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Subarachnoid hemorrhage

Incidence, risk factors, and sex differences

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A dissertation for the degree of
Philosophiae Doctor

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To Line and Ingvild

2 LIST OF PAPERS

I. Lindekleiv H, Njølstad I, Ingebrigtsen T, Mathiesen EB. Incidence of aneurysmal subarachnoid hemorrhage in Norway 1999-2007. *Acta Neurologica Scandinavia*. 2011 123(1):34-4.

II. Sandvei MS, Lindekleiv H, Romundstad PR, Müller T, Vatten L, Ingebrigtsen T, Njølstad I, Mathiesen E, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage – BMI and serum lipids: 11-years follow-up of the HUNT and the Tromsø Study in Norway. *Major Revision, Acta Neurologica Scandinavia*

III. Lindekleiv H, Sandvei MS, Njølstad I, Løchen M-L, Romundstad PR, Vatten L, Ingebrigtsen T, Vik A, Mathiesen EB. Sex differences in risk factors for subarachnoid hemorrhage. The HUNT and Tromsø studies. *Neurology. 2011;76(7):637-43.*

IV. Lindekleiv HM, Valen-Sendstad K, Mardal K-A, Morgan M, Faulder K, Magnus JH, Romner B, Ingebrigtsen T. Sex differences in intracranial arterial bifurcations. *Gender Medicine 2010;7(2):149-55.*

3 INTRODUCTION

Subarachnoid hemorrhage (SAH) is bleeding into the subarachnoid space surrounding the brain. SAH may occur spontaneously, or following traumatic brain injury. Spontaneous SAH is in 85% of cases caused by rupture of an intracranial aneurysm. This is called aneurysmal SAH (aSAH). An intracranial aneurysm is a disorder involving localized dilation of an intracranial artery. About 95% of intracranial aneurysms are saccular outpouchings of the arterial wall. The remaining aneurysms are either mycotic or fusiform widening of an artery. Saccular aneurysms are located at the major bifurcations of large intracranial arteries, either in the anterior cerebral artery, internal carotid artery, middle cerebral artery or basilar artery. A diagram of the arterial circulation at the base of the brain is shown in Figure 3.1. Non-aneurysmal spontaneous SAH is usually perimesencephalic hemorrhage, or less frequently due to arteriovenous malformations, cerebral neoplasms, arterial inflammation, or venous thrombosis.[1]

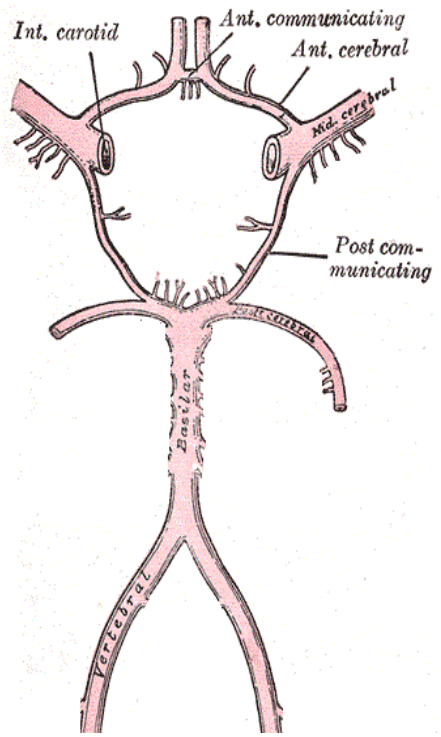

Figure 3.1 Diagram of the arterial circulation at the base of the brain (Adapted from Gray H. Anatomy of the Human Body, 1918. Figure 519)

3.1 Diagnosis and treatment of aSAH

SAH is suspected in patients with sudden onset of severe headache, which may be followed by confusion, focal neurological deficits, or loss of consciousness. The diagnosis of SAH is confirmed by detection of blood in the subarachnoid space on non contrast-enhanced computed tomogram of the brain or through lumbar puncture. Cerebral angiography is then performed to determine the presence of an intracranial aneurysm, either through endovascular catheter angiography (digital subtraction angiography) or computed tomography angiography.[1]

In Norway, the government is responsible for hospital services through state ownership of regional health authorities. Patients with verified aSAH are usually accepted for immediate admission into one of the five public neurosurgical centers (Haukeland University Hospital in Bergen, St Olavs Hospital in Trondheim, Ullevål and Rikshospitalet in Oslo, and the University Hospital of North Norway in Tromsø). The treatment for aSAH is exclusion of the aneurysm from the

circulation through endovascular embolization or microsurgery.[2] The case fatality of aSAH is 50%, with 20% of surviving patients remaining dependent on help for activities of daily living.[3] Non-aneurysmal, perimesencephalic SAH does not require invasive treatment and the patients have a normal life expectancy.[4]

3.2 Incidence of aSAH

The incidence of aSAH is 9.1 per 100,000 person-years (95% confidence interval, CI: 8.8-9.5), according to a meta-analysis of 51 studies from 21 countries.[5] The incidence increase with age, leveling off at the sixth decade. The incidence of aSAH is 50-70% higher in women than men,[6, 7] with the female preponderance occurring after 50 years of age.[5]

Regional variations exist, with the highest incidence in Finland (19.7 per 100,000 person-years, 95% CI: 18.1-21.3) and Japan (22.7 per 100,000 person-years, 95% CI: 21.9-23.5), whereas the lowest incidence is observed in South and Central America (4.2 per 100,000 person-years, 95% CI: 3.1-5.7).[5] These differences are explained by regional differences in demography, genetic factors, case finding, and prevalence of risk factors for aSAH at the population level.[5] Only one study has investigated within-country differences in the incidence of aSAH. This study from Sweden found that the incidence rates increased from south to north, with a mean incidence of 11.3 per 100,000 person-years.[8] Previous regional studies of aSAH in Norway have found varying incidence, from 9.9 to 25.6 per 100,000 person-years.[9-12] This indicates that regional differences also exist in Norway.

Temporal trends in the incidence of aSAH are uncertain, as a result of small number of patients with aSAH in incidence studies, and increased diagnosis of aSAH in the 1990s due to increased availability of computed tomography.[13] In the aforementioned meta-analysis, a 0.6% annual decrease in the incidence of aSAH was observed between 1955 and 2003.[5] This is moderate compared to the decline of other types of stroke in industrialized countries.[14-16] It is therefore uncertain whether implementation of stroke preventive treatments and reductions in cardiovascular risk factors, at the population level, have translated into a reduction of aSAH episodes.

3.3 Risk factors for aSAH

In a meta-analysis of 14 prospective cohort studies on risk factors for aSAH, the statistically significant risk factors for aSAH were current smoking (relative risk, RR: 2.2, 95% CI: 1.3-3.6), hypertension (RR: 2.5, 95% CI: 2.0-3.1), and excessive alcohol consumption (>150 g

per week, RR: 2.1, 95% CI: 1.5-2.8).[17] Ethnicity, use of oral contraceptives or hormone replacement therapy, were not statistically significant risk factors.

The association between body mass index, serum lipids, and the risk for aSAH is unclear. Some studies have reported a risk reduction with increasing body mass index or serum lipids,[12, 18-23] whereas other studies have found no such association.[10, 24, 25]

In a meta-analysis of prospective studies[18, 25-34], the risk for ever-smoking women (RR 2.7, 95% CI: 1.8-4.1) were 1.9 times higher than ever-smoking men (1.4, 95% CI: 0.9-2.1), compared to non-smokers. No sex differences in current smoking were observed (for women: RR 2.2, 95% CI: 1.7-2.8; for men: RR 2.2, 95% CI: 1.7-3.0). Hypertension was more hazardous in women (RR 3.3, 95% CI: 2.1-5.3) than men (RR 2.3, 95% CI: 1.8-3.0). No sex differences were observed with respect to excessive alcohol consumption, defined as >150 g per week. (RR 4.0, 95% CI: 0.8-19.1 in women. RR 2.2, 95% CI: 1.5-3.2 in men).[17] Retrospective case-control studies have reported conflicting results. One study found statistically significant increased risk of aSAH in male compared to female smokers,[35] another study found statistically significant higher risk of aSAH in female compared to male smokers,[36] whereas other studies found no statistically significant sex differences.[18, 37-40]

3.4 The gender gap in aSAH

The female preponderance in incidence of aSAH is caused by a corresponding female preponderance in the prevalence of intracranial aneurysms.[41] In other parts of the arterial vasculature, the prevalence of aneurysms is higher in men than women (abdominal aortic aneurysms are found four times more often in men than in women).[42] The gender gap in aSAH has been sparsely investigated, and the suggested explanations are systemic factors such as hormonal influences and intrinsic weakness of the female arterial wall.[19, 43] Epidemiological studies have found that premenopausal females are at reduced risk for SAH compared with age-matched postmenopausal females.[5, 44] The increased risk after age 50 has been attributed to the influence of hormonal factors, however studies on the use of oral contraceptives and hormone replacement therapy on the risk for SAH have yielded conflicting results.[19, 45-47] The second theory for the gender gap, intrinsic weakness of the female arterial wall, remains to be proven.[43]

The sex difference in the prevalence of intracranial aneurysms is not constant, but varies with the different intracranial arteries: women have more aneurysms in the internal carotid, middle cerebral, and basilar artery, whereas anterior cerebral artery aneurysms are equally encountered in men and women.[43, 48-50] This uneven distribution proposes a

physiological factor: local sex differences in the different intracranial arteries. Sex differences in local hemodynamic stress of the intracranial arteries have not been subject to scientific studies. However, such sex differences are plausible as aneurysms arise where arteries are exposed to the maximum hemodynamic forces. And the hemodynamic forces vary with the different intracranial arteries due to geometrical differences.[51, 52]

3.5 Computational fluid dynamics simulation

The hemodynamic forces acting upon the arterial wall are not possible to measure directly in patients, but can be estimated with computational fluid dynamics simulation. Computational fluid dynamics simulation is a technique traditionally used in engineering to simulate the forces acting upon for instance turbines and oil pipes. Biomechanical application allows simulation of blood flow throughout arteries and calculation of the resulting hemodynamic forces acting upon the arterial wall. The simulations involve discretizing the vessel into small cells to form a volume mesh, and then applying algorithms to solve the equations of motion. The motion of viscous fluids is described by the Navier-Stokes equation, which is solved for each cell. In the present thesis, computational fluid dynamics simulations are used to calculate a hemodynamic force named wall shear stress. When blood (a Newtonian fluid, i.e. a fluid that has a constant viscosity at a given temperature) flows along the vessel wall, a stress will be applied parallel to the vessel wall; this is called wall shear stress. Shear stress at a point is given by:

$$\mu \times (\delta\upsilon/\delta y)$$

μ is the dynamic viscosity of blood, υ is the dynamic velocity of the blood along the vessel wall, and y is the diameter of the vessel. Abnormal shear stress has been suggested as a causative factor in the formation and rupture of intracranial aneurysms.[53-55]

4 AIMS OF THE THESIS

I To study the incidence of aSAH in Norway, with a focus on time trends and regional variations

II To study serum lipids and body mass index as risk factors for aSAH

III To study sex differences in the established risk factors for aSAH (smoking, hypertension, and alcohol consumption)

IV To explore a new hypothesis for the female preponderance of intracranial aneurysms and aSAH: that sex differences in vessel size and blood flow velocity result in higher hemodynamic forces acting upon the female arterial wall.

5 MATERIAL AND METHODS

5.1 Paper I: "Incidence of aSAH in Norway"

5.1.1 Data source

Data were collected retrospectively from the Norwegian Patient Register, the national hospital discharge registry. For each hospital discharge, date of admission and discharge, discharge destination (home, another hospital, death), procedure codes, hospital identification code, gender, age and county of residence were recorded. One main diagnosis and a set of secondary diagnoses indicating co-morbidities were recorded. During the study period, the data from the Norwegian Patient Register contained no patient identifiers that would allow tracking of repeat hospitalizations.

5.1.2 Inclusion and exclusion criteria

We identified all cases with a diagnosis of non-traumatic SAH admitted to Norwegian hospitals from January 1st, 1999 to December 31st, 2007, using the codes I60.0–I60.9 from the International Classification of Diseases, version 10. January 1, 1999 was chosen as the starting point for this study as this represents the date when version 10 of the International Classification of Diseases was implemented in Norwegian hospitals. As one could not assume that each hospitalization represents an individual patient and that all SAHs were aneurysmal, the following strategies were used: (i) We excluded cases that were not admitted as an emergency. (ii) We excluded admissions to non-neurosurgical hospitals if the patient survived >2 days. This was done to eliminate non-aSAHs and repeated hospitalizations as a result of transfer between hospitals. (iii) We excluded hospitalizations in neurosurgical centers if length-of-stay was <3 days and if discharge destination was home. This was done to eliminate re-admissions, as the lack of unique patient identifiers precluded the tracking of patients who were transferred between hospitals. (iv) We excluded cases with secondary diagnoses of arteriovenous malformation (Q28.2) or traumatic SAH (S06).

The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Medical Research Ethics approved this study.

5.1.3 Sample

Using the appropriate ICD-10 codes for SAH, we identified 11,618 hospital admissions in Norway between January 1, 1999 and December 31, 2007. Of these, 7475 were excluded

according to the pre-established exclusion criteria, leaving a total of 4,143 patients available for the analysis (Figure 5.1)

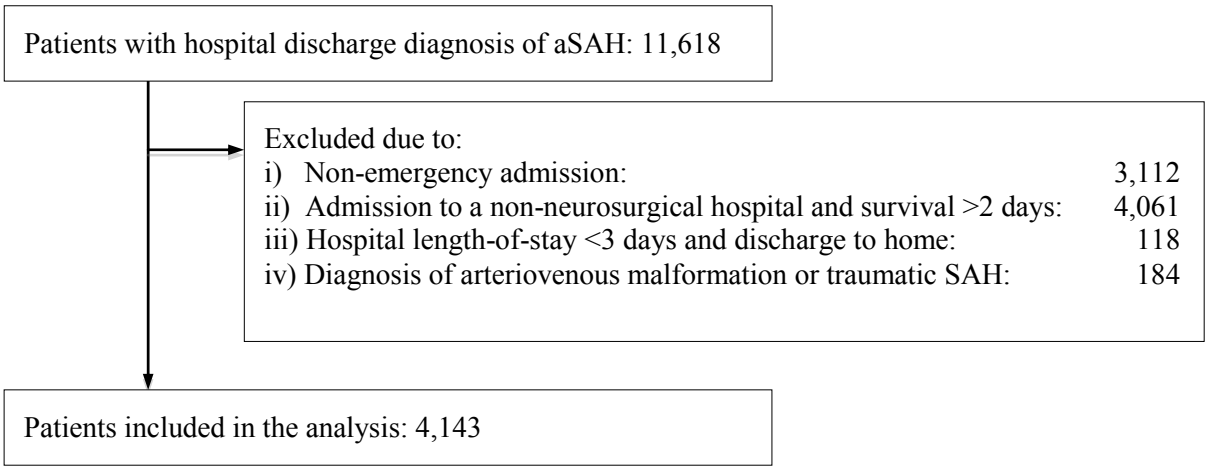

Figure 5.1 Flowchart of patient inclusion, Paper I

5.1.4 Statistical analyses

The source population consisted of all Norwegian citizens with 41.3 million person-years at risk, compiled from annual census data between 1999 and 2007, by gender, age and region. The annual incidence rates were calculated by dividing the number of all events by person-years, after direct standardization to the entire study period (1999– 2007). To analyze regional differences in incidence rates, the 19 Norwegian counties were allocated into five areas based on the Norwegian Regional Health Authorities; southern (Telemark, Buskerud, Vestfold, Vest-Agder and Aust-Agder), western (Rogaland, Hordaland and Sogn og Fjordane), eastern (Akershus, Østfold, Oslo, Hedmark and Oppland), central (Sør Trøndelag, Nord Trøndelag and Møre og Romsdal) and northern (Nordland, Troms and Finnmark). The number of cases never reaching hospital alive was calculated by subtracting the number of hospitalized patients with fatal outcome from the total number of deaths caused by SAH from the Norwegian Causes of Death Registry. Analysis of overall P for trend over time was performed using annual incidence and mortality rates of SAH. The overall national mortality rates were established from statistics published by the Norwegian Causes of Death Registry, available at http://www.ssb.no/dode. Data were available from 1999 through 2006. Data from 2007 were not available at the time of analysis.

5.2 Paper II and III: ” Risk factors for aSAH - body mass index and serum lipids” and ”Sex differences in risk factors for aSAH”

5.2.1 Study population

The Tromsø study and Nord-Trøndelag Health Study (HUNT) are two prospective, population-based cohort studies. The Tromsø study is conducted in the municipality of Tromsø, Troms county, Norway, and the HUNT study is conducted in the county of Nord-Trøndelag, Norway. The design of both studies includes repeated population health surveys to which total birth cohorts are invited.

The fourth survey of the Tromsø study (Tromsø 4) was conducted between 1995 and 1997. All residents aged 25 and older were invited to participate. Of the eligible population, 27,158 participated (77%).[56] Two-hundred-and-seventy-six participants were excluded because of not consenting to medical research (n=201), not officially registered as inhabitants of the municipality at the date of attendance (n=44), or previous SAH (n=31), leaving a total of 26,882 subjects to be followed up in the present analyses.

The second survey of the HUNT study (HUNT 2) was conducted between 1995 and 1997, and all residents aged 20 years and older were invited to participate. Of the eligible population, 65,628 participated (71.2%).[57] In Paper III, 48 persons were excluded because of death (n=3), not officially registered as inhabitants of the county at the date of attendance (n=2), or previous SAH (n=43) before entering the study, leaving a total of 65,580 participants to be followed up in the present analyses. The combined cohort of Paper III consisted of 92,462 persons, with 1,002,148 person-years of observation.

After Paper III had been published, we became aware of a data file error concerning the HUNT cohort. A total of 55 participants (not 2) were not registered as inhabitants of the municipality at the date of attendance. One participant with previous SAH had erroneously not been classified as such. Furthermore, 12,711 persons that moved from Nord-Trøndelag county during the follow-up period had erroneously been assigned follow-up time to the end of follow-up and not to the date of emigration. This was corrected in Paper II, in which 102 participants were excluded because of death (n=3), not officially registered as inhabitants of the county at the date of attendance (n=55), or previous SAH (n=44) before entering the study, leaving a total of 65,526 participants to be followed up in the present analysis. The combined cohort of Paper II consisted of 92,408 persons. After correcting the follow-up time of the 12,711 persons that emigrated from the HUNT study area, the total follow-up time was reduced from 1,002,148 to 977,895 person-years. This has been corrected in Paper II.

The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Ethics in Medical Research approved this study. All participants gave their informed, written consent to participate.

5.2.2 Data source

In the Tromsø 4 and HUNT 2 surveys, information on cardiovascular risk factors, menstruation status, and use of antihypertensive treatment, and hormone replacement therapy at baseline was obtained by self-reported questionnaires and physical examinations.[56,57]

Based on the self-reported questionnaires, the participants' smoking status was classified as never (reference category), former, or current smoking. Alcohol consumption was classified as abstinent, drinking <1 time per month (reference category), 1-4 times per month, and >4 times per month. Height and weight were measured with the participants wearing light clothes without shoes; height was measured to the nearest cm and weight to the nearest half kg. Body mass index was calculated as weight (kg) divided by the squared value of height (m). In the analysis, body mass index was treated both as a continuous variable and according to weight groups defined by the World Health Organization: <18.5 as underweight, 18.5-24.9 as normal weight, 25-29.9 as overweight, and ≥30 kg/m^2 as obese. In the categorical analyses, we used the normal weight group as the reference.

Blood pressure was measured in a seating position by trained nurses using an automatic device (Dinamap, Critikon, Tampa, FL, USA). Cuff size was adjusted after measuring the arm circumference. After 2 min of seated resting, three recordings were made at 1-min intervals. The mean value of the second and third measurement was used in the analysis. Hypertension was defined as systolic blood pressure >140 mmHg or current use of antihypertensive drugs. Women who did not use hormone replacement therapy were classified as premenopausal if they were still menstruating. Women who were not pregnant or no longer menstruating, women who were hormone replacement therapy-users and women aged ≥55 years were classified as postmenopausal.

A non-fasting blood sample was drawn from all participants. Serum samples were analyzed for total cholesterol, high-density lipoprotein-cholesterol (HDL cholesterol), and triglycerides on a Hitachi 911 Autoanalyzer, by enzymatic colorimetric methods with commercial kits (CHOD-PAP, Boehringer-Mannheim) at the Central Laboratory at Levanger Hospital (HUNT 2) and at the Department of Laboratory Medicine, University Hospital of

North Norway (Tromsø 4). Serum HDL cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride.

5.2.3 Inclusion and exclusion criteria

Patients were included as aSAH cases if the diagnosis had been verified by cerebral angiography or autopsy, or if the medical history was highly suggestive for fatal aSAH, but the patient had died before undergoing cerebral angiography and was not autopsied. A medical history highly suggestive of fatal aSAH was defined as (i) sudden headache and/or unconsciousness, (ii) death < 4 weeks, and (iii) findings on non-contrast enhanced computed tomography scans were typical for aSAH (massive basal SAH). All criteria had to be fulfilled. In HUNT, all cases were reviewed and consented by two neurosurgeons. In the Tromsø Study, an independent endpoint committee of one neurologist and two experienced physicians validated the aSAH cases. A neurologist and a neuroradiologist validated cases suggestive for fatal aSAH.

5.2.4 Case identification

The national 11-digit identification number allowed linkage of the baseline data to national and regional registers, and ensured a complete follow-up status for all-cause mortality. For the HUNT population, information about SAH was obtained by linkage to the diagnosis register at St Olavs University Hospital, the only hospital with a neurosurgical department serving the HUNT population. All patients who survive the acute phase of the SAH are treated at the department, and people who live in the region but experience a nonfatal SAH outside the area, are usually transferred to the department after acute treatment elsewhere. An identical procedure was followed in the Tromsø Study, using information from the University Hospital of North Norway, the only hospital in the area that serves the study participants. Further, information from both studies was linked to the National Causes of Death Register at Statistics Norway, using codes for aSAH according to the International Classification of Diseases, version 9 (code 430) and 10 (code I60). Individuals who had died or emigrated from Nord-Trøndelag or Tromsø were identified through the Population Register of Norway. Data on emigration from the study areas were available from the Population Register of Norway.

Follow-up time was assigned from the date of examination in each study (from 1994 to 1997) until the first aSAH occurred, until death from other causes, emigration, or to the end of follow-up, December 31, 2007, whichever occurred first. Hospitals charts for the identified patients were reviewed. Case fatality was defined as death ≤30 days after aSAH.

5.2.5 Sample

We identified 120 incident cases of aSAH (102 verified by angiography or at autopsy and 18 with a medical history highly suggestive of fatal aSAH). Of these patients, 69 were from the Nord-Trøndelag and 51 from the Tromsø cohort. After Paper III had been published, the search for aSAH cases was extended, and two additional incident aSAH cases were found. This was corrected in Paper II, leaving a total of 122 incident cases of aSAH (103 verified by angiography or at autopsy and 19 with a medical history highly suggestive of fatal aSAH). Of these patients, 71 were from the Nord-Trøndelag and 51 from the Tromsø cohort.

A flowchart of patient inclusion (Paper II) is depicted in Figure 5.2.

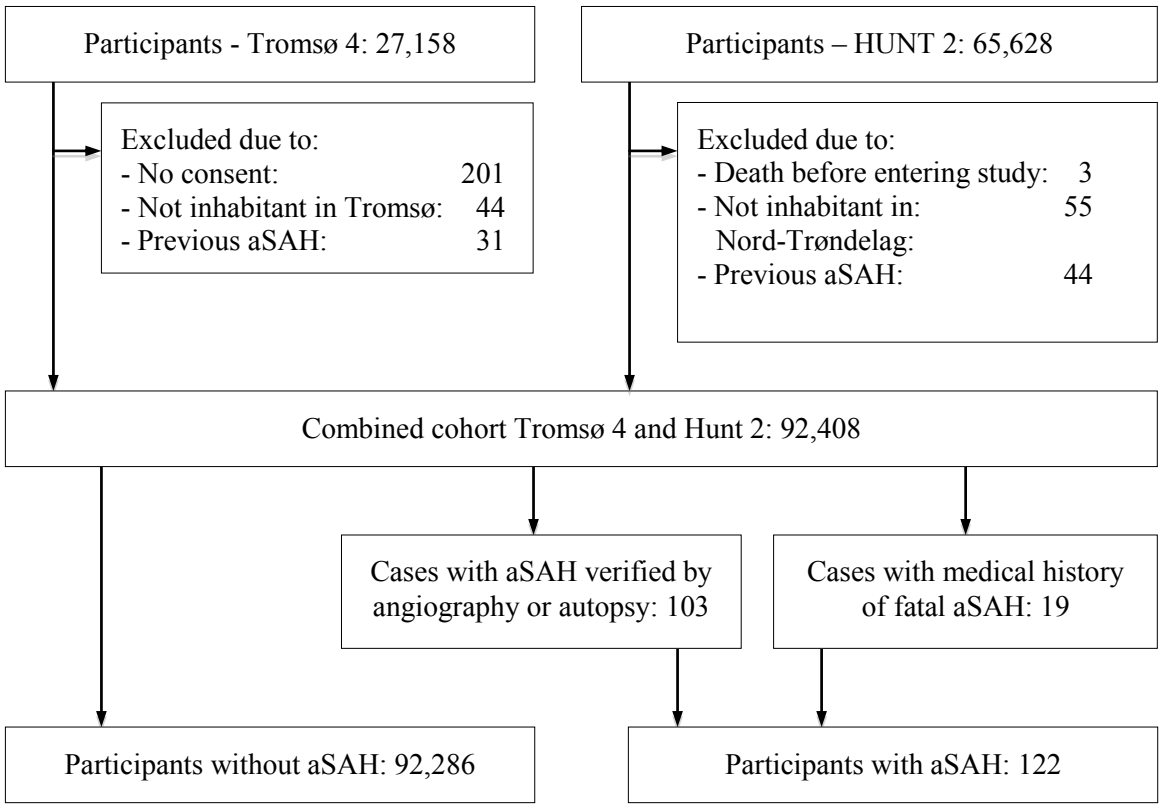

Figure 5.2 Flowchart of patient inclusion (Paper II)

5.2.6 Statistical analyses

Cox proportional hazards model was used to estimate hazard ratios (HRs) of aSAH with 95% CI. The analyses were stratified by sex. The analyses were performed with and without the 18 aSAH-patients that were not verified by angiography or at autopsy. Departure from the proportional hazards assumption was evaluated by Schönfeld's residuals and by inspection of

the log-log plots. Possible statistical interaction between sex and the risk factors for aSAH (hypertension, smoking and alcohol consumption) was assessed using the log likelihood ratio test. Possible biological (i.e. additive) interaction between sex and the risk factors for aSAH was assessed by calculating the relative excess risk due to interaction (RERI) with 95 % CIs.[58-60] RERI values >0 indicate increased risk of aSAH associated with the risk factor in question among women as compared to men, and RERI values <0 indicate decreased risk of aSAH associated with the risk factor among women as compared to men. All analyses were performed using Stata for Windows (Version 10.0, Stata Corp, Texas).

5.3 Paper IV: ”Sex differences in intracranial arterial bifurcations”

5.3.1 Study population

Data from a previously published study of 55 patients undergoing diagnostic cerebral digital subtraction angiography were available for analysis.[61] The indications for cerebral angiography were acute or previous SAH, ischemic cerebrovascular events, symptoms suspicious of other cerebrovascular disease, or family history of intracranial aneurysms.

5.3.2 Data source

We evaluated bifurcation geometry by analyzing measurements of vessel radii and bifurcation angles on three-dimensional reconstructions of the digital subtraction angiograms. The terminal bifurcation of the internal carotid artery and the division of the M1 segment of the middle cerebral artery into two main branches were studied. Five measurements were performed: diameter of the parent vessel, largest branch, and the smallest branch; and the angle formed between the parent vessel and the largest branch and the smallest branch, respectively. The diameter of the parent vessel was measured midway between the last branch point and the bifurcation of interest. In the branches, the diameters were measured 5 mm beyond the apex of the bifurcation, or if a new branch arose before this, at the most distal location before the next bifurcation. These points were identified on oblique images oriented along the flow axis of the vessel. The diameters were measured at eight different centripetal in a plane oriented 90 degrees on the flow axis. In order to measure the bifurcation angles, three points were defined in the three-dimensional volume to measure an angle: the center of the parent vessel at the point where the diameter was measured, the center of the bifurcation, and the center of the branch at the point where the diameter was measured.[61]

The average radii and angles were calculated and idealized male and female models of the middle and internal cerebral artery bifurcations were developed using Star-CD (pro-STAR Version 3.26.003, CD-Adapco, New York, USA). The models were smoothed in the intersections to give physiological correct appearance. The vessel length was set at 20 mm for the parent vessel and 15 mm for the branches, enabling fully developed flow at the outlets.

5.3.4 Sample

Of the 55 available patients, six patients with only imaging of the basilar artery were excluded, leaving data from 49 patients (32 females and 17 males) with available angiograms of the middle cerebral (n=52) or internal carotid artery (n=47) available for analysis.

5.3.5 Computational fluid dynamics simulations

Computational fluid dynamics simulations were used to calculate hemodynamic forces in the models. Earlier published data on average sex specific blood flow velocities (mean flow velocity: 75 cm/s for the female middle cerebral artery, 64 cm/s for male middle cerebral artery; 42 cm/s for the female internal carotid artery, and 34 cm/s for the male internal carotid artery) were used as stationary inflow boundary condition to the numerical simulations.[62] We modeled blood as a Newtonian incompressible fluid with density of 1025 kg/m3 and viscosity of 0.0035 kg/m×s. The vessel walls were assumed rigid. To represent the downstream geometry, the outlets were assigned a resistance boundary condition of the form $R=p_0+C\times Q$, where p_0 is the pressure (85 mmHg), Q is the flow rate, and C is the resistance coefficient (5.97 Pascal×seconds×meters^{-3}).[63] The Navier-Stokes equations, describing the flow, were solved using the finite element method, with a Chorin/Temam splitting scheme using second order elements in space.[64, 65] Tests showed that approximately 2×10^5 cells were sufficient to achieve numerical convergence. The code was implemented in FEniCS (www.fenics.org).

5.3.6 Statistical analyses

Preliminary assumption testing was conducted to check for normality, linearity, and univariate outliers. No notable violations were found, permitting the calculation of means, standard deviations and use of independent samples t-test when comparing between groups. Probability values are two-tailed. SPSS release 15.0 (SPSS, Inc., Chicago, IL) was used for calculations. The computational simulations could not be subjected to statistical tests.

6 SUMMARY OF RESULTS

6.1 Paper I: ”Incidence of aSAH in Norway”

The crude incidence rate of aSAH in Norway between 1999 and 2007 was 10.0 per 100,000 person-years (95% CI: 9.7– 10.3). The incidence was higher in women (12.0 per 100,000 person-years; 95% CI: 11.5–12.5) than men (8.1 per 100,000 person-years; 95% CI: 7.7–8.4). The crude overall mortality rate was 3.2 per 100,000 person-years (95% CI: 3.0–3.4).

A significant decrease in annual incidence was observed in the period, from 11.1 per 100,000 person-years (95% CI: 10.5–11.6) in the period 1999–2001 to 8.9 per 100,000 person-years (95% CI: 8.4–9.4) in the period 2005–2007 (P for trend <0.001), with a concurrent decrease in the annual mortality rate of SAH, from 3.5 per 100,000 person-years in 1999–2000 (313 cases), to 2.9 per 100,000 person-years in 2005–2006 (266 cases; P for trend 0.02).

Regional variations were observed in incidence rates, from 8.4 per 100,000 person-years (95% CI: 7.7–9.0) in the southern region, 10.4 per 100,000 person-years (95% CI: 9.5–11.2) in the central region, to 11.9 per 100,000 person-years (95% CI: 10.8–12.9) in the northern region, adjusted for gender and age. The highest incidence of aSAH was found in the northernmost county Finnmark with 17.4 per 100,000 person-years (95% CI: 14.2–20.5).

6.2 Paper II: ”Risk factors for aSAH - body mass index and serum lipids”

A total of 122 aSAH cases were identified over 977,895 person-years of observation.

There was a positive association between female sex (HR 1.9, 95% CI: 1.3-2.7), systolic hypertension (HR 2.6, 95% CI: 1.6-3.7), current smoking (HR 5.7, 95% CI: 3.4-9.4), and the risk of aSAH. Overweight (body mass index 25.0-29.9) participants were at lower risk of aSAH, compared to normal weight (body mass index 18.5-24.9) participants (HR 0.7, 95% CI: 0.4-1.0, adjusted for age, sex, smoking and alcohol consumption.

Among participants <50 years of age, a statistically significant, inverse relationship between HDL cholesterol and the risk of aSAH was observed (HR 0.6, 95% CI: 0.4-0.9, adjusted for sex, age, smoking, and alcohol consumption). No further association between total serum cholesterol, HDL cholesterol, triglycerides or alcohol consumption, and the risk of aSAH was observed.

6.3 Paper III: ”Sex differences in risk factors for aSAH”

A total of 120 aSAH cases were identified over 1,002,148 person-years of observation. Mean age at diagnosis was 58.6 years for women (standard deviation, SD 1.6, range 35-90) and 58.9 years for men (SD 2.1, range 30-87). On average, aSAH was diagnosed 72 months after baseline measurements (SD 43, range 0-147 months). The 30-day case fatality for aSAH was 38% (n=30) for women and 39% (n=16) for men.

In these sex-specific analyses, increased risk of aSAH was observed in female compared to male current smokers. The sex difference in current cigarette smoking increased after adjusting for age and alcohol consumption (HR 8.9 for women, 95% CI: 4.7-17.0, vs HR 2.8 for men, 95% CI: 1.3-6.1) The RERI for sex and current cigarette smoking was 3.1 (95% CI 0.5-5.8), indicating significant higher risk of aSAH associated with current cigarette smoking in women than in men (additive or biological interaction).

No sex differences were observed with respect to hypertension or alcohol consumption.

6.4 Paper IV: ”Sex differences in intracranial arterial bifurcations”

The diameters of the male vessels were significantly larger than the female vessels ($p<0.05$), with the exception of the largest branch of the internal carotid artery. No significant sex differences in the bifurcation angles were observed.

Computational fluid dynamics simulations based on averaged models showed both increased wall shear stress and a larger affected area in the female middle cerebral artery and internal carotid artery bifurcations. The maximum wall shear stress in the middle cerebral artery was 19 % higher in the female bifurcation (33.2 Pascal, Pa) than the male (27.8 Pa). The maximum wall shear stress in the internal carotid artery was 50 % higher in the female bifurcation (15.2 Pa) than in the male (10.1 Pa). These values were reflected through a higher pressure drop in the female than the male bifurcations (664 versus 502 Pa for the middle cerebral artery and 344 versus 202 Pa for the internal carotid artery).

7 DISCUSSION

The main findings of this thesis are: (i) that the incidence of aSAH in Norway decreased from 1999 to 2007, with significant regional variations indicating an increasing gradient from south to north; (ii) overweight is inversely associated with the risk of aSAH, compared to normal weight, but no overall association between HDL, LDL, total serum cholesterol, triglycerides, and the risk for aSAH is observed; (iii) current cigarette smoking is a stronger risk factor for aSAH in women than in men; and (iv) sex differences in arterial size and blood flow velocity result in higher hemodynamic forces acting upon the female arterial wall.

7.1 Internal and external validity of the studies

Internal validity is defined as validity of inference for the source population of study subjects. Three types of errors may threaten the internal validity: (i) selection bias: distortions that result from procedures used to select subjects and from factors that influence study participation; (ii) information bias: different consequence of errors in the measurement of exposure and/or disease in subjects; and (iii) confounding factors: the extraneous factors responsible for difference in disease frequency between the exposed and unexposed.

External validity pertains to the ability to generalize the findings to the general population.[66]

7.1.1 Paper I

Paper I describes a sample selected from a non-validated, national hospital discharge registry without person identifiers. Possible selection bias includes regional and temporal differences in the hospitalization of patients with suspected aSAH. This may explain the somewhat higher observed age- and sex-adjusted incidence rates in counties where the five hospitals with neurosurgical wards are located than in the surrounding counties. However, patients with aSAH have serious symptoms (such as severe headache with rapid onset and/or loss of consciousness), and usually reach medical attention rapidly. Thus, the number of patients hospitalized for aSAH probably closely represents the true number of aSAH cases. As the Norwegian Patient Register did not contain patient identifiers, a validation study was not possible. However, a Swedish study comparing the World Health Organization's "Multinational monitoring of trends and determinants in cardiovascular disease" (MONICA) stroke registry with hospital discharge registries, found that 94% of incident stroke cases was registered in the Swedish national hospital discharge registry.[67]

Information bias may exist due to measurement errors (erroneous inclusion of non-aSAH cases or classification of aSAH cases as healthy, and counting aSAH cases more than once), as hospital discharge registries are prone to errors in coding. In order to prevent this, a number of precautions were taken to eliminate non-aSAHs, readmissions and repeated hospitalizations as a result of transfer between hospitals, as described in the Methods section. Further, erroneous classification of rebleedings as incident cases may have artificially increased the estimated incidence rates. As the risk of rebleeding is low after surgical or endovascular treatment (1.3% during the first 8 years following the first episode),[68] the effect would be small. However, as long as these measurement errors affected the comparison groups (time periods and regions) equally, the resulting information bias would be non-differential.

Confounding factors, such as distance to a neurosurgical ward and availability of radiological imaging may exist. However the serious symptoms of aSAH, the widespread availability of computed tomography in Norway since mid-1990s, and the extensive air ambulance service in remote parts of Norway, make it less likely that his has affected the observed incidence rates.

As the study population was drawn from the entire Norwegian population, the findings may be generalized to the general population on the condition that the study is internally valid. In conclusion, the internal validity of Paper I is limited by the identification of cases from a national hospital discharge registry that did not include patient identifiers, and this precluded a validation study. Nevertheless, the observed incidence rates are in accordance with incidence rates observed from other Western European countries,[5] implying that the findings of Paper I are valid.

7.1.2 Paper II and III

Paper II and III describe a prospective cohort. In prospective cohort studies, selection bias is negligible with respect to the association between risk factors and disease, as information on exposure is ascertained before the development of disease.

The possibility of information bias in outcome is limited, but may be caused by either erroneous classification of healthy as SAH cases or SAH cases as healthy. The former is unlikely due to the rigorous case validation, whereas the latter is possible due to deaths outside hospital that were not autopsied.

After Paper III was published, the identification of aSAH cases was extended and two additional incident aSAH cases identified, as well as one participant with previous SAH. In

Paper III, data on participants that emigrated from the HUNT study area during follow-up were not available. Censoring these patients reduced the total follow-up time with 1,002,148 – 977,895 = 24,253 person-years. The error introduced by this is limited due to the large number of participants and aSAH cases, and is therefore unlikely to change the effect estimates of Paper III.

The number of out-of-hospital deaths caused by aSAH is difficult to measure. A meta-analysis of 18 population-based studies found that 12.4% of aSAH patients died before receiving medical attention.[69] Another study of 142 survivors after out-of-hospital cardiac arrest found aSAH in 16.2% of the patients.[70] This implies that out-of-hospital deaths occasionally are caused by aSAH. As only a minority of out-of-hospital deaths is autopsied, it is likely that some cases of sudden aSAH deaths in the present study have erroneously been classified as healthy. Biased estimates of the association between exposure and disease may also be caused by errors in exposure measurements. The present study examined exposure data from self-reported questionnaires (smoking status, alcohol consumption, use of hormone replacement therapy, and menstruation/menopause status) and laboratory measurements (blood pressure, non-fasting serum lipids (triglycerides, HDL-, LDL, and total-cholesterol). With respect to the self-reported questionnaires, possible bias includes recall bias. With respect to the laboratory data, there may be errors in measurement due to variations in the measured variables. There is a circadian variation in blood pressure,[71] and blood pressure increases in a clinical setting (the white coat effect).[72] To minimize this potential error, blood pressure was measured three times by trained nurses using an automatic device and the mean value of the second and third measurement was used in the analysis. Non-fasting serum lipids were used in the Tromsø study. Whereas there is considerable variation in triglyceride levels throughout the day (>20%), the circadian variation in HDL-, LDL-, and total-cholesterol is negligible (<10%).[73] However, as exposure data in cohort studies are measured before disease occurrence, the potential measurement errors can be assumed to be non-differential with respect to disease.

The observed sex differences may have been caused by unknown confounding factors we were unable to adjust for. One might speculate whether the observed sex differences are caused by changes in risk factors levels that occurred during follow up. Unpublished data from the Tromsø study show that this is less likely (Table 7.1). Further, information on family history of stroke (hemorrhagic and ischemic) and not subtypes of stroke (aSAH) was available.

In the present study, the analysis of hereditary factors as a risk factor for aSAH and possible interaction between smoking and hereditary factors are not specific for aSAH, but include hereditary factors for stroke in general.

Due to the high response rate and the prospective, population-based, cohort design to which total birth cohorts were invited, there are probably no major threats to the external validity of these two studies. In conclusion, the results of Paper II and III should be considered valid.

Age	Percentage of current smokers		
	Survey 4 (1994/5)	Survey 5 (2001)	Survey 6 (2008)
Men			
30-39 years	39.0	29.6	21.1
40-49 years	40.4	33.6	21.2
50-59 years	37.6	36.9	20.2
60-69 years	34.9	27.1	16.9
70-79 years	26.8	21.7	16.5
80-84 years	20.9	18.2	10.5
Women			
30-39 years	40.9	43.8	25.0
40-49 years	42.8	35.9	25.9
50-59 years	36.7	31.4	25.0
60-69 years	30.8	28.1	19.8
70-79 years	17.8	18.4	14.5
80-84 years	8.7	12.2	6.8

Table 7.1 Percentage of current smokers among men and women who attended the fourth survey of the Tromsø study, by age and survey

7.1.3 Paper IV

Paper IV describes computational fluid dynamics simulations based on radiological measurements of the middle cerebral and internal carotid artery in consecutive patients undergoing diagnostic cerebral angiography. Selection bias is possible, as the study population was small and the sample size skewed, with a female-to-male ratio of almost 2:1.

Further, the study population consisted of patients undergoing diagnostic angiography, and not healthy volunteers, only the middle cerebral and internal carotid artery were examined, and the computational fluid dynamics simulations were based on idealized male and female models, developed from the geometric measurements, and not patient specific models.

Information bias is possible in either the measurements of the vessels or in the computational fluid dynamics simulations. The former is unlikely due to high inter- and intraobserver agreement, whereas the latter is possible as computational fluid dynamics is an evolving method. Further, the analysis did not include sex differences in dynamic blood viscosity – one of the parameters that determine shear forces. Several factors contribute to the viscosity of blood: the number of red blood cells (higher in men), the number of plasma proteins (such as fibrinogen, higher in women), and body temperature. Blood viscosity in women varies with the menstrual cycle and menopause status.[74] Although blood viscosity is somewhat higher in men than women,[75] it was difficult to determine the precise values for blood viscosity in the intracranial arteries, and the same value was used for both genders in the simulations. It is not unlikely that adjusting for sex differences in blood viscosity would somewhat attenuate the observed sex differences in shear forces. There may also be other confounding factors that, if different between females and males, produce different mechanical loads on the arterial walls in men and women.

In conclusion, the results of Paper IV must be interpreted with caution. The hypothesis presented, that sex differences in anatomy and blood flow velocity cause the gender gap in aSAH, deserves prospective investigation in future studies.

7.2 The incidence of aSAH

Paper I found that the crude incidence of aSAH in Norway decreased from 11.1 per 100,000 person-years (95% CI: 10.5–11.6) in the period 1999–2001 to 8.9 per 100,000 person-years (95% CI: 8.4–9.4) in the period 2005–2007. Significant regional variations were observed, indicating an increasing gradient from south to north.

The decline in the incidence of aSAH is congruent with results from a meta-analysis covering populations in 21 countries.[5] Possible explanations include a coincidental decline in the prevalence of unfavorable risk factors. The number of daily smokers in Norway aged 16–74 years declined from 34% in 1996 to 24% in 2006.[76] Among 40–42-year-old men, the proportion with systolic blood pressure ≥160 mmHg declined from 3.9% in 1996 to 2.2% in 1999. The corresponding decline in women was from 2.1% to 1.3%.[77] The larger decline of incidence rates in men than in women may partially be explained by the fact that the

percentage of female smokers remained unchanged for about 30 years until 2003, whereas the percentage of male smokers dropped significantly during the same period.[76] The role of cardiovascular risk factors is further supported by the high incidence rate in Finnmark, a county that for several decades has had a higher mortality of ischemic heart disease and stroke than the other counties in Norway.[78] It is unlikely that increased treatment of unruptured aneurysms has significantly influenced the decline in incidence rates, as the annual rupture rate for incidentally discovered aneurysms is low.[68]

The observed regional variations in the incidence rates of aSAH were as reported for Sweden, with a higher incidence rate in the northern region compared with the southern region.[8] A possible explanation for the regional variations in incidence rates is regional variations in the risk factors of aSAH (such as smoking and blood pressure). As mentioned before, the northernmost county in Norway, Finnmark, has for several decades had a higher mortality of cardiovascular diseases than the other Norwegian counties.[78] Smoking is more frequent in the eastern and northern parts of Norway compared with the southern and western, with the highest prevalence in the northernmost county Finnmark.[76] There are, however, no corresponding geographical differences in blood pressure distribution in the general population.[79] The Finnmark population is a mixture of Sami, Norse and Finnish descendents. Possibly, a larger proportion of the population of Finnish heritage in Finnmark may contribute to the higher incidence rates of aSAH, as the population of Finnish heritage in Finnmark has a higher incidence of unfavorable risk factors and ischemic disease than the general population,[78] and the incidence of aSAH is higher in Finland than in other parts of the world.[13]

The age- and sex-adjusted incidence rates are higher in counties with neurosurgical wards than in the surrounding counties. This might be due to easier access to high-specialized hospital services, resulting in better diagnostic precision and higher hospitalization rate for people living in these areas. One might also speculate whether the higher incidence rate observed in the capital county Oslo could be partly attributed to a relatively high proportion of immigrants from low-income countries. The proportion of people with ancestry from Asia, Africa, Latin America, European countries outside the European Union and Oceania, except Australia and New Zealand, is 19.5% in Oslo, whereas the average for Norway is 6.7%. Increased incidence of cardiovascular disease in persons migrating from poorer countries to high-income industrialized countries is thought to be a result of unfavorable changes in dietary and other life-style habits with increased exposure to cardiovascular risk factors. Similar changes are seen in developing countries. Feigin et al. found that incidence rates for

SAH in the period 2000–2008 were almost twice as high in low- to middle-income countries compared with high-income countries, suggesting that those countries have entered the 'epidemiological transition'.[80]

7.3 Risk factors for aSAH

Paper II found that overweight (body mass index 25-29.9) participants were at lower risk of aSAH, compared to normal weight (body mass index 18.5-24.9) participants (HR 0.7, 95% CI: 0.4-1.0). The pathophysiological explanation for this is uncertain. Although the finding is supported by other studies,[18, 23] the confidence intervals suggest a cautious interpretation. No overall association between total serum cholesterol, HDL cholesterol, triglycerides, body mass index, and the risk of aSAH were observed.

Among participants <50 years of age, a statistically significant, inverse relationship between HDL cholesterol and the risk of aSAH was observed (HR 0.6, 95% CI: 0.4-0.9, adjusted for sex, age, smoking, and alcohol consumption). The biological explanation for an age-dependent relationship between HDL-cholesterol and the risk for aSAH is not clear. However, a strong, inverse association between HDL-cholesterol and the risk of coronary heart disease and ischemic stroke has been observed.[81-85] This effect appears to be stronger in middle than in old age.[84, 85] It is therefore possible that the present study's observation of the protective effect of HDL-cholesterol on the risk of aSAH may be true, although it needs to be confirmed in future prospective studies.

7.4 Aspects on the causes for the gender gap in aSAH

7.4.1 Previous studies exploring causes for the gender gap in aSAH

The causes for the disproportional incidence of aSAH in women have been sparsely investigated. The gender gap in aSAH is usually explained by systemic factors, including: i) hormonal and menstrual factors, and ii) intrinsic weakness of the female arterial wall.[5, 19, 43, 44]

Studies have previously investigated menopause status, age at menarche, parity, use of oral contraceptives and hormone replacement therapy. The importance of menopause in the gender gap of aSAH is indirectly supported by the fact that the female preponderance of aSAH occurs between 45 and 55 years of age.[5] Studies on the effect of menopause status on the risk for aSAH are however sparse. In a study by Longstreth at al of 103 women with aSAH and 206 age-matched controls, premenopausal women were at reduced risk for aSAH compared with age-matched postmenopausal women (OR 0.2, 95% CI: 0.1-0.7)[45] The

Australasian Cooperative Research on Subarachnoid Hemorrhage) study of 286 women with aSAH and 286 age-matched controls found no significant difference in the risk for aSAH between pre- and postmenopausal women (OR 1.0, 95% CI: 0.6-1.6, adjusted for age).[19]

The effect of age at menarche on the risk for aSAH is sparsely investigated. A study of 124 cases and 248 controls did not find that early age at menarche (<13 years) were associated with increased risk for aSAH in parous women (OR 0.9, 95% CI: 0.7-3.2, adjusted for age, hypertension, and smoking).[86] Similar findings were observed in the Australasian Cooperative Research on Subarachnoid Hemorrhage study.[19]

Increased parity is possibly a protective factor for aSAH. Gaist et al, in a nested case-control of 887 aSAH cases, found that the OR for aSAH declined with increasing parity (1 child: reference; 2 children: OR=0.8, 95% CI: 0.7-1.0; 3 children: OR=0.7, 95% CI: 0.6-0.9; 4 children: OR=0.7, 95% CI: 0.5-1.1; ≥5 children: OR=0.7, 95% CI: 0.3-1.4). The effect was reduced when adjusting for daily cigarette consumption before first childbirth.[87] A protective effect of parity has also been reported with respect to the mortality of aSAH.[88] The Australasian Cooperative Research on Subarachnoid Hemorrhage study however did not find that parous women had significantly reduced risk for aSAH (OR 0.9, 95% CI: 0.6-1.5) compared to nulliparous women.[19]

No decisive effect of hormone replacement therapy and oral contraceptives on the risk for aSAH has been found. One prospective cohort has examined use of oral contraceptives and SAH mortality, but the number of SAH cases (n=7) was too small to draw a conclusion.[89] The Australasian Cooperative Research on Subarachnoid Hemorrhage study found no association between ever use of oral contraceptives and aSAH (OR 0.9, 95% CI: 0.5-1.5, adjusted for age).[19] Similar findings were reported by Longstreth et al (OR 0.5, 95% CI: 0.3-1.1, adjusted for age), and in the World Health Organization's Collaborative Study on Cardiovascular Disease and Steroid Hormone Contraception (European population OR 1.6, 95% CI: 0.9-2.8, unadjusted).[45, 90] The Nurses' Health Study, a prospective cohort of 121,700 female nurses, examined the use of hormone replacement therapy and the risk of aSAH. No association between current (RR 0.9, 95% CI: 0.6-1.3, adjusted for age) or past use (RR 0.9, 95% CI: 0.6-1.3, adjusted for age) and the risk of aSAH was observed.[91] The Australasian Cooperative Research on Subarachnoid Hemorrhage study found that ever use of hormone replacement therapy was associated with reduced risk for aSAH (OR 0.64, 95% CI: 0.41-0.98), whereas Longstreth et al found that a reduced risk for aSAH with hormone replacement therapy was limited to those who had ever smoked.[19, 45]

The second theory for the gender gap, that intrinsic weakness of the arterial wall plays a role in promoting intracranial aneurysms in females, is motivated by the more frequent occurrence of multiple aneurysms in women than in men.[43] However the theory remains to be proven.

7.4.2 A new factor: sex differences in the vascular vulnerability to smoking

Paper III found that current cigarette smoking was approximately twice as hazardous in women as in men (HR 6.5, 95% CI 3.56-11.9 vs HR 3.5, 95% CI 1.6-7.4). After adjusting for age, hypertension, and alcohol consumption, current cigarette smoking was 3.4 times more hazardous in female than male participants (HR 9.8, 95% CI 5.1-18.7 vs HR 2.9, 95% CI 1.3-6.3). There were no statistically significant sex differences in HRs with respect to age, systolic blood pressure or alcohol consumption.

To our knowledge, this is the first population-based cohort with case verification that demonstrates sex differences in risk factors for aSAH. Sex differences in risk factors for aSAH have previously been investigated in a meta-analysis[17] of prospective studies.[18, 25-34]. This meta-analysis found hypertension and ever smoking more hazardous in women than men, but not current smoking or excessive alcohol consumption (>150 g per week). However, the meta-analysis included only three studies of men and women from the same population, of which two studies only examined alcohol consumption and not cigarette smoking,[33, 34] and the third study consisted of cases identified using a national hospital discharge registry that were not validated.[18] Retrospective case-control studies have reported conflicting results. One study found statistically significant higher risk of aSAH in male compared to female smokers,[35] one study found statistically significant higher risk of aSAH in female compared to male smokers,[36] whereas other studies found no statistically significant sex differences.[18, 37-40]

The finding of sex differences in cigarette smoking suggest that health interventions aimed at reducing the gender gap in aSAH should focus on reducing daily smoking in women at risk for aSAH. This appears to be supported by findings in the World Health Organization's MONICA project, where an increased incidence of SAH in women was found only in populations where the prevalence of smoking was approximately evenly distributed in both sexes, whereas no sex difference in incidence or a male preponderance was found in populations where relatively fewer women smoked.[92, 93] A similar difference in susceptibility to the harmful effects of smoking have been noted between ethnic groups, which may help to explain the differences in incidence of aSAH between ethnic groups.[94, 95]

Although the pathogenesis of intracranial aneurysms is not fully understood, a major theory is that aneurysm formation is initiated through an inflammatory response following endothelial injury. Jamous et al induced intracranial aneurysms in rats through renal hypertension and common carotid artery ligation, and found that intracranial aneurysm formation starts through endothelial injury, leading to the formation of an inflammatory zone, followed by a partial tear or defect in the inflammatory zone.[96] Expansion of this defect forms the nidus of the intracranial aneurysm. Hemodynamic stress is considered an important contributor to the initial endothelial injury, as aneurysms usually arise where arteries are exposed to the maximum wall shear stress [51, 52]. Studies have found that abnormal wall shear stress alters the balance of endothelial cell–derived mediators involved in the regulation of vascular tone, hemostasis, vascular cell growth, and matrix production.[97] Hemodynamic forces are considered a factor contributing to focal degeneration of the internal elastic lamina and subsequent aneurysm development.[54]

The mechanisms of how cigarette smoking augments the formation of intracranial aneurysms are not well understood. However, smoking affects both hemodynamic forces and tissue inflammation. Smoking augments hemodynamic forces through vessel diameter and blood viscosity. Nicotine activates the sympathetic nervous system, with subsequent vasoconstriction and increased pulse rate.[98] Compared to non-smokers, smokers have reversible increases in blood viscosity, due to increased hematocrit and plasma fibrinogen levels.[99-101] The subsequent effect on hemodynamic forces has recently been demonstrated through computational fluid dynamics simulations.[102] The effect of smoking on tissue inflammation may be mediated by direct effect of tobacco combustion products on the vessel wall or through increased blood concentration of white blood cells and increased monocyte-endothelial cell adhesion.[103-105] One might speculate that sex differences may be augmented by hormonal factors and the physiological changes the female vasculature undergo during menarche, pregnancy, and menopause.[106] However, Paper III did not find that age at menarche, parity, menopause status or the use of hormone replacement therapy were significant risk predictors of aSAH in women or influenced the effect of smoking on the risk of aSAH in women.

The risk for aSAH is increased in relatives of patients with aSAH.[107] Further, a gene-environment interaction with smoking for aSAH has been suggested. A case-control study of 339 aSAH cases and 1,016 matched controls found that compared to non-smokers, the odds ratio (OR) for current smokers without a family history of aSAH was 3.1 (95% CI: 2.2-4.4), and for current smokers with a family history of aSAH 6.4 (3.1-13.2).[108] The present thesis

did not find that a family history of stroke (hemorrhagic and ischemic) influenced the differential effect of smoking on the risk of aSAH in women and men. One might also speculate whether there are differences in risk factors according to the site of intracranial aneurysms, although this has not been proven.[109, 110]

7.4.3 A new hypothesis: local sex differences in the intracranial arteries?

Paper IV explores a new hypothesis for the gender gap in aSAH: local sex differences in the hemodynamic forces acting upon the wall of the different intracranial arteries. The hypothesis is motivated by the empirical observation that sex differences in the frequency of intracranial aneurysms vary with the different intracranial arteries. In a study by Horiuchi et al of 2577 patients treated surgically for aSAH, the female-to-male ratio of ruptured intracranial aneurysms varied from 1.1:1 for the anterior cerebral artery, 2.1:1 for the internal carotid artery, 1.5:1 for the middle cerebral artery, and 1.3:1 for the basilar artery.[48] Similar findings have been reported by other studies.[43, 49, 50] This uneven sex distribution suggests that a physiologic factor may be involved — a local sex difference in the different intracranial arteries and not only systemic sex differences.

Paper IV found that the diameter of the middle cerebral and carotid artery was smaller in females than males. The average diameters were used to create idealized, averaged bifurcations of the middle cerebral and internal carotid artery for females and males. Computational fluid dynamics simulations revealed higher wall shear stress in the female middle cerebral (19%) and internal carotid (50%) artery bifurcations compared with the male bifurcations. The findings of Paper IV, that the female arterial wall is exposed to higher hemodynamic forces than the male arterial wall, is caused by females having smaller intracranial arteries and increased blood flow velocity compared with males. Given a constant mass flow, a smaller vessel diameter causes increased blood flow velocity and higher wall shear stress. Sex differences in wall shear stress at the apex of the bifurcation are likely caused by sex asymmetries in the diameters of the parent vessels and branches. The small sample size in Paper IV precluded statistical analyses of this. However, the computational models assessed all factors caused by differences in the vessel diameters of females and males. The simulations showed that the sum of all sex differences in the vessel diameters caused higher wall shear stress at the apex of the female intracranial bifurcation. It is possible that sex differences in bifurcation geometry and blood flow velocity, causing higher shear forces in female intracranial artery bifurcations, over decades may result in more aneurysms in females than in males. This may be augmented by the physiologic changes the female

cardiovascular system undergoes during menopause, such as spontaneous increase in proinflammatory molecules,[111] increased vascular constrictor factors and myointimal hyperplasia, as well as decreased plasma volume and cardiac output.[112]

7.5 Directions for future research

Knowledge about the incidence and risk factors for aSAH is important for public health planning, education, and identifying patients with increased risk for the disease. The internal validity of incidence studies based on hospital discharge registries without person identifiers is limited due to possible measurement errors. Future studies should therefore be conducted using validated, person identifiable registries. The political decision in 2007 to include person-identified medical data in the Norwegian Patient Register, and in 2010 to establish a Norwegian registry of cardiovascular diseases will enable this in the future.

Knowledge about the etiological factors that cause the female preponderance of aSAH is important as it might give valuable insight into the pathogenesis of aSAH, and if reversible causes are found, health interventions may reduce the burden of aSAH in women. The present thesis suggests a health intervention program focused on reducing daily smoking in women at risk for aSAH. Future research might evaluate such health intervention, although the low incidence of aSAH would require a large number of participants.

The effect of body mass index, hormonal and reproductive factors should be further addressed in a population-based cohort study. The fact that the sex differences in the prevalence of aSAH are not constant, but vary with the intracranial arteries should lead to examinations of potential sex differences in the different intracranial arteries. The hypothesis put forward in Paper IV, that sex differences in the anatomy of the intracranial arteries contribute to the female preponderance of intracranial aneurysms, should be examined in a properly statistically powered, prospective trial using advanced radiological imaging of the intracranial vasculature in healthy volunteers. This information may be available from for instance the third survey of the HUNT study (performed between 2006 and 2008), which included cerebral magnetic resonance angiography of healthy volunteers. Further, differences in risk factors for aSAH according to the site of intracranial aneurysms, adjusted for age and sex, should be investigated as this may yield knowledge on the etiology of aneurysm formation.

8 CONCLUSIONS

Incidence of aSAH in Norway decreased from 1999 to 2007, with significant regional variations indicating an increasing gradient from south to north.

Overweight (body mass index 25.0-29.9) was inversely associated with the risk of aSAH, compared to normal weight (body mass index 18.5-24.9). No overall association between HDL, LDL, total serum cholesterol, triglycerides, and the risk for aSAH was observed.

Current cigarette smoking is a stronger risk factor for aSAH in women than in men, compared to never smoking. No statistically significant sex differences with respect to systolic blood pressure and alcohol consumption were observed.

Sex differences in arterial size and blood flow velocity result in higher hemodynamic forces acting upon the female arterial wall. This is a new hypothesis that may partially explain why intracranial aneurysms and SAH are more likely to occur in females than males.

9 REFERENCES

1. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet 2007;369:306-18.
2. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809-17.
3. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 2009;8:635-42.
4. Greebe P, Rinkel GJ. Life expectancy after perimesencephalic subarachnoid hemorrhage. Stroke 2007;38:1222-4.
5. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry 2007;78:1365-72.
6. ACROSS. Epidemiology of aneurysmal subarachnoid hemorrhage in Australia and New Zealand: incidence and case fatality from the Australasian Cooperative Research on Subarachnoid Hemorrhage Study. Stroke 2000;31:1843-50.
7. Eden SV, Meurer WJ, Sanchez BN, et al. Gender and ethnic differences in subarachnoid hemorrhage. Neurology 2008;71:731-5.
8. Koffijberg H, Buskens E, Granath F, et al. Subarachnoid haemorrhage in Sweden 1987-2002: regional incidence and case fatality rates. J Neurol Neurosurg Psychiatry 2008;79:294-9.
9. Ellekjaer H, Holmen J, Indredavik B, Terent A. Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate. Stroke 1997;28:2180-4.
10. Isaksen J, Egge A, Waterloo K, Romner B, Ingebrigtsen T. Risk factors for aneurysmal subarachnoid haemorrhage: the Tromso study. J Neurol Neurosurg Psychiatry 2002;73:185-7.
11. Njølstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. A 14-year follow-up of the Finnmark Study. Circulation 1996;94:2877-82.
12. Sandvei MS, Romundstad PR, Muller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. Stroke 2009;40:1958-62.
13. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. Stroke 1996;27:625-9.
14. Islam MS, Anderson CS, Hankey GJ, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. Stroke 2008;39:776-82.
15. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-33.
16. Vibo R, Korv J, Roose M. The Third Stroke Registry in Tartu, Estonia: decline of stroke incidence and 28-day case-fatality rate since 1991. Stroke 2005;36:2544-8.
17. Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 2005;36:2773-80.
18. Knekt P, Reunanen A, Aho K, et al. Risk factors for subarachnoid hemorrhage in a longitudinal population study. J Clin Epidemiol 1991;44:933-9.

19. Mhurchu CN, Anderson C, Jamrozik K, Hankey G, Dunbabin D. Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: an international population-based, case-control study. Stroke 2001;32:606-12.
20. Broderick JP, Viscoli CM, Brott T, et al. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stroke 2003;34:1375-81.
21. Tokuda Y, Stein GH. Serum lipids as protective factors for subarachnoid hemorrhage. J Clin Neurosci 2005;12:538-41.
22. Ohkuma H, Tabata H, Suzuki S, Islam MS. Risk factors for aneurysmal subarachnoid hemorrhage in Aomori, Japan. Stroke 2003;34:96-100.
23. Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke 2002;33:1321-6.
24. Feigin V, Parag V, Lawes CM, et al. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke 2005;36:1360-5.
25. Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. Lancet 2001;357:922-5.
26. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. N Engl J Med 1991;325:756-62.
27. Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation and decreased risk of stroke in women. JAMA 1993;269:232-6.
28. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med 1988;319:267-73.
29. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. Stroke 1989;20:1460-5.
30. Iso H, Jacobs DR, Jr., Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med 1989;320:904-10.
31. Kurth T, Kase CS, Berger K, Schaeffner ES, Buring JE, Gaziano JM. Smoking and the risk of hemorrhagic stroke in men. Stroke 2003;34:1151-5.
32. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke. The Honolulu Heart Program. JAMA 1986;255:2311-4.
33. Klatsky AL, Armstrong MA, Friedman GD, Sidney S. Alcohol drinking and risk of hemorrhagic stroke. Neuroepidemiology 2002;21:115-22.
34. Sankai T, Iso H, Shimamoto T, et al. Prospective study on alcohol intake and risk of subarachnoid hemorrhage among Japanese men and women. Alcohol Clin Exp Res 2000;24:386-9.
35. Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. Stroke 1993;24:639-46.
36. Okamoto K, Horisawa R, Ohno Y. The relationships of gender, cigarette smoking, and hypertension with the risk of aneurysmal subarachnoid hemorrhage: a case-control study in Nagoya, Japan. Ann Epidemiol 2005;15:744-8.
37. Anderson CS, Feigin V, Bennett D, Lin RB, Hankey G, Jamrozik K. Active and passive smoking and the risk of subarachnoid hemorrhage: an international population-based case-control study. Stroke 2004;35:633-7.
38. Longstreth WT, Jr., Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. Stroke 1992;23:1242-9.

39. Fogelholm R, Murros K. Cigarette smoking and subarachnoid haemorrhage: a population-based case-control study. J Neurol Neurosurg Psychiatry 1987;50:78-80.
40. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. Stroke 1986;17:831-5.
41. Inagawa T, Hirano A. Autopsy study of unruptured incidental intracranial aneurysms. Surg Neurol 1990;34:361-5.
42. Harthun NL. Current issues in the treatment of women with abdominal aortic aneurysm. Gend Med 2008;5:36-43.
43. Kongable GL, Lanzino G, Germanson TP, et al. Gender-related differences in aneurysmal subarachnoid hemorrhage. J Neurosurg 1996;84:43-8.
44. Johnston SC, Colford JM, Jr., Gress DR. Oral contraceptives and the risk of subarachnoid hemorrhage: a meta-analysis. Neurology 1998;51:411-8.
45. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study. Ann Intern Med 1994;121:168-73.
46. Falkeborn M, Persson I, Terent A, Adami HO, Lithell H, Bergstrom R. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. Arch Intern Med 1993;153:1201-9.
47. Pedersen AT, Lidegaard O, Kreiner S, Ottesen B. Hormone replacement therapy and risk of non-fatal stroke. Lancet 1997;350:1277-83.
48. Horiuchi T, Tanaka Y, Hongo K. Sex-related differences in patients treated surgically for aneurysmal subarachnoid hemorrhage. Neurol Med Chir (Tokyo) 2006;46:328-32.
49. Kassell NF, Drake CG. Timing of aneurysm surgery. Neurosurgery 1982;10:514-9.
50. Rosenorn J, Eskesen V, Schmidt K, et al. Clinical features and outcome in 1076 patients with ruptured intracranial saccular aneurysms: a prospective consecutive study. Br J Neurosurg 1987;1:33-45.
51. Alnaes MS, Isaksen J, Mardal KA, Romner B, Morgan MK, Ingebrigtsen T. Computation of hemodynamics in the circle of Willis. Stroke 2007;38:2500-5.
52. Wang Z, Kolega J, Hoi Y, et al. Molecular alterations associated with aneurysmal remodeling are localized in the high hemodynamic stress region of a created carotid bifurcation. Neurosurgery 2009;65:169-77; discussion 77-8.
53. Jou LD, Lee DH, Morsi H, Mawad ME. Wall shear stress on ruptured and unruptured intracranial aneurysms at the internal carotid artery. AJNR Am J Neuroradiol 2008;29:1761-7.
54. Ferguson GG. Physical factors in the initiation, growth, and rupture of human intracranial saccular aneurysms. J Neurosurg 1972;37:666-77.
55. Meng H, Wang Z, Hoi Y, et al. Complex hemodynamics at the apex of an arterial bifurcation induces vascular remodeling resembling cerebral aneurysm initiation. Stroke 2007;38:1924-31.
56. Available at: http://tromsoundersokelsen.uit.no/tromso/. Accessed June 16th, 2011. English translations of the questionnaires: http://www.biomedcentral.com/1472-6823/10/21.
57. Available at: http://www.ntnu.no/hunt/english/. Accessed June 16th, 2011. English translations of the questionnaires: http://www.ntnu.edu/hunt/data/que.
58. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575-9.
59. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology 1992;3:452-6.
60. Li R, Chambless L. Test for additive interaction in proportional hazards models. Ann Epidemiol 2007;17:227-36.

61. Ingebrigtsen T, Morgan MK, Faulder K, Ingebrigtsen L, Sparr T, Schirmer H. Bifurcation geometry and the presence of cerebral artery aneurysms. J Neurosurg 2004;101:108-13.
62. Krejza J, Szydlik P, Liebeskind DS, et al. Age and sex variability and normal reference values for the V(MCA)/V(ICA) index. Am J Neuroradiol 2005;26:730-5.
63. Alastruey J, Parker KH, Peiro J, Byrd SM, Sherwin SJ. Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. J Biomech 2007;40:1794-805.
64. Témam R. Sur l'approximation de la solution des équations de Navier-Stokes par la méthode des pas fractionnaires. Archive for Rational Mechanics and Analysis 1969;33:377-85.
65. Chorin A. The numerical solution of the Navier-Stokes equations. Mathematics of Computation 1968;22:745-62.
66. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
67. Merlo J, Lindblad U, Pessah-Rasmussen H, et al. Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. Eur J Epidemiol 2000;16:235-43.
68. Stegmayr B, Eriksson M, Asplund K. Declining mortality from subarachnoid hemorrhage: changes in incidence and case fatality from 1985 through 2000. Stroke 2004;35:2059-63.
69. Huang J, van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. Neurosurgery 2002;51:1101-5; discussion 5-7.
70. Inamasu J, Miyatake S, Tomioka H, et al. Subarachnoid haemorrhage as a cause of out-of-hospital cardiac arrest: a prospective computed tomography study. Resuscitation 2009;80:977-80.
71. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978;1:795-7.
72. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? JAMA 1988;259:225-8.
73. Bookstein L, Gidding SS, Donovan M, Smith FA. Day-to-day variability of serum cholesterol, triglyceride, and high-density lipoprotein cholesterol levels. Impact on the assessment of risk according to the National Cholesterol Education Program guidelines. Arch Intern Med 1990;150:1653-7.
74. Larsson H, Persson S, Hedner P, Odeberg H, Gustafson A. Studies on blood viscosity during the menstrual cycle and in the postmenopausal period in healthy women. Acta Obstet Gynecol Scand 1989;68:483-6.
75. Rosenson RS, McCormick A, Uretz EF. Distribution of blood viscosity values and biochemical correlates in healthy adults. Clin Chem 1996;42:1189-95.
76. Lund M, Lindbak RL. Norwegian Tobacco Statistics 1973-2006. Oslo: SIRUS; 2007.
77. Tverdal A. [Significant decline in blood pressure levels after 1996--fact or artefact?]. Tidsskr Nor Laegeforen 2001;121:1821-5.
78. Njølstad I, Arnesen E, Lund-Larsen PG. Cardiovascular diseases and diabetes mellitus in different ethnic groups: the Finnmark study. Epidemiology 1998;9:550-6.
79. National health screening service. The Cardiovascular disease study in Norwegian counties : Results from second screening. Oslo: National Health Screening Service; 1988.

80. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355-69.
81. Despres JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B. HDL-cholesterol as a marker of coronary heart disease risk: the Quebec cardiovascular study. Atherosclerosis 2000;153:263-72.
82. Miller NE, Thelle DS, Forde OH, Mjos OD. The Tromso heart-study. High-density lipoprotein and coronary heart-disease: a prospective case-control study. Lancet 1977;1:965-8.
83. Tanne D, Yaari S, Goldbourt U. High-density lipoprotein cholesterol and risk of ischemic stroke mortality. A 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. Stroke 1997;28:83-7.
84. Chirovsky DR, Fedirko V, Cui Y, Sazonov V, Barter P. Prospective studies on the relationship between high-density lipoprotein cholesterol and cardiovascular risk: a systematic review. Eur J Cardiovasc Prev Rehabil 2009;16:404-23.
85. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829-39.
86. Okamoto K, Horisawa R, Kawamura T, et al. Menstrual and reproductive factors for subarachnoid hemorrhage risk in women: a case-control study in nagoya, Japan. Stroke 2001;32:2841-4.
87. Gaist D, Pedersen L, Cnattingius S, Sorensen HT. Parity and risk of subarachnoid hemorrhage in women: a nested case-control study based on national Swedish registries. Stroke 2004;35:28-32.
88. Yang CY, Chang CC, Kuo HW, Chiu HF. Parity and risk of death from subarachnoid hemorrhage in women: evidence from a cohort in Taiwan. Neurology 2006;67:514-5.
89. Vessey MP, Villard-Mackintosh L, McPherson K, Yeates D. Mortality among oral contraceptive users: 20 year follow up of women in a cohort study. BMJ 1989;299:1487-91.
90. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1996;348:505-10.
91. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med 1996;335:453-61.
92. Ingall T, Asplund K, Mahonen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke 2000;31:1054-61.
93. Molarius A, Parsons RW, Dobson AJ, et al. Trends in cigarette smoking in 36 populations from the early 1980s to the mid-1990s: findings from the WHO MONICA Project. Am J Public Health 2001;91:206-12.
94. Zacharia BE, Grobelny BT, Komotar RJ, Sander Connolly E, Mocco J. The influence of race on outcome following subarachnoid hemorrhage. J Clin Neurosci 2010;17:34-7.
95. Zacharia BE, Hickman ZL, Grobelny BT, et al. Epidemiology of aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am 2010;21:221-33.
96. Jamous MA, Nagahiro S, Kitazato KT, et al. Endothelial injury and inflammatory response induced by hemodynamic changes preceding intracranial aneurysm formation: experimental study in rats. J Neurosurg 2007;107:405-11.
97. Li YS, Haga JH, Chien S. Molecular basis of the effects of shear stress on vascular endothelial cells. J Biomech 2005;38:1949-71.

98. Haass M, Kubler W. Nicotine and sympathetic neurotransmission. Cardiovasc Drugs Ther 1997;10:657-65.
99. Ernst E, Matrai A, Schmolzl C, Magyarosy I. Dose-effect relationship between smoking and blood rheology. Br J Haematol 1987;65:485-7.
100. Lowe GD. Blood viscosity and cardiovascular disease. Thromb Haemost 1992;67:494-8.
101. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. Eur Heart J 1999;20:344-53.
102. Singh PK, Marzo A, Howard B, et al. Effects of smoking and hypertension on wall shear stress and oscillatory shear index at the site of intracranial aneurysm formation. Clin Neurol Neurosurg 2010;112:306-13.
103. Sunyer J, Munoz A, Peng Y, et al. Longitudinal relation between smoking and white blood cells. Am J Epidemiol 1996;144:734-41.
104. Kalra VK, Ying Y, Deemer K, Natarajan R, Nadler JL, Coates TD. Mechanism of cigarette smoke condensate induced adhesion of human monocytes to cultured endothelial cells. J Cell Physiol 1994;160:154-62.
105. Dovgan PS, Edwards JD, Zhan X, Wilde M, Agrawal DK. Cigarette smoking increases monocyte adherence to cultured endothelial cell monolayer. Biochem Biophys Res Commun 1994;203:929-34.
106. Wildman RP, Colvin AB, Powell LH, et al. Associations of endogenous sex hormones with the vasculature in menopausal women: the Study of Women's Health Across the Nation (SWAN). Menopause 2008;15:414-21.
107. Bor AS, Rinkel GJ, Adami J, et al. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. Brain 2008;131:2662-5.
108. Woo D, Khoury J, Haverbusch MM, et al. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. Neurology 2009;72:69-72.
109. Lindner SH, Bor AS, Rinkel GJ. Differences in risk factors according to the site of intracranial aneurysms. J Neurol Neurosurg Psychiatry 2010;81:116-8.
110. Nakaoka H, Takahashi T, Akiyama K, et al. Differential effects of chromosome 9p21 variation on subphenotypes of intracranial aneurysm: site distribution. Stroke 2010;41:1593-8.
111. Pfeilschifter J, Koditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. Endocr Rev 2002;23:90-119.
112. Moulton A. Cardiovascular changes in menopause. In: Selfer D, Kennard E, eds. Contemporary Endocrinology: Menopause : Endocrinology and Management. Totowa, N.J.: Humana Press; 1999:35-52.

10 PAPERS I-IV

Paper I

Paper II

Paper III

Paper IV

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