UiT The Arctic University of Norway

Faculty of Health Sciences

Intracranial artery disease in the general population

The Tromsø Study

Liv-Hege Johnsen

A dissertation for the degree of Philosophiae Doctor. February 2024

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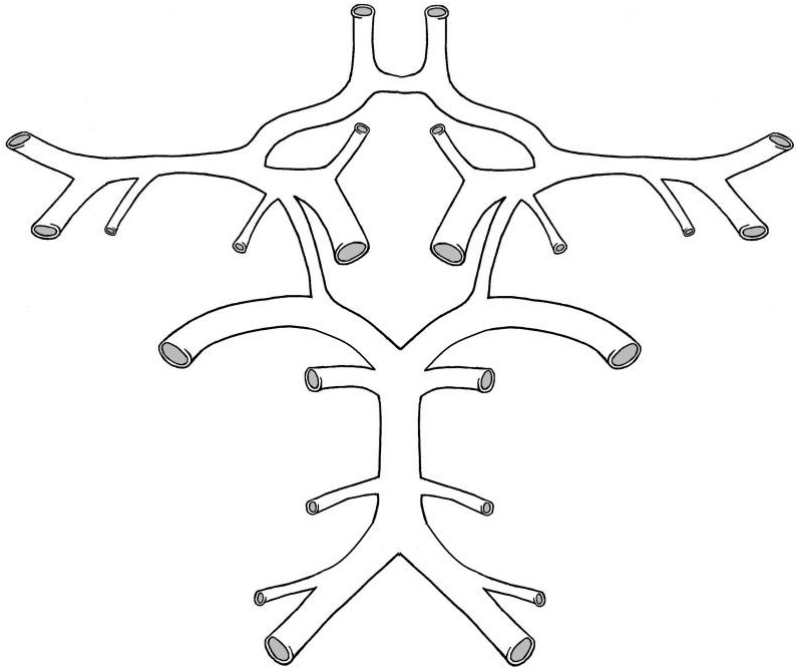

Intracranial arteries. Illustration by Ida Bjørnnes Holen

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“It does not matter how slowly you go as long as you do not stop”

Confucius, Chinese philosopher and reformer (551 BC – 479 BC)

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I recently read the following on Instagram: "*Enjoy your four years of PhD, because those five years will be the best seven years of your life*!" [@research_goes_slowly]

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Table of Contents

Summary

Intracranial aneurysms (IAs) and intracranial artery stenoses (ICAS) are diseases of the brain's arteries which can cause stroke. An IA is an outpouching of the artery wall that can rupture and lead to aneurysmal subarachnoid hemorrhage (aSAH), a type of stroke that often affects relatively young individuals, with both high mortality and the potential for severe disability. ICAS is a narrowing of a brain artery, most commonly caused by atherosclerosis, which can result in ischemic strokes due to reduced or blocked blood flow to the brain.

Data on the prevalence of both unruptured IAs (UIAs) and ICAS in Western populations is limited, and definitions of both UIAs and ICAS are varying across studies. The definitions vary concerning the threshold for the size of UIAs, the extent of arterial stenosis, and whether extradural lesions are included or not. Data on the prevalence of intradural UIAs, along with the incidence of aSAH, is necessary to calculate the risk of aneurysm rupture. ICAS is considered a significant cause of strokes in Asians and African Americans, but has been considered as less important in Western populations. The lack of prevalence data on UIA and ICAS in the Western population was the main motivation for this study.

This MRI study, which is a sub-study of the population-based Tromsø Study, is a cross-sectional study using 3-dimensional time-of-flight 3 Tesla MR angiography to identify UIAs and ICAS in 1878 adults aged 40-84 years. 3D T2-fluid attenuated inversion recovery (FLAIR) sequences, 3D T1-weighted sequences and susceptibility weighted images (SWI) were used for assessment of cortical infarcts, lacunes, white matter hyperintensities and brain parenchymal fraction (BPF) as a proxy for brain atrophy.

We found that the prevalence of UIAs ≥2 mm was 6.6%. Depending on the definition in terms of size and location, the prevalence ranged from 3.8% for intradural UIAs ≥3 mm to 8.3% for both intra- and extradural UIAs ≥1 mm. Together with data on the incidence of

aSAH, we calculated the annual risk of rupture for UIAs in the Tromsø population, which was 0.03% for UIAs<5 mm and 1.6% for UIAs ≥5 mm. The results support that UIAs ≥ 5 mm should be considered for prophylactic repair, while restraint should be exercised for UIAS < 5 mm.

The prevalence of ICAS ≥ 50% in our population was 6.0% and relatively similar to the prevalence of stenoses in the carotid arteries. We found an independent association between ICAS and age, male gender, hypertension, hyperlipidemia, current smoking, higher body mass index, and diabetes mellitus. Furthermore, we found that ICAS were associated with cortical brain infarctions, lacunes in the thalamus, periventricular white matter hyperintensities and brain atrophy.

Sammendrag

Intrakranielle aneurismer og stenoser er sykdommer i hjernens arterier som kan forårsake hjerneslag. Et aneurisme er en utposning av arterieveggen som kan sprekke og gi aneurismatisk subaraknoidalblødning (hjernehinneblødning), en tilstand som rammer relativt unge vokse og som både har høy dødelighet og potensial for alvorlig funksjonsnedsettelse. Arterielle stenoser er innsnevringer i hjernens arterier, oftest forårsaket av aterosklerose. Slike innsnevringer kan gi hjerneinfarkt grunnet redusert eller opphevet blodtilførsel til hjernen.

Det er begrensede data om forekomsten (prevalensen) av både aneurismer og stenoser i den vestlige befolkning, og definisjonene av både aneurismer og stenoser varierer mellom studier. Definisjonene varierer med hensyn til både størrelsen på aneurismene, grad av stenose og om ekstradurale lesjoner er inkludert eller ikke. Kunnskap om forekomsten av aneurismer sammenholdt med antallet nye tilfeller av hjernehinneblødning i en befolkning over en tidsperiode (insidensen) er nødvendig for å beregne hvor stor risikoen er for at et aneurisme skal sprekke og føre til hjernehinneblødning.

Intrakranielle stenoser anses som å være en viktig årsak til hjerneslag blant asiater og afroamerikanere, men har tradisjonelt vært ansett som en mindre viktig årsak i vestlige befolkninger. Mangelen på data om forekomsten av intrakranielle aneurismer og stenoser i vestlig befolkning var hovedmotivasjonen for denne studien.

Denne MRI-studien, som er en delstudie av den befolkningsbaserte Tromsøundersøkelsen, er en tverrsnittstudie som bruker 3-dimensjonal time-of-flight 3 Tesla MR-angiografi for å identifisere intrakranielle aneurismer og stenoser hos 1878 voksne i alderen 40-84 år. 3D T2-fluid attenuated inversion recovery (FLAIR) sekvenser, 3D T1-vektede sekvenser og susceptibility weighted images (SWI) ble brukt for vurdering av

kortikale infarkter, lakuner, hvitsubstansforandringer og brain parenchymal fraction (BPF) som er en proxy for hjerneatrofi.

Vi fant at forekomsten av intradurale aneurismer ≥2 mm var 6.6%. Avhengig av definisjon med tanke på størrelse og lokalisasjon varierte forekomsten på mellom 3.8% for intradurale aneurismer ≥3 mm til 8.3% for både intra- og ekstradurale aneurismer≥1 mm. Sammen med data om insidensen av aneurismatisk hjernehinneblødning beregnet vi den årlige risikoen for ruptur for aneurismer i Tromsøs befolkning. Den var 0.03% for aneurismer < 5 mm og 1.6% for aneurismer ≥ 5 mm. Resultatene gir støtte for at aneurismer ≥ 5 mm bør vurderes for profylaktisk behandling, mens man bør være tilbakeholden med behandling av aneurismer < 5 mm.

Prevalensen av intrakranielle stenoser ≥ 50% i vår populasjon var 6.0%, og dermed relativt lik prevalensen av stenoser i halspulsårene. Vi fant en uavhengig assosiasjon mellom stenoser og alder, mannlig kjønn, hypertensjon, hyperlipidemi, nåværende røyking, høyere kroppsmasseindex og diabetes mellitus. Videre fant vi at stenoser ≥ 50% var assosiert med kortikale hjerneinfarkter, lakuner i thalamus, periventrikulære hvitsubstansforandringer og hjerneatrofi.

List of papers

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

Paper I Johnsen LH, Herder M, Vangberg T, Kloster R, Ingebrigtsen T, Isaksen JG, Mathiesen EB. **Prevalence of unruptured intracranial aneurysms: impact of different definitions - the Tromsø Study**. *J Neurol Neurosurg Psychiatry.* 2022;93:902-7.

Paper II Johnsen LH, Herder M, Vangberg T, Isaksen JG, Mathiesen EB. **Prevalence of intracranial artery stenosis in a general population using 3D-time of flight magnetic resonance angiography.** *J Stroke Cerebrovasc Dis.* 2023;32:107399.

Paper III Johnsen LH, Herder M, Vangberg T, Isaksen JG, Mathiesen EB. **Association between intracranial artery stenosis and cortical infarcts, lacunes, white matter hyperintensities and brain atrophy in a general population.** (Submitted)

Abbreviations

ACOM	anterior communicating artery
ACA	anterior cerebral artery
BMI	body mass index
BPF	brain parenchymal fraction
CFR	case fatality rate
CTA	computed tomographic angiography
DSA	digital subtraction angiography
ECAS	extracranial carotid artery stenosis
ICA	internal carotid artery
ICAD	intracranial atherosclerotic disease
ICAS	intracranial artery stenosis
ICV	intracranial volume
LDL	low-density lipoproteins
MCA	middle cerebral artery
MRI	magnetic resonance imaging
MRA	magnetic resonance angiography
PCOM	posterior communicating artery
PCA	posterior cerebral artery
STRIVE	Standards for Reporting Vascular Changes on Neuroimaging
SAH	subarachnoid hemorrhage
SVD	small vessel disease
TCCS	transcranial color-coded sonography
TOF	time-of-flight
UIAs	unruptured intracranial aneurysms
WMHs	white matter hyperintensities
VR	volume rendering

MRA-VICAST method	MRA-Visual grading system for IntraCranial Stenosis
MRA-WASID method	WASID method applied on MRA

1 Introduction

Intracranial artery disease refers to pathological processes in the arteries within the skull or at the skull base. Intracranial aneurysms (IAs) and intracranial atherosclerotic disease (ICAD) are two examples of such conditions, both hypothesized to be initiated by endothelial dysfunction.[1,2] More than 90% of the IAs are of saccular type and defined as berry-like, spherical, sharply circumscribed sacs connected to the vessel by a neck.[1] IAs arises from weakening and thinning of the arterial wall and have the potential to grow and rupture, causing aneurysmal subarachnoid hemorrhage (SAH). ICAD involves thickening of the arterial wall. Progressive ICAD leads to narrowing of the arterial lumen and may evolve to intracranial artery stenosis (ICAS). Hypoperfusion, plaque rupture or intraplaque hemorrhage leading to in-situ or artery-to-artery thromboembolism or occlusion of perforating branches are the main mechanisms for ischemic stroke (IS) related to ICAS.[3-5] Together with intracranial hemorrhage (ICH), which occurs when an artery ruptures and bleeds into the brain parenchyma and/or into the ventricular system, SAH and IS constitute the three entities that collectively form the relatively heterogenous term "stroke".[6] Stroke is the second most common cause of death worldwide and the third-leading cause of death and disability combined.[7] Of all globally incident strokes reported in 2019, 62.4% were ischemic, 27.9% were attributed to ICH and 9.7% to SAH.[7] Unruptured intracranial aneurysms (UIAs) and ICAS are frequently diagnosed incidentally. Due to the growing availability and utilization of advanced neuroimaging, this tendency is likely to increase.[8,9] Data on the prevalence of both UIAs and ICAS varies depending on the type of study, the study population and definitions employed. Since strategies in management of both UIAs and ICAS are challenging, data on prevalence in the general populations is warranted.[10,11]

1.1 Pathophysiology of intracranial artery disease

Predilection sites for both saccular IAs and ICAS are regions of arteries that are exposed to complex blood flow such as the vicinity of branch points, bifurcations, and sharp curvatures where disturbed flow occurs.[1,2] Local factors such as hemodynamic forces, play a major role in the regional localization of both IA and ICAS. These factors include blood-pressure derived tension stresses and flow-generated endothelial shear stress, the latter suggested to be most important.[2] Shear stress is the tangential force that the flowing blood in motion exerts on the vessel walls that surround it, thus affecting the endothelium -the innermost layer in the vessel wall.[12] Wall shear stress is product of the blood viscosity and the shear rate at the wall. Shear rate describes how fast the blood velocity increases from areas at the arterial wall towards the central areas of the lumen. This phenomenon manifests as a decrease in the shear rate at the center of the lumen, followed by a gradual increase towards the vessel wall.[2] Shear stress and other mechanical forces that are exerted on the vessel wall,[13] alter the functions of the endothelial cells,[14] leading to endothelial dysfunction which is characterized by increased permeability of the vessel wall. The hemodynamic-induced endothelial dysfunction predispose the vessel wall to changes, and is hypothesized to initiate the formation of both IAs and atherosclerotic lesions.[1,2,12-14]

In addition to be the primary hemodynamic cause of formation of IAs, wall shear stress is also the cause of growth and rupture of IAs.[1] While high shear stress is commonly attributed to the formation of IAs, either by damaging endothelial cells or leading to loss of endothelial cells and fragmentation of the internal elastic lamina of the vessel wall,[1] it is noteworthy that both high and low shear stress are suggested to be implicated in aneurysm growth and rupture.[15,16] Low wall shear stress is commonly observed at the end of IAs such as the neck and dome regions of IAs, regions that are observed to demonstrate marked inflammatory vessel wall remodeling and loss of smooth muscle cells.[17] As the geometry,

composition, and strength of the distended vessel wall progressively deteriorate during the enlargement process, it becomes increasingly unable to withstand the stresses caused by the internal blood flow, ultimately leading to aneurysm rupture.[1]

In the case of atherosclerosis, low shear stress on the vessel wall is suggested to be the cause of both development and progression of atherosclerosis.[2] The increased permeability due to endothelial dysfunction, leads to accumulation of cholesterol-containing low-density lipoproteins (LDL) in the intima of the vessel wall.[14] This initiates a complex series of inflammatory and biochemical reactions involving accumulation of extracellular matrix, activation of the endothelium, infiltration of inflammatory cells, intimal thickening, fibrous cap formation, and angiogenesis.[18] Due to escalated inflammatory activation, the plaque grows gradually, leading to progressive stenosis and if the blood flow is compromised due to aforementioned mechanisms for stroke due to ICAS, IS may occur.[14]

1.2 Intracranial aneurysms

1.2.1 Subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH), constituting 80-85% of all SAH cases,[12] is a devastating condition with a high mortality rate.[19-21] With the advent of new and improved diagnostic and treatment options mortality tends to decrease.[19,22] A systematic review of 22 studies on sixteen populations from ten countries found that the short-term SAH case fatality rate (CFR) have declined during the last 40 years in all but two populations in Finland and Estonia.[19] During the period 1980-2000, the pooled weighted average of the overall 1-month CFR was 41% and during 2001-2020 it declined to 31%. In Europe the CFR changed from 41% to 33% when comparing these two periods.[19] SAH primarily affects relatively young patients, resulting in premature death, long-lasting disability and reduced quality of life.[23] However, approximately 20-30% of aSAH survivors are rendered permanently dependent.[23,24] The incidence of aSAH varies considerably based on geographic location, age, and gender.[25]

Register-based or regional studies have reported conflicting data on the reduction of SAH incidence over time.[25] In 2010, the global incidence of aSAH was estimated to be 6.1 per 100.000 person-years, representing a decline from 10.2 per 100 000 person-years in 1980.[25] ·Notably, Finland and Japan have significantly higher incidences of 16.6 and 28.0 per 100 000 person-years, respectively, with Japan experiencing an increasing trend.[25] Data from the Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag, the HUNT Study) reported an incidence of aSAH of 16.4 per 100 000 person-years.[26] In Northern Norway the crude incidence of aSAH in hospitalized patients was reported to be 10.0 per 100 000 person-years in the period 1999-2007,[27] declining to 5.4 per 100 000 person-years from 2007-2019.[21]

Unruptured IAs (UIAs) can be treated using microsurgical clipping or endovascular techniques to prevent future bleeding. However, these interventions carry significant risks.[28] In order to make informed decisions on prophylactic treatment, the best possible knowledge for evaluating the future rupture risk is essential. The rupture risk can be estimated when both the prevalence of UIAs and the incidence of aSAH is known. A high prevalence of UIAs, relative to the incidence of aSAH, suggest a lower risk of rupture, whereas a low prevalence indicates a higher likelihood of UIAs rupturing. Therefore, accurately determining the true prevalence of UIAs in populations becomes a crucial factor for such risk evaluation.

1.2.2 Prevalence of intracranial aneurysms

Estimating the true prevalence of UIAs in the general population is challenging due to the absence of large-scale population-based screening studies. Based on autopsy studies and angiographic studies, the prevalence is estimated to be between 0.2-9 %.[29,30] Three cross-sectional population-based studies utilizing magnetic resonance angiography (MRA) have been published. The Rotterdam Scan Study reported a prevalence of 2.3% in 5800 participants ≥45 years with a mean age of 64.9 years,[31] while a corresponding study of 4813 participants (age range 35-75 years) with a mean age 53.1 years from Shanghai, China, found

an overall prevalence of 7.0%.[32] In Norway, the HUNT study reported a prevalence of 1.9% in 1006 subjects aged 50–65 years with a mean age of 58.5 years.[2]

1.2.3 Risk factors for aneurysms and subarachnoid hemorrhage

The impact of well-known epidemiological risk factors will influence individual risk, but a fundamental challenge lies in conducting studies that can differentiate risk factors for aneurysm development from those of aneurysm rupture. The most important epidemiological risk factors for aSAH are smoking, hypertension, female gender, prior aSAH and family history of aSAH.[29,33-36] High intake of alcohol and caffeine has also been shown to increase risk, but controversy exists and thresholds for dangerous quantities are not established.[33,35] Genetic factors are probably involved in SAH, supported by the higher SAH incidence in Finland and Japan.[25,30,37] and the existence of familial aggregation, found in 10-11% of European SAH patients.[30,37] Incidence of SAH is increasing nonlinearly with age, with incidence peak for men in the 6th decade, for women in the 8th decade.[30]

Large-sized aneurysms are associated with increased risk of rupture.[28,29] The ISUIA 2 study found that aneurysms below 7 mm had an annual rupture risk of 0 to 2 %.[28] However, the majority of ruptured aneurysms are small, with 90% in the ISAT study being less than 10 mm and 52% less than 5 mm.[38] Despite their low rupture risk, there is controversy surrounding the management of UIAs less than 7.0 mm because they are a common cause of aSAH.[39] Studies stratifying the risk by location and size indicate that small aneurysms are not a homogenous group. Aneurysms located in the posterior circulation and the posterior communicating artery,[28] as well as aneurysms sized 4-6 mm located in the anterior communicating artery or the distal anterior artery, have higher rupture risk than small aneurysms in general. [28,29,40]

Various classifications of aneurysm morphology and relating this to risk of rupture has been proposed.[41] A case series of 29 aneurysms from a nationwide retrospective data collection, which assessed aneurysm morphology before and after rupture, concluded that post-rupture morphology should not be considered an adequate surrogate for the pre-rupture morphology in the evaluation of rupture risk.[42] A matched case-control study from the same cohort found that a straighter inflow angle may predispose an aneurysm to changes that further increase risk of rupture, while traditional parameters of aneurysm morphology may be of limited value in predicting IA rupture.[43]

1.3 Intracranial artery stenosis

1.3.1 Ischemic stroke

In Caucasians, extracranial carotid artery stenosis (ECAS) has been considered as an important cause of stroke, while intracranial artery stenosis (ICAS) has been regarded as less significant.[8,44] However, it has been suggested the actual impact of ICAS in Western populations may have been underestimated.[10,45-47] Among Asians, Hispanics and African Americans, ICAS has long been recognized as a common cause of stroke.[48-51] Some suggest that intracranial atherosclerotic disease is the most common cause of stroke globally, affecting up to 30-50% of Asian populations and 5-10% of White populations.[44,49,52,53] Recent studies suggest that the prevalence of ICAS is comparable to that of extracranial stenosis.[10,54]

The reported incidence and significance of ICAS in stroke patients vary considerably among countries and regions. ICAS is most common in stroke patients of Asian descent.[48,49] In a 6 years follow-up of the population-based Rotterdam study, intracranial internal carotid artery (ICA) calcification contributed to 75% of all strokes.[55]

1.3.2 Prevalence of intracranial artery stenosis

Data on the prevalence of asymptomatic ICAS is limited. A study on selected asymptomatic patients from a predominantly white cohort referred to Doppler ultrasound examination of the

carotid arteries, found ICAS in 13% of patients, as detected by transcranial doppler (TCD).[56] A review of four studies of 2593 asymptomatic individuals reported a prevalence of ICAS ranging from 3.5% to 13% depending on the age and the ethnic origin of the population studied.[47] There are a few population-based studies. Most of them are from Asia, with prevalence ranging from 4.7– 15.7%.[57-63] The Atherosclerotic Risk in Communities (ARIC) Study on 1765 participants (mean age 76 years) reported a prevalence of ICAS>50% of 8% in Caucasians assessed by MRA and high-resolution vessel wall imaging.[54] The Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) Study performed transcranial color-coded duplex (TCCD) on 933 participants (mean age 66.3 years), and reported a prevalence of ICAS>50% of 3.3% in asymptomatic participants with moderate to high vascular risk.[64,65] The population-based Rotterdam Study reported intracranial internal carotid artery calcification in 82% of the 2495 participants (mean age 69.6 years) using non-enhanced CT as a surrogate marker for intracranial atherosclerosis.[66] However, other studies using different diagnostic criteria and modalities reported considerably higher prevalence of intracranial atherosclerosis. An autopsy study on 5035 autopsy specimens found severe intracranial atherosclerosis in 43%, 65% and 80% of subjects aged 60-69, 70-79 and 80 and above, respectively.[67] A Chinese autopsy study of 114 consecutive patients, of which 85% were >40 years, reported ICAS>50% in 31.4%,[68] and French autopsy study found intracranial atherosclerotic plaque in 62% and ICAS in 43% of 333 patients with fatal stroke.[69]

1.3.3 Risk factors for intracranial artery stenosis

Most evidence regarding risk factors for ICAS is derived from hospital-based observational studies and clinical trials on symptomatic patients. The most consistently identified risk factors for ICAS appear to be age, hypertension and diabetes mellitus type 2.[5] Metabolic syndrome has been reported in nearly half of patients.[70,71] Several studies have found no association between smoking and ICAS.[64,72,73] Few studies have reported sex-specific results;

however, in the population-based Rotterdam study, smoking and excessive alcohol intake were identified as strong risk factors for intracranial artery calcification in men, while diabetes and hypertension were significant in women.[66] The ARIC Study reported that age, higher systolic blood pressure, and higher low-density lipoprotein cholesterol levels were associated with increased odds of ICAS.[54] In the Barcelona-AsIA study, diabetes, age and hypertension were associated with intracranial atherosclerosis in asymptomatic subjects with moderate-to-high vascular risk.[64]

1.3.4 Intracranial artery stenosis and structural brain changes

Possible mechanisms of stroke associated with ICAS include in-situ or artery-to-artery embolism, hypoperfusion, branch occlusive disease, or combination of these mechanisms.[74-76] which are likely to cause following infarct patterns: territorial pattern, border-zone pattern, perforator pattern and mixed pattern, respectively.[77] ICAS has, in several studies, also been associated with lacunar infarcts, white matter hyperintensities (WMHs) and brain atrophy, neuroimaging markers that are predominantly attributed to small vessel disease (SVD).[78,79] The etiology of SVD is not well understood, but as for ICAS and IA, endothelial dysfunction may be central for the initiation and development of SVD.[80]

1.3.4.1 Territorial and border-zone infarcts

Territorial infarcts are located cortical, subcortical or both, distal to a stenotic vessel, and are restricted to the territory supplied by a single intracranial artery.[77] Border-zone infarcts or watershed infarcts are located at the boundaries or junctions between two or three vascular territories, areas that are particularly vulnerable to reduced blood flow. In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, which enrolled symptomatic stroke patients, the most common stroke pattern observed was territorial. This pattern accounted for 44% of the anterior circulation strokes and 58% of posterior circulation strokes.[77]

1.3.4.2 Lacunar infarct and lacunes

Lacunar ischemic stroke is a specific subtype of ischemic stroke due to small (<2 cm), subcortical (hemispheric deep grey matter, white matter or the brainstem) infarcts caused by occlusion of a perforator artery, hence causing a perforator pattern.[81] Three possible mechanisms for lacunar infarcts have been suggested; 1) atherosclerotic occlusion at the orifice of the perforating artery or branch atheromatous disease, 2) atherotromboembolism from the carotid or intracranial arteries which occludes the perforating artery or 3) progressive intrinsic pathology in the arterial wall eventually leading to occlusion of the perforator artery, an entity associated with SVD.[81] Lacunar stroke constitutes 15-25% of all ischemic strokes in Western populations.[6,80-84]

A lacune is defined as a round or ovoid, subcortical, fluid filled cavity up to 15 mm in diameter. In addition to be the end tissue damage from a perforator/lacunar infarct, lacunes can also be the end tissue damage from small subcortical hemorrhages, incidental diffusion-weighted-imaging-positive lesions, or end-stage cavitation in WMHs.[85,86] In the newly updated "Standards for Reporting Vascular Changes on Neuroimaging" (STRIVE-2)-criteria, the term lacune is restricted to a cavitated lesion. Only when there is a reasonable certainty that the lacune follows a vascular insult the term "of presumed vascular origin" is added, which would be the case in lacunar infarcts.[86]

Independent association between ICAS and lacunes have been observed in two population-based studies from China. In the Shunyi Study, with 1237 participants, an association was found between lacunes and ICAS of any degree.[87] The PRECISE (Polyvascular Evaluation for Cognitive Impairment and Vascular Events) Study, with 3061 participants, reported an association between lacunes and ICAS≥50%.[88] Similarly, independent relationships were found between high burden of calcification in the proximal intracranial carotid and vertebrobasilar arteries, as a proxy for intracranial atherosclerosis, and

lacunes in the population-based Rotterdam Study with 1489 participants.[89] Within the WASID study patient cohort, subcortical lesions in the distribution of a perforating vessel originating at the site of a stenosis occurred in 15% and 36% of the ischemic strokes in the anterior and posterior circulation, respectively.[77] Another report from the WASID cohort showed a comparable risk of recurrent stroke in patients who initially represented with lacunar and non-lacunar strokes. As non-lacunar stroke was the most probable outcome for all patients, regardless of index stroke pattern, the authors suggested that the pathophysiology of lacunar strokes may be more closely related to stenosis than SVD.[90]

1.3.4.3 White matter hyperintensities

The Shunyi Study identified an independent association between ICAS of any degree and WMHs.[87] The PRECISE Study found that higher atherosclerotic burden was associated with higher WMH burden,[91] but not with ICAS≥50%.[88] The Rotterdam Study reported an independent association between high burden of calcification in the proximal intracranial arteries and WMHs.[89] ICAS was found to be independently associated with both progressive deep and moderate-to-severe periventricular WMHs in a Korean study on acute stroke patients,[92] though no association was found between intracranial or extracranial artery stenosis (ECAS) and WMHs in a study of 333 Chinese patients with cerebral atherosclerosis.[93]

1.3.4.4 Brain atrophy

Brain atrophy is a common observation in patients with atherosclerotic disease[94] and carotid stenosis have been suggested as risk factors for brain atrophy.[95,96] However, the relationship between ICAS and brain atrophy has not been extensively studied. The Shunyi Study found an independent association between ICAS and general brain atrophy, while larger arterial calcification volumes were associated with smaller white matter volumes in Rotterdam Study.[97] A small clinical study from USA on 68 patients with stroke-like symptoms showed

an independent association between high-grade calcifications in the cavernous part of the intracranial carotid artery and central brain atrophy, although not cortical atrophy.[98] Conversely, the SMART-MR Study in the Netherlands, which assessed vessel wall lesions on 7T MRI in 130 patients, did not find any association between ICAS burden and brain atrophy.[99]

1.4 Diagnostic imaging

Digital subtraction angiography (DSA), computed tomographic angiography (CTA), transcranial color-coded sonography (TCCS), and magnetic resonance angiography (MRA) with or without contrast enhancement are available modalities for evaluating intracranial arteries. DSA is still considered the gold standard for imaging and confirming both UIAs and ICAS, due to its excellent visualization of the intracranial vasculature.[100-102] However, its invasive nature, procedural risks, costs and limited availability make CTA and MRA the most frequently used diagnostic tools in clinical practice.[102,103] CTA and DSA expose patients to ionizing radiation,[102] and administration of intravenous iodine contrast, which may potentially cause allergic reactions, damage to the kidneys and radiation-induced cancer. Gadolinium-based contrast, used in contrast-enhanced MRA (CE-MRA) accumulate in the body and may potentially cause the lethal, progressive multiorgan fibrosing condition nephrogenic systemic fibrosis (NSF) in people with reduced kidney function.[104,105] DSA, CTA and CE-MRA visualize contrast-enhanced blood in the arterial lumen, enabling the depiction of ICAS and UIAs. However, these modalities face limitations in distinguishing between different causes of luminal stenosis, such as vasculitis versus atherosclerosis,[106] as assessment of the thin vessel walls of the intracranial arteries is challenging (CTA) or even impossible (DSA and CE-MRA). Three-Dimensional-Time-Of-Flight-MRA (3D-TOF-MRA) is a non-invasive MRA technique, that does not rely on contrast agent.[107] Instead, it depicts the flow of blood in the artery rather than directly imaging the arterial lumen itself. Loss of laminar flow and

turbulence within the artery can disrupt the signal, potentially resulting in an inaccurate impression of stenosis. Slow and turbulent flow result in flow saturation and phase dispersion, which may hinder complete delineation of UIAs.[108] TCCS, also a non-invasive modality, possess some capability to evaluate the vessel wall, mainly in the middle cerebral artery (MCA), but primarily estimates the degree of stenosis by assessing the flow velocity across an arterial stenosis.[109]

Intracranial high-resolution vessel wall imaging (HR-VWI) is a relatively recently developed technique which requires high spatial resolution and can assess the culprit vessel wall itself by offering optimal contrast in delineating the intracranial arterial wall and pathology therein. However, like CE-MRA, HR-VWI is also dependent on gadolinium-based contrast.[106]

1.4.1 Digital subtraction angiography

DSA is an invasive technique based on the injection of a radiopaque iodinated contrast agent from a catheter into the vessel of interest, obtaining a sequence of X-ray images showing the flow of the contrast through the vasculature.[102,110,111] The high spatial resolution of the DSA images,[112] is providing a very detailed map of the arterial tree which exceeds that of conventional CTA technology [102,110,113] and that of the typical MRA.[100,110] The high resolution that DSA offers, has made DSA to the superior modality in accurate assessment of the degree of ICAS, and in detecting and verifying UIAs < 3 mm.[111] The hemodynamic real-time assessment of the vasculature provided by DSA remains unparalleled, offering valuable insight into adverse hemodynamic conditions.[111] Two-dimensional (2D) DSA acquisitions are limited by overlap of the vessels located in the path of the X-rays as well as foreshortening of tortuous vessels twisting out of the image plane.[111] This can result in image artifacts that affect the contrast intensity and geometry visualization, which particularly can be a limitation

in assessment of aneurysm geometry. Rotational three-dimensional (3D) DSA overcomes these limitations, by offering a more comprehensive view.[111]

DSA is essential in planning and performing intraarterial intervention such as coiling and stenting of IAs and thrombectomy and stenting of symptomatic ICAS. However, continuous improvement of other non-or-minimal invasive modalities, such as photon counting detector CT systems may pose a potential challenge to the superiority of DSA in diagnosing both UIAs and ICAS in the future. Photon counting detector CT provides significantly higher resolution than DSA, with an in-plane spatial resolution of 0.125 mm compared to 0.3 mm provided by DSA,[112,114] thereby surpassing the resolution capabilities of DSA.

The most commonly used method for assessment of ICAS on DSA is the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method.[115] This method was developed for DSA and defines the stenosis as percent stenosis based on prestenotic (D_{normal}) and intrastenotic ($D_{stenosis}$) diameters in the following equation: percent stenosis =[(1-($\frac{Dstenosis}{Dnormal}$))] x 100.

1.4.2 Computed tomographic angiography

Conventional computed tomography (CT) utilizes X-rays and computer processing to produce detailed cross-sectional images or three-dimensional images. Conventional CTA combines the principles of CT with angiography to create cross-sectional or 3D-images of the blood vessels, offering a minimally invasive alternative to DSA. CTA provides comprehensive visualization of the vascular system by acquiring images during the first pass of intravenous iodinated contrast agent.[116.] Compared to DSA, the technique is widely available, quick to perform, less distorted from motion artifacts and less dependent on hemodynamic effects than MRA. However, similar to DSA, CTA exposes patients to ionizing radiation and requires

administration of intravenous iodine contrast, with associated risks. Limitations with CTA includes limited soft tissue resolution, posing challenges in the context of thrombosed UIAs. In cases of ICAS, calcified areas may exhibit a blooming effect, appearing larger than their actual size, potentially impacting the accuracy of ICAS assessment.[100] Additionally, CTA is reliant on precise timing of contrast injections to avoid suboptimal image quality, and is unable to evaluate blood flow dynamics.[100]

There are three main possible post-processing techniques for reconstruction of CTA images;[117] 1) multiplanar reformation (MPR) that allows adjustment of 2D images in arbitrary planes 2) maximum intensity projections (MIP), which enables viewing of both contrast filling and calcification in a vessel, and 3) volume rendering (VR) which provides 3D-images of the vessels. Software developments allowing free rotation of both MIP and 3D-VR reconstructions have increased the detection of both UIAs and ICAS.

Similar to the measurement of ICAS on DSA, the WASID method is applicable when working with CTA.[102,118]

1.4.3 Transcranial color-coded sonography

Transcranial color-coded sonography (TCCS) is a non-invasive method that utilizes ultrasound waves to measure blood flow velocity through specific acoustic windows in the skull.[109] When ultrasound waves emitted from the transducer probe encounter moving blood cells, the Doppler effect induces a change in the frequency of the waves. This change in frequency is detected by the transducer, and the observed alterations in frequency are translated into color-coded images. These images aid in identifying the direction and speed of blood flow in the vessels. The detection of intracranial stenosis with ultrasound is based on the principle that reduction in the vessel lumen results in an increase in blood flow velocity

(BFV). This flow velocity is then compared to BFV thresholds that vary for different major intracranial arteries.[109]

TCCS integrates the Doppler effect with ultrasound brightness mode (B-mode), a conventional ultrasound imaging technique that depicts the anatomical structure and morphology of the tissues.[109] Dependent on appropriate acoustic windows and operator`s skills, TCCS can visualize the circle of Willis, the carotid siphon, vertebrobasilar arteries and posterior cerebral arteries, and thereby assess both UIAs and ICAS. However, visualizing certain vessel, particularly those located deeper in the brain or behind bony structures, can be challenging. Limited soft tissue resolution can also be a concern when dealing with stenotic vessel wall assessment and thrombosed UIAs.[109]

1.4.4 Magnetic resonance angiography

MRA is a magnetic resonance imaging technique for visualizing blood vessels, and the assessment can be done with or without contrast agents.[107] Time-of-flight (TOF) MRA was among the earliest MRA methods, but suffered from long scan times and low sensitivity.[119] The introduction of gadolinium-based contrast agent in contrast-enhanced MRA (CE-MRA) significantly enhanced the visibility of the blood vessels on angiograms. The belief that gadolinium-based contrast was entirely safe to administer, led to less emphasis on advancing non-contrast MRA techniques. However, concerns arose in 2006 regarding the association between intravenous administration of gadolinium-based contrast agents and NSF,[104,105,119] prompting renewed interest in non-contrast MRA methods. Progress in non-contrast MRA techniques had been relatively slow due to limited alternatives and the need for improvements in scanner hardware and software. Today, multiple non-contrast MRA techniques are available, reflecting advancements in this field.[107]

1.4.4.1 Time-of flight magnetic resonance angiography

Time-of-flight MRA is now a widely used non-contrast MR imaging method for visualizing blood vessels, relying on the inflow effect of blood.[119] This effect arises from the difference in exposure to radiofrequency (RF) excitation between spins in stationary tissue and spins in inflowing blood. When a section (slice or slab) of tissue is repeatedly exposed to RF excitation, stationary spins become saturated, causing the longitudinal magnetization in that section to approach a low steady-state value resulting in low image signal intensity. However, the inflowing blood entering that particular section has not been exposed to the repeated RF excitation, thus arriving with fresh longitudinal magnetization, leading to high image signal intensity. This difference in the signal intensity between stationary tissue and flowing blood enables visualizing of blood flow without the use of contrast agents.[119] The inflow effect of blood depends on the refilling rate of the section. Blood velocity, repetition time (TR), and cross-sectional area of the vessel (related to the section thickness) are factors that determine the percentage of refreshed blood within a section. In 3D-TOF-MRA the slab thickness poses a challenge for inflow-based techniques. If the slab is thick, high blood velocity is required to refresh the slab, therefore most often 3D-TOF-MRA operates in the partial saturation regime. Enhanced inflow refreshment can be achieved by using multiple, thinner slabs to reduce the critical replacement velocity, and various methods are available to increase the inflow effect and reduce acquisition time.[119]

As the inflow effect is dependent on the vessel orientation relative to the imaging section, the optimal refreshment occurs for arteries running perpendicular to the thinnest dimension of the section volume. Vessels lying parallel with the imaging plane (in-plane) may experience lower refreshment rates and vessels protruding downward to the more caudal section will become saturated like stationary tissue, causing the signal to decrease.[119] This signal decrease can pose challenges in assessing ICAS, particularly for the carotid siphon,

MCA and vertebral arteries as they have entered the skull, as these arteries all have curved and possibly in-plane parallel lying courses.[119] Large aneurysms may be incompletely delineated on 3D-TOF-MRA due to saturation of slow flow and intravoxel phase dispersion in the presence of irregular flow, making detection challenging.[108]

Intracranial angiography is the most common application of MRA, and in particular, 3D-TOF-MRA has been used for diagnostic imaging of UIAs as well as ICAS. Development of MRI scanners with higher field strengths has significantly enhanced the signal-to-noise ratio (SNR) and increased the resolution.[119] In addition to improved SNR, higher field strength lengthens T1, thus resulting in reduced signal form stationary tissue. Further, multichannel receiver coil arrays generate higher SNR, which can be exchanged for higher resolution. Faster scan times is possible due to high bandwidth data acquisition hardware combined with faster and stronger gradients that facilitate shorter echo times (TEs) and TRs, and the application of parallel imaging and/or compressed sense in non-contrast MRA that have reduced shot durations and/or the total number of shots.[119] These technical improvements have propelled the overall progress of MRI, and has been particularly crucial in making non-contrast MRA applications feasible for routine clinical use. Presently, the high resolution of 3D acquisition allows for excellent visualization of small intracranial vessels. Given the negligible physiological motion in the head, long scan times exceeding five minutes are deemed acceptable for acquiring high-resolution images.[119]

As for CTA post-processing techniques for 3D-TOF-MRA includes MPR, MIP and 3D-VR. In terms of both aneurysm detection and morphology, the utilization of newer postprocessing techniques, particularly the implementation of VR, has significantly contributed to an excellent identification of aneurysm shape and enhanced detection capabilities.[120] The development of high-tesla MRI such as 3T MRI, improves image quality and the detection rate of UIAs, also those smaller than 3 mm.[120-122] Results even suggest that

aneurysms as small as 1 mm can be reliably detected with the VR algorithm.[123] However, the spatial resolution is still a limiting factor as discrimination between aneurysm and infundibula (small physiological symmetrical funnel-shaped enlargements at the origin of cerebral arteries) is challenging.[124]

As for DSA, the WASID method is the most common method for assessing ICAS on 3D-TOF-MRA. Recently, another method for assessment of ICAS has been introduced.[125] This method, called MRA-Visual grading system for IntraCranial Stenosis (MRA-VICAST method) was developed based on the hypotheses that: 1) TOF-MRA images may exaggerate the severity of ICAS, 2) reduced flow signal can be observed in the post-stenotic segment due to slow turbulent flow if the severity of the stenosis exceeds a certain level, and 3) subjective steps in the caliper measurement can impact the result.[125] In the MRA-VICAST method stenosis is graded as 1) mild (<50%) if the flow diameter of the stenotic segment is decreased but the flow diameter of the post-stenotic segment is preserved (equal to that of the pre-stenotic segment); 2) moderate (50%-69%) if the flow diameter of the stenotic segment is thread-like or non-existent (invisible), but the flow diameter of the post-stenotic segment is preserved; 3) severe (70%-99%) if the flow diameter of the stenotic segment is thread-like or non-existent (invisible) and the post-stenotic flow diameter is diffusely decreased compared to that of the pre-stenotic segment; and 4) occlusion where there is no distal flow.[125]

1.4.5 Diagnostic performance

Over the years, advancements in both hardware and software have improved the diagnostic performance of CTA, MRA, transcranial ultrasound. All modalities have been subjected to testing for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy when compared to DSA.

1.4.5.1 Intracranial aneurysms

TCCS plays a limited role in diagnosing UIAs compared to CTA and MRA. However, studies suggest that the detection of UIAs less than 5 mm is more accurate when using contrast-enhanced TCCS compared to non-contrast TCCS.[126]

Systematic reviews and meta-analyses of CTA performance reveal sensitivities ranging from 84% to 96%, specificities at 85%, and an overall accuracy of 89%.[127-129] The performance tends to be somewhat lower for smaller aneurysms, particularly those measuring less than 3 mm, with a reported sensitivity of 61%.[128]

Systematic reviews and meta-analyses of MRA indicate a sensitivity range of 80-95%, specificity between 87-95%, PPV of 97%, NPV of 77%, and an overall accuracy of 90%. Some studies report that sensitivity drops to 38% for aneurysms smaller than 3 mm.[128-131] However; 3T showed higher diagnostic performance compared to studies with lower field strength in one of these meta-analysis,[130] in line with a study conducted on 3T that reported sensitivity of 100% for UIAs, specificity of 84%, PPV of 98%, NPV of 100%, and an overall accuracy of 98%. Still, the performance was better for aneurysms measuring ≥3 mm.[132] Furthermore, no effects on diagnostic performance were observed between contrast-enhanced MRA (CE-MRA) and time-of-flight (TOF) techniques. Comprehensive meta-analyses, spanning studies from 1950-2017.[127] and 1988-2014,[128,130] concluded that both CTA and MRA have high and equivalent diagnostic value for intracranial aneurysms.[128,130]

1.4.5.2 Intracranial stenosis

For intracranial stenosis, the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial compared MRA and Transcranial Doppler (TCD) to identify ICAS of 50-99%. The PPV for MRA and TCD was 59% and 36%, respectively while NPV was reported as 91% for MRA and 86% for TCD [101] The study indicated that both methods reliably exclude the presence of ICAS. A systematic review on transcranial TCD and TCCS

compared to DSA, CTA, and MRA on patients with acute ischemic stroke reported a summary estimate of both sensitivity and specificity at 95%.[133] Studies on CTA report sensitivities of approximately 97%, specificities of 99.5%, and NPV of 99%.[118,134] In a two observer study on 3D-TOF-MRA at 3T the sensitivity was approximately 78-85%, specificity was 95%, PPV was 75-79%, and NPV was 95-97% when using a 50%–99% threshold of diameter stenosis.[135] The newly proposed MRA-VICAST method compared to the MRA WASID method against DSA, showed a sensitivity of 94.7% vs. 97.3%, specificity of 96.5% vs. 57.9%, PPV of 97.3% vs. 75.3%, NPV of 93.2% vs. 94.3%, and an overall accuracy of 95.5% vs. 80.3%.[125]

In addition to the modalities above, other and more advanced radiological techniques are emerging to profile pathological features of both intracranial aneurysms and stenoses. Studies report that HR-VWI provides more accurate stenosis measurements than 3D-TOF-MRA compared to CTA for stenosis >50% with a sensitivity of 82% for HR-VWI and 64% for MRA. Specificity was 75% for both HR-VWI and 3D-TOF-MRA which can indicate VWI as more reliable for quantitative evaluation relative to MRA.[136]

1.5 Knowledge gaps and rationale for the thesis

Data on prevalence of UIAs is limited and varies between studies.[11] Knowledge on prevalence is essential for estimation of rupture risk, which has important implications for treatment decisions. There is a lack of consistency in the definitions of UIAs across studies, both regarding threshold for size and whether extradural UIAs are included or not.[26,31,32] Given these differing definitions, investigation of how the prevalence changes by altering the definition of UIA would be interesting. Such exploration would also facilitate meaningful comparisons between studies. In light of the increasing incidence of aSAH by age and the increasing proportion of elderly individuals in the population, determination of the prevalence of UIAs across a broad age span of the adult population is important. In this population-based

cross-sectional study of inhabitants of Tromsø Municipality, we aimed to provide data on the prevalence of UIAs. As we also, through an institutional specific quality register at the Neurosurgical Department at the University Hospital in North Norway (UNN), are able to achieve data on the incidence of aSAH in the same population, this study offers a unique possibility to estimate risk of rupture of UIAs in the Tromsø population.

Knowledge on the prevalence and risk factors of ICAS and its impact on structural brain lesion in Caucasians populations is scarce.[10] Increased knowledge in this area is important both for risk estimation and for identifying modifiable risk factors that can be a target of prevention of clinical manifestations of the disease.[66] In our population-based cross-sectional study we aim to provide data on prevalence of ICAS and study the association between ICAS and cardiovascular risk factors and structural brain changes, such as cortical infarcts, WMHs, lacunes and brain atrophy.

The data obtained from this study may also serve as baseline for future prospective studies on incidence, risk factors and clinical implications of UIAs and ICAS.

2 Aims of the thesis

The objectives of this thesis were

1. To study the prevalence, distribution and size of unruptured intracranial aneurysms (UIAs) in a general adult population and explore how the definition of UIA influences prevalence estimates.
2. To study the prevalence, distribution and severity of intracranial artery stenosis (ICAS) in a general adult population and the association between ICAS and cardiovascular risk factors.
3. To study the association between intracranial artery stenosis (ICAS) and cortical infarcts, white matter hyperintensities, lacunes and brain atrophy in a general population.

3 Subject and Methods

3.1 The Tromsø Study

3.1.1 Study design and study population

The Tromsø Study is an ongoing, extensive, multiphase and multipurpose health and research study primarily involving adult inhabitants of the municipality of Tromsø, Norway.[137.138] The study was initiated in 1974 as "The Tromsø Heart Study"[139] The study employs a repeated cross-sectional surveys design, inviting total birth cohorts and selected samples, based on the official population registry. The Department of Community Medicine (ISM) at UiT The Arctic University of Norway conducts the studies in collaboration with the Norwegian Institute of Public Health, the University Hospital of North Norway (UNN) and Tromsø City Council. Over the years, the study has gradually expanded to encompass various diseases.[137.138] Data from the study contribute to several international collaborative projects and form part of a broader Norwegian collaborative study involving multiple community studies to facilitate larger prospective studies. Currently, the Tromsø Study comprises seven surveys which were conducted in 1974 (referred to as Tromsø 1), 1979–1980 (Tromsø 2), 1986–1987 (Tromsø 3), 1994–1995 (Tromsø 4), 2001-2002 (Tromsø 5), 2007–2008 (Tromsø 6), and 2015-2016 (Tromsø 7).[138] The surveys encompass questionnaire data, clinical measurements and sampling of biological specimens. Additionally, clinically oriented examinations have been conducted in large subgroups beyond the core protocol. Information on the variables registered in the different surveys are accessible on the Helsedata website.[140]

3.1.1.1 The seventh survey of Tromsø Study

The seventh survey was conducted in 2015–2016, where 21 083 (65%) of 32 591 invited citizens aged 40 years and older attended the first visit.[138] The attendance was lower for men, individuals under 50 and above 80 years, individuals who never have attended the survey, and for individuals born outside of Norway. The standard questionnaires covered a range of

topics, including prevalent cardiovascular diseases, cardiovascular symptoms, diabetes, physical activity, smoking habits, drinking habits, use of blood-pressure lowering medication, cholesterol-lowering medication and diabetes medication[138] (Appendix I - Questionnaire). All participants underwent a physical examination which included measurements of blood pressure, pulse, height, weight, hip and waist circumference. Blood samples including measurements of cholesterol, and glycated hemoglobin (HbA1c) were analyzed using established methods.

3.1.1.2 Participants in the MRI study

A subsample consisting of 75%, who were randomly drawn from 10-year age bands in men and women, and of 25% who had participated in the 2nd visit of the 6th Tromsø Study was invited to a second visit for various extended clinical examinations, and 8346 (90.2%) of the 9253 invited attended.[138] Due to limited capacity for MRI, we chose to invite the 3027 participants who had also been examined with ultrasound of the carotid arteries to participate in a magnetic resonance imaging (MRI) study of the brain and intracranial arteries conducted between January 2016 and November 2017. (Appendix II – invitation brochure to the MRI Study) In addition to attendance at the ultrasound examination, inclusion criteria for the MRI study were informed consent and meeting standard safety measures, including claustrophobia and weight exceeding 150 kg. (Appendix III -checklist for MRI scanning).

Participants who attended the ultrasound examinations from January 2016 till August 2016, received oral and written information about the MRI study upon attendance. Those who expressed interest were contacted by telephone and interviewed based on an MRI safety checklist to determine their eligibility for inclusion in the study. Of the 2033 that were invited at the ultrasound station, 1332 invited attended the MRI study. Since the financial arrangements for the MRI study were not clarified until December 2015, 994 participants who had attended ultrasound examination before that time, were invited to attend the MRI study

by letters sent by mail. (Appendix IV – invitation letter to the MRI Study). Of those invited by mail, 546 attended the MRI study.

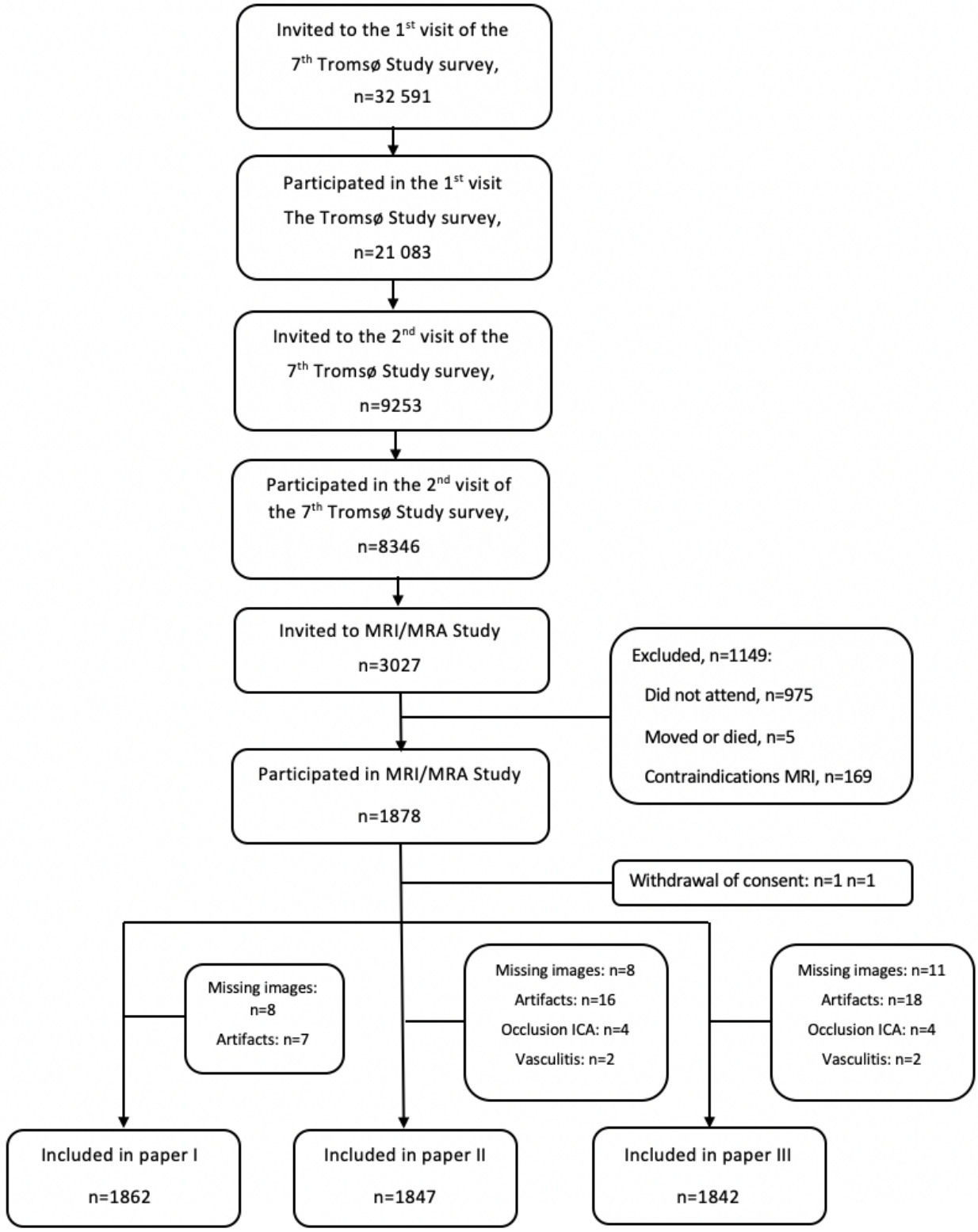
In total, 1878 (62.0%) out of 3027 invited participated in the MRI study, 880 (46.9%) men and 998 women (53.1 %). (Figure 1) Of the 1149 individuals who did not participate in the MRI study, 169 were excluded because of contraindications for MRI, and five were excluded because they had moved or died before the MRI examination. Of the 1878 subjects who underwent MRA scanning, 3D-TOF-MRA images were missing in eight participants and one participant later withdrew consent.

In paper I image quality was deemed as insufficient for assessment of UIAs in seven participants, leaving 1862 participants who were included in the final analysis.

In paper II image quality was deemed as insufficient for assessment of ICAS in 16 participants. Four participants had occlusion of the extracranial carotid artery, and two participants had findings consistent with vasculitis, leaving 1847 participants who were included in the final analysis.

In paper III, the 1847 participants included in paper II were eligible for analysis. In two participants the quality of the fluid attenuated inversion recovery (FLAIR) images was insufficient for assessment, and for three participants the FLAIR images were missing, leaving 1842 participants who were included in the final analysis.

Figure 1: Flow chart of participants in the MRI study



3.1.1.3 Assessment of images and handling of findings

Initial screening of all images was done by an experienced professional in neuroimaging and head- and neck radiology. In cases with potential clinically relevant findings in need of treatment or follow-up, participants were contacted and referred to relevant outpatient clinics at (neurosurgeon, neurologist, head and neck specialist and internist) at the University Hospital of North Norway, Tromsø for clinical follow-up and management according to department policies.

Participants with UIAs were referred to the neurosurgical outpatient clinic. In cases of uncertainty and in cases of UIAs less than 2 mm, the images were presented and discussed in a multidisciplinary meeting with the author, a neuroradiological endovascular interventionists and a neurosurgeon specialized in aneurysm surgery. Decisions were made by consensus. Patients with definite and possible ICAS were discussed with a vascular neurologist and referred to follow-up at the neurological outpatient clinic

3.1.1.4 Ethics

The study received approval from the Regional Committee of Medical and Health Research Ethics North Norway (file no. 2014/1665) and was conducted in adherence to relevant guidelines and regulations. In both Tromsø 7 and the MRI Study, each participant signed a written informed consent after receiving information brochures upon invitation. In the brochures the dual aim of the Tromsø Study is presented (Appendix 4).

3.1.1.5 Funding

The MRI/MRA study was funded by the Northern Norway Regional Health Authority. The main funding sources of the 7th wave of the Tromsø Study were UiT The Arctic University of Norway, North Norwegian Regional Health Authority, Norwegian Ministry of Health and Care Services, University Hospital of North Norway, and Troms County, in addition to the subprojects' own funding from a variety of sources.

3.1.2 Assessment of cardiovascular risk factors

Information on risk factors were obtained by questionnaires and physical measurements. All measurements were done at the date of the first visit.[138]

Blood pressure was measured with a Dinamap ProCare 300 (GE Healthcare, Norway). Measurements were done in a seated position on the right arm three times at one-minute intervals after two minutes seated rest.[138] Weight and height were measured with light clothing and no footwear with a Jenix DS-102 scale (DongSahn Jenix, Seoul, Korea). Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering medication and/or self-reported hypertension.

Non-fasting blood samples were obtained with a light tourniquet released after venipuncture. Serum samples were processed after 30–60 minutes in room temperature, centrifuged for 10 minutes at 2000***g***, transferred within 1 hour to plastic tubes, kept between 1°C and 10°C.[138] Total cholesterol, LDL and HDL levels were analyzed by standard enzymatic methods.131 Hyperlipidemia was defined as serum total cholesterol ≥7 mmol/L and/or serum LDL ≥5 mmol/L and/or use of cholesterol lowering medication.

HbA1c was measured by high performance liquid chromatography.[138] Diabetes was defined as HbA1c ≥6.5% and/or self-reported diabetes and/or current use of diabetes medication.

Information on smoking habits were obtained from questionnaires. Smoking status was defined as daily current smoking.

3.1.3 Data from imaging: scanning and assessment

3.1.3.1 MRI Acquisition and processing

The participants were scanned with a 3 Tesla (3T) Siemens Skyra MR scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. The MRI protocol included a 3D time-of-flight MRA sequence (3D-TOF-MRA), a 3D T2 fluid-attenuated-inversion-recovery sequence (FLAIR), a 3D T1-weighted sequence, and a susceptibility weighted sequence (SWI). Total scan time was 22 minutes.

3D-TOF-MRA images were acquired with a 3D transversal fast low angle shot (FLASH) sequence with flow compensation (TR/TE = 21/3.43 ms, GRAPPA parallel imaging acceleration factor 3, FOV 200 x 181 mm, slice thickness 0.5 mm, 7 slabs with 40 slices each). Reconstructed image resolution was 0.3 x 0.3 x 0.5 mm. Acquired voxel size: 0.55 x 0.52 x 1 mm.

3D-FLAIR images were acquired with a 3D turbo spin-echo sequence with variable flip angle (TR/TE/TI = 5000 ms/388 ms/1800 ms, partial Fourier = 7/8). The T1w and FLAIR scans were acquired sagittally with 1 mm isotropic resolution, GRAPPA parallel imaging acceleration factor 2, FOV = 256 mm, 176 slices, 1 mm slice thickness, 256 x 256 image matrix.

3D T1-weighted images were acquired with a 3D magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (flip angle=9°, TR/TE/TI=2300 ms/4.21 ms/996 ms).

Susceptibility weighted images (SWI) were acquired transversally (flip angle = 15°, TR/TE = 28/20 ms, GRAPPA parallel imaging acceleration factor 3, partial Fourier = 7/8, FOV = 220 x 220 mm, slice thickness 1.3 mm, 88 slices). Reconstructed image resolution was

0.6 x 0.6 x 1.6 mm. To ensure consistent slice prescription across examinations, the slice prescription was automatically aligned to a standardized brain atlas.[141]

3.1.3.2 Assessment of intracranial arteries

Assessment of UIAs and ICAS was conducted on a Sectra workstation, Sectra IDS7 (v22.1.12.4835), by two experienced neuroradiologists (MH and LHJ) utilizing source images and reconstructions of the 3D-TOF-MRA images with MIP, MPR and 3D-VR.

Paper I: Assessment and definition of intracranial aneurysms

For UIAs, additional single arterial segmentation of the 3D-VR reconstructions was performed to optimize the evaluation of morphology, when needed. The UIAs were measured on MPR of the axial 3D-TOF-MRA source images. The threshold for window width and window level was allowed to be changed to discriminate between small aneurysms and infundibula.

All visible abnormal focal saccular dilatations were measured from the center of the neck plane to the dome apex, and then perpendicular to this axis. Additionally, any diameter between any two points in the aneurysm sac that was greater than these two diameters was recorded, and the maximum diameter defined the aneurysm size. Fusiform aneurysms (n=5) were excluded.

We categorized aneurysm locations on the internal carotid artery (ICA) according to the Bouthiller classification.[142] Aneurysms located in and distal to the clinoid segment (C5) were defined as intradural. The C7-segment of the ICA was further subdivided into the posterior communicating artery (PCOM), the anterior choroid artery and terminus. We categorized UIAs located to the anterior cerebral artery (ACA) as A1-segment, anterior communicating artery (ACOM) and distal anterior cerebral artery, the middle cerebral artery

(MCA) as M1-segment, bifurcation of M1 and M2-segment, the posterior cerebral artery as P1-segment and P2-segment and vertebrobasilar arteries as basilar artery, superior cerebellar artery, posterior inferior cerebellar artery and anterior inferior cerebellar artery. The sizes were categorized as; 1–1.9 mm, 2–2.9 mm, 3–4.9 mm, 5–6.9 mm and ≥7mm.

Paper II: Assessment and definition of intracranial artery stenosis

ICAS was defined as a ≥50% focal narrowing of the intracranial arterial flow diameter of the petrocavernous and the supraclinoid segments of the ICA, the A1- and A2-segments of the ACA, the M1- and M2- segments of the MCA, the intracranial vertebral arteries, the basilar artery, PCOM or the P1- and P2- segments of the PCA. Four participants who at the carotid ultrasound examination were diagnosed with extracranial occlusion of the ICA and two participants with intracranial vasculitis were excluded from the analysis. Nine participants had insufficient image quality, leaving 1847 participants who were assessed for ICAS.

We used both the WASID method[115] and the MRA-VICAST method[125] in the assessment of ICAS. MIP and 3D-VR reconstructions were assessed to detect probable stenosis. If a stenosis was suspected on these reconstructions, assessment was made both by measurement on fixed reconstructed MIP images and orthogonal on the vessels on the MPR reconstructions as well as visually grading of MIP images. The stenoses were graded as 50%-69% (moderate), 70-99% (severe) and 100% (occlusion). We were not able to successfully apply the MRA-VICAST method in the petrocavernous and supraclinoid part of ICA, consequently only the MRA-WASID method was used in these segments.

3.1.3.3 Assessment of structural brain changes

Visual assessment of cortical infarcts, lacunes and WMHs was conducted on a Sectra workstation, Sectra IDS7 (v22.1.12.4835), by two experienced neuroradiologists (MH and LHJ) utilizing 3D-FLAIR, T1-weighted and SWI images.

Cortical infarcts

The T1-weighted, 3D- FLAIR, and SWI images were used for visual assessment of cortical infarcts. A cortical infarct was defined as a hyperintense lesion >4 mm on FLAIR images located in the cerebral cortex with or without loss of tissue or extension into the deep white matter.[143] Cortical infarcts were registered according to vascular territory (anterior and posterior circulation) and hemisphere.[144] Image quality for assessment cortical infarcts was sufficient in 1842 participants.

Lacunes

The T1-weighted, 3D- FLAIR, and SWI images were used for visual assessment of lacunes in accordance with the STRIVE-2 criteria.[86] and defined a lacune as a round or ovoid subcortical, fluid-filled cavity (with signal resembling CSF) up to 15 mm in diameter that is likely to be end tissue damage from recent small subcortical infarct, small subcortical hemorrhage or end stage cavitation within a WMH. The lacunes were registered according to vascular territory (anterior and posterior circulation), location (basal ganglia, thalamus, subcortical white matter) and hemisphere. Image quality for assessment lacunes was sufficient in 1842 participants.

White matter hyperintensities

We assessed WMHs of presumed vascular origin on 3D-FLAIR images with the Fazekas four-point scale according to recommendation in the STRIVE-1 and-2.[85,86,145,146] In the periventricular region, WMH lesions were graded as 0 = absent WMH lesions, 1 = “caps” or pencil-thin lining, 2= smooth “halo,” and 3 = irregular hyperintensities extending into the deep white matter, while deep WMHs were graded as 0 = absence or a single punctate WMH lesion, 1 = multiple punctate lesions, 2 = beginning confluency of lesions, and 3 = large confluent lesion. Seven participants were excluded from the visual scoring of WMHs due to

white matter changes consistent with multiple sclerosis (MS). One participant was excluded because artifacts on the FLAIR series made WMHs scoring impossible, leaving 1834 participants with Fazekas score.

Automated segmentation of WMHs in periventricular, in deep and in total white matter were used for estimation of burden of WMH by use of an open source fully convolutional neural network (U-Net architecture) algorithm.[147] To reduce false positives errors, we added additional post-processing steps (i.e. using grey matter mask to remove false positives in grey matter), and the final pipeline was validated on a subset of 30 cases that had acceptable similarity coefficients, or Dice scores, which on was average 0.519.[148] As the Dice score is sensitive to smaller volumes, the scores were judged as acceptable. Segmented WMH was then divided into deep WMHs and periventricular WMHs by a 10 mm rule.[149] using dilated ventricle masks for defining the set of periventricular WMHs. Both T1w and FLAIR were used to manually check for segmentation errors.[148] Due to insufficient quality of the FLAIR images, failure in the automatic segmentation algorithms, or presence of focal atrophy (e.g., larger territorial stroke lesions, MS, large arteriovenous malformations or tumors) that could severely affect the automated measurements, 95 participants were excluded from the automated segmentation of WMHs, leaving 1747 to be included in the automated WMH analysis.

Brain parenchymal fraction

We used FreeSurfer (v.6.0, surfer.nmr.mgh.harvard.edu) to estimate intracranial volume (ICV) and brain parenchymal volume from the T1-weighted images. Brain parenchymal fraction (BPF) was used as a proxy of whole brain atrophy.[150-152] BPF was defined as the ratio between brain parenchymal volume and the intracranial volume. Brain parenchymal volume included total grey and white matter and excluded ventricles and the cerebrovascular space

surrounding the brain. The intracranial volume was limited by the internal tabule. Insufficient image quality led to exclusion of 99 participants from the analysis, leaving 1743 participants with adequate data.

3.1.4 Statistical methods

Statistical analyses were performed using Stata for Mac (version 17: StataCorp LP, TX). Continuous variables are presented as means with 95% confidence intervals (CI) or standard deviations (SD) or median and interquartile range (IQR) depending on distribution. Categorical variables are presented as counts (percentages). Differences between groups were evaluated using a two-sample t-test for summary data, and z-test was used to compare proportions in one sample (paper I, II and III). Logistic regression was used for calculating the odds ratio (OR) of the association between cardiovascular risk factors and presence of ICAS (paper II). Logistic regression models were fitted to calculate the odds ratio (OR) for moderate-to-high Fazekas score (score 2 and 3), presence of lacunes or cortical infarcts. In these models ICAS (yes/no) served as predictor variable while Fazekas score (2-3 vs 0-1), lacune (yes/no) or cortical infarct (yes/no) were the outcome variables (paper III). BPF and WMH volumes were log-transformed to approximate normal distribution, and linear regression was used to assess the association between ICAS and log-transformed total WMH volume and log-transformed BPF (paper III). Both the logistic and linear regression analyses (paper II and III) were performed in unadjusted models (Model 1), adjusted for age and sex (Model 2) and adjusted for age, sex, hypertension, hyperlipidemia, current smoking and diabetes (Model 3). Two-sided p values <0.05 were considered statistically significant.

4 Main results - summary of papers

4.1 Paper I

The mean age of participants was 63.8 years (range 40-84 years) and 52.6% were women. A total of 131 intradural saccular aneurysms ≥2 mm was detected in 122 of the 1862 participants, giving an overall prevalence of intradural UIAs ≥ 2mm of 6.6% (95% CI 5.4–7.6). The prevalence was 7.5% (95% CI 5.9–9.2) in women and 5.5% (95% CI 4.1–7.2) in men. There was no consistent difference in size of aneurysms in men and women. Fifty-six of the 131 UIAs (42.7%) were located in the internal carotid artery, 14 (10.7%) in the anterior cerebral artery, 50 (38.2%) in the middle cerebral artery and 11 in the posterior circulation (8.4%).

The overall prevalence changed according to different definitions of UIAs by size and location. The overall prevalence of intradural aneurysms ≥3 mm was 3.8% (95% CI 3.0–4.8). The prevalence was 7.4% (95% CI 6.2–8.6) when the cutoff was set at ≥1 mm and increased to 8.3% (95% CI 7.1–9.7) when both intra- and extradural aneurysms were included.

4.2 Paper II

A total of 157 ICAS were found in 111 of the 1847 participants. The overall prevalence of ICAS was 6.0 % (95 % confidence interval (CI) 5.0–7.2), 4.3 % (95 % CI 3.1–5.7) in women and 8.0 % (95 % CI 6.3–10.0) in men. The prevalence increased by age from 0.8 % in 40-54 years age group to 15.2 % in the 75-84 years age group.

The distribution of ICAS per arterial segment showed that 52.2% were located to the ICA, 33.1% in the posterior circulation, 3.8% in the ACA and 10.8% in the MCA. The degree of stenosis was moderate (50%–69%) in the majority of vessels (80.9%). The per participant

prevalence of ICAS was 3.8% in the ICA, 0.3% in ACA, 0.8% in MCA and 2.3% in the posterior circulation.

The risk of ICAS was independently associated with higher age (OR 1.11, 95% CI 1.08–1.14) and male sex (OR 1.77, 95% CI 1.17–2.68). An independent association was also seen for hypertension (OR 2.32, 95% CI 1.33–4.03), hyperlipidemia (OR 1.66, 95% CI 1.10–2.51), current smoking (OR 2.11 CI 95% 1.20–3.69), higher BMI (OR 1.05 CI 95% 1.00–1.11) and diabetes (OR 1.86 CI 95% 1.04–3.33).

4.3 Paper III

The 111 participants (6.0%) with ICAS had significantly more cortical infarcts (23.4% vs. 5.5%) and lacunes (27.0% vs. 7.7%) compared to participants without ICAS (1731). This was more pronounced for cortical infarcts in the anterior circulation, and for lacunes in the posterior circulation. An independent association was found between ICAS and cortical infarcts (OR 2.31, 95% CI 1.36 – 3.95) and lacunes (OR 2.01, 95% CI 1.24 – 3.28). The association between ICAS and lacunes was mainly driven by the lacunes in thalamus (OR 4.74, 95% CI 1.76 – 12.72). Subgroup analysis showed a significant difference between those with cortical infarcts and ICAS in the supplying arteries and those with only cortical infarcts without ipsilateral ICAS, both in the anterior (14.5% vs 3.6%) and posterior circulation (17.5% vs. 3.4%).

The proportion with moderate-to-severe Fazekas score (≥2) was higher in the ICAS group than in the non-ICAS group, both for deep (41.4% vs. 22.0%) and periventricular (67.6% vs. 29.8%) WMHs. ICAS was independently associated with moderate-to-severe periventricular Fazekas score (OR 2.00, 95% CI 1.26 – 3.17) and BPF (β -coefficient -0.01482, 95% CI -0.0246 – -0.0051), but there was no significant association between ICAS and deep moderate-to-severe WMH score or WMH volumes.

5 Discussion

5.1 Methodological considerations

Epidemiology is defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems."[153] According to the renowned epidemiologist Kenneth Rothman the objective of epidemiological studies is "to obtain valid and precise estimates of disease frequency or the effect of an exposure on the disease occurrence in the source population"[154] Validity refers to the degree to which inferences drawn from a study is valid. Lack of validity is due to deficiencies in the study design, data collection or data analysis.[155] To generate valid, reliable, and generalizable knowledge, accuracy is essential. Accuracy refers to the extent to which measurements or estimation accurately reflect the true value of the attribute being measured.[153] Threats to accuracy are lack of precision (random errors) and bias (systematic errors).[154] There are two types of validity: internal and external, the former being a prerequisite for the latter.[155]

5.1.1 Internal validity

Internal validity refers to the degree to which a study is free from bias or systematic error,[153] and the extent to which the observed results represents the truth in the population being studied.[155] Three types of errors that may threaten internal validity; selection bias (population), information bias (collection, analysis and interpretation of data) and confounding.[156]

5.1.1.1 Selection bias

The validity of studies reporting incidence or prevalence of disease or exposure in the source population relies on a sample of study participants that represents the actual population. If the study sample diverges from the overall population regarding exposure and outcome of interest, selection bias occurs, and the results and conclusions drawn will not be

representative for the population intended to study.[155,157.] The Tromsø Study ensures invitation of a representative study population by inviting total birth cohorts based on the official population registry,[138] but low attendance rates in population-based studies may threaten validity. Non-responders often differ from those who respond in regard to many demographic, socioeconomic, cultural, life-style, and medical characteristics.[157] The overall attendance rate in the 7th survey of the Tromsø Study was 65%,[138] which is fairly high when compared to similar contemporary studies.[158,159] Still, we may assume that some degree of selection bias has occurred. This is partly reflected in the lower attendance rate in men, in individuals under 50 and above 80 years, in individuals who never have attended the survey, and in individuals born outside of Norway.[138] Furthermore, the healthy entrant effect may also apply to our study. The term refers to the tendency of healthier individuals to participate more readily than their less healthy counterparts.[156] and this effect may occur as a consequence of lower attendance rates among the sickest.[159] The Norwegian, population-based HUNT study reported a higher prevalence of various chronic diseases, including cardiovascular diseases and diabetes mellitus, among non-responders compared to those who attended the study.[160] In the MRI Study we implemented exclusion criteria to ensure the safety of our participants. Subjects with e.g. cochlear implants, pacemakers and claustrophobia; devices and conditions that represents relative contraindications for undergoing an MRI procedure were excluded (Figure 1, Appendix III). We cannot exclude that also other types of selection bias may have influenced attendance in the MRI study. Thirty-eight percent of the eligible participants who participated in the carotid ultrasound examination did not attended the MRI study. These subjects had already attended two visits and are therefore different than non-responders, since they already have shown great interest in attending the study.

5.1.1.2 Information and misclassification

Information bias occurs if information or data is inaccurately reported, measured or recorded.[156] Incorrectly measured or classified exposure and disease status will distort the effect estimate, as it places participants in incorrect exposure, covariate, or outcome categories.[153] In order to reduce misclassification bias, the use of standardized, validated assessment tools is important. In the Tromsø study, measurements of blood pressure, weight and height were performed by standardized methods and by trained personnel.[138] By using calibrated equipment the risk of information bias on these parameters is limited.

Data on hypertension, diabetes, smoking status, alcohol consumption and use of medications were collected through self-administered questionnaires. As questionnaires are subject to errors in recall and reporting, they may introduce information bias. By creating composite variables, such as for diabetes, which go beyond the self-reported yes/no variable, we incorporated additional factors like HbA1c, the use of antidiabetic tablets and insulin usage. This had an additive effect on the count of individuals with diabetes, encompassing those who did not respond the variable in the questionnaire and those with undiagnosed diabetes. Composite variables were also generated for hyperlipidemia and hypertension encompassing cholesterol levels and blood pressure measurement, respectively, in addition to the self-reported variables, which included medication use. Self-reported smoking status and alcohol consumption may be prone to underreporting.[161,162,] However, in a Finnish study which compared serum contine level with self-reported smoking status the validity of self-reported smoking status was high.[161]

We used 3D-TOF-MRA for assessment of UIAs and ICAS. This is a suitable modality for population-based studies, as it provides images of the intracranial arteries without administration of intravenous contrast agents and/or ionizing radiation. If MRI safety

protocols are followed, there is minimal risk of harming the participants. In clinical practice, 3D-TOF-MRA is used for both imaging of intracranial artery occlusions as well as aneurysms. However, 3D-TOF-MRA does not necessarily depict the actual anatomical arterial lumen. It captures a signal from the luminal laminar blood flow, but turbulence in the blood flow will disturb the signal and give the impression of a luminal irregularity, which may differ from the true arterial lumen. Nevertheless, 3D-TOF-MRA is regarded a good method with high sensitivity and specificity for detection of UIAs and has also been recommended as a screening tool.[130,163] In particular, due to its higher resolution, 3Tesla MRA or higher field strengths can overcome the problems with irregular flow, and show a higher diagnostic performance compared to lower field strengths. Also modern postprocessing techniques with the possibility to do freehand 3D reconstructions which enables dynamic viewing from all directions instead of fixed reconstructions in standard planes, improves the accuracy of evaluation, resulting in fewer false positives.[123,130] Spatial resolution is however still often a limiting factor which due to flow pattern images may create an illusion of aneurysms.

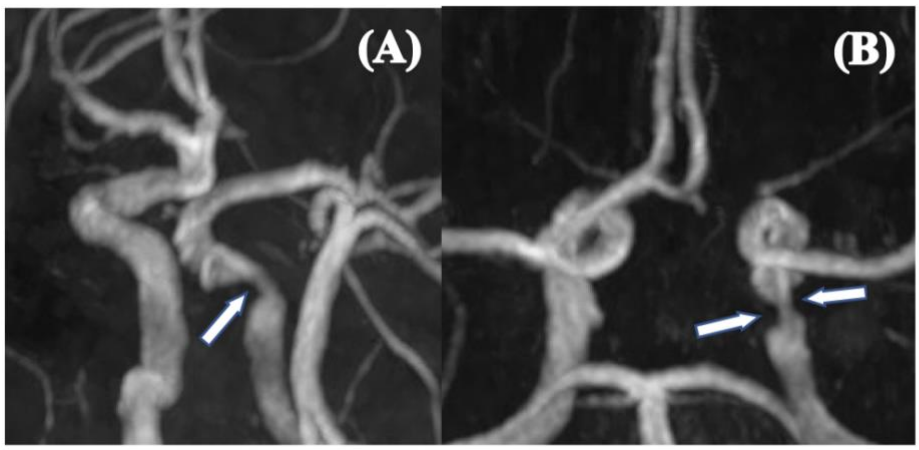
In paper I, all 1862 images and reconstructions were evaluated twice by the same reader. The intraobserver ICC was 0.98. The interobserver reliability was assessed in 100 examinations, drawn from a random sample of 160 examinations enriched with 30 known aneurysms, which were read by two observers. The Cohen's kappa (κ) for interobserver reliability on detecting aneurysms was high (0.79, SE 0.10). The interobserver intraclass correlation coefficient (ICC) for measurement of the size of the aneurysms was 0.93. Interobserver discrepancies in measurements of UIAs were resolved by consensus between the two observers.

Narrowing of an intracranial artery is relatively easily visualized and detected when the source images are reconstructed with maximum intensity projections (MIP) and 3D-volume rendering (3D-VR). However, assessing and interpreting the severity of ICAS on 3D-TOF-MRA images is not as straightforward and is prone to errors. The decreased inflow signal in vessels that are oriented parallel to the imaging plane (in-plane saturation) or vessels that extend downward to the more caudal and saturated section of the imaging slab makes interpretation challenging.[119] Due to this, assessment of ICAS in the carotid siphon, the middle cerebral artery and the vertebral arteries as they enter the skull, is challenging in particular, due to the curved courses of these arteries.[108] The WASID-method[115] tends to overestimate stenosis when applied to 3D-TOF-MR, resulting in low PPV.[102,125] Due to the relatively low spatial resolution of TOF-MRA compared with DSA, there is a risk of measurement error when manually placing calipers on vessels with blurred borders, especially in the smaller vessel.[102,125] To address these limitations, the MRA-VICAST method was developed, classifying the degree of stenosis based the signal and flow diameter in the post-stenotic segment, offering higher accuracy compared to the WASID-method.[118] Both 3D-TOF-MRA assessments by the MRA-WASID and MRA-VICAST methods have been validated against DSA in clinical studies.[101,121]

In paper II, images and reconstructions were assessed for arterial narrowing by two experienced neuroradiologists. All stenosis measured as ≥45% by the MRA-WASID method or assessed as a moderate/severe stenosis by the MRA-VICAST method induced additional assessment by both observers to reach consensus. Grading of ICAS in the ACA, MCA and the posterior circulation were based on assessment done by both the WASID and MRA-VICAST methods and by consensus among the two observers.

Stenosis in the ICA was exclusively assessed using the MRA-WASID method, as we were unable to apply the MRA-VICAST criteria in the petrocavernous and supraclinoid parts of the artery, despite strong indication of ≥50% stenosis on 3D-VR, MIP and MPR caliper flow diameter measurements. This issue might be attributed to the thickness of the TOF-MRA slab, which can lead to unreliable post-stenotic signal, particularly as the tortuous carotid siphon requires coverage by multiple slabs. Consequently, the signal on both sides of a stenosis and the flow diameter may be the same even in cases with highly suspicious stenosis (Figure 2).

Figure 2. Maximum intensity projection (MIP) reconstructions image of the of the left ICA



The arrow(s) points to reduced flow diameter in the precavernous part of the left ICA on A) sagittal oblique MIP and B) coronal oblique MIP, which do not meet the MRA-VICAST criterion of reduced signal intensity distal to the stenosis. It can be disputed whether the flow diameter is smaller in the supraclinoid part of the left ICA, but immediately distal to the stenosis the flow diameter appears to be the same as in the pre-stenotic proximal petrous part.

Reprinted from Supplemental Materials from paper II. With permission from J Stroke Cerebrovasc Dis.

The tortuosity within in the carotid siphon, leading to loss of laminar flow, coupled with in-plane artifacts, poses challenges in accurately assessing flow diameter when employing the WASID-method with 3D-TOF-MRA. Moreover, the presence of focal atheroma and calcifications in this region, can contribute to an additive appearance of a narrower flow diameter compared to the actual luminal diameter at the affected site. Additionally, the potential loss of signal due to air-bone interface susceptibility artifacts near the sphenoid sinuses introduces another challenge in assessing stenosis within the carotid siphon, often creating an illusion of stenosis.[164] Consequently, these factors may result in an overestimation of a both presence and grade of stenosis in the carotid siphon.

As shown in a CTA study, the luminal diameter of ICA decreases approximately 40% from the petrous to the terminal segment.[165] This normal narrowing of the artery is most prominent distal to the origin of the ophthalmic artery. According to the WASID method, in cases of pre-cavernous, cavernous and post-cavernous stenosis, the normal diameter of ICA (D_{normal}) should be measured at the "widest, non-tortuous, normal portion of the petrous carotid artery that have parallel margins".[115] Hence, apart from the effects of tortuosity and the focal wall changes of ICA, which can disrupt the flow signal in the artery and create the perception of a more severe stenosis, there is a potential for overestimating stenosis grade, particularly in the post-cavernous ICA, where the artery narrowing is most pronounced. This overestimation hinges on the precise location where the measurement of D_{normal} within the petrous segment is taken. It is important to note that this issue is not solely restricted to the application of the WASID method on 3D-TOF-MRA. However, due to the factors outlined earlier, the impact on assessments using 3D-TOF-MRA is more pronounced compared to DSA and CTA, which provides true luminographies of the arteries.

In paper II, interobserver and inter-method agreement was assessed in 120 examinations enriched with known cases with one or more stenoses. The κ values for inter-

method (MRA-WASID vs. MRA-VICAST) and interobserver agreement ranged from 0.76 to 0.81, which can be characterized as substantial agreement.[166]

In paper III, we assessed structural brain changes and explored their association with ICAS. Cortical infarctions were visually assessed and reported based on vascular territory, based on the brain vascular territory map from the e-Anatomy atlas by IMAIOS as a reference.[144] Evaluating cortical infarcts by vascular territory can be challenging due to the significant variability, as demonstrated by angiographic and autopsy series.[144,167] Therefore, the localization of infarcts in imaging may not necessarily be reliable to a dedicated artery, especially in the border zones between the territories of the ACA, MCA and PCA.

The accurate assessment of lacunes can be challenging and requires thorough evaluation, as perfect differentiation of lacunes from perivascular spaces is not always possible based solely on size or T2-hyperintense rim.[86] The assessment of lacunes should consider factors like shape, co-located perivascular spaces, and surrounding tissue signal. Although we adhered to the STRIVE-2 criteria for reporting lacunes and WMHs, it is a possibility that lacunes have been misinterpreted as perivascular space and vice versa.

Periventricular and deep WMHs were assessed and graded according to Fazekas grading scale[145] and by volumetric assessment. All automated segmentations underwent visual inspection and were manually corrected or excluded, if necessary. Semi-automated and automated methods are available for assessing WMHs, but the reproducibility and comparability of these methods are variable. Deep learning based algorithms are in development, but still require validation.[86,152] Hence, well validated visual scores, such as the Fazekas score, remain useful.[86] The performance of different software for extracting WMHs is variable, and may underestimate WMH volumes, indicating that some of these automated

methods cannot be considered as valid substitutes for manually segmented WMHs.[168] Other studies show that Fazekas scores correspond with distinct ranges of WMH volumes.[169,170]

Brain volume measurements were assessed using an automated tissue-classification technique. BPF was defined as the ratio of brain parenchymal volume to intracranial volume. In this study, BPF is used as a proxy for brain atrophy. Even if longitudinal studies would provide more precise data on the degree of brain atrophy in an individual over time, single time point analyses can also provide information of brain atrophy by expressing brain volume as a fraction of intracranial volume. Intracranial cavity volume reflects the sum of an individual`s maximum brain volume, hence controlling for head size in cross-sectional studies is mandatory.[152] Assessment of global cortical atrophy, medial temporal lobe atrophy, and Koedam score of parietal atrophy all have visual rating scales recommended in assessment of brain atrophy.[171] However, these methods were not utilized in our study.

Missing data is a challenge as it may lead to invalid conclusions. The amount of missing data in our study were quite limited, but in general, missing data can reduce statistical power, cause bias in the estimation of parameters and reduce the representativeness of the samples, hence complicate the analysis of the study.[172] In our study, use of composite variables for hypertension, hyperlipidemia and diabetes based on the data from both questionnaires and physical measurements reduced the number of missing data. In paper III complete subject analysis were made for linear regression analysis, which resulted in that participants with ICAS was reduced from 111 to 101, and 100 for analysis of association between ICAS and BPF and automatic segmented WMHs, respectively. Missing data for these variables was due to lower image quality due to artifacts or pathologies, and we cannot exclude that the reason for this was missing not at random.[173]

5.1.1.3 Confounding

In epidemiological studies, confounders or confounding variables are factors that are associated with both the exposure (causally or non-causally) and the outcome variable (causally). Confounders can distort the association between an exposure and an outcome due to their effect on both the exposure and the outcome.[156] Hence, confounding can be defined as a "mixing" of effects. Both overestimation, underestimation or reversal of the direction of an effect can occur due to confounding variables, and result in an association influenced by the confounder, rather than the actual risk factor of interest.[156.] Strategies to minimize bias due to confounders in epidemiological studies, are stratification and multivariable adjusted models which include potential confounders. We performed age-and sex stratified analyses of prevalence of UIAs and ICAS (paper I and II) and multivariable logistic regression analyses with adjustment for age and sex and other possible confounders (paper II and III). However, we cannot exclude that residual confounding may have distorted our results.

5.1.2 External validity

The external validity of a study refers to the ability to generalize the study findings to other populations.[157] The Tromsø population is not substantially different from other Western populations with regard to risk factor levels and incidence of cardiovascular diseases,[137] and may be seen as representative for a Western, mostly urban (80%) Caucasian population (85% of Norwegian origin) in a high-income country with high education levels, and high access to social services.[138]

5.1.3 Statistical power

A low number of participants in population based-studies reduces statistical power. The number of participants in this study was limited, resulting in relatively wide confidence intervals for the age- and sex-specific prevalence estimates, especially for the oldest age groups. In paper III, the number of participants with structural changes was limited, which

may have increased both the probability of type II errors (incorrect acceptance of the null hypothesis or false negatives) and type I errors (incorrect rejection of the null hypothesis or false positives).[154]

5.2 Discussion of main results

5.2.1 Prevalence of UIAs

In paper I, we found that the overall prevalence of intradural saccular UIAs ≥2 mm was 6.6%. The prevalence of UIAs in our study is significantly higher than the previously reported prevalence from European studies, of 1.9% in the HUNT Study,[26] and 2.3% in the Rotterdam Scan study.[31] Our results are closer to the prevalence of 7.0% found in the Chinese Shanghai study.[32]

Our study included participants from 40 –84 years, with a mean age of 63.8 years, which was slightly lower than the mean age of 64.9 years in the Rotterdam Scan Study.[31] The mean age of the HUNT Study participants was approximately five years lower (58.5 years),[26] while the mean age in the Shanghai Study[32] was more than ten years lower (53.1 years). In comparison to the prevalence in our population, we would anticipate a higher prevalence in the Rotterdam study`s population, given similar age composition. Conversely, a lower prevalence in the Shanghai Study would be expected, due to its younger population. The discrepancy, particularly between our study and the Asian study, is intriguing and could suggest the possibility of unequal age distribution in prevalence of UIAs across different ethnicities.

It is likely that some of the difference in prevalence across studies are explained by differences in MRI hardware and imaging techniques. The present study and the Shanghai study[32] used 3T MRI for assessment of UIAs, while the HUNT study[26] and the Rotterdam Scan Study[31] employed 1.5T MRI. We used 3D-TOF-MRA to assess UIAs. Being a non-

invasive imaging modality, 3D-TOF-MRA is a suitable and frequently employed tool for assessment UIAs in population-based studies and was also utilized by both the HUNT and the Shanghai studies. In the Rotterdam Study, however, UIAs were assessed using proton density weighted (PDW) images, which is not an angiography sequence. The use of 3T MRI may contribute significantly to the higher prevalence observed in the present and the Shanghai studies, as studies investigating the accuracy of MRA in diagnosing intracranial aneurysms found that 3T performed better than imaging with lower field strengths.[121,122,130] However, it is worth noting that even with 3T achieving adequate spatial resolution remains challenging, particularly in discriminating UIAs from infundibula when the spatial resolution is lower than the diameter of the arteries studied.[124] This limitation can potentially increase the likelihood of false-positive findings and lead to an overestimation of the prevalence of UIAs.

New and comprehensive post-processing techniques such as 3D-VR-reconstructions, in particular, and 3D-MIP reconstructions of 3D-TOF-MRA have an impact on detection rate of UIAs, and can partially attribute to the discrepancy in prevalence across studies. 3D-VR-reconstruction and 3D-MIP reconstructions offer significant improvement of the assessment of UIAs by enabling dynamic viewing of the arteries from all directions, surpassing the limitations of assessing solely source images and fixed MIP- reconstructions in standard planes which can obscure arteries of interest. Additional highlighting of single arteries is also an available post-processing technique to avoid overlap of arteries. Consequently, these techniques can enhance accuracy and reduce false-positive detections.[122,130] The Shanghai Study[32] used the same post-processing techniques as we did in our study. In the HUNT Study,[26] UIAs were assessed on source images and MIP-reconstructions, but not 3D-VR-reconstructons. Assessment of UIAs in the Rotterdam Study was made on PDW images without possibility for 3D-reconstructions.[31]

Differences in prevalence across studies could be attributed to varying definitions of UIAs in terms of threshold for size and intra- and/or extradural location. We defined an UIA as an abnormal focal dilatation of an intradural artery, setting a threshold for size of ≥2 mm in our main analysis. The Shanghai study shared our size threshold (≥ 2 mm), but included extradural UIAs in the C3- and C4-segments of the ICA.[32] The definition of what should be regarded intracranial artery differs, encompassing either exclusively intradural arteries or extending to include the extradural segments of the ICA at the base of the skull. As aSAH is caused by intradural UIA rupture, our primary focus was to explore the prevalence of intradural UIAs. Extradural UIAs will not cause aSAH, unless protruding through dura.[174] Since the dural rings cannot reliably be determined on MRI, UIAs situated in the C5-segment of ICA is potentially located intradural,[175] and were therefore included in our definition of UIA. The HUNT Study[26] and the Rotterdam Scan Study[31] did not provide precise definitions based on size or intra- or extradural location. As the mean size of the UIAs was 5.6 mm in HUNT and 4.5 mm in the Rotterdam Scan study compared to 3.8 mm in our study and 3.5 mm in the Shanghai Study[32], we can assume that smaller UIAs were not included in the two former studies, something that can be explained by the use of 3T, 3D-TOF MRA and improved post-processing abilities. Given the inconsistency in defining UIAs, we further explored how different UIA definitions would impact prevalence and the prevalence varied substantially, ranging from 3.8% (95% CI 3.0–4.8) for intradural aneurysms ≥3 mm to 8.3% (95% CI 7.1–9.7) when both intra- and extradural aneurysms ≥1 mm were included.

The location-wise distribution of UIAs differed between our study and the Shanghai Study.[32] In both studies, UIAs were most prevalent in the ICA, but 81% of the UIAs were located in ICA in the Shanghai Study, only 42.8% of the UIAs were located in ICA in our study. The most striking difference was for UIAs located in the MCA, as 38.2% of the UIAs in our study were located here, whereas only 4.1% of the UIAs in the Shanghai study. This

difference, though to a lesser extent, also applied to the proportion of UIAs located in the posterior circulation which was 8.5% in our study compared to 2.4% in the Shanghai Study. The HUNT[26] and Rotterdam[31] studies reported proportions of MCA aneurysms comparable to those observed in our study, but a lower proportion of posterior circulation aneurysms. Various MRI-based prevalence studies from Asia have reported proportions of UIAs in the middle cerebral artery ranging from 9% to 28.6%.[121,176-179] The disparate distribution of UIAs between European and Asian population-based studies, particularly the difference in the proportion of MCA aneurysms, is intriguing. This may suggest that the distribution of UIAs probably varies across populations, a factor that should be considered when estimating rupture risk based on aneurysm location.

In the present study, approximately 80% of the UIAs, which applies to 1.5% of the participants, were smaller than 5 mm compared to 90% in the Shanghai Study.[32] Only 9 (0.5%) of the 1862 participants had UIAs ≥7 mm. Out of the total 131 UIAs measuring ≥2 mm, a significant majority, 122 (93%) were found to be <7 mm in size. According to the findings from the ISUIA2 Study, these smaller UIAS carry a low risk of rupture.[28] In the case of UIAs located in the posterior circulation, as well as UIAs in PCOM, 4-6 mm sized UIAs in ACOM and UIAs in the distal ACA, the risk of rupture is somewhat higher.[28,38-40,180] According to this, this assumed elevated risk of rupture applies to 29 (22%) of the 131 UIAs observed in our study.

In a subset of the data on the incidence of aSAH from 2007-2019,[21] derived from the quality register at the Neurosurgical Department at UNN, the annual incidence of aSAH in the Tromsø population is found to be 1.52 per 100.000 for aneurysms <5 mm and 2.44 per 100.000 for aneurysms ≥5mm. Based on these numbers and the observed prevalence in the present study, we were able to calculate the annual risk of rupture for UIAs in the Tromsø

population. For UIAs ≥5 mm the annual risk of rupture was estimated as 1.6%, and for UIAs <5mm the annual risk of rupture was 0.03%. This result suggests that not all aneurysms <7 mm are harmless,[28.38.39.40.180] and supports the consideration of prophylactic repair for aneurysms ≥5 mm. Conversely, our findings indicate a very low rupture risk for UIAs <5mm, which supports restraint with prophylactic repair of such lesions.

5.2.2 Prevalence of ICAS

In paper II we found that the overall prevalence of ICAS in the middle-aged and elderly population was 6.0%; 8.0% in men and 4.3% in women. A 15-fold increase in prevalence was observed from the 40-54 years age group to the 75-84 years age group.

The overall prevalence of ICAS in our study is lower than the previously reported prevalence of 8.0% in Whites in the population-based US ARIC Study,[54] but higher than the prevalence of 3.3% in the Spanish AsIA Study.[64] Some of the difference across studies can be explained by differences in age distribution. The mean age of the study participants in the ARIC Study was approximately twelve years higher than participants in our study, and ten years higher than in the AsIA study. The higher prevalence in the ARIC study aligns with expectations given the generally higher prevalence of ICAS in elderly.[8] The lower prevalence of ICAS in the AsIA Study may be attributed to their exclusion of subjects with a history of stroke, transient ischemic attack, or coronary disease.

The differing prevalence of ICAS can also be attributed to the use of different imaging modalities. The present study and the ARIC Study used 3D-TOF-MRA on 3T in assessment of ICAS, while the assessment in the AsIA Study primarily relied on transcranial color-coded duplex (TCCD) with occasional employment of contrast agent when needed. TCCD is likely to exhibit poorer diagnostic performance than MRA,[101] limited by poor acoustic windows and challenges in assessing the more distal parts of the arteries. The ARIC Study conducted

additional high-resolution MRI sequences to identify and measure the intracranial vessel wall (HR-VWI) and incorporated assessment of more peripheral segments of the arteries.[54] The higher prevalence of ICAS in the ARIC Study may be due to inclusion of more distal arteries compared to our study.

We used both the WASID-method and MRA-VICAST method to assess ICAS. We believe that the combined use of the MRA-VICAST and MRA-WASID methods has reduced the likelihood for false positives in the assessment of ICAS, due to the limitations of the MRA-WASID method. ICAS in the ACA, MCA and the posterior circulation were assessed by both methods, and the results were thoroughly compared in order to determine whether ICAS≥50% was present or not. The emphasis in our evaluation leaned toward the MRA-VICAST method, which may have contributed to the observed lower prevalence of ICAS in the ACA and MCA compared to studies exclusively utilizing the MRA-WASID.[8,54] Still, it must be noted that as we were unable to apply the MRA-VICAST method to assess ICAS in the ICA, the prevalence of ICAS in the ICA in our study may be overestimated.

Differing definitions may also contribute to differing prevalence of ICAS across studies. We defined ICAS as a focal narrowing of the intracranial arterial flow diameter of ≥50% and included the petrocavernous ICA-segment. Differences in definition what should be regarded as an intracranial artery also apply to prevalence-studies on ICAS[8,66] The ARIC study included the cavernous and supraclinoid part of ICA,[54] while the AsIA study included the siphon and terminal ICA.[64] Given the inconsistency in definitions across the studies we performed analyses excluding ICAS with their main stenosis in the petrous and cavernous segments of the ICA and the overall prevalence changed to 5.9% and 5.6%, respectively.

In our study, approximately one half of all ICAS were located to the ICA, giving a per-vessel prevalence of ICAS in ICA of 3.8%. The prevalence of ICAS in the posterior

circulation was 2.5%, accounting for one third of all ICAS. Only 10.8% of the ICAS were located to the MCA and 3.8% in the ACA with a per-vessel prevalence of ICAS of 0.3% and 0.8%, respectively. This differs from the AsIA study, where ICAS were more evenly distributed: 32.1% in ICA, 16.6% in ACA, 29.4% in MCA, and 21.9% in the posterior circulation.[64] In the ARIC study, ICAS of any size was most prevalent in ICA (16%). However, ICAS ≥50% was most commonly identified in PCA (4%).[54]

We observed that the arteries predominately affected by ICAS in our population were the proximal intracerebral arteries and that ICAS distal to the circle of Willis was relatively rare. This distribution of ICAS in ICA and the vertebral arteries corresponds to the distribution of calcified atheroma detected in intracranial arteries on CT scans. The reported prevalence of calcifications in ICA and the vertebrobasilar arteries in the Rotterdam Study was 82% and 21%, respectively.[66,181] These finding also aligns with studies that have shown that ICAS tend to be more common in vessels with large diameters.[54,182]

The prevalence of ICAS in our study is higher than expected and similar to the estimated prevalence of extracranial carotid stenosis in the Tromsø population, which was 5.3% in men and 2.7% in women.[183] This observation may support the suggestion that the actual impact of ICAS in Western populations have been underestimated.[10,45-47]

5.2.3 Association between cardiovascular risk factor and ICAS

The traditional cardiovascular risk factors age, male sex, hypertension, hyperlipidemia, current smoking, BMI and diabetes mellitus were all independently associated with presence of ICAS in our study. Apart from age and sex, these are modifiable risk factors which are associated with cardiovascular disease, and could be responsive to preventive measures.[184] Hypertension and age were reported to be associated with ICAS in both the ARIC and AsIA studies. In the ARIC Study higher low-density lipoprotein cholesterol levels were also

associated with increased odds of ICAS,[54] while the Barcelona-AsIA study reported that diabetes was associated with intracranial atherosclerosis in asymptomatic subjects with moderate-to-high vascular risk.[64] None of these studies reported independent association between ICAS and sex, current smoking or BMI.[54,64]

5.2.4 Association between ICAS and structural brain changes

We found an independent association between ICAS and cortical infarcts. Cortical infarcts are typically linked to large artery atherosclerosis, and notably, our study observed stronger effect estimates for infarcts in the vascular territory of the stenosis. This finding aligns with previous studies that have reported cortical/subcortical infarcts within a territory supplied by a single large artery as a common subtype of stroke in patients with ICAS.[77,185,186]

We found an independent association between presence of ICAS and lacunes. This is in line with previous population-based studies on ICAS and artery calcifications.[87.88.89] A statistical association does however not imply causality. Lacunar infarctions are often thought to be caused by penetrating arteriolar vessel disease, and an association between ICAS disease and lacunes could be due to coexistence of large and small vessel disease.[187.188] Studies on symptomatic patients have shown conflicting results. A Korean MRI/MRA study on symptomatic patients with >50% stenosis reported an association between lacunar infarcts and MCA disease.[189] Conversely, no association was found between flow velocity in in the MCA (as an indicator of arterial narrowing) and lacunar stroke in a Scottish study.[85] Another Korean Study using HR-MRI found that branch atheromatous disease was frequently observed in patients suspected of having small-vessel occlusions even in patients with normal parent arteries on MRA.[190]

The association between ICAS and lacunes was primarily driven by lacunes in thalamus, whereas no independent association was found between ICAS and lacunes in the

anterior circulation. This might be due to insufficient power, as the frequency of lacunes in the anterior circulation was relatively low. We might also have underestimated the number of lacunes in the basal ganglia and subcortical white matter. Due to possible coexistence with dilated perivascular space, lacunes can be misinterpreted as dilated perivascular space and vice versa.[86] Assessment of lacunes in the thalamic subcortical grey matter is somewhat less challenging as presence of perivascular dilatation is relatively rare in this area.

The proportion of participants with moderate-to-severe Fazekas score both in deep and periventricular white matter was higher in the ICAS group compared to the non-ICAS, and moderate-to-severe periventricular Fazekas score were independently associated with ICAS. However, no association was found between ICAS and deep WMHs assessed by Fazekas. Neither did we reveal an association between ICAS and automatic segmented volumes of WMHs, in contrast to the Shunyi Study which found an association with WMHs ICAS of any degree,[87] and the Rotterdam Study that reported an association with WMHs and calcifications.[89] The PRECISE Study did not reveal any association between ICAS≥50% and WMHs,[88] nor did a Chinese patient-based study with ICAS verified by DSA.[93] Conversely, a patient-based MRI/MRA study from Korea, found that the presence of ICAS>50% and higher number of ICAS lesions were independently associated with deep WMH burden assessed by Fazekas score, and also moderate-to-severe periventricular Fazekas score.[92] This association between ICAS and moderate-to-severe periventricular WMHs assessed by Fazekas score is intriguing, as other studies on symptomatic patients have shown association between periventricular WMHs and markers of ICAD.[187,191] The lack of association between ICAS and WMHs, as assessed by automated segmentation, contrasts findings reported in other population-based studies.[87,89] This may be attributed to several factors, including insufficient statistical power and disparities in the segmentation algorithms and processing tools used across different studies. The variance in findings regarding the association between ICAS and

periventricular Fazekas scores, and ICAS and volumetric assessment of periventricular WMHs within our study, could lie in the differing methodologies employed in assessing WMH pathology. While Fazekas score is a qualitative assessment, volumetric analysis of WMHs provides a quantitative measure. The assessment of WMHs through the Fazekas score, considers features like bridging between lesions and confluency of the WMHs, and may not necessary align with WMH volumes.

We identified an independent association between ICAS and whole brain atrophy assessed as BPF. Similarly, the Shunyi Study.[87] reported an association between ICAS of any degree and general brain atrophy. In the Rotterdam study, larger calcification volumes were linked to smaller white matter volumes.[192] Clinical studies have shown diverging results. High grade of calcifications in the cavernous part of the intracranial carotid artery has been reported to be age independently associated with central brain atrophy, although not cortical atrophy.[98] In contrast, a study on vessel wall lesions did not find any association between ICAS burden and brain atrophy.[99]

In general, the association between ICAS/ ICAD and structural brain changes exhibits some variability across studies. This can be attributed to differences in imaging modality, MRI field strength, MRI sequences and assessment methods, together with different definitions of predictor- and outcome-variables and the population studied.[87-89,99,191] Our predictor variable; ICAS≥50%, represents a relatively advanced stage of ICAD, and includes only relatively proximal intracranial arteries. This makes direct comparison between studies challenging. Still, our results generally align with observations in previous studies and suggest that ICAS may play a role in structural brain changes.

The underlying mechanism between ICAS and structural brain changes is not known. As for lacunar infarction, WMHs and brain atrophy are often thought of as manifestations of

SVD.[152] Although categorized as distinct pathologies, large and small vessel disease may coexist and interact, and one hypothesis does not necessarily exclude the other.[187.188] This may suggest that primary prevention of ICAS could have a role in prevention of SVD and the neurological consequences of these conditions.[193.194] Consequently, further research is needed to fully understand these associations and their underlying mechanisms.

6 Conclusions, implications and future perspectives

The overall prevalence of UIAs ≥2 mm in adults aged 40-84 years in our study was 6.6%. This is higher than previously observed in Western populations. Depending on definition by size and intra- or extradural location, the prevalence ranged from 3.8% for intradural aneurysm ≥3 mm to 8.3% for intra- and extradural aneurysms ≥1 mm.

The majority of UIAs are small and less than 7 mm (93%), and according to the ISUIA 2 study, they are regarded as having a low risk of rupture. Based on the observed prevalence of UIAs in the present study and a subset of data from the retrospective registry study of aSAH, in the same population, on the incidence of UIAs,[21] we have calculated that the annual risk of aneurysm rupture in our population is 1.6% for UIAs ≥5 mm and 0.03% for UIAs <5 mm. This indicates that not all aneurysms <7 mm are harmless, and supports that aneurysms ≥5 mm should be considered for prophylactic repair. Further, our findings indicate that the rupture risk of UIAs <5mm is very low, which supports restraint with prophylactic repair of such lesions. Longitudinal follow-up studies and further analysis of aneurysm size and localization in aSAH patients compared to the MRA screening group from the same general population might provide additional knowledge on size- and location-specific rupture risk.

The overall of prevalence of ICAS ≥50% in our population was 6.0%, which is relatively high and similar to the prevalence of extracranial internal carotid stenosis in

previous population-based studies. Age, male sex, and the five modifiable risk factors associated with cardiovascular disease; hypertension, hyperlipidemia, current smoking, BMI and diabetes mellitus, were all independently associated with presence of ICAS.

ICAS was associated with cortical infarcts in both the anterior and posterior circulation, lacunes in the thalamus, periventricular WMHs assessed by Fazekas score and brain atrophy, the three latter being entities predominately attributed to SVD. These findings might suggest that the impact of ICAS could be stronger than previously assumed, and may be a target for primary prevention. Although further research is needed to fully understand these associations and their underlying mechanisms, this may suggest that primary prevention of ICAS could have a role also in prevention of SVD.

Inconsistent definitions of both UIAs and ICAS across studies makes comparison between studies challenging. In order to compare results from different populations more robust and consistent radiological definitions are needed.

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Paper I

Paper II

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Prevalence of intracranial artery stenosis in a general population using 3D-time of flight magnetic resonance angiography

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ABSTRACT

Background: Data on prevalence of intracranial artery stenosis (ICAS) in Western populations is sparse. The aim of the study was to assess the prevalence and risk factors for ICAS in a mainly Caucasian general population.
Methods: We assessed the prevalence of ICAS in 1847 men and women aged 40 to 84 years who participated in a cross-sectional population-based study, using 3-dimensional time-of-flight 3 Tesla magnetic resonance angiography. ICAS was defined as a focal luminal flow diameter reduction of ≥50 %. The association between cardiovascular risk factor levels and ICAS was assessed by multivariable regression analysis.
Results: The overall prevalence of ICAS was 6.0 % (95 % confidence interval (CI) 5.0–7.2), 4.3 % (95 % CI 3.1–5.7) in women and 8.0 % (95 % CI 6.3–10.0) in men. The prevalence increased by age from 0.8 % in 40-54 years age group to 15.2 % in the 75-84 years age group. The majority of stenoses was located to the internal carotid artery (52.2 %), followed by the posterior circulation (33.1 %), the middle cerebral artery (10.8 %) and the anterior cerebral artery (3.8 %). The risk of ICAS was independently associated with higher age, male sex, hypertension, hyperlipidemia, diabetes mellitus, current smoking and higher BMI.
Conclusions: The prevalence of ICAS in a general population of Caucasians was relatively high and similar to the prevalence of extracranial internal carotid artery stenosis in previous population-based studies.

Introduction

Intracranial artery stenosis (ICAS) is a common cause of stroke in Asians, Hispanics and African Americans[1–4], with high risk of stroke recurrence.[4,5] In Caucasians extracranial carotid artery atherosclerosis has been considered the predominant cause of stroke, whereas ICAS has been of minor importance,[5,6] but the real impact of ICAS in western populations may however have been underestimated.[7–9]

The reported prevalence of ICAS varies with study design and study population and is dependent on diagnostic criteria and examination modality. A French autopsy study of 333 patients with fatal stroke found ICAS in 43 % of the cases[10] and a Chinese autopsy study of 114 patients reported ICAS in 31.4 %.[11] A review of 48 imaging-based studies of patients with TIA or ischemic stroke estimated that 12.1 % of Caucasians had at least one intracranial stenosis.[6,12]

Data on prevalence of ICAS in the general population is limited. Population-based studies have mainly been conducted on Asian populations, with prevalence ranging from 4.7 to 15.7 %.[13,14] The

Abbreviations: ICAS, intracranial artery stenosis; ECAS, extracranial carotid artery stenosis; TOF-MRA, time-of flight magnetic resonance angiography; MRA-WASID method, The Warfarin-Aspirin Symptomatic Intracranial Disease method on TOF-MRA; MRA-VICAST method, Visual grading system for IntraCranial Arterial STenosis on TOF-MRA.

All authors can be contacted by calling the University Hospital of North NorwayThe imaging in this study was performed at the Department of Radiology, University Hospital of North Norway. All authors are academically affiliated to the Department of Clinical Medicine, Faculty of Medicine, UiT The Arctic University of Norway, Tromsø, Norway.Cover title: Prevalence of intracranial artery stenosis in a general population

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Atherosclerotic Risk in Communities (ARIC) study reported a prevalence of 8 % in Caucasians.[15] In the Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) study, the reported prevalence of ICAS >50 % was 3.3 %.[16,17]

In the population-based Rotterdam study, calcification of the intracranial internal carotid artery on non-contrast enhanced computer tomography (CT) was used as a surrogate marker for intracranial atherosclerosis, which was found in 82 % of the participants.[18]

In the present study, we aimed to determine the prevalence, distribution and severity of ICAS ≥ 50 % in a general Norwegian population aged 40 years and older using 3D-TOF 3T MRA, and to study the association between presence of ICAS and cardiovascular risk factors.

Material and methods

Study participants

Started in 1974, the Tromsø Study is a large longitudinal and multipurpose population health study of adult inhabitants in the municipality of Tromsø.[19,20] The study design is repeated cross-sectional surveys to which total birth cohorts and selected samples are invited, based on the official population registry. We invited 3027 men and women who participated in the seventh survey in 2015–2016 to participate in a magnetic resonance imaging (MRI) study. Of these, 975 did not respond, 169 were excluded because of contraindications for MRI, and five had moved or died before the MRI examination. We excluded participants with missing images ($n = 8$), insufficient image quality ($n = 16$), extracranial internal carotid artery occlusion evaluated on ultrasound examination ($n = 4$), generalized intracranial artery disease (moya-moya and vasculitis; $n = 2$), and one participant who withdrew his/her consent, leaving 1847 participants in the final analysis. Details on the sampling and flow chart (Supplemental Figure I) of participants are provided in the Supplemental material.

Cardiovascular risk factors

Information on smoking habits, physical activity, use of medication and cardiovascular disease was obtained from questionnaires. Standardized measurements of blood pressure, height and weight were recorded by trained personnel. Serum total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and hemoglobin A1c (HbA1c) were analyzed by standard enzymatic methods. Diabetes was defined as HbA1c ≥6.5 % and/or self-reported diabetes and/or use of diabetes medication. Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥ 90 mmHg and/or use of blood pressure-lowering medication and/or self-reported hypertension. Hyperlipidemia was defined as serum total cholesterol ≥7 mmol/L and/or serum LDL ≥5 mmol/L and/or use of cholesterol lowering medication.

MR angiography and assessment of intracranial artery stenosis

Participants were scanned at the University Hospital of North Norway, Tromsø, with a 3 Tesla (3T) Siemens Skyra MR scanner (Siemens Healthcare, Erlangen, Germany). We used 3D time-of-flight MRA (3D-TOF-MRA) acquired with a 3D transversal fast low angle shot sequence with flow compensation; repetition time/echo time 21/3.43 ms, parallel imaging acceleration factor 3, field of view 200 × 181 mm, slice thickness 0.5 mm, 7 slabs with 40 slices each and reconstructed image resolution of 0.3 × 0.3 × 0.5 mm. Maximum intensity projection (MIP) reconstructions and volume-rendered (VR) reconstructions of the source images were made to optimize stenosis detection.

Images and reconstructions were evaluated by two experienced neuroradiologists (MH and LHJ) on a Sectra workstation, Sectra IDS7 (v22.1.12.4835). ICAS was defined as a ≥50 % focal narrowing of the intracranial arterial flow diameter. Stenosis location was defined as the petrocavernous and the supraclinoid segments of the internal carotid artery (ICA), the A1/A2 segments of the anterior cerebral artery (ACA), the M1/M2 segments of the middle cerebral artery (MCA), the intracranial vertebral arteries, the basilar artery and the P1/P2 segments of the posterior cerebral arteries (PCA).

We used two different grading methods: 1) the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method,[21] and 2) the MRA-VICAST method.[22] The WASID method, originally developed for digital subtraction angiography (DSA), calculates degree of stenosis by measuring the diameter at the site of the stenosis and at a reference site in the same artery proximal to the stenosis. Measurements were made both on fixed reconstructed MIP images and orthogonal on the vessels with multiplanar reconstructed (MPR) images. The MRA-VICAST method is a recently proposed visual grading system for intracranial arterial stenosis on MRA based on physical characteristics of the TOF-MRA. The signal intensity and flow diameter in the artery distal to the site of stenosis assessed on MIP images is used to evaluate the grade of stenosis which is classified into four groups according to severity of stenosis: < 50 % (mild), 50 %-69 % (moderate), 70-99 % (severe) and 100 % (occlusion). We were not able to successfully apply the MRA-VICAST method in the petrocavernous and supraclinoid part of ICA, consequently only the MRA-WASID method was used in these segments.

Cohen's kappa (κ) for interobserver agreement on ICAS ≥ 50 % was 0.76 (SE 0.02). κ for inter-method agreement (MRA-WASID vs. MRA-VICAST) was 0.81 (SE 0.02). Details on interobserver and inter-method agreement are available in the Supplemental material.

A stenosis measured as ≥45 % by the MRA-WASID method and/or a moderate/severe stenosis assessed by the MRA-VICAST method induced additional assessment by both observers to reach consensus.

Statistical analysis

The data were analyzed with Stata for Mac (version 17: StataCorp LP, TX). Continuous variables are presented as means with standard deviations (SD) and categorical variables as counts (percentages). Differences between participants with and without ICAS were evaluated using a two-sample t-test for summary data, and z-test was used to compare proportions in one sample. Prevalence of ICAS is presented stratified by sex and age groups.

Logistic regression was used for calculating the odds ratio (OR) of the association between cardiovascular risk factors and presence of ICAS. The analyses were performed in univariable models (Model 1), of each variable adjusted for age and sex (Model 2), and in multivariable analyses of all risk factors (Model 3). All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

A total of 157 ICAS were found in 111 of the 1847 participants. The mean age of participants was 63.8 (SD ±10.6) years and 53.2 % were women. Participants with ICAS had higher BMI, lower HDL and higher total cholesterol, and higher proportions of hypertension, diabetes, cardiovascular disease and use of lipid-lowering and antihypertensive medication than participants without ICAS (Table 1). LDL levels and current smoking status were similar in the two groups. There was a 15-fold increase in prevalence from the 40-54 years age group to the 75-84 years age group (Table 2). Twelve percent of participants with ICAS reported previous stroke compared to 2.4 % in those without ICAS.

The distribution of ICAS per arterial segment showed that 52.2 % were located to the ICA, 33.1 % in the posterior circulation, 3.8 % in the ACA and 10.8 % in the MCA (Table 3). The degree of stenosis was moderate (50 %–69 %) in the majority of vessels (80.9 %). The per participant prevalence of ICAS was 3.8 % in the ICA, 0.3 % in ACA, 0.8 % in MCA and 2.3 % in the posterior circulation (Table 4).

The risk of ICAS was independently associated with higher age (OR

Table 1
Characteristics of participants with and without intracranial arterial stenosis (ICAS)*.

	All participants (n = 1847)	ICAS* (n = 111)	No ICAS (n = 1736)	p-value
Male sex, n (%)	864 (46.8)	69 (62.2)	795 (45.8)	<0.001
Age (years), mean (SD)	63.8 (10.6)	72.4 (7.5)	63.3 (10.5)	<0.001
Body mass index, kg/m2	27.1 (4.2)	28.2 (3.9)	27.0 (4.2)	0.006
Serum total cholesterol, mmol/L	5.51 (1.10)	5.30 (1.21)	5.53 (1.10)	0.035
Serum HDL cholesterol, mmol/L	1.63 (0.50)	1.45 (0.36)	1.64 (0.51)	<0.001
Serum LDL cholesterol, mmol/L	3.58 (1.02)	3.47 (1.09)	3.58 (1.01)	0.325
Use of cholesterol-lowering medication, %	421 (23.4)	57 (52.3)	364 (21.5)	<0.001
Hyperlipidemia	633 (34.3)	64 (57.7)	569 (32.8)	<0.001
Mean diastolic blood pressure, mmHg	75.2 (9.9)	76.1 (9.3)	75.1 (9.9)	0.274
Mean systolic blood pressure, mmHg	134.0 (20.7)	145.7 (20.5)	133.3 (20.5)	<0.001
Hypertension	988 (53.5)	94 (84.7)	894 (51.5)	<0.001
Use of antihypertensive medication	561 (30.8)	60 (55.0)	501 (29.3)	<0.001
Current smoking	246 (13.3)	19 (17.1)	227 (13.1)	0.224
Cardiovascular disease, %	286 (15.5)	49 (44.1)	237 (13.7)	<0.001
Coronary heart disease, %	207 (11.2)	38 (34.2)	169 (9.7)	<0.001
Stroke, %	53 (3.0)	13 (12.3)	40 (2.4)	<0.001
Diabetes mellitus, %	138 (7.5)	18 (16.2)	120 (6.9)	<0.001

Numbers are means (SD) or n (%)
* Intracranial arterial stenosis was defined as a lumen reduction of ≥ 50%.

1.11, 95 % CI 1.08–1.14) and male sex (OR 1.77, 95 % CI 1.17–2.68) (Table 5). An independent association was also seen for hypertension (OR 2.32, 95 % CI 1.33–4.03), hyperlipidemia (OR 1.66, 95 % CI 1.10–2.51), diabetes mellitus (OR 1.86, 95 % CI 1.04–3.33), current smoking (OR 2.11 CI 95 % 1.20–3.69) and higher BMI (OR 1.05 CI 95 % 1.00–1.11).

Discussion

In this study, the overall prevalence of ICAS in the middle-aged and elderly population was 6.0 %. The majority of ICAS were located to the intracranial ICA. Age, male sex, hypertension, hyperlipidemia current smoking and BMI were independently associated with presence of ICAS.

The prevalence of ICAS in our study is lower than the previously reported prevalence of 8.0 % in Whites in the population-based US ARIC Study,[15] but higher than the prevalence of 3.3 % in the Spanish AsIA Study.[16] Differences both in inclusion criteria and imaging methodology can probably explain the variation in prevalence between the studies. The ARIC study participants were 67 to 90 years old with a mean age of 76 (SD±5) years, which is approx. 12 years higher than the mean age in our study (63.8, SD ±10.6 years) and 10 year more than in the AsIA study (66.3 years). The AsIA Study included subjects with a moderate to high vascular risk but excluded subjects with a history of stroke or transient ischemic attack or a history of coronary disease. Stenosis was assessed by transcranial color-coded duplex (TCCD), which is likely to be less sensitive for detection of stenosis than MRI.[23] Like our study, ARIC used a 3T scanner using 3D-TOF MRA, but included more peripheral segments of the arteries and performed additional high-resolution MRI sequences to identify and measure the intracranial vessel wall, which may have increased the possibility to detect stenotic plaques.

DSA remains the gold standard in assessment of stenosis against which 3D-TOF-MRA, contrast enhanced MRA (CE-MRA), TCCD and CT angiography (CTA) are compared.[24] TCCD estimates grade of stenosis based upon the flow velocity in the artery across a stenosis, whereas CTA, CE-MRA and DSA are visualizing the contrast enhanced blood in the arterial lumen. 3D-TOF-MRA is depicting an inflow-enhancement effect which is dependent on flow velocity, repetition time and cross-sectional area of the vessel.[25] This inflow is strongly influenced by hemodynamics and has limited ability for visualization of the fine

Table 3
Distribution of intracranial arterial stenosis per arterial segment and across categories of degree of stenosis.

Vessel location	≥50% stenosis, n (%)	50-69% stenosis, n	70-99% stenosis, n	Occlusion, n
ICA	82 (52.2)	70	12	0
ACA	6 (3.8)	4	2	0
MCA	17 (10.8)	11	5	1
VA	26 (16.6)	22	1	3
BA	2 (1.3)	2	0	0
PCA	21 (13.4)	17	4	0
PCOM	3 (1.9)	1	2	0
Number (%) of vessels with ICAS	157	127 (80.9)	26 (16.6)	4 (2.5)
Per participant (prevalence, %)	111 (6.0)	88 (4.8)	20 (1.1)	3 (0.2)

Table 4
Per-participant location of intracranial arterial stenosis in men and women.

Stenosis site	Women	Men	Total
Internal carotid artery	26 (2.6)	44 (5.1)	70 (3.8)
Anterior cerebral artery	4 (0.4)	2 (0.2)	6 (0.3)
Middle cerebral artery	8 (0.8)	6 (0.7)	14 (0.8)
Posterior cerebral/vertebrobasilar artery	16 (1.6)	26 (3.0)	42 (2.3)

Values are number (percentage) of stenosis ≥50 %.

Table 2
Prevalence (%) of intracranial stenosis ≥50 % stratified by age group and sex.

	Total	40–54 years	55–64 years	65–74 years	75–84 years
Men					
No. with stenosis/No. of participants	69/864	1/156	10/233	29/323	29/152
Proportion with stenosis (95% CI)	8.0 (6.3–10.0)	0.6 (0.00– 3.5)	4.3 (0.2–7.8)	8.9 (6.1–12.6)	19.1 (13.2–26.2)
Women					
No. with stenosis/No. of participants	42/983	2/222	5/277	20/346	15/138
Proportion with stenosis (95% CI)	4.3 (3.1–5.7)	0.9 (0.1–3.2)	1.8 (0.6–4.2)	5.8 (3.6–8.8)	10.9 (6.2–17.3)
Total					
No. with stenosis/No. of participants	111/1847	3/378	15/510	49/669	44/290
Proportion with stenosis (95% CI)	6.0 (5.0–7.2)	0.8 (0.2–2.3)	2.9 (1.6–4.8)	7.3 (5.5–9.6)	15.2 (11.2–19.8)

Table 5
Association between cardiovascular risk factors and presence of intracranial arterial stenosis.

	Model 1			Model 2			Model 3		
	OR	95 % CI	p-value	OR	95 % CI	p-value	OR	95 % CI	p-value
Male Sex	1.94	1.31-2.89	0.001	1.79	1.19-2.69	0.005	1.77	1.17-2.68	0.007
Age, years	1.11	1.09-1.14	<0.001	1.11	1.08-1.14	<0.001	1.11	1.08-1.14	<0.001
BMI, kg/m^2	1.06	1.02-1.11	0.006	1.08	1.03-1.13	0.003	1.05	1.00-1.11	0.026
Hypertension	5.21	3.08-8.80	<0.001	2.87	1.67-4.95	<0.001	2.32	1.33-4.03	0.003
Diabetes mellitus	2.61	1.52-4.46	<0.001	2.42	1.39-4.24	0.002	1.86	1.04-3.33	0.036
Hyperlipidemia	2.79	1.89-4.12	<0.001	2.01	1.34-3.01	0.001	1.66	1.10-2.51	0.016
Current smoking	1.37	0.82-2.29	0.226	1.90	1.11-3.26	0.020	2.11	1.20-3.69	0.009

OR: odds ratio, CI: confidence interval
Model 1: univariable analysis, Model 2: each variable adjusted for age and sex, Model 3: multivariable model with all variables included.

structures in the arteries, especially where the hemodynamics is complex and vessels change direction, such as the carotid siphon and at junctions of arteries.[26] When applied on TOF-MRA, the WASID method tends to exaggerate the severity of ICAS, resulting in low positive predictive value.[22,24] The MRA-VICAST method was developed to compensate for this weakness of the MRA-WASID method. The MRA-VICAST method bases grading of stenosis on assessment of reduction of the flow signal. A stenosis of a certain severity will induce an irregular flow distal to the stenosis that will cause a reduced flow signal in the post-stenotic segment with the consequence that the flow diameter appears thinner than the actual luminal diameter. According to MRA-VICAST, this means that a stenosis is considered as ≥50 % if the flow signal is thread-like or invisible in the stenotic segment, and the flow diameter distal to the site the stenosis is reduced (pseudo--narrowing) or even absent. In the present study, assessment of ICAS in the ACA, MCA and the posterior circulation was made by comparing the evaluation of stenosis vs. no-stenosis by using both the WASID and MRA-VICAST methods. Decision on stenosis and grading was made after consensus between the observers and the assessment by the MRA-VICAST method was weighted heaviest. This may have contributed to the lower prevalence of ICAS in the ACA and MCA in our study compared to studies that have used the MRA-WASID method alone.[12,15]

Stenosis in the ICA was assessed only by the MRA-WASID method as we were not able to detect ICAS which met the criteria of the MRA-VICAST method despite strong indication of ≥50 % stenosis on 3D-reconstructions, MIP and MPR caliper flow diameter measurements. This might be related to the slab thickness of the TOF-MRA, which can cause the post-stenotic signal to be unreliable as the carotid siphon has to be covered by more than one slab. Thus, the signal on both sides of a stenosis may be the same even in cases with highly suspicious stenosis (Supplemental Figure II).

Because of its tortuosity the flow diameter in ICA siphon is difficult to measure. The WASID method requires that in cases of precavernous, cavernous and postcavernous stenosis, the normal diameter of ICA (D_{normal}) should be measured at the "widest, non-tortuous, normal portion of the petrous carotid artery that have parallel margins".[21] As the caliber of the ICA normally decreases on its intracranial course from the petrous segment to the terminus,[27] especially distal to the origin of the ophthalmic artery,[21] both the lumen diameter of the D_{normal} in DSA-WASID and the flow diameter of the D_{normal} in MRA-WASID will consequently be larger than the lumen diameter/flow diameter just proximal to a supraclinoid stenosis. This might, both in assessment of stenosis on DSA and MRA, lead to an overestimation of the grade of a stenosis in the postcavernous ICA. But on TOF-MRA, the assessment is even more challenging due to loss of laminar flow which is especially pronounced in irregular, atherosclerotic vessels. Hence, the flow diameter may additionally be reduced in the postcavernous segment compared to the flow diameter at the site of the D_{normal}, either giving an illusion of a stenosis or exaggerate it. The relatively high proportion of ICA stenosis in the present study might partially be explained by this.

MRI techniques such as intracranial high-resolution vessel wall imaging has proven to be reliable for assessing the arterial vessel wall and is a promising tool for detection and especially verification of stenosis which can complement TOF-MRA or CE-MRA.[28,29] CE-MRA offers better diagnostic accuracy than TOF-MRA when compared to DSA and provides an advantage in evaluating ICAS and large artery occlusion.[30]

The traditional cardiovascular risk factors age, male sex, hypertension, hyperlipidemia, current smoking, BMI and diabetes mellitus were all independently associated with presence of ICAS. Apart from age and sex, these are modifiable risk factors which are associated with cardiovascular disease and could be responsive to preventive measures.[31] The proportion with a history of cardiovascular disease was higher in participants with ICAS, most pronounced for stroke. Due to the cross-sectional design, no inferences can be made with regards to the temporal relationship between history of stroke and ICAS.

The definition of what should be regarded as an intracranial artery is not consistent across prevalence studies. While we and others defined the petrocavernous segment as intracranial,[12,18] others have excluded the petrous part, but not the cavernous segment.[15,16] Still others have included only the intradural segment.[6] If we exclude participants with the main stenosis in the petrous segment of the ICA, the overall prevalence is essentially unchanged (from 6.0 % to 5.9 %), while the prevalence of intradural stenosis is 5.6 %.

The prevalence of 8.0 % in men and 4.3 % in women in our study is similar to the estimated prevalence of extracranial carotid stenosis (ECAS) in the Tromsø population (5.3 % in men and 2.7 % in women).[32] A meta-analysis from four population-based studies (n = 23,706) reported that the prevalence of ECAS≥50 % increased from 0.3 % in men aged <50 years to 10.6 % in men ≥80 years, and from 0 % to 5.9 % in women in the same age groups.[33] This might suggest that the impact of ICAS could be stronger than previously assumed, especially in the elderly, and may be a target for primary prevention.

Strengths and limitations

The strength of this study is the population-based study design, with a balanced age distribution.[34] Still, the number of participants in this study was limited, resulting in relatively wide confidence intervals for the age- and sex-specific prevalence estimates, especially for the oldest age groups. Lower participation rate in the oldest age groups due to disease or disability may have led to underestimation of the prevalence of ICAS in the elderly. The mean age and the proportion of women were somewhat higher in non-attendees (mean age 65.0 years, 55.0 % women) than in attendees of the MRI study (mean age 63.8 years, 53.2 % women).

As DSA is an invasive method not feasible in population-based studies, we used 3D-TOF-MRA in our study with the limitations discussed above. However, we believe that the combined use of the MRA-VICAST and MRA-WASID methods has reduced the likelihood of errors in the assessment of stenosis. We are not aware of any population-based validation studies of TOF-MRA, but the MRA-WASID and MRA-VICAST methods have both been validated against DSA in clinical studies.[22,35]

Conclusions

The overall of prevalence of ICAS ≥50 % in our population was 6.0 %. The prevalence is relatively high and similar to the prevalence of extracranial internal carotid stenosis in previous population-based studies. This might suggest that the impact of ICAS could be stronger than previously assumed and may be a target for primary prevention.

Ethical approval

The Tromsø Study was approved by the Norwegian Data Inspectorate. The 7th survey of the Tromsø Study (REK Nord 2014/940) and the MRA study was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (REK Nord 2014/1665). Participants gave informed consent to participate in the study before taking part. The study adheres to the tenets of the Declaration of Helsinki.

Author contributions

Conceptualization: EBM and JGI; Data curation: LHJ, TV and EBM; Formal analysis: LHJ and EBM; Funding acquisition; EBM; Methodology: LHJ, MH and EBM; Project administration: EBM; Supervision: EBM, TV, JGI and MH; Validation: LHJ and MH; Writing-original draft: LHJ; Writing-review & editing: LHJ, MH, TV, JGI and EBM. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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Supplementary Materials

Prevalence of intracranial artery stenosis in a general population using 3D-time of flight magnetic resonance angiography. The Tromsø Study.

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Supplemental Material and Methods

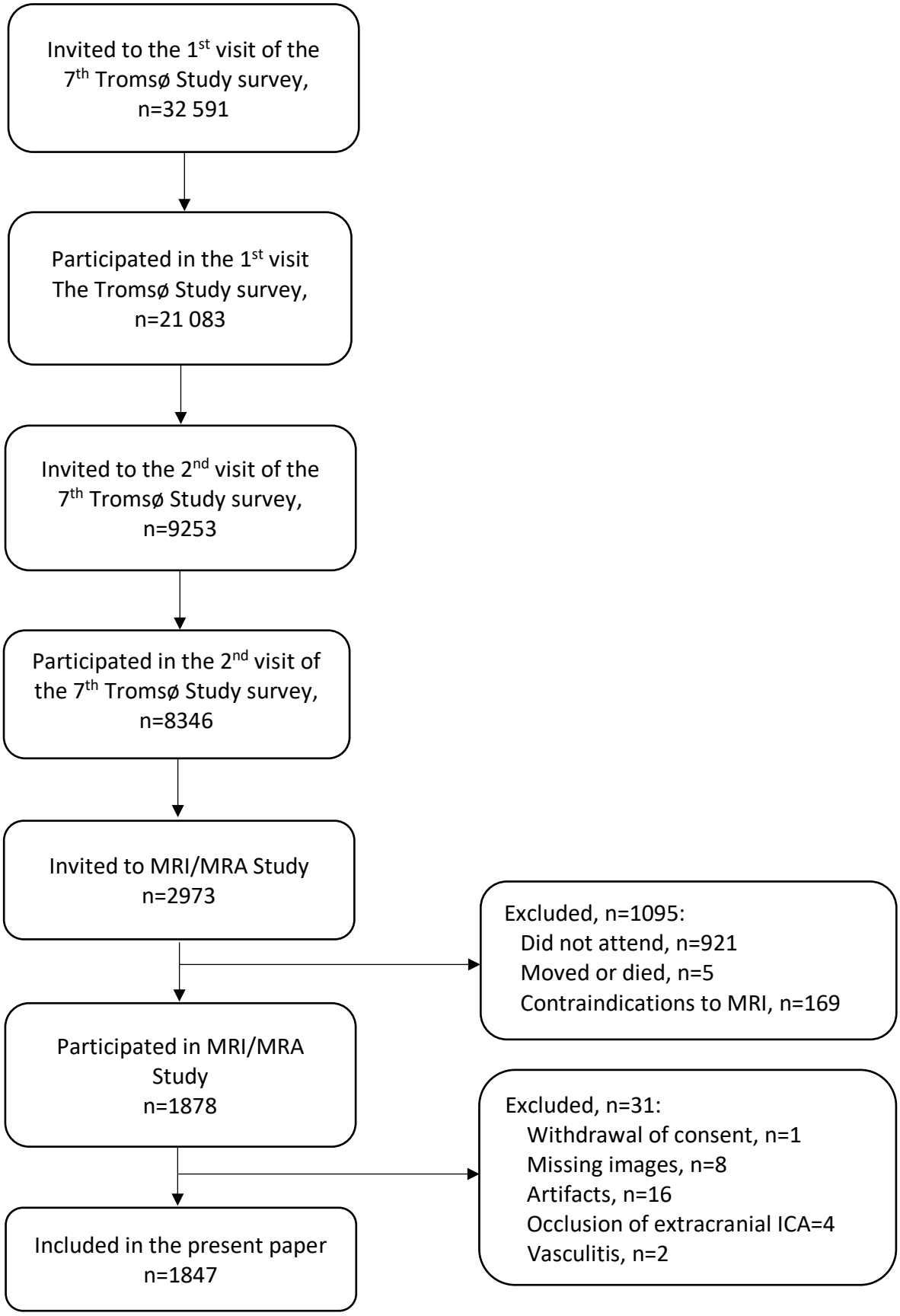
Study participants

The seventh survey of the Tromsø Study was conducted in 2015–2016, where 21 083 (64.7%) of 32 591 invited citizens aged 40 years and older attended the first visit. A pre-marked subsample of 13 028 subjects, which consisted of a random sample of 20% of all inhabitants aged 40–59 years and 50% aged 60–84 years (n=9925, 76% of the eligible) and of previous participants of the 2nd visit of the 6th survey (n=3103, 24%), was eligible for the 2nd visit, of whom 50% were pre-marked for ultrasound examination of the precerebral carotid arteries. The main survey took place from March 2015 through November 2016, while the carotid ultrasound examinations for logistic reasons started five months later (August 2015). A total of 8346 subjects attended the second visit (64% of the eligible). Due to limited MRI capacity, we invited all 3027 participants who were examined with ultrasound of the carotid arteries to participate in a magnetic resonance imaging (MRI) study conducted between January 2016 and November 2017.

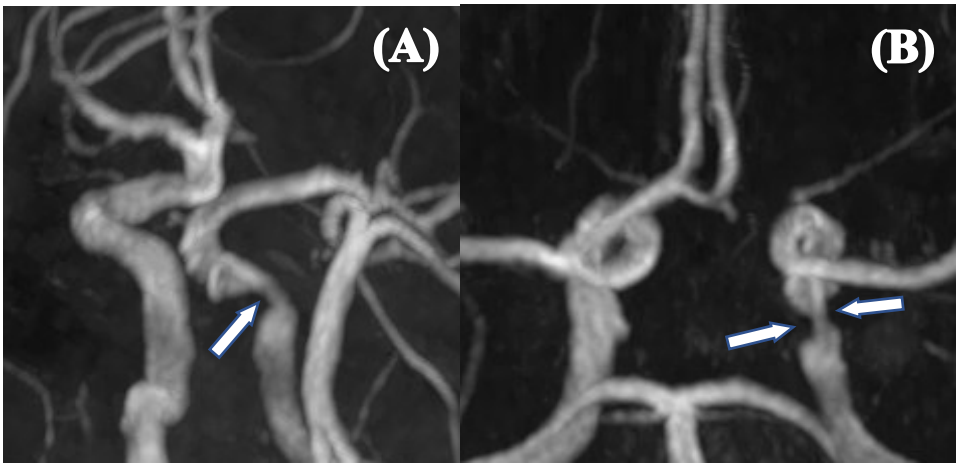
Interobserver and inter-method agreement

Interobserver and inter-method agreement was assessed in 120 examinations enriched with 44 cases with one or more stenoses. κ for inter-method agreement (MRA-WASID vs. MRA-VICAST) was assessed for the A1/A2 segments, the M1/M2 segments, the intracranial vertebral arteries, the basilar artery and the P1/P2 segments. Cohen's kappa (κ) for interobserver agreement on detection of ICAS in the ICA assessed with MRA-WASID was 0.77 (SE 0.04), while κ for interobserver agreement for ICAS in ACA, MCA and posterior circulation assessed by both MRA-WASID and MRA-VICAST was 0.76 (SE 0.02). Results for interobserver agreement on ICAS and for inter-method agreement (MRA-WASID vs. MRA-VICAST) are described in the main manuscript.

Supplemental Figure I. Flow chart of participation in the study



Supplemental Figure II. Maximum intensity projection (MIP) reconstructions image of the of the left ICA.



The arrow(s) points to reduced flow diameter in the precavernous part of the left ICA on A) sagittal oblique MIP and B) coronal oblique MIP, which do not meet the MRA-VICAST criterion of reduced signal intensity distal to the stenosis. It can be disputed whether the flow diameter is smaller in the supraclinoid part of the left ICA, but immediately distal to the stenosis the flow diameter appears to be the same as in the pre-stenotic proximal petrous part.

Paper III

Association between intracerebral artery stenosis and cortical infarcts, lacunes, white matter hyperintensities and brain atrophy.

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Tables: 3

Figures: 1

Keywords: Cerebrovascular Disease/Stroke, intracranial stenosis, infarcts, lacunes, white matter hyperintensities, brain parenchymal fraction, epidemiology

Word count: 3364

Abstract

Background: Intracranial artery stenosis (ICAS) is a significant contributor to cortical infarcts, and studies have also shown associations between ICAS and structural brain changes, such as lacunes, white matter hyperintensities (WMHs) and brain atrophy. We aimed to assess the associations between ICAS and cortical infarcts, lacunes, WMHs and brain parenchymal fraction (BPF) in a general population.

Methods: We included 1842 participants (981 women and 861 men) aged 40 to 84 years who participated in a cross-sectional population-based study. Three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) was used for the assessment of ICAS, while 3D T2-fluid attenuated inversion recovery (FLAIR) sequences, 3D T1-weighted sequences and susceptibility weighted images (SWI) were used for evaluation of brain structure. ICAS was defined as a ≥50% focal narrowing of the intracranial arterial flow diameter. WMHs were assessed by the Fazekas score and volumetric measurements. BPF was used as a proxy for brain atrophy.

Results: The 111 participants (6.0%) with ICAS had significantly more cortical infarcts (23.4% vs. 5.5%) and lacunes (27.0% vs. 7.7%) compared to participants without ICAS (1731). There was an independent association between ICAS and cortical infarcts (OR 2.31, 95% CI 1.36-3.95), lacunes (OR 2.01, 95% CI 1.24 – 3.28), mainly driven by lacunes in thalamus (OR 4.74, 95% CI 1.76 – 12.72). ICAS was independently associated with moderate-to-severe periventricular Fazekas score (OR 2.00, 95% CI 1.26 – 3.17) and BPF (β -coefficient -0.01482, 95% CI -0.0246 – -0.0051). There was no significant association between ICAS and deep moderate-to-severe WMH score or WMH volumes.

Conclusion: ICAS was associated with cortical infarcts and lacunes in the thalamus. The results also indicate a relationship between ICAS and periventricular WMHs and brain atrophy.

Non-standard Abbreviations and Acronyms

ICAS: intracranial artery stenosis

SVD: small vessel disease

WMHs: white matter hyperintensities

What is already known on this topic: Intracranial artery stenosis (ICAS) has been linked to structural brain changes such as cortical infarcts, lacunes, white matter hyperintensities (WMHs) and brain atrophy. Information is mainly limited to clinical patient series and reports from population-based studies are scarce.

What the study adds: ICAS was associated with cortical infarcts and with lacunar stroke, most pronounced for lacunes in the thalamus. ICAS was independently associated with higher risk of moderate-to-severe periventricular Fazekas score and lower brain parenchymal fraction, but not with deep moderate-to-severe WMH score or WMH volumes.

How this study might affect research, practice or policy: The study results indicate a possible relationship between ICAS and lacunes, periventricular WMHs and brain atrophy and adds to the current knowledge on ICAS as a risk factor for cortical infarcts.

Introduction

Intracranial atherosclerotic stenosis is an important cause of ischemic stroke, affecting 5-10% of White populations and up to 30-50% of Asian populations.[1] The most common stroke pattern among symptomatic stroke patients in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial was cortical and/or subcortical infarcts within the territory supplied by a single stenotic artery, constituting 44% of the anterior and 58% of posterior circulation strokes.[2]

Intracranial artery stenosis (ICAS) has been associated with lacunar strokes and white matter hyperintensities (WMHs), neuroimaging markers predominantly attributed to small vessel disease (SVD).[3] Two population-based studies from China, the PRECISE (Polyvascular Evaluation for Cognitive Impairment and Vascular Events) Study[4] and the Shunyi study,[5] have shown an independent association between ICAS and lacunes. Similarly, the population-based Rotterdam Study, reported independent relationships between intracranial artery calcification and lacunes and WMHs.[6] Results from clinical and population-based studies on the association between ICAS and WMHs are diverging.[4,5,7-9] An independent association was found between ICAS and WMHs in the Shunyi Study,[5] while no association was found between ICAS≥50% and WMHs in the PRECISE Study.[4]

Atherosclerosis and carotid stenosis have been suggested as risk factors for brain atrophy,[10,11] but the relationship between ICAS and brain atrophy has not been extensively studied. ICAS was shown to be associated with brain atrophy in the Shunyi Study,[5] and with smaller white matter volumes in the Rotterdam Study.[12] A small clinical study showed an independent association between calcifications in intracranial internal carotid artery and central brain atrophy,[13] while a study on patients with symptomatic atherosclerotic disease showed no association between vessel wall lesion burden and brain atrophy.[14]

The aim of this study was to investigate the relationship between the presence of ICAS and cortical infarcts, lacunes, WMHs and brain parenchymal fraction (BPF) as a proxy for whole brain atrophy, in a general Norwegian population aged 40 years and older.

Material and Methods

Study participants

The Tromsø Study, initiated in 1974, is a population health study involving adult residents in the municipality of Tromsø, Norway. It comprises seven surveys, with the most recent conducted in 2015-2016.[15,16] The study employs repeated cross-sectional surveys, inviting total birth cohorts and selected samples based on the official population registry. In the seventh survey, 21 083 individuals (64.7% of the 32 591 invited citizens aged 40 years and older) attended the first visit. A subset was invited to a second visit involving extended clinical examinations. Of the 9253 individuals invited, 8346 (90.2%) participated. Individuals who underwent carotid artery ultrasound examinations (n=3027) were invited to participate in the magnetic resonance imaging (MRI) study conducted in 2016–2017. Of these, 975 did not attend, 169 were excluded due to MRI contraindications, and five had either relocated or passed away prior to MRI examination. Additional exclusions included participants with either missing or insufficient image quality for the 3D TOF-MRA or 3D FLAIR (n=8 and n=18, respectively), extracranial internal carotid artery occlusion detected on ultrasound examination (n=4), generalized intracranial artery disease (moya-moya and vasculitis; n=2). One participant withdrew consent, resulting in a final study cohort of 1842 individuals.

Cardiovascular risk factors

Data on smoking status, use of medication and cardiovascular disease history was obtained through questionnaires. Trained personnel conducted standardized measurements of blood

pressure, height and weight. Serum levels of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and glycated hemoglobin (HbA1c) were analyzed using established methods. Diabetes was defined as HbA1c ≥6.5% and/or self-reported diabetes and/or use of diabetes medication. Hypertension was defined as a mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering medication and/or self-reported hypertension. Hyperlipidemia was defined as serum total cholesterol ≥7 mmol/L and/or serum LDL ≥5 mmol/L and/or use of cholesterol-lowering medication.

MRI Acquisition and Processing

Participants were scanned at the University Hospital of North Norway, Tromsø, with a 3 Tesla (3T) Siemens Skyra MR scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. The MRI protocol encompassed the following sequences: a 3D T1-weighted sequence, a 3D T2 fluid-attenuated-inversion-recovery sequence (FLAIR), a 3D time-of-flight magnetic resonance angiography (3D-TOF-MRA) sequence and a susceptibility weighted sequence (SWI). Total scan time was 22 minutes.

3D-TOF-MRA images were acquired with a 3D transversal fast low-angle shot (FLASH) sequence with flow compensation (TR/TE = 21/3.43 ms, GRAPPA parallel imaging acceleration factor 3, FOV 200 x 181 mm, slice thickness 0.5 mm, 7 slabs with 40 slices each). Reconstructed image resolution was 0.3 x 0.3 x 0.5 mm. Acquired voxel size 0.55 x 0.52 x 1 mm. Scan time 6.5 minutes.

3D-FLAIR images were acquired with a 3D turbo spin-echo sequence with variable flip angle (TR/TE/TI = 5000 ms/388 ms/1800 ms, partial Fourier = 7/8). The T1w and FLAIR scans were acquired sagittally with 1 mm isotropic resolution, GRAPPA parallel imaging

acceleration factor 2, FOV = 256 mm, 176 slices, 1 mm slice thickness, 256 x 256 image matrix.

3D T1-weighted images were acquired with a 3D magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (flip angle=9°, TR/TE/TI=2300 ms/4.21 ms/996 ms).

Susceptibility-weighted images (SWI) were acquired transversally (flip angle = 15°, TR/TE = 28/20 ms, GRAPPA parallel imaging acceleration factor 3, partial Fourier = 7/8, FOV = 220 x 220 mm, slice thickness 1.3 mm, 88 slices). Reconstructed image resolution was 0.6 x 0.6 x 1.6 mm.

ICAS was defined as a ≥50% focal narrowing of the intracranial arterial flow diameter assessed on 3D-TOF-MRA. Stenosis location was defined as the petrocavernous and the supraclinoid segments of the internal carotid artery (ICA), the A1/A2 segments of the anterior cerebral artery (ACA), the M1/M2 segments of the middle cerebral artery (MCA), the intracranial vertebral arteries, the basilar artery and the P1/P2 segments of the posterior cerebral arteries (PCA). Details on the assessment of stenosis on 3D-TOF-MRA are presented elsewhere.[17]

Assessment of brain parenchyma

Visual rating of cortical infarcts, lacunes and WMHs were assessed by two experienced neuroradiologists (LHJ and MH) using Sectra IDS7 (v22.1.12.4835). Cortical infarcts were defined as hyperintense lesions >4 mm on FLAIR images[18] located in the cerebral cortex with or without loss of tissue or extension into the deep white matter and registered according to vascular territory.[19] Classification and scoring of lacunes and periventricular and deep WMHs of presumed vascular origin were performed following the STRIVE-2 criteria.[20] A lacune was defined as a round or ovoid subcortical, fluid-filled cavity (with signal resembling CSF) up to

15 mm in diameter that is likely to be end tissue damage from recent small subcortical infarct, small subcortical hemorrhage or end-stage cavitation within a WMH. We assessed WMHs of presumed vascular origin on FLAIR-images with Fazekas four-point scale[21,22] for periventricular white matter (WM) (0 = absent, 1 = "caps" or pencil-thin lining, 2= smooth "halo," and 3 = irregular hyperintensities extending into the deep WM) and for deep WM (0 = absence or a single punctate lesion, 1 = multiple punctate lesions, 2 = beginning confluency of lesions, and 3 = large confluent lesion).

Automated segmentation of WMHs was done with a fully convolutional neural network (U-Net architecture) algorithm.[23] Segmented WMH was then divided into deep WMHs and periventricular WMHs using a 10 mm threshold,[24] giving three volumetric measures of WMH; total WMH volume, deep WMH volume and periventricular WMH volume.

FreeSurfer (v.6.0, surfer.nmr.mgh.harvard.edu) was utilized to estimate intracranial volume (ICV) and brain parenchymal volume from the T1-weighted images and a fully convolutional neural network algorithm with T1w and FLAIR images as input to estimate WMH volumes.[23,25] Brain parenchymal fraction (BPF), as a proxy of whole brain atrophy, was defined as the ratio between brain parenchymal volume (BPV) and ICV. BPV included total grey and white matter and excluded ventricles and the cerebrovascular space surrounding the brain. The intracranial volume was limited by the internal tabule.

Eight participants were excluded from the Fazekas scoring, due to white matter changes indicative of multiple sclerosis (n=7) or artifacts (n=1), leaving 1834 participants with Fazekas scores. From the automated measurements, 99 BPF and 95 WMH values were absent, due to missing images, insufficient quality of the T1 or FLAIR images, failure in the automatic segmentation algorithms, or presence of focal pathology (e.g., larger territorial

stroke lesions, multiple sclerosis, large arteriovenous malformations or tumors) that could severely affect the automated measurements.

Statistical analysis

We conducted data analysis using Stata for Mac (version 17: StataCorp LP, TX). Continuous variables are presented as means with standard deviations (SD) or as medians with interquartile range (IQR), depending on the distribution. Categorical variables are presented as counts (percentages). We assessed differences between participants with and without ICAS using a two-sample t-test for continuous variables and chi-square for categorical data. BPF and WMH volumes were log-transformed to approximate normal distribution.

Logistic regression models were fitted to calculate the odds ratio (OR) for moderate-to-high Fazekas score (scores 2 and 3), the presence of lacunes or cortical infarcts. In these models ICAS (yes/no) served as the predictor variable while Fazekas score (2-3 vs 0-1), lacune (yes/no), or cortical infarct (yes/no) were the outcome variables. Linear regression was used to assess the association between ICAS and log-transformed WMH volumes and log-transformed BPF. Both the logistic and linear regression analyses were performed in unadjusted models (Model 1), adjusted for age and sex (Model 2) and adjusted for age, sex, hypertension, hyperlipidemia, current smoking and diabetes (Model 3). Subgroup analyses were conducted to explore the association between ICAS and lacunar/cortical infarcts within their respective vascular territories both in the anterior and posterior circulation. Subgroup analyses also included analyses of ICAS and lacunes in basal ganglia, thalami and subcortical WM. Two-sided p values <0.05 were considered statistically significant. Cohen's kappa (κ) for interobserver agreement on Fazekas grading was 0.80 (SE 0.02).

Results

Characteristics of all participants and stratified according to the presence of ICAS are shown in Table 1. Participants with ICAS (n=111) tended to be older, had higher BMI, lower HDL cholesterol, and higher proportions of hypertension, diabetes mellitus, cardiovascular disease and use of lipid-lowering and antihypertensive medication than participants without ICAS. Total cholesterol, LDL-cholesterol levels and current smoking status were similar between the two groups.

Participants with ICAS had a higher proportion of cortical infarcts compared to those without ICAS (23.4% vs. 5.5%, Table 2). This was most pronounced in the anterior circulation. In multivariable-adjusted analysis, there was an independent association between ICAS and presence of cortical infarcts (OR 2.31, 95% CI 1.36 – 3.95) (Table 3, Model 3). The proportion of cortical infarcts in the vascular territory of a stenosis was higher compared to the proportion of all cortical infarcts in those without ICAS, both in the anterior (14.5% vs 3.6%, $p<0.01$) and posterior circulation (17.5% vs. 3.4%, $p<0.01$). An independent association between ICAS and cortical infarcts within the vascular territory of the stenosis was found both in the anterior (OR 2.59, 95% CI 1.33 – 5.04) and the posterior circulation (OR 3.04, 95% CI 1.24 – 7.43) (Figure 1). The association was strongest between ICAS and posterior cerebral infarcts (OR 3.89 CI 95% 1.22 – 12.40), whereas no significant association was found between ICAS and cerebellar infarcts (OR 2.14 CI 95% 0.70 – 6.49).

The proportion of participants with lacunes was higher in participants with ICAS compared to those without ICAS (27.0% vs. 7.7%, Table 2), most pronounced in the posterior circulation. In the adjusted analysis, there was an independent association between ICAS and the presence of lacunes (OR 2.01, 95% CI 1.24 – 3.28) (Table 3, Model 3). This was primarily driven by lacunes in the posterior circulation (OR 4.03, 95% CI 1.52 – 10.66) (Figure 1), especially by lacunes in the thalamus (OR 4.74, 95% CI 1.76 – 12.73). No

independent association was observed between ICAS and lacunes in the anterior circulation (Figure 1).

The proportion with moderate-to-severe Fazekas score (≥2) was higher in the ICAS group than in the non-ICAS group, evident in both deep (41.4% vs. 22.0%) and periventricular (67.6% vs. 29.8%) WMHs. The volumes of total, deep and periventricular WMHs were significantly larger in the ICAS group (Table 2). ICAS was associated with moderate-to-severe periventricular WM Fazekas score (OR 2.00, 95% CI 1.26 – 3.17) (Table 3, Model 3), but not with deep WM Fazekas score (OR 1.06, 95% CI 0.69 – 1.64) nor periventricular WMHs volume (β-coefficient 0.145, 95% CI -0.056 – 0.346).

Participants with ICAS had lower BPF compared to those without ICAS (0.65 vs. 0.69, Table 2) and ICAS was independently associated with lower BPF (β-coefficient -0.015, 95% CI -0.025 – -0.005) (Table 3, Model 3).

Discussion

In this study, we found that ICAS was independently associated with the presence of cortical infarcts, lacunes, moderate-to severe periventricular Fazekas scores, and lower BPF. No association was found between ICAS and moderate-to-severe deep white matter Fazekas score or automatically segmented WMH volumes.

Cortical infarcts are associated with large artery atherosclerosis.[2,25] In our population the prevalence of cortical infarcts was 6.6%. We found an independent association between ICAS and cortical infarcts in general, with stronger effect estimates for infarcts in the vascular territory of the stenosis. This finding aligns with previous studies that have shown that territorial cortical and subcortical infarcts are the most common stroke subtype in patients with ICAS.[2,25,26]

We identified an independent association between the presence of ICAS and lacunes. This was primarily driven by lacunes in the posterior circulation, especially by lacunes in the thalamus, whereas no independent association was found between ICAS and anterior circulation lacunes. The relatively low frequency of lacunes of 8.9% in our population suggests that there might be insufficient power to detect a possible association between ICAS and anterior circulation lacunes. Our findings are in line with previous population-based studies. The PRECISE Study, with 3061 participants, found an independent association between ICAS≥50% and lacunes.[4] The Shunyi Study, including 1237 participants, reported an association between ICAS of any degree and lacunes.[5] The Rotterdam Study, with 1489 participants, reported that a high burden of calcification in the intracranial internal carotid artery (ICA) and vertebrobasilar arteries was independently associated with lacunes.[6] The WASID Study Group reported that 15% and 36% of the ischemic strokes in the anterior and posterior circulation, respectively, were subcortical and in the distribution of a perforating vessel originating at the site of a stenosis.[2] Patients presenting with lacunar and non-lacunar strokes had a comparable risk of recurrent, predominantly non-lacunar stroke, suggesting that the pathophysiology of lacunar strokes may be more closely related to stenosis than SVD.[28] A Korean MRI/MRA study on 920 symptomatic patients with >50% stenosis, also found an association between lacunar infarcts and disease in the middle cerebral artery (MCA).[29] Conversely, no association was found between flow velocity in in the MCA (as an indicator of arterial narrowing) and small cortical or lacunar strokes.[30]

The proportion of participants with moderate-to-severe Fazekas scores in deep and periventricular white matter was higher in the ICAS-group than in the non-ICAS group. However, only moderate-to-severe periventricular Fazekas score was independently associated with ICAS. The association between ICAS and WMHs exhibits some variability across studies. The PRECISE Study reported an independent association between intracranial

atherosclerotic burden and modified WMH burden,[31] but not between ICAS≥50% and WMHs.[4] The Shunyi Study found an association between ICAS and WMHs,[5] and the Rotterdam Study found an association between calcifications in the proximal intracranial arteries and WMHs.[6] In a Chinese study on 333 patients no association was found between severity of WMHs and ICAS verified by digital subtraction angiography (DSA),[9] whereas ICAS was independently associated with WMHs in a study involving 679 Korean acute stroke patients.[8] Other patient-based studies have shown independent associations between ICAS and moderate-to-severe periventricular WMHs assessed by Fazekas.[32,33] Previous studies have shown that Fazekas scores largely correspond with distinct ranges of WMH volume.[34,35] The lack of association between ICAS and WMHs assessed by automated segmentation in our study, contrasts reports from other population-based studies. This discrepancy could be attributed to insufficient statistical power and disparities in the segmentation algorithms and processing tools utilized across different studies. Different methodologies could account for the conflicting results we observed regarding the association between ICAS and periventricular WMHs assessed by Fazekas score and ICAS and volumetric measurement of WMHs. Fazekas scoring, being qualitative, evaluates features such as bridging between lesions and confluency of the WMHs, which may not necessary correlate to the quantitative measurement of WMH volumes.

We identified an independent association between ICAS and lower BPF, as a proxy of brain atrophy. The Shunyi Study also reported an association between ICAS and general brain atrophy assessed as BPF,[5] while the Rotterdam study reported that larger calcification volumes were linked to smaller white matter volumes.[12] Clinical studies have shown diverging results. A previous study on 65 patients with acute stroke-like symptoms showed that high grade of calcifications in the cavernous carotid artery was independently associated with central brain atrophy, but not cortical atrophy.[13] Conversely, the SMART-MR Study on

130 patients with symptomatic atherosclerotic disease did not observe any association between burden of vessel wall lesions and brain atrophy.[14] Brain atrophy is a common finding in patients with atherosclerotic disease.[36] However, the precise underlying causes driving the progression of brain atrophy remain largely unknown.

In general, the association between ICAS/intracranial atherosclerotic disease (IAD) and structural brain changes exhibits some variability across studies, which can be attributed to differences in imaging modality, MRI field strength, MRI sequences, assessment methods, inconsistent definitions of predictor- and outcome-variables and population examined. While the PRECISE Study used both atherosclerotic burden and ICAS ≥50% as predictor variables in their analyses,[4] the Shunyi Study reported data for ICAS of any degree.[5] The Rotterdam Study and some patient-based studies used calcifications in arteries as a proxy for ICAS, [6,13,32] while others assess vessel walls for atherosclerotic burden.[14,33] Our predictor variable, ICAS≥50%, represents a relatively advanced stage of IAD, and includes only relatively proximal intracranial arteries. Expanding the predictor variable to include more distal arteries, branches from the vertebrobasilar arteries and ICAS<50% would most likely have a strong impact on our results. Given the differences above, direct comparison between studies is challenging. Still, our results generally align with the trends observed in previous studies and suggest that ICAS may play a role in structural brain changes. While IAD and manifestations of SVD are often categorized as distinct pathologies, it is suggested that their pathology may interact, and one hypothesis does not necessarily exclude the other.[33,37] Consequently, further research is needed to fully understand these associations and their underlying mechanisms.

Strengths and limitations

Strengths of our study is its population-based design, and a relatively large number of participants. However, selection bias may have occurred due to lower participation among

individuals with certain medical conditions, such as stroke, cognitive impairment and conditions limiting participation in a study using MRI, leading to potential underestimation of the prevalence of both ICAS and structural brain changes. The mean age and the proportion of women were higher in non-attendees than in attendees of the MRI study (mean age 65.0 vs. 63.8 years, 55.0% vs. 53.2% women, respectively). Since the study predominantly comprises Caucasians, its findings may not be directly applicable to other populations and ethnic groups. Further, the cross-sectional design of this study makes it impossible to establish a cause–effect relationship, which can only be explored further in longitudinal studies.

The choice of imaging modalities and definitions of ICAS vary between studies. We defined ICAS as a luminal narrowing of a proximal artery of ≥50%, a cutoff commonly used in a clinical setting for extracranial and intracranial stenosis. Other cutoffs and inclusion of stenosis in more distal arterial branches could have influenced results.

The differentiation between anterior and posterior circulation stenosis and lesions within their respective vascular territories, together with the application of the newly revised STRIVE-2 criteria to assess lacunes are strengths of this study. However, accurately assessment of lacunes can be challenging and require thorough evaluation, as perfect differentiation of lacunes from perivascular spaces is not always possible based on size or T2-hyperintense rim alone criteria.[20] With this in mind, there is a possibility that lacunes have been misinterpreted as perivascular space and vice versa.

Conclusions

In this population-based study we found that ICAS ≥50% was associated with cortical infarcts in both the anterior and posterior circulation and with lacunes in the thalamus. ICAS was also associated with periventricular WMHs assessed by Fazekas score and a lower brain parenchymal fraction as a proxy for brain atrophy.

Ethics approval

The present study was approved by the Regional Committee of Medical and Health Research Ethics North Norway (file no. 2014/1665) and carried out in accordance with relevant guidelines and regulations. The Tromsø Study was approved by the Norwegian Data Inspectorate. The 7th survey of the Tromsø Study and the MRA study was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (REK Nord 2014/940 and 2014/1665). The study adheres to the tenets of the Declaration of Helsinki. All participants gave written, informed consent.

We followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement for reporting.

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Contributors

Study conception and design: EBM, JGI; Data collection: LHJ; Imaging analysis: LHJ, MH; Analysis and interpretation of the results: LHJ, MH, EBM, TV; Manuscript draft: LHJ. All authors provided critical review, edited and approved the final manuscript. EBM is guarantor of the study.

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Disclosures

None

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Table 1. Characteristics of participants with and without intracranial arterial stenosis (ICAS)*

	All participants (n=1842)	ICAS* (n=111)	No ICAS (n=1731)	p-value
Male sex, n (%)	861 (46.7)	69 (62.2)	792 (45.8)	<0.001
Age, years	63.8 (10.6)	72.4 (7.5)	63.3 (10.5)	<0.001
Mean systolic blood pressure, mmHg	134.0 (20.7)	145.7 (20.5)	133.2 (20.5)	<0.001
Mean diastolic blood pressure, mmHg	75.1 (9.9)	76.1 (9.3)	75.1 (9.9)	0.271
Serum total cholesterol, mmol/L	5.52 (1.10)	5.30 (1.21)	5.53 (1.10)	0.032
Serum HDL cholesterol, mmol/L	1.63 (0.50)	1.45 (0.36)	1.65 (0.51)	<0.001
Serum LDL cholesterol, mmol/L	3.58 (1.02)	3.47 (1.09)	3.59 (1.01)	0.226
Current smoking	246 (13.4)	19 (17.1)	227 (13.1)	0.229
Body mass index, kg/m^2	27.1 (4.2)	28.2 (3.9)	27.0 (4.2)	0.006
Hypertension†	985 (53.5)	94 (84.7)	891 (51.5)	<0.001
Hyperlipidemia††	632 (34.3)	64 (57.7)	568 (32.8)	<0.001
Cardiovascular disease	286 (15.5)	49 (44.1)	237 (13.7)	<0.001
Coronary heart disease	207 (11.2)	38 (34.2)	169 (9.8)	<0.001
Previous stroke	53 (3.0)	13 (12.3)	40 (2.4)	<0.001

Diabetes mellitus[†††]	138 (7.5)	18 (16.2)	20 (6.9)	<0.001
Use of antihypertensive medication	558 (30.7)	60 (55.1)	498 (29.2)	<0.001
Use of cholesterol-lowering medication	420 (23.4)	57 (52.3)	363 (21.5)	<0.001

Numbers are means (SD) or n (%) *Intracranial arterial stenosis was defined as a lumen reduction of ≥ 50%. %. †Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering medication and/or self-reported hypertension [††] Hyperlipidemia was defined as serum total cholesterol ≥7 mmol/L and/or serum LDL ≥5 mmol/L and/or use of cholesterol lowering medication. [†††] Diabetes mellitus was defined as HbA1c ≥6.5% and/or self-reported diabetes and/or use of diabetes medication.
Information was missing in some of participants: systolic blood pressure: n=4, diastolic blood pressure: n=5, total-, HDL- and LDL- cholesterol: n=7, body mass index: n=1, coronary heart disease: n=1, previous stroke: n= 71, use of antihypertensive medication: n=27, use of lipid-lowering drugs: n=44

Table 2. Structural brain characteristics of participants with and without intracranial arterial stenosis (ICAS).

	All participants (n=1842)	ICAS (n=111)	No ICAS (n=1731)	p-value
Cortical infarct	121 (6.6)	26 (23.4)	95 (5.5)	<0.001
Cortical infarct, anterior circulation	77 (4.2)	21 (18.9)	56 (3.2)	<0.001
Cortical infarct, posterior circulation	70 (3.8)	9 (8.1)	61 (3.5)	0.014
Lacune	164 (8.9)	30 (27.0)	134 (7.7)	<0.001
Lacune, anterior circulation	142 (7.7)	21 (18.9)	121 (7.0)	<0.001
Lacune, posterior circulation	42 (2.3)	14 (12.6)	28 (1.6)	<0.001
Fazekas scale, DWM*				<0.001
Grade 0	290 (15.8)	2 (1.8)	288 (16.7)	
Grade 1	1119 (61.0)	63 (56.8)	1056 (61.3)	
Grade 2	348 (19.0)	34 (30.6)	314 (18.2)	
Grade 3	77 (4.2)	12 (10.8)	65 (3.8)	
Fazekas scale, PVWM*				<0.001

Grade 0	308 (16.8)	3 (2.7)	305 (17.7)	
Grade 1	937 (51.1)	33 (29.7)	904 (52.5)	
Grade 2	483 (26.3)	65 (58.6)	418 (24.3)	
Grade 3	106 (5.8)	10 (9.0)	96 (5.6)	
Total WMH volume, **cm^3	2.12 (1.10–5.73)	5.57 (2.79–11.09)	2.00 (1.06–5.21)	<0.001
Deep WMH volume, **cm^3	0.70 (0.44–1.49)	1.10 (0.61–2.56)	0.68 (0.44–1.41)	<0.001
Periventricular WMH volume, ** cm^3	1.34 (0.56–4.04)	4.50 (2.02–8.05)	1.25 (0.54–3.74)	<0.001
Brain parenchymal fraction†	0.68 (0.66–0.71)	0.65 (0.63–0.68)	0.69 (0.66–0.71)	<0.001

Numbers are n (%) or median (IQR; interquartile range). DWM: deep white matter, PVWM: periventricular white matter, WMH: white matter hyperintensities. *Assessed in 1834 participants. **Assessed in 1747 participants
†Brain parenchymal fraction was calculated as brain parenchymal volume divided by intracranial volume and assessed in 1743 participants

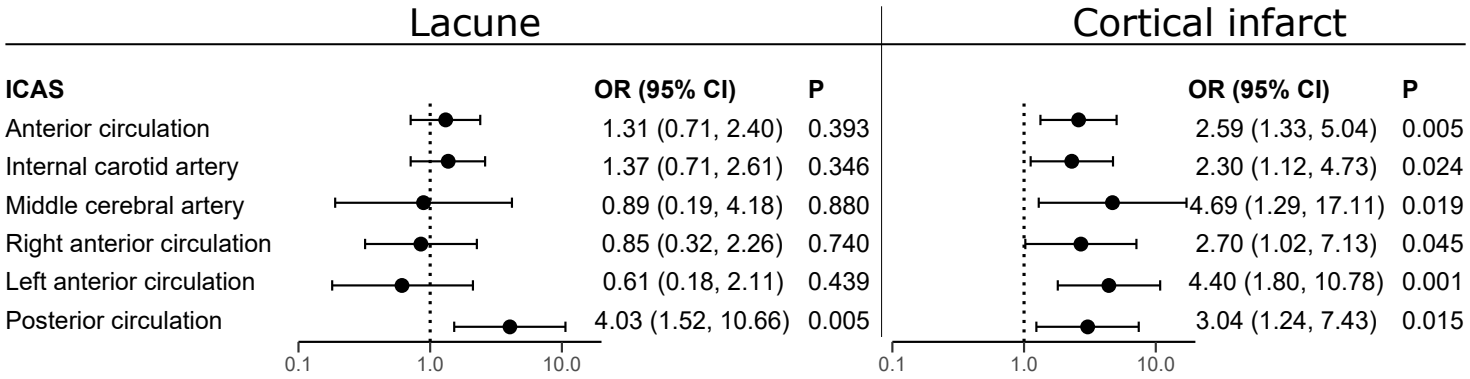
Table 3. Association between presence of intracranial artery stenosis and structural brain changes

	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Cortical infarct (yes/no)	5.27 (3.24–8.56)	<0.001	2.66 (1.58–4.46)	<0.001	2.31 (1.36–3.95)	0.002
Lacune (yes/no)	4.41 (2.80–6.95)	<0.001	2.38 (1.47–3.86)	<0.001	2.01 (1.24–3.28)	0.005
Fazekas, DWM (0/1 vs. 2/3)	2.51 (1.69–3.72)	<0.001	1.23 (0.80–1.89)	0.348	1.06 (0.69–1.64)	0.787
Fazekas, PVWM (0/1 vs. 2/3)	4.90 (3.25–7.39)	<0.001	2.36 (1.50–3.73)	<0.001	2.00 (1.26–3.17)	0.003
	β-coefficient* (95% CI)		β-coefficient* (95% CI)		β-coefficient* (95% CI)	
WMH volume	0.774 (0.549–0.999)	<0.001	0.187 (0.005–0.370)	0.044	0.125 (-0.057–0.306)	0.179
Deep WMH volume	0.039 (0.196–0.590)	<0.001	0.085 (-0.101–0.273)	0.371	0.013 (-0.056–0.356)	0.887
Periventricular WMH volume	0.959 (0.695–1.223)	<0.001	0.208 (0.006–0.409)	0.043	0.145 (-0.056–0.346)	0.158

Brain parenchymal fraction†	-0.0516 (-0.0642– -0.0390)	<0.001	-0.01488 (-0.0245– -0.0052)	0.003	-0.01482 (-0.0246– -0.0051)	0.003

OR: odds ratio, CI: confidence interval, DWM: deep white matter, PVWM: periventricular white matter, WMH: white matter hyperintensities.
Model 1: univariable analysis, Model 2: adjusted for age and sex, Model 3: multivariable model adjusted for age, sex, hypertension, hyperlipidemia, diabetes and current smoking.
*β-coefficients (95%CI) were calculated from log-transformed values.
†Brain parenchymal fraction was calculated as brain parenchymal volume divided by intracranial volume.

Figure 1. Forest plot of odds ratios (95% CI) for lacunes and cortical infarct in vascular territories of intracranial artery stenosis (ICAS).



OR: odds ratio. CI: confidence interval.
Analyses are logistic regression with ICAS as the independent variable and lacune and cortical infarct as outcome variables, adjusted for age, sex, hypertension, hyperlipidemia, diabetes and current smoking

Appendix I

Questionnaire 1, the 7th Tromsø Study 2015-2016

Tromsø-undersøkelsen
2015–2016

KONFIDENSIELT

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Bruk blokkbokstaver. Du kan ikke bruke komma.

Dato for utfylling: ☐☐☐☐☐☐

HELSE OG SYKDOMMER

1.1 Hvordan vurderer du din egen helse sånn i alminnelighet?

Meget god	God	Verken god eller dårlig	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

1.2 Hvordan synes du at helsen din er sammenlignet med andre på din alder?

Mye bedre	Litt bedre	Omtrent lik	Litt dårligere	Mye dårligere
☐	☐	☐	☐	☐

1.3 Har du eller har du hatt?
Sett ett kryss per linje.

	Nei	Ja nå	Før, ikke nå	Alder første gang
Høyt blodtrykk	☐	☐	☐	☐☐
Hjerteinfarkt	☐		☐	☐☐
Hjertesvikt	☐	☐	☐	☐☐
Atrieflimmer *(hjerteflimmer)*	☐	☐	☐	☐☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐	☐☐
Hjerneslag/hjerneblødning	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Nyresykdom *(unntatt urinveisinfeksjon)*	☐	☐	☐	☐☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐	☐☐
Astma	☐	☐	☐	☐☐
Kreft	☐	☐	☐	☐☐
Revmatoid artritt *(leddgikt)*	☐	☐	☐	☐☐
Artrose *(slitasjegikt)*	☐	☐	☐	☐☐
Migrene	☐	☐	☐	☐☐
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	☐	☐☐

1.4 Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?

☐ Nei ☐ Ja

TANNHELSE

2.1 Hvordan vurderer du din egen tannhelse?

	1	2	3	4	5	
Svært dårlig	☐	☐	☐	☐	☐	Svært god

2.2 Hvor fornøyd eller misfornøyd er du med tennene eller protesene dine?

	1	2	3	4	5	
Svært misfornøyd	☐	☐	☐	☐	☐	Svært fornøyd

BRUK AV HELSETJENESTER

3.1 Har du, grunnet egen helse, i løpet av de siste 12 måneder vært hos:

	Nei	Ja	Antall ganger
Fastlege/allmennlege	☐	☐	☐☐
Legevakt	☐	☐	☐☐
Psykiater/psykolog	☐	☐	☐☐
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	☐☐
Tannlege/tannpleier	☐	☐	☐☐
Apotek *(for kjøp/råd om medisiner/behandling)*	☐	☐	☐☐
Fysioterapeut	☐	☐	☐☐
Kiropraktor	☐	☐	☐☐
Akupunktør	☐	☐	☐☐
Alternativ behandler *(homøopat, soneterapeut, healer etc)*	☐	☐	☐☐
Tradisjonell helbreder *(hjelper, «læser» etc)*	☐	☐	☐☐
Har du kommunisert via internett med noen av tjenestene over?	☐	☐	☐☐

3.2 Har du i løpet av de siste 12 måneder vært på sykehus?

	Nei	Ja	Antall ganger
Innlagt på sykehus	☐	☐	☐☐
Konsultasjon ved sykehus uten innleggelse:			
Ved psykiatrisk poliklinikk	☐	☐	☐☐
Ved annen sykehuspoliklinikk	☐	☐	☐☐

BRUK AV MEDISINER

4.1 Bruker du, eller har du brukt, noen av følgende medisiner? *Sett ett kryss per linje.*

	Aldri	Nå	Før, ikke nå	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Annen medisin mot hjertesykdom *(f.eks. blodfortynnende, rytmestabiliserende, nitroglycerin)*	☐	☐	☐	
Insulin	☐	☐	☐	
Tabletter mot diabetes	☐	☐	☐	
Stoffskiftemedisin *(Levaxin/thyroxin)*	☐	☐	☐	

4.2 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner? *Sett ett kryss per linje.*

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende uten resept	☐	☐	☐	☐
Magesyrehemmende medisiner	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

4.3 Skriv alle medisiner (reseptfrie og reseptbelagte) du har brukt regelmessig siste 4 uker. *Ikke regn med reseptfrie vitamin-, mineral- og kosttilskudd, urter, naturmedisin etc.*

Får du ikke plass til alle medisinene, bruk eget ark.

KOSTHOLD

5.1 Spiser du vanligvis frokost hver dag?

☐ Nei ☐ Ja

5.2 Hvor mange porsjoner frukt og grønnsaker spiser du i gjennomsnitt per dag? *Med porsjon menes f.eks. et eple, en salatbolle.*

Antall porsjoner

5.3 Hvor ofte spiser du vanligvis disse matvarene? *Sett ett kryss per linje.*

	0–1 pr. mnd.	2–3 pr. mnd.	1–3 pr. uke	4–6 pr. uke	1 eller mer pr. dag
Rødt kjøtt *(alle produkter av storfe, får, svin)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei)*	☐	☐	☐	☐	☐
Feit fisk *(laks, ørret, uer makrell, sild, kveite)*	☐	☐	☐	☐	☐

5.4 Hvor mange glass/beger drikker/spiser du vanligvis av følgende? *Sett ett kryss per linje.*

	Sjelden/ aldri	1–6 pr. uke	1 pr. dag	2–3 pr. dag	4 eller mer pr. dag
Melk/yoghurt tilsatt probiotika *(Biola, Cultura, Activia, Actimel, BioQ)*	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker:					
med sukker	☐	☐	☐	☐	☐
med kunstig søtning	☐	☐	☐	☐	☐

5.5 Hvor mange kopper kaffe og te drikker du daglig? *Sett 0 for de typene du ikke drikker daglig.*

	Antall kopper
Filterkaffe *(trakterkaffe)*	
Kokekaffe og/eller presskannekaffe	
Pulverkaffe	
Espressobasert kaffe *(fra kaffemaskin, kapsler etc)*	
Sort te *(f.eks. Earl Grey)*	
Grønn/hvit/oolong te	
Urtete *(f.eks. nype, kamille, Rooibos)*	

HELSEBEKYMRING

	Ikke i det hele tatt	Litt	Noe	En hel del	Svært mye
6.1 **Tror du at det er noe alvorlig galt med kroppen din?**	☐	☐	☐	☐	☐
6.2 **Er du svært bekymret over helsen din?**	☐	☐	☐	☐	☐
6.3 **Er det vanskelig for deg å tro på legen din dersom hun/han forteller deg at det ikke er noe å bekymre seg for?**	☐	☐	☐	☐	☐
6.4 **Er du ofte bekymret for muligheten for at du har en alvorlig sykdom?**	☐	☐	☐	☐	☐
6.5 **Hvis du blir gjort oppmerksom på en sykdom (f.eks. via TV, radio, internett, avis eller noen du kjenner), bekymrer du deg da for selv å få sykdommen?**	☐	☐	☐	☐	☐
6.6 **Opplever du at du plages av mange ulike symptomer?**	☐	☐	☐	☐	☐
6.7 **Har du tilbakevendende tanker (som er vanskelig å bli kvitt) om at du har en sykdom?**	☐	☐	☐	☐	☐

FYSISK AKTIVITET

7.1 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?** *Sett kryss i den ruta som passer best.*

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks. ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks. pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

7.2 **Angi bevegelse og kroppslig anstrengelse i din fritid det siste året.** *Hvis aktiviteten varierer gjennom året, ta et gjennomsnitt. Sett kryss i den ruta som passer best.*

- ☐ Leser, ser på TV / skjerm eller annen stillesittende aktivitet
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka *(inkludert gang eller sykling til arbeidsstedet, søndagsturer etc)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking etc minst 4 timer i uka
- ☐ Trener hardt eller driver konkurranseidrett regelmessig flere ganger i uka

7.3 **Siste uka, omtrent hvor lang tid tilbrakte du <u>sittende</u> på en typisk hverdag og fridag?** *F.eks. ved arbeidsbord, hos venner, mens du så på TV / skjerm.*

☐☐ timer sittende på en hverdag *(både jobb og fritid)*

☐☐ timer sittende på en fridag

ALKOHOL

8.1 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2–4 ganger hver måned
- ☐ 2–3 ganger per uke
- ☐ 4 eller flere ganger per uke

8.2 **Hvor mange enheter alkohol (flaske øl, glass vin eller drink) tar du vanligvis når du drikker?**

1–2	3–4	5–6	7–9	10 eller flere
☐	☐	☐	☐	☐

8.3 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ Aldri
- ☐ Sjeldnere enn månedlig
- ☐ Månedlig
- ☐ Ukentlig
- ☐ Daglig eller nesten daglig

RØYK OG SNUS

9.1 **Har du røykt/røyker du daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

9.2 **Har du brukt/bruker du snus eller skrå daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

SPØRSMÅL OM KREFT

10.1 **Har du noen gang fått**

	Nei	Ja	**Hvis ja:** alder første gang	**Hvis ja:** alder siste gang
Utført mammografi	☐	☐		
Målt PSA (prostataspesifikt antigen)	☐	☐		
Utført tykktarmsundersøkelse (koloskopi, avføringsprøve)	☐	☐		

10.2 **Har noen i din nære biologiske familie hatt**

	Egne barn	Mor	Far	Mormor	Morfar	Farmor	Farfar	Tante	Onkel	Søsken
Brystkreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostatakreft	☐		☐		☐		☐		☐	☐
Tykktarmskreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

UTDANNING OG INNTEKT

11.1 **Hva er din høyeste fullførte utdanning?** *Sett ett kryss.*

- ☐ Grunnskole/framhaldsskole/folkehøyskole inntil 10 år
- ☐ Fagutdanning/realskole/videregående/gymnas minimum 3 år
- ☐ Høyskole/universitet mindre enn 4 år
- ☐ Høyskole/universitet 4 år eller mer

11.2 **Hva var din husstands samlede bruttoinntekt siste år?** *Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.*

- ☐ Under 150 000 kr
- ☐ 150 000–250 000 kr
- ☐ 251 000–350 000 kr
- ☐ 351 000–450 000 kr
- ☐ 451 000–550 000 kr
- ☐ 551 000–750 000 kr
- ☐ 751 000 –1 000 000 kr
- ☐ Over 1 000 000 kr

FAMILIE OG VENNER

12.1 **Hvem bor du sammen med?**

	Nei	Ja	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

12.2 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

12.3 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

12.4 **Hvor ofte deltar du vanligvis i foreningsvirksomhet som syklubb, idrettslag, politiske, religiøse eller andre foreninger?**

Aldri, eller noen få ganger i året	1–2 ganger i måneden	Omtrent 1 gang i uka	Mer enn 1 gang i uka
☐	☐	☐	☐

SPØRSMÅL TIL KVINNER

13.1 **Hvor gammel var du da du fikk menstruasjon første gang?**

Alder

13.2 **Er du gravid nå?**

☐ Nei ☐ Ja ☐ Usikker

13.3 **Hvor mange barn har du født?**

Antall barn

13.4 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.** *Angi så godt du kan. Hvis flere barn, bruk ekstra ark.*

	Fødselsår	Fødselsvekt i gram	Ammet ant. mnd.
Barn 1			
Barn 2			
Barn 3			
Barn 4			
Barn 5			
Barn 6			

SPØRSMÅL TIL MENN

14.1 **Har du fått behandling for betennelse i prostata eller urinblæra?**

☐ Nei ☐ Ja

14.2 **Har du fått utført steriliseringsoperasjon?**

☐ Nei ☐ Ja **Hvis ja:** hvilket år

Tusen takk for ditt bidrag.

Appendix II

Invitation to the MRI Study

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Tromsø-
undersøkelsen

Tromsøundersøkelsen 2015-2017

Invitasjon til MR-undersøkelse av hjernens blodårer

Dette er et spørsmål til deg om å delta i et forskningsprosjekt hvor hensikten er å undersøke forekomsten av innsnevringer (stenoser) og utposninger (aneurismer) i hjernens blodårer. Både innsnevringer og utposninger er viktige årsaker til hjerneslag. Vi vet imidlertid ikke sikkert hvor vanlige disse tilstandene i befolkningen. Tromsøundersøkelsen er godt egnet til å fremskaffe ny kunnskap om dette.

Med denne studien ønsker vi å få økt kunnskap om:

- Forekomst av innsnevring og utposning på hjernens blodårer
- Hvilke faktorer som er forbundet med økt risiko for å få dette
- Sammenhengen mellom slike blodåreforandringer og hjerneslag

Undersøkelsen er en del av den sjuende Tromsøundersøkelsen og utgår fra forskningsgruppen Hjerne og sirkulasjon, Institutt for klinisk medisin ved Universitetet i Tromsø, i samarbeid med Universitetssykehuset Nord Norge. Du blir forespurt om å delta i denne undersøkelsen fordi du har deltatt i den sjuende Tromsøundersøkelsen og er i riktig aldersgruppe.

Hva innebærer studien?

Deltakerne i studien vil bli undersøkt med magnetisk resonans, såkalt MR-undersøkelse av hjernens blodårer og hjernevevet. MR-undersøkelsen foregår på **Universitetssykehuset Nord Norge** og varer ca. 20 minutter.
Resultatene av bildene vil kobles sammen med øvrige opplysninger om deg samlet inn i forbindelse med Tromsøundersøkelsen.

Kontaktinformasjon

Prosjektleder professor Ellisiv B. Mathiesen Tlf. 776 46 418
Overlege Liv-Hege Johnsen, tlf. 776 28 307
Forskningstekniker Sissel Martinsen, tlf. 918 13 982

UNIVERSITETET I TROMSØ

Mulige fordeler og ulemper

For de fleste deltakerne vil studien verken ha fordeler eller ulemper. Hos noen vil det kunne påvises forandringer i hjernens blodårer, og eventuelt andre forandringer i hjernevevet (for eksempel svulster). I noen tilfeller kan det være en fordel å få påvist slike tilstander slik at man kan få behandling og forebygging for å redusere risiko for fremtidig død eller funksjonshemming. I andre tilfeller kan det tenkes at eventuell behandling vil være risikofylt eller at behandling ikke er mulig. Å påvise en potensielt farlig tilstand som ikke gir plager i øyeblikket og som ikke kan kureres, kan oppleves som en belastning.

Hva skjer hvis det påvises noe unormalt?

Hvis det påvises forandringer i blodårene eller i hjernen som krever videre utredning eller behandling, blir du informert om dette pr brev og /eller telefon. Du får da tilbud om henvisning til nærmere undersøkelse hos spesialist ved nevrologisk eller nevrokirurgisk poliklinikk, Universitetssykehuset Nord Norge, Tromsø.

Personer som ikke kan delta

MR-undersøkelsen innebærer ingen bruk av røntgenstråler eller inntak av legemidler eller kontrast, og anses som ufarlig. Følgende forhold begrenser likevel deltakelse:

- Implantater: Undersøkelsen kan gi skade, forskyvning og/eller oppvarming av metall-implantater. Dersom du har metall-implantater i kroppen, kan du ikke delta. Alle metallgjenstander (smykker, øredobber, piercing, klær med metallknapper osv.) og sminke må fjernes før undersøkelsen.
- Klaustrofobi: Du må ligge på rygg i MR maskinen, som kan føles litt trang og bråkete. Personer med klaustrofobi bør derfor ikke delta.
- Graviditet: Det er ikke påvist skader ved MR-undersøkelser av gravide, men for sikkerhets skyld anbefales det ikke at gravide tar MR. Du kan derfor ikke delta hvis du er gravid.

Hva skjer med prøvene og informasjonen om deg?

MR bildene og informasjonen som registreres om deg skal kun brukes som beskrevet i hensikten med studien. Alle opplysningene og prøvene behandles uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Resultatene av MR-undersøkelsen kobles mot øvrige data fra Tromsøundersøkelsen og slettes ikke. Selve MR bildene blir oppbevart i røntgenarkivet til Universitetssykehuset Nord Norge,
Tromsø. Det er ikke mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du tar samtykket med deg på undersøkelsen, har du glemt det får du nytt når du møter. Du kan når som helst og uten å oppgi noen grunn, trekke ditt samtykke. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Hvis du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte

Forskningstekniker Sissel Martinsen på tlf. 918 13 982
Prosjektleder professor Ellisiv B. Mathiesen på tlf. 776 46 418
Tromsøundersøkelsen ved tel 776 20700 eller epost tromsous@uit.no

Personvern, biobank, økonomi og forsikring

Studien er finansiert av UiT Norges arktiske universitet. Som deltaker i denne studien er du omfattet av Norsk pasientskadeerstatning. Opplysninger som registreres om deg er forhold som vedrører hjernens blodkar (innsnevringer og utposninger) og eventuelle forandringer i selve hjernevevet. UiT Norges arktiske universitet ved universitetsdirektøren er databehandlingsansvarlig institusjon.

Godkjenning

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk (2014/1665/REK nord).

Timeavtale

For å delta i studien, ber vi deg kontakte forskningstekniker Sissel Martinsen, tlf. 918 13 982, for å avtale tid for MR-undersøkelsen. Ved oppmøte til time er det fint om du tar med deg dette skrivet.

Samtykke til deltakelse i prosjektet MR-undersøkelse av hjernens blodårer

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Tromsø-undersøkelsen

Jeg er villig til å delta i prosjektet

Sted og dato: *Deltakers signatur*

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato: *Signatur*

Rolle i prosjektet

Takk for at du deltar og bidrar til viktig forskning. Ditt bidrag teller!

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Appendix III

Safety check-list for MRI-scanning

Navn deltaker:

Fødselsnr:

Tlf.nr:

Løpenr:

Time til MR:

SMS sendt:

MR sjekkliste		
Viktige opplysninger om deltakeren	**Ja**	**Nei**
Metall-fremmedlegeme i øyet		
Cochlea (øre) implantat		
Vaskulære kateter av metall		
Pacemakerelektrode		
Nevrostimulator		
Insulin/morfin-pumpe		
Gravid		
Klaustrofobi		
HVIS JA PÅ OVERNEVNTE SPØRSMÅL, EKSKLUDERES DELTAKEREN		
Intracranielle vaskulære klips/coiler		
Metall etter tidligere kirurgi		
(klips, hjerteklaff, shunt, aorta stentgraft, proteser, plater, skruer?		
Hvis ja, på overnevnte spørsmål:		
Implantat, når og hvor implantert? Typebetegnelse?		
Kan lege ved Tromsøundersøkelsen få tillatelse til å gå inn i		
journalen for å sjekke type metall?		
Kommunikasjonsproblemer/nedsatt hørsel		
Kan du ligge på ryggen i ca 30 min		
Metall som kan fjernes (gebiss, proteser, sminke, piercing,		
høreapparat)		
Sted, dato og underskrift:		

Appendix IV

Invitation letter to the MRI scanning

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Tromsø-
undersøkelsen

Tromsøundersøkelsen

Invitasjon til MR-undersøkelse av hjernens pulsårer

I 2015 deltok du i den 7. Tromsøundersøkelsen – tusen takk for det!

Som en del av Tromsøundersøkelsen gjennomfører vi for tiden en oppfølgingsstudie med MR-undersøkelse av hjernens blodårer. Vi utvider nå undersøkelsen med flere deltakere, og i den forbindelse kontakter vi deg.

Sammen med dette brevet finner du et skriv med informasjon om studien, forespørsel om deltakelse og samtykkeskjema.

Dersom du ønsker å delta, ber vi deg ta kontakt med oss for å avtale time. Du kan da ringe forskningstekniker **....., tlf. 918 13 982.**
Vedkommende vil kunne svare på spørsmål og gi mer informasjon om studien.

Med vennlig hilsen

Tromsøundersøkelsen

Kontaktinformasjon

Forskningstekniker Sissel Martinsen, tlf. 918 13 982
Prosjektleder professor Ellisiv B. Mathiesen, tlf. 77 64 64 18
Overlege Liv-Hege Johnsen, tlf. 77 62 83 07

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