.00-15.05)).

Conclusions: The incidence of pSAH has not changed substantially over time in Finland. The majority of pSAH cases were aneurysmal and women with aneurysm had considerable mortality and morbidity. Counselling of pregnant women about smoking cessation and

monitoring of blood pressure and symptoms of pre-eclampsia are important interventions to prevent pSAH.

Non-standard Abbreviations and Acronyms

aSAH	aneurysmatic subarachnoid hemorrhage
AVM	arteriovenous malformation
BMI	body mass index
CI	confidence interval
CT	computer tomography
GCS	Glasgow Coma Scale
GTWG	Get With The Guidelines
HDR	Hospital Discharge Register
HELLP	hemolysis, elevated liver enzymes, low platelets
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	interquartile range
MBR	Medical Birth Register
mRS	modified Rankin Scale
NCSP	NOMESCO Classification of Surgical Procedures
NOMESCO	Nordic Medico-Statistical Committee
non-aSAH	nonaneurysmatic subarachnoid hemorrhage
OR	odds ratio
pSAH	pregnancy-related subarachnoid hemorrhage
RCD	Register of Causes of Death
SAH	subarachnoid hemorrhage

SD	standard deviation
SIPP-FIN	Stroke in Pregnancy and Puerperium in Finland
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

Introduction

Subarachnoid hemorrhage (SAH) is more common among women,[1] and female sex hormones are suspected to have a role in the pathogenesis of SAH.[2,3] Data on SAH during pregnancy and puerperium (pregnancy-related SAH, pSAH), the period of the most turbulent hormonal changes in a woman's life, are limited. Although pSAH is rare, it causes high mortality and morbidity. In an American study, pSAH was associated with 4.1% of all pregnancy-related in-hospital deaths.[4] In the UK, 1.4% of all direct and indirect maternal deaths during 1997-2005 were caused by pSAH.[5]

In a nationwide analysis from the US the incidence of pSAH was 5.8-8.5/100,000 deliveries.[4,6] The incidence of pSAH was reported to increase from 4.16% to 6.33% in a 12-year period (2002-2014).[6] However, this increase was speculated to be caused by improved diagnostics and the ICD coding system. Whether pregnancy increases the risk of SAH and whether the risk is especially high in specific stages of pregnancy or puerperium are controversial. In a Swedish population-based study,[7] both late pregnancy (after 28 weeks) and delivery increased the risk for SAH compared to nonpregnant women and women in early pregnancy, while a Dutch study[8] found no association between pregnancy or puerperium and the incidence of aneurysmal SAH.

Some studies have noted that the causes of SAH in pregnant patients are different from those in non-pregnant patients such that a smaller proportion are caused by intracerebral aneurysms.[4,9] In addition, pregnant women with SAH were found to have less risk factors, such as hypertension, diabetes, and smoking, compared to non-pregnant women of similar age with SAH.[6,10] Regarding the outcome of patients with SAH, pregnant SAH patients were reported to be discharged faster and have a better survival rate than non-pregnant same-aged women with SAH.[4,6,10]

The objectives of this study were to examine the incidence trends, etiology, risk factors, and outcomes of pSAH in a nationwide population-based cohort study in Finland covering 30 years from 1987 to 2016. The pSAH patients are a subcohort of the Stroke in Pregnancy and Puerperium in Finland (SIPP-FIN) study.[11]

Methods

This manuscript follows the STROBE reporting guideline[12].

Data availability

Because the data collected for this study contains potentially identifying and sensitive patient information, the data cannot be shared in open data depositories. De-identified aggregated data that support the findings of this study can be made available to qualified investigators on reasonable request to the corresponding author.

Study design

We performed a retrospective nationwide population-based cohort study and nested case-control study in Finland. The cohort includes all women with a pregnancy resulting in delivery during the period 1987-2016 (n=1,773,728 deliveries). From the cohort, all women with SAH during pregnancy or puerperium and three matched controls with no pregnancy-associated stroke were included in the nested case-control study.

Register data

Hospital Discharge Register (HDR) and the Medical Birth Register (MBR) from 1987 to 2016 were utilized to identify women with an ICD-9, ICD-10, or surgical procedure code indicating a cerebrovascular event or its treatment in HDR up to 9 months (270 days) before or up to 3 months (90 days) after the delivery date in MBR. The diagnostic codes used to identify patients with pSAH were 6740A, 430* (ICD-9), O99.4, I60*, I67* (ICD-10), AAL00, AAL20, PAG14, PA2GT, PA2HT, PA2JT, PA2KT, PA2LT, and PA2MT (NOMESCO Classification of Surgical Procedures, NCSP). The register linkages were performed automatically by using the unique personal identifier given to all citizens and permanent residents of Finland since 1964-1967.

The HDR has collected data on all inpatient hospitalizations since 1969 and on outpatient visits in public hospitals since 1998 in Finland and includes information on healthcare facility, admission and discharge dates, diagnosis in ICD-8 (1969-1986), ICD-9 (1987-1995), or ICD-10 (since 1996), and surgical procedures (national classification 1983-1996 and NCSP since 1997).[13] The MBR registers all live births and stillbirths with gestational age of

≥22 weeks or with birth weight of ≥500 g and includes baseline characteristics of the mother, data on healthcare, interventions during pregnancy and delivery, and the outcome of the newborn.[14] Both the HDR and MBR are maintained by the Finnish Institute for Health and Welfare and reporting is mandatory for all healthcare facilities.

To identify out-of-hospital deaths, the Register of Causes of Death (RCD) was searched with ICD codes 6740A and O99.4 from 1987 to 2016. Causes of deaths and death certificates for register-identified cases and controls by the end of 2016 were obtained from the RCD to determine mortality attributed to SAH. The RCD is maintained by Statistics Finland and includes all deaths and physician-confirmed ICD codes for causes and date of death. Death certificates provide additional information on events preceding the death.

Pregnancy-related SAH cohort and definitions

For cases, patient records were obtained from healthcare facilities where the ICD codes for SAH or SAH-related procedure codes in HDR were coded. Patient records were obtained from the specialties of emergency, general and internal medicine, obstetrics and gynecology, neurology, neurosurgery, radiology, and laboratory medicine. Further records were ordered if considered necessary after the first review. The diagnosis and temporal connection of SAH and pregnancy were verified by a stroke neurologist (P.I., K.A., or K.R.). Complex cases were assessed by a panel of all three neurologists and disagreements were resolved by consensus. The Glasgow Coma Scale (GCS) and the Hunt and Hess score at hospital admission were extracted from patient records if possible. For some patients they were registered in the medical chart, whereas for the rest they were calculated based on the description of patient's neurological status.

We defined pregnancy to start from conception and the postpartum period (puerperium) to last until 12 weeks (84 days) after delivery. Puerperal time extending over the usual 42 days was used since the risk of stroke seems to be elevated beyond this period.[15,16]

We used the American Heart Association/American Stroke Association consensus definition of SAH.[17] The presence of bleeding in the subarachnoid space needed to be confirmed by imaging or lumbar puncture. The etiology of SAH was registered (e.g. cerebral aneurysm, arteriovenous malformation, intracranial artery dissection, reversible cerebral vasoconstriction syndrome, moyamoya, undefined). We differentiated between aneurysmal SAH (aSAH) and non-aneurysmal SAH (non-aSAH).

Case-control study of risk factors

Three controls matched by delivery year, age, parity, and geographical area were identified from the MBR for each case. Multiparas (≥3 deliveries) were grouped together to facilitate finding controls for extremes. Due to extreme age and a sparsely inhabited geographical area, no controls were available for one case and only two controls for another case.

Data from the HDR and MBR on baseline characteristics of the mother (e.g. previous pregnancies and deliveries, monitoring of the current pregnancy (mother's weight and height before pregnancy, follow-up visits, smoking habits, risk factors, diseases and interventions related to pregnancy), delivery (e.g. best estimate of gestational age at the time of delivery, method of delivery, mother's diagnoses during delivery)), and the outcome of the newborn were used in the risk factor analyses. Data from medical records was not used since they were not available for the controls.

Outcomes and statistical analysis

The study outcomes included the incidence of pSAH for 5-year study periods and 5-year age groups, good functional outcome defined as modified Rankin Scale (mRS) from 0 to 2, the maternal mortality rate and the mortality at 1 year from pSAH onset.

The incidence is reported per number of births. Incidence rates were calculated for 5-year periods (1987-1991, 1992-1996, 1997-2001, 2002-2006, 2007-2011, 2012-2016) and 5-year age groups (<20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥45). We also describe the incidence by pregnancy trimesters (conception-12+0 weeks, 12+1-28+0 weeks, over 28+1 weeks) and by postpartum week. Confidence intervals (CI) for incidence rates were calculated based on Poisson distribution. The Cochran-Armitage test for trend was used to study incidence trends over time periods and age groups.

We measured functional outcome by mRS at three months and at the end of the follow-up. Good outcome was defined as scores 0-2. MRS was estimated based on all available patient records during follow-up of the patients by a stroke neurologist qualified for mRS (P.I., K.A., or K.R.).

We defined maternal mortality as the number of deaths from SAH during pregnancy and childbirth or within 42 days of termination of pregnancy. Furthermore, overall mortality at 1 year from SAH onset was studied. Causes of deaths and death certificates for register-identified cases and controls by the end of 2016 were obtained from the RCD to determine mortality attributed to SAH.

Data are presented as percentages for dichotomous variables, mean and standard deviation (SD) for continuous variables, and median and interquartile range (IQR) for categorical variables. $\chi 2$ or Fisher's exact test for dichotomous variables, T-test for continuous variables, and Jonckheere-Terpstra test for ordered alternatives (GCS, Hunt and Hess score, mRS) were used to test the statistical significance of differences between aSAH and non-aSAH as well as between cases and controls in baseline characteristics, risk factors, and outcomes. All data available was used in the analysis and missing data is indicated in the Tables. P-value <0.05 was considered statistically significant. In the case-control study, unconditional logistic regression analysis was used to obtain OR estimates. Typically, conditional logistic regression is used in matched case-control studies. However, our data, matched on a few demographic variables only, are loose-matching data, i.e. matching between cases and controls is not unique. For example, a 30-year old primipara case can be matched to several same age primipara controls. In such circumstances, unconditional logistic regression has been shown to unbiasedly estimate the effect of exposure and give a shorter 95% CI than the conditional model[18]. Age-adjusted odds ratios were calculated for those variables showing an association with $p<0.20$ in the univariate analysis. Multivariate logistic regression analysis was used to model the effects of risk factors on pSAH. Variables showing a trend towards an association with pSAH in univariate analysis ($p<0.20$) were entered into the model. Backward elimination was used to find variables with an independent association. Statistical analyses were performed by IBM SPSS statistics, version 25.

Ethical approval

The study has been approved by the Ethics Committee of Helsinki University Hospital (HUS/2228/2016), and the register-keeping organizations the Finnish Institute of Health and

Welfare (THL/750/5.05.00/2017) and Statistics Finland (TK-53-783-17, TK-53-591-20) granted permission to use their register data in this study.

Results

Demographics of SAH cases

During 1987-2016 there were 57 incident cases of pSAH per 1,773,728 deliveries. The study flowchart is provided in Supplemental material (Table S1). By linking HDR and MBR data, we identified 864 potential cases of pregnancy-associated stroke, of which 254 were validated from medical records. Most common causes of exclusion included stroke at young age not associated with pregnancy, stroke mimics and vascular anomalies without stroke. In addition to 54 pSAH cases identified from HDR and MBR, three further cases were identified from the death certificates, 2 women who died at home and 1 woman who died at hospital and was originally diagnosed with intracerebral hemorrhage.

Demographics of pSAH cases are summarized in Table 1 separately for aneurysmal and non-aneurysmal pSAH. Intracranial aneurysm was the cause of SAH in 44 cases (77.2%) and 13 cases were non-aneurysmatic (22.8%). The mean age of women was 33 (±5.2) years, ranging from 23 to 45 years.

Incidence of pSAH in the study period and in age groups

Unadjusted incidence of pSAH was 3.21 (95%CI 2.46-4.13) per 100,000 deliveries: 2.48 (95%CI 1.82-3.30) for aSAH and 0.73 (95%CI 0.41-1.22) for non-aSAH. When observed in

5-year periods, the highest incidence was found in the first period 1987-1991 (4.45, 95%CI 2.54-7.23), after which the incidence appeared to decrease until 2002-2006, thereafter slightly increasing (Figure 1). However, no significant linear trends were detected (P=0.145).

The incidence of pSAH increased with age of the mother, from no cases among women aged below 20 years to 12.31 (95%CI 5.49-24.17) per 100,000 deliveries among women aged 40 years or over (P<0.0001)(Figure 2).

Incidence of pSAH during the trimesters and puerperium

During pregnancy there were 42 SAHs, of which 8 (14%) took place during the 1st trimester, 17 (30%) during the 2nd trimester, and 17 (30%) during the 3rd trimester. 15 cases of SAH took place in puerperium at a median of 3 weeks (1.5-5.0), clustering at the beginning of the postpartum period (Figure 3). No significant trend emerged in overall incidence during pregnancy or puerperium (P=0.25). The incidence of aSAH tended to increase as the pregnancy progressed and stayed at the same level in early puerperium. The incidence of non-aSAH peaked during the 2nd trimester.

Clinical presentation and complications

Details on clinical presentation at hospital admission were available for 54 women. Data were not available for two women who died at home and one woman with basilar artery aneurysm. The presentation of pSAH was typical in most patients, with a severe headache of rapid onset and mostly mild neurological symptoms. At hospital admission, the median GCS was 15 (14-15) and the Hunt and Hess score 2 (1-3). Patients with aSAH had on average lower GCS

(P=0.038) and higher Hunt and Hess scores (P=0.009) than patients with non-aSAH (Table 1). One-third of women (n=20, 36%) lost consciousness at onset. The aSAH patients received intensive care significantly more often than non-aSAH patients (P=0.023). Overall, 21.1% of patients developed angiographic evidence of vasospasm and 12.3% hydrocephalus with no significant differences between aSAH and non-aSAH cases (Table 1).

Etiology of non-aneurysmal pSAH

In 13 cases, an aneurysm was not found. Three women had an arteriovenous malformation (AVM), one patient moyamoya syndrome and pre-eclampsia, one patient HELLP syndrome, and one patient postpartum angiopathy, which caused vasospasms in the anterior and middle cerebral arteries. Seven women had no obvious cause for SAH, but four of them had typical radiological findings of perimesencephalic SAH.

Delivery

The most common method of delivery was spontaneous vaginal delivery in 19 cases (35%), followed by elective cesarean section in 16 cases (29%). However, in women who sustained SAH during pregnancy, the most common method was an elective cesarean section (38%), followed by emergency cesarean section (28%) and spontaneous vaginal delivery (23%). Other methods, such as vacuum extraction or forceps delivery, were more commonly used to facilitate the delivery than in mothers who suffered SAH during puerperium. Among these women, spontaneous vaginal delivery was most common (67%).

Prognosis of pSAH

The mean follow-up time was 9.1±8.9 years. There were seven maternal deaths, resulting in maternal mortality rate of 12%, but no other deaths within one year of the end of pregnancy. All deaths occurred within 10 days of onset of SAH and among women with aSAH (Table 1). Two patients died suddenly at home, never making it to hospital. For surviving women, the median mRS was 1 at discharge (0-3), 1 at three months (0-2), and 0 at end of follow-up (0-3). Patients with non-aSAH had significantly better recovery, with all patients, except for one , reaching mRS 0 (no symptoms) already at three months (p=0.003)(Figure 4). Good recovery (defined as mRS 0-2) was achieved by 68.2% of aSAH patients and 92.3% of non-aSAH patients (p=0.150).

Risk factor analysis

We compared pSAH cases and controls (pregnant women without pSAH or other stroke matched by delivery year, age, parity and geographical area) by the known SAH risk factors available in register data (Table 2). Smoking beyond 12 gestational weeks, hypertension prior to pregnancy, and pre-eclampsia were associated with risk of pSAH in bivariate analysis. In multivariate analysis, only smoking beyond 12^{th} gestational weeks (adjusted OR 3.08, 95%CI 1.45-6.52) and hypertension prior to pregnancy (adjusted OR 11.96, 95%CI 0.23-116.01) were independently associated with risk of pSAH.

Other potential risk factors documented in patient charts included current alcohol abuse (n=2, 3.5%), past or current substance abuse (n=5, 8.8%), prior antiplatelet use (n=2, 3.5%), and prior trauma within one month (n=1, 1.8%). One patient suffered from polycystic kidney disease, one patient had undergone chemotherapy to the head, and one patient developed

HELLP syndrome. One patient had sustained a previous SAH. Among aSAH patients, 6.8% had positive family history of SAH. Two patients had at least one first-degree relative with SAH and one patient had 5 relatives with operated cerebral aneurysm.

Discussion

To our knowledge, our study is the first nationwide population-based study on SAH during pregnancy and puerperium where data have been validated from patient records. We observed a stable incidence of pSAH during the study period. Cerebral aneurysms were the cause of SAH in most cases with a mortality rate of 16% and only 68% of women reaching good recovery. The proportion of non-aneurysmal SAH was slightly higher than that reported in the general population and patients with non-aSAH had excellent outcome. In addition to the typical risk factors for SAH (age, smoking and chronic hypertension), pre-eclampsia-eclampsia was associated with a higher risk of pSAH, but this association disappeared after adjustment of other risk factors.

According to our results, the unadjusted incidence of pSAH was 3.2 per 100,000 deliveries. The incidence of SAH in our study is lower than the incidence of 5.8-8.5 per 100,000 deliveries reported in nationwide register-based studies in the USA[4,6]. Furthermore, Bateman et al[4] and Limaye et al.[6] reported an increase in the incidence of pSAH – a trend we did not find. This might be explained by a few important differences in the healthcare systems and population structures of Finland and USA. First, the Finnish healthcare system provides every pregnant woman with a free-of-charge, extensive follow-up during pregnancy, focusing on screening and treating potential risk factors for pregnancy such as smoking or high blood pressure. Second, in the American studies[4,6] the highest risk for pSAH was encountered by

black women. The Finnish population, however, is genetically quite homogeneous, lacking significant ethnic representation.

We found that intracranial aneurysms were the most common etiology of pSAH (77%) but non-aSAH (23%) comprised a larger proportion of SAH than reported for the general Finnish population (roughly 8%).[19] Similarly, in a review by Bateman et al.[4], non-aSAHs were more common in pregnant women than in the rest of the population, being a possible explanation for the better outcomes of pSAH patients. In their cohort, only 3 of 12 patients suffered an aSAH. In a Japanese study of intracranial hemorrhage in pregnancy, the most common cerebral vascular malformations were AVMs (25.8%), aneurysms (16.5%), and moyamoya disease (10.3%).[20] In our complete SIPP-FIN stroke cohort including 103 non-traumatic intracranial hemorrhages during pregnancy or puerperium, 41 women had aneurysms (39.8%), 11 AVMs (10.7%), and only one moyamoya disease (1.0%).[11] The incidence of SAH has been reported to be relatively high in Finland, but the older studies may have been misinterpreted due to several reasons, including lack of population-based comparison data from other countries, and differences in study settings and risk factors.[21] Whether these differences between reported incidences reflect true discrepancies in the prevalence or rupture of these cerebrovascular malformations in different populations remains to be clarified by further studies.

We found some important differences between aSAH and non-aSAH. First, the incidence of aSAH increased towards the end of pregnancy, and the risk was highest in the 3rd trimester. Previous studies[9,20,22,23] also support the increasing trend towards the end of pregnancy, all indicating that rupture of the aneurysm is most common in the 3rd trimester. By contrast, the incidence of non-aSAH peaked in the 2nd trimester in our study. Most women (61%) with non-aSAH did not have any underlying vascular abnormality. We also found that patients

with non-aSAH had a milder presentation as well as a better recovery than patients with aSAH. Age did not have as distinct effect on non-aSAH as in aSAH. No other major differences in the risk factor profiles were identified. Previous comparisons in the literature could not be found.

Our study indicates that the incidence of pSAH rises significantly with mother's age. Mother's high age is known to increase the risk of stroke in pregnancy,[24–26] but there is a lack of studies addressing pSAH alone. In our cohort, other important risk factors for pSAH were smoking, hypertension prior to pregnancy, and pre-eclampsia/eclampsia. All these factors have also earlier been shown to increase the risk for pSAH.[4,22,27]

A 1997 systematic review by Hop et al.,[28] analyzing 21 population-based studies from 1960 onwards, showed that the case-fatality rate from SAH varied between 32% and 67%, whereas 10-20% of patients became disabled. However, the 2002 meta-analysis by Huang et al.[29] that included 18 population-based studies from 1965-2001 reported that the combined risk of sudden death was 12.4%, with aneurysm ruptures of the posterior circulation being the most fatal, with a sudden death rate of 44.7%. In our data, early death before any treatment was observed in 8.8% of cases, all of whom were patients with aSAH. The one-year mortality rate was 12.3%. The survival rate of patients with non-aSAH was 100%. Thus, the case-fatality rate in our cohort of pSAH patients is lower than described in SAH in general. Lower mortality among pSAH patients has been shown in the 2012 nationwide data analysis by Bateman et al.[4] and the 2015 analysis of data from the GTWG Stroke registry by Leffert et al.[10] Hackett et al.[30] state in their population-based study from 1995-1998 that one year after SAH 56% of patients were alive, of whom, however, 46% were disabled. In our cohort, 75.4% of patients with pSAH recovered well (mRS 0-2).

Our study has limitations. Although it is nationwide, the number of pSAH cases is relatively low due to the small population of Finland and the low incidence of pSAH. This limits the statistical power of our study. In addition, the Finnish population is very homogeneous in terms of racial and ethnic composition, and until recently, over 90% of the population were of Finnish origin, restricting the generalizability of our results to other more heterogeneous populations. Definition of the puerperal period varies between studies. We defined the duration of puerperium to extend up to 12 weeks due to the elevated stroke risk during this period, but consequently our results may be difficult to compare with earlier studies using the conventional 6-week period. MBR does not contain data on the pregnancies that ended before week 22 due to spontaneous or induced abortion. Therefore, we might have underestimated the incidence of SAH during the 1st trimester. Finally, we have estimated clinical grading scales that are normally performed bedside (GCS, Hunt and Hess score) or by interviewing (mRS), from patient records, which may have led to more favorable estimates and thus they must be interpreted with caution.

Summary/Conclusions

According to our results, there is no significant increase in the incidence of pSAH during 1987-2016 in Finland. However, the incidence does rise significantly with mother's age. We found that the main risk factors for pSAH were smoking, hypertension prior to pregnancy, and pre-eclampsia/eclampsia. Most pSAH cases were of aneurysmatic origin. Patients with aSAH had a higher mortality rate than patients with non-aSAH. Our results underline the importance of counseling pregnant women about smoking cessation and careful monitoring

of blood pressure and symptoms of pre-eclampsia particularly in women at high risk of hypertensive disorder of pregnancy.

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Conflicts of Interest/Disclosures

None.

Supplemental Materials

Checklist

Online Figure S1

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559 **Table 1. Risk factors, presentation, pregnancy factors, and prognosis of Subarachnoid**

560 **hemorrhage (SAH) patients.**

Variable	All women	Aneurysmal SAH	Non-aneurysmal SAH	P-value
N	57 (100%)	44 (77.2%)	13 (22.8%)	
Age (mean ±SD)	33.2 ±5.2	32.8 ±7.0	33.3 ±4.6	0.793
Risk factors*				
Smoking beyond 12th gestational week	17 (29.8%)	14 (31.8%)	3 (23.1%)	0.506
Alcohol abuse	2 (3.5%)	2 (4.5%)	0 (0%)	1.000
Substance abuse				
Current	3 (5.3%)	2 (4.5%)	1 (7.7%)	0.547
Past	2 (3.5%)	2 (4.5%)	0 (0%)	1.000
Chronic hypertension	10 (17.5%)	8 (18.2%)	2 (15.4%)	1.000
Prior antihypertensives	5 (8.8%)	4 (9.1%)	1 (7.7%)	1.000
Diabetes, type I or II	1 (1.8%)	0 (0%)	1 (7.7%)	0.232
Migraine	10 (17.5%)	7 (15.9%)	3 (23.1%)	0.685
Polycystic kidney disease	1 (1.8%)	1 (2.3%)	0 (0%)	1.000
Prior chemotherapy of the head	1 (1.8%)	1 (2.3%)	0 (0%)	1.000
Previous stroke	1 (1.8%)	0 (0%)	1 (7.7%)	0.236
Prior antiplatelet	2 (3.5%)	1 (2.3%)	1 (7.7%)	0.434
Prior trauma	1 (1.8%)	1 (2.3%)	0 (0%)	1.000
Family history of SAH†	3 (5.3%)	3 (6.8%)	0 (0%)	1.000
Clinical presentation and diagnostics*				
Glasgow Coma Scale, median (IQR)	15 (14-15)	15 (13-15)	15 (15-15)	0.038
Hunt and Hess, median, (IQR)	2 (1-3)	2 (2-3)	1 (1-2)	0.009
Loss of consciousness at onset	20 (36.4%)	18 (42.9%)	2 (15.4%)	0.102
Systolic Blood Pressure at admission, mean±SD	142 ±33	137 ±24	157 ±48	0.264
Lumbar puncture	19 (34.5%)	12 (27.9%)	7 (58.3%)	0.099
SAH in brain imaging	44 (80.0%)	37 (86.0%)	7 (58.3%)	0.054
Angiography	51 (89.5%)	38 (86.4%)	13 (100%)	0.319
Conventional angiography	42 (76.4%)	31 (72.1%)	11 (91.7%)	0.478
CT angiography	11 (20.0%)	8 (18.6%)	3 (25.0%)	0.700
Magnetic angiography	9 (16.4%)	6 (14.0%)	3 (25.0%)	0.412
Angiographic vasospasm	12 (21.1%)	11 (25%)	1 (7.7%)	0.225
Hydrocephalus	7 (12.3%)	6 (13.6%)	1 (7.7%)	1.000
Intensive care	33 (57.9%)	29 (65.9%)	4 (30.8%)	0.023
Pregnancy-associated factors*				
Pregnant	42 (73.7%)	31 (79.5%)	11 (84.6%)	0.478
Pregnancy week, median (IQR)	24 (15-31)	24.5 (13-31)	20 (15.5-32)	0.925
Trimester				
1. 1st	8 (14.0%)	7 (15.9%)	1 (7.7%)	0.667
2. 2nd	17 (29.8%)	11 (25%)	6 (46.2%)	0.176
3. 3rd	17 (29.8%)	13 (29.5%)	4 (30.8%)	1.000

Puerperium	15 (26.3%)	13 (29.5%)	2 (15.4%)	0.478
Delivery method				
Spontaneous vaginal	19 (34.5*[1])	13 (30.2%)	6 (46.2%)	0.336
Breech birth/vacuum extraction/forceps delivery	7 (12.7%)	5 (11.6%)	2 (15.4%)	0.664
Elective cesarean section	16 (29.1%)	13 (30.2%)	3 (23.1%)	0.734
Emergency cesarean	14 (23.6%)	11 (25.6%)	2 (15.4%)	0.710
Gestational hypertension	6 (10.5%)	5 (11.6%)	1 (8.3%)	1.000
Pre-eclampsia/eclampsia	8 (14.5%)	6 (14.0%)	2 (16.7%)	1.000
HELLP syndrome	1 (1.8%)	0 (0%)	1 (8.3%)	0.236
Gestational diabetes	4 (7.0%)	3 (7.0%)	1 (8.3%)	1.000
Prognosis#				
Follow-up time, years±SD	9.1 ±8.9	9.6 ±9.1	7.3 ±8.4	0.003
Early death before any treatment	5(8.8%)	5(11.4%)	0 (0%)	0.579
Mortality (maternal and 1-year)	7 (12.3 %)	7 (16.3%)	0 (0%)	0.186
mRS at 3 months, median (IQR)	1 (0-2)	1 (0-3)	0 (0-0)	0.003
Good recovery (mRS 0-2) at 3 months	43 (75.4%)	30 (68.2%)	12 (92.3%)	0.150
mRS at end of follow-up, median (IQR)	0 (0-3)	1 (0-3)	0 (0-1)	0.245

Data are presented as percentages for dichotomous variables, mean±standard deviation (SD) for continuous variables, and median and interquartile range (IQR) for categorical variables. $\chi 2$ or Fisher's exact test for dichotomous variables, T-test for continuous variables, and Jonckheere-Terpstra test for ordered alternatives were used to test the significance of differences between aneurysmal and non-aneurysmal SAH. P-value <0.05 was considered statistically significant. *Data not available for two women who died at home and for one woman whose admission details were not registered. †2 patients with 1st degree family members and 1 patient with 10 intracranial hemorrhage cases and 5 aneurysmal operations in the family #Modified Rankin Scale (mRS) data was not available from one woman. CT= computer tomography, HELLP= Hemolysis, Elevated Liver enzymes and Low Platelets, mRS=modified Rankin scale.

Table 2. Stroke risk factors in subarachnoid hemorrhage (SAH) cases and controls.

Variable	Cases (n=54)	Control (n=164)	P-value	Age-adjusted OR (95%CI)*
Smoking beyond 12th gestational week	17 (29.3%)	21 (12.8%)	0.003	3.27 (1.56-6.86)
Hypertension				
Hypertension prior to pregnancy	4 (6.9%)	1 (0.6%)	0.016	12.72 (1.39-116.46)
Gestational hypertension	6 (10.3%)	8 (4.9%)	0.200	2.32 (0.75-7.13)
Pre-eclampsia/Eclampsia	5 (8.6%)	4 (2.4%)	0.049	3.88 (1.00-15.05)
Any hypertensive disorder of pregnancy	12 (21.4%)	12 (7.3%)	0.006	3.48 (1.44-8.41)
Diabetes				
Diabetes, type I or II	1 (1.7%)	0 (0%)	0.255	nd
Gestational diabetes	3 (5.2%)	19 (11.6%)	0.209	0.40 (0.11-1.45)
BMI > 30 (n=58)#	1 (7.1%)	5 (11.4%)	1.000	0.69 (0.068-6.99)
Migraine	1 (1.7%)	0 (0%)	0.255	nd

$\chi 2$ or Fisher's exact was used to test for significance. Age-adjusted ORs were calculated by logistic regression. BMI=body mass index (kg/m^2). *nd=non-determined since there were no cases in the control group. #BMI was available for only 14 cases and 44 controls since it has been included in Medical Birth Register since 2004.

Figure legends

Figure 1. Incidence of pregnancy-related subarachnoid hemorrhage (SAH) by 5-year periods in 1987-2016. aSAH=aneurysmal SAH, non-aSAH=non-aneurysmal SAH.

Figure 2. Incidence of pregnancy-related subarachnoid hemorrhage (SAH) per 100,000 deliveries for 5-year age groups. aSAH=aneurysmal SAH, non-aSAH=non-aneurysmal SAH.

Figure 3. Timing of subarachnoid hemorhage (SAH) during trimesters and puerperium. aSAH=aneurysmal SAH, non-aSAH=non-aneurysmal SAH.

Figure 4. Modified Rankin Scale for aneurysmal and nonaneurysmal subarachnoid hemorrhage (SAH) at three months from the onset of SAH.

Subarachnoid Hemorrhage during Pregnancy and Puerperium

A population-based cohort study (n=1,773,728 deliveries) in Finland for the period 1987-2016 with a nested case-control study for risk factor analysis

Medical Birth Register & Hospital Discharge Register

Register of Causes of Death

57 pregnancy-related Subarachnoid Hemorrhages

Incidence 3.2 cases per 100,000 deliveries

77% aneurysmal

Etiology

23% non-aneurysmal

Good recovery* 68%

Outcome

Good recovery* 92%

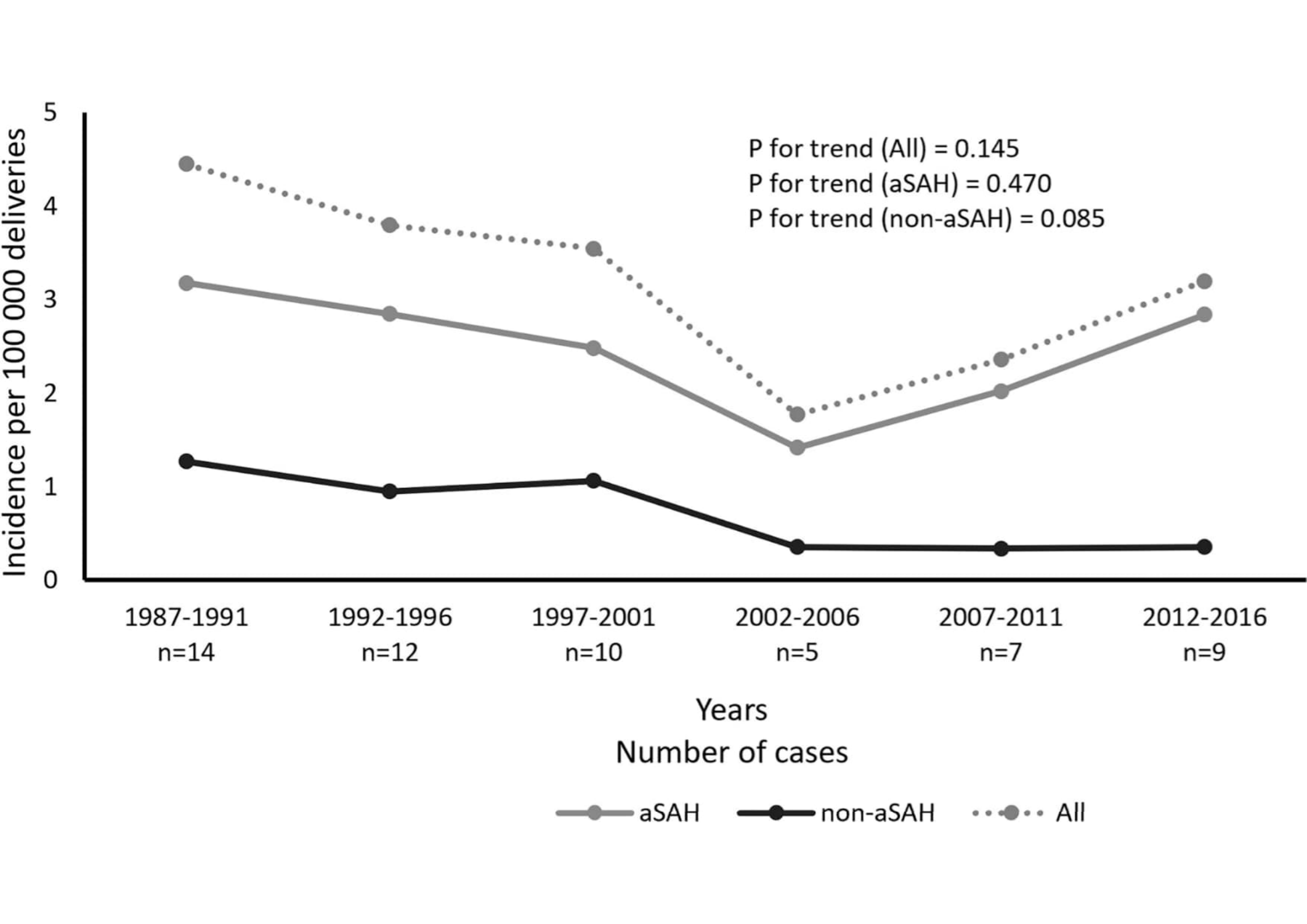
*Good recovery = mRS 0-2 at 3 months, p=0.003

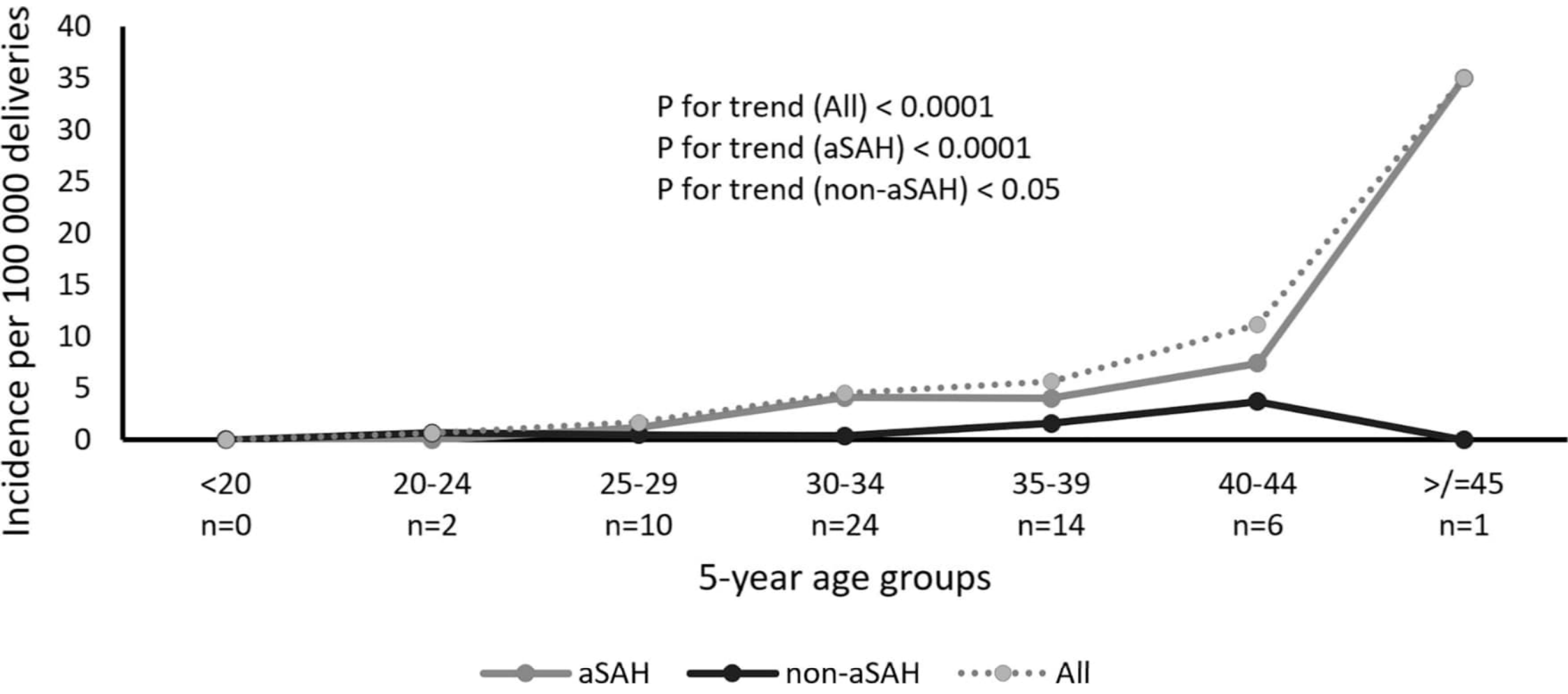
Risk factors

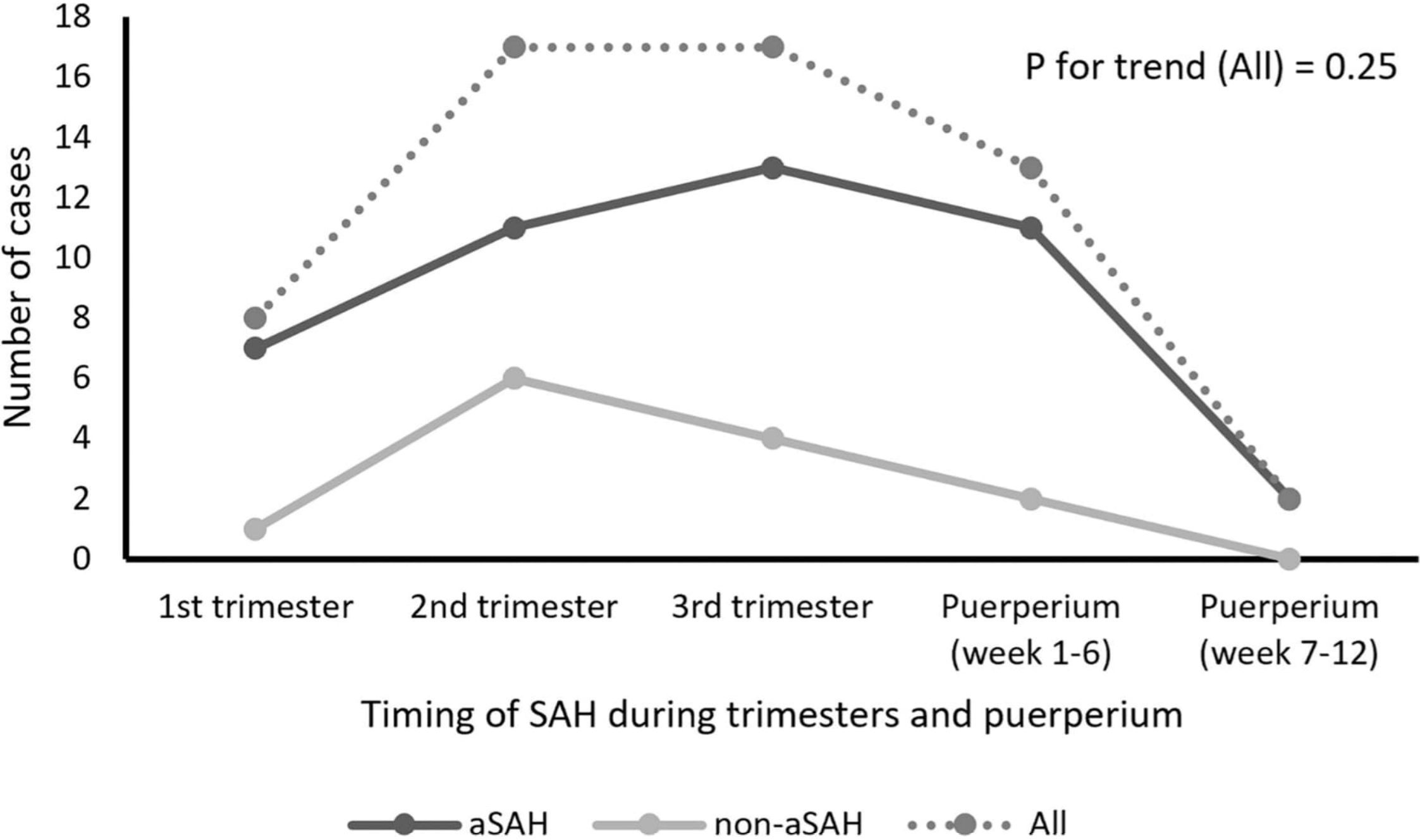
- Chronic hypertension
  Age-adj. OR 12.72 (95% CI 1.39-116.46)
- Pre-eclampsia/eclampsia
  Age-adj. OR 3.88 (95% CI 1.00-15.05)
- Smoking during pregnancy
  Age-adj. OR 3.27 (95% CI 1.56-6.86)

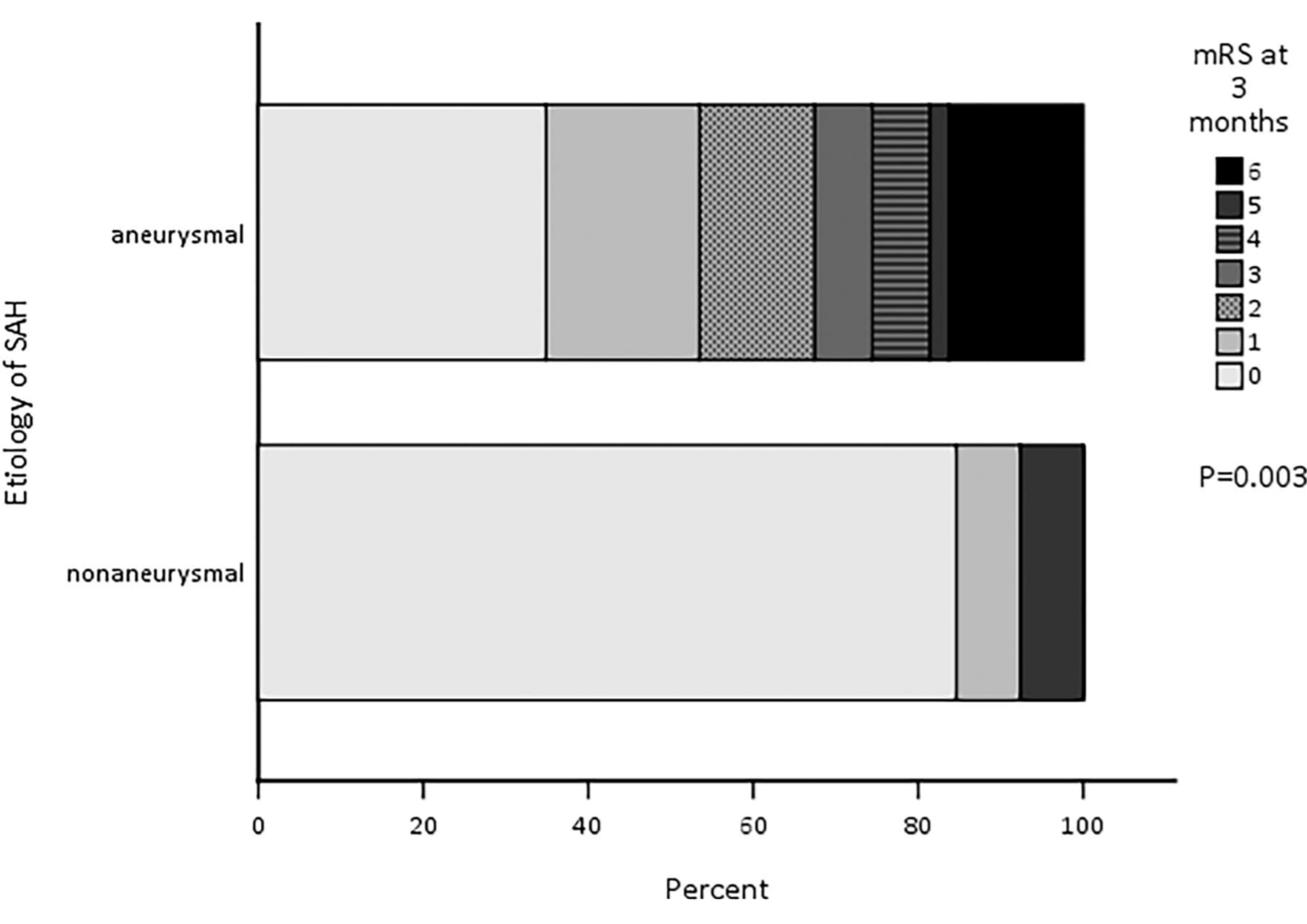
Incidence

- Did not change during the study period
- Increased by mother's age
  (P < 0.0001)


Incidence per 100 000 deliveries
5
4
3
2
1
0
P for trend (All) = 0.145
P for trend (aSAH) = 0.470
P for trend (non-aSAH) = 0.085
1987-1991
n=14
1992-1996
n=12
1997-2001
n=10
2002-2006
n=5
2007-2011
n=7
2012-2016
n=9
Years
Number of cases
aSAH
non-aSAH
All


Incidence per 100 000 deliveries
40
35
30
25
20
15
10
5
0
P for trend (All) < 0.0001
P for trend (aSAH) < 0.0001
P for trend (non-aSAH) < 0.05
<20
n=0
20-24
n=2
25-29
n=10
30-34
n=24
35-39
n=14
40-44
n=6
>/=45
n=1
5-year age groups
aSAH
non-aSAH
All


18
16
14
12
10
8
6
4
2
0
Number of cases
P for trend (All) = 0.25
1st trimester
2nd trimester
3rd trimester
Puerperium (week 1-6)
Puerperium (week 7-12)
Timing of SAH during trimesters and puerperium
aSAH
non-aSAH
All


mRS at 3 months
6
5
4
3
2
1
0
P=0.003
Etiology of SAH
aneurysmal
nonaneurysmal
0
20
40
60
80
100
Percent