Marie Søfteland Sandvei

Incidence, mortality, and risk factors for aneurysmal subarachnoid hemorrhage

Prospective analyzes of the HUNT and Tromsø studies

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
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Forekomst, dødelighet og risikofaktorer for subaraknoidalblødning

Prospektive analyser av HUNT og Tromsøundersøkelsen

Subaraknoidalblødning (SAB) utgjør omtrent 1-7 % av alle hjerneslag. Forekomsten har blitt estimert til å ligge mellom 7 og 10 per 100.000 personår. Det virker som forekomsten er relativt stabil over tid og mellom land, unntatt i Finland og Japan, hvor forekomsten er høyere. Noen studier har antydet at forekomsten har gått noe ned de senere tiår, mens sykeligheten og dødeligheten etter SAB fortsatt er høy. Siden blødningen er relativt sjelden, har det vært vanskelig å påvise risikofaktorer i prospektive studier, men røyking, høyt blodtrykk, høyt alkoholinntak og det å være kvinne er kjent å øke risikoen. Det er mer usikkerhet vedrørende kroppsmasseindeks (KMI) og serumlipider. Det er også lite kunnskap om hvilke kjennetegn ved pasientene som fører til økt risiko for død etter SAB.

Vi registrerte alle som fikk SAB etter deltakelse i befolkningsundersøkelsene HUNT 1 og 2 (1984-86 og 1995-97) og Tromsø 3 og 4 (1985-87 og 1994-95) ved hjelp av diagnoseregistrene på sykehusene som populasjonene sogner til og Dødsårsaksregisteret. Vi identifiserte til sammen 214 pasienter. Vi estimerte forekomst og overlevelse, og studerte effekten av risikofaktorer ved hjelp av Cox og Poisson regresjonsanalyser. De fire artiklene omhandler forekomst og dødelighet av SAB (artikkel I, HUNT 1 og 2 og Tromsø 3 og 4), risikofaktorer for SAB (artikkel II, HUNT 1), KMI og serum lipider og risiko for SAB (artikkel III, HUNT 2 og Tromsø 4) og kjønnsforskjeller i risikofaktorer for SAB (artikkel IV, HUNT 2 og Tromsø 4).

Vi fant at forekomsten av SAB fra 1984 til 2007 var 10,3 per 100.000 personår, 13,3 hos kvinner og 7,1 hos menn. Insidensen kan ha økt litt siden 1984, noe som kan skyldes endring i diagnostikk, men den har vært stabil siden 1995. 30 dagers letalitet var 36 % og tenderte til å øke med alder, men forble stabil over de 23 årene i oppfølgningen.

Vi fant en lineær og positiv sammenheng mellom systolisk og diastolisk blodtrykk og risiko for SAB. Røykere hadde høyere risiko for SAB enn dem som aldri hadde røykt, og det kan virke som om risikoen assosiert med røyking er høyere hos kvinner enn hos menn. Det kan også virke som om overvekt (KMI 25-29.9) er negativt assosiert med risiko for SAB. Derimot fant vi ingen sammenheng mellom totalkolesterol, HDL-kolesterol eller triglyserider og risiko for SAB i totalpopulasjonen, men hos deltakere under 50 år var HDL-kolesterol negativt assosiert med risiko.

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Table of Contents

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I started my research as a medical research student (forskerlinjestudent) in 2004 at the Department of Circulation and Medical Imaging. I would therefore like to thank my former supervisors, Stig Arild Slørdahl, for introducing me to the world of research, and Brage Høyem Amundsen, for helping me during the first important years.

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Bodø, May 2011
Marie Søfteland Sandvei

List of Papers

The thesis is based on the following four papers. The papers will be referred to by their Roman numbers.

I. Sandvei MS, Mathiesen, EB, Vatten LJ, Müller, TB, Lindekleiv H, Ingebrigtsen Tor, Njølstad I, Wilsgaard T, Løchen M-L, Vik A, Romundstad PR. **Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts 1984-2007.** Neurology *(in press)*.

II. Sandvei MS, Romundstad PR, Müller 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.

III. Sandvei MS, Lindekleiv H, Romundstad PR, Müller TB, Vatten LJ, Ingebrigtsen T, Njølstad I, Mathiesen, EB, Vik, A. **Risk factors for aneurysmal subarachnoid hemorrhage - BMI and serum lipids: 11-year follow-up of the HUNT and the Tromsø Study in Norway.** Acta Neurologica Scandinavica *(in press)*.

IV. 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 aneurysmal subarachnoid hemorrhage: a cohort study.** Neurology. 2011;76:637-43.

Abbreviations

aSAH	Aneurysmal subarachnoid hemorrhage
BMI	Body mass index
CSF	Cerebrospinal fluid
CI	Confidence interval
CT	Computer tomography
DAG	Directed acyclic graph
DIND	Delayed ischemic neurological deficit
DSA	Digital subtraction angiography
ECG	Electrocardiography
ICD	International classification of diseases
ICH	Intracerebral hemorrhage
OC	Oral contraceptive
HDL	High-density lipoprotein
HR	Hazard ratio
HRT	Hormone replacement therapy
HUNT	Nord-Trøndelag Health Study
RERI	Relative excess risk due to interaction
SAH	Subarachnoid hemorrhage
SD	Standard deviation
WHO	World Health Organization

1 Introduction

1.1 Summary

Subarachnoid hemorrhage (SAH) is a type of stroke and accounts for about 1-7 % of all strokes. The annual incidence of SAH has been estimated to range from 7 to 10 per 100,000 person years. The incidence seems to be relatively stable over time and in different countries, except for Finland and Japan, where incidence seems to be higher. There may have been a decrease in the incidence of SAH over recent decades in high-income countries, but compared to the decrease in other types of stroke, the decrease in SAH is likely to be modest. In addition, morbidity and mortality remains high. Due to the low incidene of SAH, it has been difficult to identify risk factors in prospective studies, but smoking, hypertension, excessive alcohol consumption and female sex has consistently been shown to increase the risk of SAH. There is more uncertainty regarding body mass index (BMI) and serum lipids. There is also little knowledge about the pre-ictal characteristics of the patients leading to increased risk of death after SAH.

We identified all patients who experienced an aneurysmal SAH (aSAH) after participating in the population studies HUNT 1 and 2 (1984-86 and 1995-97) and Tromsø 3 and 4 (1985-87 and 1994-95) using the patient administrative databases at the hospitals serving the study populations, and the Cause of Death Registry. We identified 214 patients in total. We estimated the incidence and survival of aSAH, and studied the association of risk factors using Cox and Poisson regression analyses. The four papers concern incidence and mortality from aSAH (paper I, HUNT 1 and 2 and Tromsø 3 and 4), risk factors for aSAH (paper II, HUNT 1), BMI and serum lipids and the risk of aSAH (paper III, HUNT 2 and Tromsø 4), and sex differences in risk factors for aSAH (paper IV, HUNT 2 and Tromsø 4).

We found that the incidence of aSAH from 1984 to 2007 was 10.3 per 100,000 person years, 13.3 in women and 7.1 in men. The incidence may have increased since 1984, which could be due to changes in diagnostics, but the incidence has remained stable since 1995. Thirty days case fatality was 36 % and tended to increase with age, but remained stable during the 23 years of follow up.

We found a positive linear association between systolic and diastolc blood pressure and the risk of aSAH. Smokers had higher risk of aSAH than never smokers, and it may seem that the risk associated with smoking is higher among women than men. Overweight (BMI 25-29.9) may be negatively associated with risk of aSAH. On the other hand, we found no

association between total serum cholesterol, HDL cholesterol or triglycerides with the risk of aSAH in the total population. However, among participants under 50 years of age, HDL cholesterol was negatively associated with risk.

Clarifications

At the beginning of the thesis, I would like to clarify the literature and the terms used in the thesis.

In section 1.2, literature published up to June 2011 have been used, to give an introduction to the current status of research related to the clinical presentation, diagnostics, treatment, complications and follow up of subarachnoid hemorrhage. However, sections 1.3-1.6 introduce the field of incidence, morbidity and mortality of SAH as well as risk factors for SAH, which is the main topic for this thesis. Therefore, in these sections, only papers published in or before 2007 have been included, as this was the status of the field of research before we started our work in 2008.

In this thesis, "aSAH" has been used when describing only aneurysmal subarachnoid hemorrhages (SAH), "SAH" has been used when describing all types of spontaneous SAHs. "SAH" is also used when describing several studies where some deal with only aSAH and some deal with all types of spontaneous SAH.

1.2 Subarachnoid hemorrhage – clinical presentation, diagnostics, treatment, complications and follow up

Subarachnoid hemorrhage (SAH) is a type of stroke and accounts for about 1-7% of all strokes.[1] SAH can occur spontaneously or as a result of trauma. The spontaneous, primary bleedings are usually caused by the rupture of a saccular aneurysm of an artery on the basis of the brain (aSAH; 85%) or a perimecencephalic bleeding (10%).[2, 3] The last 5% consists of a variety of rare conditions (cerebral arteriovenous malformations, arterial dissection etc). Traumatic SAHs are usually excluded from studies of SAH, as it is in this thesis.

Clinical presentation

The cardinal symptom of aSAH is sudden severe headache, often described by the patient as "the worst headache of my life". But headache also accounts for about 1 - 2 % of all emergency department visits, of which very few (about 3 % or less) are SAHs.[4, 5] Even in the emergency department, the positive predictive value of almost instantaneous severe headache

is only about 39 %.[6] Other symptoms of aSAH include symptoms of meningism; nausea, vomiting, photophobia and neck stiffness in addition to headache. Loss of consciousness is also common, and can be transient at onset (in about 50 % of all cases) or persisting. Epileptic seizures (in about 6 %), and focal neurological symptoms such as dysphasia, sensory or motor symptoms are other symptoms of SAH.[7] Sudden death or death before the patient reaches medical attention occurs in about 10 %.[8-10] A recent study proposed that any alert patient with an acute non-traumatic headache reaching maximum intensity within one hour and with one or more of these seven findings; age ≥ 40 years, witnessed loss of consciousness, complaint of neck pain or stiffness, onset with exertion, arrival by ambulance, vomiting, diastolic blood pressure ≥ 100 mmHg or systolic blood pressure ≥ 160 mmHg, should undergo rapid and thorough investigation to rule out aSAH.[11]

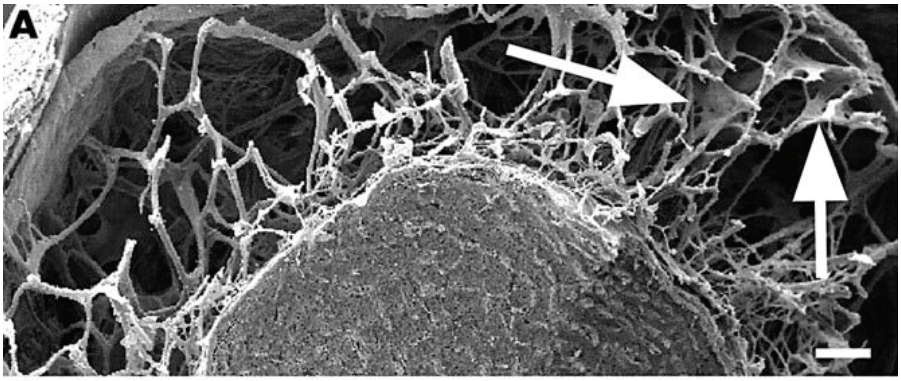

Figure 1. Scanning electron microscopy overview of the subarachnoid space in the bulbar segment. (Reprinted from British Journal of Ophthalmology, Killer HE et al, vol 87, 2003[12] with permission from Br J Ophtalmol)

Pathological aspects

The disease is called subarachnoid hemorrhage because the bleeding is located under ("sub") the middle of the meninges; the arachnoid mater, and thus fills the subarachnoid space with blood. The arachnoid mater was named because of its spider web-like appearance. This is shown in Figure 1, which is the scanning electron microscopy appearance of the arachnoid mater in the subarachnoid space around the optic nerve.[12] The intracerebral arteries at the base of the brain, where intracranial aneurysms usually occur (as shown in Figure 2), run in the subarachnoid space. Therefore, the blood usually enters the subarachnoid space when the aneurysm ruptures. However, intracranial aneurysms can also rupture into the brain tissue,

mimicking primary intracerebral hemorrhage, or into the ventricular system, and sometimes even into the subdural space.[13, 14]

The process of aneurysm origin, growth and rupture is not well understood. Aneurysms usually occur at sites with increased wall shear stress (WSS), as in the distal carina of arterial bifurcations.[13, 15] The most common sites for aneurysms are shown in Figure 2.[13] Wall pressures and WSS seem to be increased when there are deviations from normal anatomy in the circle of Willis.[16] In animal models, intracranial aneurysms have been induced by ligation of one of the common carotid arteries, leading to increased wall pressures and WSS in the contralateral arteries. In addition, hypertension has been induced by renal infarction.[17, 18] It has been proposed that the development of aneurysms is initiated by endothelial damage and disruption of the internal elastic lamina due to increased WSS.[17] The process may further include local inflammation and destruction of the vessel wall components by macrophages, proteolytic enzymes, and cytokines including interleukins, interferon-gamma and tumor necrosis factor-alpha. This leads to expansion of the defect, and the formation of a saccular aneurysm.[17, 19] Weaknesses in the components of the arterial walls probably increases the risk of intracranial aneurysms, as patients with inherited connective tissue disorders are at increased risk.[20]

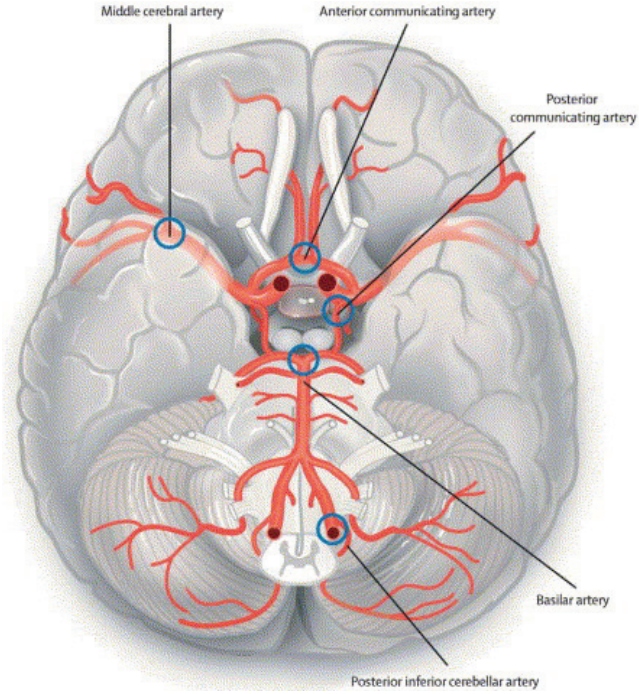

Figure 2. Base of the brain, with most common sites of aneurysms (circles). (Reprinted from Lancet, van Gijn J et al, volume 369, 2007[13] with permission from the Lancet)

Diagnostics

The diagnosis of SAH is usually established by computer tomography (CT), as seen in Figure 3. CT scan is the first investigation that should be performed when SAH is suspected, and should be performed as soon as possible after the onset of headache.[13] If a SAH is suspected and the CT scan is normal, a lumbar puncture should be performed.[21, 22] SAH is present if the supernatant of the cerebrospinal fluid (CSF) is yellow (xanthochromous) after centrifugation, as analyzed by spectrophotometry. The yellow color is caused by bilirubin, which is present due to degradation of hemoglobin. Bilirubin is only synthesized in vivo. Therefore, if the blood stained CSF (taken more than 6 or preferably 12 hours after onset of symptoms) turns clear after centrifugation, it is caused by a traumatic tap and not by a SAH.[2, 14]

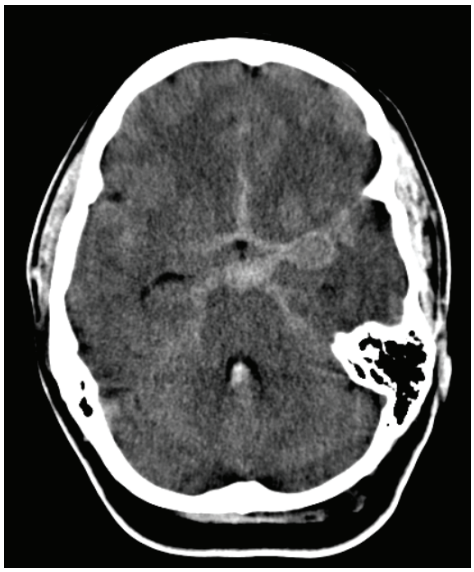

Figure 3. Conventional CT image of a subarachnoid hemorrhage. The subarachnoid blood is seen as white in the basal cisterns and the aneurysm is also visible.

To identify the cause of SAH, CT angiography is usually performed (Figure 4). Its sensitivity for detecting aneurysms with a diameter of more than 3 mm, has been shown to be 96%, and less for smaller aneurysms,[23] and may have improved with advances in CT technology.[24] In case of a negative CT angiography and a strong suspicion of SAH, four vessel catheter digital subtraction angiography (DSA) should be performed, as DSA is considered the gold standard for imaging intracranial aneurysms.[25]

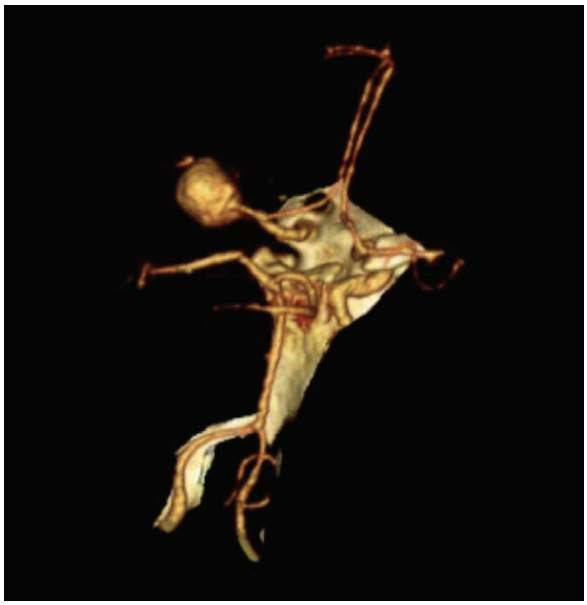

Figure 4. Reconstruction of CT angiography showing a large aneurysm in the left middle cerebral artery.

Treatment

Angiography is not only used to identify aneurysms as causes of SAH, but also to plan the treatment. Treating the aneurysm is important to prevent rebleeding, which is a serious complication of aSAH. The traditional method of treatment has been neurosurgical clipping of the aneurysm. This was first performed by the American neurosurgeon Walter E. Dandy in 1937.[26] In short, the procedure includes a craniotomy under general anesthesia. The neurosurgeon gently retracts the brain and dissects the subarachnoid space to locate the aneurysm, and then places a titanium clip around the neck of the aneurysm. The clip stays there permanently and excludes the aneurysm from the circulation, thus preventing it from rebleeding. Numerous advances in the management and surgical techniques, including better microsurgical techniques and instruments, introduction of the operation microscope, advances in anesthetics and intensive-care medicine and better diagnostic facilities, have reduced the risk associated with this procedure.[27] But still, the clinical condition of several patients is judged too bad to undergo surgical treatment after aSAH, aneurysms of the posterior circulation and closer to the midline can be harder to treat by neurosurgical clipping, and neurosurgical clipping has complications.[28, 29]

In 1990, a new treatment modality for intracranial aneurysms, endovascular coiling, was introduced for clinical use.[30] In short, a catheter is led from the femoral artery to the parent artery of the aneurysm, guided by DSA. Thereafter, detachable platinum coils are introduced into the aneurysm sac. Thrombosis occurs when the coils react with blood, and circulation in the aneurysm is stopped, thereby preventing rebleeding. Endovascular coiling of intracranial aneurysms has been widely used since 1995, and it was shown to give better outcome than neurosurgical clipping in the International Subarachnoid Aneurysm Trial.[27] Coiling is therefore now usually preferred if allowed by the anatomy and position of the aneurysm and its relation to adjoining arteries.[13, 31] However, there is increased risk of rebleeding after coiling, and several authors have raised concerns about the ISAT, so the debate about the ideal treatment for intracranial aneurysms is still ongoing.[32]

Complications

In addition to coiling or clipping of the ruptured aneurysm, the aSAH patients require specialized intensive medical treatment. The three main neurological complications in patients who survive the initial hours after aSAH are rebleeing, delayed ischemic neurologic deficit (DIND, also referred to as clinical or symptomatic vasospasm and delayed cerebral ischemia), and hydrocephalus.[13]

Most deaths occur within the first three weeks after aSAH. Apart from the initial bleeding, rebleeding is the event that causes most deaths from aSAH; after rebleeding, 75 % of patients die or remain dependent on others for activities of daily living.[33] For untreated, ruptured aneurysms, the risk of rebleeding is 3 to 4 % - and possibly higher - during the first 24 hours, and 1 to 2 % per day during the first month. The long term risk is 3 % per year after 3 months.[22, 34, 35]

To prevent rebleeding, the aneurysm should be occluded, and this is now usually done early (within 3 days after ictus).[7, 13, 22, 36] Early treatment allows for better and more aggressive treatment and prevention of symptomatic vasospasm and DIND, but on the other hand, early operation may be a risk factor for DIND.[37] Blood pressure should be monitored to maintain cerebral perfusion pressure and prevent ischemic stroke.[22] A short course of fibrinolytic agents, such as tranexamic acid, may be helpful immediately after after aSAH to prevent ultraearly rebleeding, followed by early treatment of the aneurysm.[22, 38, 39]

DIND occurs in about 30 % of all patients, most often between days 4 and 10 after ictus,[37] and is a significant source of morbidity after aSAH.[40, 41] Thick clots of subarachnoid blood, especially when completely filling any cistern or fissure, are strong predictors for

DIND.[42, 43] DIND has traditionally been thought to be caused by vasospasm in the proximal intracranial vessels, which is seen as constriction on angiography and increased pulsatility on transcranial Doppler examination.[41, 44] Therefore, studies have often used angiographic vasospasm as a surrogate end point for functional outcome. However, more recent literature has reported an imperfect association between angiographic vasospasm and DIND.[41, 44, 45] It has been suggested that other mechanisms of injury, such as microvascular dysfunction and complex neuronal - glial interactions may play a role.[40] However, the etiology of both angiographic vasospasm and DIND is still poorly understood.[41] Nitric oxide, endothelin-I, lipid peroxidation, and bilirubin oxidative products may play a part, but the results have been conflicting and the end points in the studies have differed,[41] thus complicating comparison between studies.

Although relatively little is known about the pathogenesis of DIND, different treatment strategies have been tried to prevent it.[22, 40, 41] In some randomized controlled trials, endothelin receptor antagonists and lipid peroxidation inhibitors have decreased the incidence of vasospasm and/or DIND, but not improved outcome.[41, 46] Also, clinical trials investigating the effect of magnesium have been inconclusive.[40] Studies that have evaluated the effect of statins to prevent DIND, have shown a decrease in radiographic vasospam. However, there are limited and conflicting results regarding their effect on outcome.[40, 47-49] At St Olavs Hospital, Trondheim University Hospital, statins are used in patients with increased risk of DIND. However, the only drug that has been shown to improve outcome after aSAH, is the dihydro-pyridine-type calcium channel blocker nimodipin, though its precise mechanism of action, except for its cerebral antivasoconstrictive and antiischemic effect, remains unclear.[40, 50, 51] Nimodipin is therefore used routinely after aSAH. However, it has not been shown to have any effect on angiographic vasospam. Interestingly, the similar L-type calcium channel blocker nimocardipin was found to reduce the incidence of angiographic vasospasm, but had no impact on outcome after three months.[52]

Hemodynamic therapy, also called triple-H therapy (including hypervolemia, hemodilution and hypertension), may also be used prophylactically and as treatment for vasospasm and DIND. The rationale for the triple-H therapy is that the autoregulation of cerebral perfusion following intracranial hemorrhage is impaired.[2, 53] Cerebral blood flow therefore varies directly with systemic blood pressure, and can be increased by increasing perfusion pressure (through hypertension and hypervolemia) or decreasing viscosity (through hemodilution), according to Hagen-Poiseuille law.[41] However, recent studies have found that hypertension alone may improve cerebral perfusion and that there is no additional effect of

hypervolemic and hemodilutional therapy, although randomized controlled trials are needed.[41, 54] The incidence of DIND did not differ between groups randomly assigned to normovolemic or hypervolemic therapy in the two randomized clinical trials that have been performed to my knowledge.[55, 56] In addition, the risk of deliberately increasing blood pressure and blood volume includes rebleeding from an untreated aneurysm, increased cerebral edema or hemorrhagic transformation in areas of infarction, in addition to pulmonary edema, myocardial infarction and congestive heart failure.[55, 57] The use of triple-H therapy as prophylaxis is therefore controversial, but it is used as treatment for established vasospasm.[22, 41]

Acute hydrocephalus is another well-documented complication after aSAH, and is reported to occur in about 20-30 % of patients.[22] The standard care for this condition is external ventricular drainage, which usually leads to rapid improvement.[58] However, rebleeding and ventriculitis are possible complications, although the reports about increased risk of rebleeding from untreated aneurysms are conflicting.[22, 58, 59]

In addition to the neurological complications, aSAH patients may experience several systemic complications, such as severe hypertension, hypoxemia, electrolyte disturbances, and electrocardiographic (ECG) changes.[13] These ECG changes may mimic acute myocardial infarction and may thus lead to erroneous examinations and treatment.[60] In an echocardiographic study performed in SAH patients at St Olavs Hospital, Trondheim University Hospital, we found indices of a hyperdynamic and hypervolemic circulation shortly after ictus as compared to one week later and compared to healthy controls, but we found no signs of reduced global left ventricular function.[61]

1.3 Incidence of aneurysmal subarachnoid hemorrhage

Several studies have evaluated the incidence of SAH in different countries and time periods. The annual incidence of aSAH has been found to range from 7 to 10 per 100,000 person years in most regions of the world.[62-80] However, the incidence seems to be higher in Finland (about 20 per 100,000 person years)[63, 65, 81, 82] and Japan (about 23 per 100,000 person years).[63, 83-88] In Central and South America, India and China, the incidence seems to be lower (about 4 per 100,000 person years).[63, 65, 89-93] The incidence of SAH is sparsely investigated in Africa, and there are indications that the incidence of SAH is not as low as previously believed, because few high-quality studies have been performed.[94-97] There may have been a decrease in the

incidence of SAH over recent decades in high-income countries, but compared to the decrease in other types of stroke the decrease in SAH is likely to be modest.[63, 82]

However, different study designs and case finding procedures have been employed in studies of the incidence and case fatality of SAH, and the different approaches complicate comparisons between studies.[98, 99] First, there is a mixture of studies with only aneurysmal SAHs or with a combination of both aneurysmal and non-aneurysmal SAHs.[63-65, 73, 78, 90, 92, 100] This may be because the incidence of aSAH is relatively low, and because until a few decades ago, the distribution of CT and angiography was relatively low in high-income countries, something that is still true in low-income countries. Most cases (80-85%) of SAH are aneurysmal, i.e. caused by a ruptured arterial aneurysm.[2, 3] aSAH is a serious disease; at least one-third of the patients die during the first month,[101] and prehospital case fatality is also very high (about 10 %.).[8, 10, 65, 100] In comparison, two-thirds of non-aneurysmal SAHs are so-called perimesencephal bleedings, which usually represent a milder disease, with excellent prognosis.[3, 102] Combining these two types of SAH will therefore lead to a higher incidence and a lower case fatality as compared to studying only aSAHs.

Second, many studies of SAH use hospital discharge registers and causes of death registers, and estimates of incidence and case fatality are typically made without careful validation of the cases.[62, 68, 69, 71, 72, 103, 104] In such register studies, one does not know whether angiography or autopsy is performed, and thus cases will consist of a combination of aneurysmal and non-aneurysmal SAHs. Incidence rates will also tend to be overestimated in register studies, since the diagnoses may not be carefully validated. However, the estimated positive predictive value of SAH in register studies has ranged from 75 to 93%.[69, 105, 106] Taken together, the results of those studies may lead to an overestimate of incidence rates and a corresponding underestimate of case fatality, compared to the results of studies that have restricted the cases to aneurysmal SAHs. In general, it may seem that studies performed by neurosurgeons use strict diagnostic criteria and only include aneurysmal SAHs, while studies performed by epidemiologists include all types of spontaneous SAH, but are larger and use better epidemiological and statistical methods.

Third, there have been different routines for autopsy and different intensity of diagnostics, especially in very ill and old patients, in different countries over time. As a consequence, different proportions among the possibly eligible patients have been indentified and included in different studies. At the extremes are China, where the autopsy rate is very low due to cultural tradition,[65] and Japan, where even patients dead on arrival at hospitals will have a CT scan performed, at least in studies.[84, 87]

Fourth, the incidence will differ as to whether probable cases of aSAH are included or if only cases with aneurysms confirmed by angiography or autopsy are included.[107] This may be relevant for elderly patients in particular, since less vigorous diagnostics may have been performed in these patients. If only patients with confirmed aneurysms are included in the study, several patients will be excluded, although they may have had an aSAH. On the other hand is it important to avoid false positive cases.

Fifth, incidence is often estimated in specified age groups and the rates are standardized to the general population. This may give different incidence estimates compared to studies that have included strokes in all age groups. In addition, some studies provide only crude incidence rates or rates adjusted to the population of the country they were performed in, making it hard to compare incidence rates across countries.

Sixth, many studies of SAH include relatively few patients, and thus, many studies have limited statistical power and therefore low precision in the estimates of effect. Community-based studies with "hot pursuit" identification of incident strokes, that may be necessary for comparison of stroke incidence in different places and over times, as described by Malmgren et al[98] and Sudlow et al,[99] take longer time to conduct and require much work and resources. Therefore, many studies have been carried out in small areas over short time periods, and include few cases of SAH, the smallest group of strokes.[70, 76, 79, 80, 89-91, 108-112]

Finally, in both register studies and community-based studies, the population at risk for developing first-ever SAH comes from census population data in the study area. These can be unreliable in developing countries. Since few populations have censuses each year, the number of person years in the denominator often has to be estimated from one or two censuses and multiplied by the number of years studied.[64, 65, 83, 113] Some people may therefore contribute to person years in the estimations of incidence even if they already had a SAH, or have emigrated or died from other causes during follow up. On the other hand, in population-based cohort studies performed in countries with population registers, the participants can be followed from baseline and censored when they experience a SAH, move out of the catchment area of the study, or die. Thus, the cohort approach makes the incidence estimates more precise.

1.4 Morbidity and mortality of aneurysmal subarachnoid hemorrhage

aSAH is a serious disease with high morbidity and mortality. Thirty days case fatality has ranged from 8 % to 67 % in different studies, but in most studies, thirty days case fatality

varies from 30 to 50 %.[65, 66, 68-71, 73, 76, 77, 79, 81, 85, 88, 91, 95, 100, 109-111, 113-128] In addition, 10-20 % of all patients remain dependent on others for activities of daily life after the SAH,[101] and even patients with good recovery, who have resumed independent living (about 30 %), experience problems after the SAH.[2, 129-133] These problems include changes in personality (often anxiety, irritability or emotionality), cognitive dysfunction, reduced working capacity, higher depression scores than the general population, and generally lower quality of life.[130-132, 134, 135] There are indices of improvement of functional outcome and quality of life between 4 and 18 months after ictus.[132] Because of the high morbidity and mortality, and because the bleeding often occurs at a relatively young age, the loss of productive life years in the general population is comparable to that from cerebral infarction, the most common type of stroke.[136]

Thirty days case fatality after aSAH may have improved somewhat over the last four decades, by about 0.5 % per year.[101] This may be due to advances in surgical and medical treatment of the patients. The introduction of endovascular coiling in the 1990s may also have improved prognosis, as patients whose aneurysms or clinical status made them unsuitable for neurosurgical clipping of the aneurysm, now can be treated with endovascular coiling. Corresponding to the decrease in case fatality, however, the proportion of patients who are dependent on others for activities of daily life may have increased.[101]

The same discussion as in section 1.3 about different study designs and case finding procedures that have been employed in incidence studies of SAH, also apply for the estimates of case fatality. Thus, inclusion of non-aneurysmal SAHs, use of registers without case validation, different intensity of diagnostics and case finding, and small sample size, will make estimates less precise and studies less comparable.

Several characteristics of aSAH have been associated with early death or long term dependency on others, as was also mentioned in section 1.2.[7, 13, 29, 33, 137-140] These characteristics mainly include the patients' neurological condition at admission (evaluated by Glasgow Coma Scale score and Hunt and Hess grade or the World Federation of Neurological Surgeons scale grade), age, the amount of blood in the initial CT image, and the clinical management of the patient. However, few studies have used pre-ictal patient information to predict outcome.[140-143] One study found that the risk of death from SAH in smokers was almost half that of nonsmokers,[141] whereas other studies have reported no differences in outcome according to smoking status.[142, 143] Hypertension was associated with poor outcome in one study,[140] while another found no association.[143] Heavy drinking and low income has also been found to impair the outcome after SAH.[143, 144] Regarding radiographic vasospasm and DIND, one study reported that use of aspirin before the aSAH was associated with

reduced risk of DIND with permanent neurological deficit and reduced risk of cerebral infarction, as compared to those who had not used aspirin.[145] Other studies have found that pre-ictal smoking increases the risk of vasospasm and DIND,[146-148] but as discussed in section 1.2, this does not necessarily correlate with outcome. In addition, smoking after ictus, when cerebral blood flow is reduced, may increase the risk of vasospasm.[149]

1.5 Risk factors for aneurysmal subarachnoid hemorrhage

Since aSAH often occurs in relatively young people and both mortality and morbidity are high, defining risk factors for development of aneurysms and aSAH is important from a public health perspective. However, due to the low incidence of aSAH, it has been difficult to identify risk factors in prospective studies. Many studies of SAH have been retrospective in design, and therefore possibly prone to bias in selection and information.[150-160] In addition, most of these studies selected patients (for instance hospitalized patients, only one sex or excluding those dying shortly after ictus) or studied only a few risk factors. Prospective studies have been also performed. However, many prospective studies have included a small number of SAH cases, and the case finding and case ascertainment have varied. In addition, several studies have included limited age groups and only either men or women.[161-169]

Nonetheless, smoking, hypertension and female sex have consistently been found to be associated with increased risk of SAH.[150, 151, 153, 154, 156, 158, 160, 164, 170-180] Excessive alcohol consumption (defined in different studies from 150 grams of ethanol per week to 480 grams of ethanol per week) has also been found to be associated with increased risk.[150, 152, 153, 161, 163, 171, 172, 181] However, studying risk associated with alcohol consumption can be difficult; self report of alcohol consumption has been found to be unreliable, leading to misclassification. In addition, since studies of risk factors of SAH have generally been relatively small, it has not been easy to define a “threshold consumption”, over which alcohol consumption is associated with increased risk of SAH, and the cut-off points for light, moderate and heavy alcohol consumption have varied between studies. This may be the reason why several studies have found no association between alcohol consumption and risk of SAH.[154, 172, 173]

Other factors have less consistently been associated with risk of SAH. The associations of body mass index (BMI) and serum lipids with risk of SAH remain uncertain.[172] Some studies have reported a negative association of BMI with risk of SAH,[156, 170, 171, 182] while others have found no association.[173, 174, 183]

The association of total serum cholesterol has also shown inconsistent results: some studies have reported no association,[167, 168, 170, 173, 174, 184] whereas others have reported a negative association with the risk of SAH.[154-156, 182, 185] One study also found a positive association, but this was a relatively small, retrospective case-control study and therefore prone to bias.[158] Also, most studies with negative associations were retrospective case-control studies, and the results may therefore be distorted by bias and reverse causality.[154-156, 172, 182]

Few studies have assessed HDL cholesterol with the risk of SAH, but two studies have reported an inverse association between HDL cholesterol and the risk of SAH.[158, 183] Also, few studies have assessed the effect of serum triglycerides in relation to SAH, but one hospital-based case-control study found a negative association.[155]

The association of regular physical activity and the risk of SAH is not clear.[172, 186, 187] However, moderate to extreme physical exertion have been associated with increased risk of SAH in the hours following the activity,[187, 188] but the number of cases associated with this physical exertion was low in these studies. Other activities that may precipitate a SAH include defecation, micturition and sexual activities.[188, 189] It is likely that transient elevations in blood pressure during these activities may cause rupture of an intracranial aneurysm.[187-189]

The results from studies that have assessed the influence of meteorological and temporal factors on the incidence of SAH have varied, but there are indications that the incidence may be somewhat higher in the winter and spring,[190] in the morning (as compared to the night) and on Sundays (as compared to Mondays).[190]

People with a family history of aSAH are at increased risk of developing aSAH, [69, 153, 160, 171] and the population attributable proportion of a positive family history has been estimated to about 10 %.[191] In addition, certain heritable diseases have been associated with increased risk of aSAH. Thus, patients with autosomal dominant polycystic kidney disease have increased risk of aSAH, but they constitute a very small proportion of all SAH patients.[192] These patients tend to experience the bleeding at a young age, with an equal sex distribution (no female preponderance), and a greater tendency for large aneurysms.[192] There is also evidence that the risk of SAH is increased in patients with other heritable connective tissue disorders such as Ehlers-Danlos syndrome type IV, neurofibromatosis type I, and Marfan's syndrome.[20]

Other risk factors that have been associated with increased risk of SAH include excessive coffee consumption,[174] and cocaine use.[156] In addition, it has been suggested that non-white ethnicity may be a risk factor for SAH,[172, 181, 182, 193, 194] and that low socioeconomic

status is associated with increased risk of SAH.[144, 156, 171, 181, 182, 195] However, the association of socioeconomic status may be explained by differences in risk factor profiles.[144, 172]

Genetic studies of aSAH have also been performed, but these will not be discussed here, since the genetic studies comprise a large and complicated field of study which is not directly relevant the work in this thesis.

The association of endogenous and exogenous hormonal factors with the risk of SAH have also been studied. These studies will be discussed in the following section.

1.6 Sex differences in risk factors for aneurysmal subarachnoid hemorrhage

Unlike other cardiovascular diseases, aSAH affects women more often than men.[63, 64, 196] Therefore, some studies have evaluated the association of exogenous hormonal factors, such as use of hormone replacement therapy (HRT) and oral contraceptive pills (OC), and endogenous hormonal factors, such as age at menarche and menopause, number of children and age at first birth, with risk of SAH.

HRT has been found to be negatively associated with the risk of SAH, although the associations did not reach statistical significance in all studies.[165, 172, 182, 197-199] This may be because of lack of power due to few cases using HRT or dilution because of different types of HRT and different exposure times of the women. One hypothesis as to why HRT might be protective in relation to SAH, is that the fall in estrogen at menopause may lead to a fall in collagen in the connective tissue, as it does in skin and bone after menopause.[200] This may thereby predispose to formation of intracranial aneurysms, which may be prevented in some part by the use of HRT.[201] The finding that the gender discrepancy in SAH seems to increase after menopause,[63] may support this hypothesis. However, as relatively few women use HRT over a relatively short time period, this does probably not affect the incidence of SAH to a large extent.

Concerning OC, it may seem that earlier versions of the pill, containing larger doses of estrogen than the modern pills, could have increased the risk of SAH, compared to never using OC.[157, 162, 202-204] However, the increased risk was not consistent across studies, and there seems to be no association of the new formulations of OCs and risk of SAH.[172, 182, 199, 204] One study found a higher six months case fatality among ever users of OCs as compared to never users.[203]

Concerning endogenous hormonal factors, one study found that having the first child after the age of 22 years was associated with decreased risk of SAH.[182] However, that study found no associations of other endogenous hormonal factors, such as age at menarche, parity, breast-feeding status, menopausal status, age at menopause, reason for menopause or number of fertile years. Another study found that a relatively higher proportion of SAHs had occurred shortly before or during menstruation.[199]

Taken together, studies of hormonal factors and the risk of SAH may indicate that estrogen may be protective, at least in postmenopausal women.[182] The results may also indicate that changes in serum levels of estrogen, rather that the absolute level, may increase the risk of SAH.[199] Changes in serum levels of estrogen occurs at menopause but are reduced by the use of HRT. Serum levels of estrogen also vary throughout the menstrual cycle, and the fall before menstruation is probably higher in women using older OCs containing high levels of estrogen than in women not using OCs or using newer versions containing lower levels of estrogen. However, changes in serum levels of estrogen would not explain why women are at higher risk of SAH as compared to men several years after menopause.

An alternative approach to study the sex difference in the incidence of SAH could therefore be to compare the distribution and strength of risk factors for SAH in men and women. As discussed above, the major risk factors for SAH are smoking, hypertension and excessive alcohol intake. These factors are traditionally more prevalent in males than in females, although women have been approaching men in the prevalence of smoking during the last decades.[205, 206] As SAH is more common in women, there may be sex differences in the association of these risk factors, but relatively few studies have explored this question. A meta-analysis of prospective studies found that the risk for aSAH in female ever smokers was 1.9 times than in men; hypertension was 1.3 times more hazardous in females, and excessive alcohol intake (≥150 g per week) was 1.8 times more hazardous.[172] However, the metaanalysis mainly compared studies that investigated risk factors for aSAH in either a female[164-166] or a male[161, 167-169, 178] population; only three of the studies included males and females from the same population.[163, 170, 181] Two of these studies only examined the effect of alcohol consumption, and not blood pressure or hypertension.[163, 181] In the third study, cases were identified using a national hospital discharge registry and were not validated.[170] In one study not included in the metaanalysis, the association between cigarette smoking and the risk of SAH seemed to be stronger in women than in men. However, this paper only included 36 cases of all types of spontaneous SAH.[128] Retrospective case-control studies have reported conflicting results regarding the strength of risk factors in men and women. One study found

higher risk of aSAH in male compared to female smokers,[150] other studies reported higher risk of SAH in female compared to male smokers (although it did not reach statistical significance in two),[151, 207, 208] whereas other studies found no sex differences in the strength of smoking as a risk factors for SAH.[152, 179] The relationship between hypertension and the risk of SAH have been reported as stronger in women than men in one case-control study, although it did not reach statistical significance.[151]

2 Objectives

Main objective

To estimate the incidence, mortality and case fatality from aSAH, and to assess effects of selected risk factors in large prospective population-based studies in Norway. The specific objectives of the papers are as follows:

Study I

To assess the incidence rates, case fatality and pre-ictal risk factors for aSAH mortality during the time period from 1984 until 2007 and for different age groups in two large prospective studies of the general population.

Study II

To assess the association of common life style factors (systolic and diastolic blood pressure, smoking, alcohol consumption, physical activity and BMI) with the risk of developing aSAH in a large prospective study of the general population.

Study III

To assess the association of BMI and blood lipids with the risk of developing aSAH in two large prospective studies of the general population.

Study IV

To investigate sex differences in the major established risk factors for aSAH (smoking, systolic blood pressure, and alcohol consumption) in two large prospective studies of the general population.

3 Materials and Methods

3.1 The Nord-Trøndelag Health Study (HUNT)

Nord-Trøndelag is one of 19 Norwegian counties and is located in the central part of Norway (Figure 5). The population is stable at about 131,000 inhabitants (2010),[209] with a net migration out of the county of 0.3% per year (1996-2000). The population is also homogenous, with predominantly Caucasian inhabitants. The age- and sex-distribution is comparable to Norway as a whole, and the mortality and living conditions are similar to those of the 18 other counties in Norway.[210, 211] The population is served by two local hospitals, in Levanger and Namsos, and one central university hospital, St Olavs Hospital, Trondheim University Hospital, in Trondheim. Nord-Trøndelag is therefore a suitable community for performing prospective cohort studies.

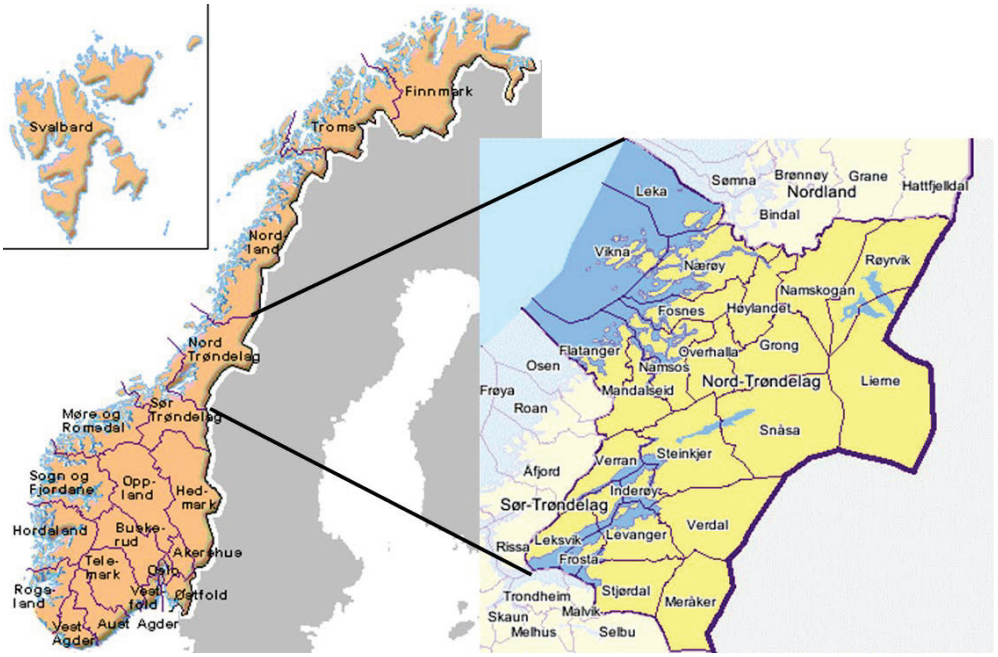

Figure 5. Norway and Nord-Trøndelag county. Adapted from Holmen et al, Norwegian Journal of Epidemiology 2003.[211]

The Nord-Trøndelag Health Study (HUNT) is a population-based study that has been performed three times. From these studies, we use data from the two first waves of the HUNT Study, HUNT 1 (1984-1986), and HUNT 2 (1995-1997). The studies have been thoroughly described elsewhere.[210, 211]

All residents aged 20 years and older in Nord-Trøndelag County in Norway were invited to participate in the HUNT Study. Of the eligible population, 77,232 (88.1 %) participated in HUNT 1, and 65,628 (71.2 %) participated in HUNT 2. Of these, 47,715 participated in both studies. In total, as described in paper I, 169 persons who were not officially registered as inhabitants of the county at attendance (n=154) or due to previous SAH (n=15) were excluded from the study, leaving a total of 94,976 people to be included in the study (HUNT 1 or 2, or both). The numbers of participants in the individual papers differs somewhat since (i) we did not have information on emigration from Nord-Trøndelag to other Norwegian counties in papers II and IV, (ii) the case finding was done in three stages, as described further in section 3.4, and (iii) participants who experienced an aSAH before attendance in HUNT 2 was excluded from papers III and IV. The specific numbers of participants are described in the individual papers.

The clinical measurements, laboratory tests, and self-reported information from the HUNT studies that were used in this thesis are described in section 3.5.

The HUNT Study is a collaboration between the Faculty of Medicine, the Norwegian University of Science and Technology, the Norwegian Institute of Public Health, and Nord-Trøndelag County Council. The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Ethics in Medical Research approved this study. In HUNT 2, all participants gave their informed, written consent to participate.

3.2 The Tromsø study

Tromsø is the largest city in Northern Norway (Figure 6) and the seventh largest city in Norway, with its 67,000 inhabitants (2010).[209] Its population is also relatively stable.

The Tromsø Study is a population-based study that has been performed six times.[212] In this study, we use data from the third and fourth waves of the Tromsø Study. Between 1986 and 1987 (Tromsø 3), all resident men aged 20 to 61 years and all resident women aged 20 to 56 years in Tromsø, Norway were invited to participate in the Tromsø 3 study. Between 1994 and 1995, all residents aged 24 years and older were invited to participate in the Tromsø

4 study. Of the eligible population, 20,606 participated (75.2 %) in Tromsø 3, and 27,158 participated (77 %) in Tromsø 4. Of these, 15,423 participated in both studies.

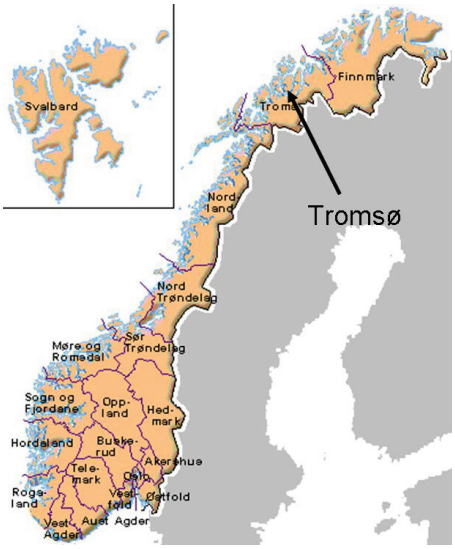

Figure 6. Tromsø. Adapted from Holmen et al, Norwegian Journal of Epidemiology 2003.[211]

In total, as described in paper I, subjects who did not consent to medical research (n=203), subjects who participated without being invited (n=65) and subjects not officially registered as inhabitants of the municipality (n=80), were excluded from the study. Also, subjects with a known history of SAH (n=30) were excluded, leaving a total of 31,753 people included in the study. In papers III and IV, using only Tromsø 4, we excluded 276 participants due to no consent 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. The participants of Tromsø 4 gave informed, written consent to participate. The study was approved by The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Ethics in Medical Research.

3.3 The Cause of Death Registry

In Norway, the reporting of deaths by physicians and public health officers to the national Cause of Death Registry is mandatory. The registry is owned by the Norwegian Institute of

Public Health, but the data are collected and organized by Statistics Norway. In addition to using information from the local physicians and public health officers, Statistics Norway collects supplementary information from other sources, such as the Cancer Registry of Norway, the Medical Birth Registry of Norway, and autopsy reports. The classification is based on International Classification of Diseases (ICD) codes. Both the underlying and other causes of death are reported. The unique 11-digit identification number of every Norwegian citizen enables linkage of data from the Cause of Death Registry with other data, such as data from the HUNT and the Tromsø studies. In paper II, the information on causes of death was complete through December 31, 2005. In papers I, III and IV information on causes of death was complete through December 31, 2007.

3.4 Study variables

3.4.1 Definition and ascertainment of aneurysmal subarachnoid hemorrhage

We used several techniques to identify aSAH patients. First, data from both the HUNT and the Tromsø studies were linked to the National Causes of Death Register at Statistics Norway, as described in section 3.3, using codes for subarachnoid hemorrhage according to the International Classification of Diseases (ICD) version 8, 9 and 10 (codes 430 (ICD 8 and 9) and I60 (ICD 10)). Second, we did searches in the hospitals serving the study populations, as described further below. For the HUNT population, the case finding for this study was performed in three stages. I will describe the case finding in the order it was chronologically performed, although this does not correspond to the sequence of the papers.

3.4.1.1 Case finding for paper II

St Olav's Hospital, Trondheim University Hospital, is the only hospital with a neurosurgical department that serves the HUNT population. All patients who survive the acute phase of the SAH are treated at the neurosurgical department, and people who live in the area but experience a nonfatal SAH outside the area, are usually transferred to this department after acute treatment elsewhere.

We identified all patients submitted to St Olav's Hospital, Trondheim University Hospital who were diagnosed with SAH from January 1, 1984 until December 31, 2005. In the search we used three different strategies. First, a computerized search of the St. Olav's

Hospital, Trondheim University Hospital's patient administrative database was used to identify patients diagnosed with SAH according to the International classification of diseases (8th and 9th revision code 430, and 10th revision, code I60). Second, we did a manual search in operation protocols of the department of neurosurgery for patients who were operated with clipping of an aneurysm, or patients who had received an external drain between 1984 and 1986, during a period when the patient administrative database was not complete. Third, as mentioned above, we could identify patients from the catchment area of the HUNT Study who died from SAH from 1984 to 2005 based on information from the Cause of Death Registry in Norway.

The 1373 patients who were identified through these procedures were individually linked to the database of the HUNT Study. Among all the identified patients 225 had participated in the HUNT 1 study. Of these, 94 were excluded from further analyses, as they were non-aneurysmal SAH, traumatic SAH, SAH caused by arteriovenous malformation, other types of cerebral bleeding, or SAH likely caused by antithrombotic or anticoagulation therapy. Also, some patients were erroneously coded in the hospital charts, the diagnostics were too sparse, or the hospital charts could not be found, and there was therefore probably erroneous coding in the hospital charts or the Cause of Death Registry, respectively. In addition, five patients had SAH prior to participating in HUNT 1 and were therefore excluded. Paper I thus included 132 patients who had a verified diagnosis of aSAH after participation in HUNT 1.

3.4.1.2 Additional case finding for paper IV in the HUNT population

In addition to the patients identified for paper II, we extended the search in the patient administrative database at St. Olav's Hospital, Trondheim University Hospital and the Cause of Death Registry until December 31, 2007. We identified 18 patients who had aSAH in 2006 or 2007, and excluded 43 patients with SAH prior to participation in HUNT 2 or Tromsø 4.

In total, paper IV included 69 patients who had a verified diagnosis of aSAH after participation in HUNT 2, in addition to those who had participated in Tromsø 4 (n=51), as described below.

3.4.1.3 Additional case finding for papers I and III in the HUNT population

As mentioned above, St Olav's Hospital, Trondheim University Hospital is the only hospital with a neurosurgical department that serves the HUNT population, and all patients who survive the acute phase of the SAH are treated at this neurosurgical department. We first

thought that we would be able to identify practically all SAH patients who survive the acute phase by searching in the patient administrative database in this hospital, and practically all SAH patients who die shortly after ictus by linkage to the Cause of Death Registry. However, as it is especially important to identify all patients in a paper of incidence, we decided to expand the search before writing paper IV. As paper III was to be submitted after the extended search was performed, these patients were also included in paper III.

We used three techniques to ascertain that we did not miss any SAH patients. First, we searched in the patient administrative database in the local hospitals in Nord-Trøndelag; Levanger and Namsos Hospitals. We identified three new patients with aSAH after participation in the HUNT study, and seven patients who had SAH before participation and who therefore were excluded from further analyses.

Second, we confirmed our search strategy by searching also for patients who had had surgical clipping or endovascular coiling of an aneurysm at St Olav's Hospital, Trondheim University Hospital, in case of misencoding. By this search we found one new aSAH patient who had participated in the HUNT Study.

Third, two experienced neurosurgeons (T.B.M. and A.V.) and a radiologist reviewed the CT images for patients who had received the diagnosis of ICH at a local hospital and who died within 6 months in the years 2003 to 2007. This was also done in case of misencoding, as some ICHs can be caused by ruptured aneurysms. The 6 months limit was set because aSAH patients not treated for their aneurysm are likely to experience recurrent bleeding within 6 months and thereafter die or be identified as aSAH case. We found no new patients who had participated in the HUNT study in this search.

In total, paper I included 157 patients who had a verified diagnosis of aSAH after participation in HUNT 1 or 2, in addition to those who had participated in Tromsø 3 or 4 (n=57), as described below. Paper III included 71 patients who had a verified diagnosis of aSAH after participation in HUNT 2, in addition to those who had participated in Tromsø 4 (n=51).

3.4.1.4 Case finding in the Tromsø population

In Tromsø, a similar procedure was followed at the University Hospital of North Norway, Tromsø, which is also the local hospital for the Tromsø population. Adjudication of hospitalized and out-of hospital first-ever aSAH was performed by an independent end point committee and based on data from hospital and out-of hospital journals, autopsy records, and

death certificates. The end point committee also adjudicated other types of stroke, thus, also finding misencoded ICHs (n=2).

In total, paper III and IV included 51 patients who had a verified diagnosis of aSAH after participation in Tromsø 4, and paper I included 57 patients who had a verified diagnosis of aSAH after participation in Tromsø 3 or Tromsø 4.

3.4.1.5 Definition of aSAH

All patients had a CT scan showing SAH of aSAH found at autopsy. Patients with conventional or CT angiographic evidence of an aneurysm or with an aneurysm found during operation, and patients identified with aSAH at autopsy were included as cases of aSAH (paper I, n=185; paper II, n=111; paper III, n=103; paper IV, n=102). Some cases (paper I, n=29; paper II, n=21; papers III, n=19; paper IV, n=18) of SAH were also included, despite the fact that angiography or autopsy was not performed, because the medical history was highly suggestive of fatal aSAH. The inclusion criteria for these patients were (1) sudden headache and/or unconsciousness, (2) massive basal SAH on CT scans, and (3) death within four weeks. All criteria had to be fulfilled, and all cases were independently reviewed and consented by two classified neurosurgeons (T.B.M and A.V) for the HUNT population and the independent end point committee for the Tromsø population. Patients were excluded, despite fulfilling all the inclusion criteria, if the CT scan showed an intracerebral hemorrhage (ICH), unless a typical localization of the ICH close to a possible aneurysm was found. Patients were excluded if they had SAH before participation, if the SAH was non-aneurysmal or if they had been coded with the wrong diagnosis.

Individuals who had died or emigrated from Nord-Trøndelag or Tromsø, were identified through the Population Register of Norway. Data on emigration from the Tromsø study area to other areas within Norway was available from the Population Register of Norway for use in all papers, while emigration from the HUNT study area to other areas within Norway was not available until preparation of papers I and III, and is therefore not included in papers II and IV. This leads to a somewhat different number of participants and follow-up time in the papers. Follow-up time was assigned from the baseline date of examination (HUNT 1 (1984-86), HUNT 2 (1995-97), Tromsø 3 (1986-87) or Tromsø 4 (1994-95) in paper I; HUNT 1 in paper II; and HUNT 2 or Tromsø 4 in papers III and IV) until the first aSAH or until the end of follow-up on December 31, 2005 (paper II) or December 31, 2007 (papers I,III and IV), whichever occurred first. Data were censored for date of registered emigration or death from causes other than first-ever aSAH. In paper I,

patients who participated in two studies were followed from the first date of attendance, but for aSAH patients, data on exposure related to survival were collected from the study attended most recently before ictus.

3.4.2 Self-administered questionnaires

In all studies, the participants filled in a questionnaire that was included with the invitation (questionnaire 1), and attended a clinical examination conducted by trained nurses. A second questionnaire (questionnaire 2) was handed out at the clinical examination and should be completed and returned by mail in a pre-stamped envelope. The questionnaires can be found at http://www.ntnu.edu/hunt/data/que (HUNT) and http://www.tromsoundersokelsen.no (Tromsø, Norwegian only).

According to their answers in the questionnaires, participants were classified as never smokers (reference), former smokers, or current smokers. In paper IV, only cigarette smokers were included as smokers, whereas participants smoking cigars and pipes were also included as smokers in papers I-III.

The questions concerning alcohol consumption differed somewhat in the four studies. In paper II (HUNT 1), we classified the participants according to alcohol consumption during the last 14 days; as total abstinent, no consumption during the last 14 days, but not totally abstinent (reference), 1-4 times, ≥ 5 times or too much. In papers III and IV (HUNT 2 and Tromsø 4), we classified participants as (0) total abstinent, (1) drinking less than once a month (reference), (2) 1-4 times per month and (3) > 4 times per month. In paper I, the categories from HUNT 2 and Tromsø 4 used in papers III and IV were kept and the categories from HUNT 1 and Tromsø 3 were reclassified to fit into these categories. For Tromsø 3, those answering "never or a few times per year" were categorized as (1); those answering "1-2 times per month" or "once a week" were categorized as (2); and those answering "2-3 times per week" or "practically every day" were categorized as (3). For HUNT 1, those answering "not during the last 14 days, but not totally abstinent" were categorized as (1); those answering "1-4 times" were categorized as (2); and those answering "≥ 5 times or too much" were categorized as (3). After this reclassification, the distribution of participants in the different categories was fairly similar between studies.

For physical activity in paper II, we used a score constructed by Nilsen et al,[213] combining the three questions concerning physical activity; the average frequency of recreational physical exercise in a week, the average duration, and the intensity of the activity.

A summary score was calculated by summarizing the responses according to the following equation: 1/5 x frequency + 1/3 x intensity + 1/4 x duration. The participants were then divided into four separate categories according to their score as highly active, moderately active, having low activity and no activity (reference).

3.4.3 Clinical measurements

Among other measurements, clinical measurements included blood pressure, height, and weight.

In paper II (HUNT 1), blood pressure was measured using a calibrated mercury manometer with a standard cuff size (12 x 14 cm) after a minimum of 2 minutes' rest.[210] The first pulse sound (Phase 1) was recorded as systolic pressure, and the level when the pulse disappeared (Phase 5) was recorded as diastolic blood pressure. Both pressures were registered with an accuracy of 2 mm Hg, and the measurements were repeated 2 minutes after the first recording. In the analyses, we used the average value of the 2 measurements of systolic and diastolic blood pressure; and in the few cases with only one measurement; this was used instead of the average. In papers III and IV (HUNT 2 and Tromsø 4), blood pressure was measured using an automatic device (Dinamap, Critikon, Tampa, FL, USA). Cuff size was adjusted after measuring the arm circumference. Three recordings were made at 1-minuntes intervals after 2 min of seated resting.[214] The mean value of the second and third measurement was used in the analysis. In paper I, blood pressure measurements from HUNT 1 and 2 and Tromsø 4 as described above was used in the analyses for participants from these studies. For participants in Tromsø 3, blood pressure was measured the same way as in HUNT 2 and Tromsø 4, except for 2-minutes intervals instead of 1-minutes.[215]

In paper II, we grouped the participants into the seven categories of systolic and diastolic blood pressure. In papers III and IV, we treated systolic blood pressure as a continuous variable and estimated hazard ratios according to a 10 mmHg increase. In addition, in papers I, III and IV, we estimated risk associated with hypertension, defined as systolic blood pressure ≥140 mmHg and/or current use of antihypertensive treatment.

Body mass index (BMI) was calculated as weight (in kg) divided by the squared value of height (in meters). BMI was divided into groups according to the World Health Organization (WHO) classification; <18.5 underweight, 18.5-24.9 normal weight (reference), 25-29.9 overweight, and obese ≥30 kg/m^2.

3.4.4 Serum lipids

A non-fasting blood sample was drawn from all participants in the HUNT 2 and Tromsø 4 studies. 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, Mannheim, Germany) at the Central Laboratory at Levanger Hospital and at the Department of Laboratory Medicine, University Hospital of North Norway, for the HUNT 2 and Tromsø 4 population, respectively. Serum HDL cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride. In paper III, low HDL cholesterol were defined as HDL cholesterol <1.29 mmol/L and <1.03 mmol/L for women and men, respectively,[216] and elevated triglycerides were defined as triglycerides ≥1.7 mmol/L.[216] In these analyses, we adjusted for number of hours since last meal.

3.5 Ethical Approval

The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Ethics in Medical Research approved this study as well as the HUNT and the Tromsø studies. In HUNT 2 and Tromsø 4, all participants gave their informed, written consent to participate.

3.6 Statistical analyses

In all papers, we used the Cox proportional hazards model to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Departure from the proportional hazards assumption was evaluated by Schönfelds residuals and by inspection of the log-log plots. Some study factors (eg, BMI, alcohol consumption, smoking) was categorized, and the risk of aSAH was estimated for each category and compared with a defined reference category. Other study factors (serum lipids, and blood pressure in papers II and III) were treated as continuous variables.

In paper I, we estimated crude incidence rates by sex, study population (HUNT or Tromsø) and age-group (20-29 years, 30-39 years…and ≥ 70 years). Poisson regression was employed to estimate trends in incidence rates over the following time-intervals; 1984-1989, 1990-1994, 1995-1999, 2000-2004, and 2005-2007, thus allowing the assessment of crude changes in the incidence rates over time, and adjusted for age (in 10-years categories), sex and

study population. We also estimated standardized incidence rates using the European and the WHO World Populations as standards. In these analyses, the incidence was assumed to be null in the group below 20 years of age, as the study included very few participants below 20 years of age and the incidence is known to be very low in this age group.[83] Students t-test was used to assess whether mean age at aSAH occurrence differed between groups and linear regression was used to assess whether age at diagnosis changed over time.

The difference between the date of aSAH and the date of death or censoring was defined as the survival time. In order to study survival after aSAH, the analysis was restricted to the first six months following aSAH. Survival was illustrated using Kaplan-Meier plots adjusted for age, and Cox proportional hazards model were used to assess survival by sex, smoking and blood pressure adjusted for age at aSAH. Case fatality was estimated after 1, 3, 7, and 30 days, and after 6 months following the date of aSAH. Multiple logistic regression analysis was used to assess 30 days case fatality according to time period, with adjustment for age and study population.

In paper II, we adjusted for age (in 10-years categories) and sex. In subsequent analyses, we also adjusted for other potentially confounding factors (systolic blood pressure, smoking, alcohol consumption, BMI, physical activity, marital status, and education). However, as there was a substantial amount of missing data on smoking and alcohol consumption, these estimates were not presented in the table.

In paper III, we adjusted for age (as a continuous variable), sex, smoking and alcohol consumption, as we considered these to be potentially confounding factors in the association of BMI and serum lipids and the risk of aSAH. To facilitate direct comparisons of the strength of effects related to continuous risk factors in paper III, we estimated HRs per standard deviation (SD) increase for the respective factors. We also assessed whether the estimated associations differed between men and women using appropriate interaction terms. Furthermore, we divided the participants' follow up time into two strata; one for participants younger than 50 years of age, and another for participants 50 years of age or older.

In paper IV, we wanted to investigate potential sex differences in the major established risk factors for aSAH. The concept of interaction in clinical and epidemiological research has created confusion because it describes two different phenomena.[217] On the one hand, statistical interaction equals effect-measure modification and refers to the need to include an interaction, or product term in a statistical model for the model to fit the data well.[217, 218] As the most widely used statistical models (logistic regression and Cox regression) are multiplicative, statistical interaction usually implies departure from a multiplicative model,

meaning that the risk of disease in a person with both risk factors is higher (or lower) than would be expected from multiplying the risk of each of them. On the other hand is the biological interaction, also called departure from an additive model, meaning that the risk of disease in a person with both risk factors is higher (syngergism) or lower (antagonism) than would be expected from adding the risk of each of them together.

Therefore, in paper IV, the possible multiplicative (i.e. statistical) interaction between sex and the risk factors for aSAH (hypertension, smoking and alcohol consumption) was assessed using the log likelihood ratio test. Possible additive (i.e. biological) interaction between sex and the risk factors for aSAH was assessed by calculating the relative excess risk due to interaction (RERI) with 95 % CIs.[219, 220] This measure has been shown to perform well in Cox proportional hazards models.[221] RERI was calculated as $RERI=HR_{11}- HR_{10}- HR_{01}+1$ where HR_{ij} is the hazard ratio for *i* = sex (1 = women, 0 = men) and *j* = the risk factor in question (1 = present, 0 = absent). If there is no additive interaction present, the RERI value will be 0. RERI values > 0 indicate that the risk of aSAH in women with the risk factor in question is higher than would be expected when adding the risk of being a woman and the risk associated with the risk factor in question. Thus, there is increased risk of aSAH associated with the risk factor in question among women as compared to men. RERI values < 0 indicate decreased risk of aSAH associated with the risk factor among women as compared to men.

In paper IV, we adjusted the sex-specific analyses of smoking for age (in 5-years categories), alcohol consumption and family history of stroke (information on family history of SAH was not available).

All analyses were performed using the statistical software Stata for Windows (Version 10.0 or 11.0, Stata Corp, College Station, Texas).

4 Main results

4.1 Paper I

Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts 1984 - 2007

The crude incidence rate was 10.3 per 100,000 person years, 13.3 for women and 7.1 for men. The results indicated an age-dependent increase of 2 % per 10 years higher age (HR 1.02, 95% CI 1.01-1.03), and suggested an increase over time (HR 1.02, 95 % CI 1.00-1.04 per 5-year period, after adjustment for age, sex and study population). After 1995, the incidence has remained stable (HR 0.99, 95 % CI 0.95-1.03). The incidence was higher in the Tromsø as compared to the HUNT population (11.9 vs 9.8 per 100,000 person years), after adjustment for age and sex. The crude incidence rate for all types of spontaneous SAH (n=272; aneurysmal, non-aneurysmal, or SAH where the diagnostics were too sparse to establish whether it was aneurysmal) was 13.1 per 100,000 person years, 15.8 for women and 10.1 for men.

Case fatality for aSAH at 1, 3, 7 and 30 days, and at 6 months, was 14 % (95 % CI 10-19), 20 % (95 % CI 14-25), 24 % (95 % CI 19-30), 36 % (95 % CI 29-42) and 40 % (95 % CI 34-47), respectively. The 30-day case fatality tended to increase by age (OR 1.3, 95 % CI 1.0-1.6 per 10 years of age), and remained stable during the 23 years of follow-up (OR 1.01, 95 % CI 0.97-1.06 per year, adjusted for age and study population).

Six months survival of never smoking patients was lower than among current smokers (age-adjusted HR 1.8, 95 % CI 1.0-3.2), and lower among patients with systolic hypertension than in patients without (age-adjusted HR 1.4, 95 % CI 0.9-2.2). However, since the risk of aSAH was higher among current smokers than never smokers, current smokers were at higher risk of dying from aSAH than never smokers (HR 5.6, 95% CI 3.3-9.5).

4.2 Paper II

Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study. The HUNT study in Norway

Systolic and diastolic blood pressures were positively associated with risk (p for trend=0.001 and <0.001, respectively). Compared to the reference level (< 130 mmHg), the risk related to systolic blood pressure between 130-139 mmHg was more than two-fold higher (HR 2.3,

95 % CI 1.4-3.8, adjusted for age and sex), and for systolic blood pressure ≥ 170 mmHg, risk was more than three-fold higher (HR 3.3, 95 % CI 1.7-6.3). For diastolic pressure, the results showed similarly strong positive associations. The risk of aSAH was higher in former (HR 2.7, 95 % CI 1.4-5.1) and current (HR 6.1, 95% CI 3.6-10.4) smokers, compared to never smokers. Compared to being normal weight (BMI 18.5-24.9), there was a lower risk (HR 0.6, 95% CI 0.4-1.0) associated with being overweight (BMI 25-29.9). For alcohol, only total abstinence significantly reduced the risk of aSAH (HR 0.3, 95% CI 0.1-0.7). Physical activity did not affect the risk of aSAH.

4.3 Paper III

Risk factors for aneurysmal subarachnoid hemorrhage - BMI and serum lipids: 11-year follow-up of the HUNT and the Tromsø Study in Norway

People who were overweight (BMI 25-29.9) were at lower risk of aSAH, compared to people in the normal weight group (BMI 18.5-24.9): the HR adjusted for age, sex, smoking and alcohol consumption associated with overweight was 0.7 (95 % CI 0.4-1.0). There was no over all association of total serum cholesterol, HDL cholesterol, triglycerides or alcohol consumption with the risk of aSAH. There was also no association of low HDL cholesterol or elevated levels of triglycerides with the risk of aSAH.

In age-specific analyses, HDL cholesterol was inversely associated with the risk of aSAH (HR 0.6, 95 % CI 0.4 to 0.9 pr SD increase adjusted for age, sex, smoking and alcohol consumption) in participants younger than 50 years of age, and in participants 50 years and older, there was no clear association of HDL cholesterol (HR 1.2, 95 % CI 1.0 to 1.5 pr SD increase adjusted for age, sex, smoking and alcohol consumption). The age-specific analyses also suggested that the inverse association of overweight was restricted to people 50 years and older, and not present in people younger than 50 years.

4.4 Paper IV

Sex differences in risk factors for aneurysmal subarachnoid hemorrhage: a cohort study

Current smoking was associated with increased risk of aSAH in both women and men (HR 8.88 (95 % CI 4.65-17.01) and HR 2.81 (95 % CI 1.30-6.08), respectively, adjusted for age, alcohol consumption, and family history of stroke). The RERI for sex and current cigarette smoking, adjusted for age, alcohol consumption, and family history of stroke, was 3.65 (95%

CI 0.87 to 6.43), indicating higher risk of aSAH associated with current cigarette smoking in women than in men (additive interaction). There was no evidence of additive interactions between sex and hypertension or alcohol consumption and the risk of aSAH. There was also no evidence of multiplicative interaction between sex and smoking, hypertension or alcohol consumption and the risk of aSAH (all p-values >0.1).

5 Discussion

In these studies, our main goal has been to estimate the incidence, mortality and case fatality from aSAH, and to assess effects of selected risk factors in large prospective population-based studies in Norway. Briefly, our main results may be summarized as follows:

- The incidence of aSAH is 10.3 per 100 000 person years, 13.3 for women and 7.1 for men. The incidence increases with age, and has increased slightly over the last 23 years. Since 1995, the incidence has remained stable.

- Case fatality for aSAH at 1, 3, 7, and 30 days, and at 6 months, was 14 %, 20 %, 24 %, 36 % and 40 %, respectively. Case fatality increases with age, but has remained stable over the last 23 years.

- Never smokers seem to have worse six months survival after aSAH than current and former smokers, but smokers have higher mortality from aSAH than never smokers, since the risk of aSAH is higher in smokers than in never smokers.

- Increasing systolic and diastolic blood pressure as well as female sex and current smoking increase the risk of aSAH. Current cigarette smoking is more strongly associated with increased risk of aSAH in women as compared to men.

- Overweight might reduce the risk of aSAH. There were no over all associations of total cholesterol, HDL cholesterol, or triglycerides with the risk of SAH in the general population. Before the age of 50 years, HDL cholesterol was negatively associated with the risk.

5.1 Strengths of the study

This study has several strengths. First, it is a prospective cohort study. A general advantage of cohort studies is that the temporality criterion for causation, that effect precedes outcome, is fulfilled, and reverse causality is avoided. In addition, cohort studies are relatively immune to recall bias, as further discussed in section 5.4.3. As the incidence of aSAH is low, relatively few prospective population-based studies have been performed.

Second, the study is population based, and the HUNT and the Tromsø studies consist of the majority of adults in the populations of Nord-Trøndelag and Tromsø. The population base of the study makes the findings easier to generalize, minimizes the risk of selection bias, and gives us the opportunity to do sub analyses in different groups. Many studies of SAH are not population-based or have studied limited age groups or only either men or women.

Third, we have good criteria for case finding and case ascertainment. The unique 11-digit identification number of all Norwegian citizens ensures complete follow up of all-cause mortality and enables us to link the study participants to discharge registers and autopsy registers. We reviewed the charts of all identified patients. All cases without proven aneurysm were independently reviewed and consented on by two classified neurosurgeons (HUNT) or a neurologist and neuroradiologist (Tromsø) before they were included as possible aSAHs or excluded from the study. Specifically, it is important that we have been careful only to include aneurysmal SAHs, as aneurysmal and nonaneurysmal SAH are two distinctively different diseases, as mentioned in section 1.3.

Fourth, the study population is large, HUNT being one of the largest population-based cohort studies worldwide. However, as aSAH is a relatively rare disease, the number of cases is anyhow somewhat limited, as discussed in section 5.2.

Fifth, our study group consisted of both experienced neurosurgeons, a neurologist and epidemiologists. Together we had expertise in the main fields and good qualifications for performing epidemiologic studies of aSAH.

Therefore, I believe our population-based prospective cohort study, with good criteria for case finding and case ascertainment, can give important insight to the epidemiology of aSAH.

5.2 Limitations of the study

However, our study also has limitations. First, the case finding was done retrospectively. In the HUNT population, case finding was done from 2008 to 2010, whereas in the Tromsø population, case finding was done repeatedly at two to three years intervals. Although we searched in overlapping sources, both at the local and regional hospitals and via the Cause of Death Registry, inaccurate coding of disease in the hospital registries could have resulted in loss of some patients, despite the precautions that were taken against this. In addition, we could have lost patients who died shortly after the bleeding without autopsy. However, the 1 day case fatality of 14 % is similar to figures observed in Japanese studies, where the

diagnostics of SAH appear to be very rigorous. Therefore, we find it unlikely that we failed to include many eligible patients in our study, maybe except for the first years of observation, mostly due to changes in diagnostics.

We included 29 patients with only suspected aneurysmal SAH. This could be a limitation, as we are not absolutely sure an aneurysm is the cause of the SAH in these patients. However, patients had to fulfill strict criteria to be included, and we performed sensitivity analyses comparing results for aSAH with and without these patients, which showed essentially identical results. We therefore consider it more correct to include these patients than to exclude them, since they are most likely aSAH patients. It can also be considered a strength that we critically reviewed all potential cases and included those who fulfilled the criteria instead of excluding all patients who did not have a verified aneurysm. Several of these patients died before they were subject to angiography or operation, and a bias towards less serious cases of aSAH could be introduced by excluding them. Since we had relatively strict criteria for inclusion of these patients, it is more likely that we excluded aneurysmal SAHs than that we included false positive cases.

As the incidence of aSAH is relatively low, we do not have a large number of aSAH patients in our studies, despite the large cohorts. We combined information from two separate populations, the HUNT and the Tromsø population, to increase the statistical power and precision in papers I, III and IV. The relatively narrow confidence intervals of most of the estimates indicate that precision is relatively good. However, we had limited power to detect small differences within sub groups, for instance over time (in paper I), between different age groups (in paper III), and between men and women (in paper IV).

As mentioned above, we combined information from two separate populations, which could be a possible limitation. However, both population studies share a number of core questions and standardized measurements,[214] and the case finding and case ascertainment were done using similar procedures. We therefore believe the populations are comparable and that combining them was helpful to increase the sample size and power of the study. When appropriate, we have mentioned the differences between the populations in the respective papers.

In paper III, only non-fasting lipid values were available. Total cholesterol and HDL cholesterol levels are not strongly influenced by recent food intake, whereas triglyceride levels tend to be increased following a meal. However, both fasting and non-fasting triglyceride levels have been positively associated with the risk of cardiovascular disease.[222] Nonetheless, we adjusted for time since last meal in the analyses, but the results remained

identical to unadjusted estimates. In addition, the use of cholesterol-lowering medication could influence the results. However, very few (about 1 %) of the Tromsø population used such medication, and there is no information on use in the HUNT population, but the use is not likely to differ substantially from that in Tromsø. Therefore, it seems unlikely that adjustment for cholesterol lowering medication would have substantially altered the results.

Finally, the estimates from epidemiological studies may be distorted by random error that reduces the precision, or by systematic errors that may interfere with the validity of the results.[223] These elements will therefore be discussed more thoroughly in the following sections.

5.3 Precision (lack of random error)

The results of epidemiological studies may always be influenced by chance. Error caused by chance is called random error, and often referred to and quantified as the precision of the estimated associations. In general, there are two ways of increasing precision in a study; one is to increase the study size and the other is to avoid misclassifications in the measurements of the study. As mentioned above, the number of aSAH cases in our study was relatively small. The combination of the two cohorts and the inclusion of patients with suspected aSAH but without angiography or autopsy, increased statistical power and thereby the precision of the findings. Nonetheless, we had limited power to detect small differences within sub groups. However, the main findings of the study were precisely estimated, as indicated by narrow confidence intervals.

Most questions and measurements in the HUNT and Tromsø studies are regarded as good, as indicated by the strength and precision of the results from several studies. We therefore believe they are good tools for studying associations with the risk of aSAH, maybe with alcohol consumption as a possible exception. This will be discussed in section 5.4.3.

5.4 Validity (lack of systematic error)

As mentioned above, random error is caused by chance. The other main type of error in an epidemiologic study is systematic error, often referred to as bias. The opposite of bias is validity, and validity and precision are both components of accuracy.[223] Validity can be divided in internal and external validity. Internal validity is how the inferences drawn from the study apply to the members of the population of the study. External validity is how the

inferences apply to people outside of that population. External validity is also called generalizability and will be discussed further in section 5.4.4. In studies of causation, internal validity is considered a prerequisite for external validity.[223] Most violations of internal validity can be classified in three groups; confounding, selection bias and information bias.

5.4.1 The role of confounding

Confounding can be seen as mixing of effects; the effect of the exposure on the outcome is distorted by the effect of another exposure that is associated with, and is a common cause of both the exposure of interest and the outcome. Confounding can lead to both an overestimation, underestimation and a change in the direction of the estimated effect of interest.[223]

Age and sex are the most obvious confounders in the present studies. This is because the risk of aSAH increases with age, and the distribution of different exposures (e.g. smoking and blood pressure) varies with age. We therefore adjusted for age in all papers. Correspondingly, aSAH is more frequent in women, and the distribution of exposures will tend to differ by sex. In paper IV, we handled this by conducting sex-specific analyses, whereas in the other papers, we adjusted for sex.

In paper III, where the aim was to assess the associations of BMI and serum lipids with the risk of aSAH, we also adjusted for smoking and alcohol consumption. From the directed acyclic graph (DAG)[224, 225] in Figure 7, we can see that these factors may be confounding the association of BMI and risk of aSAH. This is because they are both risk factors for aSAH,[172] and simultaneously, both smoking and high alcohol consumption are associated with low BMI.[226] Therefore, if we had failed to take smoking and alcohol consumption into account (i.e. controlled for them), we could erroneously have found that low BMI was associated with increased risk of aSAH, when in fact there was no association at all, since smoking and alcohol consumption are both associated with both BMI and with the risk of SAH. A similar reasoning may apply for serum lipids.

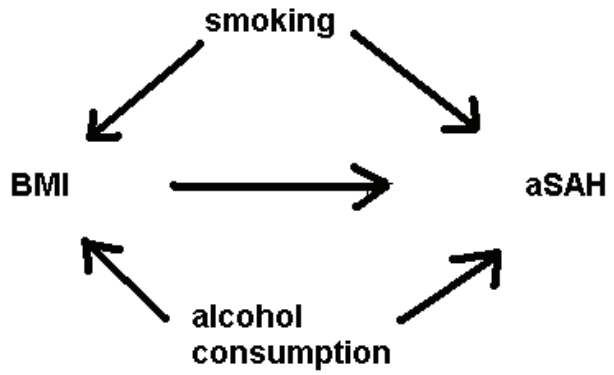

Figure 7. Directed acyclic graph of the association between BMI and aSAH

In paper IV, we also adjusted for family history of stroke, since family history is a potential confounder for the association of smoking and the risk of aSAH. For instance, people may be less likely to smoke if a relative had a stroke at a young age and the risk of aSAH is higher if a first-degree relative has experienced the disease.[69, 160] Since we did not have specific information on family history of SAH, we had to use total strokes instead. This may have led to residual confounding.

In paper II, we chose to show only the unadjusted estimates in the tables. This was done because the amount of missing data on smoking and alcohol consumption in HUNT 1 would lead to a smaller sample size and less precise adjusted estimates. We did, however, include all potential confounders (age, sex, systolic blood pressure, smoking, alcohol, BMI, physical activity, marital status and education) in a multivariable model, and these adjustments did not substantially influence the results.

In all papers, the estimates remained nearly identical after adjustment for potentially confounding factors, implying that little confounding was present. Nonetheless, we cannot exclude residual confounding by other, unmeasured factors or by the questionnaire's inability to reflect the true exposure (for instance for alcohol consumption). In any case, the decision on whether a factor should be regarded as a potential confounder, should be made based on a priori empirical substance knowledge, and not after scrutiny of the results.[225]

5.4.2 The role of selection bias

Selection bias arises when the relation between exposure and outcome differs between the participants and those who are theoretically eligible to participate.[223] Self-referral to studies is usually considered a source of selection bias that may be a threat to validity, because those who chose to participate may differ from those who did not participate.[223, 227] In both the HUNT and the Tromsø studies, all of the general population was invited, and the studies have a relatively high attendance rate. In addition, non-participation studies have been performed. Non-attendance was mostly caused by outside obligations, such as work, and the non-attendees did not systematically differ from those who attended in any respect that is likely to influence their risk of aSAH. However, there may be one exception, since elderly non-participants tended to have higher morbidity and mortality than elderly participants.[211]

5.4.3 The role of information bias

Information bias arises due to measurement errors that may distort the association of exposure and effect. For discrete variables (e.g. smoking, disease) measurement errors are usually called misclassification, and often referred to as either differential or nondifferential, according to whether the misclassification is dependent on the actual values of other variables (differential misclassification) or not (nondifferential misclassification).

Several of the measurements in the present studies were prone to misclassification. For example, random errors will occur in the measurement of serum lipids and blood pressure. There may also be information bias in the reporting of smoking and alcohol consumption. Excessive alcohol consumption has consistently been shown to be a risk factor for SAH,[172] but in this study, the only evident association was a negative association related to being abstinent from alcohol (Paper II). However, if only half of the participants acknowledge their excessive alcohol consumption, the risk difference and risk ratios between the exposure groups will be biased towards the null value due to nondifferential misclassification. In addition, the category of people who drink alcohol five or more times per month may consist of both people who drink one glass of wine every Saturday and some Fridays and people with excessive alcohol consumption. When combining these into one category, we may introduce a nondifferential misclassification bias, masking the association between excessive alcohol consumption and the risk of aSAH.

An inherent assumption in this type of studies is that exposures remain stable over the follow-up period. However, this may not be the case for several exposures. For instance, participants could have started treatment for hypertension or hypercholesterolemia after detection of elevated blood pressure or serum cholesterol in the population study. BMI, alcohol consumption and smoking habits are also factors that are prone to change over time. The likelihood that exposures change will increase with time, and in our study, some participants had the aSAH several years after baseline measurements. Therefore, we cannot exclude the possibility that treatment or behavior changes subsequent to the baseline findings could have influenced later risk of aSAH. However, little is known about the importance of temporal changes in risk factors, and how such changes may interact in the development and rupture of intracranial aneurysms. Therefore, previous exposures, detected at baseline in the population studies, may be just as important as exposures shortly before the bleeding. The strong associations we found for systolic blood pressure and for smoking suggest that baseline measurements can give important information that is highly relevant in relation to the risk of aSAH. In addition, in the Framingham study, with biannual examinations of all participants, both the baseline measurements of systolic and diastolic blood pressures, the measurements from the closest examination prior to SAH, and the mean systolic and diastolic blood pressures based on all examinations were associated with increased risk of SAH, and analogous findings were done in relation to temporal information on smoking.[128]

The misclassifications mentioned above are likely to be nondifferential, meaning the misclassifications do not depend on future aSAH occurrence. For instance, the measurement of blood pressure and the reporting of alcohol consumption are not likely to be related to the development of aSAH. Whereas most other types of biases are unpredictable in the way they may distort the estimates of effect, nondifferential misclassification will in most cases introduce a bias towards the null value since it increases the similarity of the exposure groups.[223] Several of the estimates of this thesis are therefore likely to be underestimates of the true effects.

Detection bias and recall bias are examples of differential misclassification. Recall bias is usually a minor problem in a cohort study, since people are asked about their habits and examined long before they potentially experience the study outcome, which in our cases was aSAH.

There may, however, have been a source of detection bias in our study. Younger people who experience symptoms of aSAH may be more likely to be diagnosed than severely ill elderly people, and young people who suddenly die are more likely to undergo autopsy

than elderly people, although this may have changed during the last decades, leading to more elderly patients being detected in the last part of the study, as discussed further in 5.5.1. This misclassification would lead to an underdiagnosis of aSAH in the elderly and a biased higher risk for younger compared to elderly people. However, we found a strong incidence increase related to age.

The Cause of Death Registry ensured that we had complete follow-up information for all-cause mortality in our study. Data on emigration from Statistics Norway enabled us to censor participants when they moved away from Nord-Trøndelag (in papers I and III) and Tromsø (in papers I, III and IV). Loss of follow up, which is usually a major problem in prospective cohort studies of the general population, is therefore unlikely to play an important role in these studies. However, in papers II and IV, we only had information about people who emigrated from Nord-Trøndelag out of Norway. Census data show that about 2500 persons from Nord-Trøndelag move to other Norwegian counties each year,[209] and most of these are young people, maybe students, who may move back after a few years. Nonetheless, this may have led to an overestimation of person-time in these two studies. However, as we mainly study risk factors for aSAH in these papers, this has probably not influenced our results to a large degree. In the incidence study (paper I), we had information on all migration from both Nord-Trøndelag and Tromsø.

We used strict criteria to include the aSAH cases, and we therefore believe that the specificity of the aSAH cases is close to 100 %, implying that there are no false positive cases. The sensitivity, however, may be moderate because we most likely did not detect all patients and because we had to exclude patients with potential aSAH if the diagnostics performed were too sparse. For most risk factors, this misclassification is likely to be nondifferential. For age, however, the misclassification could be differential, as discussed above. In cases with perfect specificity and imperfect sensitivity, the hazard ratio will be biased towards the null,[223] but when the risk of disease is low, as with aSAH, this bias will be small. We therefore believe that misclassification of outcome had little impact on the estimated effects of risk factors. However, our incidence estimates will probably be somewhat underestimated, especially in the oldest age groups.

5.4.4 External validity (generalizability)

It is an important objective of epidemiological studies to obtain estimates of effect that are valid for relevant target populations.[228] This study is based on population studies with high

participation rates including adults of both sexes. The external validity of our results would be limited if the associations of interest differed between those who were included in the studies and those who were not, or between the adult population of Nord-Trøndelag and Tromsø and other adult populations. There is, to our knowledge, no substantial evidence to indicate that such differences exist. However, the study consists of mainly Caucasian participants and may therefore be less generalizable to other ethnic groups.

5.5 Appraisal of the principal findings

5.5.1 Incidence of aSAH

We estimated the incidence of aSAH to 10.3 per 100,000 person years. Although comparisons between studies can be difficult due to different study designs and case finding procedures,[98, 99] our estimate corresponds well to the findings of other studies from high-income countries.[63, 64, 68-71, 103, 104, 229] However, as discussed in section 1.3, the estimates in other studies may both be over- and underestimated. We reviewed all patient charts manually and validated all aSAH cases. There may have been changes in diagnostics over the last decades, and especially older patients may have more diagnostic tests performed during the recent years even if they are critically ill. Due to our strict criteria for the aSAH diagnosis, we excluded patients with insufficient diagnostic information. Of these excluded patients, more were older than 70 years of age and died within two weeks during the two first time periods (1984-94) as compared to after 1995. This may have contributed to our finding of no decrease in incidence or case fatality during the last 23 years, whereas a moderate decline has been suggested in some other studies.[9, 63, 82, 101, 116]

We found that the incidence was somewhat higher in the northernmost population (Tromsø) compared to the HUNT population in the middle of Norway. A north-south gradient pattern in the incidence of SAH in Norway and Sweden has been previously suggested,[103, 104] but the underlying reason is unclear. The prevalence of current smoking, which is the strongest risk factor for aSAH in this population, was higher in the Tromsø population. Another possibility could be the higher proportion of inhabitants with Finnish and Sami origin in the north. In the Tromsø 3 study population, 6 % were of Finnish and 3 % of Sami origin. It is well known that Finns have higher risk of SAH.[63] In addition, inhabitants of Sami and Finnish origin in northern Norway have less favourable cardiovascular risk factor profiles,

and inhabitant of Finnish origin are at higher risk of ischemic heart disease as compared to inhabitants of majority Norwegian origin.[230]

5.5.2 Mortality of aSAH

We found a 30 days case fatality of 36 %. Although different study designs and end points complicate the comparison between studies, our estimate corresponds well to the findings of several other studies.[1, 9, 64, 65, 69-71, 73, 85, 91, 103, 116, 117, 120, 124, 229, 231, 232] We did, however, not find a decrease in the 30-days case fatality, as has been suggested in other studies,[9, 101, 103, 116-118] while others have found no decrease.[75, 85, 233] As discussed above, this may be due to differences in diagnostics, especially since case fatality increases with age.[103, 141] In addition, our number of aSAH cases may be too low to detect small changes in 30-days case fatality.

Our findings that never smokers may have poorer 6-months survival than current smokers, and the similar tendency of poorer 6-months survival in patients without hypertension as compared to hypertensive patients were surprising. However, in one previous retrospective study without strict criteria for case ascertainment where smoking status was determined by medical records, a poorer survival was found in never smokers.[141] Other studies have found no association between smoking and survival.[142, 143] One possible explanation for this association, if one should assume it is causal, is that smokers may experience less severe aSAHs and less early rebleeding because of elevated serum levels of fibrinogen[226, 234] and other thrombogenic factors.[235] Another possibility is that the increased risk of vasospasm found in smokers[146, 147] may reduce the severity of the initial hemorrhage.[141] The better survival may also be attributed to a younger age at hemorrhage,[141, 146] but the finding persisted after controlling for age, so age is likely not an explanation for the survival differences. Hypertension is used as treatment for vasospasm, [22] which may in part explain why hypertensive patients may have better survival. Finally, smoking and hypertension could possibly lead to a milder type of aSAH than aSAHs associated with other possibly unknown risk factors.

5.5.3 Risk factors for aSAH

We found strong, positive associations between smoking and hypertension and the risk of aSAH. The consistency of these findings across different study types and populations,[151, 153, 154, 170-175, 236] the dose-response relationships,[150, 151, 156, 173, 208] as well as the associations of

smoking and hypertension with other cardiovascular diseases,[205, 237] suggests that these associations may be causal. The mechanisms of how smoking increases the risk of aneurysm formation and rupture are not well understood. Smoking may elevate wall shear stress through nicotine-induced sympathetic activation[238] and increased levels of hematocrit and plasma fibrinogen.[226, 234, 239] Smoking may also increase inflammation within arterial walls by direct effect of tobacco combustion products or through increased blood concentration of white blood cells and increased monocyte-endothelial cell adhesion.[240] Other proposed mechanisms for the increased risk of SAH associated with smoking include increased blood pressure, endothelial dysfunction, enhanced atherosclerosis, and increased degradation of elastin in the arterial walls due to reduced activity of the protease inhibitor α1-antitrypsin.[179, 208, 241]

The mechanisms of how hypertension increases the risk of aneurysm formation and rupture are not well understood. However, studies have suggested that hypertension may cause intimal lesions,[15] and accelerate the process of aneurysm formation due to tensile stress in the presence of altered hemodynamics.[18, 19] Transient elevations of blood pressure have also been proposed to increase the risk of rupture in an intracranial aneurysm.[187-189]

We found that overweight may be associated with reduced risk of aSAH. This finding is in accordance with some previous studies,[156, 170, 171, 182] where others have found no association.[173, 174, 183] If this association is true, the mechanisms are uncertain. It has been suggested that low BMI could be a marker of preclinical disease or "poor health", and that higher morbidity and mortality in people with low BMI may be due to confounding or reverse causation.[242-244] It is also possible that a negative association of overweight with the risk of aSAH could be confounded by smoking or alcohol consumption.[170, 171] However, the association was only slightly attenuated after adjustment for smoking and alcohol consumption. It is unlikely that the negative association of BMI is mediated by serum lipids, since we found no clear association of any serum lipid and the risk of aSAH, except a negative association of HDL cholesterol in participants younger than 50 years of age.

Few studies have assessed the association of HDL cholesterol and the risk of SAH, but one study has reported a negative association.[183] Studies of ischemic heart disease and ischemic stroke have found a protective effect of HDL that is stronger in middle age than in old age.[196, 245] Similar age-dependent effects may therefore be plausible in relation to aSAH.

We found no associations between total serum cholesterol or triglycerides and the risk of aSAH. Some studies have found no association of total serum cholesterol,[167, 168, 170, 173, 174, 184] while others have found a negative association.[154-156, 182, 185] However, in these retrospective studies, the blood samples were drawn after the bleeding had occurred, and the

results may therefore be distorted by reverse causality. Few studies have assessed the effect of triglycerides in relation to SAH, but one retrospective study found a negative association.[155]

5.5.4 Sex differences in risk factors for aSAH

Our results suggest that current cigarette smoking is more strongly associated with increased risk of aSAH in women than in men. This was also suggested in a meta analysis of prospective studies.[172] However, as mentioned in section 1.6, the studies in that meta-analysis had limitations, as the studies either included only one sex,[161, 164-169, 178] only studied the association of alcohol consumption,[163, 181] or had un-validated cases from a national hospital discharge register.[170]

The possible mechanisms for the increased risk of intracranial aneurysms and aSAH in women have been sparsely investigated. The proposed mechanisms include hormonal factors,[63, 159, 182, 199] arterial wall weaknesses due to decreased estrogen after menopause,[201] and local sex differences in the hemodynamic forces acting upon the intracranial arteries.[246]

Our results, suggesting that sex differences in the vulnerability to cigarette smoking contribute to the sex difference in aSAH incidence is supported by the findings in the WHO MONICA study. In this study, an increased incidence of SAH in women as compared to men was evident only in populations where the prevalence of current smoking was approximately evenly distributed in the two sexes. No sex difference or a male preponderance was found in populations where few women smoked.[65, 206]

6 Conclusions

1. We found evidence for a moderate incidence increase in aSAH during 23 years of follow up, but the increase may be explained by changes in diagnostic procedures. Thirty day case fatality has remained fairly stable.

2. We found strong positive associations between blood pressure (systolic and diastolic) and current smoking with the risk of aSAH, whereas being overweight may be associated with reduced risk.

3. We found no over all associations of total cholesterol, HDL cholesterol, or triglycerides with risk, but before the age of 50 years, HDL cholesterol was negatively associated with the risk of aSAH in this large, prospective population-based study.

4. We found that current cigarette-smoking women have higher risk of aSAH as compared to current cigarette-smoking men.

7 Future perspectives

As the years pass, more patients will experience aSAH after participation in the HUNT and Tromsø studies. This will increase the power and precision of estimates from these studies, which will open the possibility to study subgroups, for instance whether risk factors differ for different types of aneurysms, such as aneurysms in the anterior and posterior circulation.

Also, as full-blood samples are available for all participants at baseline, it will be possible to perform studies on genes associated with aSAH. Although it is well-known that genetic factors play an important part in the genesis of intracranial aneurysms, the genetic basis is poorly understood. Identifying susceptible genes may give better understanding of the formation and rupture of intracranial aneurysms, and may also lead to development of pharmacological therapies.[247] Our prospective population studies with verified aSAH cases may contribute to this field.

The decision whether to surgically or endovascularly treat unruptured intracranial aneurysms or follow them conservatively is a controversy in neurosurgery. The prevalence of unruptured intracranial aneurysms is uncertain because of selection bias in earlier studies, and it is seen as unethical to study the natural course of high-risk unruptured intracranial aneurysms. Therefore, the knowledge about rupture risk, as well as the factors that may increase rupture risk, remain uncertain. In HUNT 3, 1000 participants aged 50 to 65 years underwent MRI including angiography. There is information on incidence of aSAH in the same population, and it is therefore possible to estimate rupture risk of unruptured intracranial aneurysms. The participants of the MRI study also participated in HUNT 1 and 2, and the association of life style factors with the risk of unruptured intracranial aneurysms can be assessed.

8 References

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162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
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2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY

243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE

271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN

297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS

324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN
326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1*GENE MUTATION
327. Ingebjørg S. Juel : INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97
334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING
335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA
342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT

350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION
352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY
354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.
362. Kjetil Høydal : EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.
363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS
368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES

379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM
383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES
393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION
395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS
399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY

410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA
412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS
415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?
422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH
424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?
425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE
433. Lars Adde: PREDICTION OF CEREBRAL PALSY IN YOUNG INFANTS. COMPUTER BASED ASSESSMENT OF GENERAL MOVEMENTS
434. Magnus Fasting: PRE- AND POSTNATAL RISK FACTORS FOR CHILDHOOD ADIPOSITY
435. Vivi Talstad Monsen: MECHANISMS OF ALKYLATION DAMAGE REPAIR BY HUMAN AlkB HOMOLOGUES

436. Toril Skandsen: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. MAGNETIC RESONANCE IMAGING FINDINGS, COGNITION AND RISK FACTORS FOR DISABILITY
437. Ingeborg Smidesang: ALLERGY RELATED DISORDERS AMONG 2-YEAR OLDS AND ADOLESCENTS IN MID-NORWAY – PREVALENCE, SEVERITY AND IMPACT. THE PACT STUDY 2005, THE YOUNG HUNT STUDY 1995-97
438. Vidar Halsteinli: MEASURING EFFICIENCY IN MENTAL HEALTH SERVICE DELIVERY: A STUDY OF OUTPATIENT UNITS IN NORWAY
439. Karen Lehrmann Ægidius: THE PREVALENCE OF HEADACHE AND MIGRAINE IN RELATION TO SEX HORMONE STATUS IN WOMEN. THE HUNT 2 STUDY
440. Madelene Ericsson: EXERCISE TRAINING IN GENETIC MODELS OF HEART FAILURE
441. Marianne Klokk: THE ASSOCIATION BETWEEN SELF-REPORTED ECZEMA AND COMMON MENTAL DISORDERS IN THE GENERAL POPULATION. THE HORDALAND HEALTH STUDY (HUSK)
442. Tomas Ottemo Stølen: IMPAIRED CALCIUM HANDLING IN ANIMAL AND HUMAN CARDIOMYOCYTES REDUCE CONTRACTILITY AND INCREASE ARRHYTHMIA POTENTIAL – EFFECTS OF AEROBIC EXERCISE TRAINING
443. Bjarne Hansen: ENHANCING TREATMENT OUTCOME IN COGNITIVE BEHAVIOURAL THERAPY FOR OBSESSIVE COMPULSIVE DISORDER: THE IMPORTANCE OF COGNITIVE FACTORS
444. Mona Løvlien: WHEN EVERY MINUTE COUNTS. FROM SYMPTOMS TO ADMISSION FOR ACUTE MYOCARDIAL INFARCTION WITH SPECIAL EMPHASIS ON GENDER DIFFERECES
445. Karin Margaretha Gilljam: DNA REPAIR PROTEIN COMPLEXES, FUNCTIONALITY AND SIGNIFICANCE FOR REPAIR EFFICIENCY AND CELL SURVIVAL
446. Anne Byriel Walls: NEURONAL GLIAL INTERACTIONS IN CEREBRAL ENERGY – AND AMINO ACID HOMEOSTASIS – IMPLICATIONS OF GLUTAMATE AND GABA
447. Cathrine Fallang Knetter: MECHANISMS OF TOLL-LIKE RECEPTOR 9 ACTIVATION
448. Marit Følsvik Svindseth: A STUDY OF HUMILIATION, NARCISSISM AND TREATMENT OUTCOME IN PATIENTS ADMITTED TO PSYCHIATRIC EMERGENCY UNITS
449. Karin Elvenes Bakkelund: GASTRIC NEUROENDOCRINE CELLS – ROLE IN GASTRIC NEOPLASIA IN MAN AND RODENTS
450. Kirsten Brun Kjelstrup: DORSOVENTRAL DIFFERENCES IN THE SPATIAL REPRESENTATION AREAS OF THE RAT BRAIN
451. Roar Johansen: MR EVALUATION OF BREAST CANCER PATIENTS WITH POOR PROGNOSIS
452. Rigmor Myran: POST TRAUMATIC NECK PAIN. EPIDEMIOLOGICAL, NEURORADIOLOGICAL AND CLINICAL ASPECTS
453. Krisztina Kunszt Johansen: GENEALOGICAL, CLINICAL AND BIOCHEMICAL STUDIES IN *LRRK2* – ASSOCIATED PARKINSON'S DISEASE
454. Pål Gjerden: THE USE OF ANTICHOLINERGIC ANTIPARKINSON AGENTS IN NORWAY. EPIDEMIOLOGY, TOXICOLOGY AND CLINICAL IMPLICATIONS
455. Else Marie Huuse: ASSESSMENT OF TUMOR MICROENVIRONMENT AND TREATMENT EFFECTS IN HUMAN BREAST CANCER XENOGRAFTS USING MR IMAGING AND SPECTROSCOPY
456. Khalid S. Ibrahim: INTRAOPERATIVE ULTRASOUND ASSESSMENT IN CORONARY ARTERY BYPASS SURGERY – WITH SPECIAL REFERENCE TO CORONARY ANASTOMOSES AND THE ASCENDING AORTA
457. Bjørn Øglænd: ANTHROPOMETRY, BLOOD PRESSURE AND REPRODUCTIVE DEVELOPMENT IN ADOLESCENCE OF OFFSPRING OF MOTHERS WHO HAD PREECLAMPSIA IN PREGNANCY
458. John Olav Roaldset: RISK ASSESSMENT OF VIOLENT, SUICIDAL AND SELF-INJURIOUS BEHAVIOUR IN ACUTE PSYCHIATRY – A BIO-PSYCHO-SOCIAL APPROACH
459. Håvard Dalen: ECHOCARDIOGRAPHIC INDICES OF CARDIAC FUNCTION – NORMAL VALUES AND ASSOCIATIONS WITH CARDIAC RISK FACTORS IN A POPULATION FREE FROM CARDIOVASCULAR DISEASE, HYPERTENSION AND DIABETES: THE HUNT 3 STUDY
460. Beate André: CHANGE CAN BE CHALLENGING. INTRODUCTION TO CHANGES AND IMPLEMENTATION OF COMPUTERIZED TECHNOLOGY IN HEALTH CARE

461. Latha Nrugham: ASSOCIATES AND PREDICTORS OF ATTEMPTED SUICIDE AMONG DEPRESSED ADOLESCENTS – A 6-YEAR PROSPECTIVE STUDY
462. Håvard Bersås Nordgaard: TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS – A CLINICAL AND EXPERIMENTAL STUDY

Cotutelle with University of Ghent: Abigail Emily Swillens: A MULTIPHYSICS MODEL FOR IMPROVING THE ULTRASONIC ASSESSMENT OF LARGE ARTERIES

2011

463. Marte Helene Bjørk: DO BRAIN RHYTHMS CHANGE BEFORE THE MIGRAINE ATTACK? A LONGITUDINAL CONTROLLED EEG STUDY
464. Carl-Jørgen Arum: A STUDY OF UROTHELIAL CARCINOMA: GENE EXPRESSION PROFILING, TUMORIGENESIS AND THERAPIES IN ORTHOTOPIC ANIMAL MODELS
465. Ingunn Harstad: TUBERCULOSIS INFECTION AND DISEASE AMONG ASYLUM SEEKERS IN NORWAY. SCREENING AND FOLLOW-UP IN PUBLIC HEALTH CARE
466. Leif Åge Strand: EPIDEMIOLOGICAL STUDIES AMONG ROYAL NORWEGIAN NAVY SERVICEMEN. COHORT ESTABLISHMENT, CANCER INCIDENCE AND CAUSE-SPECIFIC MORTALITY
467. Katrine Høyer Holgersen: SURVIVORS IN THEIR THIRD DECADE AFTER THE NORTH SEA OIL RIG DISASTER OF 1980. LONG-TERM PERSPECTIVES ON MENTAL HEALTH
468. MarianneWallenius: PREGNANCY RELATED ASPECTS OF CHRONIC INFLAMMATORY ARTHRITIDES: DISEASE ONSET POSTPARTUM, PREGNANCY OUTCOMES AND FERTILITY. DATA FROM A NORWEGIAN PATIENT REGISTRY LINKED TO THE MEDICAL BIRTH REGISTRY OF NORWAY
469. Ole Vegard Solberg: 3D ULTRASOUND AND NAVIGATION – APPLICATIONS IN LAPAROSCOPIC SURGERY
470. Inga Ekeberg Schjerve: EXERCISE-INDUCED IMPROVEMENT OF MAXIMAL OXYGEN UPTAKE AND ENDOTHELIAL FUNCTION IN OBESE AND OVERWEIGHT INDIVIDUALS ARE DEPENDENT ON EXERCISE-INTENSITY
471. Eva Veslemøy Tyldum: CARDIOVASCULAR FUNCTION IN PREECLAMPSIA – WITH REFERENCE TO ENDOTHELIAL FUNCTION, LEFT VENTRICULAR FUNCTION AND PRE-PREGNANCY PHYSICAL ACTIVITY
472. Benjamin Garzón Jiménez de Cisneros: CLINICAL APPLICATIONS OF MULTIMODAL MAGNETIC RESONANCE IMAGING
473. Halvard Knut Nilsen: ASSESSING CODEINE TREATMENT TO PATIENTS WITH CHRONIC NON-MALIGNANT PAIN: NEUROPSYCHOLOGICAL FUNCTIONING, DRIVING ABILITY AND WEANING
474. Eiliv Brenner: GLUTAMATE RELATED METABOLISM IN ANIMAL MODELS OF SCHIZOPHRENIA
475. Egil Jonsbu: CHEST PAIN AND PALPITATIONS IN A CARDIAC SETTING; PSYCHOLOGICAL FACTORS, OUTCOME AND TREATMENT
476. Mona Høysæter Fenstad: GENETIC SUSCEPTIBILITY TO PREECLAMPSIA : STUDIES ON THE NORD-TRØNDELAG HEALTH STUDY (HUNT) COHORT, AN AUSTRALIAN/NEW ZEALAND FAMILY COHORT AND DECIDUA BASALIS TISSUE
477. Svein Erik Gaustad: CARDIOVASCULAR CHANGES IN DIVING: FROM HUMAN RESPONSE TO CELL FUNCTION
478. Karin Torvik: PAIN AND QUALITY OF LIFE IN PATIENTS LIVING IN NURSING HOMES
479. Arne Solberg: OUTCOME ASSESSMENTS IN NON-METASTATIC PROSTATE CANCER
480. Henrik Sahlin Pettersen: CYTOTOXICITY AND REPAIR OF URACIL AND 5-FLUOROURACIL IN DNA
481. Pui-Lam Wong: PHYSICAL AND PHYSIOLOGICAL CAPACITY OF SOCCER PLAYERS: EFFECTS OF STRENGTH AND CONDITIONING
482. Ole Solheim: ULTRASOUND GUIDED SURGERY IN PATIENTS WITH INTRACRANIAL TUMOURS
483. Sten Roar Snare: QUANTITATIVE CARDIAC ANALYSIS ALGORITHMS FOR POCKET-SIZED ULTRASOUND DEVICES
484. Marit Skyrud Bratlie: LARGE-SCALE ANALYSIS OF ORTHOLOGS AND PARALOGS IN VIRUSES AND PROKARYOTES

485. Anne Elisabeth F. Isern: BREAST RECONSTRUCTION AFTER MASTECTOMY – RISK OF RECURRENCE AFTER DELAYED LARGE FLAP RECONSTRUCTION – AESTHETIC OUTCOME, PATIENT SATISFACTION, QUALITY OF LIFE AND SURGICAL RESULTS; HISTOPATHOLOGICAL FINDINGS AND FOLLOW-UP AFTER PROPHYLACTIC MASTECTOMY IN HEREDITARY BREAST CANCER
486. Guro L. Andersen: CEREBRAL PALSY IN NORWAY – SUBTYPES, SEVERITY AND RISK FACTORS
487. Frode Kolstad: CERVICAL DISC DISEASE – BIOMECHANICAL ASPECTS
488. Bente Nordtug: CARING BURDEN OF COHABITANTS LIVING WITH PARTNERS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE OR DEMENTIA
489. Mariann Gjervik Heldahl: EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER BASED ON MR METHODOLOGY
490. Lise Tevik Løvseth: THE SUBJECTIVE BURDEN OF CONFIDENTIALITY
491. Marie Hjelmseth Aune: INFLAMMATORY RESPONSES AGAINST GRAM NEGATIVE BACTERIA INDUCED BY TLR4 AND NLRP12
492. Tina Strømdal Wik: EXPERIMENTAL EVALUATION OF NEW CONCEPTS IN HIP ARTHROPLASTY
493. Solveig Sigurdardottir: CLINICAL ASPECTS OF CEREBRAL PALSY IN ICELAND. A POPULATION-BASED STUDY OF PRESCHOOL CHILDREN
494. Arne Reimers: CLINICAL PHARMACOKINETICS OF LAMOTRIGINE
495. Monica Wegling: KULTURMENNESKETS BYRDE OG SYKDOMMENS VELSIGNELSE. KAN MEDISINSK UTREDNING OG INTERVENSJON HA EN SELVSTENDIG FUNKSJON UAVHENGIG AV DET KURATIVE?
496. Silje Alvestad: ASTROCYTE-NEURON INTERACTIONS IN EXPERIMENTAL MESIAL TEMPORAL LOBE EPILEPSY – A STUDY OF UNDERLYING MECHANISMS AND POSSIBLE BIOMARKERS OF EPILEPTOGENESIS
497. Javaid Nauman: RESTING HEART RATE: A MATTER OF LIFE OR DEATH – PROSPECTIVE STUDIES OF RESTING HEART RATE AND CARDIOVASCULAR RISK (THE HUNT STUDY, NORWAY)
498. Thuy Nguyen: THE ROLE OF C-SRC TYROSINE KINASE IN ANTIVIRAL IMMUNE RESPONSES
499. Trine Naalsund Andreassen: PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENETIC ASPECTS OF OXYCODONE TREATMENT IN CANCER PAIN
500. Eivor Alette Laugsand: SYMPTOMS IN PATIENTS RECEIVING OPIOIDS FOR CANCER PAIN – CLINICAL AND PHARMACOGENETIC ASPECTS
501. Dorthe Stensvold: PHYSICAL ACTIVITY, CARDIOVASCULAR HEALTH AND LONGEVITY IN PATIENTS WITH METABOLIC SYNDROME
502. Stian Thoresen Aspenes: PEAK OXYGEN UPTAKE AMONG HEALTHY ADULTS – CROSS-SECTIONAL DESCRIPTIONS AND PROSPECTIVE ANALYSES OF PEAK OXYGEN UPTAKE, PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK FACTORS IN HEALTHY ADULTS (20-90 YEARS)
503. Reidar Alexander Vigen: PATHOBIOLOGY OF GASTRIC CARCINOIDS AND ADENOCARCINOMAS IN RODENT MODELS AND PATIENTS. STUDIES OF GASTROCYSTOPLASTY, GENDER-RELATED FACTORS, AND AUTOPHAGY
504. Halvard Høilund-Kaupang: MODELS AND METHODS FOR INVESTIGATION OF REVERBERATIONS IN NONLINEAR ULTRASOUND IMAGING
505. Audhild Løhre: WELLBEING AMONG SCHOOL CHILDREN IN GRADES 1-10: PROMOTING AND ADVERSE FACTORS
506. Torgrim Tandstad: VOX POPULI. POPULATION-BASED OUTCOME STUDIES IN TESTICULAR CANCER
507. Anna Brenne Grønskag: THE EPIDEMIOLOGY OF HIP FRACTURES AMONG ELDERLY WOMEN IN NORD-TRØNDELAG. HUNT 1995-97, THE NORD-TRØNDELAG HEALTH STUDY
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512. Karin Fahl Wader: HEPATOCYTE GROWTH FACTOR, C-MET AND SYNDECAN-1 IN MULTIPLE MYELOMA
513. Gerd Tranø: FAMILIAL COLORECTAL CANCER
514. Bjarte Bergstrøm: INNATE ANTIVIRAL IMMUNITY – MECHANISMS OF THE RIG-I-MEDIATED RESPONSE
515. Marie Søfteland Sandvei: INCIDENCE, MORTALITY, AND RISK FACTORS FOR ANEURYSMAL SUBARACHNOID HEMORRHAGE. PROSPECTIVE ANALYZES OF THE HUNT AND TROMSØ STUDIES