UiT The Arctic University of Norway

Faculty of Health Sciences
Department of Clinical Medicine

Temporal trends in intracerebral hemorrhage in a general population

Incidence, risk factors, case fatality and long-term mortality

The Tromsø Study

Maria Carlsson

A dissertation for the degree of Philosophiae Doctor. August 2021

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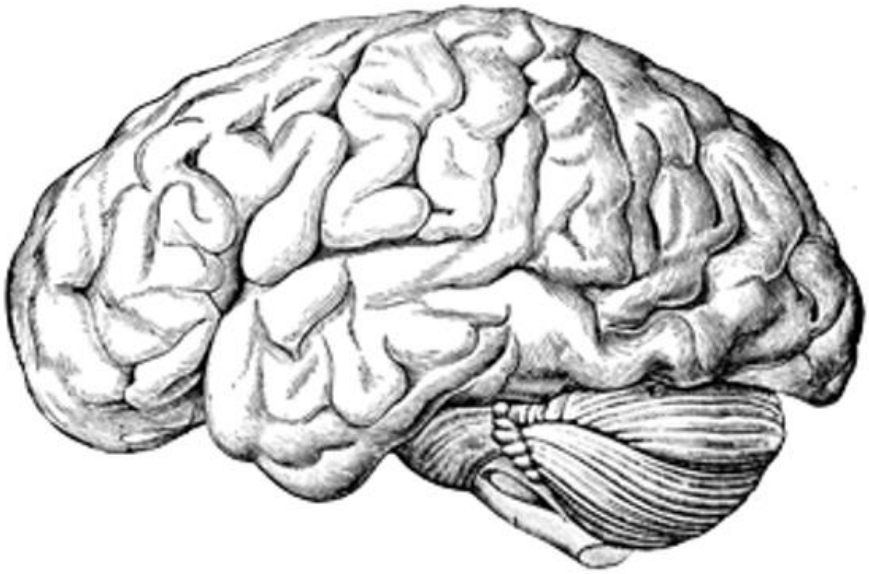

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«*L'acqua che tocchi de' fiumi è l'ultima di quelle che andò e la prima di quella che viene. Così il tempo presente.*»

“In rivers, the water that you touch is the last of what has passed and the first of which comes; so with present time”

Leonardo da Vinci, 1452-1519, Codex Trivulziano fol 34 r., Milan

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Table of Contents

Summary

Intracerebral hemorrhage (ICH) is the second most common subtype of stroke. The prognosis is poor. However, it is to a large degree a preventable disease. The aim of our study was to analyse the association between cardiovascular risk factors and risk of ICH, and to assess the impact of changes in risk factor levels over time on incidence rates of ICH. In addition, we aimed to analyse short- and long-term mortality after ICH. The Tromsø study is an ongoing, longitudinal population-based study with repeated health surveys, with >45,000 attendees, providing an unique opportunity to assess longitudinal data on ICH epidemiology in a general population in a well-defined geographical area. Age, male sex, systolic and diastolic blood pressure were significantly associated with increased risk of ICH. Incidence rates were stable in the overall population in the period 1995-2013. In women incidence rates decreased, whereas incidence rates in men were stable. Lower blood pressure levels, and a steeper decrease in blood pressure in women may have contributed to the difference in trends. Despite an increase in treatment of hypertension, less than half of attendees of the last survey who had hypertension were on blood pressure-lowering drugs. Of these, two-thirds had uncontrolled hypertension. One-month case fatality and 5-year mortality rates remained stable. Participants who survived the first 30 days after ICH had a more than 60% increased 5-year risk of death compared with controls matched by birth-year and sex. The main cause of death was cardiovascular disease. Smoking, serum cholesterol and use of anticoagulant drugs at time of ICH were associated with increased risk of 5-year mortality after ICH.

Our results indicate that there is a need for improved primary prevention of ICH. The stable short- and long-term mortality rates probably reflect the limited treatment possibilities of ICH and emphasize the urge for improved treatment strategies in the acute phase and a need for better knowledge on secondary prevention after ICH.

Sammendrag

Intracerebral blødning (ICB) er den nest hyppigste type av hjerneslag. Prognosen etter ICB er alvorlig, men det er en sykdom som i stor grad kan forebygges. Vi ønsket å undersøke hvilke risikofaktorer som øker risikoen for ICB, og om endringer i risikofaktorer over tid har påvirket forekomsten av ICB. I tillegg ønsket vi å undersøke kort- og langtidsdødelighet etter ICB. Tromsøundersøkelsen er en pågående longitudinell populasjonsbasert studie med repeterte målinger med over 45,000 deltakere. Undersøkelsen gir en unik mulighet til å analysere endringer over tid i insidens og dødelighet og risiko-faktorer for ICB i befolkningen. Vi fant at alder, mannlig kjønn, systolisk og diastolisk blodtrykk var signifikant assosiert med risikoen for ICB. Insidensraten av ICB var stabil i den samlede befolkningen i perioden 1995-2013. Vi observerte imidlertid en nedgang i insidens av ICB hos kvinner. Insidensratene hos menn var stabile. Lavere blodtrykksnivåer og en større nedgang i blodtrykk hos kvinner kan ha bidratt til forskjellen i trend. Blant deltakere med hypertensjon økte andelen som ble behandlet og hadde velregulert blodtrykk. Til tross for dette var mindre enn halvparten av deltakere med hypertensjon i siste del av studien medikamentelt behandlet. To tredeler av disse hadde ukontrollert hypertensjon. Det var ingen endring i 30-dagers fatalitet og 5-års dødelighet. Blant deltakere som var i live 30 dager etter ICB var risikoen for død i løpet av 5 år mer enn 60% høyere sammenlignet med kontroller matchet for fødselsår og kjønn. Forskjellen kunne forklares av en økt risiko for død av kardiovaskulær sykdom hos pasienter med ICB. Røyking, serum kolesterol og bruk av antikoagulantia på blødningstidspunktet var assosiert med økt risiko for 5-års dødelighet.

De stabile insidensratene viser at det er behov for en forbedret forebygging av ICB. Stabile trender i kort- og langtidsdødelighet indikerer at det er et behov for mer effektiv behandling av ICB. I tillegg er det behov for økt kunnskap om sekundærprofylakse etter ICB.

List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals:

Paper I. Carlsson M, Wilsgaard T, Johnsen SH, Vangen-Lønne AM, Løchen ML, Njølstad I, Mathiesen EB. Temporal trends in incidence and case fatality of intracerebral hemorrhage: the Tromsø Study 1995-2012. Cerebrovasc Dis Extra. 2016;6(2):40-9.

Paper II. Carlsson M, Wilsgaard T, Johnsen SH, Johnsen LH, Løchen ML, Njølstad I, Mathiesen EB. The impact of risk factor trends on intracerebral hemorrhage incidence over the last two decades – The Tromsø Study. Int J Stroke. 2019;14(1):61-68.

Paper III. Carlsson M, Wilsgaard T, Johnsen SH, Johnsen LH, Løchen ML, Njølstad I, Mathiesen EB. Long-term survival, causes of death and trends in five-year mortality after intracerebral hemorrhage. The Tromsø Study. Accepted for publication in Stroke on April 2, 2021.

Abbreviations

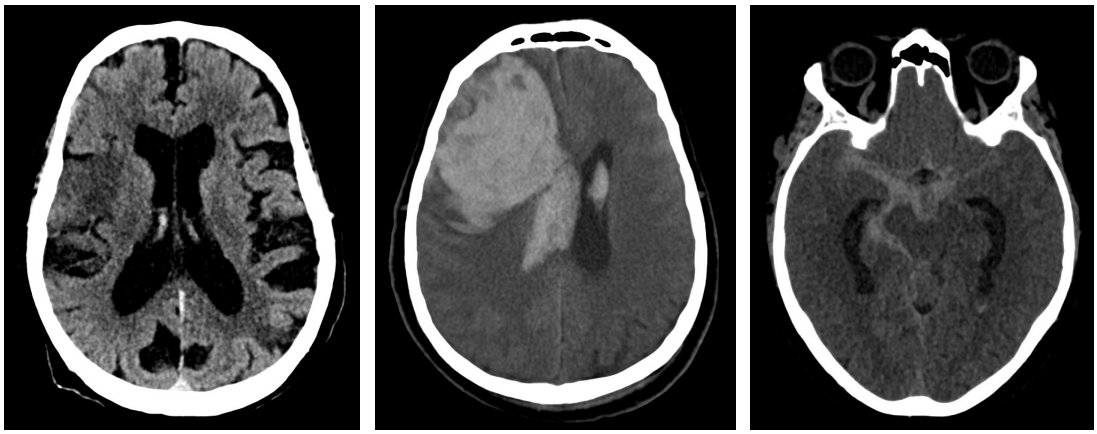
AIC	Akaike information criterion
BMI	Body mass index
CHARTS	The Cerebral Haemorrhage Anatomical RaTing instrument
CI	Confidence Interval
CT	Computed tomography
CVD	Cardiovascular disease
DALY	Disability adjusted life years
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DNR	Do not resuscitate
DOAC	Direct oral anticoagulants
GCS	Glasgow Coma Scale score
HDL	High-density lipoprotein
HR	Hazard Ratio
ICD	International classification of diseases for mortality and morbidity statistics
ICH	Intracerebral hemorrhage
INR	International normalized ratio
IRR	Incidence rate ratio
IS	Ischemic stroke
LDL	Low-density lipoprotein
MRI	Magnetic resonance imaging
OR	Odds ratio
RCT	Randomised controlled study
RIND	Reversible ischaemic neurological deficit
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
SD	Standard deviation
TIA	Transient ischemic attack
UNN	University Hospital of North Norway
VKA	Vitamin K antagonist
WHO	World Health Organization

1 Introduction

1.1 Stroke and stroke epidemiology

Stroke is the second leading cause of death and disability worldwide.[1] In Norway, stroke is the third leading cause of death.[2, 3] A stroke is caused by blockage (ischemic stroke (IS)) or rupture (hemorrhagic stroke) of a brain artery, leading to a sudden death of brain cells.[4] Hemorrhagic stroke can be further classified into intracerebral hemorrhage (ICH; bleeding into the brain parenchyma and/or into the ventricular system) and subarachnoid hemorrhage (SAH; bleeding into the subarachnoid space). Worldwide, 73-90% of strokes were ischemic, 9-27% ICH and 1-10% SAH in the period 2000-2008, with the highest proportion of hemorrhagic strokes in low-to middle income countries.[5] The symptoms of a stroke depend on the area of the brain affected, with limb paresis, speech disturbances and facial palsy being the most common in IS and ICH,[6, 7] and sudden headache the most common in SAH.[8] The symptoms of IS and ICH are similar, and brain imaging by computed tomography (CT) / magnetic resonance imaging (MRI) or autopsy are essential to differentiate the different types of stroke (Figure 1).[6]

Figure 1. CT scans of stroke subtypes



Ischemic stroke | Intracerebral hemorrhage | Subarachnoid hemorrhage

Print of radiological images on the courtesy of Liv Hege Johnsen, MD, Department of Radiology, University Hospital of North Norway

1.1.1 A historical perspective on stroke

The disease was first described by Hippocrates in 400 BC, including symptoms as acute brain pain, diplopia, vertigo, ataxia, saliva, urine loss and fecal incontinence, and by Hippocrates referred to by the term apoplexia ("to strike down").[9] Apoplexia, however, encompassed several different neurologic diseases in addition to what we today would define as a stroke.[9] Hippocrates linked the pathogenesis of apoplexia to the humoral theory; where it was believed that blood held the spirit of humans, and that an interference with the flow of the spirit to the brain would result in apoplexy.[10] His proponent, Galen (born AD 131) believed that the causes of apoplexy were due to an influx of blood into the brain or from accumulation of phlegm and black bile in the cerebral ventricles blocking the transmission of the animal spirit.[11] The first recorded use of 'stroke' as a lay term was in 1599, attributing the sudden onset of symptoms to a 'stroke of God's hand'.[10] In 1658 Johan Jakob Webfer published four cases observing the association with apoplexy and cerebral hemorrhage.[12] In later scientific publications, based on an increasing amount of autopsies, apoplexy was associated with cerebral hemorrhage, tumors and cerebral abscesses.[13] In 1689 the term stroke was introduced into medicine by William Cole in "A physio-medical essay concerning the late frequencies of apoplexies".[14] In the early 19th century a link between arterial occlusive disease and areas of cerebral softening was recognised,[15] and in the early 20th century causes of apoplexy were reclassified as hemorrhagic or ischemic.[13] In the 1960s, a stroke was defined as a sudden, focal neurological deficit of vascular origin with a neurological deficit remaining for more than seven days.[16] Symptoms lasting less than 24 hours were defined as a transient ischemic attack (TIA) and those lasting between 24 hours and 7 days as a reversible ischemic neurological deficit (RIND).[16] In 1970, the World Health Organization (WHO) defined stroke as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function,

lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.[17] Recently, a new definition of IS that incorporates tissue criteria based on brain imaging in individuals with symptoms lasting <24 hours has been included in the International classification of diseases for mortality and morbidity statistics (ICD) 11 criteria of IS.[18]

Figure 2. Treatment of chronic apoplexy.

Miniature from a textbook of surgery written by the Arab physician Abu al-_Qasim Khalaf Ibn Abbas az-Zahrawi, born in the 10th century (ABU´L QASIM, Codex Series Nova 2641, Fol 6ra. Reprinted in: (1979) Chirurgia). From: https://digital.onb.ac.at/RepViewer/viewer.faces?doc=DTL_7060734&order=1&view=SINGLE, with permission from Austrian National Library

1.1.2 Stoke epidemiology

Stroke is a major challenge for public health; in 2017 there were 11.9 million incident stroke cases, 104.2 million prevalent stroke cases, 6.2 million stroke deaths and 132 million stroke-related disability adjusted life years (DALYs) worldwide.[1] In addition to the

direct consequences of a stroke for the individuals affected and their families, it contributes to a large economic burden for society with yearly expenses in Europe estimated to 60 billion Euro and in Norway to 926 million Euro.[19]

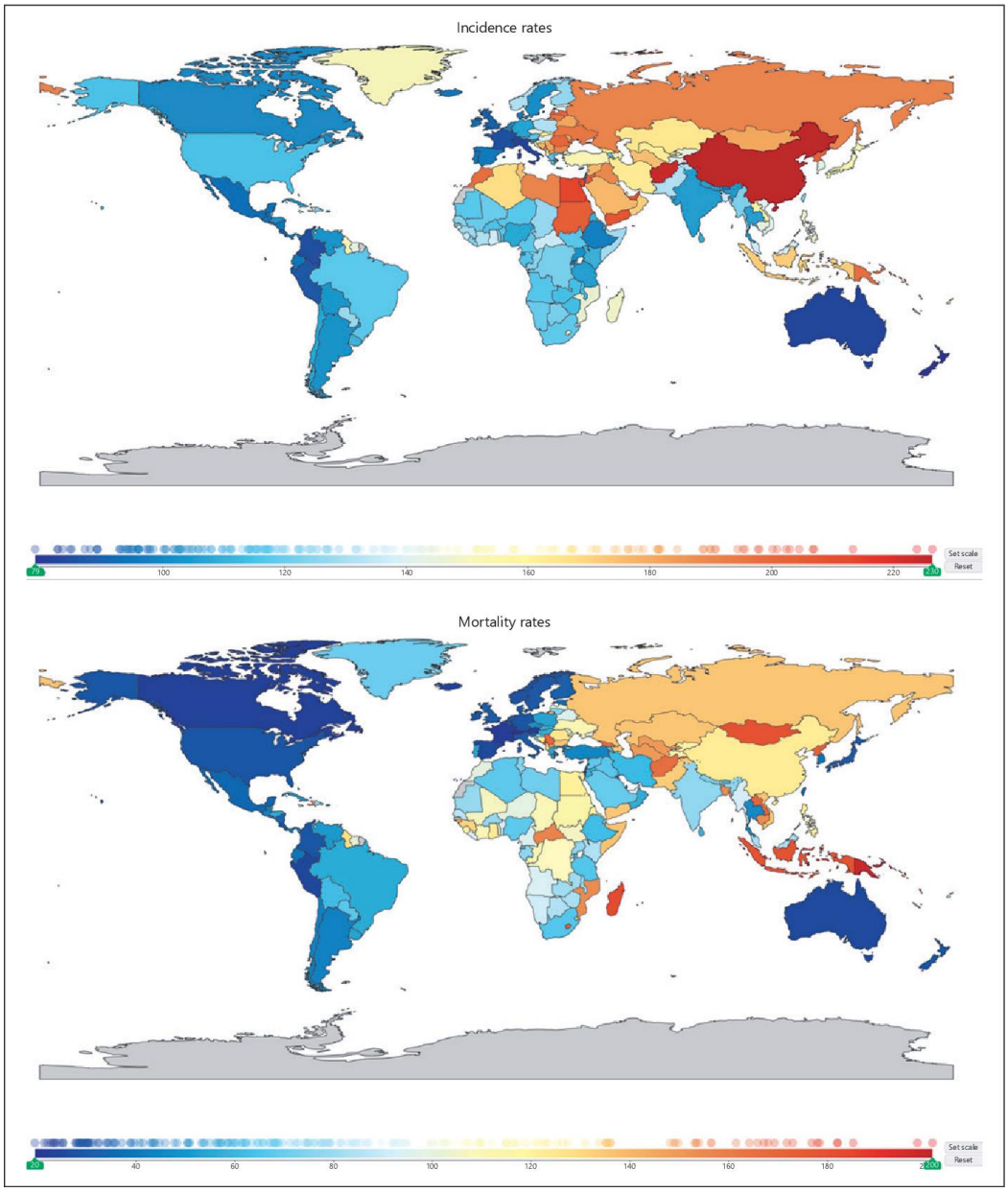
Globally, the age-adjusted stroke incidence, prevalence, mortality and DALYs decreased in the period 1990-2017.[1] Despite this, the absolute number of people with incident stroke and people who died, survived or remained disabled from stroke almost doubled.[1] There are regional differences in incidence rates and time trends. Previously, highest incidence rates of stroke were observed in high-income countries.[5] Since the 1970s, an epidemiological transition has been observed with a decrease in incidence and mortality rates in high-income countries and a concomitant increase in low- and middle-income countries.[5] After 2000, the overall stroke incidence rates in low- to middle-income countries have exceeded the level of stroke incidence in high-income countries, probably due to health and demographic transitions.[5] Currently, approximately 80% of strokes, 87% of stroke-related deaths and 89% DALYs occur in low- and middle-income countries.[1] Patients in low- and middle-income countries are younger at stroke onset, have more severe strokes with a higher proportion of ICH.[20] In addition, access to health services is lower in these countries.[20] Global age-standardised stroke incidence and mortality rates in 2017 are shown in Figure 3.

In addition to differences according to country income levels, trends may vary between countries within income groups. An example of this is a study from Sweden, showing stable incidence and mortality rates of stroke during the period 1987 to 2006 despite reports of a decrease in incidence and mortality in other high-income countries.[21]

In Norway, a decrease in stroke mortality has been observed since the 1960´s.[22] At initiation of the present study, it was unknown if the decrease was due to lower incidence rates or case fatality rates or both.[22] In 2012 the Norwegian Stroke Registry was established

with mandatory registration of hospitalised strokes in Norway.[23] Before this, data on stroke incidence and case fatality from well-defined Norwegian cohorts were few.[24, 25]

Figure 3. Global age-standardised stroke incidence and death rates per 100,000 people in 2017.



Reprinted from Krishnamurthi R, V, Ikeda T, Feigin V,L: Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. Neuroepidemiology 2020;54:171-179. doi: 10.1159/000506396. With permission from S Karger AG, Basel.

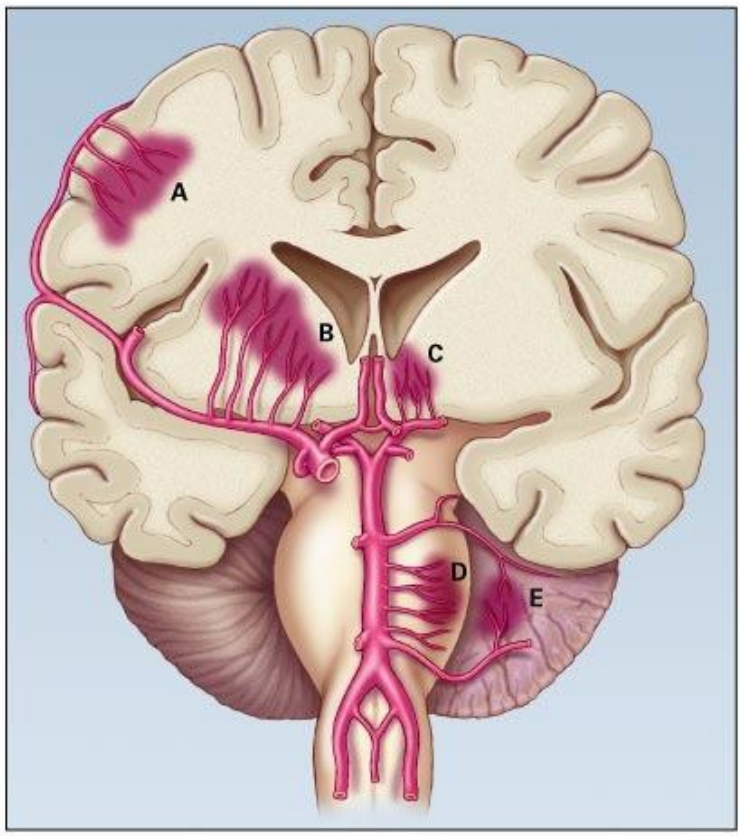
1.2 Intracerebral hemorrhage

An ICH is caused by a rupture of a blood vessel which causes a hemorrhage in the cerebral parenchyma; in some cases with extension into the ventricles and/or into the subarachnoid and dural spaces. Despite accounting for only 9-27 % of all strokes worldwide,[5] ICH contributes largely to the burden of stroke. Hemorrhagic strokes (ICH and SAH combined) are associated with greater worldwide DALYs lost compared with IS and contribute to approximately half of all stroke deaths.[26] Only 12%-39% live independently after an ICH.[27] One-month case fatality rates of ICH range between 13%-61% with a median of 40%.[27] Five-year survival rates have been estimated to 29%.[28]

1.2.1 Pathophysiology

Intracerbral hemorrhage is a heterogeneous condition. The most frequent causes are deep perforating vasculopathy and sporadic cerebral amyloid angiopathy (CAA).[29] A lower proportion is secondary bleedings caused by trauma, underlying lesions (e.g. brain tumors, vascular lesions and IS) or hematologic disease.[29] Intracerebral hemorrhage may be classified as non-lobar and lobar ICH (Figure 4). Non-lobar ICH are mainly due to deep perforating vasculopathy caused by hypertension,[30] and are located in subcortical structures, basal ganglia, thalamus, brainstem or cerebellum. Lobar ICH are located to cortico-subcortical areas of the brain lobes, often near or reaching the cerebral convexities. The most common cause of lobar ICH is CAA, which is a chronic degenerative process in leptomeningeal and cortical blood vessels causing a progressive loss of smooth muscle cells and a simultaneous accumulation of amyloid-β.[31]

Figure 4. The most common locations of intracerebral hemorrhage (ICH)



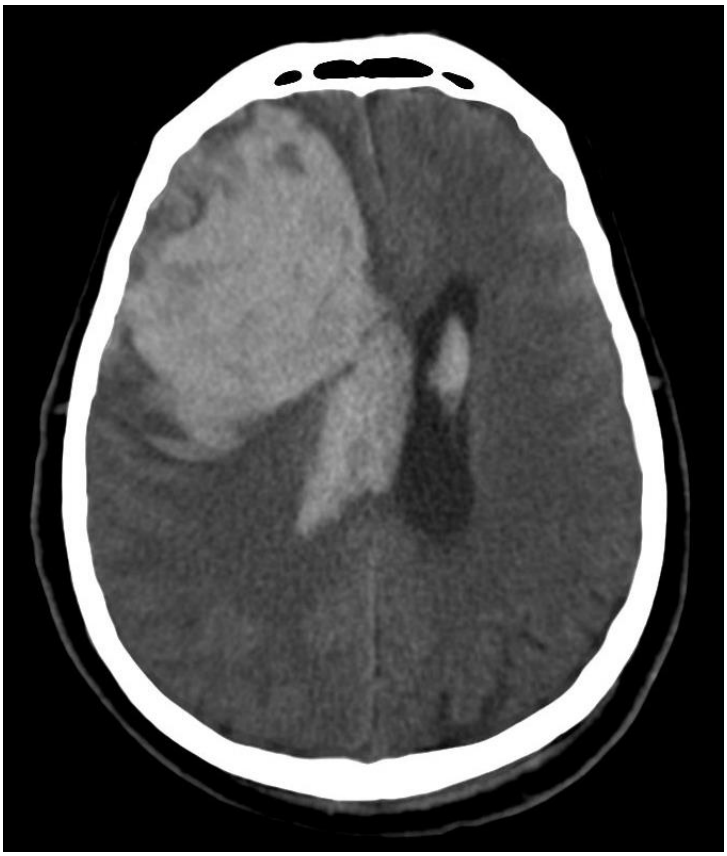
Lobar ICH: Lobar areas of the brain, originating from penetrating cortical branches of the anterior, middle, or posterior cerebral arteries (A).
Non-lobar ICH: Basal ganglia, originating from ascending lenticulostriate branches of the middle cerebral artery (B). Thalamus, branches originating from ascending thalmogeniculate branches of the posterior cerebral artery (C). The pons, originating from paramedian branches of the basilar artery (D). The cerebellum, originating from penetrating branches of the posterior inferior, anterior inferior, or superior cerebellar arteries (E).

1.2.2 Mechanisms of brain injury

In the acute phase after an ICH the hematoma causes damage of brain cells by different mechanisms. Mass effect of the hematoma may cause twisting of surrounding tissue with successively tearing of other diseased microvessels causing further rupture of blood vessels and enlargement of the hematoma.[32] In addition, degradation products of extravasated blood

(heme, iron and thrombin) may trigger toxic and inflammatory cascades, which in turn may cause an edema surrounding the hemorrhage.[32] Mass effect of the hemorrhage and edema in addition to hydrocephalus caused by intraventricular hemorrhage, may cause an increase in intracranial pressure, which may lead to further death of brain cells, and to death. Death within the first phase after an ICH is mainly a direct consequence of the ICH.[33] High age, low Glasgow Coma Scale score (GCS), infratentorial origin of ICH, high ICH volume and presence of intraventricular hemorrhage have been associated with an increased risk of one-month case fatality after ICH.[34] In addition, use of antithrombotic drugs at time of ICH increases the risk of hematoma expansion and early death.[35, 36]

Figure 5. ICH with high volume and extension into the cerebral ventricles



Print of radiological image on the courtesy of Liv Hege Johnsen, MD, Department of Radiology, UNN

1.2.3 Treatment

Treatment possibilities of ICH are few. Stroke unit care has been associated with a significant decrease in short- and long-term mortality after an ICH.[37, 38] In ICH associated with use of anticoagulants, reversal of anticoagulant drugs may reduce hematoma expansion and mortality.[39] Lowering of blood pressure in the first hours after ICH may improve functional outcome, but has not shown any effect on mortality.[40] Surgery is indicated in selected ICH patients.[41] However, randomised controlled studies (RCT) have failed to demonstrate benefit in terms of mortality or functional outcome.[41]

1.2.4 Risk factors

Non-modifiable risk factors

Age

Increasing age is a strong risk factor for ICH.[42] The association may be explained by changes in the cardiovascular system caused by ageing in addition to a cumulative effect of a long-term exposure of risk factors.[42]

Sex

Studies on differences in ICH incidence according to sex are diverging, with some studies showing an excess risk in men, and others similar risk between sexes.[27, 43, 44] In a meta-analysis of epidemiological studies, men had higher overall incidence rates of ICH, but there were geographical variations.[44] Interactions between sex, ethnicity and age have been suggested to influence differences in ICH incidence between sexes.[44]

Ethnicity

Asian countries have the highest incidence rates of ICH.[27] In US, Blacks, American Indians and Hispanic/Latino Americans have a higher incidence of ICH compared with Whites[42] and in New Zeeland, incidence rates are higher among Maori/Pacifics and Asians compared with Whites.[45] Among Blacks and Hispanics in US, the excess risk has been most pronounced in young and middle-aged individuals.[42] The association between race and risk of ICH is complex, and it remains unclear whether differences between races are genetic, environmental, or an interaction between the two.[42] Higher prevalence of and poorer control of risk factors, e.g. blood pressure, have been suggested as a contributing factors to the observed differences. [45-47]

Genetics

Studies indicate that up to 44% of ICH risk can be explained by genetic variation.[48] However, few genes have been linked to the risk of ICH.[48] The most common and well documented genetic risk factor for ICH is APOE.[48] The APOE ε2 and ε4 alleles are associated with amyloid biology, and both have been associated with an increased risk of first-ever and recurrent lobar ICH.[49-51] Locuses 1q22, 2q33 and 13q34, which have been linked to the risk of white matter hyperintensities, have been associated with non-lobar ICH.[49, 52] In addition, genetic variations within the genes COL4A1 and COL4A2 have been associated with an increased risk of ICH.[49] A high burden of risk alleles for elevated blood pressure has been associated with an increased risk of deep ICH and of presence of hypertension in a population of European ancestry,[53] and an increased risk of ICH in carriers of a genetic variant associated with high levels of high density lipoprotein (HDL)-cholesterol has been reported.[54]

A small minority of ICH cases are caused by Mendelian forms of ICH.[49] These tend to appear at a younger age and affects Whites more often.[49] Examples of these forms are familial CAA, usually affecting the beta-amyloid precursor protein gene, and mutations in the COL4A1 gene, causing autosomal dominant syndromes with perinatal ICH and porencephaly, adult-onset ICH, microbleeds, lacunar strokes and leukoaraiosis.[49]

Modifiable risk factors

Hypertension

Hypertension is the single most important modifiable risk factor for ICH.[42, 55, 56] In a meta-analysis on 11 case control studies, individuals with hypertension had a more than 3.5-fold increased risk of ICH compared with individuals with normal blood pressure.[55] The risk of ICH increases with increasing blood pressure levels and treatment of hypertension is the most effective measure for preventing ICH.[42, 55]

Serum cholesterol and use of statins

Studies on the association between serum cholesterol and ICH have been diverging. An inverse relationship with total cholesterol, HDL and low-density lipoprotein (LDL) has been reported in several studies,[55, 57] whereas others have found no association.[55, 58, 59] A possible association with use of statins and risk of ICH has been debated.[60, 61] In the vast majority of trials there has been no association between statin treatment and hemorrhagic stroke.[60]

Diabetes mellitus

Studies on the risk of ICH in individuals with diabetes mellitus (DM) have been inconsistent. Whereas some studies have showed an increased risk in individuals with DM,[62] others have

found no association.[63] The authors of a large, multinational case control study (INTERSTROKE), including 3,059 ICH patients, reported an inverse association with DM.[56] In a meta-analysis on 19 case-control studies and three cohort-studies, an association with DM was found in unadjusted data from case-control studies.[64] When analysing data of sixteen of the case-control studies in which cases and controls were comparable for age and sex, the association was no longer significant.[64] There was no significant association in the cohort-studies.[64]

Smoking

Studies on the association between smoking and ICH have been conflicting.[42] In the INTERSTROKE study, there was no association between smoking and ICH.[56] Contrary to this, the authors of recent published review concluded that cigarette smokers have an increased risk of ICH.[65] In another review, current smoking was associated with ICH in three cohort studies, but not in 10 case control studies.[55]

Physical activity

Studies on the association with physical activity and hemorrhagic stroke are limited. In the INTERSTROKE study, as well as in a large meta-analysis on physical activity and stroke, with 31 observational studies included, high level compared with low level physical activity reduced the risk of ICH/hemorrhagic stroke.[56, 66]

Antithrombotic drugs

Use of antithrombotic drugs are probably not a direct cause of ICH, but exacerbate spontaneous bleedings caused by an underlying artheriopathy.[67] There are two classes of

antithrombotic drugs; antiplatelet and anticoagulant drugs. Antiplatelet drugs have been associated with a small increase in the risk of ICH, with a higher risk associated with dual antiplatelet therapy. [68] Up to the last decade, vitamin K antagonists (VKA) were the only oral anticoagulants available. The relative risk of ICH in individuals on VKA is approximately 7-10 compared with the general population.[69] The risk increases with increasing levels of international normalized ratio (INR).[69] The last decade, treatment with direct oral anticoagulant drugs (DOACs) has been approved.[70] Use of DOACs has been associated with a lower risk of ICH compared with use of VKA, with an annual risk of 0.3-0.6% in VKA users and 0.1-0.2% in DOAC users, respectively.[67] In a Norwegian study based on the Norwegian Patient Registry and Norwegian Prescription Database, the risk of ICH associated with use of antithrombotic drugs was higher than in RCTs.[71] Combination therapies with warfarin plus aspirin and clopidogrel, warfarin plus aspirin, rivaroxaban plus aspirin, and aspirin-dypiridamole plus clopidogrel were associated with the highest risks of ICH.[71]

Alcohol intake

An increased risk of ICH associated with high use of alcohol has been suggested in several studies.[56, 72] In a review on eight case control studies, high alcohol intake was associated with ICH, with a dose-response effect.[55] However, in the three cohort studies included, there was no association with alcohol intake and ICH.[55] In addition to a possible increased risk in individuals with prolonged heavy drinking, an immediate increased risk of ICH within the first 24 hours as well as within the first week after heavy alcohol intake has been reported.[73]

Body mass index

The association between body mass index (BMI) and ICH has not been clear. Associations between high as well as low BMI in addition to an inverse association with BMI and risk of ICH have been reported.[63, 74, 75] In other studies there has been no association with BMI and ICH.[76]

Illicit drugs

Use of illicit sympathomimetic drugs, particularly cocaine and amphetamines, has been associated with increased risk of ICH.[77] This relationship may be due to drug-induced hypertension, vasculitis or vasospasm.[77]

Risk factors according to ICH location

Few studies have assessed the association with risk factors according to ICH location.[78-84] Whereas hypertension has been strongly linked to non-lobar ICH, its role in lobar ICH has been less clear.[85] A probable, although less strong association with lobar ICH has been suggested.[85] The associations with other cardiovascular risk factors have been diverging.[78-84] In a recent, large meta-analysis, encompassing 42 studies with a total of 26,174 ICH patients, hypertension, DM, male sex, alcohol overuse, underweight and being Black or Hispanic compared with being White were associated with non-lobar ICH.[84] Hypertension was the only risk factor associated with lobar ICH, although with a less strong association compared to non-lobar ICH.[84]

1.2.5 Incidence rates and time trends in incidence of ICH

Incidence rates of ICH vary between populations.[27] In the period 1980 to 2008, an incidence rate of 24.6 per 100 000 person-years, ranging between 1.8 and 129.6 per 100,000 person-years was reported, with the highest incidence rates in Asian people.[27] Studies on time trends in incidence rates of ICH over the last three decades have shown diverging results. The majority of studies have shown stable or decreasing incidence rates.[5, 27, 83, 86-97] In a few studies, an increase in ICH incidence has been observed.[98, 99]

Two large meta-analyses of 56 and 36 studies, showed stable global ICH incidence rates in 1980-2006 and 1980-2008, respectively.[5, 27] The authors of a review from the Global Burden of Disease Study reported a decrease in incidence of hemorrhagic stroke (ICH and SAH combined) in high-income countries and a significant increase in low- to middle-income countries between 1990 and 2010.[100] At initiation of our study there were two Norwegian publications on ICH incidence.[24, 25] In a population-based study from Innherred, covering the years 1994-1996, incidence rate of ICH adjusted to the European population was 0.32 per 1,000.[24] In a hospital-based study from southern Norway covering the years 2005-2009 adjusted incidence rates of ICH were 0.13 per 1,000.[25] This could indicate a fall in incidence rates between the two study periods. However, due to differences in study-design direct comparisons between these studies are limited.

1.2.6 The impact of risk factor trends on incidence trends of ICH

During the last decades systolic blood pressure (SBP) levels have decreased in several countries globally, with the largest declines occurring in high-income countries of Australasia, North America, and Western Europe.[101] In addition, there has been a decrease in

the prevalence of smoking, and cholesterol levels in Western Countries.[101] BMI and DM prevalence have increased.[101] Time trends in alcohol use have been less clear.[101] Use of blood pressure-lowering, antithrombotic and lipid-lowering drugs have increased.[101-104]

Most studies on the association between risk factor trends and stroke incidence have covered trends in total stroke incidence.[96, 105] Few studies have used individual data from repeated surveys with registration of premorbid risk factors.[96, 97, 105] Studies on the impact of changes in risk factors on ICH incidence are scarce.[21, 83, 92, 93, 97] Hypertension has consistently been shown to be the strongest modifiable risk factor for ICH.[42] Despite a decrease in blood pressure levels, stable incidence rates of ICH have been reported in several studies during the last three decades.[5, 27, 83, 86, 87, 92, 93, 95, 97] The authors of two European studies have raised a concern that a change in risk factor profile of ICH with an increase in ICH associated with an increased use of antithrombotic drugs in the elderly may have outweighed the effect of a decrease in ICH associated with hypertension.[93, 97]

1.2.7 Time trends in 1-month case fatality rates

Studies on trends in 1-month case fatality are scarce and have shown diverging results. Whereas some studies have shown stable case fatality rates, [27, 88, 90, 95, 106] others have shown decreasing rates.[89, 91, 98, 107-110] In two large meta-analyses on 36 and 30 studies and with a total of 8,145 and 7,736 ICH patients, respectively, 1-month case fatality rates were stable in the periods 1983-2006 and 1985-2015.[27, 106] In two Norwegian studies covering the periods 1994-1996 and 2005-2009, unadjusted 1-month case fatality rates were 37.8 and 36.6, respectively.[24, 25]

1.2.8 Long-term survival

There are few studies on long-term survival after ICH.[28, 88, 107, 108, 111] The majority of early deaths are a direct consequence of the ICH event, whereas other causes of death contribute to a larger degree in ICH survivors.[33] Despite this, studies on ICH patients who survive the early phase are scarce.[28] Cumulative 5-year survival rates in ICH patients have ranged between 27 and 57%.[28, 112-114] Few studies have assessed temporal trends in long-term mortality rates and the results have been diverging.[28, 88, 107, 108, 111] Most of the studies were published after initiation of the present study. The components of the ICH score are the most studied prognostic factors for long-term survival, and there is limited knowledge on the impact of traditional cardiovascular risk factors.[28, 34]

1.3 Knowledge gaps and rationale for the thesis

In summary, stroke is to a large degree a preventable disease.[56] Studies on trends in incidence, case fatality and long-term mortality rates of stroke are important to assess the impact of preventive measurements, to identify emerging risk factors and to assess the effect of therapeutic interventions. Ischemic stroke and ICH have different risk factor profiles and outcome after ICH is poorer compared to IS.[26, 42] Knowledge on trends in incidence, 1-month case fatality and long-term survival in ICH patients is limited. Although the pathophysiology differs according to ICH location, there are few studies on cardiovascular risk factors according to ICH location. There is little knowledge on the impact of risk factor trends on ICH incidence. Data on long-term survival after ICH, especially in ICH survivor cohorts are few. The lack of Norwegian data on time trends in incidence, 1-month case fatality and long-term survival rates of ICH was an additional motivation for this study.

2 Aims of the thesis

The objectives of this theses were

1. To analyse trends in incidence and 1-month case fatality rates of ICH over time, in a well-defined general Norwegian population.
2. To analyse the association with risk factors and ICH overall and according to ICH location, and the impact of risk factor trends on time trends in ICH incidence.
3. To compare differences in long-term survival rates, causes of death and risk factors for death in 30-day survivors of ICH and the general population, and to analyse time trend in long-term mortality rates of ICH.

3 Subjects and Methods

3.1 The Tromsø-study

3.1.1 Study design and study population

The Tromsø Study is an ongoing, longitudinal population-based cohort study with repeated health surveys.[115] The study was initiated in 1974 with the primary aim to assess the increasing coronary heart disease mortality which was observed in the years 1951-1970.[116] Tromsø is the regional center in Northern Norway and is located 400 km north of the Arctic Circle at 69° N (Figure 6). The population has increased from 42,200 in 1974 to the current population of 77,000 inhabitants,[117] the majority living in the city centre. The increase in population has been mainly due to the establishment of large educational institutions, health care institutions and other knowledge based industries.[116] The vast majority of the inhabitants are of Caucasian origin.[118] The municipality is served by one hospital; The University Hospital of North Norway (UNN). The distances in the area are long and the nearest hospital in the county, outside Tromsø municipality, is located 300 km away by road, 134 km by air.

Since the initiation of the Tromsø Study, seven surveys have been conducted (Tromsø 1-7); in 1974, 1979-1980, 1986-1987, 1994-1995, 2001-2002, 2007-2008 and 2015-2016, respectively. Eligible for the present thesis were attendendees of Tromsø 1-6. Based on the official population registry, full birth cohorts and random samples of residents in the municipality of Tromsø have been invited to attend the surveys.[119] A total of 40,051 individuals have attended at least one of Tromsø 1-6.[119] Table 1 shows attendance rates, age- and sex distribution in the six first surveys which the present work is based upon.

Table 1. Year of survey, age, number and attendance rate of eligible participants in the 1st -6th surveys of The Tromsø Study

Survey year	Men			Women		
	Age group, years	Participants, n	Attendance rate, %	Age group, years	Participants, n	Attendance rate, %
1974	20-49	6,595	74.4	-	-	-
1979-80	20-54	8,477	73.8	20-49	8,143	81.8
1986-87	12-64	10,963	71.8	12-67	10,863	79.0
1994-95	25-97	12,865	69.6	25-97	14,294	74.9
2001-02	30-89	3,511	75.7	30-89	4,619	80.9
2007-08	30-87	6,054	62.9	30-87	6,930	68.4

To the first survey (Tromsø 1), only men aged 20-49 years were invited. From the second surveys and onwards both sexes have attended. The age span of invited attendees has varied between the surveys. From the fourth study and onwards elderly have been invited. In the 5th and 6th studies the lower age limit has been 30 years. The 4th study, carried out in 1994-1995, was the largest of the surveys. The attendance rates to the study have generally been high, although there has been a decrease from approximately 75% in the first surveys to 66% in the 6th survey.[119] Repeated measurements are available for a large part of the attendees with 23,342 individuals attending two or more of the 1st-6th surveys.[119]

The surveys include questionnaire data (Appendix), clinical measurements and sampling of biological specimens (Table 2). Since the 4th survey, additional clinically oriented examinations have been performed on large subgroups (N= 7,965, 5,939 and 7,307 in Tromsø 4, 5 and 6, respectively), in addition to the core protocol. Variables registered in the different surveys are available at the NESSTAR website of the Tromsø study (http://tromsoundersokelsen.uit.no/tromso/).

Table 2. Overiew of data collected in the 1st – 6th surveys of The Tromsø Study.

	Tromsø Study survey number					
Type of information	1	2	3	4	5	6
Marital status, age, sex	x	x	x	x	x	x
Questionnaire data	x	x	x	x	x	x
Interview	x	x	x	x	x	x
Measured weight and height	x	x	x	x	x	x
Measured waist and hip circumference				x	x	x
Measured blood pressure	x	x	x	x	x	x
Blood samples*	x	x	x	x	x	x
Electrocardiography (ECG) †			x	x	x	x
Echocardiography†				x	x	x
Ultrasound examination of the carotid artery†				x	x	x
Ultrasound examination of the abdominal aorta†				x	x	
Spirometry†					x	x
Bone mineral densitometry†				x	x	x
Urinary analyses†				x	x	x
Examination of vision acuity†					x	x
Cognitive testing†					x	x
Eye examination†						x
Pain sensitivity						x

*Analyses of blood lipids were performed in all surveys. Other blood samples differed between studies, please see http://tromsoundersokelsen.uit.no/tromso/).

† Examinations performed on subgroups of the attendees

After inclusion in the study, the participants are continuously followed up with registration of several clinical end points, including cardiovascular diseases (CVD) and death.[119] The longitudinal design with repeated surveys gives an unique possibility to study trends in prevalence of risk factors and incidence rates of diseases in a cohort in a well-defined geographical area. Since the 1970´s, the differences in CVD mortality in Norway have decreased, and the rates in North Norway are now similar to the rest of the country.[120]

Figure 6. Location of Tromsø

Source: Kartverket

Paper I

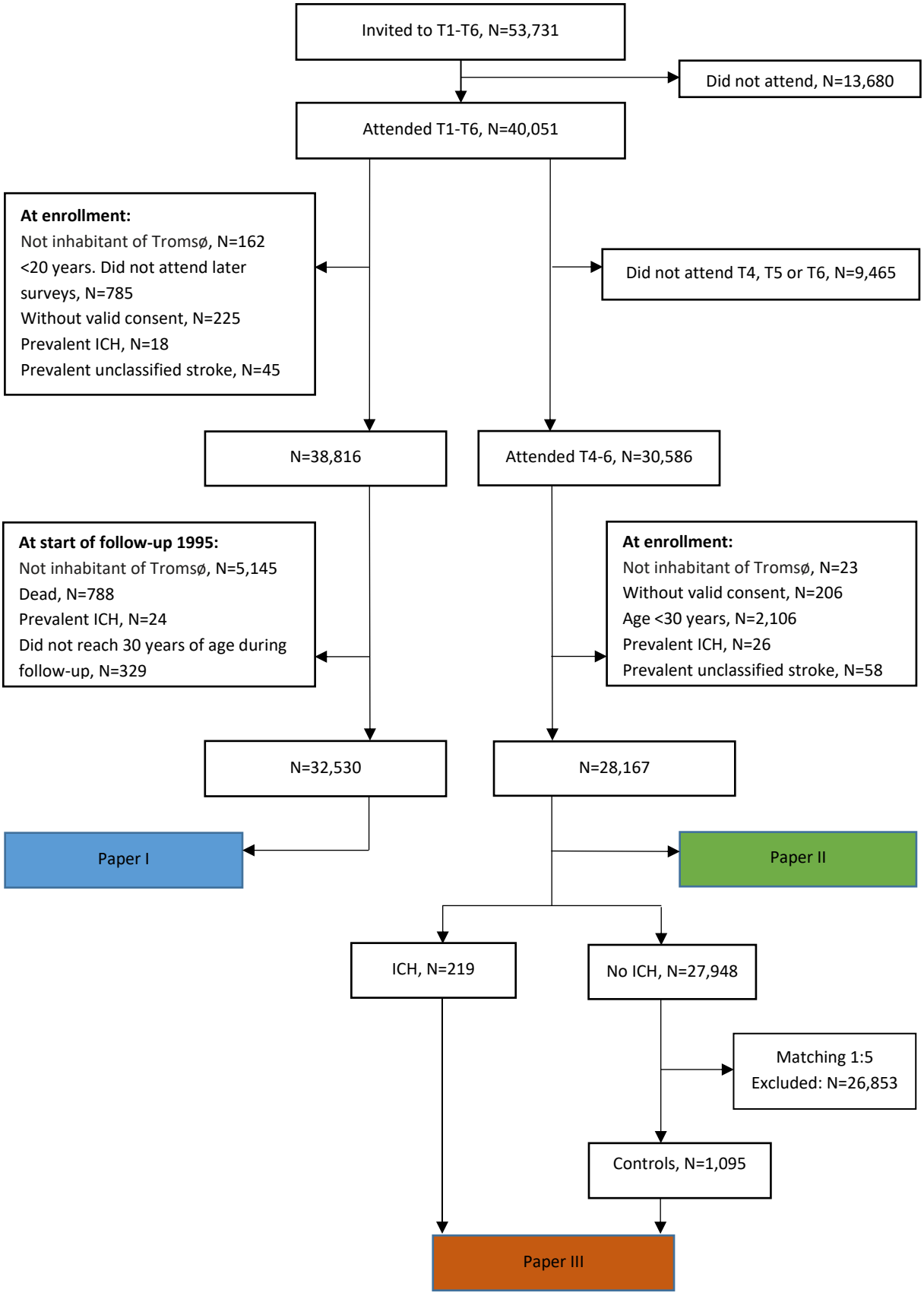
Individuals who had attended at least one of the 1st-6th Tromsø were eligible for Paper I. Selection of participants is shown in Figure 7. Of the 53,731 individuals who were invited, 40,051 attended at least 1 of the 6 surveys (Table 1, Figure 7). Individuals who were not officially registered as inhabitants of the Tromsø municipality at the date of enrolment (n=162), individuals who were younger than 20 years at enrolment and did not attend later studies (n=785), those who did not have valid written consent to medical research (n=225),

and individuals who had prevalent ICH (n=18) or unclassified stroke (n=45) were excluded. Because older birth cohorts were not enrolled in the earliest surveys, and individuals <30 years were not enrolled in the two latest surveys, analyses were limited to individuals aged ≥ 30 years in the period 1 January 1995 to 31 December 2012. Individuals who emigrated out of the municipality (n=5,145), died (n=788) or suffered an ICH (n=24) before 1995 or did not reach 30 years of age during follow-up (n=329) were censored, leaving 32,530 individuals (16,771 women and 15,759 men) to be included. For individuals who were younger than 30 years when first attending a survey, start of follow-up was assigned from the date they turned 30 years. Participants were followed up until the first-ever ICH event, emigration out of the municipality, death or end of study (31 December 2012).

Paper II-III

Eligible for paper II-III were participants who attended at least one of the 4th- 6th surveys performed in 1994-1995, 2001 and 2007-2008 (n=30,586) (Table 1, Figure 7). Participants who were not officially registered as inhabitants of Tromsø municipality (n=23) at date of inclusion and participants without valid written consent (n=206) were excluded. In addition, we excluded participants aged <30 years (n=2,106) and participants with prevalent ICH (n=26) or unclassified stroke (n=58), leaving 28,167 individuals (14,794 women and 13,373 men) to be included. The endpoint registry had been updated since Paper I, and participants in Paper II and III were followed up with registration of first-ever ICH until 31 December 2013, and with registration of date of death and cause of death until 31 December 2016. During this period 219 ICH were registered. In paper III, the 219 ICH cases were matched 1:5 with individuals of same birth-year and sex, who did not suffer an ICH during follow-up (n= 1,095).

Figure 7. Flow chart of the study population



3.1.2 Ethics

The Tromsø Study has been approved by the Regional Committee for Medical and Health Research Ethics (REK) (REK nr 2009/2536 og 2006/121) and the Data Inspectorate of Norway, In addition the study has an approved biobank (biobanknumber 277 and 2397). Data collected may only be used for approved research purposes, and projects must have their own approval from the REK. Research on incidence and mortality of stroke, and on CVD risk factors are covered by the existing approvals of the Tromsø study. All data are anonymised and every individual has a unique code, which is blinded for the researchers. The regulations for consent to research has changed since the initiation of the study, with stricter regulations during the last decades. Written consent has been used since Tromsø 4th. The attendees have the possibility to withdraw from the study at any time point and without being required to provide their reason for withdrawal. Information on the possibility to withdraw consent is available in the invitations to the study in addition to the homepage for the Tromsø study (https://uit.no/research/tromsostudy). Employees of the Tromsø study have a duty of confidentiality. The attendees have not received compensation for attending the study.

3.1.3 Funding

The study has been funded by UiT The Arctic University of Norway since the first survey in 1974. In addition, there have been contributions from the National Screening Services, the Research Council of Norway, the Northern Norway Regional Health Authority, the Norwegian Council on Cardiovascular Diseases, the Odd Berg Research Foundation, the Dam Foundation and the Norwegian National Budget.

3.2 Ascertainment of risk factors

3.2.1 Data from clinical examinations and blood samples

Blood pressure

Blood pressure was measured with three recordings separated by a 1-minute interval, after a 2-minute seated rest, using Dinamap Vital Signs monitor 1846 (Criticon inc. Tampa, FL, USA) in the 1994-1995 and 2001 surveys and Dinamap Pro care 300 Monitor (GE Healthcare, Norway) in the 2007-08 survey. The proper cuff size was selected based on the circumference of the upper right arm in the individual participant. We used the mean value of the two last recordings. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and/or use of blood pressure-lowering drugs.

BMI

Weight was measured with light clothing and no footwear. Height was measured in standing position. BMI was calculated as weight divided by the square of height (kg/m2).

Serum cholesterol, HDL and triglycerides

Non-fasting blood samples were drawn at date of attendance. Serum cholesterol, HDL and triglycerides were analysed by standard enzymatic colorimetric methods at UNN.

3.2.2 Data from questionnaires

Information on previous and current diseases, smoking status, use of alcohol and physical activity, as well as use of blood pressure-lowering, lipid-lowering, antidiabetic and antithrombotic drugs were collected through standardised questionnaires (Appendix). In addition, use of medication used on a regular basis was retrieved through lists of brand names

of medication, written by the participants and checked by health personnel at the study site. In order to supplement the information from the questionnaires, a short interview was included in the surveys with topics as family history of coronary heart disease, current and former use of medications etc.

Diabetes mellitus

Diabetes mellitus was self-reported in questionnaires by answering the question: Do you have, or have you had DM? Serum glucose and HbA1c were measured in the 5th-6th surveys, but not in the surveys prior to these, and was therefore not included in the definition of DM.

Smoking

Smoking status was asked for in questionnaires and defined as daily current smoker (cigarettes and/or pipe and/or cigarillos/cigars).

Alcohol consumption

Alcohol consumption was asked for in questionnaires. The questions concerning the amount of alcohol intake differed between the surveys and alcohol consumption was categorised as teetotalism yes/no in the overall analysis on the association of alcohol consumption and risk of ICH, and on time trend in alcohol consumption. Additional analyses on the association between the amount of alcohol consumption and risk of ICH were performed based on answers from questionnaires in the the 5th-6th surveys. In these analyses, the amount of alcohol intake was categorised as teetotalism, moderate alcohol consumption (1-7 glasses per week in women, 1-14 glasses per week in men) and high alcohol consumption (>7 glasses per week in women, >14 glasses per week in men).

Physical activity

Information on physical activity was self-reported in questionnaires and defined as strenuous leisure physical activity (i.e. become sweaty and out of breath) for at least 1 hour per week.

Use of blood pressure-lowering, lipid-lowering and antithrombotic drugs

Use of blood pressure-lowering drugs at attendance was self-reported in questionnaires by answering the following question: Do you use blood pressure-lowering drugs? Response categories: 1) Now, 2) Previously, but not now, 3) Never. Use of lipid-lowering drugs was self-reported in questionnaires by answering the following question: Have you during the last 14 days used lipid-lowering drugs? Response categories: 1) Yes 2) No. In 1994-95 this question was limited to individuals aged <70 years, and information from additional list of the brand names of medication used on regular basis was available only for participants aged 55-74 years and selected 5-10% samples of participants aged 25-54 and 75-85 years. In 2001-2002 and 2007-2008, use of lipid-lowering drugs was asked for in all age groups. Use of antithrombotic drugs at attendance was collected through lists of the brand names of medication used on regular basis written by participants and checked by health personnel at the study site. Data were collected for attendees of the second visit of the survey in 1994-1995, and in all attendees of the surveys in 2001 and 2007-2008.

3.2.3 Data from medical records

Information on use of antithrombotic drugs at time of ICH was obtained retrospectively from the medical record of each subject suffering an ICH during follow-up. Antithrombotic drugs were further divided into antiplatelet drugs and anticoagulant drugs. Anticoagulant drugs were defined as use of vitamin-K antagonists, DOACs, treatment with

high dose heparin or high dose low molecular weighted heparin, or thrombolytic treatment of indications other than IS.

3.3 Ascertainment of clinical endpoints

3.3.1 Case ascertainment and definition of ICH

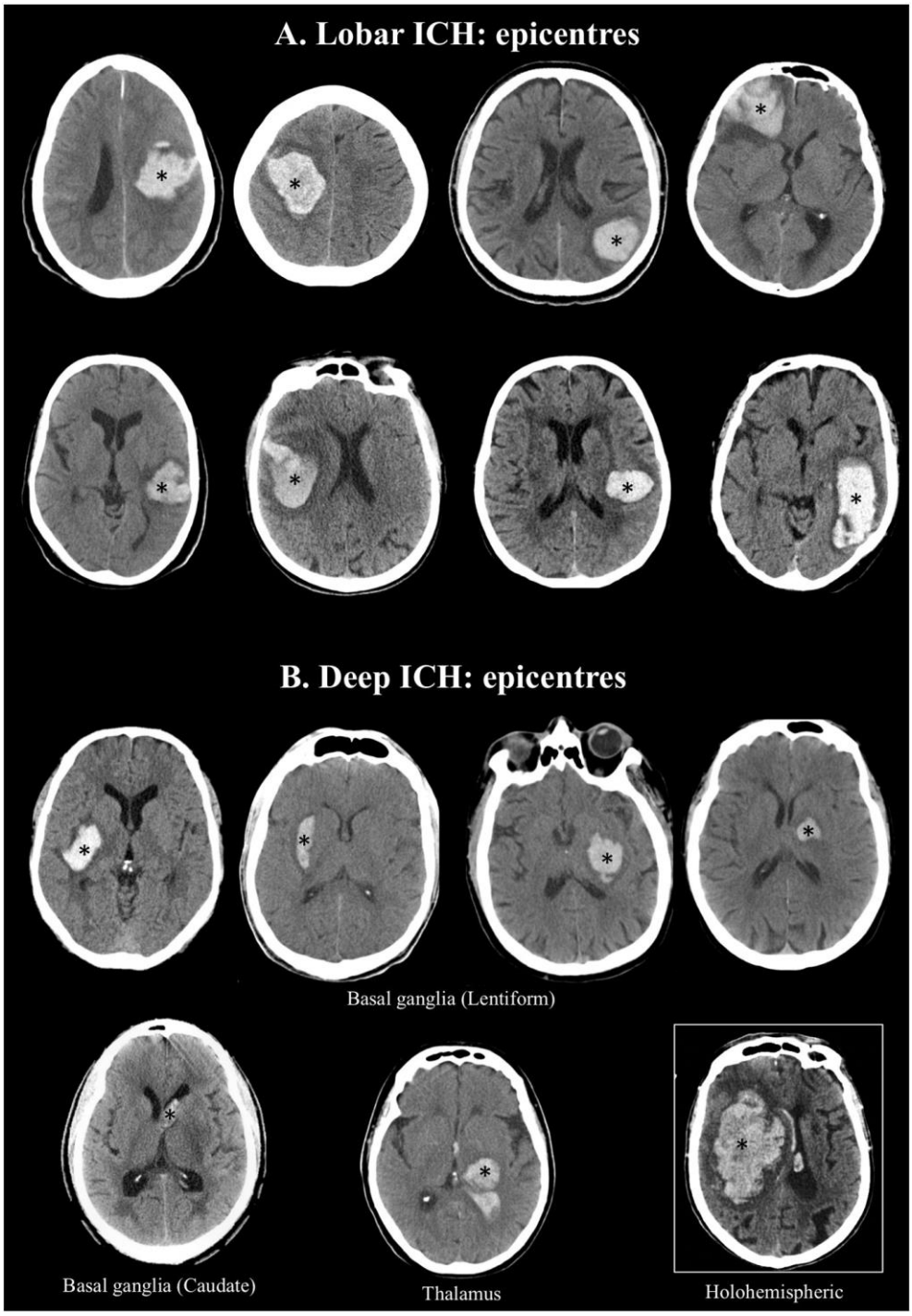
All attendees were continuously followed up with registration of first-ever ICH. Follow-up time was assigned from date of first attendance until first-ever ICH, death, emigration from Tromsø or to end of follow-up (31 December 2012 in Paper I, and 31 December 2013 in Paper II-III), whichever came first. Stroke was defined according to the WHO definition; "rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting ≥24 hours or leading to death, with no apparent cause other than vascular origin".[17] Strokes were registered by linkage to the discharge and out-patients diagnosis registry at UNN, using unique 11-digit personal identification numbers. Searches were performed for ICD versions 8 and 9 diagnosis codes 430–438, and ICD-10 diagnosis codes I60–I69 (cerebrovascular disease (CVD)). From 2006, ICD-10 codes G45 (TIA), G46 (vascular syndromes of brain in cerebrovascular diseases) and G81 (hemiplegia) were added to the search. In addition, systematic text searches were made for the words 'stroke', 'ischemic stroke' and 'intracerebral hemorrhage' in the medical records of all participants with ICD-8 to ICD-10 diagnosis codes 410–414 and I20–I25 (ischemic heart disease), 798/R96 (sudden death, cause unknown), R98 (unattended death) and 799/R99 (other ill-defined and unknown causes of morbidity and mortality). An independent endpoint committee reviewed all cases separately by use of medical records from the hospital (including autopsy reports). Cases retrieved from the National Causes of Death registry were additionally validated by medical records from nursing homes, general practitioners,

emergency services and/or death certificates, when available. We included ICH diagnosed by CT, MRI and/or autopsy. Strokes where imaging or autopsy had not been conducted in the acute stage were categorised as unclassified. ICH caused by hemorrhagic transformation of IS, trauma, brain surgery, hematologic disease or brain tumor were excluded. An independent endpoint committee reviewed each case separately by use of hospital medical records (including autopsy reports).

Registration of ICH location

All CT and MRI scans in ICH patients were assessed retrospectively by the author, who is a senior consultant in neurology. ICH location was defined using a validated rating instrument (CHARTS; Figures 8 and 9).[121] In cases where radiologic examinations were not available (n=35), location was assessed by radiology reports and/or autopsy reports. In uncertain cases, the scans were additionally validated by a neuroradiologist at UNN, and consensus made in cooperation with a senior consultant in neurology at UNN. ICH location was categorised as lobar, non-lobar (deep/infratentorial), uncertain and other location (intraventricular or located to the corpus callosum). Intracerebral hemorrhages with uncertain location were further categorised as probably lobar, probably deep, and holohemispheric. In analyses stratified on location, probable lobar and probable deep ICH were included in the analyses as lobar and non-lobar ICH, respectively. Cases with multiple ICH affecting solely lobar (n=7) or non-lobar (n=3) regions were categorised according to location. Multiple ICH affecting both regions (n=1), ICH located to the corpus callosum (n=2), intraventricular ICH (n=3), holohemispheric ICH (n=13) and ICH with missing location (the radiologic examination and radiologic report were not available at the time of the retrospective assessment) (n=1) were included in analyses of ICH overall, but excluded from analyses stratified on location. All ratings were performed blinded for risk factors.

Figure 8. Examples of the main anatomical patterns of intracerebral hemorrhage (ICH)



*Presumed epicentres of the main bulk of ICH, in the slice with the largest axial ICH diameter

Figure 9. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS) rating form

Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS)

Patient ID: _ _ _ _ _ _ _ _ _ _ Date of Birth: _ _/_ _/_ _ _ _ Date of CT/MRI: _ _/_ _/_ _ _

Please assign each ICH into an anatomical category based on the following procedure:

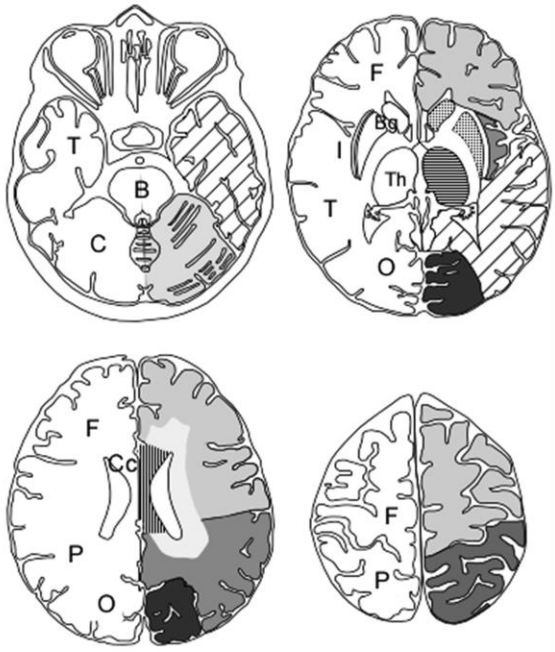
- Review multiple axial slices to visualize the location and spread of ICH. Other imaging planes may also be helpful.
- Classify the site of ICH as **LOBAR**, **DEEP AND INFRATENTORIAL**, or **UNCERTAIN** using the definitions below.
- Note the typical sites of origin and patterns of extension seen in deep ICH (basal ganglia and thalamus – see examples).†
- Define the epicentre of the ICH on the **axial slice with the biggest ICH diameter**; helpful for irregularly-shaped lobar ICH.
- Compare the epicentre to the corresponding anatomy in the unaffected hemisphere; helpful for deep ICH and minimal midline shift.
- Categorise ICH as Lobar (Insular) if it involves only the thin rim of insula grey matter; may be hard to distinguish from basal ganglia.
- There is an option to make note of any intraventricular haemorrhage (**IVH**) or convexity subarachnoid haemorrhage (**cSAH**).

1. LOBAR ICH: the main bulk and the presumed epicentre of the haematoma is located in the cerebral cortex or at the junction of the cortex and white matter (*including subcortical white matter*), and does not extend into the subcortical gray matter structures such as the basal ganglia or thalamus. Lobar ICH may be further subdivided according to lobes (see diagram).

2. DEEP AND INFRATENTORIAL: the main bulk of the haematoma located in the basal ganglia, thalamus, brainstem or cerebellum and usually does not extend into cerebral cortical grey matter. Rarer locations, including pituitary gland or cerebral peduncle should be included in the brainstem category given likely shared arterial supply and mechanisms. For cerebellar ICH, the main bulk of the haematoma originates in the cerebellum.

3. UNCERTAIN: where the ICH is difficult to distinguish visually between lobar and non-lobar origin (e.g. the ICH is too large and extends into both lobar and non-lobar areas), the location should be recorded as "Uncertain". The rater should still try to categorise the ICH as "Probable lobar" or "Probable non-lobar" on their best judgement, but for those ICH involving the majority of a hemisphere (including deep and lobar areas) the category "Holohemispheric" should be used.

Please tick boxes and enter the number of ICHs. *Sub-regions are optional, depending on the study question*		R	L
1. Lobar ☐	1.1 Frontal (F)		
	1.2 Parietal (P)		
	1.3 Temporal (T)		
	1.4 Occipital (O)		
	1.5 Insular (I)		
2.Deep and Infratentorial ☐	2.1 Basal ganglia (Bg)		
	2.1.1 Lentiform		
	2.1.2 Caudate		
	2.2 Thalamic (Th)		
	2.3 Brainstem (B)		
	2.4 Cerebellar (C)		
3. Uncertain ☐	3.1 Probable lobar		
	3.2 Probable deep		
	3.3 Holohemispheric		
Other location (e.g. Corpus callosum (Cc)):…… ……			
IVH present		Y	N
cSAH extension (adjacent to the ICH or elsewhere)		Y	N



† Weisberg et al. Neuroradiology 1990; Chung et al. Brain 1996

3.3.2 Dates of death and causes of death

Dates for death and emigration out of the municipality were obtained from the Population Registry of Norway. Causes of death were retrieved from the Norwegian Cause of Death Registry through 31 December, 2016. Causes of death were defined as CVD (ICD 9 codes 390-459 and ICD 10 codes I00-I99), malignancy (ICD 9 codes 140-208 and ICD 10 codes C00-C97) and chronic lower respiratory diseases (asthma excluded) (ICD 9 490-492, 494 and 496 and ICD 10 codes J40-44 and J47). CVD was further classified as ischemic heart disease (ICD 9 codes 410-414 ICD 10 codes I20-I25), IS (ICD 9 code 434 and ICD 10 code I63), ICH (ICD 9 code 431 and ICD 10 code I61), unspecified stroke (ICD 9 code 436 and ICD 10 code I64), stroke sequelae (ICD 9 code 439 and ICD 10 code I69) and "other". Causes of death not classified as CVD, malignancy or chronic lower respiratory diseases were classified as "other".

3.4 Statistical methods

Statistical analyses were performed using STATA version 13.0 (StataCorp LP, College Station, Tex., USA) (Paper I), StataCorp (2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) (Paper II) and StataCorp. (2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.), (Paper III). For all analyses, a two-sided p value <0.05 was considered significant.

Crude incidence rates of ICH per 1,000 person-years were calculated (Paper I and II). In addition, age- and sex adjusted incidence rates were calculated by the direct method using the European standard population of 1976 (Paper I) and 2013 (Paper II) as references. Age adjusted incidence rate ratios (IRR) between men and women were calculated. Time trends in incidence rates, adjusted for age or age and sex were assessed by Poisson regression models

(Paper I and II). Incidence rates ratios were calculated from each Poisson regression model (Paper I and II).

Thirty-day case fatality rates were calculated (Paper I and III). Analysis of time trend in 30-day case fatality rates was performed using a logistic regression model, adjusted for age and sex, and odds ratio (OR) for time trend was calculated (Paper I).

Hazard ratios (HR) for the association between risk factors and ICH overall and according to ICH location (lobar and non-lobar) were assessed by Cox proportional hazards models (Paper II). To account for dependencies between repeated measurements, trends in risk factors and use of blood pressure-lowering, lipid-lowering and antithrombotic drugs were analysed in age- and sex-adjusted general estimated equations models (GEE) (Paper II). Odds ratio for treatment with antithrombotic drugs at time of ICH was calculated by logistic regression and adjusted for age and sex (Paper II).

In paper III, cumulative survival rates in ICH cases and controls matched for birth year and sex were assessed by Kaplan Meier estimates. Hazard ratios for mortality between cases and controls during follow-up through 2016, and HR of risk factors for 5-year mortality in 30-day survivors were analysed by stratified univariate and multivariable Cox proportional hazards regression models. Differences in effect of a risk factor between cases and controls were assessed by including interaction terms between ICH status (yes/no) and each risk factor (e.g. ICH status x SBP). Model selection was performed using backward selection. When interaction was significant, separate HRs were calculated for cases and controls. Analyses on risk of death in cases according to ICH location and use of antithrombotic drugs were performed using a Cox proportional hazard model adjusted for cardiovascular risk factors. Fisher´s exact test was used to compare causes of death within five years between cases and

controls. Time trend in 5-year survival rates in cases was assessed using logistic regression adjusted for age and sex.

In analyses of time trends in incidence, 30-day case fatality and 5-year mortality rates, tests of linearity were performed using fractional polynomials (Paper I-III). Tests of interaction between age and time and sex and time were performed by including two-way interaction terms (age × time and sex × time) in regression models (Paper I-III).

Further details on statistical methods are described in the papers.

4 Main results – summary of papers

4.1 Paper I

In paper I, 32,530 individuals were followed-up with registration of first-ever primary ICH during the period 1995-2012. A total of 226 first-ever ICH (122 in men, 104 in women) were registered during 453,152 person-years. The crude and age- and sex-adjusted incidence rates in the overall population were 0.50, 95% CI 0.44–0.57 and 0.42, 95% CI 0.37– 0.48 per 1,000 person-years, respectively. Incidence rates increased steeply with increasing age; compared with the age group 45-54 years, individuals in age groups 65-74 years and ≥85 years had a 9-fold and 30-fold higher risk of ICH, respectively (crude incidence rates 0.12, 95% CI 0.07-0.20, 1.08, 95% CI 0.85-1.39 and 3.65, 95% CI 2.61-5.11 per 1,000 person-years.) Women were on average 5 years older than men at the time of ICH. Age-adjusted incidence rates were higher in men compared with women 0.53, 95% CI 0.43-0.62 and 0.33, 95% CI 0.26-0.39 per 1,000 person-years respectively. Incidence rates in the overall population remained stable over time: IRR 0.73, 95% CI 0.47–1.12. There was no significant time trend in incidence rates in analyses stratified on sex or on age, although a borderline significant decrease in incidence rates in women was observed: IRR 0.52, 95% CI 0.27–1.00. Among the 226 individuals with ICH, 54 died within the first 30 days after the ICH event, resulting in a 30-day case fatality rate of 23.9%, 95% CI 18.3–29.5. The risk of death was highest within the first days after the ICH; of the individuals who died within the first 30 days, 48.2% died within the first two days and 74.1% died within the first seven days. Thirty-day case fatality rate was higher in the elderly; 34.3%, 95% CI 25.1–43.5 in individuals aged ≥75 years to be compared with 14.9%, 95% CI 8.4–21.3 in individuals aged <75 years. There was no change in 30-day case fatality rates during the observation period; OR 0.83, 95% CI 0.27–2.52.

4.2 Paper II

In paper II, 28,167 individuals were followed-up with registration of ICH during the period 1994-2013. We registered 219 first-ever ICH (96 women and 123 men) during a follow-up of 396,976 person-years. ICH location was lobar in 40% non-lobar in 51%, and holohemispheric/other location in 9%. Individuals with ICH were older, more likely to be males, and had higher age- and sex-adjusted blood pressure levels at baseline compared with ICH-free individuals. The crude prevalence of hypertension in ICH patients was 84%. Twenty-five percent used anticoagulant drugs and 28% antiplatelet drugs at time of ICH. None of the ICH cases were on DOACs.

Age, male sex, SBP, DBP, and hypertension were independently associated with the risk of ICH, whereas there was no association between total cholesterol, HDL-cholesterol, triglycerides, BMI, DM, daily smoking, teetotalism or physical activity and risk of ICH. There was no significant dose-dependent association with alcohol intake and risk of ICH. Individuals with drug-treated hypertension and blood pressure levels <140/90 mm Hg, had no significantly increased risk of ICH compared with individuals without hypertension (HR 1.74, 95% CI 0.79-3.84), whereas individuals who were on blood pressure-lowering drugs, but with SBP levels ≥140 mm Hg and/or DBP levels ≥90 mm Hg had a similar risk for ICH as individuals with untreated hypertension (HR 3,43, 95% CI 2.12-5.55 and HR 3.36, 95% CI 2.24-5.03, respectively).

In analyses stratified on ICH location, we found a significant association with age, SBP, DBP and hypertension and ICH of both lobar and non-lobar location, whereas male sex was

significantly associated with non-lobar ICH only. Hypertension was stronger associated with non-lobar (HR 5.08, 95% CI 2.86–9.01) than with lobar (HR 1.91, 95% CI 1.12–3.25) ICH.

During the study period blood pressure levels, serum lipid levels and smoking prevalence decreased significantly. Contrary to this, BMI levels and DM prevalence increased. The proportion of physically active individuals increased, and the rate of teetotalers decreased. There was an increase in use of blood pressure-lowering, lipid-lowering and antithrombotic drugs. Among individuals with hypertension, the proportion of individuals treated with blood pressure-lowering drugs increased from 18% in 1994-1995 to 46% in 2007-2008. The rate of individuals with well controlled hypertension increased from 21% in 1994-1995 to 35% in 2007-2008. Blood pressure levels were lower and the SBP decrease was steeper in women compared with men; from 138.2 (95% CI 137.7-138.5) to 131.0 mm Hg (95% CI 130.2-131.8) in women and from 140.5 (95% CI 140.1-140.8) to 136.1 mm Hg (95% CI 135.2-136.9) in men. The increase in use of blood pressure-lowering drugs was similar in men and women; in 1994-1995, 6.2% of men used blood pressure-lowering drugs to be compared with 15.6% in Tromsø 2007-2008. In women, corresponding rates were 5.6% and 15.0%. We did not observe any significant change in use of antithrombotic drugs at ICH onset over time; OR 1.84, 95% CI 0.90-3.76 for use of antithrombotic drugs at time of ICH in 2008-2013 with 1994-2001 as reference (p for trend=0.10).

Incidence rates in the overall population remained stable during the observation period (IRR 0.81, 95% CI 0.52–1.27). In analyses stratified on sex there was a significant, 54% decrease in incidence rates in women (IRR 0.46, 96% CI 0.23-0.90), whereas incidence rates in men (IRR 1.27, 95% CI 0.69-2.31) were stable. Incidence trends according to age group were stable (IRR 0.89, 95% CI 0.48-1.66 and IRR 0.78, 95% CI 0.41-1.48 in individuals aged

<75 years and ≥75 years, respectively). Interaction analyses revealed a significant interaction between sex and location. In analyses stratified on sex and location a decrease of non-lobar ICH in women (IRR 0.26, 95% CI 0.09-0.71) was observed, whereas the incidence rate in lobar ICH in women were stable (IRR 1.17, 95% CI 0.42-3.26). In men, incidence rates of both non-lobar (IRR 1.34, 95% CI 0.60-3.02) and lobar ICH (IRR 1.58, 95% CI 0.58-4.29) were stable.

4.3 Paper III

In paper III, a total of 219 ICH cases and 1,095 controls, randomly chosen from the original cohort and matched for birth-year and sex, were followed up with registration of date of death and causes of death during long-term follow-up (median follow-up 4.8 years, maximum follow-up 21.4 years). Mean age at ICH was 74 years (SD 11). Individuals with ICH had higher SBP levels and a higher prevalence of hypertension, whereas other cardiovascular risk factors were similar distributed between cases and controls. In cases, the risk of death was highest during the initial phase after the ICH, and thereafter levelled off. Thirty day-case fatality rates were 24.2% (n=53) in cases and 0.6% (n=6) in controls, respectively. Cumulative 1-, 5-, 10-, 15- and 20-years survival rates were 65%, 47%, 25%, 15% and 6% in cases and 94%, 70%, 51%, 33% and 22% in controls. In 30-day survivors, cumulative 1-, 5-, 10-, 15- and 20-years survival rates were 86%, 62%, 34%, 20% and 8% in cases and 95%, 73%, 55%, 36% and 25% in controls. The risk of death was significantly higher in 30-day survivors of ICH compared with controls (HR 1.62, 95% CI 1.27-2.06) during long-term follow up.

In both cases and controls, the major cause of death was CVD, with a significantly higher proportion in cases; accounting for 61% and 34 % of all deaths, respectively. In cases, the increased risk of death of CVD was driven by death from ICH and stroke sequelae. The risk of death by malignancy was significantly higher in controls than in cases. There was no difference in the risk of death by chronic obstructive respiratory diseases or other causes of death.

Smoking was associated with the risk of death within five years in both cases and controls, whereas there was no association with SBP or DM. Serum cholesterol was associated with risk of death in cases but not in controls. Risk of death did not differ according to ICH location. Of the four patients with holohemispheric ICH, three died during 5-year follow-up. Individuals on anticoagulant drugs at time of ICH had a significantly increased risk of death within five years, whereas there was no increased risk in individuals on antiplatelet drugs. There was no change in 5-year mortality rates during the study period (OR per year increase in calendar time 1.01, 95% CI 0.93-1.09)

5 Discussion

5.1 Methodological considerations

Epidemiology is a science that studies disease occurrence and health states in human populations.[122] Epidemiological studies aim to measure how population health indicators as disease frequency vary according to factors such as age, sex, geographic areas, race/ethnicity and time, and assesses the effect of exposures on the occurrence of diseases.[122]

5.1.1 Validity

Accuracy is essential for an epidemiological study to produce knowledge which is reliable and generalisable. There are several steps during a study where errors may occur. Errors in a study may be referred to as random or systematic.[123] Random errors may lead to lower precision of the estimates, and to an increased variability.[123] However, they usually do not threat validity.[123] Systematic errors, on the other hand, may lead to bias.[124] In epidemiological research, validity refers to the absence of bias, and depends on the accuracy of the methods used.[124] There are two types of validity: internal and external.[123]

Internal validity

Internal validity is the extent to which the observed results represent the truth in the study population (comparability) and is a prerequisite for external validity (representativeness).[123, 124] The internal validity may be threatened by measurement errors, errors in the selection of participants and in the way the data are interpreted.[123] These factors are often referred to as bias. Bias may be classified as selection bias (population), information bias (collection, analysis and interpretation of data) and confounding.[125]

Selection bias

Selection bias occurs when the study sample differs from the overall population in a way that the conclusions drawn are not representative for the population intended to study.[123] This may result in differences between study participants and non-participants in regard to the exposure and outcome of interest. Selection bias can result from the procedures used to select study participants or by factors influencing the study participation.[123] Selection bias can be further divided into non-respondent bias, attrition bias (loss to follow-up bias), and the healthy entrant effect.

Non-respondent bias

Non-respondent bias occurs when those that respond differ from those that do not respond.[125] In a population-based study validity may be threatened by low attendance rates. The Tromsø Study has aimed to include large, representative samples of the Tromsø population. Full birth cohorts and random samples of the residents in Tromsø municipality have been invited to attend.[119] The invitations are based on the official population registry.[119] Non-attendees were given one reminder.[119] The attendance rates to the surveys of the Tromsø Study have been high; in the 1st – 5th surveys, attendance rates were >75%, but somewhat lower in the 6th survey with an attendance rate of 66%.[119] In accordance with this, there has been a decrease in attendance rates in other comparable health surveys in Norway as well as internationally.[126, 127] The attendance rates in the 6th survey was however higher compared with other comparable health surveys in Norway.[128] Attendance rates were lower among the youngest and oldest (aged ≥80 years), among men and non-married.[119, 128] We cannot exclude that this may have introduced a selection bias.

Attrition bias (loss to follow-up bias)

Attrition bias occurs due to drops out or death.[123] Differential losses to follow-up is observed if the persons who are lost to follow up differ from those who remain under observation up to the event occurrence or termination of the study.[124] If the characteristics of those who were lost to follow-up are associated with the outcome measures, or if individuals lost to follow-up differ according to the distribution of exposure, attrition bias will be a particular problem.[123] All participants of the Tromsø Study are being followed-up with regard to disease incidence and mortality by linkage to the discharge and outpatient diagnosis registers at UNN, to the National Population Registry and to the National Causes of Death Registry by use of the Norwegian, unique 11-digit identification numbers.[119] The loss of follow-up in the Tromsø study can be considered as negligible.

The healthy entrant effect

Attendandees of epidemiologic studies are more likely to have favourable health profiles compared with non-attendees, which may bias estimates of prevalence, incidence and associations between exoposure and disease.[127] The healthy entrant effect may occur as a consequence of lower attendance rates among the sickest. Due to legal restrictions by the Norwegian Data inspectorate, analyses on morbidity and mortality among non-participants in the Tromsø Study have been precluded.[119] Previous analyses have shown lower mortality rates among individuals who attended all Tromsø 2-4 surveys compared with individuals who had been invited to all three, but only attended Tromsø 4.[119] In a publication from the Norwegian, population-based HUNT study, non-participants had lower socioeconomic status, higher mortality and higher prevalence of several chronic diseases compared with participants of the study.[129] However, there was little evidence supporting introduction of bias in

association and causal studies due to non-participation.[129] We cannot exclude that a healthy entrant effect may have led to lower incidence rates of ICH (Paper I and II) and higher survival rates (Paper I and III). A possible healthy entrant effect is less likely to have influenced analyses of trends over time (Paper I-III) or of comparisons between cases with ICH and controls (Paper III).

Information bias

Information bias (measurement bias) occurs when the data is being recorded inaccurately, or when the study population report incorrect information.[125] Information bias may place the participants in incorrect exposure, covariate or outcome category. If the measurement errors occur in a systematic manner; e.g. by use of non-calibrated equipment, they may lead to information bias.[123] Misclassification bias may be further categorised as differential (error that depends on the actual values of other variables) and non-differential (error that does not depend on the actual values of other variables).[122] Nondifferential errors will most often weaken a true association and thus to a degree have predictable consequences. Differential misclassification can alter estimations in any direction, and is more serious compared with nondifferential misclassification.[124] In a prospective cohort study, exposures are ascertained prior to the outcome of interest, and errors in classification tend to be similar distributed according to disease status, resulting in nondifferential misclassification.[124]

One measure to reduce misclassification bias is by use of standardised, validated assessment tools. In the Tromsø study, measurements of blood pressure, weight and height were performed by standardised methods and by trained personnel.[128] The equipment used was calibrated, limiting the risk of information bias on these parameters. Total cholesterol, triglycerides and HDL-cholesterol were measured by standardised methods at UNN. The

samples were non-fasting. However, the changes in lipid-levels in response to normal food intake are small, and fasting cholesterol levels may not be superior to non-fasting samples in assessing risk of CVD.[130]

Data on DM, smoking status, alcohol consumption, use of medications and physical activity were collected through self-administered questionnaires. Questionnaires are subject to errors in recall and reporting, and may introduce information bias. In a Norwegian study the concordance of self-reported DM was high.[131] Individuals with undiagnosed DM were not registered in our study, which may have led to lower prevalence rates of DM. We cannot exclude that this may have led to a dilution of a possible association with DM and outcomes of interest. Self-reported smoking status and alcohol consumption may be prone to underreporting.[132, 133] However, in a recent Finnish study, comparing serum contine level with self-reported smoking status the validity of self-reported smoking status was high..[132] Self-reported physical activity is often influenced by variations in recall accuracy.[134] A previous publication from the Tromsø Study showed a high correlation between self-reported and objectively measured leisure physical activity in attendees of the Tromsø Study.[134]

We may have missed some cases of ICH. However, UNN is the only hospital in the region. Due to long distances to other hospitals, admissions to other hospitals are unlikely. There is a possibility that non-hospitalised, non-fatal cases may not have been identified, e.g. due to sparse symptomatology or old age leading to non-referral/non-detection. Increasing treatment possibilities and an increased awareness of stroke may have led to higher admission rates, and a relative underestimation of incidence rates in the first part of the observation period. There is a possibility for an increased use of neuroimaging (CT and MRI) in the diagnostics of stroke during the last decades leading to an increasing recognition of ICH and

higher incidence rates in the end of the study. However, CT which has been considered the golden standard for diagnostics of ICH, has been available at the UNN since 1977.

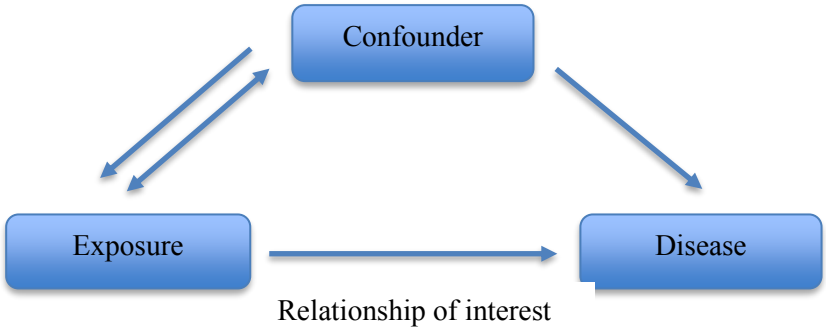
All stroke cases were validated by an independent end point committee reducing the risk of misclassification. ICH location was registered using a validated instrument. We regard the validity of ICH diagnosis and ICH location in the study as high.

Information on causes of death was based on data from the Norwegian Causes of Death Registry, which encompasses all residents, irrespective of whether they die in Norway or abroad.[135] The degree of coverage and completeness in the registry is near-complete. There is a risk of misclassification of causes of death. There have been few validation studies of the Norwegian Causes of Death Registry.[135] A previous publication showed a substantial agreement between Norwegian mortality statistics and autopsy findings for stroke and coronary deaths.[136]

Confounding

The term confounding is derived from latin and means "to mix together".[125] Confounding may result in an association between a given exposure and an outcome as a result of influence of a third variable; a confounder (Figure 10).[124] A confounder has to be associated with both the exposure and outcome.[124] The association may be either causal or non-causal.[124] The confounder shall not be an intermediate between the exposure and outcome.[124]

Figure 10. Illustration of confounding



Unidirectional arrow indicates a causal association. A bidirectional arrow indicates a non-causal association.

Confounding may result in a misleading association (overestimation, underestimation or reversal of the direction of an effect), which is due to a confounder, and not due to the risk factor of interest.[124] In order to have an impact the confounder must be unequally distributed in the groups being compared.[124] Known confounders can to some degree be handled by statistical methods; i.e. randomisation (study-participants are randomly allocated to the study-groups), excluding those with a confounding factor, matching (choosing two groups that are similar with the respect of the confounding factor, for example age and sex), stratification (dividing into two groups based on the confounding variable) and multivariable analyses (controlling for multiple factors in statistical analyses).[125, 137] Multivariable analyses were used in Paper I-III. Despite use of multivariable analyses, there may be possible confounders that we have not adjusted for. We performed analyses stratified on age and sex in paper I-II, and analyses stratified on ICH location in paper II. In Paper III, matching on birth-year and sex was performed in analyses comparing cases and controls.

External validity

External validity refers to which degree the study results apply to similar individuals outside the study population, and thus is generalisable.[123] The data in a study are collected from a study population. For the data to be valid outside the study population, the study population has to be representative for the population intended to study. External validity can be improved by using random selection.[124] The invitation to the Tromsø study was performed inviting randomly selected inhabitants of the municipality, as described earlier. The age and sex distribution of the Tromsø Study mirrors the Tromsø population in general, and risk factor levels and incidence of CVD among participants of the Tromsø study have been similar to other Western populations. The study population may be seen as representative for a Western, mostly urban, Caucasian population in a high-income country with high education levels, and high access to social services.

5.1.2 Interaction (effect modification)

Interaction describes a situation where the direction or strength of an association between two variables depend on the value of one or more other independent variables.[124] For dichotomous variables, interaction means that the effect of the exposure on the outcome differs depending on whether the categorical variable is present or not.[124] For continuous variables the effect of exposure on outcome depends on the level of the continuous variable if interaction is present.[124] Interaction may be assessed by including an interaction term (product of two or more independent variables) in a multivariable model.[138] Analyses of interactions were used in all papers. In paper I-II, interaction terms were used to assess differences in time trends in incidence and case fatality rates according to age and sex. In paper III, tests for

interaction were performed when comparing the association of cardiovascular risk factors and risk for five-year mortality between cases and controls and to assess differences in time trends of five-year mortality, according to age and sex.

5.1.3 Missing data

Missing data is a limitation in the majority of studies, and may have different reasons. Missing data may be categorised as missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR).[139] There are different measures to handle missing data. Complete subject analysis refers to the deletion of records with missing data in analyses which involves variables for which the records have missing data. The results of these analyses will be valid if cases with complete data have been randomly sampled from all the subjects in the study; i.e. the data are missing completely at random.[139] If a large proportion of subjects have missing data, this may lead to reduced power, which in turn may cause unreliable estimates despite being MCAR.[139] In these cases, alternative methods may be used.[139] In paper II, physical activity was the risk factor with most missing data (n=1,137) among the 27,948 individuals without ICH. For other cardiovascular risk factors the number of individuals with missing data ranged between 0-244. Among ICH cases, data on DM was missing in one, physical activity in two and data on ICH location in one. In multivariable analyses on the association between cardiovascular risk factors and risk of ICH with inclusion of all risk factors (model 2) in paper II, a total of 1,211 controls (4.3%) and 2 ICH cases (0.9%) were excluded due to missing data. Among 30-day survivors in paper III, data on DM were missing in one case and three controls. Smoking status was missing in one control. Data on use of antithrombotic drugs at time of ICH were missing in one case. In all papers, the

missing data were few, and considered to be MCAR. Complete subject analyses were used in all papers.

5.1.4 Repeated measurements

The Tromsø study is a longitudinal study with repeated surveys. A high proportion of attendees have attended more than one survey, and thus contribute with repeated measures of cardiovascular risk factors.[119] Repeated measurements within one individual are correlated, and may lead to incorrect estimation of the variances and incorrect inferences about the regression coefficients in statistical analyses which assume independent associations (e.g. linear regression and logistic regression).[140] To account for this, GEE were used in analyses of time trends in risk factors. Generalized estimating equations is a statistical method which permits specification of a "working correlation matrix" that accounts for the form of within-subject correlation of responses on dependent variables and thus corrects for the dependency of observations.[140]

5.1.5 Statistical power

Despite being a large population-based study, the number of incident ICH cases in our study was limited. Low statistical power may increase the probability of type II errors (incorrect acceptance of the null hypothesis).[122] In our study this could mean failing to observe a change in time trend, when there is one. A low statistical power may also lead to an increased risk that statistically significant results will be falsely positive.[122] One possibility to increase the power of the study could have been to merge data with other similar Norwegian cohort studies, e.g. the HUNT study. However, due to differences in study-design this was not

possible. Another possibility could have been to present results from the overall stroke population in the Tromsø study. However, ICH and IS have different risk factor profiles and outcome, and we believe that it is important to report data stratified on stroke subtype. There is a need for data from well conducted studies with validated ICH cases, and despite the limited number of cases, we believe that our study contributes to the knowledge on ICH.

5.2 Discussion of main results

5.2.1 Association between cardiovascular risk factors and risk of ICH

Age, male sex, SBP, DBP and hypertension were associated with the risk of ICH, whereas there was no association with total cholesterol, HDL-cholesterol, triglycerides, BMI, DM, smoking, alcohol intake or physical activity.

The association with age and blood pressure and risk of ICH is in line with previous studies.[42] Hypertension was present in 84% of ICH patients. Individuals with hypertension who were on blood pressure-lowering drugs and reached a blood pressure level <140/90 mm Hg, had no significant increased risk of ICH compared with individuals without hypertension. This finding reflects the results from previous RCTs on primary prevention of ICH which have shown a significant decreased risk of ICH in patients with hypertension treated with blood pressure-lowering drugs.[141]

Studies on the association with sex and risk of ICH have been diverging. Whereas some studies have shown similar risk between sexes, others have shown an increased risk in men.[27, 43, 44] In a recent meta-analysis, men had a higher overall ICH incidence.[44] However, there were geographical variations. In Europe, the majority of studies have shown similar

incidence rates between sexes, with the exception of Greece and Norway, where a male preponderance has been observed.[44]

There was no association with total cholesterol, triglycerides or HDL-cholesterol and the risk of ICH. Several publications have reported an inverse association with cholesterol and risk of ICH,[55, 57] whereas others have found no association.[55, 58, 59]

Alcohol intake was not associated with the risk of ICH. In some previous studies, a dose-dependent relationship with alcohol intake and risk of ICH has been reported.[56, 72] We performed analyses with alcohol intake categorised as teetotalism yes/no. This may have diluted a possible association according to amount of alcohol intake. Questions on alcohol intake differed between surveys, and analyses on the association between amount of alcohol intake and risk of ICH was limited to individuals attending the 5th and 6th surveys. These analyses did not show any dose-dependent association with alcohol intake and risk of ICH. However, due to a smaller sample size the power of these analyses may have been limited.

We found no association with BMI, DM or smoking and risk of ICH. Previous studies on the association with BMI, DM and smoking and the risk of ICH have been diverging.[42, 55, 62-64, 74-76] We used self-reported data on DM, and there is a possibility that we may have missed some cases with undiagnosed, untreated DM.

There are few studies on the association with physical activity and risk of ICH. In a large case control study as well as in a recent meta-analysis on observational studies, high level leisure time physical activity had a protective effect on risk of ICH/hemorrhagic stroke.[56, 66] Due to differences in the questionnaires according to level of physical activity we categorised physical activity as strenuous leisure physical activity (i.e. become sweaty and out

of breath) for at least 1 hour per week. We cannot exclude that there may be a possible association with higher levels of physical activity, which we were not able to identify.

Previous studies have indicated an association with use of illicit drugs and risk of ICH.[77] We did not have information on use of illicit drugs in our study-population.

One of the major strengths of this study is the use of individual data from repeated surveys with registration of premorbid risk factors. In individuals, who attended more than one study, measurements from the latest attendance before the ICH event were used. There is a possibility that risk factor levels may have changed after attendance in some individuals. However, a previous study from the Tromsø Study showed that changes in risk factors between surveys have been small and little likely to affect risk estimates for myocardial infarction and deep venous thrombosis to a larger degree.[142] The authors suggested that risk estimates based on a single measurement are generally reliable in cohort studies with long follow-up.[142]

Risk factors according to ICH location

Age, SBP and DBP were significantly associated with both lobar- and non-lobar ICH. The association with blood pressure was however substantially stronger with non-lobar than with lobar ICH. Previous studies on risk factors according to ICH location are few, and the results have been diverging.[78-84]

In a meta-analysis, an excess of hypertension was found in ICH patients with deep versus lobar ICH.[85] However, a concern was raised about methodologically issues of the studies as blinding for hypertension status when reporting ICH location, uncertain reliability of the classification of hemorrhage location and variable rates of investigation for secondary causes.[85] The ICH cases in our study were rigorously validated and registration of ICH

location was performed blinded for risk factors. We excluded individuals with ICH caused by hemorrhagic transformation of IS, trauma, brain surgery, hematologic disease and brain tumor. In addition, a validated instrument was used for assessment of ICH location.[121]

We found an association between male sex and risk of non-lobar, but not lobar ICH, which has been previously reported in studies from the US, and Mexico.[44] In a large meta-analysis on risk factors according to ICH location, the risk ratio of male sex on non-lobar ICH was 1.63, 95% CI 1.25-2.14, whereas there was no association with lobar ICH.[84] The reason for this association is not clear. In our population, the association with male sex and non-lobar ICH remained significant after adjusting for cardiovascular risk factors. We found no association with other cardiovascular risk factors and ICH, regardless of location.

5.2.2 Time trends in risk factors

Blood pressure levels, prevalence of hypertension, serum lipid levels and smoking prevalence decreased significantly during the study-period. BMI levels and prevalence of DM increased. The proportion of physically active individuals increased. The rate of teetotalers decreased. There was an increase in use of blood pressure-lowering, lipid-lowering and antithrombotic drugs during the study period. Women had lower blood pressure levels than men in all surveys, and the decrease in blood pressure was steeper in women than in men.

In accordance with our study, there has been a decrease in blood pressure levels in several Western countries during the last decades.[101] In Norway, a similar decrease in blood pressure levels has been observed in the HUNT study.[143] Higher blood pressure levels in men has been reported in other high income countries.[144] In line with our results, a steeper decrease in blood pressure levels in women compared with men has been reported in a

previous publication from the Tromsø Study in addition to two large cross-sectional studies with pooled analyses.[145-147] In the Norwegian HUNT-study, the difference in time trend in blood pressure levels between men and women was less pronounced.[143] Use of blood pressure-lowering drugs increased. However, previous publications from the Tromsø Study and the HUNT study have suggested that the observed decrease in blood pressure levels cannot be fully explained by an increased use of blood pressure-lowering drugs, but to a degree are due to changes in blood pressure in the population.[143, 145] The reason for this is not known. There was an increase in the proportion of individuals with hypertension treated with blood pressure-lowering drugs, and an increase in the proportion with well-controlled hypertension. Despite an increase in treatment of hypertension, less than half of individuals who fulfilled the criteria for hypertension in the last survey were on blood pressure-lowering drugs. Of these, two-thirds had uncontrolled hypertension. Similar results have been reported in large, multinational studies,[144, 148] and underline the need for further improvements of primary prevention of ICH. A decrease in serum lipids levels, daily smoking, and increase in BMI levels and in prevalence of DM has been observed in other Western countries, including the Norwegian HUNT study.[101, 143] In accordance with several previous studies from Western countries, use of lipid-lowering and antithrombotic drugs increased.[101-104]

5.2.3 Incidence rates of and time trends in incidence of ICH

Incidence rates increased with increasing age and were higher in men compared with women. Incidence rates in Paper I, adjusted to the European population of 1974, were 0.42, 95% CI 0.37– 0.48 per 1,000 person-years, which is higher compared to a previous meta-analysis reporting an incidence rate of 0.25 per 1,000 person-years (95% CI 0.20–0.31),[27] and three

Norwegian publications, where adjusted incidence rates ranged between 0.13-0.32 per 1,000.[24, 25, 149] Our study was limited to individuals aged ≥30 years, whereas the majority of other studies have included younger age groups, or had no lower age limit, which may have contributed to the higher incidence rates in our study.

Incidence rates of ICH in the overall population were stable in the period 1995-2013. The majority of studies from other populations have shown stable or decreasing incidence rates of ICH.[83, 86-97] In accordance with our findings, incidence rates were stable in two previous meta-analyses covering the periods 1980-2006 and 1980-2008, respectively.[5, 27] The authors of the Global Burden of Diseases reported a decrease in incidence of hemorrhagic stroke (ICH and SAH combined) in high-income countries between 1990 and 2010.[100] In a recent review on stroke incidence in high-income countries, a significant decrease in ICH incidence was observed in the period 1990-2000.[150] During the period 2001-2010 the decrease was less pronounced, and no longer statistical significant.[150] In a Norwegian study on trend in stroke incidence during the period 2010-2015, based on data from the National Patient Registry and the National Cause of Death Registry, incidence rates of ICH were stable, whereas a significant decrease in IS incidence was observed.[151] The study included both first-ever and recurrent strokes.[151] A trend towards an increased burden of primary ICH in high-income countries was reported in the latest article on stroke incidence from The Global Burden of Disease Study, underlining the importance of further surveillance of this stroke entity.[1]

Trends in incidence rates diverged between sexes. Incidence rates in men were stable, but tended to decrease over time in women. The decrease in ICH incidence in women was driven by a 74% decrease in non-lobar ICH. There are few previous studies on sex-specific trends in ICH incidence, and the results have been diverging.[92, 94, 99] To the best of our

knowledge, our study is the first study reporting incidence trends according to sex, stratified on ICH location.

There was no difference in incidence trends according to age-group in our population. Previous studies have not been consistent. In a study from the Netherlands, incidence rates were stable in individuals aged ≥75 years, whereas incidence rates in the younger decreased.[152] In two UK and French studies incidence rates increased in the elderly, and decreased in the younger.[93, 97] Contrary to this, decreasing incidence rates in individuals aged ≥75 years, and stable incidence rates in individuals aged 45–59 years was found in an US study.[88]

5.2.4 The impact of risk factor trends on incidence trends of ICH

Hypertension was the only modifiable risk factor associated with ICH and was more strongly associated with non-lobar than lobar ICH. Despite a decrease in blood pressure levels, incidence rates of ICH remained stable in the overall population. However, the trend diverged between sexes with a decreasing trend in women, driven by a decrease in non-lobar ICH. Lower blood pressure levels and a steeper blood pressure decrease in women compared with men may have contributed to the differences between sexes.

Previous studies on the association with changes in risk factor levels and incidence trends in ICH are few.[21, 83, 92, 93, 97] In addition to an association with hypertension, use of anticoagulant drugs has been associated with the risk of ICH, with a higher risk associated with vitamin K antagonists compared with DOACs.[67] Antiplatelet drugs probably increase the risk of ICH to a small degree.[68] There has been a concern that an increased use of

antithrombotic drugs in the elderly may have outweighed a decrease in hypertension associated ICH.[93, 97] In two UK and French studies on 107 and 441 ICH patients, covering the periods 1981-2006 and 1985-2008, respectively, an increase in incidence rates in individuals aged ≥75 years was observed, whereas incidence rates in younger age groups decreased.[93, 97] In the French study, the increase in the elderly was driven by an increase in lobar ICH, concomitant with an increase in use of antithrombotic drugs.[93] In a study from the US, the annual incidence of anticoagulant-associated ICH increased during the period 1988-1999.[153] Contrary to these studies, a Finnish study reported stable incidence rates of ICH associated with use of anticoagulant drugs despite a 3.6-fold increase of warfarin users in the population during the period 1993-2008.[102] During this period admission INR values above the therapeutic range decreased, suggesting improved control of anticoagulant therapy over time.[102] We did not observe any significant trend according to age-group or in incidence of lobar ICH, and there was no significant increase in ICH associated with use of antithrombotic drugs. We did not have data on INR in VKA users in our study-population. In Norway, DOACs received marketing authorization in 2011, and during the last years they have taken over for VKAs.[70] None of the ICH cases in our study population were on DOACs at time of ICH.

5.2.5 Time trend in 30-day case fatality rates

Case fatality rates in our population were approximately 24%, which is in the lower range compared with previous publications.[27] Thirty-day case fatality rates remained stable during the period 1995-2012. This is in line with several studies, including two meta-analyses including 36 and 30 studies, with a total of 8,145 and 7,736 ICH patients, respecively.[27, 88, 90, 95, 106] A decrease in 1-month case fatality rates has been reported by others.[89, 91, 98, 107-110] The

authors of a study from the Netherlands reported diverging trends according to age group with a decrease in case fatality among individuals younger than 75 years, and stable case fatality rates in individuals aged 75 years and older.[152] We found no difference in time trend according to age group. In a French study, the reduction in one-month case fatality was observed during the period 1985-2011.[110] The decrease was observed between 48 hours and 30 days, whereas the risk of death within the first 48 hours was stable. The authors concluded that the decrease probably was an effect of implementation of dedicated stroke networks, organised intensive care units and guidelines dedicated to the management of ICH patients, and that stable 1-month case fatality rates in the initial 48 hours after the ICH might be explained by limited treatment opportunities in the acute phase of an ICH.[110] The stroke unit at UNN was established in 1993, and a possible effect of this may not have been detected in our study. We cannot exclude that there may be changes in 30-day case fatality rates in our population which we did not detect due to limited power. In three previous Norwegian studies performed in 1994-1996, 2005 to 2009 and 2010-2014, respectively, 1-month case fatality rates ranged between 37% and 40%, [24, 25, 149] which may support our finding of stable 1-month case fatality rates during the last decades. The rates in these studies are however crude, which limits direct comparisons.

In the majority of cases, death during the first month after an ICH is a direct consequence of the ICH.[33] The components of the ICH score (high age, low GCS, infratentorial origin of ICH, high ICH volume and presence of intraventricular hemorrhage) have been associated with an increased risk of early death after ICH.[34] Use of anticoagulant drugs at time of ICH has been associated with an increased risk of early death.[154] In addition, early do not resuscitate (DNR) orders are an independent risk factor for early death, probably

caused by a limitation of active treatment in these patients.[155] We had limited data on the components of the ICH score, and did not have data on DNR orders.

Due to the relatively low 30-day case fatality rates in our population, we compared our results with data on 30-day case fatality in ICH patients living in Tromsø municipality who were habituated in Tromsø and registered as hospitalised at UNN with a first-ever ICH in the Norwegian Stroke Registry for the period 2012-2016 (n=79). In these patients, 30-day case fatality rate was 31.6% (personal communication, Stein Harald Johnsen), which is lower compared with previous Norwegian studies,[24, 25, 149] but higher than in our study. We cannot exclude that the lower 30-day case fatality rate in our study-population may be due to a healthy bias effect. This is, however, less likely to have had an impact on analyses in trends in case fatality rates.

5.2.6 Long-term survival

In paper III we report data on long-term survival in ICH patients and their controls, matched for birth-year and sex. Whereas death in the acute phase after ICH often is a direct consequence of the ICH, other causes of death play a larger part in ICH survivors. [33] There are few previous studies on ICH survivor cohorts, and there is little data on the impact of cardiovascular risk factors on risk long-term mortality.[28] In addition, data on trends in long-term mortality rates are scarce.[28, 88, 107, 108, 111] We aimed to compare long-term survival rates, causes of death and the impact of cardiovascular risk factors on long-term mortality in 30-day survivors of ICH and the general population. As shown in paper I, the risk of death after ICH was high in the acute phase after the ICH. After the initial phase, the risk of death flattened out. However, the risk of death during long-term follow-up was more than 60% higher in 30-

day survivors of ICH compared to controls. The finding of an increased risk of death during long-term follow-up is in line with previous studies on ICH survivors.[33, 112, 156, 157]

Among 30-day survivors, 5-year survival rate was 62% in ICH cases to be compared with 73% in controls. 10-year survival rates were and 34% and 55%, respectively. After 20 years of follow-up, 8% of ICH cases and 25% of controls were alive.

Few studies have assessed long-term survival in ICH survivor cohorts, and start of follow-up after ICH has varied. The authors of the Finnish study reported a 7-year survival rate of 67% among 3-month survivors of ICH.[156] In a Swedish study 5- and 10-year survival rates were 74% and 43% among 1-year survivors.[112]

The major cause of death was CVD in both cases and controls, accounting for 61% and 34% of all deaths, respectively. The risk of death by CVD was significantly higher in ICH patients compared with controls, driven by an increased risk of ICH and stroke sequelae. Controls had a higher risk of death by malignancy compared with cases, whereas there was no difference in risk of death by other causes. In line with our findings, CVD was the major cause of death in two previous studies on ICH survivors, with rates of 56% and 58%, respectively.[33, 112]

The increased risk of death by ICH and stroke sequelae probably mirrors high dependency rates after an ICH in addition to ICH recurrence.[27, 33, 113, 156-158] We did not have data on functional outcome after ICH, or on recurrence rates of ICH in our cases. The risk of IS in ICH patients is similar to the risk of ICH recurrence.[28, 157] The risk of death by IS was however not higher compared with the general population in our study. In a recently published study from the Netherlands on 19,444 30-day survivors of ICH, 4.4% had recurrent

ICH of which 59% were fatal, 4.2% had IS, of which 20% were fatal, and 10.1% had unclassified stroke, of which 22% were fatal.[157]

Previous studies on risk factors for long-term mortality after ICH are heterogenous, and the majority have included individuals who died within the first month after the ICH.[28] We found a significant association with smoking and all-cause mortality in both cases and controls. Previous studies on the association between smoking and long-term mortality have been inconsistent.[33, 156, 159] Serum cholesterol was associated with an increased risk of death in ICH patients, but not in controls. An inverse association with serum cholesterol and risk of ICH has been suggested in several studies, but not all.[55, 57-59] We analysed risk factors for ICH in paper II, and found no association with serum cholesterol and risk of ICH in our study-population. Data on serum cholesterol and risk of long-term mortality are few. In a Danish study, an inverse association with serum cholesterol and risk of death was reported in 7-day survivors of ICH.[160] However, the risk was no longer significant after adjusting for statin use.[160] We did not have data on statin use at time of ICH. It is unknown if statins should be withheld or started in ICH patients.[60] In some studies, use of statins has been associated with improved outcome, and reduced long-term mortality after ICH.[60] In a recent Swedish observational study on data from the Swedish Stroke Register, ICH patients who were prescribed statins at discharge, had a reduced risk of death.[161] Use of statins was not associated with recurrence of ICH.[161] However, studies based on observational data may be prone to confounding by indication bias. An association with statins and lobar ICH has been suggested,[61] and there is a possibility that risk of statin use may differ according to the underlying ICH pathology. There is a need for RCTs to increase the understanding on use of statins as secondary prevention in ICH patients, and possible differences between subgroups of ICH.

Despite being a strong risk factor for both incident and recurrent ICH,[42, 162] blood pressure was not associated with the risk of death within five years, neither in ICH cases nor in controls. This is in line with previous studies, failing to show an association with hypertension and long-term mortality in ICH patients.[25, 28, 33, 112, 156] There is a possibility that initiation of blood pressure-lowering treatment in ICH patients may have attenuated a possible association with premorbid SBP and risk of long-term mortality. We had little data on use of blood pressure-lowering drugs and blood pressure levels after the ICH in our cohort. There are few data on blood pressure-lowering and risk of all-cause mortality in ICH patients, and studies on blood pressure-lowering on all-cause mortality in stroke overall have been conflicting.[163, 164] Despite our results, lowering of blood pressure remains an important measure for secondary prevention after an ICH, as it reduces the risk of ICH recurrence as well as risk of other CVD significantly.[162, 165]

We found no association with DM and risk of death neither in cases nor in controls. Previous studies on the association with DM and long-term mortality after ICH have not been consistent.[28, 33, 112, 156, 159]

In analyses restricted to ICH patients, we found a significant association with use of anticoagulant drugs, but not antiplatelet drugs, at time of ICH and risk of 5-year mortality. There was no difference in risk of death according to ICH location. Studies on the association between anticoagulant drugs and long-term mortality in ICH survivor cohorts have shown diverging results.[33, 112, 156, 159] ICH patients on anticoagulant drugs have an increased risk larger hematoma size and of hematoma expansion,[154] which may increase the risk of poor outcome. Whether an association with anticoagulant drugs and long-term mortality after ICH could be a consequence of increased disability due to larger hematoma size in patients on

anticoagulant drugs, an increased risk of ICH recurrence in cases where anticoagulant drugs were resumed, or by an increased risk of thromboembolic events in patients where anticoagulants were withdrawn, or a combination, is unclear. Data on resumption of antithrombotic drugs after ICH are limited. However, several ongoing RCTs are addressing this question.[166] We have limited data on the resumption of antithrombotic drugs.

Infratentorial location of ICH and hematoma size are predictors for short-term mortality after ICH.[34] We found no association with ICH location and the risk of death within five years. We did not have data on ICH volume. Among the 30-day survivors of ICH four had a holohemispheric ICH, which may be considered a proxy for large hematoma size. Of these, three died within five years. Previous studies on ICH location and hematoma size have not been consistent,[28, 33, 112, 159] but they may be of less importance in ICH survivors.[33, 112, 159]

There was no change in 5-year mortality rates during follow-up. There are few studies on trends in long-term mortality rates after ICH. In a large meta-analysis, 5-year mortality rates were stable in the period 1983-1997,[28] and in a US study 3-year mortality rates were stable between 2000 and 2010.[88] Contrary to these results, a decrease in 5-year mortality rates in 2004-2008 compared with 1994-1998, was observed in a large Danish register-based study, including 24,760 ICH patients, and a decrease in 10-year mortality among 10,480 ICH patients during the period 1999-2007 was observed in a Finnish register-based study.[108] In a Dutch study on 30-day survivors of ICH in patients aged 18-49 years, 5-year mortality rates were stable.[111] The explanations of stable long-term mortality rates may be complex. Treatment possibilities of ICH are limited, and a large proportion of ICH survivors remain disabled,[27] which may increase the risk of death by medical complications. Stroke unit care reduces the risk of long-term mortality after ICH.[38] The stroke unit at UNN was established in

1993. As the start of follow-up in our study was set to 1994-1995, we may not have been able to register a possible effect of the implication of stroke unit care at our hospital.

6 Conclusions, clinical implications and future perspectives

6.1 Conclusions

Incidence rates of ICH remained stable in the overall population during the study-period. A decrease in incidence rates in women was observed, driven by a 74% decrease in non-lobar ICH, whereas incidence rates in men were stable, regardless of location. Age, male sex, SBP, DBP and hypertension were significantly associated with the risk of ICH. Hypertension was stronger associated with non-lobar ICH compared with lobar ICH. Lower blood-pressure levels in addition to a steeper decrease in blood-pressure over time in women compared with men, may have contributed to the difference between sexes. We observed no change in incidence rates according to age group. Despite an increased use of antithrombotic drugs during the study-period, there was no significant change in incidence of ICH associated with use of antithrombotic drugs.

Prevention is the most important measure to reduce the burden of ICH. Hypertension was the only modifiable cardiovascular risk factor associated with ICH, and was present in 84% of ICH cases. In the general population, individuals with hypertension, treated with blood pressure-lowering drugs, who reached a blood pressure level <140/90 mm Hg had a similar risk of ICH compared to controls without hypertension, whereas individuals with uncontrolled hypertension, whether treated or not, had a significantly increased risk of ICH. Despite an increase in use of blood pressure-lowering drugs, less than half of individuals with hypertension attending the last survey were treated and of these, two-thirds did not reach treatment goals.

Thirty-day case fatality rates remained stable. Individuals who survived the first 30 days after the ICH event had a significantly increased risk of death during long-term follow-up compared to controls matched by birth-year and sex. CVD was the major cause of death in both cases and controls, with a higher proportion in ICH cases. In ICH patients, the increased risk of death by CVD was driven by recurrent ICH and stroke sequelae. Smoking was associated with an increased risk of death within five years in both cases and controls, whereas serum cholesterol was associated with an increased risk in cases only. In individuals with ICH, use of anticoagulant drugs at time of ICH was significantly associated with 5-year mortality. ICH location was not associated with risk of death within five years. There was no change in 5-year mortality rates during the observation period.

The high proportion of individuals with untreated hypertension, and of individuals who did not reach treatment goals, indicate that there is a need for improved primary prevention of ICH. The stable short- and long-term mortality rates probably reflects the limited treatment possibilities of ICH, and stresses the urge for improved treatment strategies in the acute phase after an ICH. In addition, there is a need for better knowledge on secondary prevention after ICH.

6.2 Clinical implications and future perspectives

6.2.1 Primary prevention

We have shown that there is a need for improved treatment of hypertension to reduce the burden of ICH. Since our study, there has been a further decrease in blood pressure levels in the population of Tromsø.[167] In a recent publication using data from the 7th wave of the Tromsø study, performed in 2015-2016, blood pressure control was achieved in 22% of men

and 33% of women with hypertension, and aged 40-69 years.[168] In those on blood pressure-lowering drugs, 62% had well controlled hypertension,[168] which is higher compared with our study-population. Despite a trend of improved treatment of hypertension, there is still a considerable scope for improving the primary prevention of ICH.[168]

There has been a continuous increase in the use of antithrombotic drugs.[70, 103, 169] Due to the similar preventive effect, greater convenience and reduced risk of bleeding, DOACs have been increasingly used during the last years. In some countries, including Norway, they have overtaken for vitamin K antagonists.[67, 70, 169] DOACs were approved in Norway in 2011-2012.[70] None of the anticoagulant users in our ICH-population were on DOACs. This pattern could be expected to have changed during the recent years. In addition to changes in prescription patterns of anticoagulant drugs, an increase in dual antiplatelet therapy may be expected e.g. due to changes in guidelines on secondary prevention of IS.[170]

In the most recent publication from the Global Burden of Disease Study, an increasing proportion of ICH in high income countries was reported, underlining the importance of further surveillance on ICH epidemiology.[1] Future studies on trends in ICH incidence and possible changes in risk factor profile of ICH are important to assess the effects of trends in blood pressure levels and changes in prescription patterns of antithrombotic drugs during the recent years.

6.2.2 Acute treatment

The stable short- and long-term mortality rates in our study stresses the urge for more effective treatment opportunities of ICH to reduce early death and ICH sequelae. Treatment in stroke units reduces the risk of short- and long-term mortality,[37, 38] and reversal of

anticoagulant drugs may reduce mortality in patients on anticoagulant drugs at time of ICH.[39] Except from this, studies on use of hemostatic drugs, blood pressure-lowering and surgery in ICH patients so far have failed to show any clear benefit with respect of mortality.[40, 41, 171] However, sub-analyses suggest that hemostatic drugs may be beneficial in selected patients if started early.[172] In addition, hematoma evacuation using minimally invasive surgery with small residual ICH volume may be a promising treatment strategy.[173] Risk of hematoma expansion after ICH is largest during the first few hours after an ICH,[35] and prehospital identification and treatment of ICH may be an important measure to improve outcome after ICH. Future studies are warranted to assess timing and subgroups of patients who may benefit from different treatment strategies. In addition, there is a need for further research on novel treatments for reducing the consequences of edema and toxic effect of degradation products of hemoglobin.

Supportive care on a stroke unit or critical care unit improves outcome after ICH.[37, 155] Early prognostication after ICH is difficult, and it has been suggested that the use of prognostic scales may be a self-fulfilling prophesy, decreasing the likelihood of survival after ICH.[155] Early DNR orders reduces active treatment and increases early death after ICH.[155] In a recent publication from the UK implementation of a "bundle of care" with a combination of anticoagulation reversal, blood pressure-lowering and surgery in selected cases in addition to specialised supportive care reduced one-month case fatality substantially.[174] A substantial part of the effect was mediated through a reduction in early DNR orders.[174] These results are promising, and further research on implementation of the use of care bundle approach on a national level, and on the components to be included in a care bundle are important to assess approaches which may reduce early case fatality rates.

Further studies on short- and long-term mortality rates after ICH will be an important tool to assess effects of possible changes in future treatment regimens of ICH.

6.2.3 Secondary prevention

Secondary prevention with the aim to reduce recurrence rates of ICH and to reduce the risk of IS and other serious vascular events in ICH patients are important. We found a significant association with smoking, serum cholesterol and use of anticoagulant drugs and long-term mortality after ICH. Data on serum cholesterol and use of statins and long-term survival after ICH are few,[60, 160] and there is a need for further studies to assess this question. In addition, there is a need for knowledge on use of antithrombotic drugs in ICH patients.

Blood pressure-lowering is the most important measure to reduce recurrence rates of both lobar and non-lobar ICH.[162] Studies, however, indicate that a less than half of patients reach treatment goals after a stroke.[162, 175] There is a need for research on novel approaches to improve the rates of patients reaching treatment goals after a stroke.

ICH is a heterogeneous disease. Use of antithrombotic drugs, statins, and risk of ICH recurrence may differ according to the underlying pathology.[61] The increased use of advanced imaging techniques, genetic tests in addition to possible novel biomarkers may improve the possibilities of early identification of underlying ICH pathology.[61] Future studies should focus on identifying the underlying pathophysiology and tailoring preventive treatments according to sub-type of ICH.

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Paper I

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Original Paper

Temporal Trends in Incidence and Case Fatality of Intracerebral Hemorrhage: The Tromsø Study 1995–2012

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Key Words
Intracerebral hemorrhage · Stroke incidence · Cohort study · Epidemiology

Abstract
Background: The aim of this study was to explore temporal trends in incidence and case fatality rates of intracerebral hemorrhage (ICH) over the last two decades in a Norwegian municipality. ***Methods:*** Incident cases of primary ICH were registered in the period from 1995 through 2012 in 32,530 participants of the longitudinal population-based Tromsø Study. Poisson regression models were used to obtain incidence rates over time in age- and sex-adjusted and age- and sex-specific models. Case fatality rates were calculated and age- and sex-adjusted trends over time were estimated using logistic regression. ***Results:*** A total of 226 ICHs were registered. The age- and sex-adjusted incidence rate [95% confidence interval (CI)] in the overall population was 0.42 (0.37–0.48) per 1,000 person-years. Age-adjusted incidence rates were 0.53 (0.43–0.62) in men and 0.33 (0.26–0.39) in women. In individuals aged <75 years, the age- and sex-adjusted incidence rate was 0.27 (0.22–0.32) and in individuals aged ≥75 years, it was 2.42 (1.95–2.89) per 1,000 person-years. There was no significant change in incidence rates over time. The incidence rate ratio (95% CI) in the overall population was 0.73 (0.47–1.12) in 2012 compared with 1995. The overall 30-day case fatality (95% CI) was 23.9% (18.3–29.5) and did not change substantially over time [odds ratio in 2012 vs. 1995 = 0.83 (95% CI 0.27–2.52)]. ***Conclusion:*** No significant changes in incidence and case fatality rates of ICH were observed during the last two decades.

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Introduction

Stroke is the second leading cause of death worldwide and the third leading cause of death in Norway [1, 2]. Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes in Western countries, with an incidence rate of 0.1–0.3/1,000/year [3]. Morbidity and case fatality are high: only 12–39% of patients live independently after an ICH and case fatality rates at 1 month range between 13 and 61% (median 40%) [4]. Treatment possibilities for ICH are limited [5]. However, recent studies show that early, intensive lowering of blood pressure may improve outcome [6].

Studies of trends in incidence and 1-month case fatality rates of ICH over the last three decades have shown divergent results. While some studies have reported stable incidence rates, others have found decreasing or increasing rates [7–16]. Studies of trends in case fatality rates have reported stable as well as decreasing rates [7, 9, 11–14, 16–18]. Reviews based on studies published between 1970 and 2008 showed no significant change in incidence and case fatality rates [4, 19], while a recent review reported a decrease in incidence of intracerebral and subarachnoidal hemorrhage in high-income countries and a significant increase in low- to middle-income countries between 1990 and 2010 [20]. The aim of our study was to explore temporal trends in incidence and case fatality rates of ICH over the last two decades in a Norwegian municipality.

Methods

Study Population

The Tromsø Study is an ongoing, longitudinal population-based study started in 1974. The municipality of Tromsø is located in the northern part of Norway. The population has increased; from approximately 42,200 in 1974 to the current population of approximately 73,000 inhabitants [21, 22]. The vast majority of the population is of Caucasian origin.

Details of the study have been described earlier [23, 24]. Based on the official population registry, full birth cohorts and random samples of residents in the municipality of Tromsø have been invited to attend the surveys. To the first survey (Tromsø 1), only men were invited. Of the 53,731 individuals who were invited, 40,051 attended at least 1 of the 6 surveys (table 1) [24]. Participants are being followed up with regard to incident stroke and cardiovascular events. The Tromsø Study has been approved by the Regional Committee for Medical and Health Research Ethics and the Data Inspectorate of Norway.

Individuals who were not officially registered as inhabitants of the Tromsø municipality at the date of enrolment (n = 162), individuals who were younger than 20 years at enrolment and did not attend later studies (n = 785), those who did not have valid written consent to medical research (n = 225), and individuals who had prevalent ICH (n = 18) or unspecified stroke (n = 45) were excluded. Because older birth cohorts were not enrolled in the earliest surveys, and individuals <30 years were not enrolled in the two latest surveys (table 1), analyses were limited to individuals aged ≥30 years in the period January 1, 1995 to December 31, 2012. Individuals who emigrated out of the municipality (n = 5,145), died (n = 788) or suffered an ICH (n = 24) before 1995 or did not reach 30 years of age during follow-up (n = 329) were censored, leaving 32,530 individuals (16,771 women and 15,759 men) to be included. Individuals were followed up with registration of incident stroke from the date of first attendance. For individuals who were younger than 30 years when first attending a survey, the start of follow-up was assigned from the date they turned 30 years. Participants were followed up until the first-ever ICH event, emigration out of the municipality, death or end of study (December 31, 2012).

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Table 1. Year of survey, age, number and attendance rate of eligible participants (the Tromsø Study)

Survey year	Men			Women		
	age group, years	participants, n	attendance rate, %	age group, years	participants, n	attendance rate, %
1974	20–49	6,595	74.4	–	–	–
1979–80	20–54	8,477	73.8	20–49	8,143	81.8
1986–87	12–64	10,963	71.8	12–67	10,863	79.0
1994–95	25–97	12,865	69.6	25–97	14,293	74.9
2001–02	30–89	3,511	75.7	30–89	4,619	80.8
2007–08	30–87	6,054	62.9	30–87	6,930	68.4

Case Ascertainment

Cases were retrieved by linking the participation list to the discharge and outpatient diagnosis registers at the University Hospital of North Norway, and to the National Causes of Death Registry. The University Hospital is the only hospital serving the Tromsø region (the nearest hospital in the county being located 300 km away by road, 134 km by air). Cases of stroke were retrieved by searching for International Classification of Disease (ICD) versions 8 and 9 diagnosis codes 430–438, and ICD-10 diagnosis codes I60–I69 (cerebrovascular disease). In 2006 through 2007, ICD-10 codes G45 (transitory ischemic attack), G46 (vascular syndromes of brain in cerebrovascular diseases) and G81 (hemiplegia) were added to the search. In addition, systematic text searches were made for the words 'stroke', 'ischemic stroke' and 'intracerebral hemorrhage' in the medical records of all participants with ICD-8 to ICD-10 diagnosis codes 410–414 and I20–I25 (ischemic heart disease), 798/R96 (sudden death, cause unknown), R98 (unattended death) and 799/R99 (other ill-defined and unknown causes of morbidity and mortality).

Each case was reviewed separately by an independent endpoint committee by use of medical records from the hospital (including autopsy reports). Cases retrieved from the National Causes of Death registry were additionally validated by medical records from nursing homes, general practitioners, emergency services and/or death certificates. Stroke was defined according to the WHO criteria: 'rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin' [25]. Strokes were defined as an ICH where a parenchymal hemorrhage was identified on computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or autopsy. ICHs caused by hemorrhagic transformation of ischemic stroke, trauma, brain surgery, hematologic disease or brain tumor were excluded. Cases where neither imaging nor autopsy was performed in the acute phase were categorized as unspecified stroke.

Dates for death and emigration out of the municipality were obtained from the Population Registry of Norway. Linkage to registers was performed using the Norwegian, unique 11-digit personal identification numbers.

Statistical Analyses

Statistical analyses were conducted using STATA version 13.0 (StataCorp LP, College Station, Tex., USA). Analyses of the overall study population, stratified by age (predefined age groups: <75 and ≥75 years) and sex were conducted. The stsplit function in STATA was used to produce a new record in the data file for each year a participant was under follow-up, with updated calendar time and attained age variables. Crude incidence rates for incident primary ICH per 1,000 person-years from January 1, 1995 through December 31, 2012 were calcu-

Table 2. Incidence rates of primary ICH per 1,000 person-years (the Tromsø Study 1995–2012)

	ICH, n	Person-years at risk, n	Crude incidence rate (95% CI)	Adjusted incidence rate[a] (95% CI)
Men	122	216,279	0.56 (0.47–0.67)	0.53 (0.43–0.62)
Women	104	236,873	0.44 (0.36–0.53)	0.33 (0.26–0.39)
Age <75	121	410,607	0.29 (0.25–0.35)	0.27 (0.22–0.32)
Age ≥75	105	42,545	2.47 (2.04–2.99)	2.42 (1.95–2.89)
Overall	226	453,152	0.50 (0.44–0.57)	0.42 (0.37–0.48)

[a] Incidence rates adjusted to age/age and sex by the direct method using the European standard population of 1976 as reference.

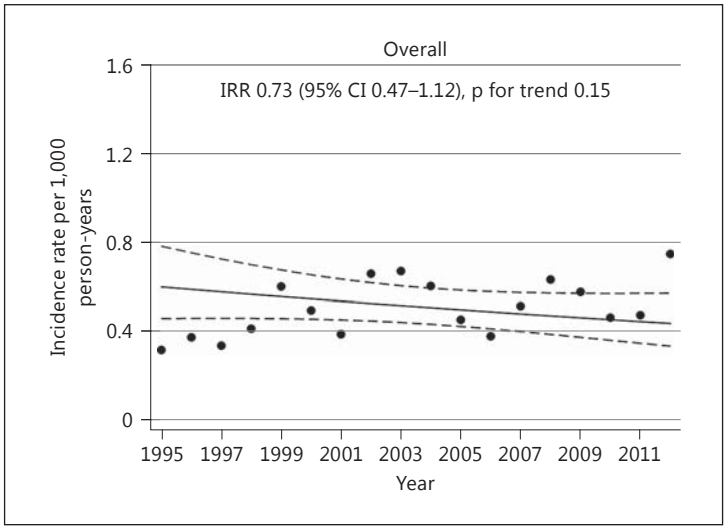

Fig. 1. Temporal trend in incidence rates of ICH, overall population. The Tromsø Study 1995–2012.

lated with the number of events registered during the study period as numerator and person-years at risk as denominator (table 2). Calendar year-specific incidence rates were estimated. In addition, crude incidence rates in 10-year age bands were calculated.

Incidence rates adjusted for age and sex were calculated by the direct method using the European standard population of 1976 as reference. Incidence rate ratios (IRRs) between men and women, with women as reference, adjusted for age, were estimated using Poisson regression.

Trends in incidence rates over time, adjusted for age or age and sex (fig. 1, 2), were obtained from a Poisson regression model. In the overall population, trend was estimated with age set at 64 years, while trends were estimated at 62 years in men, 65 in women, 58 in individuals <75 years of age and 82 in individuals aged ≥75 years, respectively. In sex-adjusted models, the mean value of sex was used. To assess a possible nonlinear trend over time, the models were fitted with fractional polynomials, with time as covariate [26]. Powers were chosen from the set: $\varphi = (-2, -1, -0.5, 0, 0.5, 1, 2, 3)$. Model selection was performed by comparing a Poisson regression model with a linear time variable with the best fitting first- and second-degree models using the Akaike Information Criteria (AIC). In the overall population and in all subgroups, the best AIC was observed in the models with a linear time term. Tests of interaction between age and time and sex and time were performed by including

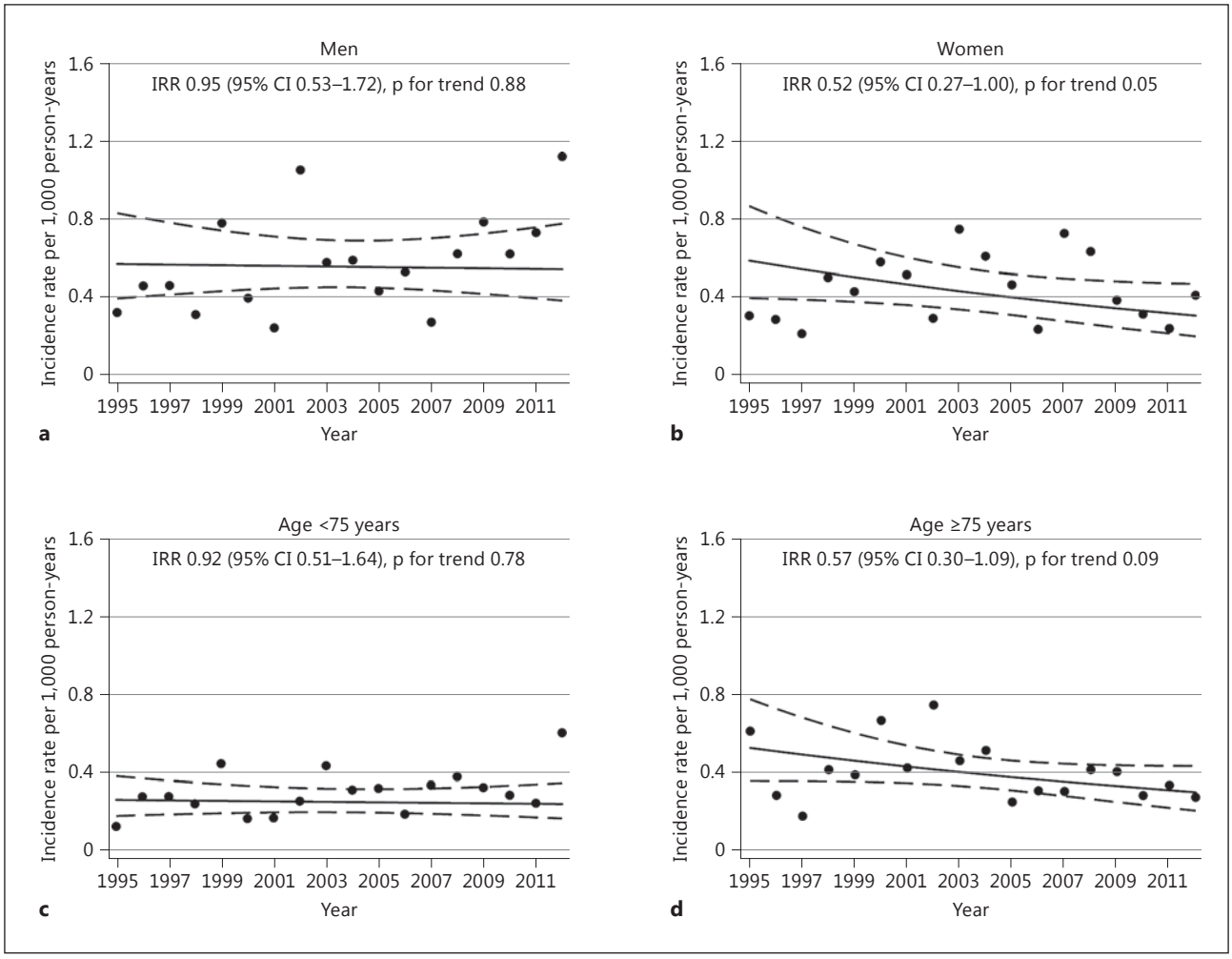

Fig. 2. Temporal trends in incidence rates of ICH, stratified by sex (**a**, **b**) or age (**c**, **d**). The Tromsø Study 1995–2012.

two-way interaction terms (age × time and sex × time) in the regression models. IRRs between 2012 and 1995 were estimated from each regression model.

Case fatality rates were calculated with the number of deaths occurring within 30 days after the event as numerator and the total number of ICH cases as denominator (table 3). Analysis of temporal trend was performed using a logistic regression model, adjusted for age and sex (fig. 3). The adjusted time trend was presented using the mean values of age and sex. The model was fitted with fractional polynomials and model selection performed using AIC as described earlier. Based on the model selection criteria, time was included as a linear term in the logistic regression model. Odds ratio (OR) was calculated for the year 2012 versus 1995. Tests of interaction between age and time and sex and time were performed by including two-way interaction terms (age × time and sex × time) in the model. Additional analyses of trends in case fatality were performed by calculating ORs between time periods (1995–2000, 2001–2006 and 2007–2012), unadjusted and adjusted for age and sex (table 3).

For all analyses, a two-sided p value <0.05 was considered significant. Power calculations based on the observed person-years at risk, the age-adjusted baseline incidence rate, and a 5% significance level showed that the smallest population effect size that would give us 80%

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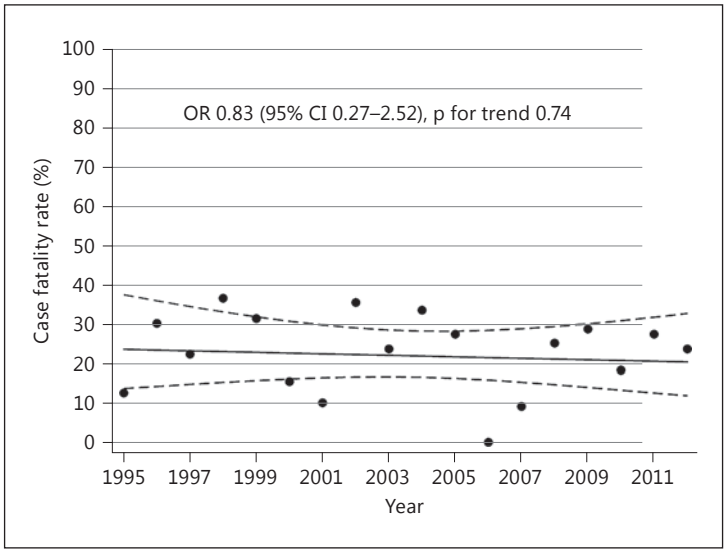

Fig. 3. Temporal trend in 30-day case fatality rates. The Tromsø Study 1995–2012.

Table 3. ORs for 30-day case fatality rates of ICH according to time period (the Tromsø Study 1995–2012)

	Year of ICH		
	1995–2000	2001–2006	2007–2012
ICH, n	67	79	80
30-day CFR, % (n)	25.37 (17)	24.05 (19)	22.50 (18)
OR (95% CI)[a]	1 (reference)	0.93 (0.44–1.98)	0.85 (0.40–1.83)
OR (95% CI)[b]	1 (reference)	0.83 (0.38–1.81)	0.85 (0.39–1.88)

CFR = Case fatality rate. [a] Unadjusted. [b] Adjusted for age and sex.

power to detect a significantly decreasing incidence trend was IRR = 0.51. In subgroup analyses, the population effect size was IRR = 0.52 in men and IRR = 0.35 in women, and IRR = 0.48 in those <75 years of age and IRR = 0.17 in those ≥75 years of age. Power calculations based on a baseline case fatality rate of 26.4% and the number of ICH being 226 showed that we would have 80% power to detect a significant linear trend in case fatality rates if the population trend over 17 years was 0.24 (OR = 0.92 per year).

Results

We registered 226 incident primary ICHs during a total of 453,152 person-years (table 2). The age- and sex-adjusted incidence rate in the overall population was 0.42 (95% CI 0.37–0.48) per 1,000 person-years, 0.53 (95% CI 0.43–0.62) in men and 0.33 (95% CI 0.26–0.39) in women (table 2). Women were on average 5 years older than men at the time of ICH. Adjusted incidence rates were 0.27 (95% CI 0.22–0.32) per 1,000 person-years in individuals aged <75 years and 2.42 (95% CI 1.95–2.89) in individuals aged ≥75 years. The incidence rates increased steeply with age: compared with the age group 45–54 years, individuals in age groups 65–74 years and ≥85 years had a 9-fold and 30-fold higher risk of ICH, respectively [crude incidence rates 0.12 (95% CI 0.07–0.20), 1.08 (95% CI 0.85–1.39) and 3.65 (95%

CI 2.61–5.11) per 1,000 person-years]. In the overall population, the incidence rate of ICH was significantly higher in men compared with women [IRR 1.63 (95% CI 1.25–2.13)]. In individuals aged <75 years, this difference remained significant [IRR 1.72 (95% CI 1.19–2.48)], while the difference between men and women in individuals aged ≥75 years was nonsignificant [IRR 1.43 (95% CI 0.97–2.11)].

Figures 1 and 2 show trends in incidence rates over time. In the overall population, the estimated incidence rate in 2012 was 27% lower than in 1995 [IRR 0.73 (95% CI 0.47–1.12)]. In women, there was a decrease by 48% [IRR 0.52 (95% CI 0.27–1.00)] and in individuals aged ≥75 years the rates decreased by 43% [IRR 0.57 (95% CI 0.30–1.09)] during the study period. However, none of these changes were statistically significant (p value for trend: 0.15, 0.05 and 0.09, respectively). Incidence rates in men and in individuals aged <75 years remained stable [IRR 0.95 (95% CI 0.53–1.72) and 0.92 (95% CI 0.51–1.64), respectively]. There were no significant interactions between age and time (p values for the overall population 0.06, others ranging between 0.21 and 0.76) or sex and time (p values for the overall population 0.21, p values for individuals <75 and ≥75 years of age 0.56 and 0.39, respectively).

Among the 226 individuals suffering an ICH, 54 died within the first 30 days after the ICH event, resulting in a 30-day case fatality rate of 23.9% (95% CI 18.3–29.5). Of the individuals who died within the first 30 days, 48.2% died within the first 2 days and 74.1% died within the first 7 days after the event. The case fatality rate was higher in individuals aged ≥75 years compared with individuals aged <75 years [34.3% (95% CI 25.1–43.5) vs. 14.9% (95% CI 8.4–21.3)]. There was no significant trend over time in 30-day case fatality rates adjusted for age and sex [OR in 2012 vs. 1995: 0.83 (95% CI 0.27–2.52)] (fig. 3; table 3). There was no interaction between age and time (p = 0.57), or sex and time (p = 0.21), suggesting that the trends did not differ by age or sex.

Discussion

We observed no significant change in incidence and case fatality rates of ICH over time. Incidence rates of ICH increased steeply with increasing age, and were higher in men compared with women. Previous studies have reported higher, however not always statistically significant, incidence rates of ICH among men [4, 27]. In line with our study, one review showed that the male predominance in stroke incidence decreased with increasing age [27].

Incidence of ICH trends differ by country income level, with increasing incidence rates in low- to middle-income countries and decreasing rates in high-income countries [20]. However, over the last three decades, results from high-income Western countries have shown diverging results. Two European population-based studies reported stable incidence rates [7, 8], whereas one Australian and one study from the USA reported a significant decrease in incidence rates [11, 12]. One population-based study from the Greater Cincinnati/Northern Kentucky region reported a significant increase in ICH rates from 1988 to 1999, driven by a change between 1988 and 1993/94 [15]. A subsequent publication from the same region showed stable incidence rates between 1993/94 and 2005 [9]. Three large register studies from the USA, Australia and Canada showed stable [10], decreasing [14] and increasing [16] admission rates, respectively.

Case fatality rates vary between studies, with reported case fatality rates ranging between 13 and 61%, the lowest rates reported in publications from Japan [4]. The case fatality rates in our cohort are in the lower range, and lower compared to two previously published studies from Norway [28, 29]. There was no significant change in case fatality rates over time, which is in line with results from a meta-analysis of studies published in the period 1980 and 2008 [4].

Strengths and Limitations

The major strengths of our study is the longitudinal, population-based design, high attendance rates, and rigorous case validation. Our study is one of few studies which provide knowledge about trends in incidence of ICH in a population within a well-defined geographical area over a long-time span, including the last decade.

There are, however, some limitations. The number of ICHs is low, leading to limited power to detect statistically significant changes in incidence and case fatality rates, especially in subgroup analyses. Cohort studies carry a risk of both selection bias and bias due to loss to follow-up. Although attendance rates in the Tromsø Study have been high, lower attendance rates have been among the youngest, among men and nonmarried individuals [23]. In addition, lower attendance rates among the elderly and diseased may have influenced incidence and case fatality rates to some degree. Legal restrictions have prohibited the possibilities of detailed analyses of morbidity and mortality according to attendance. We regard the follow-up of our participants as close to complete. Participants are followed up from the date of first attendance (independently of attendance to later surveys) until the first event, death or upon moving away from the municipality.

However, as case identification was retrospective, not hot pursuit, we may have missed some nonhospitalized, nonfatal cases. In addition, some nonhospitalized fatal cases of ICH may have been coded as nonhemorrhagic due to lack of imaging or autopsy, leading to an underestimation of the true incidence rates. There is a possibility that a higher focus on treatment of stroke during the last decades may have led to higher admission rates to the hospital, resulting in relative underestimation of incidence rates in the first part of the observation period. There is also a possibility for a higher utilization of CT/MRI scanning in the diagnostics of stroke patients during the last decades. However, CT scan has been available at our hospital since 1977, and is routinely performed as a screening procedure in all patients admitted for stroke or transient ischemic attack.

Studies from the UK and France suggest that stable incidence rates may be explained by a shift in the risk factor profile during the last decades with a decrease in ICHs associated with hypertension and a concomitant increase in ICHs associated with antithrombotic treatment in the elderly [30, 31]. Information on the use of antithrombotic treatment was unfortunately not available in our study.

Conclusion

We observed no significant change in incidence and case fatality rates in the period from 1995 through 2012.

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Disclosure Statement

The authors have no conflict of interest to disclose.

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The impact of risk factor trends on intracerebral hemorrhage incidence over the last two decades—The Tromsø Study

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Abstract

Background: Studies on the relationship between temporal trends in risk factors and incidence rates of intracerebral hemorrhage are scarce.

Aims: To analyze temporal trends in risk factors and incidence rates of intracerebral hemorrhage using individual data from a population-based study.

Methods: We included 28,167 participants of the Tromsø Study enrolled between 1994 and 2008. First-ever intracerebral hemorrhages were registered through 31 December 2013. Hazard ratios (HRs) for intracerebral hemorrhage were analyzed by Cox proportional hazards models, risk factor levels over time by generalized estimating equations, and incidence rate ratios (IRR) by Poisson regression.

Results: We registered 219 intracerebral hemorrhages. Age, male sex, systolic blood pressure (BP), diastolic BP, and hypertension were associated with intracerebral hemorrhage. Hypertension was more strongly associated with non-lobar intracerebral hemorrhage (HR 5.08, 95% CI 2.86–9.01) than lobar intracerebral hemorrhage (HR 1.91, 95% CI 1.12–3.25). In women, incidence decreased significantly (IRR 0.46, 95% CI 0.23–0.90), driven by a decrease in non-lobar intracerebral hemorrhage. Incidence rates in men remained stable (IRR 1.27, 95% CI 0.69–2.31). BP levels were lower and decreased more steeply in women than in men. The majority with hypertension were untreated, and a high proportion of those treated did not reach treatment goals.

Conclusions: We observed a significant decrease in intracerebral hemorrhage incidence in women, but not in men. A steeper BP decrease in women may have contributed to the diverging trends. The high proportion of untreated and sub-optimally treated hypertension calls for improved strategies for prevention of intracerebral hemorrhage.

Keywords

Intracerebral hemorrhage, stroke, risk factors, epidemiology, incidence, temporal trends, cohort study

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Introduction

In Western countries, intracerebral hemorrhage (ICH) represents approximately 10–15% of all strokes.[1] However, symptoms are more severe and outcome is poorer compared with ischemic stroke (IS). Treatment possibilities are limited and prevention remains the major measure to reduce the burden of ICH.

Hypertension is the most important modifiable risk factor for ICH.[2–4] Whereas non-lobar ICH has been associated with hypertensive arteriopathy, cerebral amyloid angiopathy is an important cause of lobar ICH.[5] Hypertension seems to be more strongly associated with non-lobar ICH.[6] The association with

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cholesterol, diabetes mellitus (DM), body mass index (BMI), smoking, alcohol consumption, and physical activity is less clear.[2–4] A dose-dependent relationship with alcohol intake and an inverse association with serum-cholesterol has been suggested.[2–4] Treatment with anticoagulants is associated with an increased risk of ICH and treatment with antiplatelets probably increases the risk to a small degree.[2]

In several Western countries, blood pressure (BP) levels, smoking, and cholesterol levels have declined during the last decades.[7] Trends in alcohol use vary, whereas BMI, DM prevalence, and use of anticoagulant drugs have increased.[7,8] Incidence trends of ICH have been stable[9–11] or decreasing[12,13] in the majority of previous publications from Western countries. Studies on the association between risk factor trends and stroke incidence using individual data from repeated surveys with registration of premorbid risk factor levels are scarce[9,14,15] and the majority of these have covered trends in total stroke incidence.[14,15]

Aims

We aimed to analyze temporal trends in premorbid risk factors and incidence rates of ICH over the last two decades using individual person-data from a population-based study with repeated surveys.

Methods

The Tromsø study is an ongoing population-based study with repeated study design.[16] Eligible for our study were 28,251 registered inhabitants of Tromsø aged ≥30 years who attended one or more of the three surveys conducted in 1994–1995, 2001, and 2007–2008 (Table I, Supplements). Individuals with prevalent ICH ($n = 26$) or unclassified stroke ($n = 58$) were excluded, leaving 14,794 women and 13,373 men to be included. All individuals were followed up with registration of first-ever ICH. Follow-up time was assigned from date of first attendance until first-ever ICH, death, emigration from Tromsø or to 31 December 2013, whichever came first.

Risk factors

Risk factors were registered at first date of attendance and updated at the dates of attendance in the subsequent survey(s). Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg and/or treatment with BP-lowering drugs. Non-fasting blood samples were analyzed by standard methods at the University Hospital of Northern Norway (UNN). Information on DM, smoking status, alcohol use, and physical activity was obtained from questionnaires (Supplements).

Use of medication

Information on use of BP-lowering and lipid-lowering drugs was obtained from questionnaires (Supplements). In addition, information about medication used on a regular basis (antithrombotics included) was retrieved through lists of brand names of medication, written by the participants and checked by health personnel at the study site. Information on the use of antithrombotic drugs at the time of ICH was obtained retrospectively from the medical record of each subject suffering an ICH during follow-up.

Identification of ICH events and location of ICH

Monitoring of first-ever cases of selected cardiovascular diseases among Tromsø Study participants has been going on since the study start and is performed by linkage to the discharge and out-patients diagnosis registers at UNN, the only hospital serving the municipality, and to the Causes of Death Registry of Norway, using unique 11-digit personal identification numbers. Cases were classified as ICH when a parenchymal hemorrhage was identified by computed tomography (CT), magnetic resonance imaging (MRI) and/or autopsy. Cases secondary to hemorrhagic transformation of IS, trauma, brain surgery, hematologic disease, or brain tumor were excluded. An independent endpoint committee reviewed each case by use of medical records from the hospital (including autopsy reports). Dates for death and emigration out of the municipality were obtained from the Population Registry of Norway.

CT scans, MRI scans, and radiology and autopsy reports were assessed retrospectively to record location of the ICHs. Location was defined according to an anatomical rating instrument and categorized as lobar, non-lobar (deep/infratentorial), holohemispheric, or other location (Supplements).[5]

Statistical analyses

Statistical analyses were performed using StataCorp (2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Baseline means and proportions of risk factors measured at the date of first entry to the study were adjusted for age and sex of the study sample, using linear and logistic regression models.

The association between risk factors and ICH was assessed by calculating hazard ratios (HRs) using Cox proportional hazards. The assumption of proportional hazards was tested using Schoenfelds residuals and log–log plots. In model 1, each independent variable was adjusted for age and sex. In model 2, each independent variable was adjusted for age, sex, SBP (except for hypertension and DBP), total cholesterol, high-density lipoprotein cholesterol (HDL cholesterol)

(except for triglycerides), BMI, DM, daily smoking, teetotalism, and leisure physical activity. To account for dependencies between repeated measurements, trends in risk factors and use of BP-lowering, lipid-lowering and antithrombotic drugs were analyzed in age- and sex-adjusted general estimated equations models. Age- and sex-adjusted odds ratios (OR) for treatment with antithrombotic drugs at time of ICH were calculated by logistic regression.

Age- and sex-adjusted incidence rates were calculated by the direct method using the European standard population of 2013 as reference. Incidence trends over time were obtained from age- and sex-adjusted Poisson regression models. Additional analyses stratified on sex, pre-defined age groups (<75 years and ≥75 years), and location were performed. Interaction between age and time (year of ICH) and sex and time was tested by including interaction terms (age × time, sex × time) in the regression models. Non-linearity was tested using fractional polynomials. Incidence rate ratios (IRRs) between 2013 and 1995 were estimated from each regression model.

Results

We registered 219 first-ever ICHs during a follow-up of 396,976 person-years, of which 40% were lobar, 51% non-lobar, and 9% holohemispheric/other location. Individuals with ICH were older, more likely to be males, and had higher age- and sex-adjusted BP levels at baseline compared with ICH-free individuals (Table 1, Table IIa and IIb, Supplements). Among individuals with ICH, the crude prevalence of hypertension at last attendance before ICH was 84%.

Associations between risk factors and incident ICH

Age, male sex, SBP, DBP, and hypertension were independently associated with ICH (Table 2). There was no association between ICH and serum lipids, BMI, DM,

Table 1. Baseline characteristics[a] of participants with and without first-ever intracerebral hemorrhage (ICH) during follow-up, adjusted for age and sex—the Tromsø Study

	No. ICH ($n = 27,948$)	ICH ($n = 219$)	p value[b]
Age, years	48.5 (13.6)	63.7 (11.9)	<0.001
Male sex	47.4 (13,250)	57.3 (123)	0.004
Systolic blood pressure (mm Hg)	134.0 (20.9)	142.7 (24.6)	<0.001
Diastolic blood pressure (mm Hg)	78.5 (12.1)	83.7 (15.2)	<0.001
Hypertension[c]	33.6 (10,026)	59.0 (176)	<0.001
Total cholesterol (mmol/L)	6.1 (1.3)	6.0 (1.2)	0.73
Triglycerides (mmol/L)	1.57 (1.04)	1.52 (0.97)	0.48
HDL-cholesterol (mmol/L)	1.49 (0.41)	1.49 (0.40)	0.79
Body mass index (kg/m^2)	25.5 (4.0)	25.5 (4.0)	0.93
Diabetes mellitus	1.5 (575)	0.9 (6)	0.26
Daily smoking	34.8 (9747)	34.2 (64)	0.87
Teetotalism	9.9 (3510)	9.5 (48)	0.80
Physical activity[d]	29.7 (8401)	31.5 (48)	0.61
Use of blood pressure-lowering drugs	4.8 (1957)	5.2 (36)	0.62
Use of lipid-lowering drugs	1.2 (422)	1.0 (5)	0.69

[a]Continuous variables are presented as mean (SD); categorical variables are presented as % (n).
[b]p value for difference between individuals with and without first-ever intracerebral hemorrhage adjusted for age and sex.
[c]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs.
[d]Strenuous leisure physical activity >1 h/week.

Table 2. Hazard ratios (HR)[a] for first-ever intracerebral hemorrhage by risk factors[b]—the Tromsø Study

Risk factor (SD)	HR (95% CI) Model 1[c]	HR (95% CI) Model 2[c]
Age (14.3)	3.42 (2.94–3.98)	2.84 (2.38–3.40)
Male sex	1.76 (1.35–2.30)	1.86 (1.38–2.52)
Systolic blood pressure (21.9)	1.45 (1.28–1.64)	1.46 (1.29–1.66)
Diastolic blood pressure (12.0)	1.52 (1.37–1.70)	1.55 (1.39–1.74)
Hypertension[d]	3.08 (2.10–4.54)	3.26 (2.20–4.85)
Total cholesterol (1.2)	1.06 (0.92–1.21)	1.01 (0.88–1.16)
HDL-cholesterol (0.4)	1.00 (0.87–1.15)	0.99 (0.85–1.14)
Triglycerides (1.0)	1.02 (0.89–1.17)	0.99 (0.85–1.16)
Body mass index (4.1)	1.00 (0.87–1.14)	0.93 (0.80–1.08)
Diabetes mellitus	1.15 (0.64–2.06)	1.14 (0.63–2.06)
Daily smoking	1.11 (0.81–1.52)	1.14 (0.83–1.58)
Teetotalism	1.07 (0.77–1.50)	1.04 (0.74–1.46)
Physical activity[e]	0.96 (0.69–1.33)	0.99 (0.71–1.38)

[a]HRs are expressed per SD increase in continuous variables and for presence vs. absence of categorical variables.
[b]Updated at the date of attendance in the subsequent survey(s) in individuals who were still free of ICH.
[c]Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure (except for hypertension and diastolic blood pressure) total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) (except for triglycerides), body mass index, diabetes mellitus, daily smoking, teetotalism, and physical activity.
[d]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs.
[e]Strenuous leisure physical activity >1 h/week.

daily smoking, teetotalism, or physical activity. We found no significant dose-dependent association with alcohol intake and ICH: HR 1.02 (95% CI 0.72–1.44) for moderate alcohol consumption and 1.63 (95% CI 0.64–4.16) for high alcohol consumption, respectively.

There was a significant association with age, SBP and DBP and ICH of both lobar and non-lobar location, whereas male sex was significantly associated with non-lobar ICH only (Table III, Supplements). Hypertension was more strongly associated with non-lobar (HR 5.08, 95% CI 2.86–9.01) than with lobar ICH (HR 1.91, 95% CI 1.12–3.25).

Individuals with drug-treated, well-controlled hypertension (SBP <140 mm Hg and DBP <90 mm Hg) had no significant increased risk of ICH compared with those without hypertension (HR 1.74, 95% CI 0.79–3.84), whereas the risk was increased in individuals with SBP ≥140 mm Hg and/or DBP ≥90 mm Hg despite treatment with BP-lowering drugs (HR 3.43, 95% CI 2.12–5.55). A similar increased risk was seen in those with untreated hypertension (HR 3.36, 95% CI 2.24–5.03).

Change in risk factor levels

BP levels, serum lipid levels, and smoking prevalence decreased significantly over time, whereas BMI and DM prevalence increased (Table 3). The proportion of physically active individuals increased. Use of BP-lowering, lipid-lowering, and antithrombotic drugs increased. Women had lower BP than men in all surveys, and the SBP decrease was steeper in women than in men: from 138.2 (95% CI 137.7–138.5) to 131.0 mm Hg (95% CI 130.2–131.8) in women and from 140.5 (95% CI 140.1–140.8) to 136.1 mm Hg (95% CI 135.2–136.9) in men (Table IVa and IVb, Supplements). Among individuals with hypertension, the crude proportions treated with BP-lowering drugs in 1994–1995 and 2007–2008 were 18% and 46%, respectively. In the treated group, the proportion with well-controlled hypertension was 21% in 1994–1995 and 35% in 2007–2008.

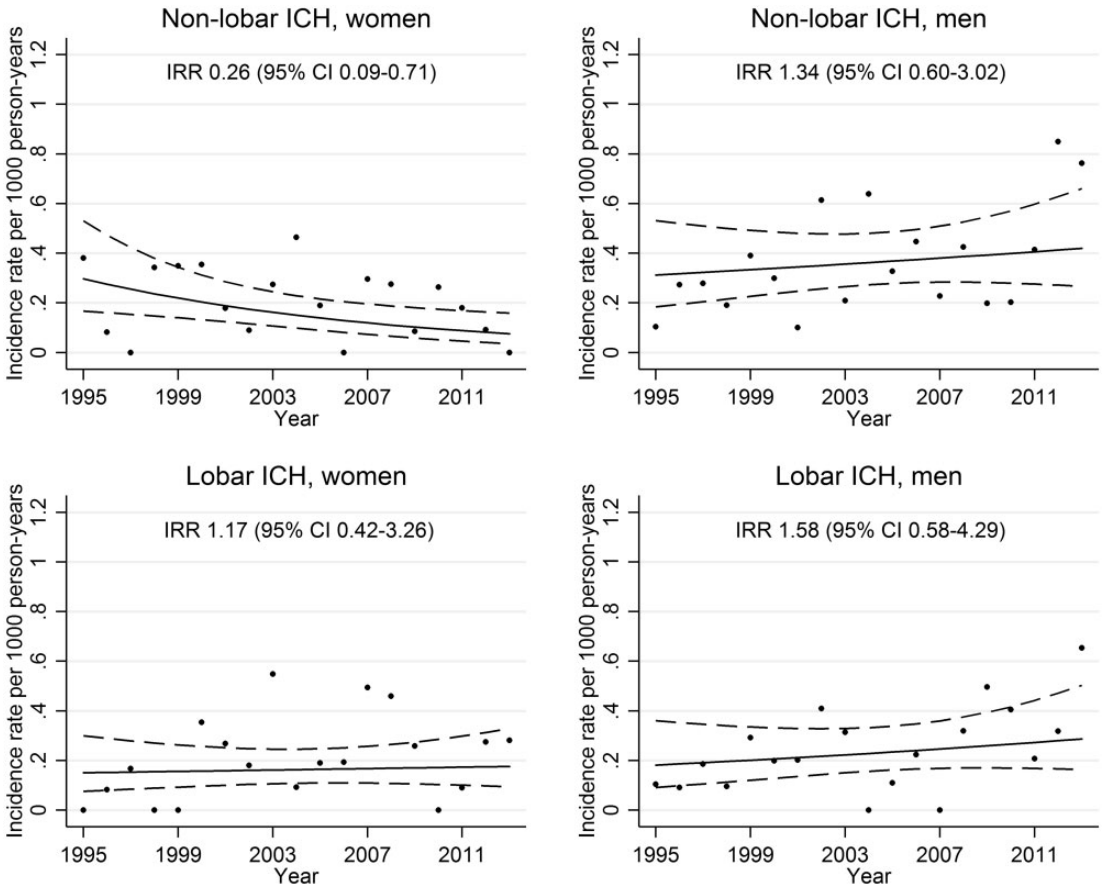
Twenty-five percent of ICH patients were treated with anticoagulants and 28% with antiplatelets. There was no significant change over time in use of

Table 3. Cardiovascular risk factor levels by survey year—the Tromsø Study

	1994–1995 ($n = 23,583$)	2001 ($n = 8016$)	2007–2008 ($n = 12,944$)	Relative change from 1994 to 2008 (%)	p value[a]
Age (years)	47.4 (47.2–47.6)	54.4 (54.0–54.7)	58.8 (58.4–59.1)		
Male sex	47.1 (46.5–47.8)	47.5 (46.5–48.4)	47.8 (46.6–49.0)		
Systolic blood pressure (mm Hg)	139.3 (139.1–139.6)	133.7 (133.1–134.3)	133.3 (132.7–133.8)	−4	<0.001
Diastolic blood pressure (mm Hg)	80.3 (80.2–80.5)	78.6 (78.3–79.0)	76.6 (76.3–77.0)	−5	<0.001
Hypertension[b]	44.6 (43.9–45.4)	38.6 (36.7–40.5)	41.6 (39.8–43.5)	−7	<0.001
Total cholesterol (mmol/L)	6.30 (6.29–6.32)	5.96 (5.92–6.00)	5.46 (5.43–5.50)	−13	<0.001
HDL-cholesterol (mmol/L)	1.52 (1.51–1.52)	1.43 (1.41–1.44)	1.49 (1.48–1.50)	−2	<0.001
Triglycerides (mmol/L)	1.60 (1.58–1.61)	1.54 (1.50–1.57)	1.52 (1.49–1.55)	−5	<0.001
BMI (kg/m^2)	25.5 (25.5–25.6)	26.3 (26.2–26.4)	26.6 (26.5–26.7)	4	<0.001
Diabetes mellitus	1.8 (1.7–2.0)	2.4 (1.9–2.9)	3.6 (3.0–4.4)	99	<0.001
Daily smoking	34.5 (33.9–35.2)	31.0 (29.6–32.5)	22.8 (21.6–24.0)	−34	<0.001
Teetotalism	13.5 (13.0–14.0)	8.6 (7.9–9.4)	8.1 (7.4–8.8)	−40	<0.001
Physical activity[c]	23.5 (22.9–24.1)	37.3 (35.2–39.5)	44.6 (42.5–46.7)	90	<0.001
Use of blood pressure-lowering drugs	5.9 (5.6–6.2)	10.6 (9.5–11.8)	15.2 (13.8–16.8)	159	<0.001
Use of lipid-lowering drugs	0.8 (0.7–0.9)	6.0 (4.7–7.7)	9.4 (7.4–11.9)	1041	<0.001
Use of antithrombotic drugs[d,e]	2.4 (2.1–2.6)	4.3 (3.6–5.3)	6.2 (5.1–7.5)	160	<0.001
Use of antiplatelets[e]	2.1 (1.9–2.4)	4.0 (3.2–5.0)	5.4 (4.4–6.7)	158	<0.001
Use of anticoagulants[e]	0.5 (0.4–0.6)	0.6 (0.4–1.0)	1.0 (0.6–1.5)	104	<0.001

Continuous variables are age- and sex-adjusted means with 95% CI. Categorical variables are age-and sex-adjusted prevalence (%) with 95% CI.
[a]Test for linear trend.
[b]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs.
[c]Strenuous leisure physical activity ≥1 h/week.
[d]Use of antiplatelets and/or anticoagulants.
[e]Calculated in the attendees of the second visit of the survey in 1994–1995 ($n = 6773$), and in all attendees of the surveys in 2001 and 2007–2008.

Figure 1. Age-adjusted incidence rate ratios (IRR) of incident intracerebral hemorrhage in 2013 compared with 1995 stratified on sex and location—the Tromsø Study.



antithrombotics at ICH onset (p for trend = 0.10) (Table Va and Vb, Supplements).

Incidence of ICH over time

The incidence rates of ICH in the overall population did not change significantly over time (IRR 0.81, 95% CI 0.52–1.27) (Table VI, Supplements). However, analyses stratified on sex showed a significant 54% decrease in incidence in women (IRR 0.46, 95% CI 0.23–0.90), whereas incidence in men remained stable (IRR 1.27, 95% CI 0.69–2.31), p value for interaction 0.02. Analyses of predefined age groups showed no significant change in incidence in individuals aged <75 years or in individuals aged ≥75 years (Table VI, Supplements). Analyses stratified on location showed no significant trend for lobar (IRR 1.36, 95% CI 0.67–2.79) or non-lobar ICH (IRR 0.71, 95% CI 0.38–1.33). However, for non-lobar ICH there was a significant interaction between sex and time (p value 0.02). Sex-stratified analyses showed a significant 74% reduction in non-lobar ICH in women, whereas incidence in men were stable (Figure 1, Table VI, Supplements).

Discussion

We showed a significant association with SBP, DBP, hypertension, age and male sex, and ICH. Hypertension was more strongly associated with non-lobar than lobar ICH.

BP levels decreased significantly over time, in line with trends in several Western countries.[7]

There was no significant change in incidence rates of ICH in the overall population. However, trends diverged between sexes; in women, incidence rates decreased significantly, driven by a 74% decrease in non-lobar ICH, whereas incidence rates in men remained stable. In line with previous publications from the Tromsø Study,[17] BP levels were lower and deceased steeper over time in women compared with men, which may have contributed to the diverging trends. Results from the majority of

previous studies from Western countries have shown stable[9–11] or decreasing.[12,13] incidence rates of ICH. Publications on sex-specific trends in ICH incidence are scarce and the results have been diverging.[11,12,18] To the best of our knowledge, sex-specific trends in ICH incidence according to location have not previously been reported.

The authors of two previous studies from UK and France suggested that a decrease in hypertension-associated ICH may have been offset by an increase in ICH associated with use of antithrombotic drugs.[9,10] In both studies incidence rates in individuals aged ≥75 years increased, whereas incidence decreased in younger age groups. In the French study, the increase in the elderly was attributed to a two-fold increase in lobar ICH, concomitant with a rise in use of antithrombotics. We did not observe any significant trend according to age-group or in incidence rates of lobar ICH. Despite an overall increase in antithrombotic use, we did not find any significant change in the risk of use of antithrombotics at time of ICH, which is in line with a previous Finnish study.[8]

Hypertension was present in 84% of ICH cases. Whereas participants with drug-treated, well-controlled hypertension did not have a higher risk of ICH compared with individuals without hypertension, individuals with uncontrolled hypertension, whether treated or not, had a significantly increased risk of ICH. Despite an increased use of BP-lowering drugs, less than half of individuals who fulfilled the criteria for hypertension in the last survey were treated and two-thirds of these had uncontrolled hypertension, similar to previous results in a large multinational study.[19]

Strengths and limitations

The strengths of this study are its prospective, longitudinal design with repeated surveys, use of individual data and updated risk factors, high attendance rates, and rigorously validated cases. The relatively low number of ICHs in the cohort precluded detailed subgroup analyses and may have caused inability to detect significant associations between risk factors and ICH. We cannot exclude that we have missed some non-hospitalized, non-fatal cases. Increased awareness of stroke and a higher degree of utilization of CT and MRI over time may have led to an underestimation of incidence rates in the beginning of the study-period. Non-attendees tended to be younger, more likely to be men and less likely to be married, indicating some degree of selection bias. Legal restrictions precluded analyses of mortality and morbidity in non-attendees.

Conclusions

We observed a significant decrease in the ICH incidence in women, driven by a 74% decrease in non-lobar ICH. Incidence rates in men remained stable. Hypertension was the most important risk factor and stronger associated with non-lobar than lobar ICH. BP levels decreased more steeply in women than in men. The majority of participants with hypertension were untreated or did not reach treatment goals. Improved strategies for detection and treatment of hypertension for primary prevention of ICH are needed.

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Authors' contributions

IN, TW, and EBM contributed to protocol development, gaining of ethical approval, and overall management of the Tromsø Study. LHJ, MC, MLL, IN, TW, and EBM contributed to data collection. MC researched the literature and drafted the manuscript. MC, TW, EBM, and SHJ did the data analysis. All authors reviewed the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

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Supplementary file

The impact of risk factor trends on intracerebral hemorrhage incidence over the last two decades. The Tromsø Study.

Supplemental methods

Risk factors

Blood pressure was measured using an automatic device with three recordings separated by a 1-minute interval, after a 2-minute seated rest. The mean value of the two last recordings was used in the present study. Weight was measured with light clothing and no footwear, and height was measured in standing position. BMI was calculated as weight divided by the square of height (kg/m^2). Diabetes mellitus was self-reported in questionnaires by answering the question: Do you have, or have you had diabetes mellitus?

Smoking was defined as daily current smoker (cigarettes and/or pipe and/or cigarillos/cigars). Alcohol consumption was categorised as teetotalism, moderate alcohol consumption (1-7 glasses per week in women, 1-14 glasses per week in men) and high alcohol consumption (>7 glasses per week in women, >14 glasses per week in men). However, questions concerning the amount of alcohol intake differed between the surveys. Because of this, analyses of the association between the amount of alcohol intake and risk of ICH were based on answers from questionnaires in the surveys performed in 1994-95 and in 2001, whereas analysis of trends in alcohol intake was limited to teetotalism yes/no.

Physical activity was defined as strenuous leisure physical activity (i.e. become sweaty and out of breath) for at least 1 hour per week. It was self-reported in the questionnaires; in 1994-95 and in 2001 by answering the following questions: "How has your physical activity in leisure time been during this last year? Think of your weekly average for the year. Time spent going to work count as leisure time." "Light activity (not sweating or out of breath): and "Hard physical activity (sweating/out of breath)". For both questions, response categories were: Hours per week: 1) None, 2) < 1 hour, 3) 1-2 hours, 4) 3 or more hours per week. In 2007-08 the questions were: "How often do you exercise (e.g. walking, skiing, swimming or work out/do sports?", response categories: 1) Never; 2) Less than once a week; 3) Once a week; 4) 2-3 times a week 5) almost daily "If you exercise – how hard do you exercise in average?", response categories: 1) Easy – you do not become out of breath or sweaty; 2) You become out of breath or sweaty; 3) Hard - you become exhausted, "For how long time do you exercise in average? ", response categories: 1) Less than 15 minutes; 2) 15-29 minutes; 3) 30-60 minutes; 4) More than 1 hour. Use of blood pressure-lowering drugs at attendance was self-reported in questionnaires by answering the following question: Do you use blood pressure-lowering drugs? Response categories: 1) Now, 2) Previously, but not now, 3) Never. Use of lipid-lowering drugs was self-reported in questionnaires by answering the following question: Have you during the last 14 days used lipid lowering drugs? Response categories: 1) Yes 2) No. In 1994-95 this question was limited to individuals aged <70 years, and information from additional lists of the brand names of medication used on a regular basis was available only for participants aged 55-74 years and selected 5-10% samples of participants aged 25-54 and 75-85 years. A comparison of self-reported use of LLD in Tromsø 6 against data from the prescription database 6 months prior to the survey showed a kappa value of 0.94 (95% CI 0.93-0.95), a sensitivity of 98% and a specificity of 99% (Anne Elise Eggen, personal communication).

Anticoagulants were defined as use of vitamin-K antagonists, novel oral anticoagulants, treatment with high dose heparin or high dose low molecular weighted heparin, or thrombolytic treatment of indications other than IS.

Identification of ICH events and location of ICH

Cases were retrieved by searching for International Classification of Disease (ICD) versions 8 and 9 diagnosis codes 430-438 and ICD 10 diagnosis codes I60-I69. In addition, systematic text searches were made for the words "stroke", "ischemic stroke" and "intracerebral hemorrhage" in the medical records of all participants with ICD 8-10 diagnosis codes 410-414 and I20-I25, 798/R96, R98 and 799/R99.

All CT and MRI scans were assessed by a senior consultant in neurology (MC). In cases where radiologic examinations were not available (n=35), location was assessed by radiology reports and/or autopsy reports. In uncertain cases, the scans were additionally validated by a neuroradiologist (LHJ) at the University Hospital of Northern Norway, and consensus made in cooperation with a senior consultant in neurology (EBM).

Location of ICH was categorised as lobar, non-lobar (deep/infratentorial), uncertain and other location (intraventricular or located to the corpus callosum). Uncertain ICH was further categorised as probably lobar, probably deep, and holohemispheric. In analyses stratified on location, probable lobar and probable deep ICHs were included in the analyses as lobar and non-lobar ICH, respectively. Cases with multiple ICHs affecting solely lobar (n=7) or non-lobar (n=3) regions were categorised according to location. Multiple ICHs affecting both regions (n=1), ICH located to the corpus callosum (n=2), intraventricular ICH (n=3), holohemispheric ICH (n=13) and ICH with missing location (the radiologic examination and radiologic report were not available at the time of the retrospective assessment) (n=1) were included in analyses of ICH overall, but excluded from analyses stratified on location. All ratings were performed blinded for risk factors.

Table I. Age span and attendance rates of eligible participants, and age- and sex distribution of attendees and non-attendees, by year of survey. The Tromsø Study 1994-2008.

		Men				Women			
		Attendees		Non-attendees		Attendees		Non-attendees	
	Age group (Years)	n* (%)†	Mean age (Years)	n*	Mean age (Years)	n* (%)†	Mean age (Years)	n*	Mean age (Years)
Tromsø 4 (1994-95)	25-97	12,865 (69.6)	46.6	5615	40.9	14,293 (74.9)	47.2	4785	44.1
Tromsø 5 (2001)	30-89	3511 (75.7)	59.9	1125	46.0	4619 (80.8)	59.4	1098	50.8
Tromsø 6 (2007-08)	30-87	6054 (62.9)	57.5	3571	54.4	6930 (68.4)	57.5	3207	58.1

*Number of subjects.
†Attendance rate

Table IIa. Crude baseline characteristics of participants with and without incident intracerebral hemorrhage (ICH) stratified by sex. The Tromsø Study.

	No ICH		ICH	
	Men N=13,250	**Women N=14,698**	**Men N=123**	**Women N=96**
Age, years	48.2 (13.0)	48.7 (14.1)	61.5 (11.4)	66.5 (12.0)
Systolic blood pressure, mm Hg	136.7 (17.8)	131.5 (23.1)	154.0 (22.8)	157.4 (26.6)
Diastolic blood pressure, mm Hg	80.6 (11.4)	76.6 (12.5)	91.1 (12.8)	86.3 (17.6)
Hypertension[†]	40.6 (5386)	31.6 (4640)	80.5 (99)	80.2 (77)
Total cholesterol, mmol/L	6.1 (1.2)	6.0 (1.4)	6.3 (1.1)	6.9 (1.3)
Triglycerides, mmol/L	1.79 (1.2)	1.36 (0.9)	1.69 (1.1)	1.64 (0.8)
HDL-cholesterol, mmol/L	1.34 (0.4)	1.63 (0.4)	1.40 (0.3)	1.64 (0.4)
Body mass index kg/m^2	25.9 (3.5)	25.1 (4.4)	26.6 (3.9)	25.8 (4.1)
Diabetes mellitus	2.1 (274)	2.1 (301)	3.3 (4)	2.1 (2)
Daily smoking	35.4 (4688)	34.4 (5059)	29.3 (36)	29.2 (28)
Teetotalism	8.5 (1125)	16.2 (2385)	11.4 (14)	35.4 (34)
Physical activity[‡]	35.9 (4753)	24.8 (3648)	30.9 (38)	10.4 (10)
Use of blood pressure-lowering drugs	7.0 (933)	7.0 (1024)	16.3 (20)	16.7 (16)
Use of lipid-lowering drugs	1.9 (248)	1.2 (174)	2.4 (3)	2.1 (2)

[*]Continuous variables are presented as mean (SD), categorical variables are presented as % (n)
[†]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs
[‡]Strenuous leisure physical activity >1 hour/week

Table IIb. Crude baseline characteristics of participants with and without incident intracerebral hemorrhage (ICH) stratified by age. The Tromsø Study.

	No ICH		ICH	
	<75 years N= 26,457	**≥75 years N=1491**	**<75 years N=179**	**≥75 years N=40**
Age, years	46.8 (11.7)	79.4 (3.9)	60.3 (10.3)	79.0 (3.2)
Male sex	48.0 (12,696)	37.2 (554)	61.5 (110)	32.5 (13)
Systolic blood pressure, mm Hg	132.4 (19.6)	160.9 (25.1)	152.5 (23.2)	168.7 (26.1)
Diastolic blood pressure, mm Hg	78.1 (11.8)	85.4 (15.4)	88.7 (14.4)	90.5 (18.7)
Hypertension†	33.2 (8788)	83.0 (1238)	76.5 (137)	97.5 (39)
Total cholesterol, mmol/L	6.0 (1.3)	6.7 (1.4)	6.7 (1.3)	6.6 (1.2)
Triglycerides, mmol/L	1.55 (1.04)	1.74 (1.06)	1.69 (1.02)	1.58 (0.69)
HDL-cholesterol, mmol/L	1.49 (0.41)	1.53 (0.45)	1.49 (0.37)	1.58 (0.52)
Body mass index kg/m^2	26.1 (4.3)	25.5 (4.0)	26.5 (4.1)	26.2 (3.9)
Diabetes mellitus	1.7 (446)	8.7 (129)	2.2 (4)	5.0 (2)
Daily smoking	36.0 (9522)	15.1 (225)	34.1 (61)	7.5 (3)
Teetotalism	10.8 (2861)	45.5 (649)	16.2 (29)	47.5 (19)
Physical activity‡	31.4 (8319)	5.5 (82)	25.1 (45)	7.5 (3)
Use of blood pressure-lowering drugs	6.2 (1638)	21.4 (319)	12.8 (23)	32.5 (13)
Use of lipid-lowering drugs	1.5 (403)	1.3 (19)	2.8 (5)	0.0 (0)

*Continuous variables are presented as mean (SD), categorical variables are presented as % (n)
†Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs
‡Strenuous leisure physical activity >1 hour/week

Table III. Hazard ratios (HR)[*] for incident intracerebral hemorrhage according to location, by risk factors[†]. The Tromsø Study.

	Lobar (n=88)		Non-lobar (n=111)	
	HR (95% CI) Model 1[‡]	HR (95% CI) Model 2[‡]	HR (95% CI) Model 1[‡]	HR (95% CI) Model 2[‡]
Age	2.59 (2.09-3.22)	2.22 (1.71-2.89)	2.49 (2.06-3.01)	1.80 (1.42-2.29)
Male sex	1.37 (0.90-2.09)	1.37 (0.86-2.18)	2.06 (1.40-3.02)	2.42 (1.57-3.73)
Systolic blood pressure	1.28 (1.04-1.57)	1.29 (1.05-1.59)	1.82 (1.53-2.16)	1.82 (1.52-2.17)
Diastolic blood pressure	1.22 (1.01-1.47)	1.22 (1.01-1.48)	1.85 (1.61-2.13)	1.89 (1.64-2.19)
Hypertension[§]	1.89 (1.12-3.18)	1.91 (1.12-3.25)	4.71 (2.71-8.19)	5.08 (2.86-9.01)
Total cholesterol	1.17 (0.95-1.44)	1.18 (0.95-1.45)	1.26 (1.04-1.51)	1.14 (0.94-1.39)
HDL-cholesterol	0.91 (0.73-1.14)	0.86 (0.68-1.09)	1.21 (0.93-1.36)	1.07 (0.88-1.31)
Triglycerides	1.08 (0.89-1.30)	1.04 (0.84-1.29)	1.03 (0.86-1.24)	0.96 (0.78-1.18)
Body mass index	0.92 (0.74-1.15)	0.84 (0.66-1.07)	1.02 (0.84-1.24)	0.90 (0.72-1.12)
Diabetes mellitus	0.81 (0.25-2.57)	0.82 (0.26-2.63)	0.44 (0.11-1.80)	0.46 (0.11-1.87)
Daily smoking	1.15 (0.72-1.84)	1.06 (0.65-1.74)	1.05 (0.69-1.60)	1.10 (0.71-1.71)
Teetotalism	1.16 (0.69-1.96)	1.11 (0.65-1.90)	1.16 (0.72-1.88)	1.13 (0.69-1.85)
Physical activity[‖]	0.85 (0.50-1.46)	0.89 (0.52-1.53)	1.08 (0.69-1.68)	1.11 (0.71-1.75)

[*]Hazard ratios are expressed per SD increase in continuous variables

[†]Updated at the date of attendance in the subsequent survey(s) in individuals who were still free of ICH

[‡]Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, SBP (except for hypertension and DBP) total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) (except for triglycerides), body mass index (BMI), diabetes mellitus (DM), daily smoking, teetotalism and physical activity

[§]Systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or use of blood pressure-lowering drugs

[‖] Strenuous leisure physical activity >1 hour/week

Table IVa. Cardiovascular risk factor levels in men by survey year. The Tromsø Study.

	1994-1995 n=11,235	2001 N=3457	2007-2008 N=6034	Relative change from 1994 to 2008 (%)	P-value*
Age	46.9 (46.7-47.2)	54.0 (53.6-54.5)	58.8 (58.3-59.2)		
Systolic blood pressure, mm Hg	140.5 (140.1-140.8)	136.0 (135.1-136.9)	136.1 (135.2-136.9)	-3	<0.001
Diastolic blood pressure, mm Hg	82.0 (81.8-82.2)	80.0 (79.5-80.6)	80.0 (79.5-80.5)	-2	<0.001
Hypertension†	49.1 (48.1-49.8)	43.5 (40.7-46.3)	47.1 (44.4-49.7)	-4	<0.001
Total cholesterol, mmol/L	6.23 (6.21-6.25)	5.90 (5.84-5.96)	5.41 (5.36-5.47)	-13	<0.001
HDL-cholesterol, mmol/L	1.37 (1.36-1.38)	1.30 (1.29-1.32)	1.33 (1.32-1.35)	-3	<0.001
Triglycerides, mmol/L	1.77 (1.75-1.79)	1.72 (1.66-1.78)	1.71(1.65-1.76)	-4	<0.001
BMI, kg/m^2	25.8 (25.7-25.8)	26.6 (26.5-26.7)	27.1 (26.9-27.2)	5	<0.001
Diabetes mellitus	1.9 (1.6-2.2)	2.6 (2.0-3.5)	4.2 (3.2-5.5)	123	<0.001
Daily smoking	36.0 (35.1-37.0)	31.2 (29.0-33.5)	21.6 (20.0-23.4)	-40	<0.001
Teetotalism	9.6 (9.0-10.1)	6.8 (5.8-7.9)	6.5 (5.6-7.5)	-32	<0.001
Physical activity‡	31.5 (30.6-32.4)	44.8 (41.7-47.8)	46.9 (44.1-49.8)	49	<0.001
Use of blood pressure lowering drugs	6.2 (5.8-6.7)	11.1 (9.5-13.0)	15.6 (13.5-17.9)	150	<0.001
Use of lipid lowering drugs	1.1 (0.9-1.3)	7.6 (5.4-10.5)	11.4 (8.4-15.5)	970	<0.001
Use of antithrombotic drugs§,‖	3.8 (3.3-4.3)	6.6 (5.2-8.4)	9.2 (7.3-11.5)	144	<0.001
Use of antiplatelets‖	3.3 (2.9-3.8)	6.1 (4.7-7.9)	8.0 (6.2-10.2)	139	<0.001
Use of anticoagulants‖	0.8 (0.6-1.0)	1.0 (0.6-1.7)	1.5 (0.9-0.2.7)	102	<0.001

Continuous variables are age- adjusted means with 95% CI. Categorical variables are age-adjusted prevalence (%) with 95% CI

*Test for linear trend

†Systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or use of blood pressure-lowering drugs

‡ Strenuous leisure physical activity ≥1 hour per week

§ Use of antiplatelets and/or anticoagulants

‖ Calculated in the attendees of the second visit of the survey in 1994-1995 (n=3 331), and in all attendees of the surveys in 2001 and 2007-2008

Table IVb. Cardiovascular risk factor levels in women by survey year. The Tromsø Study.

	1994-1995 N=12,348	2001 N=4559	2007-2008 N=6910	Relative change from 1994 to 2008 (%)	P-value*
Age	47.8 (47.5-48.0)	54.6 (54.1-55.1)	58.8 (58.3-59.3)		
Systolic blood pressure, mm Hg	138.2 (137.7-138.5)	131.8 (131.0-132.7)	131.0 (130.2-131.8)	-5	<0.001
Diastolic blood pressure, mm Hg	78.8 (78.6-79-0)	77.3 (76.8-77.8)	73.8 (73.3-74.3)	-6	<0.001
Hypertension†	39.5 (38.4-40.6)	33.3 (30.8-35.8)	36.2 (33.7-38.7)	-9	<0.001
Total cholesterol, mmol/L	6.36 (6.34-6.38)	6.02 (5.97-6.07)	5.52 (5.47-5.57)	-13	<0.001
HDL-cholesterol, mmol/L	1.65 (1.64-1.66)	1.54 (1.52-1.55)	1.63 (1.61-1.65)	-1	<0.001
Triglycerides, mmol/L	1.43 (1.42-1.45)	1.38 (1.34-1.42)	1.36 (1.32-1.40)	-5	<0.001
BMI, kg/m^2	25.3 (25.2-25.4)	26.1 (25.9-26.2)	26.2 (26.0-26.3)	3	<0.001
Diabetes mellitus	1.8 (1.5-2.0)	2.2 (1.6-2.9)	3.2 (2.4-4.2)	80	<0.001
Daily smoking	33.2 (32.3-34.1)	30.8 (28.9-32.7)	23.7 (22.1-25.4)	-29	<0.001
Teetotalism	18.2 (17.5-18.9)	11.1 (10.0-12.4)	10.3 (9.3-11.4)	-43	<0.001
Physical activity‡	16.9 (16.2-17.6)	30.5 (27.7-33.5)	42.1 (39.2-45.2)	149	<0.001
Use of blood pressure lowering drugs	5.6 (5.2-6.0)	10.1 (8.7-11.8)	15.0 (13.1-17.1)	170	<0.001
Use of lipid lowering drugs	0.6 (0.5-0.8)	4.8 (3.3-7.1)	7.9 (5.4-11.3)	1134	<0.001
Use of antithrombotic drugs§,‖	1.5 (1.2-1.8)	2.9 (2.1-4.1)	4.2 (3.0-5.9)	184	<0.001
Use of antiplatelets‖	1.3 (1.1-1.6)	2.7 (1.8-3.9)	3.7 (2.6-5.4)	188	<0.001
Use of anticoagulants‖	0.3 (0.2-0.4)	0.4 (0.2-0.8)	0.5 (0.2-1.2)	105	<0.001

Continuous variables are age-adjusted means with 95% CI. Categorical variables are age-adjusted prevalence (%) with 95% CI

*Test for linear trend

†Systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or use of blood pressure-lowering drugs

‡ Strenuous leisure physical activity ≥1 hour per week

§ Use of antiplatelets and/or anticoagulants

‖ Calculated in the attendees of the second visit of the survey in 1994-1995 (n=3 442), and in all attendees of the surveys in 2001 and 2007-2008

Table Va. Odds ratios (OR) for use of antithrombotic drugs at time of first-ever intracerebral hemorrhage by time period. The Tromsø Study.

	1994-2013 n=219	1994-2001 n=59	2002-2007 n=72	2008-2013 n=88	P for trend*
Antithrombotic drugs†‡	110 (50)	23 (39)	37 (51)	50 (57)	
OR (95% CI) §		1	1.53 (0.73-3.22)	1.84 (0.90-3.76)	0.10
Antiplatelets†	61 (28)	12 (20)	19 (26)	30 (34)	
OR (95% CI) §		1	1.29 (0.55-2.98)	1.80 (0.82-3.96)	0.13
Anticoagulants†	55 (25)	11 (19)	18 (25)	26 (30)	
OR (95% CI) §		1	1.34 (0.57-3.17)	1.65 (0.73-3.76)	0.23

*P-value for linear trend

†Numbers are n (%)

‡Antiplatelets and/or anticoagulants

§Adjusted for age and sex

Table Vb. Odds ratios (OR) for use of antithrombotic drugs in men and women at time of intracerebral hemorrhage (ICH) by time period. The Tromsø Study.

	1994-2013	1994-2001	2002-2007	2008-2013	P for trend*
Men	**n=123**	**n=30**	**n=39**	**n=54**	
Antithrombotic drugs†‡	72 (59)	15 (50)	23 (59)	34 (63)	
OR (95% CI)§		1	1.13 (0.41-3.13)	1.60 (0.60-4.23)	0.32
Antiplatelets†	41 (33)	9 (30)	12 (31)	20 (37)	
OR (95% CI)§		1	0.92 (0.32-2.62)	1.24 (0.47-3.28)	0.66
Anticoagulants†	35 (28)	6 (20)	11 (28)	18 (33)	
OR (95% CI)§		1	1.44 (0.46-4.51)	1.83 (0.63-5.32)	0.26
Women	n=96	n=29	n=33	n=34	
Antithrombotic drugs†‡	38 (40)	8 (28)	14 (42)	16 (47)	
OR (95% CI)§		1	2.12 (0.70-6.39)	2.24 (0.76-6.60)	0.16
Antiplatelets†	20 (21)	3 (10)	7 (21)	10 (29)	
OR (95% CI)§		1	2.47 (0.55-11.0)	3.51 (0.83-14.8)	0.09
Anticoagulants†	20 (21)	5 (17)	7 (21)	8 (24)	
OR (95% CI)§		1	1.34 (0.37-4.84)	1.42 (0.41-4.94)	0.60

*P-value for linear trend
†Numbers are n (%)
‡Antiplatelets and/or anticoagulants
§Adjusted for age

Table VI. Incidence rates (IR) and incidence rate ratios (IRR) of incident intracerebral hemorrhage in 1995-2013. The Tromsø study.

	Crude IR (95% CI)	Adjusted IR* (95% CI)	IRR (95% CI)†
All	0.55 (0.48-0.63)	0.60 (0.52-0.68)	0.81 (0.52-1.27)
Men	0.66 (0.55-0.79)	0.80 (0.64-0.96)	1.27 (0.69-2.31)
Women	0.45 (0.37-0.56)	0.46 (0.36-0.55)	0.46 (0.23-0.90)
<75 years	0.31 (0.25-0.37)	0.30 (0.24-0.36)	0.89 (0.48-1.66)
≥75 years	2.45 (2.04-2.96)	2.50 (2.02-2.98)	0.78 (0.41-1.48)
Lobar ICH	0.22 (0.18-0.27)	0.24 (0.19-0.29)	1.36 (0.67-2.79)
Men	0.24 (0.18-0.33)	0.30 (0.21-0.40)	1.58 (0.58-4.29)
Women	0.20 (0.15-0.28)	0.20 (0.14-0.26)	1.17 (0.42-3.26)
Non-lobar ICH	0.28 (0.23-0.34)	0.31 (0.25-0.36)	0.71 (0.38-1.33)
Men	0.36 (0.28-0.46)	0.44 (0.32-0.56)	1.34 (0.60-3.02)
Women	0.20 (0.15-0.28)	0.21 (0.15-0.27)	0.26 (0.09-0.71)

*Adjusted to age and sex by the direct method using the European standard population of 2013 as reference
†Incidence rates in 2013 compared with 1995, adjusted for age and sex

Paper III

Long-term survival, causes of death and trends in five-year mortality after intracerebral hemorrhage. The Tromsø Study.

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Abstract

Background and purpose: Data on long-term survival after intracerebral hemorrhage (ICH) are scarce. In a population-based nested case-control study, we compared long-term survival and causes of death within five years in 30-day survivors of first-ever ICH and controls, assessed the impact of cardiovascular risk factors on 5-year mortality, and analyzed time trend in 5-year mortality in ICH patients over two decades.

Methods: We included 219 participants from the population-based Tromsø Study, who after the baseline participation had a first-ever ICH between 1994-2013 and 1,095 age- and sex-matched participants without ICH. Cumulative survival was presented using the Kaplan Meier method. Hazard ratios (HR) for mortality and for the association between cardiovascular risk factors and 5-year mortality in 30-day survivors were estimated by stratified Cox proportional hazards models. Trend in 5-year mortality was assessed by logistic regression.

Results: Risk of death during follow-up (median time 4.8 years) was increased in the ICH group compared to controls (HR 1.62, 95% confidence interval (CI) 1.27-2.06). Cardiovascular disease was the leading cause of death, with a higher proportion in ICH patients (22.9% vs 9.0%, p <0.001). Smoking increased the risk of 5-year mortality in cases and controls (HR 1.59, 95% CI 1.15-2.19), whereas serum cholesterol was associated with 5-year mortality in cases only (HR 1.39, 95% CI 1.04-1.86). Use of anticoagulants at ICH onset increased risk of death (HR 2.09, 95% CI 1.09-4.00). There was no difference according to ICH location (HR 1.15, 95% CI 0.56 -2.37). 5-year mortality did not change during the study period (OR per calendar year 1.01, 95% CI 0.93-1.09).

Conclusions: Survival rates were significantly lower in cases than controls, driven by a twofold increased risk of cardiovascular death. Smoking, serum cholesterol and use of anticoagulant drugs were associated with increased risk of death in ICH patients. 5-year mortality rates in ICH patients remained stable over time.

Non-standard Abbreviations and Acronyms

ICH: Intracerebral hemorrhage

SBP: Systolic blood pressure

Introduction

Stroke is the second leading cause of death globally, causing 5.5 million deaths yearly.[1] Intracerebral hemorrhage (ICH) accounts for 10-20% of all strokes. The morbidity and mortality is high,[2] and approximately half of stroke deaths are caused by hemorrhagic stroke (ICH and subarachnoid hemorrhage combined).[1] The risk of death after an ICH is highest in the acute phase with 1-month case fatality rates ranging between 13% and 61%.[2] The components of the ICH score (age, hematoma volume, infratentorial location, presence of intraventricular hemorrhage and Glasgow coma scale score) and use of anticoagulant drugs have been associated with an increased risk of early death after ICH.[3, 4]

There are few studies on long-term survival after ICH,[5-15] and on time trends in long-term survival rates.[5, 7, 9, 12] Whereas the majority of early deaths are a direct consequence of the ICH event, other causes of death contribute to a larger degree in ICH survivors.[16] Despite this, a minority of studies on long-term survival are on ICH survivor cohorts.[5] The components of the ICH score are the most studied prognostic factors for long-term survival, and there is limited knowledge on the impact of traditional cardiovascular risk factors.[5]

The aim of our study was to compare long-term survival rates in ICH-cases with the general population, to compare causes of death within five years, and to assess the impact of cardiovascular risk factors on the risk of death in 30-day survivors. In addition, we analyzed temporal trends in 5-year mortality rates in cases.

Materials and methods

The Tromsø Study is an ongoing population-based study with repeated surveys, where inhabitants of the Tromsø municipality in Northern Norway have been invited to attend.[17] In the period 1974-2016, seven surveys have been undertaken with a total of 45,473 attendees. At attendance, data on health are collected from questionnaires, clinical examinations and biological samples, by use of standardized study protocols. Attendees are continuously being followed up with registration of several end-points, including stroke, from date of first attendance until date of death or emigration out of the municipality, whichever come first. The Tromsø Study was approved by the Regional Committee for Medical and Health Research Ethics (REK Nord 2009/2536) and the Data Inspectorate of Norway. Written informed consent was obtained from all participants. The data are owned by the UiT The Arctic University of Norway. Legal restrictions prohibit sharing of data.

Eligible for the present study were participants who attended at least one of the surveys performed in 1994-1995, 2001 and 2007-2008 (n=30,586). Participants without valid written consent (n=206) and participants who were not officially registered as inhabitants of Tromsø municipality (n=23) at date of inclusion were excluded. In addition, we excluded participants aged <30 years (n=2,106) and participants with prevalent ICH (n=26) or unclassifiable stroke (n=58) (Figure I, Table I, please see https://www.ahajournals.org/journal/str).

Assessment of cardiovascular risk factors is described in Supplemental Materials and methods (please see https://www.ahajournals.org/journal/str). Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or treatment with BP-lowering drugs. Use of antithrombotic drugs at time of ICH was registered retrospectively by use of medical records.

Strokes were registered by linkage to the discharge and out-patients diagnosis registry at the University Hospital of North Norway, the only hospital in the region, and to the Norwegian Cause of Death Registry, using unique 11-digit personal identification numbers. Searches were performed for International Classification of Disease (ICD) versions 8 and 9 diagnosis codes 430–438, and ICD-10 diagnosis codes I60–I69 (cerebrovascular disease).[18] From 2006, ICD-10 codes G45 (transient ischemic attack), G46 (vascular syndromes of brain in cerebrovascular diseases) and G81 (hemiplegia) were added to the search. In addition, systematic text searches were made for the words 'stroke', 'ischemic stroke' and 'intracerebral hemorrhage' in the medical records of all participants with ICD-8 to ICD-10 diagnosis codes 410–414 and I20–I25 (ischemic heart disease), 798/R96 (sudden death, cause unknown), R98 (unattended death) and 799/R99 (other ill-defined and unknown causes of morbidity and mortality). An independent endpoint committee reviewed all cases separately by use of medical records from the hospital (including autopsy reports). Cases retrieved from the National Causes of Death registry were additionally validated by medical records from nursing homes, general practitioners, emergency services and/or death certificates, when available. Stroke was defined according to the WHO criteria.[19] We included ICH diagnosed by computed tomography, magnetic resonance imaging and/or autopsy. ICH caused by hemorrhagic transformation of ischemic stroke, trauma, brain surgery, hematologic disease or brain tumor were excluded. An independent endpoint committee reviewed each case separately by use of hospital medical records (including autopsy reports). ICH location was defined using a validated rating instrument (CHARTS),[20] as described in a previous publication.[21] Dates for death and emigration out of the municipality were obtained from the Population Registry of Norway. Causes of death were retrieved from the Norwegian Cause of Death Registry through December 31, 2016.

A total of 219 first-ever ICH cases were registered (96 women and 123 men) between 1994-2013. Each case was matched to 5 randomly selected participants without ICH from the original population-based cohort. The controls (n=1,095) were of same birth year and sex and still alive at the date of ICH of the matched case. Assessment of risk factors and causes of death was identical in cases and controls. Baseline characteristics of cases and controls are presented in Table 1. Start of follow-up for both cases and controls was defined as date of ICH of the case in each strata. Cumulative survival rates were estimated in all cases and their matched controls. Analyses of causes of death within five years and the impact of risk factors on the risk of death were performed in cases surviving 30 days after the ICH date and their controls. Causes of death were defined as cardiovascular disease (CVD) (ICD 9 codes 390-459 and ICD 10 codes I00-I99), malignancy (ICD 9 codes 140-208 and ICD 10 codes C00-C97) and chronic lower respiratory diseases (asthma excluded) (ICD 9 490-492, 494 and 496 and ICD 10 codes J40-44 and J47). CVD was further classified as ischemic heart disease (ICD 9 codes 410-414 ICD 10 codes I20-I25), ischemic stroke (ICD 9 code 434 and ICD 10 code I63), intracerebral hemorrhage (ICD 9 code 431 and ICD 10 code I61), unspecified stroke (ICD 9 code 436 and ICD 10 code I64), stroke sequelae (ICD 9 code 439 and ICD 10 code I69) and "other". Causes of death not classified as CVD, malignancy or chronic lower respiratory diseases were classified as "other". Trend in 5-year mortality rates was analyzed in 30-day survivors of ICH. The STROBE reporting guideline was used. A STROBE checklist and flow-diagram are available online (Figure I, please see https://www.ahajournals.org/journal/str).

Statistical methods

Statistical analyses were conducted using StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. Means and proportions of risk factors were

calculated using updated risk factors from the last survey before start of follow up, except for age, which was registered at start of follow-up. Differences between cases and controls were assessed using Fisher´s exact test for categorical variables and Student's t-test for continuous variables. Cumulative survival rates were assessed by Kaplan Meier estimates. We used stratified univariate and multivariable Cox proportional hazards regression models to estimate hazard ratios (HR) for mortality between cases and controls during follow-up through 2016, and to estimate HR of risk factors for 5-year mortality in 30-day survivors. Differences in effect of a risk factor between cases and controls were assessed by including interaction terms between ICH status (yes/no) and each risk factor (e.g. ICH status*SBP). Model selection was performed using backward selection. When interaction was significant, separate HRs were calculated for cases and controls. Risk of death in cases according to ICH location and use of antithrombotic drugs was analyzed using a Cox proportional hazard model adjusted for cardiovascular risk factors (age, sex, SBP, serum cholesterol, diabetes mellitus and smoking). The assumption of proportionality was tested using Schoenfelds residuals. In 30-day survivors, data on diabetes were missing in one case and three controls. Smoking status was missing in one control. Data on use of antithrombotic drugs at time of ICH were missing in one case. The missing data were considered to be missing completely at random. Participants with missing data were excluded from multivariable analyses on the association with risk factors and 5-year mortality. Causes of death within five years were compared using Fisher´s exact test. Time trend in 5-year survival rates in cases was assessed using logistic regression adjusted for age and sex. Linearity was assessed by fitting the model with fractional polynomials of calendar time. The best fitting first- and second-degree models were compared to a model with a linear time variable using the Akaike information Criteria (AIC). Non-linear models were not superior to the linear model, and time was included as a linear term in the

logistic regression model. Odds ratio (OR) was estimated per year increase in calendar time. Interaction between age and time and sex and time was tested in separate models.

With a study-population of 166 thirty-day survivors of ICH and their 825 controls and with a total risk of death of 29% within five years, we had 80% power to show a HR=1.18 per standard deviation (SD) for a continuous variable, and a HR=1.48 for a binary variable as smoking with a prevalence of 25%.

A two-sided p-value of <0.05 was considered significant in all analyses.

Results

Median follow-up time from date of ICH was 4.8 years, with a maximum follow-up of 21.4 years. Age at ICH ranged between 42 and 96 (mean 74 (SD 11)) years. Forty-four percent of cases were women. Cases had higher SBP levels and a higher prevalence of hypertension compared with controls (Table 1). Twenty-eight percent of cases used antiplatelet drugs and 25% used anticoagulant drugs at date of ICH. Forty percent of the ICH were lobar, 51% non-lobar, 6% holohemispheric and 3% of other location.

Cumulative survival rates are shown in Figure 1 and 2. Survival rates were lower in cases compared with controls with the largest discrepancy during the earliest phase after the ICH event (Figure 1). 30-day case fatality rates were 24.2% (n=53) in cases and 0.6% (n=6) in controls. Cumulative 1-, 5-, 10-, 15- and 20-years survival rates were 65%, 47%, 25%, 15% and 6% in cases and 94%, 70%, 51%, 33% and 22% in controls.

Analyses of long-term survival and causes of death were performed in ICH patients surviving the first 30 days (n=166) and their matched controls surviving the first 30 days after start of follow-up (n=825). Trend in 5-year mortality rates was analyzed in 30-day survivors of ICH. Baseline characteristics are presented in Table II (please see https://www.ahajournals.org/journal/str). Mean age at ICH was 73 years (SD 11). Twenty-

seven percent of 30-day survivors were on antiplatelet drugs and 19% on anticoagulant drugs. Forty-three percent of the ICH were lobar, 52 % non-lobar, 2% holohemispheric and 2% had other location.

In 30-day survivors of ICH, the cumulative 1-, 5-, 10-, 15- and 20-years survival rates were 86%, 62%, 34%, 20% and 8%. Corresponding rates in controls were 95%, 73%, 55%, 36% and 25%. The risk of death was significantly higher in 30-day survivors of ICH compared with controls (HR 1.62, 95% CI 1.27-2.06).

In both cases and controls, the major cause of death was CVD (Table 2), accounting for 61% and 34 % of all deaths, respectively. In cases, the increased risk of death of CVD was driven by death from ICH and stroke sequelae. The risk of death by malignancy was significantly higher in controls than in cases; 8% vs 3%, corresponding to 31% of all deaths in controls and 8% of all deaths in cases. There was no difference in the risk of death by chronic obstructive respiratory diseases or other causes of death.

Smoking was associated with the risk of death within five years, whereas there was no association with SBP or diabetes mellitus (Table 3). There was an interaction between ICH status and serum cholesterol. Serum cholesterol was associated with risk of death in cases, whereas there was no significant association in controls. The association between having an ICH and risk of 5-year mortality increased with higher levels of serum cholesterol.

There was no difference in risk of death between individuals with non-lobar compared with lobar ICH (HR 1.13, 95% CI 0.65-1.97), or with infratentorial compared with supratentorial ICH (HR 1.15, 95% CI 0.56-2.37). Of the four patients with holohemispheric ICH, three died during 5-year follow-up. Use of anticoagulant drugs at time of ICH increased the risk of death within five years (HR 2.09, 95% CI 1.09-4.00), whereas use of antiplatelet drugs did not (HR 1.29, 95% CI 0.69-2.44).

5-year survival rates remained stable during the study period (OR per year increase in calendar time 1.01, 95% CI 0.93-1.09) (Figure 3).

Discussion

Individuals with ICH had significantly higher risk of death compared to the general population. The risk of death was highest in the acute phase, and thereafter levelled off. However, 30-day survivors of ICH had a more than 60% increased risk of death compared to controls. The increased risk persisted through long-term (up to 21 years) follow-up. This is in line with two previous studies on ICH survivor cohorts, where an excess mortality was observed during 7 and 13 years of follow-up of 140 and 172 ICH cases, respectively.[6, 22] In a Finnish study on 203 ICH survivors and with a follow-up time of 16 years, an increased risk of death was observed during the first six years after ICH, but not thereafter.[16]

The cumulative 5-year survival rate in the total ICH cohort was 47%, compared with 70% in controls. In previous studies, 5-year survival rates in ICH patients ranged between 27% and 57%,[5, 6, 8, 14] with a tendency towards lower survival rates in population-based compared with hospital-based studies.[5] The 10-year survival rate of 25% was similar with previous population-based studies, reporting rates ranging between 18% and 31%.[6, 10, 11, 14, 16, 23] Studies on survival beyond 10 years are scarce. Fifteen and 20-year survival rates in our cases were 15% and 6% respectively, which is similar to two previous studies.[10, 16]

Early death after an ICH is often a direct consequence of the ICH event,[16] and has been associated with the components of the ICH score and use of anticoagulant drugs.[3, 4] In line with this, 30-day survivors in our cohort were younger, and the proportions of holohemispheric ICH and anticoagulant drug users were lower, compared with the total ICH cohort. In ICH patients, 5- and 10-year survival rates were 62% and 34%, respectively. Corresponding rates in controls were 73% and 55%. There are little data from population-

based studies on long-term survival in ICH survivors, and start of follow-up after the ICH has varied.[6, 8, 16, 22] The authors of a study on 3-month survivors of ICH reported a 7-year survival rate of 67%,[22] whereas 5- and 10-year survival rates were 74% and 43% in a study on 1-year survivors.[6]

Differences in demographics of study populations and study design (e.g. age at ICH and differences in case ascertainment) limit direct comparisons of survival rates between studies. In addition, differences in short-term mortality rates may influence cumulative long-term survival rates. The age of cases in our study was in the higher range compared with previous publications. One month case fatality rate in our cases was lower compared with several previous studies.[8, 14, 16, 23]

CVD was the major cause of death accounting for 61% of all deaths in cases and 34% in controls. This is in accordance with two previous studies, where CVD accounted for 56% and 58% of deaths in ICH patients during long-term follow-up.[6, 16] In our study, the risk of death by CVD in cases was driven by death by ICH and stroke sequelae. Previous studies have shown high rates of disability after an ICH.[2, 5, 8] The increased risk of death by ICH may be a consequence of complications due to disability following the index ICH or of recurrent ICH.[8, 16, 22, 24] We do not have data on functional outcome or on the rate of recurrent ICH.

High blood pressure is a strong risk factor for ICH.[21] However, in line with our results several previous studies on ICH survivor cohorts failed to show an association between hypertension and long-term mortality after ICH.[5, 6, 15, 16, 22] There is a possibility that initiation of blood pressure treatment in ICH patients may attenuate a possible association with premorbid SBP levels and risk of death in long-term. Studies on secondary prevention have shown an association with lowering of blood pressure and reduced recurrence rates of ICH.[25] Data on blood pressure lowering and all-cause mortality in ICH patients are scarce, and

studies on the effect of blood pressure lowering on all-cause mortality in stroke patients (ischemic stroke and ICH combined) have been conflicting.[26, 27]

An inverse association between serum cholesterol and the risk of ICH has been suggested in several, but not all studies.[21, 28] The risk of ICH in statin users is debated.[29] Data on the association between serum cholesterol and use of statins and long-term outcome after ICH are very limited.[13, 29] We found increased long-term mortality in ICH cases with high serum cholesterol levels, as opposed to the results of a Danish study of 7-days survivors of ICH, where serum cholesterol was inversely associated with long-term mortality after ICH.[13] However, after adjusting for statin use, the association was no longer significant. Statin use at time of ICH was not registered in our cohort. In some studies, use of statins has been associated with improved outcome, and reduced long-term mortality after ICH. [29] However, randomized controlled studies are lacking, and there is a need for further studies to address this question.

Daily smoking was associated with 5-year mortality in both cases and controls, whereas there was no significant association with diabetes mellitus. Previous studies on the association between smoking and diabetes mellitus and long-term mortality have been inconsistent.[6, 15, 16, 22]

Use of anticoagulant drugs at the time of ICH was significantly associated with 5-year mortality. Studies on the association between anticoagulant drugs and long-term mortality in patients surviving the earliest phase (one month up to one year) after an ICH are diverging.[6, 15, 16, 22] Use of anticoagulant drugs at time of ICH has been associated with a larger hematoma size, and a larger risk of hematoma expansion[4] which may increase the risk of long-term mortality as a consequence of increased disability. ICH patients have an increased risk of both subsequent ICH and thromboembolic events.[5] However, data on the risks and benefits of resumption of anticoagulant drugs after an ICH are scarce. It is unclear whether an association

between anticoagulant drugs and long-term mortality could be explained by an increased rate of ICH due to resumption of anticoagulants or by thromboembolic events due to withhold of anticoagulants. Several ongoing randomized controlled studies are addressing the resumption of anticoagulant drugs after ICH.[30] We have limited data on resumption of anticoagulant drugs in our ICH cohort.

We found no association with ICH location and outcome. Four 30-day survivors of ICH had a holohemispheric ICH, which might be regarded as a proxy for large hematoma size. Of these, three died within five years. Previous studies on the association of hematoma location and hematoma size with long-term mortality have been diverging,[5] but they may be of less importance in ICH survivors.[6, 15, 16]

5-year mortality rates did not change during follow-up (Figure 3). This is in accordance with the results of a meta-analysis, where 5-year mortality rates remained stable between 1983 and 1997[5], an US study where 3-year mortality rates were stable between 2000 and 2010[12] and a Dutch study with stable 5-year mortality rates between 1998 and 2010 in 30-day survivors of ICH, aged 18-49 years.[9] In contrast, a decrease in 5-year mortality rates in 2004 to 2008 compared with 1994 to 1998, was observed in a large Danish register-based study, including 24,760 ICH patients.[7] Stroke unit care has been associated with a decrease in long-term mortality after ICH.[31] The stroke unit at the University Hospital of North Norway was established in 1993 and an effect of this may not have been shown in our study. Except for stroke unit care, treatment possibilities for ICH have remained limited, which may have contributed to the stable mortality rates. We cannot exclude that modest changes in trends might exist that we were unable to detect due to small sample sizes.

Strengths and limitations

The major strengths of our study are its prospective, population-based design, long-term follow-up and inclusion of cases and controls from the same population in a well-defined geographic area, with standardized adjudication of cases and identical, standardized registration of risk factors in both cases and controls. We regard case identification to be nearly complete, but we cannot exclude that we may have missed some non-hospitalized, non-fatal cases of ICH. Causes of death were identified by linkage to the Norwegian Cause of Death Registry, which includes all deaths of Norwegian citizens, but there is a possibility of misclassification of death causes. However, a previous publication showed substantial agreement between Norwegian mortality statistics and autopsy findings for stroke and coronary deaths.[32]

The relatively low number of ICH patients limits the possibilities of subgroup analyses. Due to limited information, we were not able to adjust for possible confounders such as socioeconomic status and other demographic data. Furthermore, we did not have complete data on the components of the ICH score, and we did not have data on treatment of ICH. Diabetes was self-reported, and we may have missed some cases. There may be some degree of selection bias to the Tromsø Study; non-attendees tended to be younger, more likely to be men and less likely to be married.[33] However, this is not likely to have influenced comparisons between cases and controls or analyses of time trends in mortality.

Conclusions

Cumulative survival rates were significantly lower in 30-day survivors of ICH compared with controls. The difference persisted through long-term follow-up. The most common cause of death within five years was CVD, with a significantly higher risk in ICH patients compared to controls, driven by death by recurrent ICH and stroke sequelae in ICH patients. Smoking, serum cholesterol and use of anticoagulant drugs at time of ICH were associated with death

within five years in cases. There was no difference in mortality according to ICH location. 5-year mortality rates did not change during the last two decades. There is a need of more knowledge on secondary prevention, including statin use and resumption of anticoagulant drugs after an ICH. In addition, stable long-term mortality rates in ICH patients may reflect the currently limited treatment opportunities of ICH and stresses the need for effective treatment strategies for ICH patients.

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Disclosures

None

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Figure legends

Figure 1. Cumulative survival in individuals with a first-ever intracerebral hemorrhage (ICH) and matched controls. The Tromsø Study.

Figure 2. Cumulative survival in 30-day survivors of a first-ever intracerebral hemorrhage (ICH) and matched controls. The Tromsø Study.

Figure 3. Time trend in 5-year mortality rates in 30-day survivors of a first-ever intracerebral hemorrhage (ICH). The Tromsø Study.

Tables

Table 1. Characteristics of individuals with first-ever intracerebral hemorrhage (ICH), and controls matched for birth year and sex*. The Tromsø Study 1994-2013.

	ICH N=219	No ICH N=1,095	P-value†
Age, years	74.2 (10.9)	74.2 (10.9)	0.98
Male sex (yes/no)	56.2 (123)	56.2 (615)	1.00
Systolic blood pressure, mm Hg	156.3 (24.2)	148.5 (23.6)	<0.001
Hypertension‡ (yes/no)	84.0 (184)	67.2 (736)	<0.001
Total cholesterol, mmol/L	6.3 (1.3)	6.4 (1.3)	0.66
Diabetes mellitus (yes/no)	5.5 (12)	5.2 (57)	0.87
Daily smoking (yes/no)	25.1 (55)	25.6 (280)	0.88

Continuous variables are presented as mean (SD), categorical variables are presented as % (n).

*Age was measured at start of follow-up, other risk factors measured at date of last attendance prior to start of follow up. All controls were alive at date of ICH of its case.

†P-value for difference between individuals with and without ICH.

‡Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering drugs.

Table 2. Causes of death within five years in 30-day survivors of first-ever intracerebral hemorrhage (ICH) and controls matched for birth year and sex*. The Tromsø Study 1994-2013.

	ICH N=166	No ICH N=825	P-value†
Cardiovascular disease	22.9 (38)	9.0 (74)	<0.001
Intracerebral hemorrhage	9.6 (16)	0.1 (1)	<0.001
Ischemic stroke	1.8 (3)	0.5 (4)	0.10
Unclassifiable stroke	2.4 (4)	1.2 (10)	0.27
Stroke sequelae	3.0 (5)	0.4 (3)	0.01
Ischemic heart disease	3.0 (5)	4.1 (34)	0.66
Other	3.0 (5)	2.7 (22)	0.79
Malignancy	3.0 (5)	8.2 (68)	0.02
Chronic obstructive lung disease‡	1.2 (2)	1.3 (11)	1.00
Other causes	10.2 (17)	7.8 (64)	0.28
Total	37.4 (62)	26.3 (217)	0.01

Causes of death are presented as % (n).

*Underlying cause of death registered in the Norwegian Cause of Death Registry. All controls were alive at date of ICH of its case.

†P-value for difference between individuals with and without ICH.

‡Asthma excluded.

Table 3. Multivariable-adjusted hazard ratios[*](HR) of 5-year all-cause mortality according to intracerebral hemorrhage (ICH) status [†] and according to cardiovascular risk factors. The Tromsø Study.

	HR (95% CI)
Systolic blood pressure (mm Hg)	1.08 (0.94-1.24)
Diabetes mellitus (yes/no)	1.57 (0.93-2.64)
Daily smoking (yes/no)	1.59 (1.15-2.19)
Total cholesterol[‡] (mmol/L) in subjects with	
No ICH	0.94 (0.81-1.10)
ICH	1.39 (1.04-1.86)
ICH[‡] (yes/no) at total cholesterol level[§]	
4 mmol/L	0.69 (0.36-1.32)
6 mmol/L	1.22 (0.88-1.70)
8 mmol/L	2.17 (1.34-3.51)

[*]HRs were calculated by stratified Cox proportional hazards regression models with backward selection. HRs are expressed per SD increase in continuous variables and presence vs absence of categorical variables. HRs for each variable were adjusted for all other variables present in the table.

[†] Cases with first-ever ICH and controls matched by birth year and sex. Cases who died within the first 30 days after ICH were excluded, as were their age- and sex-matched controls. Differences in risk between cases and controls were assessed by use of interaction terms.

[‡]Significant interaction between ICH and total cholesterol (p=0.02), indicating a difference in association with total cholesterol and 5-year all-cause mortality between cases and controls in addition to a difference in the association of ICH and 5-year all-cause mortality according to level of total cholesterol

[§]HRs for ICH were estimated by analyses with total cholesterol centered at defined levels (4, 6 and 8 mmol/L).

Figure 1. Cumulative survival in individuals with a first-ever intracerebral hemorrhage (ICH) and matched controls. The Tromsø Study.

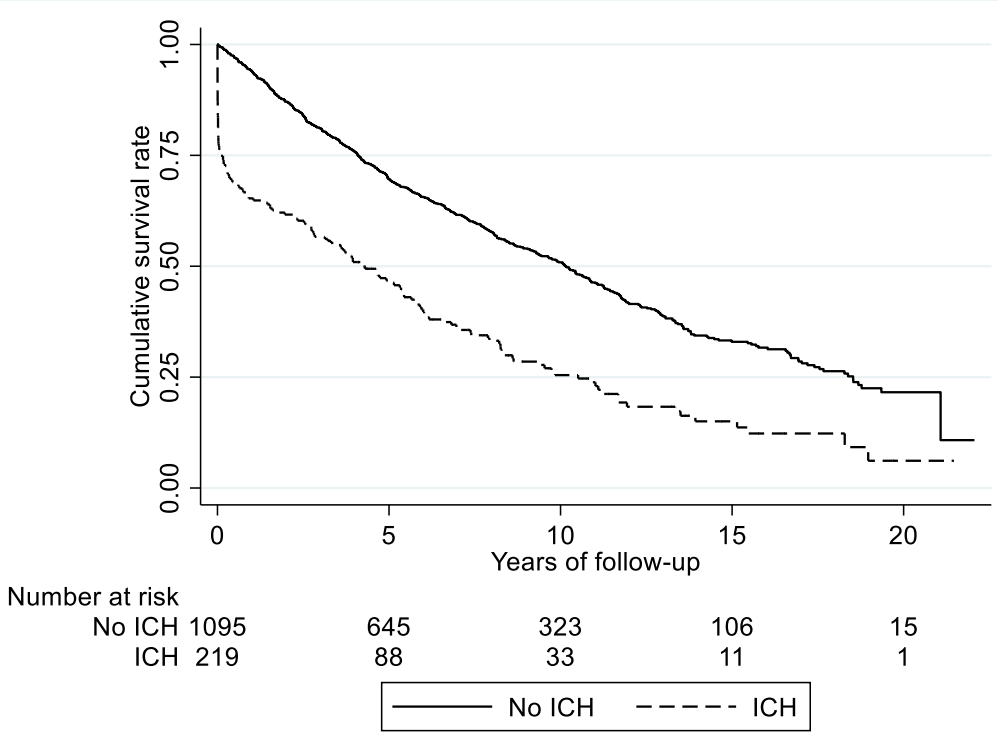


Figure 2. Cumulative survival in 30-day survivors of a first-ever intracerebral hemorrhage (ICH) and matched controls. The Tromsø Study.

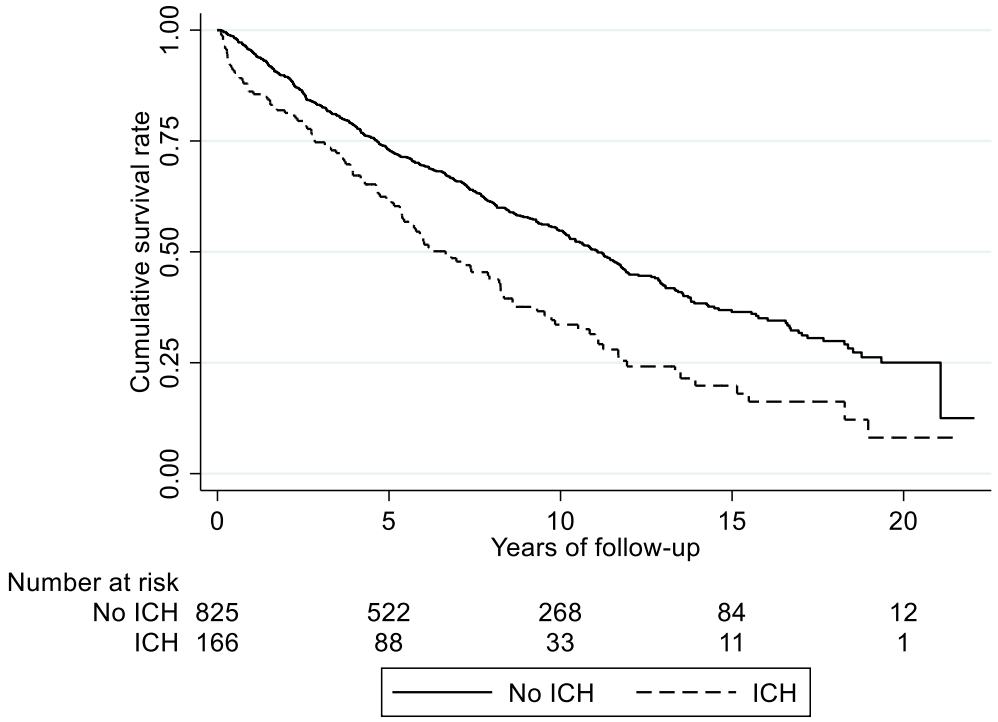
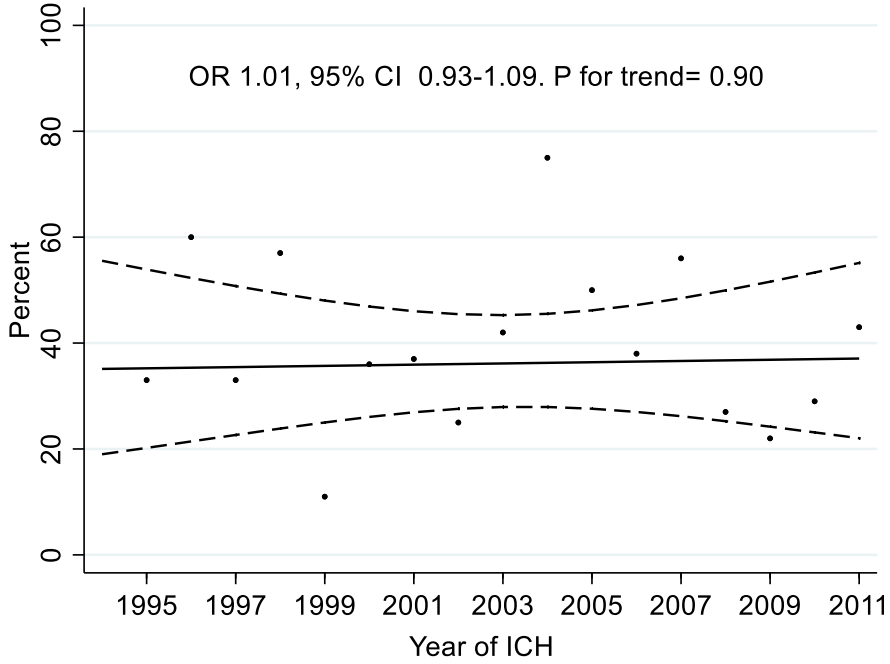


Figure 3. Time trend in 5-year mortality rates in 30-day survivors of a first-ever intracerebral hemorrhage (ICH). The Tromsø Study.



OR: Odds ratio per year increase in calendar time.
Solid line: Trend in 5-year mortality rates, adjusted for age and sex. Dashed lines: 95% CI.
Dots: Crude 5-year mortality rates.

Supplemental materials

Expanded Materials and methods

Online Figure I

Online Table I-III

STROBE check list

SUPPLEMENTAL MATERIAL

Long-term survival, causes of death and trends in five-year mortality after intracerebral hemorrhage. The Tromsø Study.

Materials and methods

Assessment of risk factors

Information on diabetes mellitus, smoking habits and use of blood pressure lowering drugs was collected through questionnaires (please see https://uit.no/research/tromsostudy). Blood pressure was measured with three recordings after a 2-minute seated rest, and by a 1-minute interval, using Dinamap Vital Signs Monitor 1846 (Critikon Inc., Tampa, FL, USA) in the 1994-1995 and 2001 surveys, and Dinamap Pro care 300 Monitor (GE Healthcare, Norway) in the 2007-2008 survey. We used the mean value of the two last recordings. Non-fasting serum-cholesterol was analyzed by standard enzymatic colorimetric methods at the University Hospital of North Norway.

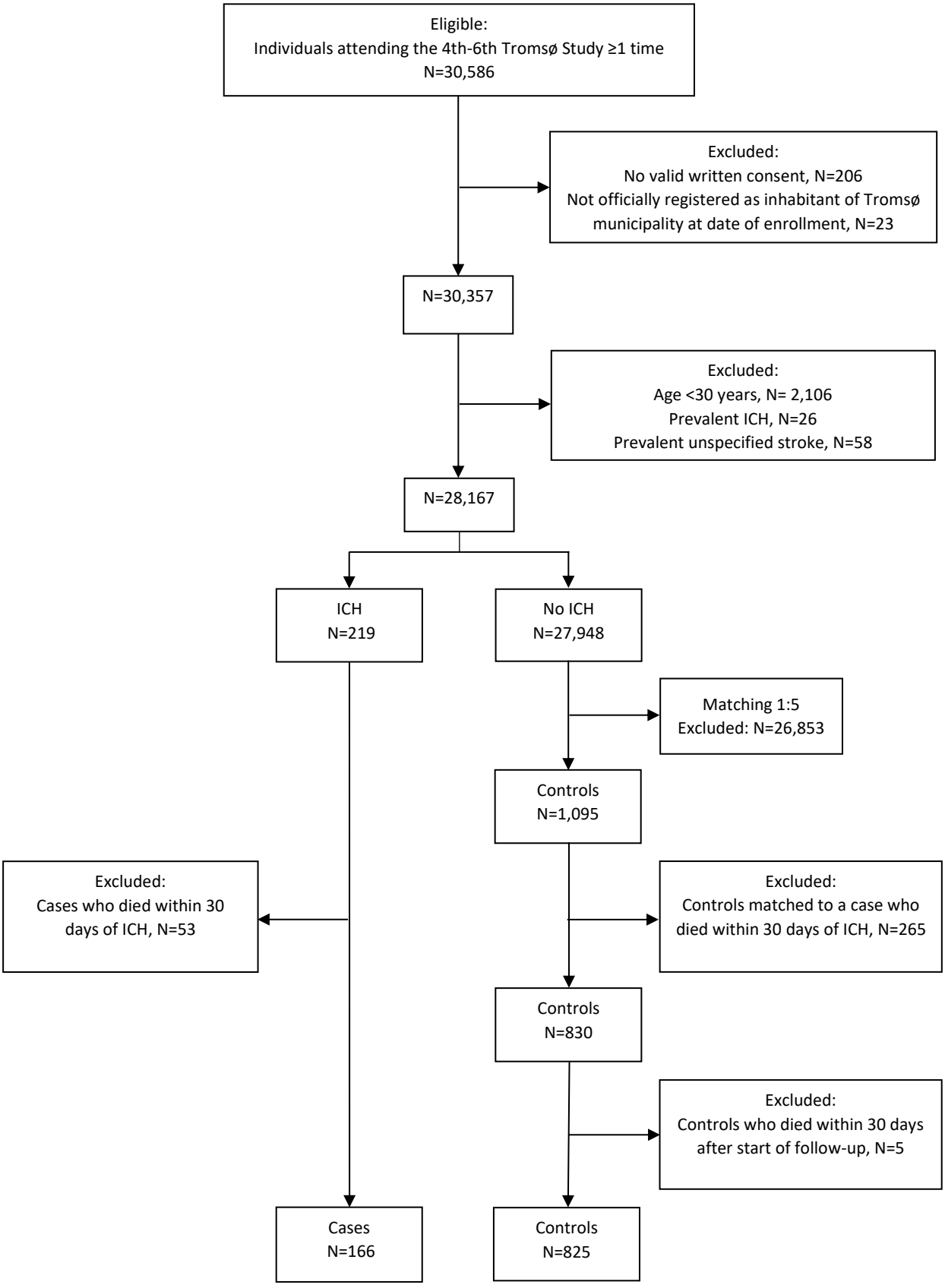


Figure I. Flow diagram. Long-term survival, causes of death and trends in five-year mortality after intracerebral hemorrhage. The Tromsø Study.

Table I. Age, sex and attendance rates of eligible participants, by year of survey. The Tromsø Study.

		Men		Women	
	Age group	n (%)	Mean age*	n (%)	Mean age*
Tromsø 4, 1994-95	25-97 years	12,865 (69.6)	46.6	14,293 (74.9)	47.2
Tromsø 5, 2001	30-89 years	3511 (75.7)	59.9	4619 (80.8)	59.4
Tromsø 6, 2007-08	30-87 years	6054 (62.9)	57.5	6930 (68.4)	57.5

*Mean age (years) of attendees at date of inclusion.

Table II. Characteristics[*] of 30-day survivors of first-ever intracerebral hemorrhage (ICH) and controls, matched by birth year and sex. The Tromsø Study.

	ICH (N=166)	No ICH (N=825)	P-value[†]
Age, years	72.6 (10.8)	72.5 (10.8)	0.96
Male sex (yes/no)	59.0 (98)	59.0 (487)	1.00
Systolic blood pressure, mm Hg	155.6 (23.8)	146.6 (22.9)	<0.001
Hypertension[‡] (yes/no)	83.1 (138)	64.2 (530)	<0.001
Total cholesterol, mmol/L	6.4 (1.3)	6.3 (1.3)	0.68
Diabetes mellitus (yes/no)	5.4 (9)	4.2 (35)	0.50
Daily smoking (yes/no)	24.7 (41)	27.0 (223)	0.53

Continuous variables are presented as mean (SD), categorical variables as % (n).

[*]Age was measured at start of follow-up, other risk factors were measured at date of last attendance prior to start of follow up. All controls were alive at the date of the ICH of their matched case.

[†]P-value for difference between individuals with and without ICH.

[‡]Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering drugs.

Table III. Hazard ratios (HR)[*] of 5-year all-cause mortality by intracerebral (ICH) status[†] and cardiovascular risk factor levels. The Tromsø Study.

	HR (95% CI)
ICH (yes/no)	1.43 (1.06-1.93)
Systolic blood pressure (mm Hg)	1.12 (0.98-1.28)
Total cholesterol (mmol/L)	1.03 (0.90-1.18)
Diabetes mellitus (yes/no)	1.44 (0.87-2.38)
Daily smoking (yes/no)	1.64 (1.19-2.24)

[*]HRs were calculated by unadjusted stratified Cox proportional hazards regression models and are expressed per SD increase in continuous variables and presence vs absence of categorical variables.

[†]Cases with first-ever ICH and controls matched by birth year and sex. Cases who died within the first 30 days after ICH were excluded, as were their age- and sex-matched controls.

Appendix I

Questionnaire, Tromsø 1 1974

A

Yes | No

Do you have, or have you had:

- A heart attack? 33
- Angina pectoris (heart cramp)? 34
- Any other heart disease? 35
- Hardened arteries in the legs? 36
- A cerebral stroke? 37
- Diabetes? 38

Are you being treated for:

- High blood pressure? 39

Do you use:

- Nitroglycerine? 40

B

Yes | No

Do you have get or discomfort in the chest when:

- Walking up hills or stairs, or walking fast on level ground? 41
- Walking at normal pace at level ground? . . . 42

If you get pain or discomfort in the chest when walking, do you usually:

1. Stop? 43
2. Slow down? .....
3. Carry on at the same pace? .....

If you stop or slow down, does the pain disappear:

1. Within 10 minutes? 44
2. After more than 10 minutes? .....

Do you get pain in the calf while:

- Walking? 45
- Resting? 46

If you get pain in the calf, then:

- Does the pain increase when you walk faster or uphill? 47
- Does the pain disappear when you stop? 48

Do you usually have:

- Cough in the morning? 49
- Phlegm chest in the morning? 50

C

Yes

Exercise and physical exertion in leisure time.
If your activity varies much, for example between summer and winter, then give an average.
The question refers only to the last twelve months:

Tick "Yes" beside the description that fits best:

1. Reading, watching TV, or other sedentary Activity? 51
2. Walking, cycling, or other forms of exercise at least 4 hours a week? .....
   (include walking or cycling to place of work, Sunday walk/stroll, etc.)
3. Participation in recreational sports, heavy gardening, etc.? .....
   (note: duration of activity at least 4 hours a week)
4. Participation in hard training or sports competitions, regularly several times a week?

D

Yes | No

Do you smoke daily at present? 52

If the answer was "Yes" in the previous question, then:

Do you smoke cigarettes daily? 53
(hand-rolled or factory made)

If you do not smoke cigarettes at present, then:

Have you previously smoked cigarettes daily? 54

If "Yes", how long is it since you stopped:

1. Less than 3 months? 55
2. 3 months to 1 year? .....
3. 1 to 5 years? .....
4. More than 5 years? .....

For those who smoke or have smoked previously:

How many years altogether have you smoked daily? 56-57
No. of years

How many cigarettes do you smoke, or did you, smoke daily? Give number of cigarettes per day 61
(hand-rolled or factory made)
No. of cigarettes

Do you smoke tobacco products other than cigarettes daily?

- Cigars or cigarillos? 62
- A pipe? 63

If you smoke a pipe, how many packs of tobacco (50 grams) do you smoke per week?
Give the average number of packs per week. 64
No. of tobacco packs

E

Yes | No

Do you usually work shifts or at nights? 67

Can you usually come home from work:

- Every day? 68
- Every weekend? 69
- Are there periods during which your working days are longer than usual? 70
  (e.g. fishing season, harvest)

During the last year, have you had:

Tick "Yes" beside description that fits best

1. Mostly sedentary work? 71
   (e.g. office work, watchmaker, light manual work)
2. Work that requires a lot of walking .....
   (e.g. shop assistant, light industrial work, teaching)
3. Work that requires a lot of walking and lifting?
   (e.g. postman, heavy industrial work, construction)
4. Heavy manual labour? .....
   (e.g. forestry, heavy farm-work, heavy construction)

During the last 12 months, have you had to move for work reasons? 72

Is housekeeping your main occupation? 73

Have you within the last 12 months received unemployment benefit? 74

Are you at present on sick leave, or receiving rehabilitation allowance? 75

Do you receive a complete or partial disability pension?

F

Yes | No | Don't know

Have one or more of your parents or sisters or brothers had a heart attack (heart wound) or angina pectoris (heart cramp)? 77

Are two or more of your grandparents of Finnish origin? 78

Are two or more of your grandparents of Sami origin? 79

Appendix IIa

Questionnaire 1, Tromsø 2 1979-1980

A

Yes | No

Do you have, or have you had:

- A heart attack? 33
- Angina pectoris (heart cramp)? 34
- Any other heart disease? 35
- Hardened arteries in the legs? 36
- A cerebral stroke? 37
- Diabetes? 38

Are you being treated for:

- High blood pressure? 39

Do you use:

- Nitroglycerine? 40

B

Yes | No

Do you have get or discomfort in the chest when:

- Walking up hills or stairs, or walking fast on level ground? 41
- Walking at normal pace at level ground? . . . 42

If you get pain or discomfort in the chest when walking, do you usually:

1. Stop? 43
2. Slow down? .....
3. Carry on at the same pace? .....

If you stop or slow down, does the pain disappear:

1. Within 10 minutes? 44
2. After more than 10 minutes? .....

Do you get pain in the calf while:

- Walking? 45
- Resting? 46

If you get pain in the calf, then:

- Does the pain increase when you walk faster or uphill? 47
- Does the pain disappear when you stop? 48

Do you usually have:

- Cough in the morning? 49
- Phlegm chest in the morning? 50

C

Yes

Exercise and physical exertion in leisure time.
If your activity varies much, for example between summer and winter, then give an average.
The question refers only to the last twelve months:

Tick "Yes" beside the description that fits best:

1. Reading, watching TV, or other sedentary Activity? 51
2. Walking, cycling, or other forms of exercise at least 4 hours a week? .....
   (include walking or cycling to place of work, Sunday walk/stroll, etc.)
3. Participation in recreational sports, heavy gardening, etc.? .....
   (note: duration of activity at least 4 hours a week)
4. Participation in hard training or sports competitions, regularly several times a week?

D

Yes | No

Do you smoke daily at present? 52

If the answer was "Yes" in the previous question, then:

Do you smoke cigarettes daily? 53
(hand-rolled or factory made)

If you do not smoke cigarettes at present, then:

Have you previously smoked cigarettes daily? 54

If "Yes", how long is it since you stopped:

1. Less than 3 months? 55
2. 3 months to 1 year? .....
3. 1 to 5 years? .....
4. More than 5 years? .....

For those who smoke or have smoked previously:

How many years altogether have you smoked daily? 56-57
No. of years

How many cigarettes do you smoke, or did you, smoke daily? Give number of cigarettes per day 61
(hand-rolled or factory made)
No. of cigarettes

Do you smoke tobacco products other than cigarettes daily?

- Cigars or cigarillos? 62
- A pipe? 63

If you smoke a pipe, how many packs of tobacco (50 grams) do you smoke per week?
Give the average number of packs per week. 64
No. of tobacco packs

E

Yes | No

Do you usually work shifts or at nights? 67

Can you usually come home from work:

- Every day? 68
- Every weekend? 69
- Are there periods during which your working days are longer than usual? 70
  (e.g. fishing season, harvest)

During the last year, have you had:

Tick "Yes" beside description that fits best

1. Mostly sedentary work? 71
   (e.g. office work, watchmaker, light manual work)
2. Work that requires a lot of walking .....
   (e.g. shop assistant, light industrial work, teaching)
3. Work that requires a lot of walking and lifting?
   (e.g. postman, heavy industrial work, construction)
4. Heavy manual labour? .....
   (e.g. forestry, heavy farm-work, heavy construction)

During the last 12 months, have you had to move for work reasons? 72

Is housekeeping your main occupation? 73

Have you within the last 12 months received unemployment benefit? 74

Are you at present on sick leave, or receiving rehabilitation allowance? 75

Do you receive a complete or partial disability pension?

F

Yes | No | Don't know

Have one or more of your parents or sisters or brothers had a heart attack (heart wound) or angina pectoris (heart cramp)? 77

Are two or more of your grandparents of Finnish origin? 78

Are two or more of your grandparents of Sami origin? 79

Appendix IIb

Questionnaire 2, Tromsø 2 1979-1980

LABEL

TR - II

ADDITIONAL QUESTIONS FOR PERSONS ATTENDING THE MASS X-RAY EXAMINATION IN TROMSØ

Together with the invitation to attend you received a questionnaire from the National Mass Radiography Service. You delivered this questionnaire at the examination.

Cardiovascular diseases are, however, a complex group of diseases. The causes are still partly unknown. In Tromsø we are therefore trying to obtain a more complete description of factors which may be of importance for the course of these diseases, such as diet, psychological pressure ("stress"), social conditions, and occurrence of disease in relatives. We hope you will take the trouble to complete this questionnaire as well, an return it to the Tromsø Board of Health in the enclosed envelope.

All information in connection with the mass x-ray examination will be treated as strictly confidential.

I YOUR OWN DIET

1. What type of bread do you usually eat?
Tick the most appropriate box.

	YES
White bread *(e.g. French bread)*	1
Ordinary bread (light texture)	2
Whole meal (brown) bread	3
Home-made (brown) bread	4

2. What type of butter of margarine do you usually eat?
Tick the most appropriate box.

	YES
Butter	1
Ordinary margarine	2
Plant margarine	3
Soft margarine spread	4

3. How many slices of bread do you usually eat **daily**?
Tick the most appropriate box.

	YES
Less than two slices	1
2-6 slices	2
7-12 slices	3
13 or more slices	4

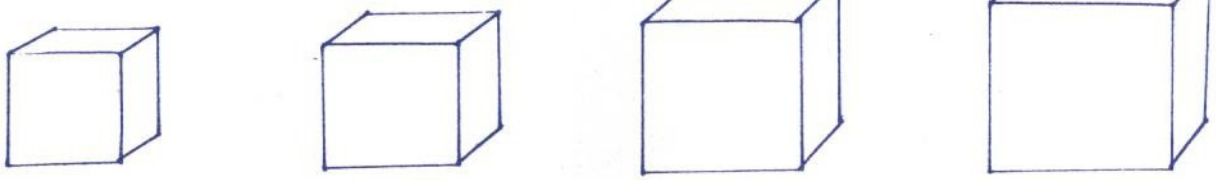
4. What type of milk do you usually drink?
Tick the most appropriate box.

	YES
Do not drink milk	1
Full cream milk: ordinary type or curdled	2
Skimmed milk: ordinary type or curdled	3
Mixture of full cream and skimmed milk	4

5. The drawings below show cubes of butter of margarine (actual size).
Tick the box above the cube which best resembles the amount you spread on a slice of bread.
If in doubt, try buttering a slice.

Do not use butter or margarine ☐

1. ☐ 2. ☐ 3. ☐ 4. ☐



6. How many glasses/cups of milk do you usually drink daily?
Tick the most appropriate box.

	YES
Do not drink milk, or drink less than 1 glass/cup	1
1-2 glasses/cups	2
3-4 glasses/cups	3
5 or more glasses/cups	4

7. How many cups of coffee do you usually drink daily?
Tick the most appropriate box.

	YES
Do not drink coffee, or drink less than 1 cup	1
1-4 cups	2
5-8 cups	3
9 or more cups	4

8. Are you a teetotaller?

	YES	No

If "No",

— How often do you usually drink beer?
Tick the most appropriate box.

	YES
Never or just a few times a year	1
Once or twice a month	2
About once a week	3
2-3 times a week	4
More or less daily	5

— How often do you usually drink wine?
Tick the most appropriate box.

	YES
Never or just a few times a year	1
Once or twice a month	2
About once a week	3
2-3 times a week	4
More or less daily	5

— How often do you usually drink spirits?
Tick the most appropriate box.

	YES
Never or just a few times a year	1
Once or twice a month	2
About once a week	3
2-3 times a week	4
More or less daily	5

9. Approximately how often during the last 12 months have you drunk so much wine, beer or spirits that you got drunk?
Tick the most appropriate box.

	YES
Have never been drunk, or have not been drunk during the last year	1
A few times during the last year	2
Once or twice a month	3
Once or twice a week	4
3 or more times a week	5

10. How often does your main meal consist of fish or fish dishes?
Tick the most appropriate box.

	YES
Less than once a week	1
Once or twice a week	2
3-4 times a week	3
5-6 times a week	4
7 times a week	5

11. How often do you eat fruit or vegetables?
Tick the most appropriate box.

	YES
Never eat fruit or vegetables	1
A few time a year	2
Once or twice a month	3
About once a week	4
2-3 times a week	5
More or less daily	6

12. How many times a month do you eat boiled or fried sausages, meat balls, other processed meat, etc.?
Tick the most appropriate box.

	YES
Never or less than once a month	1
Once or twice a month	2
3-4 times a month (up to once a week)	3
5-8 times a month (up to twice a week)	4
More than 8 times a month (more than twice a week)	5

13. Have you made any changes in your diet during the last 5 years as regards the following food items?
Tick each item in the appropriate box.

	As before	More now	Less now
Ordinary margarine or butter			
Skimmed milk			
Lean meat			
Full cream milk			
Soya margarine (soft)			
Fatty meat			

II OWN ILLNESSES PAST AND PRESENT

	YES	No
14. Have you ever had?		
Sudden paralysis or numbness on one side of your face or body, in your hand or foot		
Sudden loss of ability to speak		
Sudden loss of eye sight, complete or partial, or sudden onset of double vision		
15. Have you had a peptic ulcer?		
Do you often have a gnawing pain in the upper part of your stomach?		
Do you suffer much from heartburn or regurgitation of gastric juices?		
Do you suffer much from wind and rumbling in your stomach?		
Do you often get cramps in your stomach?		
Have you ever had your large intestine x-rayed?		
Have you ever had gallstones?		
16. Have you had kidney stones or stones in the urinary tract?		
If yes, how many times? (no. of times)		
and, when did you have the last attack? (Year)		
17. Have you ever had cancer?		
If yes, in what year was the disease discovered? (Year)		
18. Do you have, or have had you the skin disease psoriasis?		
19. Have you had allergy-induced eczema on your hands during the last 12 months?		
20. Have you been on sick leave, or been unable to work due to allergic eczema on your hands at any time during the past 3 years?		
21. Have you ever had arthritis? (chronic rheumatoid arthritis)		
22. Have you suffered from back pain during the past 12 months lasting for more than 4 weeks?		
If yes, did the back pain improve if you exercised?		
23. Have you suffered from morning stiffness in your back lasting more than 30 minutes?		
24. Have you suffered from pains lasting more than 3 months, in the joints listed below during the last 3 years?		
Knees		
Elbows		
Innermost finger joints		
Other joints		
If yes, did you suffer from stiff joints in the mornings lasting more than 30 minutes?		
25. Have you had any infectious disease during the past 14 days? (influenza, common cold, vomiting, diarrhoea, etc.)		
26. Have you taken iron tablets during the past 14 days?		

27. How often do you take painkillers such as Globoid, Novid, Dispril, Albyl, etc.? Tick the most appropriate box.

	YES	No
1-3 times a week 1		
1-3 times a month 2		
Seldom or never 3		
Have you used such painkillers during the last 14 days?		

28. Have you changed the amount of physical exercise you take in leisure time during the last five years? Tick the most appropriate box.

	YES
As before 1	
More than before 2	
Less than before 3	

III ILLNESS IN PARENTS AND SIBLINGS

29. Have any of these relatives had:

	mother	father	sister	brother
Cerebral stroke or brain haemorrhage				
Diabetes				
Arthritis (chronic rheumatoid arthritis)				
Cancer				
Kidney stones or stone in urinary tract				
Psoriasis				
Peptic ulcer				
None of the above mentioned illnesses				

IV SOCIAL CONDITIONS AND PSYCHOLOGICAL PRESSURE ("STRESS")

30. How many years of education have you had? (including primary and secondary schools) — no. of years

31. How was your family's financial situation when you were growing up? Tick the most appropriate box.

	YES
Very good 1	
Good 2	
Poor 3	
Very poor 4	

32. Do you suffer from sleeplessness? If yes, at what time of the year do you suffer from sleeplessness? Tick the most appropriate box.

	YES	No
No particular time 1		
Especially during the polar night 2		
Especially during the midnight sun season 3		
Especially in spring and autumn 4		
What form does your sleeplessness take?		
Difficult to fall asleep at night? 1		
Wake up a lot during the night? 2		
Wake up very early in the morning? ... 3		

33. Have you had difficulty sleeping in the past couple of weeks? Tick the most appropriate box.

	YES
Not at all 1	
No more than usual 2	
Rather more than usual 3	
Much more than usual 4	

34. Have you felt unhappy and depressed during the last couple of weeks? Tick the most appropriate box.

	YES
Not at all	
No more than usual 2	
Rather more than usual 3	
Much more than usual 4	

35. Have you felt unable to cope with your difficulties during the last couple of weeks? Tick the most appropriate box.

	YES
Not at all 1	
No more than usual 2	
Rather more than usual 3	
Much more than usual 4	

Appendix IIIa

Questionnaire 1, Tromsø 3 1986-1987

THE TROMSØ HEALTH SURVEY

(Applies only to the person to whom the letter is addressed.)

The health survey is coming now to your district.

You find the time and place for attendance below.

You will find an orientation on the survey in the enclosed brochure.

We would like you to fill in the form on the back and take it with you to the survey.

We ask those possibly not attending to report their absence in the attached absence report.

Yours sincerely

MUNICIPAL HEALTH AUTHORITY OF TROMSØ
COUNTY DOCTOR OF TROMS UNIVERSITY OF TROMSØ
NATIONAL HEALTH SCREENING SERVICE

Birth date | Personal number | Municipality | Circuit number

Meeting place | Gender | First letter of last name | Day and date | Time

HEIGHT | WEIGHT | ANM 70 | M | P | Ø | KODE 75 | AVVIK | ARM | MAN | APP.NR. | TSM 82

MEASUREMENT 1	MEASUREMENT 2	MEASUREMENT 3
MAR 85 S 88	MAR 91 S 94	MAR 97 S 100
HR 103 D 106	HR 109 D 112	HR 115 D 118

A FAMILY

Have one or more of your parents or siblings had a heart attack (heart wound) or angina pectoris (heart cramp)? 12

Yes | No | Don't know

B OWN ILLNESSES

Do you have, or have you had:

A heart attack? 13
Angina pectoris (heart cramp)? 14
A cerebral stroke? 15
Diabetes? 16

Yes | No

Are you being treated for:

High blood pressure? 17

Do you use:

Nitroglycerine? 18

C SYMPTOMS

Do you get pain or discomfort in the chest when:

Yes | No

Walking up hills or stairs, or walking fast on level ground? 19
Walking at normal pace at level ground? 20

If you get pain or discomfort in the chest when walking, do you usually:

Stop? 21
Slow down? .....
Carry on at the same pace? .....

1 2 3

If you stop or slow down, does the pain disappear:

After less than 10 minutes? 22
After more than 10 minutes? .....

1 2

Do you usually have:

Yes | No

Cough in the morning? 23
Phlegm chest in the morning? 24

D EXERCISE

Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The question refers only to the last year:

Tick the most appropriate box.

Reading, watching TV, or other sedentary activity? 25

1

Walking, cycling or other forms of exercise at least 4 hours a week? .....
(include walking or cycling to work, Sunday walk/stroll, etc.)

2

Participation in recreational sports, heavy gardening, etc.? .....
(note: duration of activity at least 4 hours a week)

3

Participation in hard training or sports competitions, regularly several times a week? ...

4

E SALT/ FAT

How often do you use salted meat or salted fish for dinner?

Tick the most appropriate box.

Never or less than once a month 26
Once a week or less .....
Twice a week or less .....
More than twice a week.....

1 2 3 4

How often do you add extra salt to your dinner?

Tick the most appropriate box.

Rarely or never 27
Sometimes or often .....
Always or nearly always .....

1 2 3

What type of margarine or butter do you usually use on your bread?

Tick the most appropriate box.

Do not use margarine or butter on bread 28
Butter .....
Hard Margarine .....
Soft (soya) margarine spread.....
Butter/ margarine mixtures .....

1 2 3 4 5

What type of cooking fat do you normally use in your household?

Tick the most appropriate box.

Butter or hard margarine 29
Soft (soya) margarine or oil .....
Butter/ margarine mixtures .....

1 2 3

F SMOKING

Yes | No

Do you smoke daily at present? 30

If the answer is "YES", then:

Do you smoke cigarettes daily? 31
(hand-rolled or factory made)

If you do not smoke cigarettes at present, then:

Have you previously smoked cigarettes daily? ... 32

If you answered "Yes", how long is it since you stopped:

Less than 3 months? 33
3 months to 1 year? .....
1 -5 years? .....
More than 5 years? .....

1 2 3 4

To be answered by those who smoke or who have smoked previously:

How many years altogether have you smoked daily? 34

Year

How many cigarettes do you smoke or did you smoke daily? .....
Give number of cigarettes per day 36
(hand-rolled + factory made)

Cigarettes

Do you smoke anything else other than cigarettes daily?

Cigars or cigarillos/cheroots? 40
A pipe? 41

If you smoke a pipe, how many packs of tobacco (50 grams) do you smoke per week?

Give the average number of packs per week 42

Tobacco packets

G COFFEE

How many cups of coffee do you usually drink daily?

Tick the most appropriate box.

Do not drink coffee, or less than one cup 45
1 -4 cups .....
5 -8 cups .....
9 or more cups .....

1 2 3 4

What type of coffee do you usually drink daily?

Coarsely ground coffee for brewing (boiled) 46
Finely ground filter coffee 47
Instant coffee 48
Caffeine free coffee 49
Do not drink coffee 50

H EMPLOYMENT

Yes | No

Have you within the last 12 months received unemployment benefit? 51

Are you at present on sick leave, or receiving rehabilitation benefit? 52

Do you receive a complete or partial disability pension? 53

Do you usually work shifts or at night? 54

During the last year, have you had:

Tick the most appropriate box.

Mostly sedentary work? 55
(e.g. office work, watchmaker, light manual work)

1

Work that requires a lot of walking? .....
(e.g. shop assistant, light industrial work, teaching)

2

Work that requires a lot of walking and lifting? ...
(e.g. postman, heavy industrial work, construction)

3

Heavy manual labour? .....
(e.g. forestry, heavy farm-work, heavy construction)

4

Yes | No

Is house-keeping your main occupation? ... 56

I FOLLOW-UP EXAMINATION

Has any one in your household (other than yourself) been called in to a doctor for further medical examination after the previous cardiovascular disease survey? 57

If this survey suggests that you need a further medical examination, which general practitioner do you wish to be referred to?

Write the doctor's name here?

..... 58

No particular doctor 61

Don't write here

Appendix IIIb

Questionnaire 2, Tromsø 3 1986-1987

ADDITIONAL QUESTIONS TO THE TROMSØ HEALTH SURVEY 1986-87.

Cardiovascular heart and circulatory diseases, on which the surveys of the 1974 and 1979-80 focused, are a very varied category of diseases whose causes are still partly unknown. In Tromsø we are therefore trying to obtain a more complete description of factors which may be important for the course of these diseases, such as diet, psychological pressure, "stress", social conditions and the occurrence of disease in relatives. Such a description is also important in the search of factors that contribute to cancer, a group of diseases which also we try to combat in the coming years.

When you were called in, you received a questionnaire which you handed in at the survey. The present questionnaire asks for further information about your health and includes questions on various diseases and physical and psychological complaints. We have included questions on pregnancy, birth and menstruation.

In addition, we are interested in obtaining information on the public use of medical health services in order to find out how to improve the health service.

We hope that you will take the trouble to fill in yet another questionnaire and return it to "Tromsø Board of Health" in the enclosed envelope. All information will be treated with strict confidentiality If you have any comments regarding the survey, you may write them down in the space provided on the last page of the questionnaire.

Yours sincerely

Tromsø Board of Health

Department of medicine
University of Tromsø

GENERAL STATE OF HEALTH

How is your health?
Tick the box where "Yes" is appropriate.

		Yes
Very bad	12	☐ 1
Bad		☐ 2
Neither good nor bad, "middling"		☐ 3
Good		☐ 4
Excellent		☐ 5

ILLNESSES

Do you have, or have you had:
Tick "Yes" or "No" for each question.

		Yes	No
The skin disease psoriasis	13	☐	☐
Asthma	14	☐	☐
Allergic eczema	15	☐	☐
Hay fever	16	☐	☐
Chronic bronchitis	17	☐	☐
Gastric ulcer	18	☐	☐
Duodenal ulcer	19	☐	☐
Your appendix removed	20	☐	☐
An operation for a stomach ulcer	21	☐	☐
Chronic rheumatoid arthritis	22	☐	☐
Cancer	23	☐	☐
Epilepsy	24	☐	☐
Migraine	25	☐	☐

INFECTIONS

		Number / Yes	No
How many times in the last 6 months have you had infections like a cold, influenza (flu) diarrhoea/vomiting, or similar illnesses?	26	☐	
Have you had one of these infections in the past 14 days?	27	☐	☐

ILLNESSES IN PARENTS OR SIBLINGS

Tick for the relatives who have or have ever had any of the following illnesses:

		mother	father	brother	Sister
Cerebral stroke or brain haemorrhage	28	☐	☐	☐	☐
Diabetes	32	☐	☐	☐	☐
Rheumatoid arthritis	36	☐	☐	☐	☐
Cancer	40	☐	☐	☐	☐
Psoriasis	44	☐	☐	☐	☐
Gastric or duodenal ulcer	48	☐	☐	☐	☐
Asthma	52	☐	☐	☐	☐

		Yes	No
Tick if none of the relatives have or have had any of those illnesses	56	☐	☐

MEDICINES

		Yes	No
Have you during the last year used tablets/sprays or had injections for asthma or allergies?	60	☐	☐

Have you used any of the following medicines in the past 14 days?

		Yes	No
Painkillers	61	☐	☐
Antipyretic drugs (to reduce fever)	62	☐	☐
Eczema ointment	63	☐	☐
Blood pressure medicines	64	☐	☐
Heart medicines	65	☐	☐
Sleeping pills	66	☐	☐
Nerve tablets	67	☐	☐
Migraine drugs	68	☐	☐
Epilepsy drugs	69	☐	☐
Other medicines	70	☐	☐

CONTACT DUE TO OWN HEALTH OR ILLNESS

How many visits have you made during the past year due to your own health or illness?

Number of visits

- To a GP (general practitioner) ..... 71 ☐
- To a specialist (not hospital) ..... 72 ☐
- Emergency GP ..... 85 ☐
- Medical officer at work ..... 87 ☐
- Physiotherapist ..... 89 ☐
- Chiropractor ..... 81 ☐
- Alternative practitioner (homoeopath, foot zone therapist, etc.) .. 83 ☐
- Hospital outpatient department ..... 85 ☐

Number of hospital admissions in the past year . 87 ☐

DIET

How many slices of bread do you usually eat daily?
Tick the box where "Yes" is appropriate.

Yes

- Less than 2 slices ..... 88 ☐ 1
- 2 - 4 slices ..... ☐ 2
- 5 – 6 slices ..... ☐ 3
- 7 – 12 slices ..... ☐ 4
- 13 or more slices ..... ☐ 5

What type of milk do you usually drink?
Tick the box where "Yes" is appropriate.

Yes

- Do not drink milk ..... 89 ☐ 1
- Full cream milk (ordinary or curdled) ..... ☐ 2
- Semi-skimmed milk ..... ☐ 3
- Skimmed milk (ordinary or curdled) ..... ☐ 4

How many glasses/cups of milk do you usually drink daily?

Yes

- Less than 1 glass/cup ..... 90 ☐ 1
- 1 – 2 glasses/cups ..... ☐ 2
- 3 – 4 glasses/cups ..... ☐ 3
- 5 or more glasses/cups ..... ☐ 4

FISH

How often do you eat cod/pollock or other lean fish for dinner or in a sandwich?
Tick the box where "Yes" is appropriate.

Yes

- Less than once a week ..... 91 ☐ 1
- Once a week ..... ☐ 2
- Twice a week ..... ☐ 3
- 3 or more times a week ..... ☐ 4

How often do you eat fatty fish such as herring, halibut, red fish, mackerel, salmon or trout for dinner or in a sandwich?
Tick the box where "Yes" is appropriate.

Yes

- Less than once a week ..... 92 ☐ 1
- Once a week ..... ☐ 2
- Twice a week ..... ☐ 3
- 3 or more times a week ..... ☐ 4

Do you take cod liver oil regularly?
Tick the box where "Yes" is appropriate.

Yes

- No ..... 93 ☐ 1
- During polar night ..... ☐ 2
- All year ..... ☐ 3

BREAKFAST

Yes No

Do you usually eat breakfast daily? ..... 94 ☐ ☐

DINNER

How often do you eat meat for dinner?
Tick the box where "Yes" is appropriate.

Yes

- Less than once a week ..... 95 ☐ 1
- Once or twice a week ..... ☐ 2
- 3 – 4 times a week ..... ☐ 3
- 5 or more times a week ..... ☐ 4

How often do you use fat like butter, margarine, mayonnaise, etc. with your dinner?
Tick the box where "Yes" is appropriate.

Yes

- Less than once a week ..... 96 ☐ 1
- Once or twice a week ..... ☐ 2
- 3 – 4 times a week ..... ☐ 3
- 5 or more times a week ..... ☐ 4

Yes No

Do you usually eat vegetables with your dinner? ..... 97 ☐ ☐

FRUIT

How often do you usually eat fruit?
Tick the box where "Yes" is appropriate.

Yes

- Less than once a week ..... 98 ☐ 1
- About once a week ..... ☐ 2
- 2 – 3 times a week ..... ☐ 3
- 4 – 5 times a week ..... ☐ 4
- More or less ..... ☐ 5

ALCOHOL

Yes No

Are you a teetotaller? ☐ ☐

If not,
- How often do you usually drink beer?
Tick the box where "Yes" is appropriate.

Yes

- Never or just a few times a year ..... 100 ☐ 1
- 1 – 2 times a month ..... ☐ 2
- About once a week ..... ☐ 3
- 2 – 3 times a week ..... ☐ 4
- More or less daily ..... ☐ 5

How often do you usually drink wine?
Tick the box where "Yes" is appropriate.

Yes

- Never or just a few times a year ..... 101 ☐ 1
- 1 – 2 times a month ..... ☐ 2
- About once a week ..... ☐ 3
- 2 – 3 times a week ..... ☐ 4
- More or less daily ..... ☐ 5

- How often do you usually drink spirits?
Tick the box where "Yes" is appropriate.

Yes

- Never or just a few times a year ..... 102 ☐ 1
- 1 – 2 times a month ..... ☐ 2
- About once a week ..... ☐ 3
- 2 – 3 times a week ..... ☐ 4
- More or less daily ..... ☐ 5

Approximately how often have you during the last year consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?
Tick the box where "Yes" is appropriate.

Yes

- Not at all the past year ..... 103 ☐ 1
- A few times ..... ☐ 2
- Once or twice a month ..... ☐ 3
- 3 or more times a week ..... ☐ 4

PHYSICAL ACTIVITY

How often do you take part in physical activity lasting at least 20 minutes, which makes you perspire or become breathless?
Tick the box where "Yes" is appropriate.

		Yes
Rarely or never	104	☐ 1
Weekly		☐ 2
Several times a week		☐ 3
Daily		☐ 4

If you usually take part in this type of activity at least weekly, how much time do you spend exercising?
Tick the box where "Yes" is appropriate.

		Yes
Less than 30 minutes a week	105	☐ 1
Between 30 minutes and 1 hour a week		☐ 2
Between 1 and 2 hours a week		☐ 3
More than 2 hours a week		☐ 4

CHANGE IN DIETARY HABITS AND OTHER HABITS

Have you changed any of the following habits during the last 5 years: (Tick once for each question)

		Now use more	As before	Less
Dietary fat	106	☐	☐	☐
Soya margarine or oil	107	☐	☐	☐
Skimmed or low fat milk	108	☐	☐	☐
Coffee intake	109	☐	☐	☐
Alcohol intake	110	☐	☐	☐
Physical activity	111	☐	☐	☐

MARRIAGE / PARTNER

		Yes	No
Are you married or partner	112	☐	☐

How old were you when you first married or Moved in with a partner? 113 ☐ years

HOUSEHOLD

How many people live in your household? 115 ☐ Number

		Yes	No
Is anyone in your household 10 years or younger?	117	☐	☐
Does anyone in your household need special care/assistance – other than the children?	118	☐	☐

SCHOOLING

How many years education have you had? (including primary and secondary schools) 119 ☐ years

EMPLOYMENT

Have you had paid work the entire past year?
Tick the box where "Yes" is appropriate.

		Yes
Full-time work	121	☐ 1
Part-time work		☐ 2
Unpaid work		☐ 3

How much house work do you normally do yourself?
Tick the box where "Yes" is appropriate.

All or almost all	122	☐ 1
At least half		☐ 2
More than quarter		☐ 3
Less than quarter		☐ 4

BACK AND JOINTS CONDITIONS

		Yes	No
During this last year have you suffered from back pain that has lasted longer than 4 weeks?	123	☐	☐
If yes, does the pain improve when you move around?	124	☐	☐
Have you suffered from morning stiffness in your back lasting more than 30 minutes?	125	☐	☐

During the past 3 years have you suffered from pain in any of the following joints lasting more than 30 minutes?

		Yes	No
Knees	126	☐	☐
Elbows	127	☐	☐
Innermost finger joints	128	☐	☐
Other joints	129	☐	☐

		Yes	No
If yes, have you suffered from stiff joints in the morning lasting more than 30 minutes?	130	☐	☐

NECK, HEAD AND SHOULDER COMPLAINTS

How often do you suffer from headache?
Tick the box where "Yes" is appropriate.

		Yes
Rarely of never	131	☐ 1
Once or more a month		☐ 2
Once or more a week		☐ 3
Daily		☐ 4

How often do you suffer pain in the neck or shoulder?
Tick the box where "Yes" is appropriate.

		Yes
Rarely of never	132	☐ 1
Once or more a month		☐ 2
Once or more a week		☐ 3
Daily		☐ 4

Do the pains in your head, neck or shoulder reduce your ability to work?
Tick the box where "Yes" is appropriate.

		Yes
Little or no effect	133	☐ 1
To some degree		☐ 2
To a large degree		☐ 3
Cannot do ordinary work		☐ 4

		Yes	No
Have your back, shoulder, and/or neck ever been x-rayed?	134	☐	☐

SLEEPLESSNESS/ LOSS OF CONSCIOUSNESS

		Yes	No
Have you ever suffered from sleeplessness?	135	☐	☐

If yes, what time of the year does it affect you most? Tick the box where "Yes" is appropriate.

		Yes
No particular time	136	☐ 1
Especially during the polar night		☐ 2
Especially during the midnight sun season		☐ 3
Especially in spring and autumn		☐ 4

		Yes	No
Have you at any time during the last 12 months suffered from tiredness that has affected your work performance?	137	☐	☐
Have you suffered from sudden loss of consciousness in the past year?	138	☐	☐
Have you noticed sudden changes in your pulse rate of heartbeat in the past year?	139	☐	☐

REACTION TO PROBLEMS

If you have major personal problems, do you expect to get help and support from your spouse or family? ..... 140 — Yes ☐ No ☐

In the last year, have you for a long time felt a need to seek help with personal problems, without doing so? ..... 141 — Yes ☐ No ☐

During the past 2 weeks have you felt unable to cope with your problems?
Tick the box where "Yes" is appropriate.
- Seldom or never ..... 142 — Yes ☐ 1
- Sometimes ..... ☐ 2
- Often ..... ☐ 3
- Nearly always ..... ☐ 4

During the past 2 weeks have you felt unhappy or depressed?
Tick the box where "Yes" is appropriate.
- Seldom or never ..... 143 — Yes ☐ 1
- Sometimes ..... ☐ 2
- Often ..... ☐ 3
- Nearly always ..... ☐ 4

Do you ever feel lonely?
Tick the box where "Yes" is appropriate.
- Very often ..... 144 — Yes ☐ 1
- Sometimes ..... ☐ 2
- Rarely or never ..... ☐ 3

THE REMAINING SECTION OF THE QUESTIONNAIRE APPLIES TO WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 145 — ☐ years

When did your last period start? ..... 147 — day / month / year

How many days usually pass from the first day of one period to the first day of your next period (the time lapsed between the start of two periods) ..... 153 — ☐ days

Do/ did you menstruate regularly? ..... 155 — Yes ☐ No ☐

Do you usually take painkillers during menstruation? ..... 156 — Yes ☐ No ☐

PRE-MENSTRUAL TENSION

Do you have any of the following complaints before your period:
- Are you depressed or irritable?
Tick the box where "Yes" is appropriate.
  - Hardly at all ..... 157 — Yes ☐ 1
  - Noticeably ..... ☐ 2
  - Very much so ..... ☐ 3
- Are your breasts painful?
Tick the box where "Yes" is appropriate.
  - Hardly at all ..... 158 — Yes ☐ 1
  - Noticeably ..... ☐ 2
  - Very much so ..... ☐ 3
- Do you have swollen hands/feet, put on weight, or feel bloated?
Tick the box where "Yes" is appropriate.
  - Hardly at all ..... 159 — Yes ☐ 1
  - Noticeably ..... ☐ 2
  - Very much so ..... ☐ 3

Do the complaints disappear when you get your period? ..... 160 — Yes ☐ No ☐

For these complaints, do you use?
- diuretics? ..... 161 — Yes ☐ No ☐
- other medications? ..... 162 — ☐ ☐

PREGNANY

How many children have given birth to? .... 163 — number ☐

How old were you when you got pregnant for the first time? ..... 164 — ☐ years

CONTRACEPTION

Do you use or have you ever used oral contraceptive pills or an intrauterine device? ..... 166 — Yes ☐ No ☐

If yes, for how many years altogether have you used:
- The pill? ..... 167 — ☐ years
- An intrauterine device? ..... 169 — ☐ years

How old were you when you started using:
- The pill? ..... 171 — ☐ years
- An intrauterine device? ..... 173 — ☐ years

If you have stopped taking the pill, did 6 months or more pass without menstruating without you being pregnant? 175 — Yes ☐ No ☐

Did you have to stop taking the pill due to high blood pressure? ..... 176 — Yes ☐ No ☐

CERVICAL SMEAR TEST

How many times have you had a cervical smear test in the last 3 years? ..... 177 — Number of tests ☐

How many years is it since you had your last cervical smear test? ..... 178 — ☐ years

Your comments: 179

Thank you for the help! Remember to post the questionnaire today!

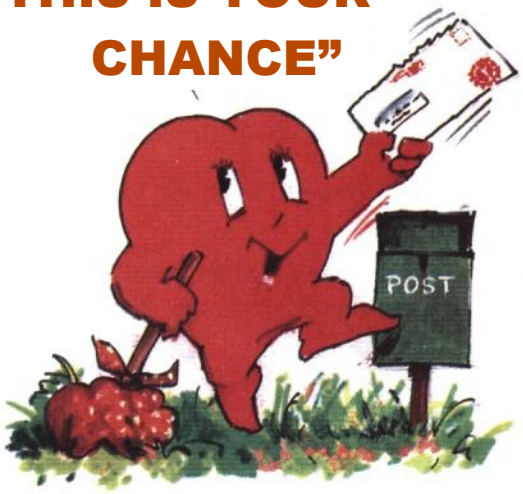
The Tromsø survey 1986-1987

Appendix IV

Questionnaire 1, Tromsø 4 1994-1995

HEALTH SURVEY
Invitation

"THIS IS YOUR CHANCE"



Date of birth **Social security No.** **Municipality** **Electoral ward No.**

Welcome to the Tromsø Health Survey!

The Health Survey is coming to Tromsø. This leaflet will tell you when and where. You will also find information about the survey in the enclosed brochure.

We would like you to fill in the form overleaf and take it with you to the examination.

The more people take part in the survey, the more valuable its results will be. We hope, therefore, that you will be able to come. Attend even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure measured recently.

Yours sincerely,
Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service

"THIS IS A REAL OPPORTUNITY- TAKE IT!"

YOUR OWN HEALTH

What is your current state of health? *Tick one box only.*

Poor	12	1
Not so good		2
Good		3
Very good		4

Do you have, or have you had:

	Yes	No	Age first time
A heart attack	13		years
Angina pectoris (heart cramp)	16		years
A cerebral stroke/ brain haemorrhage	19		years
Asthma	22		years
Diabetes	25		years

Do you use blood pressure lowering drugs?

Currently	28	1
Previously, but not now		2
Never used		3

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months? 29 Yes / No

Have you in the last two weeks felt:

	No	A little	A lot	Very much
Nervous or worried? 30				
Anxious? 31				
Confident and calm? 32				
Irritable? 33				
Happy and optimistic? 34				
Down/depressed? 35				
Lonely? 36				
	1	2	3	4

SMOKING

Did any of the adults at home smoke while you were growing up? 37 Yes / No

Do you currently, or did you previously, live together with daily smokers after your 20th birthday? 38 Yes / No

If "YES", for how many years in all? 39 ____ Years

How many hours a day do you normally spend in smoke-filled rooms? 41 ____ Hours

Put 0 if you do not spend time in smoke-filled rooms.

Do you yourself smoke:

	Yes	No
Cigarettes daily? 43		
Cigars/ cigarillos daily? 44		
A pipe daily? 45		

If you previously smoked daily, how long is it since you quit? 46 ____ Years

If you currently smoke, or have smoked previously:

How many cigarettes do you or did you usually smoke per day? 48 ____ cigarettes

How old were you when you began daily smoking? 52 ____ Age years

How many years in all have you smoked daily? 54 ____ Years

EXERCISE

How has your physical activity in leisure time been during this last year? *Think of your weekly average for the year.*

Time spent going to work counts as leisure time.

	Hours per week: None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)* 56				
Hard activity *(sweating/ out of breath)* 57				
	1	2	3	4

COFFEE

How many cups of coffee do you drink daily?

Put 0 if you do not drink coffee daily.

Coarsely ground coffee for brewing 58 ____ Cups

Other coffee 60 ____ Cups

ALCOHOL

Are you a teetotaller? 62 Yes / No

How many times a month do you normally drink alcohol? *Do not count low-alcohol beer.*

Put 0 if less than once a month. 63 ____ Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? 65

Do not count low-alcohol beer.

Put 0 if less than once a month.

Beer	Wine	Spirits
Glasses	Glasses	Glasses

FAT

What type of margarine or butter do you usually use on bread? *Tick one box only.*

Don't use butter/margarine	71	1
Butter		2
Hard margarine		3
Soft margarine		4
Butter/margarine mixtures		5
Light margarine		6

EDUCATION/WORK

What is the highest level of education you have completed?

7-10 years primary/secondary school, modern secondary school	72	1
Technical school, middle school, vocational school, 1-2 years senior high school		2
High school diploma (3-4 years)		3
College/university, less than 4 years		4
College/university, 4 or more years		5

What is your current work situation?

Paid work	73	
Full-time housework	74	
Education, military service	75	
Unemployed, on leave without payment	76	

How many hours of paid work do you have per week? 77 ____ No. of hours

Do you receive any of the following benefits?

Sickness benefit (sick leave)	79	
Rehabilitation benefit	80	
Disability pension	81	
Old-age pension	82	
Social welfare benefit	83	
Unemployment benefit	84	

ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)? 85

Yes	No	Don't know

Appendix IVb

Questionnaire 2 (<70 years), Tromsø 4 1994-1995

The Tromsø Health Survey

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.

This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are in doubt about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire ..... 17 ☐

Day Month Year

Date for filling in this form:..... 18 ...../...../.....

CHILDHOOD/YOUTH

In which Norwegian municipality did you live at the age of 1 year?

..... 24 - 28

If you did not live in Norway, give country of residence instead of municipality.

How was your family's financial situation during your childhood?

- Very good ..... 29 ☐
- Good ..... ☐
- Difficult ..... ☐
- Very difficult ..... ☐

How many of the first three years of your life

- did you live in a town/city? ..... 30 ____years
- did your family have a cat or dog in the home? ..... 31 ____years

How many of the first 15 years of your life

- did you live in a town/city? ..... 32 ____years
- did your family have a cat or dog in the home? ..... 34 ____years

HOME

Who do you live with?

Tick once for each item and give the number .		Yes	No	Number
Spouse/partner	36	☐	☐	
Other people over 18 years	37	☐	☐	_____
People under 18 years	40	☐	☐	_____

How many of the children attend day care/kindergarten? .... 43 _____

What type of house do you live in?

- Villa/detached house ..... 45 ☐ 1
- Farm ..... ☐ 2
- Flat /apartment ..... ☐ 3
- Terraced /semi-detached house ..... ☐ 4
- Other ..... ☐ 5

How big is your house? ..... 46 _____ m^2

Approximately what year was your house built? ..... 49 _____

		Yes	No
Has your house been insulated after 1970?	53	☐	☐
Do you live on the lower ground floor/basement?	54	☐	☐
If "Yes", is the floor laid on concrete?	55	☐	☐

What is the main source of heat in your home?

- Electric heating ..... 56 ☐
- Wood-burning stove ..... ☐
- Central heating system using:
  - Paraffin ..... ☐
  - Electricity ..... ☐

		Yes	No
Do you have fitted carpets in the living room?	60	☐	☐
Is there a cat in your home?	61	☐	☐
Is there a dog in your home?	62	☐	☐

WORK

If you have paid or unpaid work, how would you describe your work?

- Mostly sedentary work? ..... 63 ☐ 1
  (e.g. office work, mounting)
- Work that requires a lot of walking? ..... ☐ 2
  (e.g. shop assistant, light industrial work, teaching)
- Work that requires a lot of walking and lifting? ..... ☐ 3
  (e.g. postman, nursing, construction)
- Heavy manual work? ..... ☐ 4
  (e.g. forestry, heavy farm-work, heavy construction)

Can you decide yourself how your work should be organised?

- No, not at all ..... 64 ☐ 1
- To a small extent ..... ☐ 2
- Yes, to a large extent ..... ☐ 3
- Yes, I decide myself ..... ☐ 4

		Yes	No
Are you on call, do you work shifts or nights?	65	☐	☐

Do you do any of the following jobs (full- or part-time)?

Tick one box only for each item.		Yes	No
Driver	66	☐	☐
Farmer		☐	☐
Fisherman		☐	☐

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time.
*If you have had the condition several times, how old were you **last** time?*

	Yes	No	Age
Hip fracture 69	☐	☐	_____
Wrist/forearm fracture 72	☐	☐	_____
Whiplash 75	☐	☐	_____
Injury requiring hospital admission 78	☐	☐	_____
Gastric ulcer 81	☐	☐	_____
Duodenal ulcer 84	☐	☐	_____
Gastric/duodenal ulcer surgery 87	☐	☐	_____
Neck surgery 90	☐	☐	_____

Have you you ever had, or do you still have:
Tick one box only for each item.

	Yes	No
Cancer 93	☐	☐
Epilepsy	☐	☐
Migraine	☐	☐
Chronic bronchitis	☐	☐
Psoriasis	☐	☐
Osteoporosis 98	☐	☐
Fibromyalgia/fibrositis/chronic pain syndrome	☐	☐
Psychological problems for which you have sought help	☐	☐
Thyroid disease	☐	☐
Liver disease	☐	☐
Kidney disease 103	☐	☐
Appendectomy	☐	☐
Allergy and hypersensitivity:		
Atopic eczema (e.g. childhood eczema)	☐	☐
Hand eczema	☐	☐
Hay fever	☐	☐
Food allergy 108	☐	☐
Other hypersensitivity (not allergy)	☐	☐

How many times have you had a cold, influenza (flu), vomiting/diarrhoea, or similar in the last six months? ____ times

	Yes	No
Have you had this in the last 14 days? 112	☐	☐

ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
Tick "None" if none of your relatives have had the disease.

	Mother	Father	Brother	Sister	Child	None
Cerebral stroke or brain haemorrhage 113	☐	☐	☐	☐	☐	☐
Heart attack before age 60 119	☐	☐	☐	☐	☐	☐
Cancer 125	☐	☐	☐	☐	☐	☐
Asthma 131	☐	☐	☐	☐	☐	☐
Gastric/duodenal ulcer 137	☐	☐	☐	☐	☐	☐
Osteoporosis 143	☐	☐	☐	☐	☐	☐
Psychological problems 149	☐	☐	☐	☐	☐	☐
Allergy 155	☐	☐	☐	☐	☐	☐
Diabetes 161	☐	☐	☐	☐	☐	☐
– age when they got diabetes 167	___	___	___	___	___	

SYMPTOMS

	Yes	No
Do you cough about daily for some periods of the year? ..177	☐	☐
If "Yes":		
Is your cough productive ? 178	☐	☐
Have you had this kind of cough for as long as 3 months in each of the last two years? 179	☐	☐
Have you had episodes of wheezing in your chest? ..180	☐	☐
If "Yes", has this occurred:		
Tick one box only for each item.		
At night 181	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐
Have you noticed sudden changes in your pulse or heart rhythm in the last year? 185	☐	☐

How often do you suffer from sleeplessness?

Never, or just a few times a year 186	☐ 1
1-2 times a month	☐ 2
Approximately once a week	☐ 3
More than once a week	☐ 4

If you suffer from sleeplessness, what time of the year does it affect you most?

No particular time of year 187	☐ 1
Especially during the polar night	☐ 2
Especially during the midnight sun season	☐ 3
Especially in spring and autumn	☐ 4

	Yes	No
Have you in the last year suffered from sleeplessness to the extent that it has affected your ability to work? ..188	☐	☐

How often do you suffer from headaches?

Rarely or never 189	☐ 1
Once or more a month	☐ 2
Once or more a week	☐ 3
Daily	☐ 4

Does the thought of getting a serious illness ever worry you?

Not at all 190	☐ 1
Only a little	☐ 2
Some	☐ 3
Very much	☐ 4

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness:
*Tick **0** if you have **not** had such contact*

	Number of times the past year
To a general practitioner (GP)/Emergency GP 191	_____
To a psychologist or psychiatrist	_____
To an other medical specialist (not at a hospital)	_____
To a hospital out-patient clinic 197	_____
Admitted to a hospital	_____
To a medical officer at work	_____
To a physiotherapist 203	_____
To a chiropractor	_____
To an acupuncturist	_____
To a dentist 209	_____
To an alternative practitioner (homoeopath, foot zone therapist, etc.)	_____
To a healer, faith healer, clairvoyant	_____

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
*Put **0** for items you have **not** used.*

Medicines

Painkillers	215	_____ months
Sleeping pills		_____ months
Tranquillizers		_____ months
Antidepressants	221	_____ months
Allergy drugs		_____ months
Asthma drugs		_____ months

Dietary supplements

Iron tablets	227	_____ months
Calcium tablets or bonemeal		_____ months
Vitamin D supplements		_____ months
Other vitamin supplements	233	_____ months
Cod liver oil or fish oil capsules		_____ months

Have you in the last 14 days used the following medicines or dietary supplements?
*Tick **one** box only for **each** item.*

		Yes	No
Medicines			
Painkillers	237	❑	❑
Antipyretic drugs (to reduce fever)		❑	❑
Migraine drugs		❑	❑
Eczema cream/ointment		❑	❑
Heart medicines (not blood pressure)		❑	❑
Cholesterol lowering drugs		❑	❑
Sleeping pills		❑	❑
Tranquillizers		❑	❑
Antidepressants		❑	❑
Other drugs for nervous conditions		❑	❑
Antacids	247	❑	❑
Gastric ulcer drugs		❑	❑
Insulin		❑	❑
Diabetes tablets		❑	❑
Drugs for hypothyroidism (Thyroxine)		❑	❑
Cortisone tablets	252	❑	❑
Other medicine(s)		❑	❑
Dietary supplements			
Iron tablets		❑	❑
Calcium tablets or bonemeal		❑	❑
Vitamin D supplements		❑	❑
Other vitamin supplements	257	❑	❑
Cod liver oil or fish oil capsules		❑	❑

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? 259 _____ good friends
Do not count people you live with, but do include other relatives!

How many of these good friends do you have contact with at least once a month? ..... 261 _____

	Yes	No
Do you feel you have enough good friends? 263	❑	❑

How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?

Never, or just a few times a year	264	❑ 1
1-2 times a month		❑ 2
Approximately once a week		❑ 3
More than once a week		❑ 4

FOOD HABITS

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (10-12g)

A catering portion is enough for about ..... 265 _____ slices

What kind of fat is normally used in **cooking** (not on the bread) in your home?

Butter	266	❑
Hard margarine		❑
Soft margarine		❑
Butter/margarine blend		❑
Oils	270	❑

What kind of bread (bought or home-made) do you usually eat?
Tick one or two boxes!

	White bread	Light textured	Ordinary brown	Coarse brown	Crisp bread
The bread I eat is most similar to:	❑ 271	❑	❑	❑	❑ 275

How much (in **number** of glasses, cups, potatoes or slices) do you usually eat or drink **daily** of the following foodstuffs?
*Tick one box for **each** foodstuff.*

	0	Less than 1	1-2	3-4	5-6	More than 6
Full milk (ordinary or curdled) (glasses) 276	❑	❑	❑	❑	❑	❑
Semi-skimmed milk (ordinary or curdled) (glasses)	❑	❑	❑	❑	❑	❑
Skimmed milk (ordinary or curdled) (glasses)	❑	❑	❑	❑	❑	❑
Tea (cups)	❑	❑	❑	❑	❑	❑
Orange juice (glasses)	❑	❑	❑	❑	❑	❑
Potatoes 281	❑	❑	❑	❑	❑	❑
Slices of bread in total (incl. crisp-bread)	❑	❑	❑	❑	❑	❑
Slices of bread with						
- fish (e.g. mackerel in tomato sauce)	❑	❑	❑	❑	❑	❑
- lean meat (e.g. ham)	❑	❑	❑	❑	❑	❑
- fat meat (e.g. salami)	❑	❑	❑	❑	❑	❑
- cheese *(e.g. Gouda/ Norvegia)* 286	❑	❑	❑	❑	❑	❑
- brown cheese	❑	❑	❑	❑	❑	❑
- smoked cod caviare	❑	❑	❑	❑	❑	❑
- jam and other sweet spreads	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

How many **times per week** do you normally eat the following foodstuffs?
*Tick a box for **all** foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	almost daily
Yoghurt 290	❑	❑	❑	❑	❑	❑
Boiled or fried egg	❑	❑	❑	❑	❑	❑
Breakfast cereal/ oat meal, etc.	❑	❑	❑	❑	❑	❑
Dinner with						
- unprocessed meat	❑	❑	❑	❑	❑	❑
- sausage/meatloaf/ meatballs	❑	❑	❑	❑	❑	❑
- fatty fish (e.g. salmon/redfish) 295	❑	❑	❑	❑	❑	❑
- lean fish (e.g. cod)	❑	❑	❑	❑	❑	❑
- fishballs/fishpudding/fishcakes	❑	❑	❑	❑	❑	❑
- vegetables	❑	❑	❑	❑	❑	❑
Mayonnaise, remoulade	❑	❑	❑	❑	❑	❑
Carrots 300	❑	❑	❑	❑	❑	❑
Cauliflower/cabbage/ broccoli	❑	❑	❑	❑	❑	❑
Apples/pears	❑	❑	❑	❑	❑	❑
Oranges, mandarins	❑	❑	❑	❑	❑	❑
Sweetened soft drinks	❑	❑	❑	❑	❑	❑
Sugar-free ("Light") soft drinks	❑	❑	❑	❑	❑	❑
Chocolate	❑	❑	❑	❑	❑	❑
Waffles, cakes, etc. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALCOHOL

How often do you usually drink	beer?	wine?	spirits?
Never, or just a few times a year	❑	❑	❑ 1
1-2 times a month	❑	❑	❑ 2
About once a week	❑	❑	❑ 3
2-3 times a week	❑	❑	❑ 4
More or less daily	❑	❑	❑ 5
	308		310

Approximately how often during the last year have you consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not at all the last year ..... ❑ 1
- A few times ..... ❑ 2
- 1-2 times a month ..... ❑ 3
- 1-2 times a week ..... ❑ 4
- 3 or more times a week ..... ❑ 5

For approximately how many years has your alcohol consumption been as you described above? ..... 312 ____years

WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? Write **0** if you never have.

- before age 20 ..... 314 _____ times
- later ..... 316 _____ times

If you have lost weight deliberately, about how many kilos have you ever lost at the most?

- before age 20 ..... 318 _____ kg
- later ..... 320 _____ kg

What weight would you be satisfied with (your "ideal weight")? ..... 322 _____ kg

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

- Never ..... 325 ❑ 1
- Not more than once a month ..... ❑ 2
- Two or more times a month ..... ❑ 3
- Once a week or more ..... ❑ 4

Your comments:

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 326 _____years

If you no longer menstruate, how old were you when you stopped menstruating? ..... 328 _____years

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? ..... 330 Yes ❑ No ❑

If "Yes", how many times? ..... 331 _____ times

If you still menstruate or are pregnant: day/month/year

What date did your last menstruation period begin? 333 ___/___/___

Do you usually use painkillers to relieve period pains? ..... 339 Yes ❑ No ❑

PREGNANCY

How many children have you given birth to? ..... 340 _____ children

Are you pregnant at the moment? ..... 342 Yes ❑ No ❑ Don't know ❑

Have you during pregnancy had high blood pressure and/or proteinuria? ..... 343 Yes ❑ No ❑

If "Yes", during which pregnancy?	Pregnancy First	Later
High blood pressure 344	❑	❑
Proteinuria 346	❑	❑

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child.

Child	Year of birth:	Number of months breastfed:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

CONTRACEPTION AND ESTROGEN

Do you use, or have you ever used:	Now	Before	Never
Oral contraceptive pills (incl. minipill) ... 372	❑	❑	❑
Hormonal intrauterine device	❑	❑	❑
Estrogen (tablets or patches) 374	❑	❑	❑
Estrogen (cream or suppositories)	❑	❑	❑
	1	2	3

If you use oral contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?

376 .....

If you use or have ever used oral contraceptive pills:

Age when you started to take the pill? ..... 380 _____years

How many years in total have you taken the pill? ..... 382 _____years

If you have given birth, how many years did you take the pill before your first delivery? ..... 384 _____years

If you have stopped taking the pill:

Age when you stopped? ..... 386 _____years

Thank you for the help! Remember to mail the form today!

The Tromsø Health Survey

Appendix IVc

Questionnaire 2 (≥70 years), Tromsø 4 1994-1995

Tromsø Health Survey
for the over 70s

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. Finally, the survey should give knowledge about the older part of the population. We would therefore like you to answer the questions below.

This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are in doubt about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire .....17 ❑

Day Month Year

Date for filling in this form: .....18 ...../...../.....

CHILDHOOD/YOUTH

In which Norwegian municipality did you live at the age of 1year?

.....24 -28

If you did not live in Norway, give country instead of municipality

How was your family's financial situation during your childhood?

- Very good .....29 ❑ 1
- Good ..... ❑ 2
- Difficult ..... ❑ 3
- Very difficult ..... ❑ 4

How old were your parents when they died?

- Mother .....30 _____Years
- Father .....32 _____Years

HOME

Who do you live with?
Tick once for each item and give the number.

	Yes	No	Number
Spouse/partner 34	❑	❑	
Other people over 18 years 35	❑	❑	_____
People under 18 years 38	❑	❑	_____

What type of house do you live in?

- Villa/ detached house .....41 ❑ 1
- Farm ..... ❑ 2
- Flat/apartment ..... ❑ 3
- Terraced /semi-detached house ..... ❑ 4
- Other ..... ❑ 5

How long have you lived in your present home? .....42 _____years

	Yes	No
Is your home adapted to your needs? 44	❑	❑
If "No", do you have problems with:		
Living space 45	❑	❑
Variable temperature, too cold/too warm 46	❑	❑
Stairs 47	❑	❑
Toilet 48	❑	❑
Bath/shower 49	❑	❑
Maintenance 50	❑	❑
Other (please specify) 51	❑	❑

Would you like to move into a retirement home? ...52 ❑ ❑

PREVIOUS WORK AND FINANCIAL SITUATION

How will you describe the type of work you had for the last 5-10 years before you retired?

- Mostly sedentary work? .....53 ❑ 1
  (e.g. office work, mounting)
- Work that requires a lot of walking? ..... ❑ 2
  (e.g. shop assistant, housewife, teaching)
- Work that requires a lot of walking and lifting? ..... ❑ 3
  (e.g. postman, nurse, construction)
- Heavy manual work ..... ❑ 4
  (e.g. forestry, heavy farm-work, heavy construction)

Did you do any of the following jobs (full-time or part-time)?
Tick one box only for each item.

	Yes	No
Driver 54	❑	❑
Farmer 55	❑	❑
Fisherman 56	❑	❑

How old were you when you retired? .....57 _____Years

What kind of pension do you have?

- Basic state pension .....59 ❑
- An additional pension .....60 ❑

How is your current financial situation?

- Very good .....61 ❑ 1
- Good ..... ❑ 2
- Difficult ..... ❑ 3
- Very difficult ..... ❑ 4

HEALTH AND ILLNESS

Has your state of health changed in the last year?

- Yes, it has got worse .....62 ❑ 1
- No, unchanged ..... ❑ 2
- Yes, it has got better ..... ❑ 3

How do you feel your health is now compared to others of your age?

- Much worse .....63 ❑ 1
- A little worse ..... ❑ 2
- About the same ..... ❑ 3
- A little better ..... ❑ 4
- Much better ..... ❑ 5

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	Yes	No	Age
Hip fracture 64	❑	❑	_____
Wrist /forearm fracture 67	❑	❑	_____
Whiplash 70	❑	❑	_____
Injury requiring hospital admission 73	❑	❑	_____
Gastric ulcer 76	❑	❑	_____
Duodenal ulcer 79	❑	❑	_____
Gastric/duodenal ulcer surgery 82	❑	❑	_____
Neck surgery 85	❑	❑	_____

Have you ever had, or do you have:
Tick one box only for each item.

	Yes	No
Cancer 88	❑	❑
Epilepsy	❑	❑
Migraine	❑	❑
Parkinson's disease	❑	❑
Chronic bronchitis	❑	❑
Psoriasis 93	❑	❑
Osteoporosis	❑	❑
Fibromyalgia/fibrositis/chronic pain syndrome	❑	❑
Psychological problems for which you have sought help	❑	❑
Thyroid disease	❑	❑
Liver disease 98	❑	❑
Recurrent urinary incontinence	❑	❑
Glaucoma	❑	❑
Cataract	❑	❑
Arthrosis (osteoarthritis)	❑	❑
Rheumatoid arthritis 103	❑	❑
Kidney stones	❑	❑
Appendectomy	❑	❑
Allergy and hypersensitivity		
Atopic eczema (e.g. childhood eczema)	❑	❑
Hand eczema	❑	❑
Hey fever 108	❑	❑
Food allergy	❑	❑
Other hypersensitivity (not allergy)	❑	❑

How many times have you had a common cold, influenza (flu), diarrhoea/vomiting or similar in the last 6 months? 111 _____ times

	Yes	No
Have you had this in the last 14 days? 113	❑	❑

ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
Tick "None" if none of your relatives have had the disease.

	Mother	Father	Brother	Sister	Child	None
Cerebral stroke or brain haemorrhage 114	❑	❑	❑	❑	❑	❑
Heart attack before age 60 120	❑	❑	❑	❑	❑	❑
Cancer 126	❑	❑	❑	❑	❑	❑
Hypertension 132	❑	❑	❑	❑	❑	❑
Asthma 138	❑	❑	❑	❑	❑	❑
Osteoporosis 144	❑	❑	❑	❑	❑	❑
Arthrosis (osteoarthritis) 150	❑	❑	❑	❑	❑	❑
Psychological problems 156	❑	❑	❑	❑	❑	❑
Dementia 162	❑	❑	❑	❑	❑	❑
Diabetes 168	❑	❑	❑	❑	❑	❑
- age when they got diabetes 174	__	__	__	__	__	

SYMPTOMS

	Yes	No
Do you cough about daily for some periods of the year? 184	❑	❑
If "Yes":		
Is your cough productive? 185	❑	❑
Have you had this kind of cough for as long as 3 months in each of the last two years? 186	❑	❑
Have you had episodes with wheezing in your chest?187	❑	❑
If "Yes", has this occurred:		
Tick one box only for each item.		
At night 188	❑	❑
In connection with respiratory infections	❑	❑
In connection with physical exertion	❑	❑
In connection with very cold weather 191	❑	❑
Have you noticed sudden changes in your pulse or heart rhythm in the last year? 192	❑	❑
Have you lost weight in the last year? 193	❑	❑
If "Yes":		
How many kilograms? 194	_____ kg	

How often do you suffer from sleeplessness?

- Never, or just a few times a year .....196 ❑ 1
- 1-2 times a month ..... ❑ 2
- Approximately once a week ..... ❑ 3
- More than once a week ..... ❑ 4

If you suffer from sleeplessness, what time of the year does it affect you most?

- No particular time of year .....197 ❑ 1
- Especially during the polar night ..... ❑ 2
- Especially during the midnight sun season ..... ❑ 3
- Especially in spring and autumn ..... ❑ 4

	Yes	No
Do you usually take a nap during the day? 198	❑	❑
Do you feel that you usually get enough sleep?	❑	❑

Do you suffer from:	No	A little	A lot
Dizziness 200	❑	❑	❑
Poor memory	❑	❑	❑
Lack of energy	❑	❑	❑
Constipation 203	❑	❑	❑

Does the thought of getting a serious illness ever worry you?

- Not at all ..... 204 ☐
- Only a little ..... ☐
- Some ..... ☐
- Very much ..... ☐

BODILY FUNCTIONS

Can you manage the following everyday activities on your own without help from others?	Yes	With some help	No
Walking indoors on one level 205	☐	☐	☐
Walking up/down stairs	☐	☐	☐
Walking outdoors	☐	☐	☐
Walking approx. 500 metres	☐	☐	☐
Going to the toilet	☐	☐	☐
Washing yourself 210	☐	☐	☐
Taking a bath/shower	☐	☐	☐
Dressing and undressing	☐	☐	☐
Getting in and out of bed	☐	☐	☐
Eating	☐	☐	☐
Cooking 215	☐	☐	☐
Doing light housework *(e.g. washing up)*	☐	☐	☐
Doing heavier housework *(e.g. cleaning floor)* ..	☐	☐	☐
Go shopping	☐	☐	☐
Take the bus	☐	☐	☐

	Yes	With difficulty	No
Can you hear normal speech (if necessary with hearing aid)? 220	☐	☐	☐
Can you read (if necessary with glasses)? 221	☐	☐	☐

Are you dependent on any of the following aids? ?

	Yes	No
Walking stick 222	☐	☐
Crutches	☐	☐
Walking frame/zimmer frame	☐	☐
Wheelchair	☐	☐
Hearing aid	☐	☐
Safety alarm device..... 227	☐	☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to vour own health or illness:
Put 0 if you have not had such contact

	Number of times the past year
To a general practitioner (GP)/emergency GP 228	
To a psychologist or psychiatrist	
To an other medical specialist (not at a hospital)	
To a hospital out-patient clinic 234	
Admitted to a hospital	
To a physiotherapist	
To a chiropractor 240	
To a acupuncturist	
To a dentist	
To a chiropodist 246	
To an alternative practitioner (homoeopath, foot zone therapist, etc.)	
To a healer, faith healer, clairvoyant	

Do you have home aid?	Yes	No
Private 252	☐	☐
Municipal	☐	☐

Do you receive home nursing care? ..... ☐ ☐

Are you pleased with the health care and home assistance services in the municipality?

	Yes	No	Don't know
Assigned family GP 255	☐	☐	☐
Home nursing care	☐	☐	☐
Home assistance services	☐	☐	☐

Do you feel confident that you will receive health care and home assistance services if you need it?

- Confident ..... 258 ☐ 1
- Not confident ..... ☐ 2
- Very unsure ..... ☐ 3
- Don't know ..... ☐ 4

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the last year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
Put 0 for items you have not used.

Medicines:

- Painkillers ..... 259 _____months
- Sleeping pills ..... _____months
- Tranquillizers ..... _____months
- Antidepressants ..... 265 _____months
- Allergy drugs ..... _____months
- Asthma drugs ..... _____months
- Heart medicines (not blood pressure) ..... 271 _____months
- Insulin ..... _____months
- Diabetes tablets ..... _____months
- Drugs for hypothyroidism (Thyroxine) ..... 277 _____months
- Cortisone tablets ..... _____months
- Remedies for constipation ..... _____months

Dietary supplements:

- Iron tablets ..... 283 _____months
- Vitamin D supplements ..... _____months
- Other vitamin supplements ..... _____months
- Calcium tablets or bone meal ..... 289 _____months
- Cod liver oil or fish oil capsules ..... _____months

FAMILY AND FRIENDS

Do you have close relatives who can give you help and support when you need it? 293	Yes	No
	☐	☐
If "Yes", who can give you help?		
Spouse/partner 294	☐	
Children	☐	
Others	☐	

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? ..... 297 ____ good friends

Do not count people you live with, but do include other relatives!

	Yes	No
Do you feel you have enough good friends?..... 299	☐	☐

Do you feel that you belong to a community (group of people) who can depend on each other and who feel committed to each other (e.g. a political party, religious group, relatives, neighbours, work place, or organisation)?

- Strong sense of belonging ..... 300 ☐ 1
- Some sense of belonging ..... ☐ 2
- Not sure ..... ☐ 3
- Little or no sense of belonging ..... ☐ 4

How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ..... 301 ☐ 1
- 1-2 times a month ..... ☐ 2
- Approximately once a week ..... ☐ 3
- More than once a week ..... ☐ 4

FOOD HABITS

Number

How many meals a day do you normally eat (dinner and bread meals)? ..... 302 _____

How many times a week do you eat warm dinner? ..... 304 _____

What kind of bread (bought or home-made) do you usually eat?

Tick one or two boxes.

	White Bread	Light textured	Ordinary brown	Coarse brown	Crisp bread
The bread type is most similar to:	☐ 306	☐	☐	☐	☐ 310

What kind of fat is normally used in *cooking* (not on the bread) in your home?

- Butter ..... 311 ☐
- Hard margarine ..... ☐
- Soft margarine ..... ☐
- Butter/margarine blend ..... ☐
- Oils ..... 315 ☐

How much (in number of glasses, cups, potatoes or slices) do you usually eat/drink daily the following foodstuffs?

Tick one box for each foodstuff.

	None	Less than 1	1-2	3 or more
Milk of all types (glasses) 316	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐
Slices of bread with				
– fish (e.g. mackerel in tomato sauce)	☐	☐	☐	☐
– cheese *(e.g. Gouda/Norvegia)*	☐	☐	☐	☐
– smoked cod caviare 322	☐ 1	☐ 2	☐ 3	☐ 4

How many times per week do you normally eat the following foodstuffs?

Tick for all foodstuffs listed.

	Never	Less than 1	1	2 or more
Yoghurt 323	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐
Breakfast cereal/oatmeal, etc.	☐	☐	☐	☐
Dinner with				
– unprocessed meat	☐	☐	☐	☐
– fatty fish (e.g. salmon/red-fish)	☐	☐	☐	☐
– lean fish (e.g. cod) 328	☐	☐	☐	☐
– vegetables (fresh or cooked)	☐	☐	☐	☐
Carrots (fresh or cooked)	☐	☐	☐	☐
Cauliflower/cabbage/broccoli	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐
Oranges, mandarins, etc. 333	☐ 1	☐ 2	☐ 3	☐ 4

WELL BEING

How content do you generally feel with growing old?

- Good ..... 334 ☐ 1
- Quite good ..... ☐ 2
- Up and down ..... ☐ 3
- Bad ..... ☐ 4

What is your view of the future?

- Bright ..... 335 ☐ 1
- Not too bad ..... ☐ 2
- Quite worried ..... ☐ 3
- Dark ..... ☐ 4

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 336 _____ years

How old were you when you stopped menstruating? ..... 338 _____ years

PREGNANCY

How many children have you given birth to? ..... 340 _____ Children

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child. If you have given birth to more than 6 children, note their birth year and number of months you breastfed at the space provided below for comments.

Child	Year of birth:	Number of months breastfed:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Have you during pregnancy had high blood pressure and/or proteinuria? ..... 366 Yes ☐ No ☐

If "Yes", during which pregnancy?	Pregnancy First	Later
High blood pressure 367	☐	☐
Proteinuria 369	☐	☐

ESTROGEN

Do you use, or have you ever used estrogen:

	Now	Previously	Never
Tablets or patches 371	☐	☐	☐
Cream or suppositories 372	☐	☐	☐

If you use estrogen, what brand do you currently use?

..... 373

Your comments:

Thank you for the help! Remember to mail the form today!

Tromsø Health Survey

Appendix Va

Questionnaire 1 (<70 years), Tromsø 5 2001

Health survey

Personal Invitation

Don't write here

5.3 (Municipality) (County) (Country)

9.3 (Business) 9.4 (Occupation) 14.7 (Mark)

1. YOUR OWN HEALTH

1.1 What is your current state of health? *(Tick one only)*

Poor ☐ 1 | Not so good ☐ 2 | Good ☐ 3 | Very good ☐ 4

1.2 Do you have, or have you had?:

	Yes	No	Age first time
Asthma	☐	☐	
Hay fever	☐	☐	
Chronic bronchitis/emphysema	☐	☐	
Diabetes	☐	☐	
Osteoporosis	☐	☐	
Fibromyalgia/chronic pain syndrome	☐	☐	
Psychological problems for which you have sought help	☐	☐	
A heart attack	☐	☐	
Angina pectoris (heart cramp)	☐	☐	
Cerebral stroke/brain haemorrhage	☐	☐	

1.3 Have you noticed attacks of sudden changes in your pulse or heart rhythm in the last year? Yes ☐ No ☐

1.4 Do you get pain or discomfort in the chest when:
Walking up hills, stairs or walking fast on level ground? Yes ☐ No ☐

1.5 If you get such pain, do you usually:

Stop? ☐ 1 | Slow down? ☐ 2 | Carry on at the same pace? ☐ 3

1.6 If you stop, does the pain disappear within 10 minutes? Yes ☐ No ☐

1.7 Can such pain occur even if you are at rest? Yes ☐ No ☐

2. MUSCULAR AND SKELETAL COMPLAINTS

2.1 Have you suffered from pain and/or stiffness in muscles and joints during the last 4 weeks?
(Give duration only if you have had problems)

	No complaint	Some complaint	Severe complaint	Duration: Up to 2 weeks	Duration: 2 weeks or more
Neck/shoulders	☐	☐	☐	☐	☐
Arms, hands	☐	☐	☐	☐	☐
Upper part of your back...	☐	☐	☐	☐	☐
Lumbar region	☐	☐	☐	☐	☐
Hips, legs, feet	☐	☐	☐	☐	☐
Other places	☐	☐	☐	☐	☐
	1	2	3	1	2

2.2 Have you ever had:

	Yes	No	Age last time
Fracture in the wrist/forearm	☐	☐	
Hip fracture?	☐	☐	

3. OTHER COMPLAINTS

3.1 Below is a list of various problems. Have you experienced any of this during the last week (including today)?
(Tick once for each complaint)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
Felt afraid or anxious	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
Felt tense or upset	☐	☐	☐	☐
Tend to blame yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
Feeling of being useless, worthless	☐	☐	☐	☐
Feeling that everything is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future	☐	☐	☐	☐
	1	2	3	4

4. USE OF HEALTH SERVICES

4.1 How many times in the last 12 months have you been to/used:
(Tick once for each line)

	None	1-3 times	4 or more
General practitioner (GP)	☐	☐	☐
Medical officer at work	☐	☐	☐
Psychologist or psychiatrist *(private or out-patient clinic)*	☐	☐	☐
Other specialist *(private or out-patient clinic)*	☐	☐	☐
Emergency GP *(private or public)*	☐	☐	☐
Hospital admission	☐	☐	☐
Home nursing care	☐	☐	☐
Physiotherapist	☐	☐	☐
Chiropractor	☐	☐	☐
Dentist	☐	☐	☐
Alternative practitioner	☐	☐	☐

5. CHILDHOOD/YOUTH AND AFFILIATION

5.1 How long altogether have you lived in the county? ☐☐ year
(Put 0 if less than half a year)

5.2 How long altogether have you lived in the municipality? ☐☐ year
(Put 0 if less than half a year)

5.3 Where did you live most of the time before the age of 16?
(Tick one option and specify)

Same municipality .... ☐ 1

Another municipality in the county ..... ☐ 2 Which one: _____

Another county in Norway ☐ 3 Which one: _____

Outside Norway ..... ☐ 4 Country:: _____

5.4 Have you moved within the last five years?

No ☐ 1 | Yes, one time ☐ 2 | Yes, more than once ☐ 3

6. BODY WEIGHT

6.1 Estimate your body weight when you were 25 years old: ☐☐☐ kg

7. FOOD AND BEVERAGES

7.1 How often do you usually eat these foods?
(Tick once per line)

	Rarely /never	1-3 times /month	1-3 times /week	4-6 times /week	1-2 times /day	3 times or more /day
Fruit, berries	☐	☐	☐	☐	☐	☐
Cheese *(all types)*	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Boiled vegetables	☐	☐	☐	☐	☐	☐
Fresh vegetables/salad	☐	☐	☐	☐	☐	☐
Fatty fish *(e.g. salmon, trout, mackerel, herring)*	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

7.2 What type of fat do you usually use? *(Tick once per line)*

	Don't use	Butter	Hard margarine	Soft/light margarine	Oils	Other
On bread	☐	☐	☐	☐	☐	☐
For cooking	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

7.3 Do you use the following dietary supplements:

	Yes, daily	Sometimes	No
Cod liver oil, fish oil capsules	☐	☐	☐
Vitamins and/or mineral supplements?	☐	☐	☐

7.4 How much of the following do you usually drink?
(Tick once per line)

	Rarely /never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 glasses or more /day
Full milk, full-fat curdled milk, yoghurt	☐	☐	☐	☐	☐
Semi-skimmed milk, semi-skimmed curdled milk,low-fat yoghurt	☐	☐	☐	☐	☐
Skimmed milk, skimmed curdled milk	☐	☐	☐	☐	☐
Extra semi-skimmed milk	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Water	☐	☐	☐	☐	☐
Mineral water (e.g. Farris, Ramløsa etc)	☐	☐	☐	☐	☐
Cola-containing soft drink	☐	☐	☐	☐	☐
Other soda/soft drink	☐	☐	☐	☐	☐
	1	2	3	4	5

7.5 Do you usually drink soft drink: with sugar ☐ 1 without sugar ☐ 2

7.6 How many cups of coffee and tea do you drink daily? *Number of cups*
(Put 0 for the types you don't drink daily)

Filtered coffee ..... ☐☐

Boiled coffee/coarsely ground coffee for brewing ..... ☐☐

Other type of coffee ..... ☐☐

Tea ..... ☐☐

7.7 Approximately how often have you during the last year consumed alcohol? *(Do not count low-alcohol and alcohol-free beer)*

Never consumed alcohol ☐ 1	Have not consumed alcohol last year ☐ 2	A few times last year ☐ 3	About 1 time a month ☐ 4
2-3 times per month ☐ 5	About1 time a week ☐ 6	2-3 times a week ☐ 7	4-7 times a week ☐ 8

To those who have consumed the last year:

7.8 When you drink alcohol, how many glasses or drinks do you normally drink? *number* ☐☐

7.9 Approximately how many times during the last year have you consumed alcohol equivalent to 5 glasses or drinks within 24 hours? *Number of times* ☐☐

7.10 When you drink, do you normally drink: *(Tick one or more)*

Beer ☐ Wine ☐ Spirits ☐

8. SMOKING

8.1 How many hours a day do you normally spend in smoke-filled rooms? *Number of total hours* ☐☐

	Yes	No
8.2 Did any of the adults smoke at home while you were growing up?	☐	☐
8.3 Do you currently, or did you previously live together with a daily smoker after your 20th birthday?	☐	☐

	Yes, now	Yes, previously	Never
8.4 Do you/did you smoke daily?	☐	☐	☐

If NEVER: Go to question 9 : (EDUCATION AND WORK)

8.5 If you smoke daily now, do you smoke:	Yes	No
Cigarettes?	☐	☐
Cigars/cigarillos?	☐	☐
A pipe?	☐	☐

8.6 If you previously smoked daily, how long is it since you quit? *Number of years* ☐☐

8.7 If you currently smoke, or have smoked previously:

How many cigarettes do you or did you normally smoke per day? *Number of cigarettes* ☐☐

How old were you when you began daily smoking? *Age in years* ☐☐

How many years in all have you smoked daily? *Number of years* ☐☐

9. EDUCATION AND WORK

9.1 How many years of education have you completed? *Number of years* ☐☐
(Include all the years you have attended school or studied)

9.2 Do you currently have paid work?

Yes, full-time ☐ 1 Yes, part-time ☐ 2 No ☐ 3

9.3 Describe the activity at the workplace where you had paid work for the longest period in the last 12 months. *(e.g. Accountancy firm, school, paediatric department, carpentry workshop, garage, bank, grocery store, etc.)*

Business: _____
If retired, enter the former business and occupation. Also applies to 9.4

9.4 Which occupation/title have or had you at this workplace?
(e.g. Secretary, teacher, industrial worker, nurse, carpenter, manager, salesman, driver, etc.)

Occupation: _____

9.5 In your main occupation, do you work as self-employed, as an employee or family member without regular salary?

Self-employed ☐ Employee ☐ Family member ☐

	Yes	No
9.6 Do you believe that you are in danger of losing your current work or income within the next two years?	☐	☐

9.7 Do you receive any of the following benefits?	Yes	No
Sickness benefit (are on sick leave)	☐	☐
Old age pension, early retirement (AFP) or survivor pension	☐	☐
Rehabilitation/reintegration benefit	☐	☐
Disability pension (full or partial)	☐	☐
Unemployment benefits during unemployment	☐	☐
Social welfare benefits	☐	☐
Transition benefit for single parents	☐	☐

10. EXERCISE AND PHYSICAL ACTIVITY

10.1 How has your physical activity in leisure time been during this last year?
Think of a weekly average for the year.
Time spent going to work is count as leisure time. Answer both questions.

	Hours per week: None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)*...	☐	☐	☐	☐
Hard physical activity *(sweating/out of breath)*.....	☐ 1	☐ 2	☐ 3	☐ 4

10.2 Describe exercise and physical exertion in your leisure time. If your activity varies much e.g. between summer and winter, then give an average. The question refers only to the last year.
(Tick the most appropriate box)

Reading, watching TV or other sedentary activity? ..... ☐ 1

Walking, cycling or other forms of exercise at least 4 hours a week? ..... ☐ 2
(Include walking or cycling to work, Sunday walk/stroll,etc.)

Participation in recreational sports, heavy gardening, etc.? ☐ 3
(Note: duration of activity at least 4 hours a week)

Participation in hard training or sports competitions, regularly several times a week? ..... ☐ 4

11. FAMILY AND FRIENDS

11.1 Do you live with:
Spouse/partner?..... Yes ☐ No ☐

11.2 How many good friends do you have? *Number of friends* ☐☐
Count the ones you can talk confidentially with and who can give you help when you need it. Do not count people you live with, but do include other relatives.

11.3 How much interest do people show for what you do?
(Tick only once)

Great interest ☐ 1 | Some interest ☐ 2 | Little interest ☐ 3 | No interest ☐ 4 | Uncertain ☐ 5

11.4 How many associations, sport clubs,groups, religious communities or similar do you take part in? *Number* ☐☐
(Write 0 if none)

11.5 Do you feel that you can influence what happening in your local community where you live? *(Tick only once)*

Yes, a lot ☐ 1 | Yes, some ☐ 2 | Yes, a little ☐ 3 | No ☐ 4 | Never tried ☐ 5

12. ILLNESS IN THE FAMILY

12.1 Have one or more of your parents or siblings had a heart attack (heart wound) or angina pectoris (heart cramp)? ..... Yes ☐ No ☐ Don't know ☐

12.2 Tick for the relatives who have or have had any of the illnesses: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Cerebral stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Heart attack before age of 60 years	☐	☐	☐	☐	☐	☐
Asthma.....	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐

12.3 If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who got it earliest in life):

Don't know, not applicable	Mother's age	Father's age	Brother's age	Sister's age	Child's age
☐	☐☐	☐☐	☐☐	☐☐	☐☐

13. USE OF MEDICINES

With medicines, we mean drugs purchased at pharmacies. Supplements and vitamins are not considered here.

13.1 Do you use:

	Now	Previously, but not now	Never used
Blood pressure lowering drugs	☐	☐	☐
Cholesterol-lowering drugs	☐	☐	☐

13.2 How often have you during the last 4 weeks used the following medicines?
(Tick once for each line)

	Not used in the last 4 weeks	Less than every week	Every week but not daily	Daily
Painkillers non-prescription	☐	☐	☐	☐
Painkillers on prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐
Other prescription medicines ...	☐ 1	☐ 2	☐ 3	☐ 4

13.3 For those medicines you have checked in points 13.1 and 13.2, and that you've used during the last 4 weeks:

State the name and the reason that you are taking/have taken these (disease or symptom):
(Tick for each duration you have used the medicine)

Name of the medicine: *(one name per line)*	Reason for use of the medicine	How long have you used the medicine: Up to 1 year	1 year or more
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

If there is not enough space here, you may continue on a separate sheet that you attach

14. THE REST OF THE FORM IS TO BE ANSWERED BY WOMEN ONLY

14.1 How old were you when you started menstruating? *Age in years* ☐☐

14.2 If you no longer menstruating, how old were you when you stopped menstruating? *Age in years* ☐☐

14.3 Are you pregnant at the moment?

Yes ☐ 1 | No ☐ 2 | Uncertain ☐ 3 | Above fertile age ☐ 4

14.4 How many children have you given birth to? *Number of children* ☐☐

14.5 Do you use, or have you ever used?
(Tick once for each line)

	Now	Before, but not now	Never
Oral contraceptive pills/mini pill/ contraceptive injection	☐	☐	☐
Hormonal intrauterine device (IUD) *(not ordinary IUD)*..	☐	☐	☐
Estrogen *(tablets or patches)*	☐	☐	☐
Estrogen *(cream or suppositories)*	☐	☐	☐

14.6 If you use/have used prescription estrogen:
How long have you used it? *Number of years* ☐☐

14.7 If you use contraceptive pills, mini pill, contraceptive injection, hormonal IUD or estrogen, what brand do you use?

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Appendix Vb

Questionnaire 1 (≥70 years), Tromsø 5 2001

E

Health survey

Personal invitation

Do not write here:

E13 (Municipality) (County) (Country) E15 (Mark)

E1. YOUR OWN HEALTH

What is your current state of health? *(Tick only once)*

Poor ☐ 1 | Not so good ☐ 2 | Good ☐ 3 | Very good ☐ 4

Do you have, or have you had?:

	Yes	No	Age first time
Asthma	☐	☐	
Chronic bronchitis/emphysema	☐	☐	
Diabetes	☐	☐	
Osteoporosis	☐	☐	
Fibromyalgia/chronic pain syndrome	☐	☐	
Psychological problems for which you have sought help	☐	☐	
A heart attack	☐	☐	
Angina pectoris (heart cramp)	☐	☐	
Cerebral stroke/brain haemorrhage	☐	☐	

	Yes	No
Do you get pain or discomfort in the chest when: Walking up hills, stairs, or walking fast on level ground?	☐	☐

If you get such pain, do you usually:

Stop? ☐ 1 | Slow down? ☐ 2 | Carry on at the same pace? ☐ 3

	Yes	No
If you stop, does the pain disappear within 10 minutes?	☐	☐
Can such pain occur even if you are at rest?	☐	☐

E2. ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had:

	Yes	No	Don't know
A heart attack (heart wounds) or angina pectoris (heart cramp)	☐	☐	☐

Tick for the relatives who have or have had any of the illnesses: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Cerebral stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Heart attack before age of 60 years	☐	☐	☐	☐	☐	☐
Asthma	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐

If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who got it earliest in life)

Don't know, not applicable	Mother's age	Father's age	Brother's age	Sister's age	Child's age
☐					

E3. COMPLAINTS

Below is a list of various problems.
Have you experienced any of this during the last week (including today)?
(Tick once for each line)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
Felt afraid or anxious	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
Felt tense or upset	☐	☐	☐	☐
Tend to blame yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
Feeling of being useless, worthless	☐	☐	☐	☐
Feeling that everything is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future.	☐	☐	☐	☐
	1	2	3	4

E4. TEETH, MUSCLE AND SKELETON

How many teeth have you lost/extracted? *Number of teeth*
(disregard milk-teeth and wisdom teeth)

Have you been bothered by pain and/or stiffness in muscles and joints during the last 4 weeks?

	No complaint	Little complaint	Severe complaint
Neck / shoulders	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
Lumbar regions	☐	☐	☐
Hips, legs, feet	☐	☐	☐
Other places	☐	☐	☐

Have you ever had:

	Yes	No	Age last time
Fracture in wrist/forearm?	☐	☐	
Hip fracture?	☐	☐	

Have you fallen down during the last year? *(Tick once only)*

No ☐ 1 | Yes, 1-2 times ☐ 2 | Yes, more than 2 times ☐ 3

E5. EXERCISE AND PHYSICAL ACTIVITY

How has your physical activity been during this last year?
Think of a weekly average for the year.
Answer both questions.

	Hours per week: None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)*	☐	☐	☐	☐
Hard physical activity *(sweating/out of breath)*	☐ 1	☐ 2	☐ 3	☐ 4

E6. BODY WEIGHT

Estimate your body weight when you were 25 years old: kg.

E7. EDUCATION

How many years of education have you completed? *Number of years*

(include all the years you have attended school or studied)

E8. FOOD AND BEVERAGES

How often do you usually eat these foods?
(Tick once for each line)

	Rarely /never	1-3 times /month	1-3 times /week	4-6 times /week	1-2 times /day	3 times or more /day
Fruit, berries	☐	☐	☐	☐	☐	☐
Cheese (all types)	☐	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐	☐
Boiled vegetables	☐	☐	☐	☐	☐	☐
Fresh vegetables/salad	☐	☐	☐	☐	☐	☐
Fat fish (e.g. salmon, trout, mackerel, herring)	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

Do you use dietary supplements:

	Yes, daily	Sometimes	No
Cod liver oil, fish oil capsules	☐	☐	☐
Vitamins and/or mineral supplements	☐	☐	☐

How much of the following do you usually drink?
(Tick once for each line)

	Rarely /never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 glasses or more /day
Full milk, full-fat curdled milk, yoghurt	☐	☐	☐	☐	☐
Semi-skimmed milk, semi-skimmed curdled milk, low-fat yoghurt	☐	☐	☐	☐	☐
Skimmed milk, skimmed curdled milk	☐	☐	☐	☐	☐
Extra semi-skimmed milk	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Water	☐	☐	☐	☐	☐
Soft drink, mineral water	☐	☐	☐	☐	☐
	1	2	3	4	5

How many cups of coffee and tea do you drink daily?
(Put 0 for the types you do not drink daily) *Number of cups*

Filtered coffee

Boiled coffee/coarsely ground coffee for brewing

Other type of coffee

Tea

Approximately, how often have you during the last year consumed alcohol? *(Do not count low-alcohol and alcohol-free beer)*

Never consumed alcohol ☐ 1	Have not consumed alcohol last year ☐ 2	A few times last year ☐ 3	About 1 time a month ☐ 4
2-3 times per month ☐ 5	About 1 time a week ☐ 6	2-3 times a week ☐ 7	4-7 times a week ☐ 8

To those who have consumed the last year:

When you drink alcohol, how many glasses or drinks do you normally drink? *Number*

Approximately how many times during the last year have you consumed alcohol equivalent to 5 glasses or drinks within 24 hours? *Number of times*

E9. SMOKING

How many hours a day do you normally spend in smoke-filled rooms? *Number of total hours*

Did any of the adults smoke at home while you were growing up? ☐ Yes ☐ No

Do you currently, or did you previously live together with a daily smoker after your 20th birthday? ☐ Yes ☐ No

Do you/did you smoke daily?

Yes, now	Yes, previously	Never
☐	☐	☐

If you have NEVER smoked daily;
Go to question E11 (BODILY FUNCTIONS AND SAFETY)

If you smoke daily now, do you smoke:

	Yes	No
Cigarettes?	☐	☐
Cigars/cigarillos?	☐	☐
A pipe?	☐	☐

If you previously smoked daily, how long is it since you quit? *Number of years*

If you currently smoke, or have smoked previously:

How many cigarettes do you or did you normally smoke per day? *Number of cigarettes*

How old were you when you began daily smoking? *Age in years*

How many years in all have you smoked daily? *Number of years*

E10. BODILY FUNCTIONS AND SAFETY

Would you feel safe by walking alone in the evening in the area where you live?

Yes	A little unsafe	Very unsafe
☐ 1 2 3	☐	☐

When it comes to mobility, sight and hearing, can you:
(Tick once for each line)

	Without problems	With some problems	With great problems	No
Take a 5 minute walk in fairly high pace?	☐	☐	☐	☐
Read ordinary text in newspaper, if necessary with glasses?	☐	☐	☐	☐
Hear what is said in a normal conversation?	☐	☐	☐	☐
	1	2	3	4

Do you because of chronic health problems have difficulties with: *(Tick once for each line)*

	No difficulties	Some difficulties	Great difficulties
Move around in your home?	☐	☐	☐
Get out of your home by yourself?	☐	☐	☐
Participate in organization or other leisure time activities?	☐	☐	☐
Use public transport?	☐	☐	☐
Perform necessary daily shopping?	☐	☐	☐

E11. USE OF HEALTH SERVICES

How many times in the last 12 months have you been to/used:
(Tick once for each line)

	None	1-3 times	4 or more
A general practitioner (GP)	☐	☐	☐
Specialist *(private or out-patient clinic)*	☐	☐	☐
Emergency GP *(private or public)*	☐	☐	☐
Hospital admission	☐	☐	☐
Home nursing care	☐	☐	☐
Physiotherapist	☐	☐	☐
Chiropractor	☐	☐	☐
Municipal home care	☐	☐	☐
Dentist	☐	☐	☐
Alternative practitioner	☐	☐	☐

Are you confident that you will receive health care and home assistance if you need it?

YES ☐ 1 NO ☐ 2 Don't know ☐ 3

E12. FAMILY AND FRIENDS

Do you live: At home? ☐ 1 In an institution/shared apartment? ☐ 2

Do you live with:

	YES	NO
Spouse/ partner?	☐	☐
Other people?	☐	☐

How many good friends do you have?
Count the ones you can talk confidentially with and who can give you help when you need it. Do not count people you live with, but do include your children and other relatives.....

Number of friends ☐☐

How much interest do people show for what you do?
(Tick only once)

Great interest ☐ 1 Some interest ☐ 2 Little interest ☐ 3 No interest ☐ 4 Uncertain ☐ 5

How many associations, sport clubs, groups, religious communities, or similar do you take part in?
(write 0 if none)

Number ☐☐

E13. CHILDHOOD/YOUTH AND AFFILIATION

How long altogether have you lived in the county? ☐☐ years

How long altogether have you lived in the municipality? ☐☐ years

Where did you live most of the time before the age of 16?
(Tick one option and specify)

Same municipality..... ☐ 1

Another municipality in the county..... ☐ 2 Which one:_____

Another county in Norway ☐ 3 Which one:_____

Outside Norway ..... ☐ 4 Country: _____

Have you moved during the last five years?

No ☐ 1 Yes, once ☐ 2 Yes, more than once ☐ 3

E14. USE OF MEDICINES

With medicines, we mean drugs purchased at pharmacies. Supplements and vitamins are not considered here

Do you use?
(Tick once for each line)

	Now	previously, but not now	Never used
Blood pressure lowering drugs	☐	☐	☐
Cholesterol-lowering drugs	☐	☐	☐
Drugs for osteoporosis	☐	☐	☐
Insulin	☐	☐	☐
Tablets for diabetes	☐	☐	☐

How often have you during the last 4 weeks used the following medicines?
(Tick once for each line)

	Not used in the last 4 weeks	Less than every week	Every week, but not daily	Daily
Painkillers non-prescription	☐	☐	☐	☐
Painkillers on prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐
Other prescription medicines	☐	☐	☐	☐
	1	2	3	4

State the name of the medicines you are using now and the reason you are taking the medicines (disease or symptom):
(Tick for each duration you have used the medicine)

Name of the medicine: (one name per line):	Reason for use of the medicine:	How long have you used the medicine: Up to 1 year	How long have you used the medicine: One year or more
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

If there is not enough space here, you may continue on a separate sheet that you attach.

E15. THE REST OF THE FORM IS TO BE ANSWERED BY WOMEN ONLY

How old were you when you started menstruating? *Age in years* ☐☐

How old were you when you stopped menstruating? *Age in years* ☐☐

How many children have you given birth to? *Number of children* ☐☐

Do you use, or have you ever used estrogen? *Total number of years*

	Never	Previously	Now	
Tablets or patches	☐	☐	☐	☐☐
Cream or suppositories	☐	☐	☐	☐☐

If you use estrogen, which brand you use now?

_____

Have you ever used contraceptives pills? ..... Yes ☐ No ☐

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Appendix Vc

Questionnaire 2, Tromsø 5 2001

Label

Additional questions to the health survey in Troms and Finnmark 2001-2002

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The study is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses. This form is part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated strictly confidential.

The information you give us may later be linked with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are unsure about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed prepaid envelope. Thank you in advance for helping us.

Yours sincerely

Department of Community Medicine
University of Tromsø

National Health Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire ☐

Date of completion:

Day ☐☐ Month ☐☐ Year ☐☐☐☐

T1. NEIGHBORHOOD AND HOME

1.1 In which municipality did you live at the age of 1 year? *(If you have not lived in Norway, state country of residence instead of the municipality)*

_____

1.2 What type of house do you live in? *(Tick only once)*

- Detached house/villa ☐ 1
- Farm ☐ 2
- Flat/apartment ☐ 3
- Terraced/semi-detached house ☐ 4
- Institution/care home ☐ 5
- Other ☐ 6

1.3 How big is your house? ☐☐☐ *m² (gross)*

1.4 Are you bothered by: *(Tick once for each line)*

	No complaint	Little complaint	Severe complaint
Moisture, drought or coldness in your home	☐	☐	☐
Other forms of bad indoor climate	☐	☐	☐
Traffic noise (cars or aircraft)	☐	☐	☐
Other noise (industrial, construction, etc.)	☐	☐	☐
Neighbour noise	☐	☐	☐
Drinking water quality	☐	☐	☐
Air pollution from traffic	☐	☐	☐
Air pollution from wood/oil heating, factory etc.	☐	☐	☐

1.5 What home language did your grandparents have? *(Tick for one or more alternatives)*

	Norwegian	Sami	Kven/ Finnish	Other language
Mother's mother	☐	☐	☐	☐
Mother's father	☐	☐	☐	☐
Father's mother	☐	☐	☐	☐
Father's father	☐	☐	☐	☐

T1. NEIGHBORHOOD AND HOME (cont.)

1.6 What do you consider yourself as? *(Tick for one or more alternatives)*

Norwegian ☐ Sami ☐ Kven/ Finnish ☐ Other ☐

1.7 Do you feel that you have enough good friends? Yes ☐ No ☐

1.8 How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings or other associations? *(Tick only once)*

- Never, or just a few times a year ☐ 1
- 1-3 times a month ☐ 2
- Approximately once a week ☐ 3
- More than once a week ☐ 4

T2. PAID AND UNPAID WORK

2.1 If you have paid or unpaid work, how would you describe your work? *(Tick only once)*

- Mostly sedentary work? *(e.g. office work, mounting)* ☐ 1
- Work that requires a lot of walking? *(e.g. shop assistant, light industrial work, teaching)* ☐ 2
- Work that requires a lot of walking and lifting? *(e.g. Postman, nursing, construction)* ☐ 3
- Heavy manual labour? *(e.g. forestry, heavy farm-work, heavy construction)* ☐ 4

2.2 Can you decide yourself how your work (paid or unpaid) should be organised? *(Tick only once)*

- No, not at all ☐ 1
- To a small extent ☐ 2
- Yes, to a large extent ☐ 3
- Yes, I decide myself ☐ 4

2.3 Are you on call, do you work shifts or nights? Yes ☐ No ☐

T3. TOBACCO

3.1 Do you smoke?

Yes, daily ☐ 1 Yes, sometimes ☐ 2 No, never ☐ 3

If "Yes, sometimes"

What do you smoke?

☐ Cigarettes ☐ Pipe ☐ Cigar/cigarillos

3.2 Have you used or do you use snuff daily?

Yes, now ☐ Yes, previously ☐ Never ☐

If YES:

How many years altogether have you used snuff? ☐☐ years

T4. ALCOHOL

4.1 Are you a teetotaller? Yes ☐ No ☐

4.2 How many times a month do you normally drink alcohol? ☐☐ *Number of times*

(Do not count low-alcohol beer. Put 0 if less than once a month)

4.3 How many glasses of beer, wine or spirits do you normally drink in a fortnight?

Beer ☐☐ Wine ☐☐ Spirits ☐☐

(Do not count low-alcohol beer. Put 0 if you do not drink alcohol)

4.4 For approximately how many years has your alcohol consumption been at the same level you described above? ☐☐ years

4.5 Have you, in one or more periods in the last 5 years consumed so much alcohol that it has inhibited your work or social life?

Yes, at work ☐ 1 Yes, socially ☐ 2 Yes, both at work and social life ☐ 3 No, never ☐ 4

T5. FOOD AND DIETARY SUPPLEMENTS

5.1 Do you usually eat breakfast every day? Yes ☐ No ☐

5.2 How many times a week do you eat a warm dinner? ☐ *times*

5.3 How important is it for you to have a healthy diet?

Very ☐ 1 Somewhat ☐ 2 Little ☐ 3 Not ☐ 4

5.4 Do you use the following dietary supplements?

	Yes, daily	sometimes	No
Iron tablets	☐	☐	☐
Calcium tablets or bonemeal	☐	☐	☐
Vitamin D supplements	☐	☐	☐
Cod liver oil	☐	☐	☐

T6. BODY WEIGHT

6.1 Do you currently try to change your body weight?

No ☐ 1 Yes, I try to gain weight ☐ 2 Yes, I try to lose weight ☐ 3

6.2 What weight would you be satisfied with (your "ideal weight")? ☐☐☐ kg

T7. ILLNESSES AND INJURIES

7.1 Have you ever had:

Tick once for each question. Also give the age at the time. If you have had the condition several times, how old were you the last time

	Yes	No	Age last time
Severe injury requiring hospital admission	☐	☐	☐☐ years
Ankle fracture	☐	☐	☐☐ years
Peptic ulcer	☐	☐	☐☐ years
Peptic ulcer surgery	☐	☐	☐☐ years
Neck surgery	☐	☐	☐☐ years
Prostate surgery	☐	☐	☐☐ years

7.2 Do you have, or have you ever had:

(Tick once for each question)

	Yes	No
Cancer	☐	☐
Psoriasis	☐	☐
Thyroid disease	☐	☐
Glaucoma	☐	☐
Cataract	☐	☐
Osteoarthritis (arthrosis)	☐	☐
Bent fingers	☐	☐
Skin contractions in your palms	☐	☐
Kidney stone	☐	☐
Appendectomy	☐	☐
Hernia surgery	☐	☐
Surgery/treatment for urine incontinence	☐	☐
Epilepsy	☐	☐
Poliomyelitis (polio)	☐	☐
Parkinson's disease	☐	☐
Migraine	☐	☐
Leg ulcer	☐	☐
Allergy and hypersensitivity:		
Atopic eczema (e.g. childhood eczema)	☐	☐
Hand eczema	☐	☐
Food allergy	☐	☐
Other hypersensitivity (not allergy)	☐	☐

7.3 Have you had common cold, influenza, gastroenteritis, etc. during the last 14 days? Yes ☐ No ☐

7.4 Have you during the last 3 weeks had common cold, influenza, bronchitis, pneumonia, sinusitis, or other respiratory infection? Yes ☐ No ☐

7.5 Have you ever had bronchitis or pneumonia? Yes ☐ No ☐

7.6 Have you during the last 2 years had bronchitis or pneumonia? *(Tick only once)*

No ☐ 1 1-2 times ☐ 2 More than 2 times ☐ 3

T8. SYMPTOMS

8.1 Have you in the last two weeks felt:
(Tick once for each question)

	No	A Little	A lot	Very much
Nervous or worried	☐	☐	☐	☐
Bothered by anxiety	☐	☐	☐	☐
Confident and calm	☐	☐	☐	☐
Irritable	☐	☐	☐	☐
Happy and optimistic	☐	☐	☐	☐
Down/depressed	☐	☐	☐	☐
Lonely	☐	☐	☐	☐
	1	2	3	4

8.2 Do you cough about daily for periods of the year? ☐ Yes ☐ No

If YES:
Is your cough productive? ☐ Yes ☐ No

Have you had this kind of cough for as long as 3 months in each of the last two years? ☐ Yes ☐ No

8.3 Have you had episodes with wheezing in the chest? ☐ Yes ☐ No

If YES:
Has this occurred: *(Tick once for each question)*

	Yes	No
At night	☐	☐
In connection with respiratory infections	☐	☐
In connection with physical exertion	☐	☐
In connection with very cold weather	☐	☐

8.4 Do you get pain in the calf while walking ☐ Yes ☐ No

If YES:
How long can you go before you notice the pain? ☐☐☐ *meter*

8.5 Do you get short-winded in the following situations?
(Tick once for each question)

	Yes	No
While walking fast on level ground or slight up hills	☐	☐
While walking calmly on level ground	☐	☐
While washing or dressing yourself	☐	☐
While resting	☐	☐

8.6 Do you have to stop because of short-windedness while walking in your own pace on level ground? ☐ Yes ☐ No

8.7 Have you during the last year suffered from pain and/or stiffness in muscles and joints that have lasted continuously for at least 3 months? ☐ Yes ☐ No

If YES:
Has the complaint reduced your leisure time activity? ☐ Yes ☐ No

For how long has the complaint endured in total?

approx. ☐☐ years and ☐☐ months

Has the complaint reduced your ability to work during the last year? *(Also applies to domestic workers and pensioners (Tick once)*

No/insignificantly	To some extend	Significantly reduced	Do not know
☐ 1	☐ 2	☐ 3	☐ 4

Have you been on sick leave due to these complaints during the last year? ☐ Yes ☐ No ☐ Do not work

T8. SYMPTOMS (continue)

8.8 How often do you suffer from sleeplessness?
(Tick only once)

Never, or just a few times a year	☐ 1
1-3 times a month	☐ 2
Approximately once a week	☐ 3
More than once a week	☐ 4

8.9 If you suffer from sleeplessness monthly or more frequently, what time of the year does it affect you most?

No particular time of the year	☐ 1
Especially during the polar night	☐ 2
Especially during the midnight sun season	☐ 3
Especially in spring and autumn	☐ 4

8.10 Have you in the last year suffered from sleeplessness to the extend that it has affected your ability to work ? ☐ Yes ☐ No

8.11 Do you usually sleep during the day? ☐ Yes ☐ No

8.12 How often do you suffer from urinary incontinence?

Never	☐ 1
Not more than once a month	☐ 2
Two or more times a month	☐ 3
Once a week or more	☐ 4

8.13 Are you able to walk down 10 steps without holding on to something (e.g. a handrail) ☐ Yes ☐ No

8.14 Do you use glasses? ☐ Yes ☐ No

8.15 Do you use a hearing aid? ☐ Yes ☐ No

8.16 How is your memory?
(Tick once for each question)

	Yes	No
Do you forget what you just have heard or read?	☐	☐
Do you forget where you have placed things?	☐	☐
Is it more difficult to remember now than earlier?	☐	☐
Do you more often write memos now than earlier?	☐	☐

If "YES" on one of these questions;
Is this a problem in your daily life? ☐ Yes ☐ No

T9. MEDICINES

9.1 Do you use, or have you used any of the following medicines:

	Now	Previously, but not now	Age when used 1st time	Never used
Drugs for osteoporosis	☐	☐	☐☐ years	☐
Tablets for diabetes	☐	☐	☐☐ years	☐
Drugs for hypothyroidism (thyroxine)	☐	☐	☐☐ years	☐

9.2 Do you use any medicines which you take as injections? ☐ Yes ☐ No

If YES:
Give the name of the medicines (for injection):
(one name per line)

_____

_____

T10. ILLNESS IN THE FAMILY

10.1 Tick for the relatives who have or have ever had any of the diseases: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Heart attack (heart wound)	☐	☐	☐	☐	☐	☐
Angina pectoris (heart cramp)	☐	☐	☐	☐	☐	☐
High blood pressure	☐	☐	☐	☐	☐	☐
Aneurysm.....	☐	☐	☐	☐	☐	☐
Gastric/duodenal ulcer	☐	☐	☐	☐	☐	☐
Hip fracture	☐	☐	☐	☐	☐	☐
Psychological problems ..	☐	☐	☐	☐	☐	☐
Allergy	☐	☐	☐	☐	☐	☐
Osteoarthritis (arthrosis) ..	☐	☐	☐	☐	☐	☐
Dementia	☐	☐	☐	☐	☐	☐

10.2 How many siblings and children do you have?

	Brothers	Sisters	Children
Number	☐☐	☐☐	☐☐

10.3 Do you usually do extra caring work because of illness etc. in your close family?

Yes, daily/almost daily ☐ 1 Yes, sometimes ☐ 2 No ☐ 3

10.4 Do you/your family receive home aid or home nursing care?..... Yes ☐ No ☐

	Yes	No	Age at death
10.5 Is your mother alive?	☐	☐	☐☐☐ years
10.6 Is your father alive?	☐	☐	☐☐☐ years

T11. MOBILE TELEPHONE

11.1 Do you have (own, rent, etc.) a mobile telephone?

Yes, always ☐ 1 Yes, sometimes ☐ 2 No ☐ 3

If Yes:
What do you use your mobile telephone for, and how often do you use it? *(Tick once for each line)*

	Number of times per day				
	30 or more	10-29	2-9	1 or less	Never
Conversations..	☐	☐	☐	☐	☐
Text messaging	☐	☐	☐	☐	☐
	12345				

T12. THE REST IS TO BE ANSWERED BY WOMEN ONLY

12.1 If you have given birth, fill in each child's birth year and how many months you breastfed after delivery.
(If you did not breastfeed, write 0)

Child:	Birth year:	Number of months breastfed:
1st child	☐☐☐☐	☐☐
2nd child	☐☐☐☐	☐☐
3rd child	☐☐☐☐	☐☐
4th child	☐☐☐☐	☐☐
5th child	☐☐☐☐	☐☐
6th child	☐☐☐☐	☐☐

(If more children, use additional sheet)

T12. THE REST IS TO BE ANSWERED BY WOMEN ONLY

12.2 If you still have mensturate or are pregnant:
What date did your last menstruation start?

Day ☐☐ Month ☐☐ Year ☐☐☐☐

12.3 If you no longer menstruate; why did your periods stop? *(Tick once)*

It stopped by itself ..... ☐ 1
Uterus surgery ..... ☐ 2
Surgically removed both ovaries ..... ☐ 3
Other reason (e.g. radiation, chemotherapy) ... ☐ 4

12.4 Do you use or have you used prescribed estrogen (tablets or patches)?..... Yes ☐ No ☐

If YES:
How old were you when you started taking estrogen ? ..... ☐☐ years

If you stopped using estrogen,
How old were you when you stopped taking estrogen?..... ☐☐ years

12.5 Do you use or have you used oral contraceptive pills?..... Yes ☐ No ☐

If YES:
How old were you when you started taking the pill?..... ☐☐ years

How many years in total have you taken the pills?.... *Number of years* ☐☐

If you have given birth:
How many years did you take the pill before your first delivery?... *Number of years* ☐☐

If you stopped taking the pill:
How old were you when you stopped?.... ☐☐ years

12.6 Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? Yes ☐ No ☐

If YES:
How many times?..... ☐☐ times

12.7 How is your current menstruation status?

I have not had menstruation in the last year ☐ 1
I have regular menstruation ..... ☐ 2
I have irregular menstruation ..... ☐ 3

12.8 When you were 25-29 years old, how many days usually passed between the start of two periods?

Minimum ☐☐ days Maximum ☐☐ days Do not know ☐

The periods were of approximately equal length every time?..... Yes ☐ No ☐

How many days did a typical menstrual bleeding period last?... ☐☐ days

Thank you for the help!
Remember to mail the form today!

IE 050000-1046-1 - 25.000 - Beyer Hecos 02.01

Appendix VIa

Questionnaire 1, Tromsø 6 2007-2008

Tromsø-undersøkelsen

The form will be read electronically. Please use a blue or black pen
You can not use comas, use upper-case letters.

2007 - 2008 Confidential

HEALTH AND DISEASES

1 **How do you in general consider your own health to be?**

- ☐ Very good
- ☐ Good
- ☐ Neither good nor bad
- ☐ Bad
- ☐ Very bad

2 **How is your health compared to others in your age?**

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

3 **Do you have, or have you had?**

	Yes	No	Age first time
Heart attack	☐	☐	
Angina pectoris	☐	☐	
Stroke/brain hemorrhage	☐	☐	
Atrial fibrillation	☐	☐	
High blood pressure	☐	☐	
Osteoporosis	☐	☐	
Asthma	☐	☐	
Chronic bronchitis/Emphysyma/COPD	☐	☐	
Diabetes mellitus	☐	☐	
Psychological problems *(for which you have sought help)*	☐	☐	
Low metabolism	☐	☐	
Kidney disease, *not including urinary tract infection (UTI)*	☐	☐	
Migraine	☐	☐	

4 **Do you have persistent or constantly recurring pain that has lasted for 3 months or more?**

☐ Yes ☐ No

5 **How often have you suffered from sleeplessness during the last 12 months?**

- ☐ Never, or just a few times
- ☐ 1-3 times a month
- ☐ Approximately once a week
- ☐ More that once a week

6 **Below you find a list of different situations. Have you experienced some of them in the last week (including today)?** (Tick once for each complaint)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
You felt afraid or worried	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
You felt tense or upset	☐	☐	☐	☐
Easily blamed yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
You felt useless, worthless	☐	☐	☐	☐
Feeling that life is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future	☐	☐	☐	☐

USE OF HEALTH SERVICES

7 **Have you during the past year visited:**
If YES; how many times?

	Yes	No	No. of times
General practitioner (GP)	☐	☐	
Psychiatrist/psychologist	☐	☐	
Medical specialist outside hospital *(other than general practitioner/psychiatrist)*	☐	☐	
Physiotherapist	☐	☐	
Chiropractor	☐	☐	
Alternative medical practitioner *(homeopath, acupuncturist, foot zone therapist, herbal medical practitioner, laying on hands practitioner, healer, clairvoyant, etc.)*	☐	☐	
Dentist/dental service	☐	☐	

8 **Have you during the last 12 months been to a hospital?**

	Yes	No	No. of times
Admitted to a hospital	☐	☐	
Had consultation in a hospital without admission;			
At psychiatric out-patient clinic	☐	☐	
At another out-patient clinic	☐	☐	

9 **Have you undergone any surgery during the last 3 years?**

☐ Yes ☐ No

USE OF MEDICINE

10 **Do you take, or have you taken some of the following medications?** (Tick once for each line)

	Never used	Now	Earlier	Age first time
Drugs for high blood pressure	☐	☐	☐	
Lipid lowering drugs	☐	☐	☐	
Drugs for heart disease	☐	☐	☐	
Diuretics	☐	☐	☐	
Medications for osteoporosis	☐	☐	☐	
Insulin	☐	☐	☐	
Tablets for diabetes	☐	☐	☐	
Drugs for metabolism Thyroxine/levaxin	☐	☐	☐	

11 **How often have you during the last 4 weeks used the following medications?**(Tick once for each line)

	Not used the last 4 weeks	Less than every week	Every week, but not daily	Daily
Painkillers on prescription	☐	☐	☐	☐
Painkillers non-prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐

12 **State the names of all medications -both those on prescription and non-prescription drugs- you have used regularly during the last 4 weeks.** Do not include vitamins, minerals, herbs, natural remedies, other nutritional supplements, etc.

If the space is not enough for all medications, use an additional paper of your own.

When attending the survey centre you will be asked whether you have used antibiotics or painkillers the last 24 hours. If you have, you will be asked to provide the name of the drug, strength, dose and time of use.

FAMILY AND FRIENDS

13 **Who do you live with?** (Tick for each question and give the number)

	Yes	No	Number
Spouse/cohabitant	☐	☐	
Other persons older than 18 years	☐	☐	
Persons younger than 18 years	☐	☐	

14 **Tick for relatives who have or have had**

	Parents	Children	Siblings
Myocardial infarction	☐	☐	☐
Myocardial infarction before 60 years	☐	☐	☐
Angina pectoris	☐	☐	☐
Stroke/brain haemorrhage	☐	☐	☐
Osteoporosis	☐	☐	☐
Stomach/duodenal ulcer	☐	☐	☐
Asthma	☐	☐	☐
Diabetes mellitus	☐	☐	☐
Dementia	☐	☐	☐
Psychological problems	☐	☐	☐
Drugs/substance abuse	☐	☐	☐

15 **Do you have enough friends who can give you help when you need it?**

☐ Yes ☐ No

16 **Do you have enough friends whom you can talk confidentially with?**

☐ Yes ☐ No

17 **How often do you normally take part in organised gatherings, e.g. sports clubs, political meetings, religious or other associations?**

☐ Never, or just a few times a year
☐ 1-2 times a month
☐ Approximately once a week
☐ More than once a week

WORK, SOCIAL SECURITY AND INCOME

18 **What is the highest level of education you have completed?** (Tick one)

☐ Primary, 1-2 years secondary school
☐ Vocational school
☐ High secondary school (A-level)
☐ College/university less than 4 years
☐ College/university 4 years or more

19 **What is your main occupation/activity?** (Tick one)

☐ Full time work ☐ Housekeeping
☐ Part time work ☐ Retired/benefit recipient
☐ Unemployed ☐ Student/military service

20 **Do you receive any of the following benefits?**

- ☐ Old-age, early retirement or survivor pension
- ☐ Sickness benefit (are in a sick leave)
- ☐ Rehabilitation benefit
- ☐ Full disability pension
- ☐ Partial disability pension
- ☐ Unemployment benefits
- ☐ Transition benefit for single parents
- ☐ Social welfare benefits

21 **What was the households total taxable income last year?** Include income from work, social benefits and similar

- ☐ Less than 125 000 NOK
- ☐ 125 000-200 000 NOK
- ☐ 201 000-300 000 NOK
- ☐ 301 000-400 000 NOK
- ☐ 401 000-550 000 NOK
- ☐ 551 000-700 000 NOK
- ☐ 701 000 -850 000 NOK
- ☐ More than 850 000 NOK

22 **Do you work outdoors at least 25% of the time, or in cold buildings (e.g. storehouse/industry buildings)?**

- ☐ Yes
- ☐ No

PHYSICAL ACTIVITY

23 **If you have paid or unpaid work, which statement describes your work best?**

- ☐ Mostly sedentary work *(e.g. office work, mounting)*
- ☐ Work that requires a lot of walking *(e.g. shop assistant, light industrial work, teaching)*
- ☐ Work that requires a lot of walking and lifting *(e.g. postman, nursing, construction)*
- ☐ Heavy manual labour

24 **Describe your exercise and physical exertion in leisure time. If you activity varies much, for example between summer and winter, then give an average. The question refers only to the last year.** (Tick the one that fits best)

- ☐ Reading, watching TV, or other sedentary activity.
- ☐ Walking, cycling, or other forms of exercise at least 4 hours a week *(here including walking or cycling to place of work, Sunday-walking, etc.)*
- ☐ Participation in recreational sports, heavy gardening, etc. *(note:duration of activity at least 4 hours a week)*
- ☐ Participation in hard training or sports competitions, regularly several times a week.

25 **How often do you exercise?** (With exercise we mean for example walking, skiing, swimming or training/sports)

- ☐ Never
- ☐ Less than once a week
- ☐ Once a week
- ☐ 2-3 times a week
- ☐ Approximately every day

26 **How hard do you exercise on average?**

- ☐ Easy- do not become short-winded or sweaty
- ☐ You become short-winded and sweaty
- ☐ Hard- you become exhausted

27 **For how long time do you exercise every time on average?**

- ☐ Less than 15 minutes
- ☐ 15-29 minutes
- ☐ 30-60 minutes
- ☐ More than 1 hour

ALCOHOL AND TOBACCO

28 **How often do you drink alcohol?**

- ☐ Never
- ☐ Monthly or more infrequently
- ☐ 2-4 times a month
- ☐ 2-3 times a week
- ☐ 4 or more times a week

29 **How many units of alcohol** (a beer, a glass of wine or a drink) **do you usually drink when you drink alcohol?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 or more

30 **How often do you drink 6 units of alcohol or more in one occasion?**

- ☐ Never
- ☐ Less frequently than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

31 **Do you smoke sometimes, but not daily?**

- ☐ Yes
- ☐ No

32 **Do you/did you smoke daily?**

- ☐ Yes, now
- ☐ Yes, previously
- ☐ Never

33 **If you previously smoked daily, how long is it since you stopped?**

Number of years ☐☐

34 **If you currently smoke, or have smoked before: How many cigarettes do you or did you usually smoke per day?**

Number of cigarettes ☐☐

35 **How old were you when you began smoking daily?**

Number of years ☐☐

36 **How many years in all have you smoked daily?**

Number of years ☐☐

37 **Do you use or have you used snuff or chewing tobacco?**

- ☐ No, never
- ☐ Yes, previously
- ☐ Yes, sometimes
- ☐ Yes, daily

DIET

38 **Do you usually eat breakfast every day?**

☐ Yes ☐ No

39 **How many units of fruits or vegetables do you eat on average per day?** (units means for example a fruit, a cup of juice, potatoes, vegetables)

Number of units ☐☐

40 **How many times per week do you eat hot dinner?**

Number ☐☐

41 **How often do you usually eat these products?**
(Tick once for each line)

	0-1 times/ mth	2-3 times/ mth	1-3 times/ week	4-6 times/ week	1-2 times/ day
Potatoes	☐	☐	☐	☐	☐
Pasta/rice	☐	☐	☐	☐	☐
Meat *(not processed)*	☐	☐	☐	☐	☐
Processed meat *(sausages/meatloaf/meatballs)*	☐	☐	☐	☐	☐
Fruits, vegetables, berries	☐	☐	☐	☐	☐
Lean fish	☐	☐	☐	☐	☐
Fat fish *(e.g. salmon, trout, mackerel, herring, halibut, redfish)*	☐	☐	☐	☐	☐

42 **How much do you normally drink the following?**
(Tick once for each line)

	Rarely/ never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 or more glasses /day
Milk, curdled milk, yoghurt	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Soft drinks with sugar	☐	☐	☐	☐	☐

43 **How many cups of coffee and tea do you drink daily?** (Put 0 for the types you do not drink daily)

	Number of cups
Filtered coffee	☐☐
Boiled coffee (coarsely ground coffee for brewing)	☐☐
Other types of coffee	☐☐
Tea	☐☐

44 **How often do you usually eat cod liver and roe?** (i.e. "mølje")

☐ Rarely/never ☐ 1-3 times/year ☐ 4-6 times/year
☐ 7-12 times/year ☐ More than 12 times/year

45 **Do you use the following supplements?**

	Daily	Sometimes	No
Cod liver oil or fish oil capsules	☐	☐	☐
Omega 3 capsules *(fish oil, seal oil)*	☐	☐	☐
Vitamins and/or mineral supplements	☐	☐	☐

QUESTONS FOR WOMEN

46 **Are you currently pregnant?**

☐ Yes ☐ No ☐ Uncertain

47 **How many children have you given birth to?**

Number ☐☐

48 **If you have given birth, fill in for each child: birth year, birth weight and months of breastfeeding** (Fill in the best you can)

Child	Birth year	Birth weight in grams	Months of breastfeeding
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **During pregnancy, have you had high blood pressure?**

☐ Yes ☐ No

50 **If yes, which pregnancy?**

☐ The first ☐ Second or later

51 **During pregnancy, have you had proteinuria?**

☐ Yes ☐ No

52 **If yes, which pregnancy?**

☐ The first ☐ Second or later

53 **Were any of your children delivered prematurely (a month or more before the due date) because of preeclampsia?**

☐ Yes ☐ No

54 **If yes, which child?**

1st child ☐ 2nd child ☐ 3rd child ☐ 4th child ☐ 5th child ☐ 6th child ☐

55 **How old were you when you started menstruating?**

Age ☐☐

56 **Do you currently use any prescribed drug influencing the menstruation?**

Oral contraceptives, hormonal IUD or similar ☐ Yes ☐ No

Hormone treatment for menopausal problems ☐ Yes ☐ No

When attending the survey centre you will get a questionnaire about menstruation and possible use of hormones. Write down on a paper the names of all the hormones you have used and bring the paper with you. You will also be asked whether your menstruation have ceased and possibly when and why.

Appendix VIb

Questionnaire 2, Tromsø 6 2007-2008

Tromsø 6

- part of The Tromsø Study

FILL OUT THE FORM IN THIS WAY:

The form would be read by machine, it is therefore important that you tick appropriately:

☒ Correct

☑ Wrong

☒ Wrong

■ If you tick the wrong box, correct by filling the box like this

Write the numbers clearly 1 2 3 4 5 6 7 8 9 0

7 4 Correct

7 4 Wrong

Use only black or blue pen, do not use pencil or felt tip pen

1. DESCRIPTION OF YOUR HEALTH STATUS

Mark the statement that best fits your state of health today by ticking once in one of the boxes under each of the five groups below:

1.01 **Mobility**

- ☐ I have no problems in walking about
- ☐ I have little problems in walking about
- ☐ I am confined to bed

1.02 **Self-care**

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

1.03 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

1.04 **Pain and discomfort**

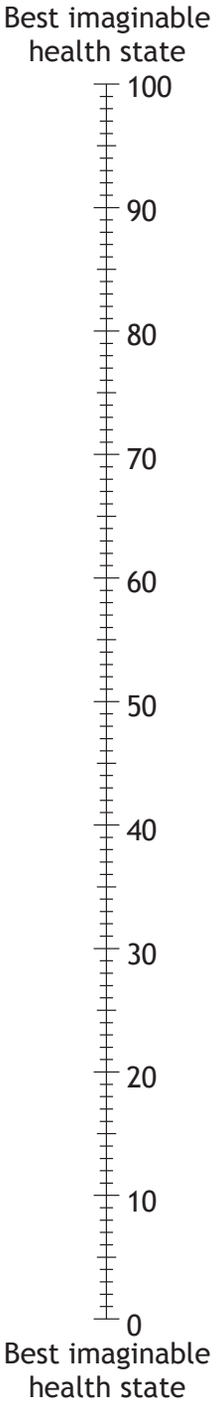
- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

1.05 **Anxiety and depression**

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

1.6 To allow you to show us how good or bad your state of health is we have made a scale (almost like a thermometer) where the best state of health you can imagine is marked 100 and the worst 0. We ask you to show your state of health by drawing a line from the box below to the point on the scale that best fits your state of health.

Your own health state today



2. CHILDHOOD/YOUTH AND AFFILIATION

2.01 **Where did you live at the age of 1 year?**

- ☐ In Tromsø *(with present municipal borders)*
- ☐ In Troms, but not Tromsø
- ☐ In Finnmark
- ☐ In Nordland
- ☐ Another place in Norway
- ☐ Abroad

2.02 **How was your family's financial situation during your childhood?**

- ☐ Very good
- ☐ Good
- ☐ Difficult
- ☐ Very difficult

2.03 **What is the importance of religion in your life?**

- ☐ Very important
- ☐ Somewhat important
- ☐ Not important

2.04 **What do you consider yourself as?** (Tick for one or more alternatives)

- ☐ Norwegian
- ☐ Sami ethnicity
- ☐ Kven/Finnish
- ☐ Another ethnicity

2.05 **How many siblings and children do you have/have you had?**

Number of siblings ..... ☐☐

Number of children ..... ☐☐

2.06 **Is your mother alive?**

☐ Yes ☐ No

If NO: her age when she died ..... ☐☐

Is your father alive?

☐ Yes ☐ No

If NO: his age when he died ..... ☐☐

2.07 **What was/is the highest completed education for your parents and your spouse/cohabitant?** (Tick once for each column)

	Mother	Father	Spouse/ cohabitant
Primary 7-10 years, 1-2 years secondary school	☐	☐	☐
Vocational school	☐	☐	☐
High secondary school (A level)	☐	☐	☐
College or university (less than 4 years)	☐	☐	☐
College or university (4 years or more)	☐	☐	☐

3. WELL BEING AND LIVING CONDITIONS

3.01 **Below are three statements about satisfaction with life as a whole. Then there are two statements about views on your own health. Show how you agree or disagree with each of the statements by ticking in the box for the number you think fits best for you.** (tick once for each statement)

	Completely disagree	1	2	3	4	5	6	7	Completely agree
In most ways my life is close to my ideal		☐	☐	☐	☐	☐	☐	☐	
My life conditions are excellent		☐	☐	☐	☐	☐	☐	☐	
I am satisfied with my life		☐	☐	☐	☐	☐	☐	☐	
I have a positive view of my future health		☐	☐	☐	☐	☐	☐	☐	
By living healthy, I can prevent serious diseases		☐	☐	☐	☐	☐	☐	☐	

3.02 **Below are four statements concerning your current job conditions, or if you are not working now, the last job you had.** (Tick once for each statement)

	Completely disagree	1	2	3	4	5	6	7	Completely agree
My work is tiring, physically or mentally		☐	☐	☐	☐	☐	☐	☐	
I have sufficient influence on when and how my work should be done		☐	☐	☐	☐	☐	☐	☐	
I am being bullied or harassed at work		☐	☐	☐	☐	☐	☐	☐	
I am being treated fairly at work		☐	☐	☐	☐	☐	☐	☐	

3.03 **I consider my occupation to have the following social status in the society**
(if you are not currently employed, think about your latest occupation)

- ☐ Very high status
- ☐ Fairly high status
- ☐ Middle status
- ☐ Fairly low status
- ☐ Very low status

3.04 **Have you over a long period experienced any of the following?** (Tick one or more for each line)

	No	Yes, as a child	Yes, as adult	Yes, last year
Been tormented, or threatened with violence	☐	☐	☐	☐
Been beaten, kicked at or victim of other types of violence	☐	☐	☐	☐
Someone in your close family have used alcohol or drugs in such a way that it has caused you worry	☐	☐	☐	☐

If you have experienced anything of the above, how much are you affected by that now?

☐ Not affected ☐ Affected to some extent ☐ Affected to a large extent

4. ILLNESS AND WORRIES

4.01 **Have you during the last month experienced any illness or injury?**

☐ Yes ☐ No

If YES: have you during the same period? (Tick once for each line)

	Yes	No
Been to a general practitioner	☐	☐
Been to a medical specialist	☐	☐
Been to emergency department	☐	☐
Been admitted to a hospital	☐	☐
Been to an alternative practitioner *(chiropractor, homeopath or similar)*	☐	☐

4.02 **Have you noticed sudden changes in your pulse or heart rythm in the last year?**

☐ Yes ☐ No

4.03 **Do you become breathless in the following situations?** (tick once for each question)

	Yes	No
When you walk rapidly on level ground or up a moderate slope	☐	☐
When you walk calmly on level ground	☐	☐
While you are washing or dressing	☐	☐
At rest	☐	☐

4.04 **Do you cough about daily for some periods of the year?**

☐ Yes ☐ No

If YES: Is the cough usually productive?

☐ Yes ☐ No

Have you had this kind of cough for as long as 3 months in each of the last two years?

☐ Yes ☐ No

4.05 **How often do you suffer from sleeplessness?** (tick once)

☐ Never, or just a few times a year
☐ 1-3 times a month
☐ Approximately once a week
☐ More than once a week

If you suffer from sleeplessness monthly or more often, what time of the year does it affect you most? (Put one or more ticks)

☐ No special time
☐ Polar night time
☐ Midnight sun time
☐ Spring and autumn

4.06 **Have you had difficulty sleeping during the past couple of weeks?**

☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.07 **Have you during the last two weeks felt unhappy and depressed?**

☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.08 **Have you during the last two weeks felt unable to cope with your difficulties?**

☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.09 **Below, please answer a few questions about your memory:** (tick once for each question)

	Yes	No
Do you think that your memory has declined?	☐	☐
Do you often forget where you have placed your things?	☐	☐
Do you have difficulties finding common words in a conversation?	☐	☐
Have you problems performing daily tasks you used to master?	☐	☐
Have you been examined for memory problems?	☐	☐

If YES to at least one of the first four questions above: Is this a problem in your daily life?

☐ Yes ☐ No

4.10 **Have you during the last last year suffered from pain and/or stiffness in muscles or joints in your neck/shoulders lasting for at least 3 consecutive months?**
(tick once for each line)

	No	A little	A lot
Neck, shoulder	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.11 **Have you suffered from pain and/or stiffness in muscles or joints during the last 4 weeks**

	No	A little	A lot
Neck, shoulder	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.12 **Have you ever had:**

	Yes	No	Age last time
Fracture in the wrist/underarm?	☐	☐	
Hip fracture?	☐	☐	

4.13 **Have you been diagnosed with arthrosis by a doctor?**
☐ Yes ☐ No

4.14 **Do you have or have you ever had some of the following:**

	Never	Little	Much
Nickel allergy	☐	☐	☐
Pollen allergy	☐	☐	☐
Other allergies	☐	☐	☐

4.15 **Have you ever experienced infertility for more than 1 year?**
☐ Yes ☐ No

If Yes: was it due to:

	Yes	No	Do not know
A condition concerning you?	☐	☐	☐
A condition concerning your partner?	☐	☐	☐

4.16 **To which degree have you had the following complaints during the last 12 months?**

	Never	Little	Much
Nausea	☐	☐	☐
Heartburn/regurgitation	☐	☐	☐
Diarrhoea	☐	☐	☐
Constipation	☐	☐	☐
Alternating diarrhoea and constipation	☐	☐	☐
Bloated stomach	☐	☐	☐
Abdominal pain	☐	☐	☐

4.17 **If you have had abdominal pain or discomfort during the last year:**

	Yes	No
Was it located in your upper stomach?	☐	☐
Were you bothered as often as once a week or more during the last 3 months?	☐	☐
Became better after bowel movement?	☐	☐
Are the symptoms related to more frequent or rare bowel movements than normally?	☐	☐
Are the symptoms related to more loose or hard stool than normally?	☐	☐
Do the symptoms appear after a meal?	☐	☐

4.18 **Have you ever had:**

	Yes	No	Age last time
Stomach ulcer	☐	☐	
Duodenal ulcer	☐	☐	
Ulcer surgery	☐	☐	

4.19 **For women: Have you ever had a miscarriage?**
☐ Yes ☐ No ☐ Do not know
If Yes: number of times

4.20 **For men: Have your partner ever had a miscarriage?**
☐ Yes ☐ No ☐ Do not know
If Yes: number of times

4.21 **Is your diet gluten-free?**
☐ Yes ☐ No ☐ Do not know

4.22 **Have you been diagnosed with Dermatitis Herpetiformis (DH)?**
☐ Yes ☐ No ☐ Do not know

4.23 **Have you been diagnosed with coeliac disease, based on a biopsy from your intestine taken in an endoscopy examination?**

☐ Yes ☐ No ☐ Do not know

4.24 **Do you have your natural teeth?**

☐ Yes ☐ No

4.25 **How many amalgam tooth fillings do you have/have you had?**

☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Have you been suffering from headache the last year?**

☐ Yes ☐ No

If No: go to section 5, food habits

4.27 **What kind of headache are you suffering from?**

☐ Migraine ☐ Other headache

4.28 **How many days per month do you suffer from headache?**

☐ Less than one day
☐ 1-6 days
☐ 7-14 days
☐ More than 14 days

4.29 **Is the headache usually:**
(tick one for each line)

	Yes	No
Pounding/pulsatory pain	☐	☐
Pressing/tightening pain	☐	☐
Unilateral pain *(right or left)*	☐	☐

4.30 **What is the intensity of your headache?**

☐ Mild *(do not hinder normal activity)*
☐ Moderate *(decrease normal activity)*
☐ Strong *(block normal activity)*

4.31 **What is the duration of the headache usually?**

☐ Less than 4 hours
☐ 4 hours – 1 day
☐ 1-3 days
☐ More than 3 days

4.32 **If you suffer from headache, when during the year does it affect you most?** (tick one or more)

☐ No special time
☐ Polar night time
☐ Midnight sun time
☐ Spring and/or Autumn

4.33 **Before or during the headache, do you have a transient:**

	Yes	No
Visual disturbances? *(flickering, blurred vision, flashes of light)*	☐	☐
Unilateral numbness in your face or hand?	☐	☐
Deterioration by moderate physical Activity?	☐	☐
Nausea and/or vomiting?	☐	☐

4.34 **Describe how many days you have been away from work or school during the last month due to headache?**

Number of days ☐☐

5. FOOD HABITS

5.01 **How often do you usually eat the following?** (tick once for each line)

	0-1 times per month	2-3 times per month	1-3 times per week	More than 3 times per week
Fresh water fish *(not farmed)*	☐	☐	☐	☐
Salt water fish *(not farmed)*	☐	☐	☐	☐
Farmed fish *(salmon, trout, char)*	☐	☐	☐	☐
Tuna fish *(fresh or canned)*	☐	☐	☐	☐
Fish bread spread	☐	☐	☐	☐
Mussels, shells	☐	☐	☐	☐
The brown content in crabs	☐	☐	☐	☐
Whale or seal meat	☐	☐	☐	☐
Pluck (liver/kidney/heart) from reindeer or elk/moose	☐	☐	☐	☐
Pluck (liver/kidney/heart) from ptarmigan/grouse	☐	☐	☐	☐

5.02 **How many time during the year do/did you usually eat the following?** (number of times)

	In adulthood	In childhood
Mølje (cod or pollack meat, liver, and roe) *(Number of times per year)*		
Gulls egg *(Number of eggs per year)*		
Reindeer meat *(Number of times per year)*		
Local mushroom and wild berries *(blueberries/lingonberries/cloudberries) (Number of times per year)*		

5.03 **How many times per month do you eat canned (tinned) foods (from metal boxes)?**

Number ☐

5.04 **Do you take vitamins and/or mineral supplements?**

☐ Yes, daily ☐ Sometimes ☐ Never

5.05 **How often do you eat?**

	Never	1-3 times per month	1-3 times per week	4-6 times per week	1-2 times per day	3 times per day or more
Dark chocolate	☐	☐	☐	☐	☐	☐
Light chocolate/milk chocolate	☐	☐	☐	☐	☐	☐
Chocolate cake	☐	☐	☐	☐	☐	☐
Other sweets	☐	☐	☐	☐	☐	☐

5.06 **If you eat chocolate, how much do you usually eat each time?**
Compared with the size of a Kvikk-Lunsj sjokolade *(a chocolate brand in the market)* and describe how much do you eat in relation to it.

¼	½	1	1 ½	2	More than 2
☐	☐	☐	☐	☐	☐

5.07 **How often do you drink cocoa/hot chocolate?**

Never	1-3 times per month	1-3 times per week	4-6 times per week	1-2 times per day	3 times per day or more
☐	☐	☐	☐	☐	☐

6. ALCOHOL

6.01 How often have you in the last year:	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Not been able to stop drinking alcohol when you have started?	☐	☐	☐	☐	☐
Failed to do what was normally expected of you because of drinking?	☐	☐	☐	☐	☐
Needed a drink in the morning to get yourself going after a heavy drinking session?	☐	☐	☐	☐	☐
Had feeling of guilt or remorse after drinking?	☐	☐	☐	☐	☐
Not been unable to remember what happened the night before because of your drinking?	☐	☐	☐	☐	☐

	Never	Yes, but not in the last year	Yes, during the last year
6.02 **Have you or someone else been injured because of your Drinking?**	☐	☐	☐
Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	☐	☐	☐

7. WEIGHT

7.01 **Have you involuntary lost weight during the last 6 months?**

☐ Yes ☐ No

If Yes: how many kilograms? ..... |__|

7.02 **Estimate your body weight when you were 25 years old:**

Number of kilograms ..... |__|__|

7.03 **Are you satisfied with your present body weight?**

☐ Yes ☐ No

7.04 **What weight would you be satisfied with (your "ideal" weight)?**

Number of kilograms ..... |__|__|

8. SOLVENTS

8.01 **How many hours per week, do you do the following leisure- or professional activities:**

Automobile repair/paint, ceramic work, painting/solvents, hair dressing, glazier, electrician. (Put 0 if you do not engage in such leisure or professional activities)

Number of hours per week on average |__|__|

8.02 **Do you use hair color preparations**

☐ Yes ☐ No

If Yes: How many times per year? |__|__|

9. USE OF HEALTH SERVICES

9.01 **Have you ever experienced that disease has been inadequately examined or treated, and that this had serious consequences?**

- ☐ Yes, this has happened to me
- ☐ Yes, this has happened to a close relative *(child, parents, spouse)*
- ☐ No

If Yes, where do you think the reason of the problem is? (tick once or more):

- ☐ With a general practitioner
- ☐ With an emergency medical doctor
- ☐ With a private practising specialist
- ☐ With a hospital doctor
- ☐ With another health personnel
- ☐ With an alternative practitioner
- ☐ with more than one person due to the failure of procedures and collaboration

9.02 **Have you ever felt persuaded to accept an examination or treatment that you do not want?**

☐ Yes ☐ No

If Yes, do you think this has had unfortunate health-related consequences?

☐ Yes ☐ No

9.03 **Have you ever complained about a treatment you have got?**

- ☐ Have never a reason for complaining
- ☐ Have considered complaining, but did not do that
- ☐ Have complained verbally
- ☐ Have complained in writing

9.04 **How long have you had your current general practitioner/other physician?**

- ☐ Less than 6 months
- ☐ 6 to 12 months
- ☐ 12 to 24 months
- ☐ More than 2 years

9.05 **At the last visit to the general practitioner, did the doctor(s) speak to you in a way so you understand them?** Answers to a scale from 0 to 10, where 0 = they were difficult to understand and 10 = they were always easy to understand

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

9.06 **How would you characterize the treatment or counselling, you got the last time you were with a doctor?** Answer on a scale from 0 to 10, where 0 = very bad treatment, and 10 = very good treatment

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

9.07 **Do you have during the last 12 months experienced that it has been difficult to be referred to special investigations (like X-ray or similar) or to specialized health service (private practising specialist or at hospital)?**

- ☐ Not applicable
- ☐ No problem
- ☐ Some problems
- ☐ Great problems

9.08 **Have you during the last 12 months experienced that it is difficult to be referred to physiotherapist, chiropractor or similar?**

- ☐ Not applicable
- ☐ No problem
- ☐ Some problems
- ☐ Great problems

9.09 **All in all, have you experienced that it is difficult or simply to be referred to specialized health services?**

- ☐ Not applicable
- ☐ Very difficult
- ☐ Somehow difficult
- ☐ Reasonably easy
- ☐ Very easy

9.10 **Have you during the last 12 months been to examination or treatment in specialized health service?**

☐ Yes ☐ No

If Yes, did the doctor(s) speak to you so that you understood them? Answer on a scale from 0 to 10, where 0 = they were difficult to understand and 10 = they were always easy to understand

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9.11 **How would you characterize the treatment or advice you got last time you were with a specialist?** Answer on a scale from 0 to 10, where 0 = very poor and 10 = very good

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9.12 **Have you ever before 2002 undergone an operation in hospital or specialist clinic?**

☐ Yes ☐ No

9.13 **Have you during the last 12 months used herbal medicine, natural means or natural medicines?**

☐ Yes ☐ No

9.14 **Have you during the last 12 months used meditation, yoga, qi gong or thai chi as own treatment?**

☐ Yes ☐ No

10. USE OF ANTIBIOTICS

10.01 **Have you used antibiotics during the last 12 months?** (all penicillin-like medicine in the form of tablets, syrups or injections)

☐ Yes ☐ No ☐ Do not remember

If YES: What did you get the treatment for? Have you taken many antibiotic treatments, tick for each treatment.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
• Urinary tract infection *(bladder infection, cystitis)*	☐	☐	☐	☐	☐	☐
• Respiratory tract infection *(ear, sinus, throat or lung infection, bronchitis)*	☐	☐	☐	☐	☐	☐
• Other	☐	☐	☐	☐	☐	☐
Treatment duration: number of days	|	|	|	|	|	|

How did you acquire the antibiotics for treatment? Have you acquired many treatments, tick for each one.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
With prescription from a doctor/dentist	☐	☐	☐	☐	☐	☐
Without contacting a doctor/without prescription:						
· Purchase from a pharmacy abroad	☐	☐	☐	☐	☐	☐
· Purchase over the internet	☐	☐	☐	☐	☐	☐
· Remnants from earlier treatment at home	☐	☐	☐	☐	☐	☐
· From family/friends	☐	☐	☐	☐	☐	☐
· Other ways	☐	☐	☐	☐	☐	☐

10.02 **Do you have antibiotics at home?**

☐ Yes ☐ No

If YES:is this after an agreement with your doctor for treatment of chronic or frequently recurring disease?

☐ Yes ☐ No

If No: how did you acquire this antibiotic? (Multiple ticks are possible)

Purchased from a pharmacy abroad ☐
Purchased over the internet ☐
Remnants from earlier treatment ☐
From family/friends ☐
Other ways ☐

10.03 **Would you consider using antibiotics without consulting your doctor?**

☐ Yes ☐ No

If YES: which conditions would you treat in such situation? (multiple ticks are possible)

Common cold ☐
Cough ☐
Bronchitis ☐
Sore throat ☐
Sinusitis ☐
Fever ☐
Influenza ☐
Ear infection ☐
Diarrhoea ☐
Urinary tract infection ☐
Other infections ☐

11. YOUR CIRCADIAN RHYTHM

We will ask you some questions about your sleeping habits

11.01 **Have you worked in a shift work schedule during the last 3 months?**

☐ Yes ☐ No

11.02 **Number of days per week which you cannot freely choose when you sleep (e.g. work days)?**

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Then I go to bed at ..... ☐☐:☐☐

I get ready to fall asleep at ..... ☐☐:☐☐

Number of minutes I need to fall asleep ..... ☐☐

I wake up at ..... ☐☐:☐☐

With help of: ☐ Alarm clock ☐ External stimulus *(noise, family members etc.)* ☐ By myself

Number of minutes I need to get up ..... ☐☐

11.03 **Number of days per week which you can freely choose when you sleep** (e.g. free days or holidays)

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Then I go to bed at ..... ☐☐:☐☐

I get ready to fall asleep at ..... ☐☐:☐☐

Number of minutes I need to fall asleep ..... ☐☐

I wake up at ..... ☐☐:☐☐

With help of: ☐ Alarm clock ☐ External stimulus *(noise, family members etc.)* ☐ By myself

Number of minutes I need to get up ..... ☐☐

12. SKIN AND DERMATOLOGY

12.01 **How often do you usually take a shower or a bath?** (tick once)

- ☐ 2 or more times daily
- ☐ 1 time daily
- ☐ 4-6 times per week
- ☐ 2-3 times per week
- ☐ Once a week
- ☐ Less than once a week

12.02 **How often do you during a day usually wash your hands with soap?** (tick once)

- ☐ 0 times
- ☐ 1-5 times
- ☐ 6-10 times
- ☐ 11-20 times
- ☐ More than 20 times

12.03 **Have you ever taken any antibiotics (penicillin and similar medicines) because of a skin disease, for example infected eczema, acne, non-healing leg ulcers, recurrent abscess?**

☐ Yes ☐ No

If Yes: How many times in average per year did you take antibiotics during the period you were most affected (tick once)

☐ 1-2 ☐ 3-4 ☐ More than 4 times

12.04 **Have you or have you ever had the following skin disorders?** (tick once for each line)

	Yes	No
Psoriasis	☐	☐
Atopic eczema (children's eczema)	☐	☐
Recurrent hand eczema	☐	☐
Recurrent pimples/spots for several months	☐	☐
Leg or foot ulcer that did not heal for 3-4 weeks	☐	☐

If Yes for the question on leg and/or foot ulcer, do you have the ulcer today?

☐ Yes ☐ No

12.05 **Have you often or always any of the following complaints?** (tick once for each line)

	Yes	No
Swelling in the ankles or legs, particularly in the evenings	☐	☐
Varicose veins	☐	☐
Eczema (red, itchy rash) on your legs	☐	☐
Leg pain when you walk, but is relieved when you stand still	☐	☐

12.06 **Have you ever had the following diagnoses by a physician?** (tick once for each line)

	Yes	No
Psoriasis	☐	☐
Atopic eczema	☐	☐
Rosacea	☐	☐

12.07 **Have you recurring large acne/abscesses that are tender/painful and often form scars in the following places?** (tick once for each line)

	Yes	No
Armpits	☐	☐
Under the breasts	☐	☐
Stomach groove/the navel	☐	☐
Around the genitalia	☐	☐
Around the anus	☐	☐
The groin	☐	☐

If Yes: Have you ever visited a physician because of abscesses?

☐ Yes ☐ No

If Yes, did you get any of the following treatments? (tick once for each line)

	Yes	No
Antibiotic ointment	☐	☐
Antibiotic tablets	☐	☐
Surgical drainage	☐	☐
A larger surgical intervention including skin removal	☐	☐
Surgical laser treatment	☐	☐

Follow-up questions

INFORMATION TO FOLLOW-UP QUESTIONS

The following pages with questions should not be answered by all. If you have answered yes to one or more of questions below, we ask you to move on to the follow-up questions on the topic or topics you have answered yes to. The first four topics are from the first questionnaire and the last question is from this form.

We have for the sake of simplicity highlighted topics with different colors so that you will find the questions that applies to you.

If you answered YES to that you have: long-term or recurrent pain that has lasted for 3 months or more, please answer the questions on page 19 and 20. The margin is marked with green.

If you answered YES to that you have undergone any surgery during the last 3 years, please answer the questions on page 21 and 22. The margin is marked with purple.

If you answered YES to that you're working outdoors at least 25% of the time, or in facilities with low temperature, such as warehouse/industrial halls, please answer the questions on page 23 The margin is marked with red.

If you answered YES to that you have used non-prescription pain relievers, please answer questions on page 24. The margin is marked with orange.

If you answered YES to that you have or have ever had skin problems (such as psoriasis, atopic eczema, non-healing leg or foot ulcerl, recurrent hand eczema, acne or abscesses), please answer the questions on page 25. The margin is marked with yellow.

If you have answered **NO** to these five questions, you are finished with your answers. The questionnaire is to be returned in the reply envelope you were given at the survey. The postage is already paid.

Should you wish to give us written feedback on either the questionnaire or The Tromsø Survey in general, you are welcome to that on page 26.

Do you have any questions, please contact us by phone or by e-mail. You can find the contact information on the back of the form. **THANK YOU** for taking the time to the survey and to answer our questions.

13. FOLLOW-UP QUESTIONS ON PAIN

You answered in the first questionnaire that you have protracted or constantly recurrent pain that has lasted for 3 months or more. Here, we ask you to describe the pain a little closer.

13.01 **How long have you had this pain?**

Number of years ☐☐ months ☐☐

13.02 **How often do you have this pain?**

- ☐ Every day
- ☐ Once a week or more
- ☐ Once a month or more
- ☐ Less than once a month

13.03 **Where does it hurt?** (Tick for all locations where you have protracted or constantly recurrent pain)

- ☐ Head/face
- ☐ Jaw/temporo-mandibular joint
- ☐ Neck
- ☐ Back
- ☐ Shoulder
- ☐ Arm/elbow
- ☐ Hand
- ☐ Hip
- ☐ Thigh/knee/leg
- ☐ Ankle/foot
- ☐ Chest/breast
- ☐ Stomach
- ☐ Genitalia /reproductive organs
- ☐ Skin
- ☐ Other locations

13.04 **What do you believe is the cause of the pain?** (Tick for all known causes)

- ☐ Accident /acute injury
- ☐ Long-term stress
- ☐ Surgical intervention/operation
- ☐ Herniated disk *(prolapse)* /lumbago
- ☐ Whiplash
- ☐ Migraine/headache
- ☐ Osteoarthritis
- ☐ Rheumatoid arthritis
- ☐ Bechterews syndrome
- ☐ Fibromyalgia
- ☐ Angina pectoris
- ☐ Poor blood circulation
- ☐ Cancer
- ☐ Nerve damage/neuropathy
- ☐ Infection
- ☐ Herpes zoster
- ☐ Another cause *(describe below)*
- ☐ Don't know

Describe the other cause:

.....

13.05 **Which kind of treatment have you received for the pain?** (Tick for all types of pain treatments you have received)

- ☐ No treatment
- ☐ Analgesic medications
- ☐ Physiotherapy/chiropractic treatment
- ☐ Treatment at a pain clinic
- ☐ Surgery
- ☐ Psycho-educative/relaxation training/ psychotherapy
- ☐ Acupuncture
- ☐ Complimentary medicine *(homeopathy, healing, aromatherapy, etc.*
- ☐ Another treatment

13.06 **On a scale of 0 to 10, where 0 corresponds to no pain and 10 corresponds to the worst possible pain you can imagine:**

How strong would you say that the pain usually is?	No pain	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Worst imaginable pain
How strong is the pain when it is in its strongest intense?	No pain	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Worst imaginable pain
To what degree does the pain interfere with your sleep?	No effect	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Impossible to sleep
To what degree does the pain interfere with performing common activities at home and at work?	No effect	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Can not do anything

14. FOLLOW-UP QUESTIONS ON SURGERY

In the first questionnaire you answered that you have undergone an operation during the last 3 years.

14.01 **How many times have you undergone surgery during the last 3 years?**

Number ..... ☐

Below, please describe the operation. If you have undergone several operations during the last 3 years, these questions concern the last surgery you underwent.

14.02 **Where in your body did you have surgery?** (If you were operated simultaneously in several places in the body, tick more than once)

Surgery in the head/neck/back
- Head/face ..... ☐
- Neck/throat ..... ☐
- Back ..... ☐

Surgery in the chest
- Heart ..... ☐
- Lungs ..... ☐
- Breasts ..... ☐
- Another surgery in the chest region ..... ☐

Surgery in the stomach/pelvis
- Stomach/intestines ..... ☐
- Inguinal hernia ..... ☐
- Urinary tract/reproductive organs ☐
- Gall bladder/biliary tract ..... ☐
- Another surgery in the stomach/pelvis ..... ☐

Surgery in the hip/legs
- Hip/thigh ..... ☐
- Knee/leg ..... ☐
- Ankle/foot ..... ☐
- Amputation ..... ☐

Surgery in the shoulder and arm
- Shoulder/overarm ..... ☐
- Elbow/underarm ..... ☐
- Hand ..... ☐
- Amputation ..... ☐

14.03 **Reason for the surgery:**
- Acute illness/trauma ..... ☐
- Planned non-cosmetic operation ..... ☐
- Planned cosmetic operation ..... ☐

14.04 **Where did you have the surgery?**
- Tromsø hospital ..... ☐
- Harstad hospital ..... ☐
- Other public hospital ..... ☐
- Private clinic ..... ☐

14.05 **How long time is it since you had surgery?**

Number of years ..... ☐ Months ..... ☐

14.06 **Do you have reduced sensitivity in an area near the surgical scar?**

☐ Yes ☐ No

14.07 **Are you hypersensitive to touch, heat or cold in an area near the surgical scar?**

☐ Yes ☐ No

14.08 **Does slight touch from clothes, showering or similar cause discomfort/pain?**

☐ Yes ☐ No

14.09 **If you had pain at the site of surgery before you had surgery, do you have the same type of pain now?**

☐ Yes ☐ No

14.10 **The pain at the site of surgery:** Answer on a scale from 0 to 10, where 0=no pain and 10=worst pain you can imagine

How strong pain did you have at the site of surgery before you had surgery	No pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Worst imaginable pain
How strong pain do you normally have at the site of surgery now	No pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Worst imaginable pain
How strong pain do you normally have at the site of surgery when it is most intense	No pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Worst imaginable pain

15. FOLLOW-UP QUESTIONS ABOUT WORK IN COLD ENVIRONMENT

In the first questionnaire you answered yes to that you work in cold environments. Here are some follow-up questions that we hope you will answer.

15.01 **Do you feel cold at work?**

- ☐ Yes, often
- ☐ Yes, sometimes
- ☐ No, never

15.02 **For how long have you been exposed to cold air below 0°C during the last winter?**

Leisure/hobbies *(hours/week)* ..... ☐☐

Work *(hours/week)* ..... ☐☐

Outdoors, with suitable clothing *(hours/week)* ..... ☐☐

Outdoors, without suitable clothing *(hours/week)* ..... ☐☐

Indoors, with no heating *(hours/week)* ☐☐

In cold, with wet clothing *(hours/week)* ..... ☐☐

Contact with cold objects/tools *(hours/week)* ..... ☐☐

15.03 **What ambient temperature prevents you from:**

	Under °C
Working outdoors	☐☐
Training outdoors	☐☐
Performing other activities outdoors	☐☐

15.04 **Have you during the last 12 months had a frostbite with blisters, sores or skin injury?**

☐ Yes ☐ No

If Yes, how many times? ..... ☐☐

15.05 **Have you had itching and/or rash in relation to cold exposure?**

☐ Yes ☐ No

15.06 **Have you during the last 12 months been involved in an accident which required medical treatment where cold was an important factor?**

	Yes	No
At work	☐	☐
In leisure time	☐	☐

15.07 **Do you experience any of the following symptoms while you are in a cold environment? If so, at what temperature do the symptoms occur?**

	Yes	No	Under °C
Breathing problems	☐	☐	☐☐
Wheezy breathing	☐	☐	☐☐
Mucus secretion from lungs	☐	☐	☐☐
Chest pain	☐	☐	☐☐
Disturbance in heart rhythm	☐	☐	☐☐
Impaired blood circulation in hands/feet	☐	☐	☐☐
Visual disturbance *(short term/transient)*	☐	☐	☐☐
Migraine *(short term/transient)*	☐	☐	☐☐
Fingers turning white *(short term/transient)*	☐	☐	☐☐
Fingers turning blue-red *(short term/transient)*	☐	☐	☐☐

15.08 **How does a cold environments and cold-related symptoms influence your performance?**

	Decrease	No effect	Improve
Concentration	☐	☐	☐
Memory	☐	☐	☐
Finger sensitivity *(feeling)*	☐	☐	☐
Finger skill *(motor)*	☐	☐	☐
Control of movement *(for example tremor)*	☐	☐	☐
Heavy physical work	☐	☐	☐
Long-lasting physical work	☐	☐	☐

16. USE OF NON-PRESCRIPTION PAINKILLERS MEDICATIONS

In the first questionnaire you answered that you had used non-prescription painkillers (analgesic) medications in the last 4 weeks. Here are some follow-up questions we hope you will answer.

16.01 **What types of non-prescription painkiller medications have you used?**

Paracetamol: *(Pamol, Panodil, Paracet, Paracetamol, Pinex)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ daily

How much you take usually daily when you use the medications?
(number of tablets, suppositories) ..... ☐☐

Acetylsalicylates: *(Aspirin,Dispril, Globoid)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much you take usually daily when you use the medications?
(number of tablets) ..... ☐☐

Ibuprofen: *(Ibumetin, Ibuprofen, Ibuprox, Ibux)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much you take usually daily when you use the medications?
(number of tablets, suppositories) ..... ☐☐

Naproxen: *(Ledox, Naproxen)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much you take usually daily when you use the medications?
(number of tablets) ..... ☐☐

Phenazone with caffeine: *(Antineuralgica, Fanalgin, Fenazon-koffein, Fenazon-koffein sterke)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ daily

How much you take usually daily when you use the medications?
(number of tablets) ..... ☐☐

16.02 **For which complains do you use non-prescription painkiller drugs?** (multiple ticks are possible)

- ☐ Headache
- ☐ Menstrual pain
- ☐ Migraine
- ☐ Back pain
- ☐ Muscle/joint pain
- ☐ Tooth pain
- ☐ Other

16.03 **Do you think you have experienced side effects of some of the medications?** (tick once for each line)

	Yes	No
Paracetamol	☐	☐
Acetylsalicylates	☐	☐
Ibuprofen	☐	☐
Naproxen	☐	☐
Phenazone with caffeine	☐	☐

16.04 **Where do you use to buy such medications?**

- ☐ Pharmacy
- ☐ Grocery
- ☐ Patrol stations
- ☐ Abroad
- ☐ Internet

16.05 **Do you combine the treatment with the use of prescribed pain-relief medications?**

☐ Yes ☐ No

17. FOLLOW-UP QUESTIONS ABOUT SKIN DISEASES

On page 15 in this questionnaire you answered that you have or have had a skin disease. Here are some follow-up questions we hope you will answer.

Answer on a scale from 0 to 10, where 0 corresponds to no symptoms and 10 correspond to worst imaginable complaints. If you answered YES to that you have or have had:

No complaint 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable complaints

17.01 **Psoriasis**
- How much are you affected by your psoriasis today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your psoriasis when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.02 **Atopic eczema**
- How much are you affected by your atopic eczema today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your atopic eczema when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.03 **Hand eczema**
- How much are you affected by your hand eczema today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your hand eczema when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.04 **Acne**
- How much are you affected by your acne today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your acne when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.05 **Abscesses**
- How much are you affected by your abscesses today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your abscesses when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.06 **Here is a list of factors that might trigger or exacerbate abscesses, tick for what you think apply to you:**

	Yes	No
Stress/psychological strain	☐	☐
Narrow/tight clothing	☐	☐
Menstrual periods	☐	☐
Pregnancy	☐	☐
Other	☐	☐

17.07 **How many episodes of abscesses do you usually have per year?** (tick once)

☐ 0-1 ☐ 4-6
☐ 2-3 ☐ More than 6

17.08 **How old were you when you got abscesses for the first time?**

☐ 0-12 years ☐ 26-35 years
☐ 13-19 years ☐ 36-50 years
☐ 20-25 years ☐ Older than 50 years

17.09 **If you no longer have abscesses, how old were you when it disappeared?**

☐ 0-12 years ☐ 26-35 years
☐ 13-19 years ☐ 36-50 years
☐ 20-25 years ☐ Older than 50 years

FEEDBACK

Should you wish to give us a written feedback on either the questionnaire or The Tromsø Study in general, you are welcome to it here:

Thank you for your help

Tromsø-undersøkelsen

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