Arterial ischaemic stroke from 2010-2015: Incidence, risk factors, atherosclerosis and 5-year outcome

The Norwegian Stroke in the Young Study, a three-generation research program

Beenish Nawaz

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Name: Beenish Nawaz

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Scientific environment

Department of Neurology, Haukeland University Hospital, Bergen
Department of Clinical Medicine, University of Bergen, Bergen
Bergen Stroke Research Group, Haukeland Univeristy Hospital, Bergen

Main supervisor: Professor Ulrike Waje-Andreassen, MD PhD

Co-supervisors: Annette Fromm, MD PhD MSc
Professor Halvor Næss, MD PhD

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List of abbreviations

AAI	Ankle-arm index
AAP	Abdominal aorta plaque
ACE	Angiotensin-converting enzyme inhibitors
ADC	Apparent diffusion coefficient
AHA	American Heart Association
ASA	American Stroke Association
ARB	Angiotensin receptor blockers
BIF	Carotid bifurcature
BMI	Body-mass index
BP	Blood pressure
CAD	Coronary artery disease
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
CCA	Common carotid artery
CE	Cardiac embolism
CFA	Common femoral artery
cIMT	Carotid intima-media thickness
cm	Centimetre
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
CVD	Cardiovascular disease
DSA	Digital subtraction angiography
DWI	Diffusion weighted imaging
EAT	Epicardial adipose tissue
ECG	Electrocardiogram
EKG	Elektrokardiogram
EVT	Endovascular thrombectomy
FH+	Positive family history
fIMT	Femoral intima-media thickness
HDL	High density lipoprotein
HR	Hazard ratio
ICA	Internal carotid artery
IMT	Intima-media thickness
IV	Intravenous
IVT	Intravenous thrombolysis
IQR	Interquartile range
LAA	Large-artery atherosclerosis
LDL	Low density lipoprotein
MELAS	Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
mm	Millimetre
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NAA	Number of areas with atherosclerosis
NOR-SYS	Norwegian Stroke in the Young Study
p	P-value
PAD	Peripheral artery disease
PET	Positron emission tomography
ICA	Internal carotid artery
SAO	Small artery occlusion
SAT	Subcutaneous abdominal adipose tissue
SD	Standard deviation
SFA	Superficial femoral artery
SOC	Stroke of other determined cause
SPSS	Statistical Package for the Social Sciences
SUC	Stroke of undetermined cause
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment classification
US	United States
VAT	Visceral abdominal adipose tissue
WHO	World Health Organization
WHR	Waist-hip ratio

Original papers

I. Nawaz B, Eide GE, Fromm A, Øygarden H, Sand KM, Thomassen L, Næss H, Waje-Andreassen U.

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II. Nawaz B, Fromm A, Øygarden H, Eide GE, Saeed S, Meijer R, Bots M, Sand KM, Thomassen L, Næss H, Waje-Andreassen U.

Prevalence of atherosclerosis and association with 5-year outcome - The Norwegian Stroke in the Young Study

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III. Nawaz B, Fromm A, Øygarden H, Eide GE, Saeed S, Meijer R, Bots M, Sand KM, Thomassen L, Næss H, Waje-Andreassen U.

Vascular risk factors and staging of atherosclerosis - The Norwegian Stroke in the Young Study

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Abstract

From 2010 to 2015, the three-generations Norwegian Stroke in the Young Study (NOR-SYS) included ischaemic stroke patients aged 15-60 years, and their parents, partners and adult offspring to gain more knowledge about vascular risk factors, atherosclerosis and cardiovascular events in families. This thesis explores the inclusion rates of three generations, incidence of ischaemic stroke and the prevalence of atherosclerotic disease at a young age in the well-defined patient population referred to Haukeland University Hospital, Norway. Our results were compared to the patients' partners, serving as controls, and related to vascular risk factors and 5-year outcome after stroke. All results were age- and sex-adjusted.

Paper I described active participation of 385 patients (96.5%), 260 controls (80.0%) and 414 (74.6%) adult offspring. The active participation rate for patients' parents was low (55.2% fathers and 57.3% mothers), and the active participation rate for partners' parents was even lower (38.4% fathers and 40.2% mothers). The mean annual incidence rate of young stroke patients ≤49 years was 15.0 per 100.000.

Paper II presented the prevalence of atherosclerosis in seven vascular areas related to 5-year outcome. Young age was defined as ≤49 years and middle-age was defined as ≥50 years. About 50% of young male patients, and about 33% of young female patients had prevalent atherosclerosis. Compared to controls, atherosclerosis was more prevalent only in young female patients. At 5-year follow up, 13.7% patients and 4.1% controls had experienced new cardiovascular events, and the occurrence rate was higher in young female patients than in young female controls. The mortality rate was low and did not differ between patients and controls (5.5% vs 3.5%). Adjusted for age and sex, the occurrence of new cardiovascular events was associated with ischaemic electrocardiogram (ECG), pathological ankle-arm index (AAI), femoral intima-media thickness (fIMT) and increased number of vascular areas with atherosclerosis (NAA) among patients, and with abdominal aorta plaques (AAP), carotid intima-media thickness (cIMT), fIMT and NAA among controls. Mortality was associated with higher age, ischaemic ECG and NAA with among patients, and with cIMT among controls.

Paper III presented the total risk factor burden related to prevalence of atherosclerosis. In total, risk factors were present among 96.4% of young male patients and 94.3% of young female patients. Compared to controls, only young female stroke patients had a higher risk factor burden. Prevalent atherosclerosis was associated with age, hypertension, diabetes mellitus, smoking and body-mass index (BMI) in a combined analysis for patients and controls, adjusted for age, sex, and all risk factors.

Abstrakt

"Norwegian Stroke in the Young Study" (NOR-SYS) er en tre generasjoners studie, som har inkludert hjerneinfarkt pasienter i alderen mellom 15-60 år, og deres foreldre, partnere og voksne barn mellom 2010-2015 for å få kunnskap om risikofaktorer, aterosklerose og kardiovaskulære hendelser i familier. Denne avhandlingen redegjør for deltakelsesratene til tre generasjoner, forekomst av hjerneinfarkt og utbredelsen av aterosklerose hos unge mennesker som ligger under ansvarsområde for Haukeland universitetssykehus i Bergen, Norge. Våre resultater av unge hjerneinfarkt pasienter ble sammenlignet med deres partnere som kontroller, og relatert til risikofaktorer og til 5-års utkom. Alle resultatene ble justert for alder og kjønn.

Artikkel I beskrev aktiv deltakelse for 385 pasienter (96.5%), 260 kontroller (80.0%) og 414 (74.6%) voksne barn. Lavere deltakelsesrate var hos pasientforeldrene (55.2% fedre og 57.3% mødre), og enda lavere hos partnerforeldre (38.4% fedre og 40.2% mødre). Forekomst av hjerneinfarkt hos pasienter ≤49 år var 15.0 per 100.000 per år.

Artikkel II presenterte utbredelse av aterosklerose i syv vaskulære områder, og relaterte det til 5-års utkom. Vi definerte ung alder ≤49 år og middel alder ≥50 år. Ca 50.0% av unge mannlige og 33.0% av unge kvinnelige pasienter hadde aterosklerose. Den totale utbredelsen av aterosklerose var kun høyere blant unge kvinnelige pasienter sammenlignet med unge kvinnelige kontroller. I løpet av en 5-års periode, fikk 13.7% pasienter og 4.1% kontroller nye vaskulære hendelser, med signifikante flere hendelser blant unge kvinnelige pasienter i forhold til unge kvinnelige kontroller. Ingen signifikant forskjell ble funnet i mortalitetsraten blant pasienter og kontroller (henholdvis på 5.5% og 3.5%). Justert for alder og kjønn, nye vaskulære hendelser var assosiert med iskjemisk elektrokardiogram (EKG), AAI, fIMT og NAA blant pasienter, og med AAP, cIMT, fIMT og NAA blant kontroller. Mortalitet var assosiert med økende alder, iskjemisk EKG og NAA blant pasienter, og med cIMT blant kontroller.

Artikkel III beskrev total risikofaktorbyrde og relaterte det til aterosklerose. Risikofaktor var tilstede hos 96.4% unge mannlige pasienter og hos 94.3% unge kvinnelige pasienter. Risikofaktorbyrden var kun høyere blant unge kvinnelige

pasienter sammenlignet med unge kvinnelige kontroller. Aterosklerose var assosiert med høy alder, hypertensjon, diabetes mellitus og kroppsmasseindex (BMI) i en kombinert analyse for pasienter og kontroller, justert for alder, kjønn og alle risikofaktorer.

Introduction

Definitions

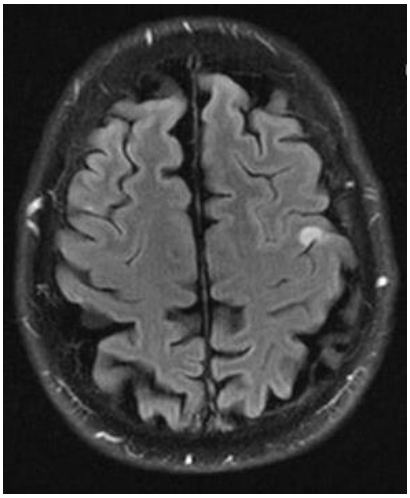
Cardiovascular disease

Cardiovascular disease (CVD) is a general term for disorders of the heart and blood vessels. CVD involving the heart includes hypertensive heart disease, rheumatic heart disease, cardiomyopathy, arrhythmias, congenital heart disease, valvular heart disease and endocarditis, whereas vascular diseases include stroke, coronary artery disease (CAD), peripheral artery disease (PAD), aortic disease and venous thromboembolism.[1-3] The underlying mechanisms vary depending on the disease, however, atherosclerosis causing stenosis or occlusion of blood vessels is the major precursor of vascular diseases involving stroke, CAD and PAD.[3]

Stroke subtypes

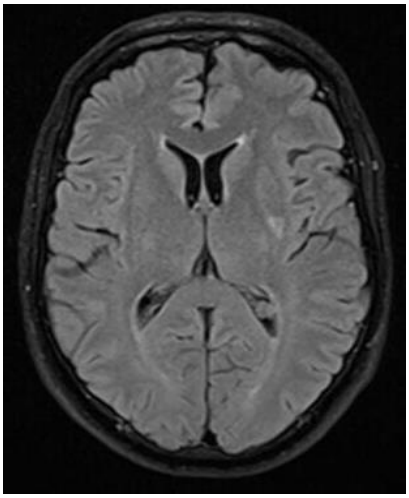
Stroke is classified into three major subtypes; ischaemic stroke, haemorrhagic stroke, and cerebral vein thrombosis. Ischaemic stroke occurs mainly as a result of a blockage of an artery in the brain either by embolism (Figure 1), or by local cerebral thrombosis (Figure 2), alternatively due to haemodynamic mechanisms (Figure 3) as a consequence of cerebral hypoperfusion distally to a severe stenosis of a major cervical or intracranial artery, or due to systemic conditions such as heart failure or severe hypotension. Cerebral vein thrombosis is caused by thrombosis of a major cerebral vein, and may be caused by pregnancy or other thrombotic conditions. Haemorrhagic stroke occurs by rupture of an intracerebral artery, leading to intracerebral haematoma or subarachnoidal haemorrhage. However, secondary haemorrhagic complications may occur in any type of stroke. It is of utmost importance to reveil the primary stroke mechanism, as management and treatment depend on the respective stroke subtype. They have to be diagnosed correctly, and need to be evaluated individually.[4-7]

Figure 1 Ischaemic stroke due to embolism



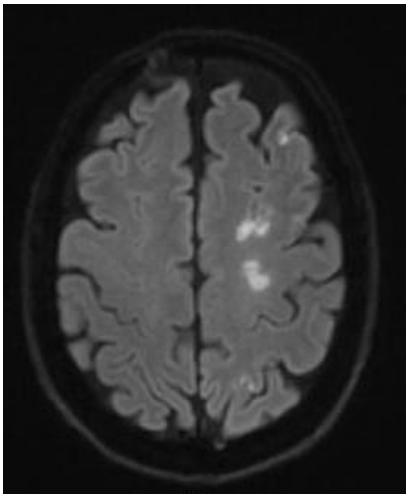
Magnetic resonance imaging (MRI) showing embolic cortical infarction in the territory supplied by the left middle cerebral artery

Figure 2 Ischaemic stroke due to local thrombosis of a small vessel



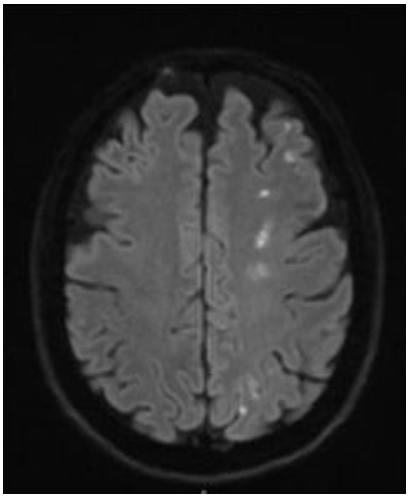
MRI showing a lacunar infarction in the left putamen

Figure 3 Haemodynamic stroke



MRI showing multiple ischaemic strokes in the watershed area in the left cerebral hemisphere

Haemodynamic stroke



Definitions of ischaemic stroke over time

The classical definition of stroke was introduced by the World Health Organization (WHO) in 1970 as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin".[8] Although still widely used, the WHO definition basically relied on clinical symptoms. The Stroke Council of the AHA/ASA defined in 2013 ischaemic stroke as an acute episode of focal dysfunction of the brain, spinal cord, or retina, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.[9] In this updated definition, the 24 hour inclusion criterion for focal dysfunction was considered misleading as permanent brain injury can occur despite subjective quick fading of symptoms, and the silent infarctions were also included in the ischaemic stroke definition due to improved stroke detection by advanced neuroimaging technology, particularly by Magnetic Resonance Imaging (MRI).[9]

Definition of young stroke

Many studies have arbitrarily chosen age limits for the definition of "young stroke", as a specific definition of "young stroke" is lacking. A lower age limit of 15-18 years, and an upper age limit of 45-49 years has often been used, however, upper age limits starting from 30 years, or up to 60 years have also been reported.[10-14] The Norwegian Stroke in the Young Study included patients up to age 60, but in this thesis, young stroke is defined as age of 15-49 years, and middle-aged stroke at age of 50-60 years.

Epidemiology

Global burden of cardiovascular disease and stroke

Cardiovasular diseases (CVD) are the leading cause of mortality and morbidity in the world, accounting globally for almost one-third of all deaths.[15] Stroke is the second leading cause of death in the world after ischaemic heart disease.[16] In 2019, approximately 18.6 million deaths were attributed to CVD and 6.55 million deaths were attributed to stroke worldwide.[17]

By 2019, the prevalence of CVD and stroke, and the total number of deaths due to CVD and stroke had increased steadily since 1990, and these changes were mainly driven by population growth, and by aging populations.[17] During this period, stroke prevalence had increased by 85.0% and stroke deaths by 43.0%.[16] However, age-standardized deaths had actually fallen for CVD and for stroke (36.0%), indicating effective preventive measures by means of public health efforts to reduce the prevalence of major vascular risk factors, and improved treatment of CVD.[16, 18]

The highest burden of CVD and stroke is seen in low- and middle-income countries with an occurrence of 70% of CVD deaths[19], where of 85% happen due to ischaemic heart disease and stroke.[20] In Europe, death rates from ischaemic heart disease and stroke are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe.[21]

Stroke is mainly considered as a disease in the elderly population as stroke incidence increases steeply with age.[22, 23] In 2020, the mean age for stroke in Norway was 75 years, and 44% occurred in females.[24]

Stroke affects around 15 million individuals each year worldwide.[11, 25] Of all incident strokes globally in 2019, 62.4% were ischaemic strokes, 27.9% were intracerebral haemorrhages and 9.7% were subarachnoidal haemorrhages.[16] Cerebral vein thrombosis comprises around 0.5-1% of all strokes.[26] The East Asian population has generally higher rates of intracerebral haemorrhages compared to the Caucasian population (28.0% vs 12.4%).[27, 28] In 2020, there were registered 8917 cases of acute

stroke in Norway with its population of 5.4 million inhabitants, where of 85% were ischaemic strokes, 14% were haemorrhagic strokes, and 1% was unspecified.[24, 29]

Incidence of young stroke

Young stroke ≤49 years accounts for around 10 – 15% of all strokes,[11, 13, 30, 31] affecting around two million young adults yearly.[10] A worldwide young stroke meta-analysis by the GOAL initiative study, recently showed a mean age of 40.8 years, with a male predominance which increased with age.[32] Several European young stroke studies have reported the annual incidence rate around 7 – 17 per 100.000.[25, 30, 33-35] Incidence remains low among the youngest individuals, ranging from 1.2 – 4.5 per 100.000 per year at age <35 years.[33] A Norwegian registry-based study of young stroke patients aged 15-49 years from 2010-2015, reported the annual incidence of 20.7 per 100.000.[36]

Young stroke incidence rates show geographical and ethnic variations. The incidence rate of young stroke is higher in low- and middle-income countries, ranging from 19-30%[37], mainly regarded due to rise in risk factors in young adults.[38] In Europe, average stroke rates have appeared higher in Eastern Europe, and lower in Southern European countries.[39, 40] Worldwide, young stroke incidence is higher in developing countries than in industrialised countries, partially due to limited health awareness, differences in occurrence of risk factors, and other causes, including pollution, presence of rheumatic heart disease, infections such as HIV or tuberculosis, moya moya disease, and sickle cell disease, or due to restricted access to health care, and resources of risk factor treatment.[41, 42] Regarding ethnic variations, the incidence has been reported higher in black and Hispanic populations compared with white populations in the United States (US).[23, 37, 43]

Several studies have reported that while the incidence of stroke in older adults is decreasing, the young stroke incidence is rising.[10, 11, 25, 30, 35, 40, 41, 44-47] A review from 2018 reported an increase of up to 40% in the incidence of stroke in young adults worldwide.[10] Suspected reasons for the increasing rates include improved awareness of young stroke, improved stroke diagnostics, and increasing prevalence of risk factors.[30]

Family history as risk factor for cardiovascular events and stroke

A positive family history (FH+) of CVD is a well-known non-modifiable risk factor for CVD in offspring, particularly among families with premature FH+.[48, 49] Premature FH+ is defined as ≥1 parent with CVD before the age of 55 years among fathers, and before the age of 65 years among mothers.[49] CAD and PAD have mainly atherosclerotic aetiology, in contrast to young stroke including many non-atherosclerotic causes, and the association between FH+ and CAD is most evident in literature.[50] Familial aggregation of CVD may directly be related to genetic factors, or indirectly by adherence to specific behaviours (e.g. smoking, alcohol use), or vascular risk factors (e.g. hypertension, diabetes mellitus, dyslipidaemia, obesity).[51, 52]

Various family-based studies have related a moderate proportion of stroke susceptibility to familial aggregation, however, there are limitations in interpretation of these studies. There is often a recall bias of FH+, and family members may have difficulties in distinguishing between ischaemic and haemorrhagic stroke.[53, 54] Hence, many former studies have combined ischaemic and haemorrhagic stroke.[55, 56] Oygarden et al reported in the NOR-SYS study that female patients more likely reported FH+ than male patients, suggesting that females have more knowledge of family history than males and knowledge is better for relatives with a female than male linkage.[57]

Earlier, stroke criteria were solely based on clinical symptoms lasting more than 24 hours, whereas modern neuroimaging technology has improved the precision of stroke diagnosis.[8] Furthermore, families usually share both genetics and environment.[53] In the Framingham study, a parental FH+ of ischaemic stroke by 65 years of age was associated with a 2.22-fold increase in ischaemic stroke risk in offspring ($p < 0.05$), after adjusting for vascular risk factors.[58]

Risk factors of young stroke

Elderly stroke is associated with the traditional vascular risk factors, mainly hypertension, dyslipidemia, diabetes mellitus and smoking, whereas young stroke has many additional risk factors, as shown in Table 1.

Table 1 Risk factors for young arterial ischaemic stroke

Risk factors	**Other risk factors**
Non-modifiable risk factors	Carotid or vertebral artery dissection
Age	Patent foramen ovale/atrial septum defect
Sex	Inflammtory processes, infections (HIV, hepatitis) and sepsis
Ethnicity	Inherited thrombophilias and acquired prothrombotic or
Low birth weight	hypercoagulable states
Positive family history of CVD	Factor V Leiden mutation
Known history of CVD	Antithrombin III, protein C or S deficiency
Congenital heart disease	Antiphopholipid syndrome
Coronary heart disease	Systemic lupus erythromatosus
Valvular heart disease	Hyperhomocyteinemia
Dilated cardiomyopathy	Sickle cell disease
Peripheral artery disease	Malignancy
	Pregnancy/Puerperium
Vascular and lifestyle risk factors	Oestrogen containing contraceptive pills
Hypertension	Postmenopausal hormone therpy
Dyslipidaemia (LDL ≥ 3.37	Metabolic syndrome
mmol/L or HDL ≤ 1.0 mmol/L)	Elevated lipoprotein (a)
Obesity (BMI ≥ 30 kg/m²)	Vasculopathy and related conditions
Overweight (BMI 25-29.9 kg/m²)	Hereditary/genetic disorders (Fabry/MELAS/CADASIL)
Abdominally obese (high WC)	Moyamoya disease
Diabetes mellitus	Arteritis (Primary/Giant cell/Takayasu/radiation-induced)
Tobacco smoking	Fibromuscular dysplasia
Physical inactivity	Reversibel vasoconstriction syndrome
Poor diet	Sneddon's syndrome/Susac syndrome
Excessive alcohol consumption	Obstructive sleep apnea
Illicit drug use	Migraine with aura
Atrial fibrillation	Short sleep duration ≤6 hours
Infective endocarditis	Air pollution

Abbreviations: CVD = cardiovascular disease; BMI = body-mass index; WC = waist circumference; MELAS = Mitochondrial encephalopathy lactic acidosis, and stroke-like episodes; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Adapted from Putaala et al.[59], von Sarnowski et al.[60], Maaijwee et al.[11], Boot et al.[41], George et al. [31], Goldstein et al.[43], Griffiths et al[35]

Some of the risk factors are either age- or sex-specific, or more common at younger ages, such as some hypercoaguable states and vasculopathies, use of contraceptive medication, pregnancy/puerperium, or use of illicit drugs.[30] The prevalence of certain

modifiable vascular risk factors (including hypertension, dyslipidaemia, diabetes and obesity), and the accumulation of multiple risk factors has increased among young stroke patients, particularly in young adults aged ≥35 years.[44] In a recent worldwide meta-analysis, the GOAL initiative study, the prevalences of common vascular risk factors were reported as following; smoking 49.2%, hypertension 36.6%, dyslipidaemia 31.7%, diabetes mellitus 13.8% and obesity 13.6%.[32] The 15 cities young stroke study across several European countries reported no differences in risk factor profiles between Northern, Southern and Central European countries.[61] Vascular risk factors have different strengths of association with young stroke, as shown in Table 2. The results are based on two European case-control studies; One Finnish population-based study of stroke patients aged 25-49 years[62], and one German study of stroke patients aged 18-55 years.[63]

Table 2 Modifiable risk factors and their risk of ischaemic stroke in the young at age between 18-55 years

Risk factor	**Odds ratio (95% Confidence interval)**
Diabetes mellitus type 1*	6.72 (3.15 – 14.33)
Diabetes mellitus type 2*	2.31 (1.35 – 3.95)
Physical inactivity**	5.9 (5.1 – 6.7)
Smoking*	1.81 (1.50 – 2.17)
Hypertension*	1.43 (1.17-1.75)
Obesity**	1.2 (1.0-1.5)
Dyslipidaemia**	0.9 (0.8-1.1)

The table is adapted from Boot et al[41], with permission from the publisher.
**Data is adapted from Kivioja et al[62], **Data is adapted from Aigner et al[63].*

Diabetes mellitus

Diabetes mellitus is a metabolic disorder causing hyperglycaemia due to insulin deficiency (type 1 diabetes) or due to insulin resistance (type 2 diabetes). The diagnosis is based on plasma glucose levels as following; HbA1c ≥48 mmol/mol (≥6.5%), or fasting plasma glucose ≥7.0 mmol/L, and/or following a glucose tolerance test with plasma glucose ≥11.1 mmol/L two hours after intake of 75 g oral glucose.[64]

Diabetes mellitus is an independent risk factor for CVD and stroke[65], and is associated with poor outcome among young stroke patients aged <65 years.[66] Diabetes accelerates vascular aging, and individuals with diabetes are particularly susceptible to large- and small-artery atherosclerosis.[67] Long-term complications of hyperglycaemia also include retinopathy, polyneuropathy and nephropathy.

Type 1 diabetes among stroke patients aged 15-49 years is associated with CAD and PAD.[68] The treatment targets for type 1 diabetes are to achieve glycemic control by HbA1c <53 mmol/mol (<7.0%) by insulin replacement, and adequate treatment of hypertension and dyslipidaemia in order to prevent long-term complications of diabetes, particularly occurrence of CVD.[64, 69] The treatment goals of blood pressure and LDL-cholesterol are strict for patients with diabetes mellitus in the American and European guidelines. Blood pressure should be <130/80 mmHg, and LDL-cholesterol <1.4 mmol/L.[70-72]

Type 2 diabetes may be a part of the metabolic syndrome that is characterized by obesity, hypertension, dyslipidaemia (high triglycerides and low HDL-cholesterol) and insulin resistance. The glycemic target for type 2 diabetes is HbA1c is <48 mmol/mol (<6.5%), however, individuals with prolonged illness, co-morbidity such as impaired kidney function and/or risk of hypoglycaemia, HbA1c between 53-64 mmol/mol (7.0-8.0%) is accepted.[64, 73] Management of type 2 diabetes consists of lifestyle changes, medical treatment of diabetes, weight control and management of comorbidities such as hypertension and dyslipidaemia.[73] Type 2 diabetes among young stroke patients aged 15-49 years is associated with obesity, PAD and stroke due to large-artery atherosclerosis.[68]

Physical inactivity

Physical inactivity is often linked to obesity, dyslipidemia and hypertension. A meta-analysis of 23 studies concluded with a strong evidence that moderate and high level of physical activity was associated with a reduced risk of ischaemic stroke.[74] According to Norwegian guidelines on physical activity, adults are recommended to

do moderate-intensity activity with a minimum of 150 minutes each weak, or vigorous-intensity activity of 75 minutes each weak, or a combination of both, and only 29% of adults aged 20-49 years met the criteria in 2015.[75, 76]

Smoking and other use of tobacco

There is a strong dose-response relationship between smoking and risk of young stroke in both sexes.[77, 78] Over the last decade, smoking is more frequently seen in young adults.[44] The prevalence is highest in Europe (28.7%), particularly in countries located in Central and Eastern Europe.[41] In Norway the proportion of daily smokers ≥30 years has declined by 34% between 1994 and 2008[79], but the daily use of snuff-tobacco, particular to Nordic countries, has increased steadily since 2002.[80]

Smokeless tobacco has been associated with increased risk of CAD and stroke.[81] Previously, no association was observed for snus in Sweden.[81, 82] However, recent analyses from the past 2 years indicate association between use of snus among males, and increased all-cause mortality and CVD-associated mortality.[83, 84]

The popularity of electronic cigarettes (e-cigarettes) has increased in recent years, and the long-term risk of CVD is unknown. No association has been shown between e-cigarette use and CVD in cross-sectional studies.[85, 86] A longitudinal study between 2013-2019 did not show any association either, however, larger studies with more cardiovascular outcome events and longer follow-up are required.[87]

Hypertension

The definition of hypertension has been changed over years. In 1993, there was a consensus of recommending non-drug treatment and monitorering blood pressure (BP) as long as BP was 140-160 mmHg systolic and/or 90-95 mmHg diastolic without any other risk factors[88]. Current hypertension definitions and treatment goals differ slightly between European guidelines from 2018, and US guidelines from 2020. In the European guidelines, hypertension is defined as BP ≥140/90 mmHg, and the treatment

goal is BP <140/90 mmHg for anybody, independent of age, and BP <130/80 mmHg is the treatment goal for individuals with diabetes mellitus, or at other high cardiovascular risk.[70] In contrast, US guidelines state hypertension as BP ≥130/80 mmHg, and the treatment goal is to keep BP as close to a normal range as possible, i.e. BP ≤130/80 mmHg for anybody. However, non high-risk individuals can initiate treatment when BP ≥140/90 mmHg.[71] For patients with severe carotid stenosis or other reason of haemodynamic stroke, blood pressure lowering should be used cautiously as tolerated, without a specific goal other than a minimum reduction of 10/5 mmHg.[89] The latest ESO guidelines recommend a BP target of <130/80 mmHg in patients with previous stroke or transient ischaemic attack (TIA), in order to reduce the risk of recurrent stroke.[90]

Hypertension in young adults is a public health burden[91], affecting almost 1 in 8 young adults at age 20-40 years.[92] Young adults with hypertension have a higher lifetime risk of CVD, stroke, subclinical organ damage, and a higher mortality, given their longer exposure to high BP.[51, 92-95] Organs affected by longstanding hypertension include the cerebrovascular system, the heart, kidneys and the retina. Typically, features of subclinical and clinical affection of the cerebrovascular system include increased carotid intima-media thickness (cIMT), and lacunar infarction due to small-artery occlusion, microhaemorrhages, and white matter hyperintensities, which eventually may lead to cognitive decline and vascular dementia.[96] Hypertensive heart disease includes left ventricular hypertrophy, impaired left ventricular function, arrhythmias and CAD.[96] Other damages, such as retinopathy, and nephropathy leading to chronic renal failure, can also be caused by diabetes mellitus.[96]

Hypertension may be primary (essential) or secondary to other conditions, such as hypothyroidism, renal artery stenosis, primary aldosteronism, Cushing syndrome and pheochromocytoma.[92] The investigation for secondary causes of hypertension is essential, as specific causes of secondary hypertension might be curable. Treatment of essential hypertension includes diet and lifestyle interventions, and drug therapy. The first-line antihypertensive drug therapy recommendation is to use one of the following four drug classes: thiazide diuretics, calcium antagonists, angiotensin converting

enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB).[71] However, fertile women should avoid the use of ACE inhibitors or ARBs because of the risk of teratogenic effects during pregnancy.[92]

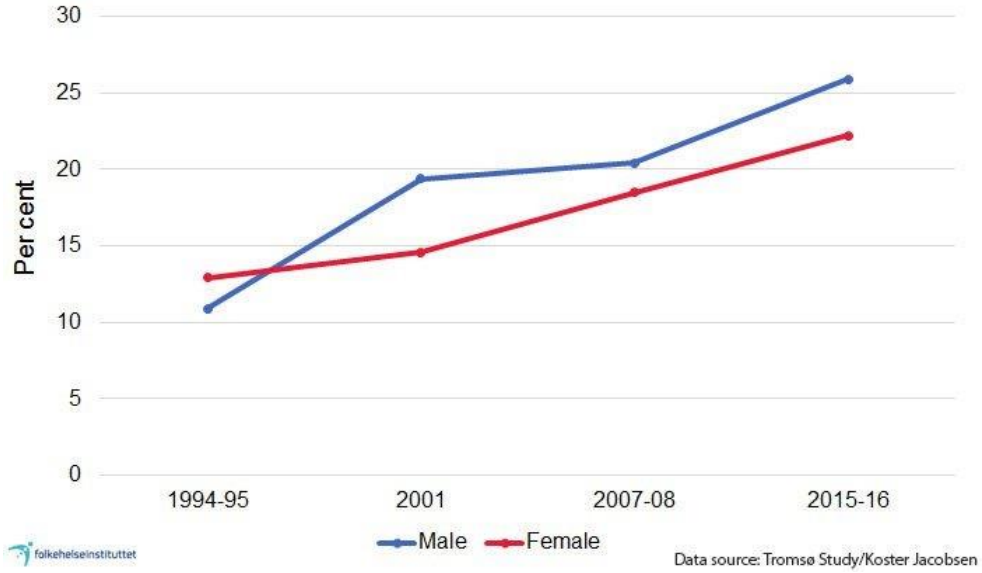
Antihypertensive drug therapy reduces the risk of CVD and stroke.[97, 98] A blood pressure reduction of 10/5 mmHg has been associated with a 41% reduction of stroke.[98] Nevertheless, adherence to antihypertensive treatment is still challenging among young adults.[99] Young adults with poor medication compliance have been associated with higher risk for future CVD events compared to adherent patients (HR 1.57; 95% CI, 1.45-1.71).[97]

Obesity

Obesity is often determined by the body mass index (BMI), calculated by kg/m^2. BMI ≥25 is defined as grade 1 or low-risk obesity/overweight, BMI 30.0-34.9 as grade 2 or moderate-risk obesity, BMI 35-39.9 as grade 3 or high-risk obesity and BMI ≥40 as health damaging obesity.[100] Obesity is one of the major health problems worldwide, and it is estimated that obesity has almost tripled between 1975 and 2016.[101] In Norway, approximately 1 in 4 middle-aged males and 1 in 5 middle-aged females are obese, and the trend has increased since 1994 (Figure 4).[102]

Obesity reflects an excess of adipose tissue that preferentially accumulates in the trunk and upper body in men, and in the hips and thighs in women.[103] In general, the major effect of obesity on cardiovascular health is mediated through the risk of metabolic syndrome (insulin-resistance, dyslipidaemia and hypertension)[104, 105], and BMI has shown a U-shaped relationship with CVD mortality.[100, 106-108] However, a protective effect of obesity on survival was shown when coexisting with CVD, a phenomenon known as the obesity paradox.[109, 110]

Figure 4 Prevalence of obesity (BMI ≥30) over time in Nothern Norway from the Tromsø studies among men and women aged 40-69 years.



Source: Public Health Report on overweight and obesity in Norway[102] with permission from the publisher.

Nevertheless, the association of obesity, measured by increased BMI, with young stroke is either weak[63], or absent when adjusted for concomitant vascular risk factors.[95] Other studies have found that increases in BMI during childhood and adolescence are positively associated with young stroke.[111, 112] Since BMI reflects body size rather than fat distribution, giving a wrong classification for well-trained subjects with a high muscle mass, other markers of abdominal adiposity, such as waist circumference, waist-hip ratio (WHR), and waist-to-height ratio have shown to be stronger associated with the risk of stroke.[113-116] A recent study reported that abdominal obesity measured with WHR is an independent risk factor for cryptogenic stroke in young adults after adjustment for concomitant risk factors.[117]

Epicardial adipose tissue (EAT) reflects visceral adiposity surrounding the heart. EAT is associated with metabolic syndrome, insulin resistance, subclinical atherosclerosis, CVD and mortality.[118-122] Two large multi-ethnic studies (the Multi-Ethnic Study of

Atherosclerosis and the Framingham Heart Study) have identified EAT as an independent predictor for CVD.[122] Among young stroke patients with embolic stroke of unknown cause, EAT thickness was significantly higher than in healthy individuals, suggesting that EAT thickness might be a novel risk factor in these patients.[123]

Subcutaneous abdominal adipose tissue (SAT) and visceral abdominal adipose tissue (VAT) have also been related to multiple vascular risk factors, metabolic syndrome, and CVD, however, the correlations with VAT have appeared to be stronger than those with SAT.[105, 107, 124] Furthermore, SAT accumulation does not seem to increase CVD risk independently from BMI, in contrast to VAT.[107, 125]

Dyslipidaemia

Dyslipidaemia is defined by high serum levels of total cholesterol and LDL-cholesterol (pure hypercholesterolaemia), low HDL-cholesterol, and/or triglycerides (mixed dyslipidemia or pure hypertriglyceridaemia). Dyslipidaemias can occur primary (familial) or secondary to unhealthy lifestyle (high intake of saturated fat, low physical inactivity, obesity, smoking, alcohol), or other conditions (other forms of obesity, diabetes mellitus).[126] Worldwide, the prevalence of dyslipidaemia is highest in Europe (54%), followed by North-America (48%), and dyslipidemia is lowest in Africa (22.6%).[41]

Dyslipidaemias, particularly with elevated LDL-cholesterol levels, are major precursors of atherosclerosis, resulting in premature CVD.[126] Familial hypercholesterolaemia is strongly associated with premature development of atherosclerosis, resulting in thicker cIMT, premature CVD and mortality in young adults compared to healthy individuals.[52] Hypertriglyceridaemias are often related to obesity, diabetes mellitus, alcoholism, or metabolic syndrome, and they are associated with atherosclerosis and acute pancreatitis.[127]

As young ischaemic stroke has various causes, dyslipidaemia has not shown an association to all-cause stroke.[63] However, young stroke patients with large- and small-artery atherosclerosis have the highest prevalence of dyslipidaemia.[41, 60, 128, 129]

Statin therapy has a major role in treatment of dyslipidaemia. Statins were developed at the end of the 1970s, and statin therapy became first common in the prevention and therapy of CAD, thereafter also in stroke medicine. In stroke medicine, the use has continuously increased during the past decades.[130] In a large meta-analysis, a statin-induced reduction of 1 mmol/L of LDL-cholesterol, caused a risk reduction of major vascular events by 22%, of stroke by 17% and of total mortality by 10% over 5 years.[72] Statins have also shown to stabilize, and even reduce atherosclerotic plaques.[131]

The European guidelines for management of dyslipidaemia from 2019 emphasizes the importance of lowering LDL-cholesterol and triglycerides together with management of other vascular risk factors by drugs and lifestyle interventions, in order to reduce atherosclerotic cardiovascular risk in adults. Class I recommendation is given to reduce LDL-cholesterol <1.8 mmol/L for individuals at high-risk, while LDL-cholesterol <1.4 mmol/L is recommended for individuals with diabetes mellitus or other very high-risk.[72] The latest ESO guidelines recommend a LDL-cholesterol <1.8 mmol/L in patients with previous stroke or TIA, in order to reduce the risk of cardiovascular events.[90]

Young stroke aetiology

Although the symptoms of stroke in young adults are similar to those in the elderly, the causes of stroke in the young are more diverse. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification from 1993 still is the most widely used causative classification system used for all ages, and ischaemic stroke is categorized into five subtypes, as shown in table 3.[132, 133]

Table 3 Trial of Org 10172 in Acute Stroke Treatment, TOAST classification[132]

TOAST subtypes	Causes of stroke	Prevalence of young stroke subtypes
LAA	Embolus or thrombosis causing >50% stenosis/occlusion of extracranial or intracranial artery	8-25%[33, 35, 134-137]
CE	Cardiac emboli of high-risk or medium-risk source such as atrial flutter, atrial fibrillation, cardiomyopathy, valvular heart disease	13-35%[33, 35, 134-137]
SAO	Lacunar infarction, ≤15 mm subcortical or brain stem lesion	10-26%[33, 134-137]
SOC	- Dissection of carotid or vertebral artery - Immunological disorders/infections - Hypercoagulable state - Haematological disorders - Hereditary disorders	15-26%[33, 134-137]
SUC	- Two or more causes identified - Negative evaluation - Incomplete evaluation - Fails to meet the criteria for the other subtypes	33-40%[33, 35, 134-137]

Abbreviations: LAA = large-artery atherosclerosis; CE = cardiac embolism; SAO = small artery occlusion; SOC = stroke of other determined cause; SUC = stroke of undetermined cause

Large-artery atherosclerosis (LAA): TOAST defines ischaemic stroke caused by LAA as a result of significant stenosis (>50%), or occlusion of a major brain artery, or an artery branch presumbly due to atherosclerosis resulting in arterio-arterial embolism.[132] Cortical or cerebellar lesions, and brain stem or subcortical hemispheric

infarcts >1.5 cm in diameter on CT or MRI are considered to be of potential LAA origin.[132] In young stroke, LAA is documented mostly among males, and increases with age.[41, 134, 135 138]

Cardioembolism (CE): Ischaemic stroke is caused by an arterial occlusion presumably due to a cardiac embolus. Clinical and brain imaging findings are similar to those described for LAA, and result in cardio-arterial embolism to the brain. TIA or ischaemic stroke in more than one vascular territory, supports the suspicion of cardiogenic stroke.[132] Cardiac embolic sources are divided into high-risk and low-risk groups. Most young patients with CE present with a persistent foramen ovale, which is either regarded as a low-risk source, or an uncertain source of CE.[35] One study showed a persistent foramen ovale prevalence of 38.3%,[134] and another up to 66.7%.[139] Of high-risk sources in young adults aged 15-49 years, most frequent were atrial fibrillation/flutter (15.1%) and cardiomyopathy (11.5%).[134] Males outnumbered females among young stroke due to CE.[134]

Small artery occlusion (SAO): Strokes are often labelled as lacunar infarcts, characterized by clinical lacunar syndromes, and without cortical affection. Radiologically, CT/MRI may present normal, or with a subcortical or brain stem lesion <1.5 cm diameter.[132] Figure 2 is showing a patient with a lacunar infarction in the left putamen. Young ischaemic stroke due to SAO has a male predominance.[41, 134, 135]

Stroke of other determined cause (SOC): This category includes rare causes of stroke, such as non-atherosclerotic vasculopathies, such as dissection of cervical or vertebral artery; hypercoagulable state, for example inherited thrombophilias, hormone treatment, pregnancy, active cancer disease, and anti-phospholipid syndrome; or other haematologic disorders, for example sickle cell disease.[132] SOC is more common in females, and in younger patients, and cervical artery dissection is the most frequent single cause of young SOC with up to 25%.[30, 41, 134, 135]

Stroke of undetermined cause (SUC): This category includes strokes with either undetermined cause or with multiple potential causes.[132] Other reasons may be due to

either incomplete evaluation, or negative evaluation despite an extensive diagnostic work-up.

TOAST has moderate interrater agreement, is easy to use in clinical practice, and is regarded as a useful tool in order to guide management decisions.[132, 140, 141] The 15 cities young stroke study was done across several European countries, and demonstrated that there were no aetiological differences according to TOAST criteria among patients from Southern, Central or Northern Europe[134]. However, TOAST determines the most probable single cause, but the challenge with young stroke patients is that a high proportion (up to 40%) has been classified into the SUC group.[142-144]

Other classifications systems such as the CSS (Causative Classification System), ASCO (Atherosclerosis, Small vessel disease, Cardioembolic source, Other Cause) and SPARKLE (Subtypes of Ischaemic Stroke Classification System) have been introduced. The CSS is meant to enhance the accuracy of TOAST, and it has an excellent interrater reliability.[145] In the ASCO system, the degree of probability to each cause is addressed, and it permits documenting the quality of the work-up.[146] The SPARKLE system is meant to improve the criteria for LAA by adding the total plaque area assessed by ultrasound, increasing the proportion of strokes classified as LAA-related.[141, 147] The newer classifications depend on the availability of modern diagnostic technology, and are difficult to use in clinical practice. Although TOAST, CSS, ASCO and SPARKLE stratify stroke aetiologies into the same five subtypes, they use different classification criteria to do so, hence, direct comparisons have been difficult.[148] LAA is defined as >50% stenosis in TOAST and ≥70% stenosis in ASCO, resulting in that LAA may be underestimated in ASCO. However, this is not in line with newer knowledge on plaque stability being more important than the degree of stenosis, and the total plaque area being a stronger predictor of stroke, myocardial infarction and death than carotid stenosis itself.[149, 150]

Imaging of acute ischaemic stroke

Advanced neuroimaging techniques, particularly magnetic resonance imaging (MRI) emerged in the 90ies, and became commonly used from the beginning of this century, revolutionizing acute stroke diagnosis and treatment. As a consequence, ischaemic stroke is earlier and more frequently detected. MRI can frequently discover smaller lesions. Moreover, MRI has also enabled the detection of clinically silent ischaemic stroke, that occurs without patient noticing any stroke symptoms. In a Finnish study of 1008 ischaemic stroke patients aged 15-49 years, 13% had clinically silent infarcts.[33] As MRI is radiation-free, it is recommended and preferred imaging modality in very young patients.[151] However, MRI is not as widely available as CT, especially in the emergency settings, and there are limitations for some patients due to implanted medical devices, metallic implants or serious claustrophobia.

Computed tomography and CT angiography

Cerebral computed tomography (CT) and CT angiography (CTA) are the primary imaging modalities worldwide in suspected stroke within the regular 4.5 hour time window for treatment with intravenous thrombolysis (IVT) due to its speed, cost and availability. CT has a high sensitivity to detect acute haemorrhages, and large well-established infarcts.[152] However, the sensitivity for the detection of acute ischaemic stroke is poor, particularly in the hyperacute time window, when ischaemic lesions are small or are located in the posterior circulation.[152]

In the setting of stroke, CTA with use of intravenous (IV) contrast, is the primary imaging modality for the thoracic aorta, the cervical arteries, and the intracranial arteries, including the visualization of ongoing intracerebral haemorrhages ("spot sign)". It is preferred to perform CTA immediately after non-contrast cerebral CT for most stroke patients, in order to identify occlusions of large proximal intracranial arteries available to endovascular thrombectomy (EVT), to assess the collateral circulation, or to identify active bleedings. In addition to the facilitation of acute stroke

treatment options, CTA adds valuable information to the aetiological work-up of ischaemic and haemorrhagic stroke.[153]

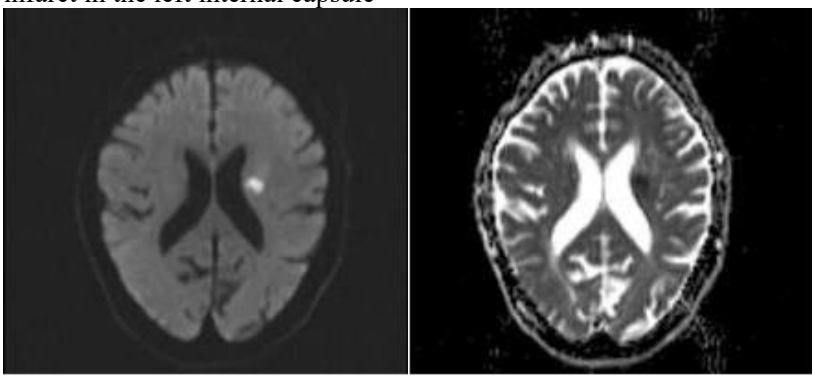
CT perfusion

CT perfusion (CTP) imaging is obtained by the administration of IV contrast, facilitating the detection of tissue at risk, and establishing a ratio between the individual ischaemic core and still salvageable tissue, the penumbra ("tissue at risk"). CTP is recommended after 4.5 hours of symptom onset, and in unknown onset stroke, in order to identify patients who are likely to benefit from IVT or EVT beyond the standard time window for acute stroke treatment.[154] Further, CTP can predict brain regions with increased risk of haemorrhage after IVT.[155]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is superior to CT in the detection of small acute ischaemic lesions. A study found that MRI had much higher sensitivity than CT in detecting ischaemic stroke (83% vs 26%).[156] The diffusion-weighted imaging (DWI), and corresponding apparent diffusion coefficient (ADC) maps are most sensitive techniques to depict early ischaemic stroke (Figure 5).[157] Persistent ischaemic stroke lesions appear later on FLAIR and/or T2 than on DWI imaging series. In clinical practice, patients with a DWI/FLAIR mismatch are likely to be within a time window when IVT and/or EVT are safe and effective.[158]

Figure 5 Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) and corresponding apparent diffusion coefficient (ADC) map showing an acute lacunar infarct in the left internal capsule



MR angiography

Non-contrast MR-angiography (MRA) of the intracranial arteries use the time-of-flight (TOF) technique.[159] It is based on a phenomenon of flow-related enhancement, resulting in a brighter signal of flowing blood in the arteries compared to stationary tissues.[160] MRA has a sensitivity of 87% and specificity of up to 98% for the detection of arterial occlusion of embolic or thrombotic origin.[152]

Digital subtraction angiography

Digital subtraction angiography (DSA) in case of ischaemic stroke is the gold standard modality for diagnosing intracranial arterial pathology, especially when cerebral arteritis or vasospasm are suspected, or when CTA and MRA are not resolving the diagnostic questions about dissections, stenoses, occlusions, malformations or collateral flow. Although DSA is superior to CTA or MRA, good quality CTA and MRA are often sufficient for routine vascular assessment as DSA uses ionizing radiation and is an invasive procedure.[161] However, DSA is necessary in conjuction of acute endovascular therapy in acute ischaemic stroke and subarachnoid haemorrhage.[161]

Atherosclerosis

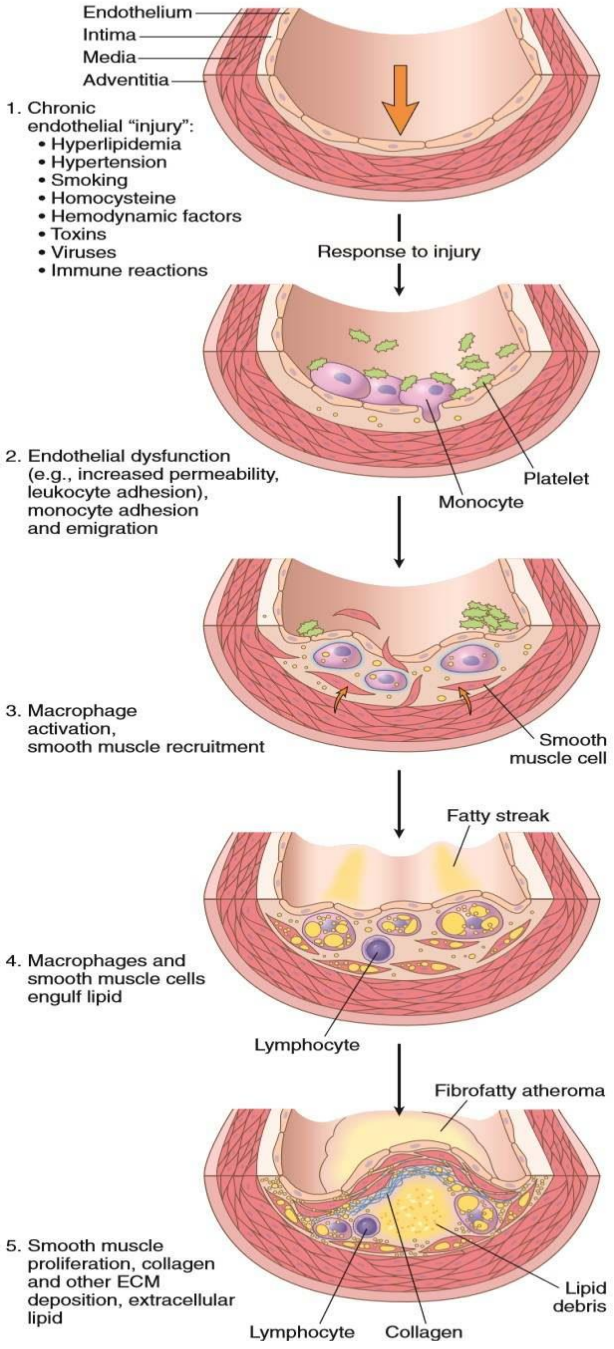
Atherosclerosis and cardiovascular disease

Atherosclerosis is a focal, progressive, chronic inflammatory disease, which may already develop gradually from early childhood.[162-164] The lesions of atherosclerosis occur principally in large and medium-sized arteries, predominantly at sites of disturbed laminar flow, such as at arterial branching points, for example at the carotid bifurcations.[165, 166] They are responsible for a number of cardiovascular events, such as acute ischaemic stroke, myocardial infarction or PAD.[167]

Pathogenesis of atherosclerosis

Atherosclerotic lesions are focal thickenings of the intima, consisting of lipids, various cell types, connective-tissue elements and debris.[168] The pathogenesis of atherosclerosis is a complex process, initated by endothelial injury and dysfunction, where the formation of a fatty streak is considered as the earliest sign of atherosclerosis.[169, 170] Fatty streaks are characterized by the focal accumulation of lipoproteins, particularly LDL-cholesterol in the vascular intimal layer, resulting in recruitment of monocytes and T-lymphocytes through activated endothelial cells.[170, 171] Here, monocytes differentiate into macrophages, which ingest and process modified and oxidized lipoproteins, forming foam cells.[170, 171] Activation of macrophages and lymphocytes lead to the release of inflammatory cytokines, chemokines, and growth factors leading to focal necrosis and smooth muscle cell proliferation with the formation of a fibrous cap that overlies a core of lipids and necrotic tissue.[167] Figure 6 shows stages of fatty streaks and atheroma formation.

Figure 6 Stages of fatty streak and atheroma formation



Adapted from Rafiaeian-Kopaei et al[170]. With permission from the publisher

Fatty streaks may either disappear, or progress into atheroma by facilitating the deposition of fibrous material, and development of a necrotic core.[172] Progressive thinning of the fibrous cap causes activation of tissue factor and leading to platelet activation, aggregetion and subsequently formation of a thrombus, causing a major cardiovascular event.[173] Expansion of atherosclerotic plaques may progress onto luminal stenosis or occlusion, however, Glagov et al demonstrated that arteries can enlarge in relation to plaque area without luminal narrowing until the atherosclerotic lesion occupies 40% of the lumina due to remodeling.[174]

The atherosclerotic plaques may be stable or unstable, and plaque stability is related to the thickness of the fibrous cap and the level of inflammation.[175] Typically ruptured plaques tend to content a thinned fibrous cap, a large lipid-rich necrotic core with a high level of inflammation, intraplaque haemorrhage, punctuate or spotty calcification and few smooth muscle cells.[176]

Composition and degree of inflammation and neovascularization in atherosclerotic plaques may be more important to stroke risk than the degree of stenosis.[177] Inflammation can be detected in carotid atherosclerosis by the use of 2-deoxy-2-[^{18}F] fluoro-D-glucose (18F-FDG) uptake on PET scan.[178] Critical narrowing of atherosclerotic lesions are not typically the cause of cardiovascular events and may not be the best predictor of CVD risk.[176] Unstable plaques are vulnerable to erosion or rupture of the fibrous cap. This causes acute thrombosis by an immediate reaction between thrombocytes and tissue factor that may lead to embolization or thrombotic occlusion, resulting in infarction long before the stenosis gets hemodynamically significant.[176] Thus, most cardiovascular events result from unstable plaques.[169, 176]

Risk factors for atherosclerosis

Atherosclerosis is a multifactorial disease. Approximately 40% of cases are attributed to genetic factors and 60% to environmental risk factors.[179] FH+ of premature CVD, age, hypertension, smoking, dyslipidaemia, diabetes mellitus and insulin resistance,

obesity, physical inactivity, unhealthy diet, inflammation, high levels of CRP, bacterial or viral infections, sleep apnea, stress and alcohol are regarded as risk factors for the pathogenesis of atherosclerosis.[170, 180-182] Many chronic infectious agents have been associated with the development of atherosclerosis, such as Chlamydia pneumonia, Helicobacter pylori, cytomegalovirus, Epstein-Barr virus, herpes simplex virus 1 and 2, human immunodeficiency virus and hepatitis C virus.[183] Acute influenza, other respiratory tract infections, and acute bacterial infections have shown to increase the risk for CVD and stroke, particularly during the winter.[184] A meta-analysis has shown that influenza vaccination protects against CVD events, and decreases mortality in patients with known CVD.[184] Hence, to avoid inflammation that may lead to plaque activation and plaque rupture, WHO and Norwegian Public Health authorities strongly recommend annual vaccination against influenza for individuals at higher cardiovascular risk, particularly for those with known CVD, diabetes or severe obesity, as important a primary prevention measure.[185, 186]

Non-invasive markers of atherosclerosis

Non-invasive surrogate markers of atherosclerosis may identify subclinical disease before the occurrence of adverse cardiovascular events, and prevent the need to perform invasive diagnostic procedures. A number of various surrogate markers of atherosclerosis have been detected over the past decades by improved diagnostics, such as duplex-sonography that enables measurements of intima-media thickness (IMT), and visualization and evaluation of atherosclerotic plaques, electrocardiogram (ECG) and ankle-arm index (AAI) measurements. Other diagnostics include carotid artery MRI features, coronary heart-CT, the evaluation of left ventricular hypertrophy, arterial stiffness, and brachial artery reactivity and other additional markers of atherosclerosis, such as the coronary artery calcium score, but are beyond the scope of this dissertation.

Ultrasonographic assessment of arteries

Ultrasonographic assessment of the large arteries is a cost-effective, widely available, reproducible and noninvasive method to measure IMT and to assess the presence and character of atherosclerotic plaques and degree of stenosis.[187] IMT is measured as the distance between the lumen-intima reflex and media-adventitia reflex of the far artery wall segment on B-mode ultrasound.[187] IMT measurement is most commonly perfomed in the carotid arteries (cIMT), but measurements in the femoral arteries (fIMT) have also gained attention. IMT is preferentially measured in the far wall, as near wall IMT measurements have not been regarded as reliable in previous studies.[188, 189] However, the Multi-Ethnic Study of atherosclerosis, showed that combined cIMT of near and far wall had the strongest association with risk factors, while far wall cIMT strongest predicted incident CAD.[190]

Increased IMT is the first structural artery wall that shows incipient atherosclerosis, and has been defined by ≥0.9 or ≥1.0 mm in some studies.[162, 191] As IMT also depends on non-modifiable risk factors, other studies have defined IMT as increased if greater

than the 75th percentile for age, ethnicity and sex.[192] Atherosclerotic plaque is defined by the European Mannheim consensus as IMT ≥1.5 mm or a focal structure that encroaches into the arterial lumen of ≥0.5 mm or by 50% of the surrounding IMT.[189]

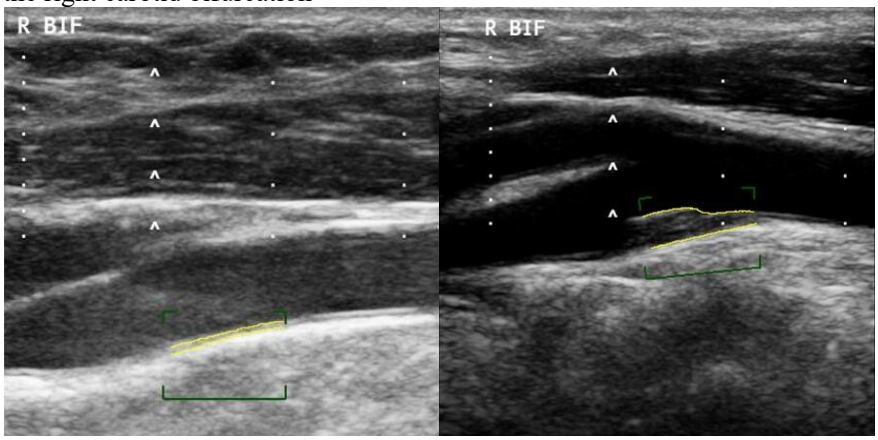
Carotid intima-media thickness

Carotid intima-media thickness (cIMT) is a well-known surrogate marker of the presence, and of progression of atherosclerosis.[193] In addition, cIMT is also an established strong predictor of future cardiovascular events.[193-195] An increased cIMT by 0.10 mm is associated with an increased risk of 18% for stroke, and 15% for myocardial infarction.[194]

Screening of cIMT routinely in general population has been regarded as controversial. US national guidelines in 2010 recommended use of cIMT routinely in asymptomatic adults at intermediate risk of CVD,[196] but in 2013 they recommended against the use of cIMT for risk assessement of first cardiovascular events.[197] A meta-analysis showed that regression of cIMT by drug therapies did not reflect reduction in cardiovascular events,[198] and another meta-analysis reported that the CVD risk prediction beyond traditional risk factors was only minimally increased by use of cIMT.[199] However, ultrasound is a valuable supplementary tool to CTA and MRA for individual evaluation of the cause of stroke, and consequences for treatment after ischaemic stroke at a young age.

The cIMT is usually measured in the distal segment of the common carotid artery (CCA), in the carotid bifurcation (BIF), and in the proximal segment of the internal carotid artery (ICA). According to meta-analyses, BIF-IMT and ICA-IMT improve stroke risk prediction better than CCA-IMT alone.[187] Figure 7 is showing normal cIMT, and a plaque in the right carotid bifurcation.

Figure 7 Measurement of normal intima-media thickness (left) and plaque (right) in the right carotid bifurcation



In general, cIMT is influenced by a number of non-modifiable risk factors such as age, male sex, ethnicity, and genetic factors, in addition to vascular risk factors such as hypertension, dyslipidaemia, blood glucose, metabolic syndrome, BMI, smoking, and cIMT increases with the number of risk factors present.[200-202] Several studies have shown that cIMT is linearly related to age, regardless of CVD or other risk factors.[203-205] The annual rate of cIMT increase varies between studies, ranging from 0.003-0.010 mm per year, even without the evidence of atherosclerosis.[205] Regarding sex differences, males have higher cIMT compared to females.[203, 206] Furthermore, a study reported that white males and females have generally lower cIMT than black males and females, respectively.[207] cIMT findings are also influenced by genetic determinants other than those influencing known risk factors.[208]

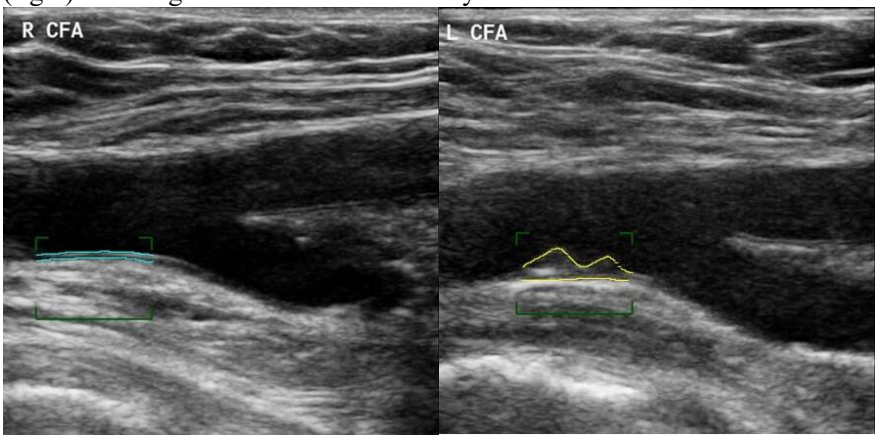
Femoral intima-media thickness

Femoral intima-media thickness (fIMT) is usually measured in the distal segment of the common femoral artery (CFA), and in the proximal segment of the superficial femoral artery (SFA). Increased fIMT and femoral artery plaques are also considered surrogate markers of CVD, although they are underutilized, and have received less

attention to date.[209-213] Several studies have found that fIMT shows a positive relation to the extent of coronary atherosclerosis,[212, 214] and carotid atherosclerosis.[211, 215] Furthermore, femoral plaques are regarded as a marker of future cardiovascular events.[209, 216, 217]

Age, sex, vascular risk factors and genetic factors influence fIMT.[212, 218, 219] No racial differences in fIMT measurements have been reported by the Bogalusa Heart study.[219] Figure 8 is showing normal fIMT, and femoral plaque in the right common femoral artery.

Figure 8 Measurement of normal femoral intima-media thickness (left), and plaque (right) in the right common femoral artery

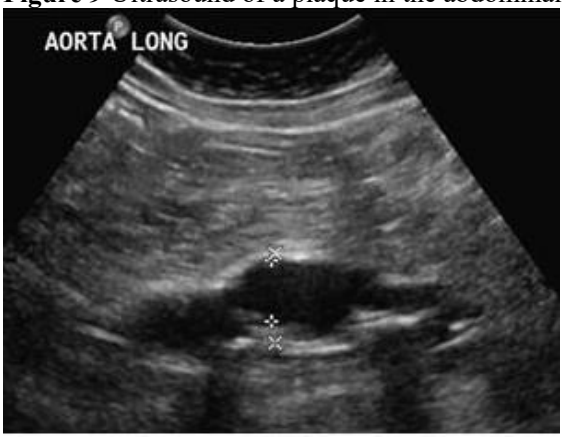


Assessment of abdominal aorta plaques and calcification

It is widely known that the abdominal aorta, and its branching points are the most common sites for atherosclerotic lesions. Usually, the lower two-thirds of the abdominal aorta contains most atherosclerosis in both sexes, and in all decades.[220] In contrast with cIMT, which is a well-established tool for CVD risk assessment, abdominal aorta atherosclerosis has been scarcely investigated. The presence of aortic atherosclerosis increases with age, and is associated with the presence and/or severity of CAD.[220, 221] More widely investigated is abdominal aorta calcification, which is a

strong predictor of cardiovascular events and death.[222, 223] Abdominal aorta calcification is assessed differently in studies by x-ray,[221, 223] by calcium scoring,[222] or by CT scan.[224] Figure 9 is showing atherosclerotic disease in the abdominal aorta visualized by ultrasound.

Figure 9 Ultrasound of a plaque in the abdominal aorta



Electrocardiogram

The electrocardiogram (ECG) gives information about the electrical function of the heart. It is an easy and quick test to detect different types of cardiac abnormalities, such as arrhythmias, conduction delays or myocardial ischaemia. ECG as a screening tool has been debated due to false positive rates resulting in misdiagnosis and overtreatment. Hence, ECG is not recommended for asymptomatic individuals or individuals at low risk for CVD due to low sensitivity to detect CAD.[225] However, it belongs to the routine diagnostics in any patient admitted for suspected stroke or other types of CVD.

Ankle-arm index

Ankle-arm index (AAI) is the ratio of the systolic BP measured at the ankle to that measured in the arm. Doppler-based BP measurements are bilaterally performed in the radial artery, the dorsalis pedis artery, and the posterior tibial artery. The AAI ratio is calculated from the lowest values measured in one of the ankles, and that measured in one of the arms. A value of ≤0.90 has a 90% sensitivity, and 98% specificity to indicate moderate to severe PAD, as determined by the gold standard of angiography.[226]

Long-term 5-year outcome

Young stroke has a worse prognosis with more recurrent cardiovascular events and higher mortality compared to controls of the same age and sex.[227] A previous Norwegian long-term follow-up study on patients with acute stroke aged <50 years in our geographical region from 1988 to 1997, showed that young stroke patients had a 10-fold higher mortality rate, and a 5-fold higher rate of recurrent cardiovascular events than age- and sex-matched controls after about 12 years.[228] After 18 years, mortality rates showed that about one in four of these patients did not reach retirement age.[228] The 5-year recurrence rate has been reported as 8.0-15.4% for stroke, and as 2.4-3.0% for myocardial infarction or other arterial events.[227, 229, 230] The 5-year mortality risk for young ischaemic stroke patients is around 9-11%.[30, 227]

Survival rates in young stroke patients are favourable when compared to elderly stroke patients.[231] However, due to higher co-morbidity rates among the elderly, it is more meaningful to compare young stroke patients to a control population of the same age.

Aims of the thesis

Paper I

- To assess the incidence of young ischaemic stroke in the region of Bergen.
- To evaluate the education and work state of young ischaemic stroke patients for future comparison of long-term outcome of stroke.
- To evaluate the active participation rates of all participants in the three generations included into the Norwegian Stroke in the Young Study (NOR-SYS).

Paper II

- To assess the prevalence of atherosclerosis in seven predefined vascular areas among young ischaemic stroke patients and controls.
- To assess the prevalence of atherosclerosis stratified by ischaemic stroke aetiology based on the TOAST classification.
- To relate the prevalence of atherosclerosis among stroke patients and controls to 5-year outcome of new cardiovascular events and death.

Paper III

- To assess the prevalence of vascular risk factors among ischaemic stroke patients and controls.
- To relate the risk factor burden to the prevalence of atherosclerosis by numeric staging of atherosclerosis among stroke patients and controls.

Subjects and methods

All three papers are mainly based on data collected in the inclusion period, and 5-year follow-up results about new cardiovascular events and mortality. My contribution to the data collection consisted of practical work with the 5-year follow-up, including the repetition of standardized ultrasound cIMT measurements among patients, partners/ex-partners and offspring.

The Norwegian Stroke in the Young Study, NOR-SYS

NOR-SYS is a population-based, prospective, long-term, three-generations family study on acute young ischaemic stroke. Stroke patients were included from 1st Sept 2010 to 31st Aug 2015, and family members were included until 31st Dec 2015. Patients aged 15-60 years, were admitted to the Department of Neurology at Haukeland University Hospital in Bergen, and the acute ischaemic stroke diagnosis was verified radiologically. Patients with stroke caused by non-arterial infarction such as subarachnoidal haemorrhage, intracerebral haemorrhage, sinus venous thrombosis, trauma or cerebral tumour were excluded from participation. Stroke aetiology was classified according to TOAST criteria by an experienced vascular neurologist, Halvor Næss, who was blinded for the ultrasonographic NOR-SYS results.

Study population and controls

Partners and/or ex-partners ≥18 years and adult offspring ≥18 years were offered participation after patients' consent, and subsequently included into NOR-SYS by informed written consent. Patients, partners, ex-partners, and adult offspring answered a standardized questionnaire on family history of CVD, own CVD history and vascular risk factors (Appendix 1). Biometric measurements such as height, weight, hip and waist circumference, AAI, BP on both arms and legs, and ECG were performed. A standardized ultrasound protocol was performed to obtain cIMT, fIMT and abdominal

aorta plaques (AAP). Ultrasound was also performed to obtain fat measurement results of epicardial adipose tissue (EAT), visceral abdominal adipose tissue (VAT) and subcutanenous abdominal adipose tissue (SAT).

Biological parents of stroke patients and partners/ex-partners were invited to participate, based on consent by NOR-SYS patients or partners/ex-partners. They returned a standardized questionnaire about own cardiovascular risk factors and CVD (Appendix 1) by written informed consent.

The 5-year follow-up was performed from 1st Sept 2015 to 31st Dec 2020 for patients and partners/ex-partners, and to 30th June 2021 for adult offspring (slightly delayed due to the Covid pandemia from March 2020). They answered a standardized questionnaire, and biometric measurements such as height, weight, hip and waist circumference, BP on both arms, and ECG were repeated. Ultrasonography was performed to obtain current cIMT measurements. Hospital records of all participants included in the 5-year follow-up were checked for new cardiovascular events. For those who did not attend the 5-year follow-up, hospital records were used only for alive-dead state, and for finding the cause of death.

Risk factor definitions

The following 12 vascular risk factors were included: prior cardiovascular events; hypertension; diabetes mellitus; dyslipidaemia; smoking; alcohol; physical inactivity; BMI; WHR; EAT; VAT and SAT.

Prior cardiovascular events, including stroke, CAD and PAD, were verified by hospital records. Uncertain information about previous stroke was substantiated by neuroradiologic imaging information. Hypertension, diabetes mellitus and dyslipidaemia were defined as present when treated before admission, or when diagnosed during hospitalization. Hypertension was defined as BP >140/90 mmHg in two separate, bilateral measurements, using an appropriate cuff size after 15-30 minutes rest in supine position, usually performed after ECG and ultrasound

diagnostics. Diabetes mellitus and dyslipidaemia were detected by blood tests taken from patients only, and defined as HbA1c >6.4% (46 mmol/mol); total cholesterol >5.0 mmol/L and/or LDL-cholesterol >3.0 mmol/L, and/or HDL-cholesterol <1.0 mmol/L, and/or triglycerides >2.5 mmol/L. Smoking was categorized as never-smoking, prior smoking when quit at least 1 year ago, and current smoking. Pack-years of smoking were calculated as the number of cigarette packs (20 cig/pack) consumed daily, multiplied by the number of years of smoking. Alcohol consumption was categorized as increased if ≥12 units/week were reported. Physical inacitivity was defined as light, moderate, or vigorous physical activity of less than 60 minutes/week. BMI was categorized as increased if ≥25 kg/m^2. WHR of ≥0.85 among females, and of ≥0.90 among males was considered increased.[9]

Fat distribution in subcutaneous and visceral departments were visualized by ultrasonography. EAT, VAT and SAT measurements were performed by use of a 5-1 MHz sector array transducer, 5-1 MHz curved array transducer, and a 9-3 MHz linear array tranducer (iU22 Philips Medical systems, Bothell, WA, USA), respectively.[232] EAT was defined as the echo-free space between the outer layer of the myocardial wall, and the visceral layer of the pericardium, measured on the free wall of the right ventricle at end-systole.[119] The mean of three maximum value measurements was calculated, and a cut-off value of 0.5 cm was used to identify individuals at higher cardiovascular risk.[10] VAT measurements were performed in a longitudinal view on the umbilicus level, and the distance between the peritoneum and the lumbal spine was used.[233] All measurements were performed at the end of expiration, and without distortion of the abdominal cavity. The vertebral column was positioned horizontally. VAT was measured at three positions (frontal median position, 10 cm lateral to the left for the median position and 10 cm lateral to the right for the median position), and the mean value of these three measurements was calculated. SAT was defined as the distance between the cutis and linea alba, and was measured under maximum decompression of the abdominal wall. The tranducer was positioned transverse, 1 cm above the umbilicus. Cut-off values for VAT and SAT are not yet established. Thus, our sex-specific high VAT and SAT definitions were based on 90th percentile cut points from a normal weight referent sample, as a similar method was used in the

Framingham Heart Study.[234] The referent sample consisted of 133 men and 99 women with normal BMI <25 kg/m^2. The 90th percentile cut-offs of VAT and SAT for referent groups were 9.6 and 3.5 cm in men, and 8.3 and 4.2 cm in women, respectively. The total risk factor burden was defined as number of risk factors present, ranging from 0 to 12.

Numeric staging of atherosclerosis

Analogue to oncological staging of tumours, the prevalence of atherosclerosis was termed as atherosclerotic staging, and defined as number of affected vascular areas out of seven examined areas, ranging from 0 to 7. Atherosclerosis was assessed by presence of signs of ischaemia on ECG, AAI ≤0.9, presence of AAP, and presence of the maximum value of in total 16 right and left mean cIMT- and fIMT segments, if ≥1.5 mm, respectively.

A 12 lead ECG was verified by the cardiologist, Sahrai Saeed, to identify signs of acute or previous myocardial ischaemia. AAI was measured with an Ultrasonic Doppler Flow Detector (Model 811-BTS, Parks Medical Electronic, Inc. Aloha, Oregon USA), and an 8.2 MHz pencil probe. AAI was assessed by systolic blood pressure bilaterally for the radial, posterior tibial and dorsalis pedis arteries. The lowest blood pressure value of the arm and ankle was used for measurement of the AAI ratio, and a cut-off value ≤0.9 indicated PAD (Appendix 2).[232]

Ultrasound imaging was performed with Philips iU22. Two patients, admitted to the Intensive Care Unit, were examined with a portable Philips CX50 ultrasound system (both systems were Philips Medical Systems, Bothell, WA, USA). Any sonographer responsible for the inclusion and the 5-year follow-up was a physician, internationally certified for the NOR-SYS ultrasound protocol in collaboration with The Vascular Imaging Center, University Medical Center, Utrecht, The Netherlands. Ultrasound imaging was performed bilaterally on carotid and femoral arteries to obtain cIMT and fIMT measurements, and on the abdominal aorta for visual identification of AAP.

Reproducibility evaluation of cIMT within (intra-observer), and between (inter-observer) sonographers of the research group, and between ultrasound equipment (inter-equipment) have been performed.[235]

Intima-media thickness protocol

cIMT and fIMT measurements were performed in high-resolution B-mode, in the probe-far wall during the end-diastolic phase of the cardiac cycle, verified by continuous ECG monitoring, and by Philips QLAB (Philips Medical Systems, Bothell, WA, USA) IMT-measuring soft-ware. High quality measurements of mean IMT were achieved from the bilateral CCA, BIF, ICA, CFA and SFA. Successful measurement required ≥70% of the point-to-point analysis out of a predefined 1 cm segment. IMT of the CCA was measured at four predefined, standardized insonation angles, using Meijer's Carotid Arc® (Appendix 3).[236] IMT of BIF, ICA, CFA and SFA were obtained from one suitable insonation angle presenting the maximum available IMT, after thorough interrogation. The maximum value of any mean IMT segment was used in the statistical analyses, and visible plaques were included into the measurement when present. Mean IMT values ≥0.9 mm were considered increased,[162, 237] and mean IMT values ≥1.5 mm were defined as atherosclerotic plaque.[189] The ultrasound protocol for IMT measurements is shown in Appendix 4.

Statistical analyses

Statistical analyses were performed under supervision of the biostatistician, Geir Egil Eide, using The IBM SPSS Statistics version 24 and Stata SE 15.1 (Paper I), Stata SE 16.0 (Paper II) and Stata SE 17.0 (Paper III).

Patients and controls were dichotomized into young aged (≤49 years), and middle-aged (≥50-60 years) in all papers. Descriptive statistics were given as mean and standard deviation (SD) in all papers. In Paper I, ischaemic stroke incidence was

analyzed with respect to calender year, age and sex using multiple logistic regression. In Paper II, Cox models and Kruskal-Wallis rank test were applied. IMT values were compared between patients, and controls by relative change. In Paper III, the Poisson regression was used to relate numeric staging of atherosclerosis to risk factors. Univariate comparisons of vascular areas, and risk factors between patients and controls were done within the four sex and age strata, using unpaired t-test, and Fisher's exact test (Paper II and III). For the unadjusted comparison of all patients to their partners, McNemar's test of symmetry was used (Paper II and III). Interactions were tested, and two sided P-values ≤ 0.05 were considered significant in all papers.

Ethical considerations

NOR-SYS was approved by the Western Norway Regional Committee (REK-Vest 2010/74) with the lowest age of 15 years for patients only, and 18 years for other study participants. The study was registered in ClinicalTrials.gov NCT01597453, and conducted in accordance with the Declaration of Helsinki.

All participants, or in a few cases, a next-of-kin family member gave written consent to participate in the study. All participants received oral, and/or written information about the purpose of the study. According to the Regional Ethics Committee decision, dropouts were followed regarding their dead-or-alive state and cause of death, as available from their medical record, only.

Summary of the papers

Paper I

Participation rates: From 2010 to 2015, NOR-SYS included 385 patients (96.5%), 260 partners (80.0%) and 414 (74.6%) adult offspring. Among living patients' parents, 91 fathers (55.2%) and 142 mothers (57.3%) participated, and among living partners' parents, 48 fathers (38.4%) and 68 mothers (40.2%) participated by returning a questionnaire. Patients had a mean age of 49.5 (± 9.8) years at study inclusion, and the male-female ratio was 2.2:1.

Young stroke incidence: The mean annual incidence rate of stroke for all patients was 30.2 per 100,000, for young patients at age 15-49 years 15.0 per 100,000, and for middle-aged patients at age 50-60 years 87.4 per 100.000. Adjusted for sex and age, the odds for incident ischaemic stroke decreased by 7% per year in the period from 2010 – 2015 ($p = 0.040$). Ischaemic stroke incidence was higher in males, except in very young females aged <25 years, and the difference was accentuated with increasing age ($p = 0.008$).

Education and work state of patients: There were 74.0% of stroke patients who had graduated from high school or university/college, and there was no sex difference in educational state ($p = 0.104$) in contrast to work state ($p <0.001$). Among male patients, 84.1% worked, and 80.3% worked fulltime. Among female patients, 74.4% worked, and 52.9% worked fulltime prior to the index stroke.

Paper II

A total of 385 ischaemic stroke patients and 260 partners as controls were included. In total, 39.5% of patients and 39.2% of controls were at age ≤49 years. The majority of patients were males (68.6%), and subsequently the majority of controls were females (70.0%). NOR-SYS ultrasonography was performed in all but two patients.

Total burden of atherosclerosis: The total burden of atherosclerosis was assessed among 324 patients and 238 controls, and described as atherosclerosis present in at least one of seven vascular areas. Male patients were more affected by atherosclerosis than female patients (67.4% vs 48.0%). Atherosclerosis was prevalent in about 50% of young male patients, and in about 33% of young female patients, and the burden was even higher among middle-aged patients (77.6% of males and 62.7% of females). Compared with controls, only young female patients showed more frequently prevalent atherosclerosis (32.7% vs 14.3%; $p = 0.024$).

Vascular areas with atherosclerosis: Ischaemic ECG and higher mean cIMT were more frequent in young and middle-aged female patients ($p = 0.044$, $p = 0.020$, $p = 0.023$ and $p < 0.001$, respectively) than in their respective controls. Mean fIMT was higher in middle-aged female patients ($p < 0.001$) than in middle-aged female controls. No differences were found among males patients and male controls regarding prevalences of ischaemic ECG, AAI, AAP, cIMT and fIMT.

TOAST subtypes and atherosclerosis: Large-artery atherosclerosis (LAA) was found in 7.3%, cardiac embolism (CE) in 26.0%, small artery occlusion (SAO) in 19.0%, stroke of other determined cause (SOC) in 10.6%, and stroke of undetermined cause (SUC) in 37.1%. Atherosclerosis was prevalent among 61.4% of all patients and in the subgroups of TOAST as following: 100% in LAA, 44.6% in CE, 65.6% in SAO, 34.4% in SOC, and 70.4% in SUC group.

Cardiovascular events and mortality at 5-year follow-up: After a mean follow-up of 5.3 years, 83.9% of patients and 84.2% of controls participated. In total, 44 patients (13.7%) patients, and 9 (4.1%) controls had experienced new cardiovascular events, with a significant difference only among young female patients and controls. The ischaemic stroke recurrence rate among patients was 7.5%. Twenty-one (5.5%) patients and 9 (3.5%) controls were deceased at the time of 5-year follow-up, without any differences between the subgroups with respect to age group and sex. CVD-related death only occurred among two patients, and none of the controls, while three patients and three controls had unknown causes of death. Logistic regression, relating 5-year

outcome to atherosclerosis, was performed in 323 patients and 219 controls. Adjusted for age and sex, the occurrence of new cardiovascular events was associated with an ischaemic ECG, AAI ≤0.9, fIMT ≥0.9 mm, and an increased number of vascular areas with atherosclerosis (NAA) among patients, and with AAP, cIMT ≥0.9 mm, fIMT ≥0.9 mm and NAA among controls. Mortality was associated with higher age, ischaemic ECG, and NAA among patients, and with cIMT ≥0.9 mm among controls.

Paper III

A total of 385 ischaemic stroke patients and 260 partners as controls were included.

The prevalence of risk factors: The most common risk factors among all stroke patients ≤60 years were dyslipidaemia (76.1%), obesity (BMI ≥25.0 kg/m^2 in 66.5%, increased WHR in 70.8%, increased EAT in 61.6%), smoking (69.6%), and hypertension (61.8%). The most common risk factors among young ischaemic stroke patients ≤49 years were obesity (BMI ≥25.0 kg/m^2 in 64.7%, increased WHR in 58.9%, increased EAT in 51.3%), dyslipidaemia (63.2%), smoking (60.5%), and hypertension (42.8%).

Risk factor burden: The risk factor burden was assessed among 346 patients and 250 controls, and defined as presence of at least one vascular risk factor. In total, 96.4% of young male patients and 94.3% of young females patients presented with at least one risk factor, and the burden was even higher among middle-aged male and female patients (100.0%). Compared to controls, only young female patients showed a significantly higher risk factor burden (94.3% vs 88.6%, p = 0.049).

Risk of atherosclerosis: The Poisson regression analysis, relating atherosclerosis to risk factors, was performed in 562 study participants (324 patients and 238 controls). Atherosclerosis was associated with age, hypertension, diabetes mellitus, smoking, and BMI in a combined analysis for patients and controls, adjusted for age, sex, and all risk factors.

Discussion

Age, ethnicity and sex

NOR-SYS was designed with a high age limit up to 60 years due to the high life expectancy in Norway,[238] and active work life up to 67 years for both sexes. The upper limit of 60 years was also regarded necessary due to the three-generation design with inclusion of adult offspring ≥18 years. However, we dichotomized our participants into young (15 – 49 years), and middle-aged (50 – 60 years) for better comparison with existing literature.

The majority of participants were Caucasians. Thus, we assume that our results are generalizable to other high-income countries, and to regions with comparable ethnicity, educational level and life-style.

Male patients were outnumbering female patients with a ratio of 2.2:1 in our study, and in both age groups separately. The higher incidence of stroke in males was also shown by other large studies,[60, 134] and a recent worldwide meta-analysis.[32]

The median age of our young stroke patients was 43 years (IQR 35-46), which is comparable to the European 15-cities young stroke study, that reported the lowest median age for Southern Europe (41 years; IQR, 34-45), followed by Central Europe (43 years; IQR, 37-46), and Northern Europe (44 years; IQR, 37-47).[61]

We also found that middle-aged patients outnumbered the young by a ratio of 1.5:1, and it is well-known that there is a steep rise in incidence of stroke from the age of 40 years.[33]

Education and work

Our stroke patients were generally well-educated, with no significant sex differences ($p = 0.104$). We found that 74.0% had a higher education than primary school, which can be compared with the national statistics on education level showing that 73.1% of

the Norwegian population had upper secondary school or tertiary education level in 2015.[239]

Inclusion into NOR-SYS between 2010 and 2015 was conducted in a very stable socioeconomic period, with very low unemployment rates around 3.7% in Norway.[240] We found 68.6% of patients working full-time, 14.5% were sick/disabled and 3.6% were unemployed before stroke onset. According to the national statistics, 67.6% of the Norwegian population aged 15-74 years worked fulltime,[241] and 9.7% of the population aged 18-67 years were sick/disabled.[242] Thus, there was a slightly larger group of sick/disabled people in our cohort aged up to 60 years compared with the national statistics.

Participation rates at inclusion and at 5-year follow-up

Participation rates at inclusion were excellent for patients, around 96.5%, and good among partners and adult offspring (80.0% and 74.6%, respectively). Stroke patients compared to partners were similar regarding mean age (49.5 years vs 50.3 years), education level higher than primary school (74.0% vs 81.1%), and full-time work state (71.7% vs 64.2%), indicating that our partners were representative as controls. The participation rate of patients and partners at 5-year follow-up was about 84.0%, hence, loss to follow-up bias was minimal. In comparison, the Third Generation Cohort of the Framingham Heart Study performed between 2002 to 2005, almost 60 years after the Original Cohort from 1948, reported a high recruitment rate among offspring with 72% returning the enrollment forms, and over 62.0% attending the first clinic examination.[243]

Some patients and partners did not consent to contact with their own parents, mainly due to severe comorbidity, or their parents were not interested. There was also a high number of deceased parents, particularly fathers. Active participation rate was highest among mothers of patients and partners, respectively. This may reflect the higher life expectancy for females in Norway, and the earlier cardiovascular morbidity and mortality among males.[238, 244] In 2021, the life expectancy in Norway was 84.7 years

for females, and 81.6 years for males.[245] CVD and cancer are the leading causes of deaths in Norway.[246] One might also speculate that only the healthiest parents returned their questionnaire, dominated by females, which showed a higher participation rate than males.[247]

Young stroke incidence

The annual incidence rate in our study for young stroke aged 15-49 years was 15 per 100.000. This is in line with results from other European young stroke studies with an upper age limit of 50 years, reporting annual incidence rates of 7-17 per 100,000.[25, 30, 33-35] The population in Western Norway is dominated by Caucasians. Thus, we compared our results to other European studies with mainly white populations. The incidence of young stroke is generally lower in white than in black populations.[23, 37] The US reported higher incidences of young stroke among Afro-Americans and Hispanics compared to whites.[41] A national Norwegian registry-based study from the same time period, and for the same age group reported the annual young stroke incidence as 20.7 per 100.000.[36] However, we could not directly compare our prospective, clinical study where the ischaemic stroke diagnosis was radiologically verified, with the national register-based study, with potentially less strict inclusion criteria. Another difference appears as our study was based on the consent of participants, while the register-based study was not dependent on consent, therefore, probably any patient with the diagnosis of ischaemic stroke, including early death, or death from stroke abroad, appeared.

Time trend studies on incidence rates during the last decades have shown an increasing incidence of young ischaemic stroke. Ekker et al reported an increased young ischaemic stroke incidence for patients at age 18-50 years by 46%, from 7.4 in 1998 to 10.8 per 100,000 in 2010.[25] Another study reported that the proportion of all stroke below the age of 55 years increased by 44%, from 12.9% in 1993/94 to 18.6% in 2005.[47] In a previous study from Hordaland county conducted from 1988 to 1997, the annual incidence for young stroke patients aged 15-49 years was 11.4 per 100.000.[248]

Direct comparison to our study was challenging, as the Hordaland study had a larger catchment area with a larger population, it only included first-ever stroke cases, and the stroke diagnosis was based on the Baltimore-Washington criteria, as stroke was diagnosed mainly by cerebral CT.[248]

There are several possible explanations for an increasing young stroke incidence. Improved stroke detection with advanced neuroimaging technology, particularly the more common use of MRI technology led to positive findings in more patients with minor stroke, and identification of ischaemic stroke even after rapidly regressive symptoms.[10, 25, 30, 40] The diagnosis of first-ever stroke is also challenged by the increasing detection of clinically silent infarctions. Higher awareness after national information campaigns may have increased the public knowledge about also young people suffering a stroke, which may have contributed to the increased detection of stroke. In addition, there is unfortunately an increase in traditional vascular risk factors among young adults.[25, 31] There is increased prevalence of hypertension, diabetes mellitus, dyslipidaemia, obesity, alcohol intake, and use of illicit drugs in the young population, particularly in men.[10, 11, 30, 33, 44, 139, 249-252] In Norway, the prevalences of smoking[79], hypertension[253] and physical inactivity[76] among the young population have decreased, however, the prevalences of use of snuff-tobacco[80], obesity[254] and diabetes mellitus[253] have increased.

Regarding sex differences, we found that the incidence of ischaemic stroke was higher in males compared to females in our study, except from very young females below the age of 25 years. Due to the small number of participants below the age of 25 years in our study (12 patients), we could not draw any conclusion, but other studies, including the Hordaland study, have previously shown the same trend for young females below the age of 30 years.[30, 61, 135, 248] These findings were attributed to the use of contraceptive medication, pregnancy and puerperium, a higher prevalence of migraine with aura, and to autoimmune disorders, such as the antiphopholipid syndrome in females.[10, 13, 25, 30, 35, 41, 59, 249] Over the years, the progestin-only pills were introduced and the oestrogen content of newer contraceptives was reduced.[255] A meta-analysis of 18 studies reported that progestin-only pills are not associated with an increased risk of

ischaemic stroke, and that a lower oestrogen dose is associated with a lower risk of ischaemic stroke when compared with higher oestrogen doses, as it was used in the first generation of oral anticonception pills.[256] The higher incidence of young stroke among males at ages beyond 35 years is attributed to clustering of risk factors in middle-aged males, and because CVD develops 7 to 10 years earlier in males than in females.[30, 257]

Prevalence of vascular risk factors

Traditional risk factors were frequently present in young patients as well as in controls in our study. We found that obesity (BMI ≥25 kg/m^2 64.7%, increased WHR 58.9%, increased EAT 51.3%), dyslipidaemia (63.2%), smoking (60.5%) and hypertension (42.8%) were the most prevalent risk factors among our young stroke patients with age up to 49 years. The worldwide GOAL meta-analysis and several European single-center or multicenter young stroke studies reported smoking, hypertension and dyslipidaemia as some of the most frequent risk factors among young stroke patients, and with no regional differences found in Europe.[32, 33, 60, 61, 139, 258, 259] Worldwide, smoking was most prevalent in North America (57.4%) and Asia (53.1%), followed by Central Europe (50.7%) and Northern Europe (49.3%).[32] Dyslipidaemia was most prevalent in Northern Europe (48.1%) and Oceania (46.6%), followed by Central Europe (41.9%).[32] Hypertension was most prevalent in Asia (46.2%) and North America (42.5%), followed by Northern Europe (36.5%).[32]

Regarding sex differences among young stroke patients, only hypertension and alcohol intake had a higher prevalence in male patients in our study. The Stroke in Young Fabry Patients (SIFAP1) study showed sex differences among several risk factors.[60] Apart from hypertension and alcohol intake, males had also higher prevalence of dyslipidaemia, smoking, CVD and diabetes mellitus, whereas females had higher prevalence of migraine.[60]

The total risk factor burden was high among our young stroke patients (95.6%), and was highest in middle-aged male and female patients (100%). Compared to controls,

we found the risk factor burden was only higher among young female patients (94.3% vs 88.6%). An increasing risk factor burden among stroke patients of increasing age has also been observed in other studies.[60, 61, 258] Several studies have reported that at least half of the patients with stroke at a young age have at least two independent risk factors for stroke.[260, 261]

Risk factor burden and its association with atherosclerosis

We found numeric staging of atherosclerosis, combined for patients and controls, and adjusted for all risk factors associated with age, hypertension, diabetes mellitus, smoking and BMI. All these variables are well-known vascular risk factors of developing atherosclerosis.[170, 180, 181] The Bogalusa Heart Study showed that hypertension, dyslipidaemia, smoking, BMI, and an increased number of risk factors were related to the extent of atherosclerosis in the aorta, and coronary arteries in even younger individuals aged 2-39 years, who died mostly due to acute trauma.[164]

In other studies, the association between obesity (defined as BMI ≥30 kg/m$^{2)}$ and young stroke has been reported as weak or absent when adjusted for vascular risk factors.[63, 95] We found that prevalent atherosclerosis was associated with increased WHR, but after adjustment for all variables, the finding became non-significant. Among stroke patients, WHR showed a positive trend. As the majority of missing WHR measurements in our study derived from patients with increased BMI, we may have underestimated its association with atherosclerosis.

In contrast, one study found that increased BMI in childhood and adolescence was associated with young stroke.[112] However, BMI as a measure of obesity has limitations as it does not take age, sex, bone structure, fat distribution or muscle mass into consideration.[262] Hence, WHR seems more robust, and more strongly associated with risk of stroke, rather than BMI.[113] In a meta-analysis of 58 prospective studies, 1 SD increase in BMI and WHR was associated with a higher risk for CAD, and ischaemic stroke for study participants aged 40-59 years, whereas the hazard ratio was attenuated for elderly subjects (≥70 years).[263] The association between WHR and ischaemic

stroke was stronger than that of BMI, and ischaemic stroke (hazard ratio 1.25 vs 1.20) when adjusted for age, sex and smoking.[263]

EAT and VAT were associated with increased numeric staging of atherosclerosis among our participants, but turned non-significant after adjustment for all variables. In contrast, other studies have found EAT and VAT to be predictors of CVD.[107, 121, 264] SAT was in our study not associated with atherosclerosis in any of our performed analyses, and therefore, we did not evaluate SAT as risk factor for atherosclerosis. The Framingham Heart Study reported stronger associations of VAT with metabolic risk factors than with SAT.[124]

We found physical inactivity associated with increased numeric staging of atherosclerosis in the regression analysis separately for patients and controls. Physical inactivity has been associated with obesity and worse cardiovascular profile before, increasing the risk of ischaemic stroke (OR 5.9).[63] It is further well-known that obesity provides an increased risk for earlier development of hypertension and diabetes mellitus.[265]

Finally, we found high risk factor matching regarding physical inactivity and smoking between patients and their partners as controls, indicating that couples share life-style and habits.[53]

Prevalence of atherosclerosis at different vascular areas

Carotid and femoral intima-media thickness

All the mean values for cIMT and fIMT established for our patients and controls were increased (i.e ≥0.9 mm).[162, 237] Middle-aged patients had higher mean cIMT and fIMT values than young-aged patients, and mean fIMT was higher among male patients than among female patients. Is is well-known that IMT increases with age and is generally higher in males.[203-205, 212]

Compared to controls, mean cIMT was higher among our female patients, and mean fIMT was higher only among middle-aged female patients. No difference was seen among male patients and controls regarding cIMT and fIMT. In general, cIMT has been associated with incident stroke,[195] while fIMT has been associated with prevalence and severity of CAD,[212, 214] and with carotid atherosclerosis.[211, 215] This may partly explain the differences in cIMT and fIMT among our female patients and controls. The fact that we did not find any differences in cIMT and fIMT among the male patients and controls in our study may reflect that atherosclerosis starts early in life, and is very common at a subclinical level, particularly in males, and even at a young age.[30, 266]

Measurements of IMT are easiest to obtain at the CCA. The accuracy of IMT measurements obtained from BIF or ICA are largely dependent on the expertise of the sonographer, and on the anatomy of the patient.[189] In NOR-SYS, most missing measurements were in the ICA (9 patients), followed by BIF (3 patients). Our measurements for patients were highest for mean BIF-IMT (1.19), followed by ICA-IMT (1.00 mm), as also shown by other studies.[203, 207] It is well-known that atherosclerosis usually starts in the carotid BIF, and ICA due to turbulences.[165]

New cardiovascular events were associated with fIMT ≥0.9 among patients, and with cIMT ≥0.9 mm and fIMT ≥0.9 mm among controls, when adjusted for age and sex. Measurements of carotid plaques were previously shown to be a stronger predictor for cardiovascular events than cIMT in various studies.[267, 268] The Tromsø Study evaluated cIMT and the total plaque area in 6584 individuals aged 25-84 years, with a 10-year follow-up, and reported that only total plaque area, but cIMT was not found predictive of ischaemic stroke.[269] In the Rotterdam study, plaque thickness predicted myocardial infarction better than IMT.[270] In NOR-SYS, plaques were included in our segmental IMT-measurements when located within the standardized and predefined anatomical site of measurement. Thus, they would lead to higher IMT values, subsequently pronouncing the association of IMT to vascular events in our study. The methods used in the different studies are not directly comparable.

Mortality was associated with an increased number of vascular areas affected by atherosclerosis among patients, and with cIMT ≥0.9 mm among controls when adjusted for age, sex and all vascular areas with prevalent atherosclerosis. Several studies have shown that cIMT is a predictor for future cardiovascular events and mortality.[187, 191, 194, 195, 271, 272]

Electrocardiogram

In our study, ischaemic ECG was found among 10.4% of stroke patients. Our female patients had a higher prevalence of ischemic ECG compared to female controls, and no differences were seen among male patients and controls. Furthermore, ischaemic ECG predicted new cardiovascular events and mortality among patients, regardless of age and sex. Accordingly, a Belgian population-based study of participants aged 25-74 years, reported that major abnormalities in ECG were strongly associated with new cardiovascular events and mortality in both sexes.[273] In another study, clinically silent ischaemic ECG was an independent predictor of cardiac mortality.[274]

Abdominal aorta plaques

We found that AAP were present in about 47% of our ischaemic stroke patients. No difference was found when compared to controls in any of the subgroups, possibly attributed to the small number of participants and a high prevalence of AAP at a subclinical level. The prevalence of AAP was higher in middle-aged patients compared to young patients (58% vs 30%, $p < 0.001$), and AAP predicted new cardiovascular events among controls, regardless of age and sex. Also several other studies have shown that aortic atherosclerosis increases with age and is associated with the presence and/or severity of CAD.[220, 221, 275]

Ankle-arm index

We found AAI ≤0.9, defining PAD, among 4.7% of our ischaemic stroke patients. No difference was found when compared to controls in any of the subgroups. Furthermore, no age or sex differences were found among patients, possibly due to small number of participants. The prevalence of PAD is generally low in young populations, and is reported as 3.5% at age 40-44 years in a recent systematic review.[276] However, it is reasonable to believe that PAD is largely underdiagnosed and underreported, as clinical features regularily appear in more advanced stages, and later-on during the course of the disease.

In NOR-SYS, a pathological AAI ≤0.9 mm predicted new cardiovascular events among our patients, regardless of age and sex. In other studies, AAI was regarded a predictor of CAD and cardiac mortality accordingly.[226, 277] Pathological AAI has also been associated with a relative risk of 2.33 (95% CI 2.02 – 2.68) for stroke.[278]

The total prevalence of atherosclerosis

Atherosclerosis is the common underlying cause of CVD morbidity and mortality worldwide. However, despite high rates of recurrent CVD and mortality after stroke at a young age, the TOAST classification shows only low rates of atherosclerosis due to its definition of at least 50% stenosis, and high rates of unknown causes of stroke, especially in the young. Therefore, we used an approach of numeric staging of atherosclerosis by measurements and evaluation of the extent of atherosclerosis in seven vascular areas, comparable with oncological staging of tumours after the diagnosis of cancer. The maximum number out of seven evaluated vascular areas affected was six among patients, and five among controls. Atherosclerosis was present at least at one of seven vascular areas among 1/2 of young male patients and 1/3 of young female patients. Among controls, the extent of atherosclerosis was equally high among males and middle-aged females, but was less present in young females. This is in agreement with current knowlegde on subclinical atherosclerosis starting early in

life and increasing with age, particularly in males.[30]Autopsy studies have confirmed a high prevalence of coronary atherosclerosis, predominantly in young and healthy male populations.[279, 280]

Atherosclerosis according to the TOAST classification

Atherosclerosis was found among 61.4% of our stroke patients. As expected, all our stroke patients with large-artery atherosclerosis (LAA) had prevalent atherosclerosis. But the prevalence of atherosclerosis was also high (65.6%) among patients with small artery occlusion (SAO), confirming previous knowledge that LAA and SAO share similar risk factors such as smoking, hypertension and diabetes mellitus.[281] The prevalence of atherosclerosis was lowest (34.4%) among patients with stroke of other determined aetiology (SOC), as causes such as coagulation defects are mostly of non-atherosclerotic origin. There were 44.6% of stroke patients with cardiac embolism and 70.4% of patients with unknown cause of the ischaemic stroke with prevalent atherosclerosis. To our knowledge, there are no comparable young stroke studies with a similar approach. Our findings indicate that TOAST is not a suitable tool in order to detect individual prevalent atherosclerosis in young and middle-aged patients.

Autopsy studies of young trauma victims were able to show early signs of atherosclerosis in coronary arteries, particularly among young healthy men, and one study even related coronary and aortic atherosclerosis to an increased number of vascular risk factors.[164, 279, 280] Other clinical studies have correlated the severity of CAD to femoral atherosclerosis.[210, 212]

Recurrent events and mortality

At 5-year follow-up, 13.7% of our patients experienced new cardiovascular events, of whom 7.5% were due to recurrent ischaemic stroke, with only a significant difference among young female patients compared to young female controls. Mortality rate was

5.5% among our stroke patients. Of note, we did not manage to include three patients with basilarisocclusion at admission due to early death. We included them into our calculation of incidence, but not into calculation of the mortality rate, as they were not included into NOR-SYS due to lacking consent. However, it is important to mention, as it describes the severity of acute ischaemic stroke when recanalization of important main arteries is not obtained.

In comparison, the population-based Hordaland study of young stroke patients at age 15-49 years from 1988-1997 in western Norway showed a recurrence rate of ischaemic stroke of 9.9%, and a mortality rate of 9.9%, after a mean follow-up of 5.7 years.[229] A Finnish study that included young stroke patients between 1994-2004, reported a cumulative 5-year recurrence rate of 11.5% for any cardiovascular event, and 9.4% for ischaemic stroke.[230] An older young stroke study, conducted between 1977-1992, reported also high recurrent rates of stroke (9.0%), and particularly a high mortality rate (21%) after a mean follow-up of 6 years.[282] Other studies of young stroke from 1974 to 2010 have also reported higher 5-year mortality rates around 9-11% than we found in our study.[30]

In our study, there was no difference in the mortality rates between patients and controls, while a Dutch study from 2013 showed a 4-fold higher mortality for young stroke patients compared to nationwide age- and sex-matched mortality rates.[283]

Young stroke patients are at a high risk of new cardiovascular events and earlier mortality, mainly due to atherosclerotic diseases.[30, 282, 284] NOR-SYS demonstrates that 5-year mortality in addition was associated with an increased number of vascular areas affected by atherosclerosis. We did not find any difference between the TOAST subgroups regarding 5-year outcome ($p = 0.109$). However, in other young stroke studies, LAA as cause of stroke was associated with the highest risk of mortality.[30]

Hence, our study indicates a trend towards improved prognosis for young stroke patients over the years, although NOR-SYS comprises a comparably small sample size. Very probable explanations are improved acute treatment of ischaemic stroke by introduction of thrombolysis, thrombectomy, and increased focus on secondary

prevention with increased focus towards healthy life-style, and more aggressive treatment of modifiable risk factors. An example is the repeated adjustment in the definition of hypertension over the past decades, resulting in earlier initiation of antihypertensive treatment.[70, 71, 90] Another example is the far more regular use of statins after the diagnosis of dyslipidaemia, with repeated adjustments of lower LDL-cholesterol treatment goals. Current guidelines state that all patients with established CVD should be subscribed statins irrespective of baseline triglycerides or LDL-cholesterol, as the use of statins was associated with a lower risk of all-cause mortality, and a lower risk of recurrent stroke among young ischaemic stroke patients.[130, 285] Since statins may have rare but serious side effects, an individual evaluation including ultrasound may spare some very young patients with normal cholesterol and normal artery wall segments for statin treatment.

Methodological considerations, strengths and limitations

NOR-SYS was originally designed as a national multi-center study, but became a single-centre, hospital-based, prospective study on acute ischaemic stroke in the region of Bergen. However, we consider NOR-SYS as well as a population-based study for several reasons. Bergen is geographically located at the western coast of Norway, and the department of Neurology has served as the responsible stroke unit for stroke patients at age 15-≤60 years on a local as well as a regional level for decades. We included only patients living in the defined geographical region of "Helse-Bergen" into NOR-SYS, including the cities of Bergen and Voss, and minor surrounding communities.

NOR-SYS did not limit study inclusion to a few days after acute ischaemic stroke. The majority of our patients were admitted and included into NOR-SYS within a week after the onset of stroke symptoms. Citizens of our region, who suffered from documented acute ischaemic stroke outside our geographical region, were included into NOR-SYS at the time of referral, and with a subsequent delay of up to 5 months,

but acute stroke that usually occurred during holidays or work abroad had then been documented by the actual hospital.

We did not make any attempt to investigate whether additional patients belonging to "Helse-Bergen" were not admitted to our hospital at all, as a previous Norwegian study's intensified search among general practitioners did not disclose any additional patients <79 years.[286]

The likelihood of sending patients with acute stroke to other hospitals in Norway, or neighbouring countries is considered as very low as Haukeland University Hospital itself has a regional function. However, we are aware of the fact that patients from our geographical region may have died from stroke suddenly abroad or at other places in Norway. In addition, there may have been patients with minor or short-lasting symptoms that did not seek health care at all. However, these patients are outside of our reach, and the confounder of non-referral may equally appear in other studies, too.

The special geographical background was also the reason for the three-generation design of NOR-SYS. We assumed our hospital, with its traditionally strong responsibility in the fields of young stroke, invasive cardiac diagnostics and interventions, and vessel-surgery and interventions, to be a rich source of medical information on CVD, gathered from several generations of patients from the area. Partners/ex-partners were chosen as controls due to their genetic role for common offspring. At the same time, similar life-style in partners may lead to better comparability between patients and controls than can be expected from randomly selected controls.[287] We found that particularly smoking and physical inactivity were shared risk factors among our patients, and their partners as controls.

During the inclusion period, no major changes were made to our stroke unit, admission routines or diagnostic criteria. Acute intervention with thrombectomy was approved in 2017 in Norway. Diagnostic MRI is a widely available procedure in Norway, aiding for more precise diagnostic of ischaemic stroke. Patients with contraindications, or who refused the use of MRI, were diagnosed by repeated CT scans, in order to visualize occurring acute ischaemic lesions in the course of the disease. In NOR-SYS,

98.5% of our stroke patients were examined by MRI.[288] The ultrasound protocol was performed by internationally certified doctors, only.

The prospective design of NOR-SYS has the advantage of a detailed collection of data serving the estimation of young stroke incidence, the prevalence of vascular risk factors, staging of several vascular areas affected by atherosclerosis, and data collection until the 5-year follow-up.

Other strengths of NOR-SYS include high participation rates for patients, partners and adult offspring, standardized diagnostic work-up of multiple risk factors including a comprehensive ultrasound protocol permitting staging of atherosclerosis, a low number of inobtainable IMT measurements, and use of mean IMT measurements which provide information on cardiovascular risk even in absence of plaques.[289]

However, NOR-SYS has several limitations. The comprehensive diagnostic work-up and ultrasound protocol were time-consuming, and they are not easy to apply in daily clinical practice outside the frame of a study design. Three young stroke patients were not included into NOR-SYS due to their severe vital condition at hospital admission, and two patients were not examined according to the ultrasound protocol due to early fatality of the stroke and morbid obesity causing insufficient imaging quality, respectively. There was a recall bias due to the fact that patients were interviewed directly, while partners received the questionnaire when meeting at the hospital, and thus had more time to prepare. The study design with partners as controls resulted in inequality of sex group sizes with a high number of male patients and a relatively low number of male controls, implying limitations for interpretation. As it is well-known that atherosclerosis is both age and sex dependent, our age and sex-matched analyses were based on small sample sizes in each studied subgroup. Regarding staging of atherosclerosis, we did not include the intracranial arterial pathology despite its certain relevance to the subject, due to substantial uncertainties in defining the cause and degree of stenosis by commonly available imaging methods.[290] The low number of outcome events, particularly the number of deaths, may limit the interpretation of our analyses. However, the Norwegian system of a 11-digit individual identification

number secured that no participants dropped-out for the alive-dead analysis. The diagnosis of diabetes mellitus and dyslipidaemia differed between patients and controls, as blood tests were only performed among patients during hospitalisation, potentially leading to underestimation of its prevalences among our controls.

Conclusions and future aspects

This thesis reflects new information on the epidemiology of ischaemic stroke among young and middle-aged patients aged 15-60 years in the region of Bergen. In addition, it identifies the burden of risk factors, and prevalence of atherosclerosis at a subclinical and clinical symptomatic level among patients and controls.

Cardiovascular diseases are the leading cause of death, and stroke is the second leading cause of death worldwide. Cardiovascular diseases are also leading among the frequent causes of admissions to hospitals. Our incidence rate of young ischaemic stroke has increased during the past decades, as also seen in other European countries, and the prevalence of vascular risk factors among young patient population is high. This thesis shows a high risk factor burden, and high prevalence of atherosclerosis in seven vascular areas without differences among male patients, and controls at any age, and among middle-aged female patients and controls. These findings emphasize the importance of early health education, and early aggressive treatment of risk factors for primary prevention as well as for secondary prevention.

The 5-year outcome of our young stroke patients are promising, as they were not different from our control subjects for most subgroups regarding occurrence of new cardiovascular events and mortality, very probably attributed to better acute treatment with thrombolysis and thrombectomy, better secondary prophylaxis, and more attention to reach clearly specified treatment goals, defined by international stroke treatment guidelines.

However, there is still a gap in our knowledge regarding understanding of underlying causes of ischaemic stroke, not well enough explained by common methods of evaluation, such as TOAST. Future research will include an increasing amount of genetic diagnostics, in order to explore substantial differences in phenotype and frequency of arterial disease despite young age, and variations in the presentation of vascular risk factors, and individual diagnosis of subclinical disease in the arteries at stroke onset. An individual extensive diagnostic work-up of young stroke patients

including arterial staging for any type of stroke, will be essential for an increased value of genetic diagnostics.

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Errata

Page 6: Corrected the reference page to “75”.

Page 11 and page 13: Missing word: “fIMT”

Page 33: Misspelling “onging” – corrected to “ongoing”.

Page 39: Deleted “excessive use of alcohol”

Page 40: Deleted “of CAD” and changed the reference number 190.

Page 50: Misspelling “vigrorous” to “vigorous”

Page 51: Deleted word: “, and.”

Page 56: Missing word: “fIMT≥0.9 mm”

Page 58: Change years from “23 years” to “60 years” and “1971” to 1948”

Page 62: Misspelling “measurments” to “measurements”

Page 64: Misspelling “infaction” to “infarction”

Paper II: Table 5 Patients: 95% CI for NAA, adjusted for age and sex is: (1.03-1.65)

Controls: 95% CI for cIMT≥0.9mm, adjusted for age and sex is: (1.09-114.5)

Paper III: Deleted word in discussion “without sex differences”

Appendix

1. a) Questionnaire to patients about vascular risk factors and events
   b) Questionnaire to partners about vascular risk factors and events
   c) Questionnaire to patients'/partners' parents about vascular risk factors and events
2. Ankle-arm index
3. Meijer's Carotid Arc®
4. Ultrasound protocol at inclusion of patients and partners

Appendix 1a) Questionnaire to patients about vascular risk factors and events

NORSTROKE Norwegian Stroke Research Registry Senter for Nevrovaskulære Sykdommer Nevrologisk avdeling Haukeland Universitetssykehus	Pasient:
Senter kode ☐☐☐	Pasient Nr. ☐☐☐☐☐

NOR-SYS Norwegian Stroke in the Young Study	Studie kode ☐☐☐	NOR-SYS familie nr. ☐☐☐

NOR-SYS Norwegian Stroke in the Young Study

Norwegian Stroke in the Young Study

Dette er et standardskjema som vi ber deg svare på for å få en god vurdering av risikofaktorene angående hjerte-kars-sykdom.

Hvem svarer?

☐ Pasienten ☐ Foreldre
☐ Partner ☐ Søsken
☐ Voksent barn ☐ Andre: .....

Utfylt skjema leveres til overlege Ulrike Waje-Andreassen

Sosialt, utdannelse, arbeid

Sivil status	☐ Gift/samboer ☐ Enke / enkemann	☐ Ugift	☐ Skilt eller separert
Bor med	☐ Ektefelle/samboer ☐ Institusjon	☐ Bor alene ☐ Ingen fast bopel	☐ Familiemedlem
Utdannelse	☐ Grunnskole	☐ Videregående	☐ Høyskole/Uni
Arbeid	☐ Elev/student ☐ Lønnet arbeid deltid ☐ Permittert, arbeidsledig ☐ Pensjonist	☐ Hjemmeværende ☐ Sykemeldt heltid ☐ Trygd/attføring heltid Hva er/var ditt yrke?	☐ Lønnet arbeid heltid ☐ Sykemeldt deltid ☐ Trygd/attføring deltid

Familie

Antall egne (hel-)søsken ☐ Antall egne barn ☐, av dem er ☐ over 18 år

Hvilke personer i din nærmeste familie har hatt hjerneslag (infarkt eller blødning)?
Hvis helt ukjent (kryss dersom du er adoptert) ☐ og gå til neste avsnitt om røyking

Hjerneslag? Hvis "Ja": Hjerneslaget skyldtes (evt. flere kryss)

	Ja	Nei	Vet ikke	Drypp/TIA	Infarkt	Blødning	Vet ikke
Far	☐	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Hjertesyk? Hvis "Ja": Hjertesykdommen skyldtes (sett flere kryss, dersom aktuelt)

	Ja	Nei	Vet ikke	Angina brystsmerter	Hjerte-infarkt	Svikt/rytme-klaffeproblem	Vet ikke
Far	☐	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Trange blodårer / "røykebein"? Hvis "Ja": Behandling ble (sett flere kryss, dersom aktuelt)

	Ja	Nei	Vet ikke	Gå-trening	Kirurgisk	Amputasjon	Vet ikke
Far	☐	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Døde noen familiemedlemmer før 70-års alder? Nei ☐ Ja ☐ Vet ikke ☐

Hvis ja, hvem døde yngre enn 70 år gammel? _____

Var døden plutselig og uventet? Nei ☐ Ja ☐ Vet ikke ☐

Vet du noe nærmere om dødsårsaken, i så fall hvilken? _____

Røyking

Kryss her hvis du aldri har røykt/brukt snus ☐

Alder røkestart ☐ Alder røkeslutt ☐ Hvis du sluttet siste år, hvor mange mnd siden? ☐ Røkt totalt år ☐

Tidligere: Antall sigaretter per dag i snitt? Før fylte 15 år ☐ 15-30 år ☐ 30-60 år ☐

Nå: Antall sigaretter per dag i snitt? ≤10 ☐ 11-20 ☐ 21-29 ☐ ≥30 ☐

Bruker du snus? nei ☐ ja ☐

Hvor mye snuser du nå per dag i snitt? <¼ boks ☐ ¼ boks ☐ ½ boks ☐ ≥1 boks ☐

Hvor lang tid etter at du våkner røyker du din første sigarett eller bruker snus? <5 min ☐ 6-30 min ☐ 31-60 min ☐ >60 min ☐

Har du hatt opphold fra å røyke / snuse? nei ☐ ja ☐ Hvis ja, hvor mange? ☐

Hvor lenge varte det lengste oppholdet? ☐ mnd ☐ år

Hvis du hadde opphold, hvordan klarte du det, hvem eller hva hjalp deg (*sett flere kryss , dersom aktuelt)*

- ☐ Ingen hjelp
- ☐ Familie/venner
- ☐ Egen lege
- ☐ Røykeavvenningskurs
- ☐ Nikotinerstatning (plasetr, tyggis, annet)
- ☐ Medikamenter
- ☐ Alternativ medisin
- ☐ Akupunktur
- ☐ Støttetelefon, internett

Alkohol

Kryss her hvis du aldri har drukket alkohol ☐

1 alkoholenhet = 1 liten fl pils = 1 glass vin = 1 drink (brennevin). 1 flaske vin = 6 enheter

Har drukket tidligere, men sluttet å drikke alkohol for mer enn 1 år siden: nei ☐ ja ☐

Antall enheter alkohol per uke i gjennomsnitt: 0-3 ☐ 4-6 ☐ 7-12 ☐ >12 ☐ >20 ☐

Antall dager per måned med inntak av alkohol i gjennomsnitt ☐

Fysisk aktivitet

Aktive treningstimer i gjennomsnitt per uke (jogging, sykling, svømming, annen trening) ☐ timer

Aktive timer med turgåing i snitt per uke (aktivitet i jobbsammenheng) ☐ timer

- ☐ Ingen spesiell fysisk aktivitet, gjør alt hage/hytte- og annet vedlikeholdsarbed på hus selv
- ☐ Ingen spesiell fysisk aktivitet, ikke spesielt vedlikeholdskrevende arbeid på huset
- ☐ Trenger hjelp til tyngre husarbeid / bære tunge handleposer
- ☐ Beveger meg kun vanlig og innendørs
- ☐ Bruker hjelpemiddel (stokk eller annet) til å bevege meg innendørs

Høyde, vekt, blodtrykk

Kryss her hvis du ikke har hatt høyt blodtrykk ☐

Høyde cm ☐ Vekt kg ☐ Dersom du har høyt blodtrykk, hvor lenge har du hatt behandling med tabletter? ☐

Sukkersyke

Kryss her hvis du ikke har sukkersyke ☐

I hvor mange år har du hatt sukkersyke? ☐ Hvor mange år har du brukt medikamenter? ☐

Hva slags behandling får du nå? kost ☐ tabletter ☐ Insulin ☐ tabletter og sprøyter ☐

Tidligere hjerneslag, hjertekarsykdom

Kryss her hvis du ikke har hatt noe av dette ☐

Har du hatt følgende:	Vet ikke	Nei	Ja	Hvis undersøkt/behandlet: Når (år), hvor (sykehus)
Hjerneslag	☐	☐	☐	
Drypp / TIA	☐	☐	☐	
Hjerneinfarkt	☐	☐	☐	
Hjerneblødning	☐	☐	☐	
Operasjon hals/hjerne pga slag		☐	☐	
Epilepsi, krampeanfall		☐	☐	
Angina, brstsmerter		☐	☐	
Hjerteinfarkt		☐	☐	
Blokking/stenting av hjertepulsåre		☐	☐	
Bypass-operasjon		☐	☐	
Annen hjerteoperasjon		☐	☐	Hvorfor?
Røykebein		☐	☐	
Operasjon på pulsårene i beina		☐	☐	
Operasjon på hovedpulsåren		☐	☐	
Blodpropp i lungene		☐	☐	
Blodpropp i arm/bein, hoven og blå		☐	☐	
Blodpropp i arm/bein, kald og hvit		☐	☐	
Blødning fra spiserør, mage, tarm		☐	☐	
Annen alvorlig blødning		☐	☐	
Hjerteflimmer av og til		☐	☐	
Hjerteflimmer kronisk		☐	☐	
Annen rytmeforstyrrelse		☐	☐	
Hjertesvikt		☐	☐	
Migrene uten synsproblemer (aura)		☐	☐	
Migrene med synsproblemer (aura)		☐	☐	
For kvinner: Menopause		☐	☐	Alder ved menopause (år):

Dersom du er behandlet av **privat hjertespesialist**, vennligst angi (omtrent) hvilket år, navn og adresse:

År: _____ Navn _____ Adr. _____

Dersom **din fastlege** har behandlet deg for brystsmerter, forbigående synsproblemer, svakhet i armer eller bein eller smerter i beina, vennligst angi (omtrent) hvilket år, navn og adresse:

År: _____ Navn _____ Adr. _____

Andre sykdommer eller plager

Kryss her hvis du ikke har hatt noe av dette ☐

Har du hatt følgende:	Nei	Ja	Innlagt i sykehus	Nei	Ja
Blodforgiftning	☐	☐		☐	☐
Nyresykdom	☐	☐		☐	☐
Kreftsykdom, helbredet	☐	☐		☐	☐
Kreftsykdom under oppfølging	☐	☐		☐	☐
Kronisk mage- eller tarmsykdom	☐	☐		☐	☐
Lever-galle sykdom/plager	☐	☐		☐	☐
Bukspyttkjertel sykdom/plager	☐	☐		☐	☐
Lungesykdom (KOLS og annet)	☐	☐		☐	☐
Multippel sklerose (MS)	☐	☐		☐	☐
Høyt stoffskifte	☐	☐		☐	☐
Lavt stoffskifte	☐	☐		☐	☐
Muskel-skjelettplager, beinskjørhet	☐	☐		☐	☐
Leddgikt / revmatologisk sykdom	☐	☐		☐	☐
Psoriasis / annen kronisk hudsykdom	☐	☐		☐	☐
Søvnproblemer	☐	☐		☐	☐

Angstplager	☐	☐	☐	☐
Hukommelsesproblemer	☐	☐	☐	☐
Depresjon	☐	☐	☐	☐

Hvis annen sykdom /plage som ikke er nevnt, vennligst angi:_____

Medikamenter

Kryss her hvis du ikke bruker noe medikament ☐

Også insulin, vitaminer, evt. p-pille eller annet hormonpreparat, evt. alternativ homeopatisk medisin

Navn	Tablett styrke	Antall tabl pr gang	Antal ggr pr dag	Navn	Tablett styrke	Antall tabl pr gang	Antal ggr pr dag

Flere medikamenter, dersom aktuelt: _____

Allergier

Kryss her hvis du ikke har hatt allergiplager ☐

	Nei	Ja	Usikker		
Medikamenter?	☐	☐	☐	Hvilket?	.....
Røntgenkontrast?	☐	☐	☐	Hvilket?	.....
Annen allergi?	☐	☐	☐	Hvilken?	.....

På hvilken måte reagerer du allergisk? _____

Infeksjoner

Kryss her hvis du ikke har hatt infeksjoner ☐

	Nei	Ja
Er du de siste 4 ukene blitt behandlet/operert pga betennelse?	☐	☐
Er du de siste ukene blitt behandlet/operert pga betennelse?	☐	☐
• Bronkitt eller lungebetennelse		☐
• Urinveisinfeksjon		☐
• Bihulebetennelse		☐
Annen type betennelse/infeksjon		☐
Tannlegebehandling pga betennelser?	☐	☐
Går du regelmessig til tannlegen?	☐	☐
Bruker du influensavaksine om høsten?	☐	☐

Aktuelt hjerneinfarkt

Evt. flere kryss dersom aktuelt

Hva var omstendighetene omkring øyeblikket du ble syk? Symptomene ble bemerket:

- Ved eller like etter vanlig aktivitet ☐
- Ved eller like etter sterk fysisk aktivitet ☐
- Vet ikke ☐

- Under positivt psykisk stress ☐
- Under negativt psykisk stress ☐
- Var ikke stresset, nøytralt stemningsleie ☐

Måltider og matvaner

	Nei	Ja
Jeg spiser stort sett regelmessig frokost, lunch og middag	☐	☐
Jeg spiser stort sett mellommåltider	☐	☐

Mellommåltider består stort sett av
☐ frukt, salat eller yoghurt
☐ brødskiver
☐ sjokolade, kake eller kjeks

På hverdager spiser jeg vanligvis det første måltidet ca. kl. _____

Fisk, kjøtt: som pålegg og middagsmat spiser jeg *(sett ett kryss)*

☐ mest fisk
☐ mest kjøtt
☐ kjøtt og fisk omtrent like mye
☐ spiser hverken kjøtt eller fisk

Fett: Jeg bruker *(sett ett kryss på det som passer best)*

☐ mest plantemargarin, olivenolje, skummet melk i tilberedningen av brød- og middagsmat (inkludert drikke og saus)
☐ mest smør, fløte, helmelk, lettmelk, bacon i tilberedingen av brød- og middagsmat (inkludert drikke og saus)
☐ en blanding av det ovennevnte i omtrent like store deler

Grønnsaker, frukt: Hyppighet av inntak *(sett ett kryss i hver linje)*

	daglig	4-6 x/uke	1-3 x/uke	<1 x/uke	nesten aldri
Grønnsaker, rå	☐	☐	☐	☐	☐
Grønnsaker, kokt	☐	☐	☐	☐	☐
Frukt, fersk	☐	☐	☐	☐	☐

Middag / matvaner hjemme: Jeg spiser

☐ hjemmelaget mat
☐ mest ferdig eller nesten ferdig mat, kjøpt i supermarket
☐ mest ferdigmat, kjøpt på veikro, bensinstasjon, kiosk, pizzeria, "fast-food" kjede
☐ spiser ikke varm middag

Middag / matvaner på reisedager: Yrket medfører ca. *(antall)* _____ reisedager. Jeg spiser

☐ oftest ikke middag men brødskiver, kald mat
☐ mest ferdigmat, kjøpt på veikro, bensinstasjon, kiosk, pizzeria, "fast-food" kjede
☐ mest restaurantmat
☐ ingen middag på dagen, venter til jeg kommer hjem, spiser et stort måltid ca. kl. _____
☐ en blanding av det ovennevnte

Salt: Jeg salter maten på tallerken oftest før jeg har smakt på den ☐ Nei ☐ Ja

Jeg spiser chips/ peanøtter: ☐ daglig ☐ 4-6x/uke ☐ 1-3x/uke ☐ < 1x/uke ☐ nesten aldri

Drikkevaner: Jeg drikker mest *(sett flere kryss for det som passer best)*

☐ Melk	☐ Juice	☐ Saft
☐ Kaffee	☐ Svart te	☐ Svart te

☐ Brus ☐ Lett-brus ☐ Vann/mineralvann

Av alkohol drikker jeg mest ☐ Vin ☐ Øl ☐ Brennevin ☐ Likør, annen ☐ Drikker ikke alkohol

Kosttilskudd og vekt

Jeg bruker ☐ Tran ☐ Vitaminer ☐ Annet kosttilskudd _____
Navn

	Nei	Ja	
Jeg har hatt mindre matlyst siste ukene før innleggelse	☐	☐	
Jeg har hatt ufrivillig vekttap siste 4 uker før innleggelsen	☐	☐	_____ kg

Appendix 1b) Questionnaire to partners about vascular risk factors and events

Norwegian Stroke in the Young Study

Kjære ektefelle, samboer, partner!
Dette er et standardskjema som vi ber deg svare på for å få en god vurdering av risikofaktorene angående hjerte-kar sykdom
Svarer du selv på disse spørsmål? ☐
Hvis ikke, hvem svarer for deg? (vennligst angi navn og familierelasjon: partner, søsken, barn eller annen relasjon)

……

Ektefelle, samboer, partner

Jeg er kvinne ☐ Jeg er mann ☐

Jer er …….. år gammel.

Sosialt, utdannelse og arbeid *Antall egne barn……..*

Utdannelse: Grunnskole… ☐ Videregående ☐ Høgskole/Univ. ☐

Arbeid:

Elev/ student ☐	Hjemmeværende ☐	Lønnet arbeid heltid ☐
Lønnet arbeid deltid ☐	Sykemeldt heltid ☐	Sykmeldt deltid ☐
Arbeidsled./permittert ☐	Trygdet/attfør. heltid ☐	Trygdet/attfør. deltid ☐
Pensjonist ☐		

Hva er/ var ditt yrke? ……..

Familiebelastning *Kryss her hvis du ikke har noen familiebelastning* ☐

Hvilke personer i din nærmeste familie har hatt hjerneslag (hjerneinfarkt eller hjerneblødning)?
Helt ukjent *(kryss dersom du er adoptert)* ☐ *og gå videre til neste avsnitt om røyking.*

Hjerneslag:	**Vet ikke**	**Nei**	**Ja: hvis ja: forårsaket av** *(sett flere kryss, dersom aktuelt)*: Drypp/ TIA	Hjerneinfarkt	Hjerneblødning	Vet ikke
Far	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐

Hjertesyk:	**Vet ikke**	**Nei**	**Ja: hvis ja: forårsaket av** *(sett flere kryss, dersom aktuelt):* Angina/ brystsmerter	Hjerteinfarkt	Svikt, rytme-, klaffeproblemer	Vet ikke
Far	☐	☐	☐	☐	☐	☐

Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Trange blodårer / "røykebein":

	Vet ikke	**Nei**	**Ja: hvis ja: behandlet med** *(sett flere kryss, dersom aktuelt):*				
				Amputasjon	Bevarende inngrep	Gå-trening	Vet ikke
Far	☐	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
	☐						
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Røyking *Kryss her hvis du aldri har røkt/ bruker snus* ☐

Tidligere røyker:

Alder ved røykestart ☐☐ alder i år

Alder ved røykeslutt ☐☐ alder i år

Hvis du sluttet siste år, hvor mange mndr siden ☐☐ antall mnd

Røykt i totalt antall år ☐☐ antall år

Aktiv røyker:

Hvor mange sigaretter har du røykt per dag i snitt?

Før fylte 15 år ☐☐ stykk

15-30 år ☐☐ stykk

31-60 år ☐☐ stykk

Hvor mange sigaretter røyker du nå per dag?

10 eller mindre ☐ 11 – 20 ☐ 21 - 30 ☐ 30 eller mer ☐

Bruker du snus? Nei ☐ Ja ☐

Hvor mye snuser du per dag?

Mindre enn 1/4 boks ☐ 1/4 boks ☐ 1/2 boks ☐ 1 boks eller mer ☐

Hvor lang tid etter at du våkner røyker du din første sigarett eller bruker snus?

Innen 5 minutter ☐ 6-30 min ☐ 31 – 60 min ☐ etter 60 min ☐

Har du hatt opphold fra å røyke / snuse? Nei ☐ Ja ☐ Hvis ja, hvor mange? ☐☐

Hvor lenge varte det lengste oppholdet? ☐☐ antall mnd ☐☐ antall år

Hvis du hadde opphold, hvordan klarte du det, hvem eller hva hjalp deg? *(sett flere kryss, dersom aktuelt)*

Ingen hjelp	☐	Røykavvenningskurs	☐	Alternativ medisin	☐
Familie/ venner	☐	Nikotinerstatning (plaster, tyggis, annet)	☐	Akupunktur	☐
Lege	☐	Medikamenter	☐	Annet	☐

Alkohol

Kryss her hvis du aldri har drukket alkohol ☐

En enhet alkohol = 1 liten flaske pils = 1 glass vin = 1 drink (brennevin). 1 fl vin = 6 enheter.

Hvor mange enheter drikker du i snitt pr uke?

Antall enheter alkohol	*0- 1*	*1-3*	*4-6*	*7-12*	≥12	≥20
per uke i gjennomsnitt	☐	☐	☐	☐	☐	☐

Antall dager **per måned** med inntak av alkohol i gjennomsnitt ☐☐

Fysisk aktivitet

Aktive treningstimer i gjennomsnitt per uke gjennomsnitt per uke (jogging, sykling, svømming, annen trening) ☐☐ antall timer

Aktive timer med turgåing i ☐☐ antall timer

Ingen spesiell fysisk aktivitet, gjør all hage- hytte- og annen vedlikeholdsarbeid på hus selv ☐
Ingen spesiell fysisk aktivitet, ingen spesiell vedlikehold krevende arbeid på huset ☐

Trenger hjelp til tyngre husarbeid/ bære tunge handleposer. ☐
Beveger meg kun vanlig og innendørs ☐
Bruker hjelpemiddel (stokk eller annet) til å bevege meg innendørs ☐

Høyde, vekt og blodtrykk

Kryss her hvis du ikke har hatt høyt blodtrykk ☐

Høyde ☐☐☐ cm

Vekt ☐☐☐ kg

Dersom du har høyt blodtrykk, hvor lenge har du hatt behandling med tabletter? ☐☐ antall år

Sukkersyke

Kryss her hvis du ikke har sukkersyke ☐

I hvor mange år har du hatt sukkersyke? ☐☐ antall år

Hva slags behandling får du nå? Kost ☐ Tabletter ☐ Insulin ☐

Hvor lenge har du brukt medikamenter? ☐☐ antall år

Tidligere hjerneslag, hjertekarsykdom ***Kryss her hvis du ikke har hatt noen av tilfellene nedenfor*** ☐

Har du hatt følgende:	*Nei*	*Ja*	*Årstall første gang*	*Årstall siste gang*	*Hvis behandlet, evt. i hvilket sykehus?*
Angina/ brystsmerter	☐	☐	|___|	|___|	……..
Hjerteinfarkt	☐	☐	|___|	|___|	…….....
Blokking kransåre hjertet	☐	☐	|___|	|___|	……..
Bypass-operasjon	☐	☐	|___|	|___|	……...
Operert hjerteklaff	☐	☐	|___|	|___|	……
Operert medfødt hjertefeil	☐	☐	|___|	|___|	……
Drypp/ Hjerneslag	☐	☐	|___|	|___|	……
Operasjon på halsårene	☐	☐	|___|	|___|	……
Epilepsi, krampeanfall	☐	☐	|___|	|___|	……
Røykebein	☐	☐	|___|	|___|	……
Operasjon pulsårene bena	☐	☐	|___|	|___|	……
Operasjon på hovedpulsåren	☐	☐	|___|	|___|	……
Blodpropp i bena	☐	☐	|___|	|___|	……
Blodpropp i lungene	☐	☐	|___|	|___|	……
Operasjon av årekunter	☐	☐	|___|	|___|	……
Blødning fra spiserør, mage eller tarm	☐	☐	|___|	|___|	……...
Annen alvorlig blødning	☐	☐	|___|	|___|	……
Hjerteflimmer av og til	☐	☐	|___|	|___|	……...
Hjerteflimmer kronisk	☐	☐	|___|	|___|	……
Annen rytmeforstyrrelse	☐	☐	|___|	|___|	……
Hjertesvikt	☐	☐	|___|	|___|	……
Migrene uten synsproblemer (aura)	☐	☐	|___|	|___|	……..
Migrene med synsproblemer (aura)	☐	☐	|___|	|___|	……..

Dersom du har blitt behandlet av **privat praktiserende hjertespesialist**, vennligst angir (omtrent) hvilket år, navn og adresse:

Årstall…… Dr.…… Adresse……..

Dersom **din fastlege** har behandlet deg for brystsmerter, forbigående synsproblemer,
svakhet i armer eller bein eller smerter i beina, vennligst angir (omtrent) hvilket år, navn og adresse

Årstall…… Dr.…… Adresse……..

Andre sykdommer eller plager — ***Kryss her hvis du ikke har noen annen sykdom eller plage***….☐

Har du eller har du hatt følgende?	Nei	Ja	*Vært innlagt på sykehus?* Nei	Ja
Nyresykdom	☐	☐	☐	☐
Kreftsykdom, helbredet	☐	☐	☐	☐
Kreftsykdom nå	☐	☐	☐	☐
Sure oppstøt eller brystsvie	☐	☐	☐	☐
Sår mage-tarm	☐	☐	☐	☐
Kronisk tykktarmsykdom	☐	☐	☐	☐
Astma/kr. bronkitt/KOLS	☐	☐	☐	☐
Annen lungesykdom....	☐	☐	☐	☐
Multippel sklerose (MS)	☐	☐	☐	☐
Høyt stoffskifte	☐	☐	☐	☐
Lavt stoffskifte	☐	☐	☐	☐
Osteoporose/benskjørhet	☐	☐	☐	☐
Muskel/skjelett plager	☐	☐	☐	☐
Leddgikt	☐	☐	☐	☐
Annen reumatol.sykdom	☐	☐	☐	☐
Depresjon	☐	☐	☐	☐
Søvnproblem	☐	☐	☐	☐
Redusert hukommelse	☐	☐	☐	☐
Angst	☐	☐	☐	☐
Annen sykdom eller plage	☐	☐	Hvis ja, hvilken sykdom/ helseplage? ……..	

Medikamenter (også insulin/ vitaminer/ p-piller / annet hormonpreparat alternativ/homøopatisk medisin) ***Kryss her hvis du ikke bruker medikament*** ☐

Navn	*Tablett styrke*	*Ant tabl pr gang*	*Antall ggr pr dag*
……..	…….	…….	…….
……..	…….	…….	……..
……..	…….	…….	…….

Flere medikamenter, dersom aktuelt: ……..

Allergi — ***Kryss her hvis du ikke har hatt noen allergiplager*** ☐

Er du allergisk mot:	*Nei*	*Ja*	*Usikker*	
Medikamenter?	☐	☐	☐	Hvilket? ……
Røntgenkontrast?	☐	☐	☐	Hvilket? ……
Annen allergi?	☐	☐	☐	Hvilken? ……..……

På hvilken måte reagerer du allergisk?

Infeksjoner	***Kryss her hvis du ikke har hatt noen infeksjoner*** ☐

Er du de siste 14 dager blitt behandlet/ operert pga betennelser?	*Nei*	*Ja*
Bronkitt eller lungebetennesle	□	☐
Urinveisinfeksjon	☐	☐
Bihulebetennelse	☐	☐
Tannlegebehandling pga betennelser?	☐	☐
Går du regelmessig til tannlege?	☐	☐
Bruker du influensavaksine om høsten?	☐	☐

Hjertelig takk for hjelpen!

Appendix 1c) Questionnaire to patients'/partners' parents about vascular risk factors and events

NOR-SYS Norwegian Stroke in the Young Study

Norwegian Stroke in the Young Study

HELSE VEST

Kjære pårørende!
Dette er et standardskjema som vi ber deg svare på for å få en god vurdering av risikofaktorer og forekomst av hjerte-karsykdom i familien din. I tilfelle noen andre svarer for deg, vennligst angi familierelasjon til deg: ……..

Familie, ref. nr:

Pasientens eller partnerens far/mor

Jer er …….. år gammel.

Utdannelse og arbeid

Antall egne barn ☐

Utdannelse: Grunnskole ☐ Videregående ☐ Høgskole/Univ. ☐

Arbeid:

Elev/ student ☐	Hjemmeværende ☐	Lønnet arbeid heltid ☐
Lønnet arbeid deltid ☐	Sykemeldt heltid ☐	Sykmeldt deltid ☐
Arbeidsled./permittert ☐	Trygdet/attfør. heltid ☐	Trygdet/attfør. deltid ☐
Pensjonist ☐		

Hva er/ var ditt yrke? ……..

Familiebelastning

Hvilke personer i din nærmeste familie har hatt hjerneslag (hjerneinfarkt eller hjerneblødning)?
Helt ukjent *(kryss dersom du er adoptert)* ☐ *og gå videre til neste avsnitt om røyking.*

Hjerneslag:	**Vet ikke**	**Nei**	**Ja: hvis ja: forårsaket av** *(sett flere kryss, dersom aktuelt)*:				
				Drypp/ TIA	Hjerneinfarkt	Hjerneblødning	Vet ikke
Far	☐	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Hjertesyk:	**Vet ikke**	**Nei**	**Ja: hvis ja: forårsaket av** *(sett flere kryss, dersom aktuelt):*				
				Angina/ brystsmerter	Hjerteinfarkt	Svikt, rytme-, klaffeproblemer	Vet ikke
Far	☐	☐	☐	☐	☐	☐	☐

Farmor	☐	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐	☐
Egne søsken	☐	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐	☐

Trange blodårer / "røykebein":

	Vet ikke	**Nei**	**Ja: hvis ja: behandlet med** *(sett flere kryss, dersom aktuelt):* Amputasjon	Bevarende inngrep	Gå-trening	Vet ikke
Far	☐	☐	☐	☐	☐	☐
Farmor	☐	☐	☐	☐	☐	☐
Farfar	☐	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐	☐
Mormor	☐	☐	☐	☐	☐	☐
Morfar	☐	☐	☐	☐	☐	☐
	☐					
Egne søsken	☐	☐	☐	☐	☐	☐
Egne barn	☐	☐	☐	☐	☐	☐

Røyking *Kryss her hvis du aldri har røkt/ bruker snus* ☐

Alder ved røykestart ____ alder i år

Alder ved røykeslutt ____ alder i år

Hvis du sluttet siste år, hvor mange mndr siden ____ antall mnd

Røykt i totalt antall år ____ antall år

Dersom du fortsatt røyker: Hvor mange sigaretter røyker du nå per dag?

10 eller mindre ☐ 11 – 20 ☐ 21 - 30 ☐ 30 eller mer ☐

Bruker du snus? Nei ☐ Ja ☐

Fysisk aktivitet

Aktive treningstimer i gjennomsnitt per uke gjennomsnitt per uke (jogging, sykling, svømming, annen trening) ____ antall timer

Aktive timer med turgåing i ____ antall timer

Ingen spesiell fysisk aktivitet, gjør all hage- hytte- og annen vedlikeholdsarbeid på hus selv ☐

Ingen spesiell fysisk aktivitet, ingen spesiell vedlikehold krevende arbeid på huset ☐

Trenger hjelp til tyngre husarbeid/ bære tunge handleposer. ☐

Beveger meg kun vanlig og innendørs ☐

Bruker hjelpemiddel (stokk eller annet) til å bevege meg innendørs ☐

Høyde, vekt og blodtrykk ***Kryss her hvis du ikke har hatt høyt blodtrykk*** ☐

Høyde ____ cm Vekt ____ kg

Dersom du har høyt blodtrykk, hvor lenge har du hatt behandling med tabletter? ____ antall år

Sukkersyke ***Kryss her hvis du ikke har sukkersyke*** ☐

I hvor mange år har du hatt sukkersyke? ____ antall år

Hva slags behandling får du nå? Kost ☐ Tabletter ☐ Insulin ☐

Hvor lenge har du brukt medikamenter? ____ antall år

Tidligere hjerneslag, hjertekarsykdom ***Kryss her hvis du ikke har hatt noen av tilfellene nedenfor*** ☐

Har du hatt følgende:	*Nei*	*Ja*	*Årstall første gang*	*Årstall siste gang*	*Hvis behandlet, evt. i hvilket sykehus?*
Angina/ brystsmerter	☐	☐	|___|	|___|	……..
Hjerteinfarkt	☐	☐	|___|	|___|	…….....
Blokking kransåre hjertet	☐	☐	|___|	|___|	……..
Bypass-operasjon	☐	☐	|___|	|___|	……...
Operert hjerteklaff	☐	☐	|___|	|___|	……
Operert medfødt hjertefeil	☐	☐	|___|	|___|	……
Drypp/ Hjerneslag	☐	☐	|___|	|___|	……
Operasjon på halsårene	☐	☐	|___|	|___|	……
Epilepsi, krampeanfall	☐	☐	|___|	|___|	……
Røykebein	☐	☐	|___|	|___|	……
Operasjon pulsårene bena	☐	☐	|___|	|___|	……
Operasjon på hovedpulsåren	☐	☐	|___|	|___|	……
Blodpropp i bena	☐	☐	|___|	|___|	……
Blodpropp i lungene	☐	☐	|___|	|___|	……
Operasjon av årekunter	☐	☐	|___|	|___|	……
Blødning fra spiserør, mage eller tarm	☐	☐	|___|	|___|	……...
Annen alvorlig blødning	☐	☐	|___|	|___|	……
Hjerteflimmer av og til	☐	☐	|___|	|___|	……...
Hjerteflimmer kronisk	☐	☐	|___|	|___|	……
Annen rytmeforstyrrelse	☐	☐	|___|	|___|	……
Hjertesvikt	☐	☐	|___|	|___|	……
Migrene uten synsproblemer (aura)	☐	☐	|___|	|___|	……..
Migrene med					

synsproblemer (aura) ☐ ☐ |___| |___I ……..

Dersom du har blitt behandlet av **privat praktiserende hjertespesialist**, vennligst angir (omtrent) hvilket år, navn og adresse:

Årstall…… Dr.…… Adresse……..

Dersom **din fastlege** har behandlet deg for brystsmerter, forbigående synsproblemer,
svakhet i armer eller bein eller smerter i beina, vennligst angir (omtrent) hvilket år, navn og adresse

Årstall…… Dr.…… Adresse……..

Medikamenter	***Kryss her hvis du ikke bruker medikament*** ☐	
Navn	*Tablettstyrke* *Tabletstyrke*	*Navn*
……..	…….	……..
……..	…….	……..
……..	…….	……..

Flere medikamenter, dersom aktuelt: ……..

Hjertelig takk for hjelpen!

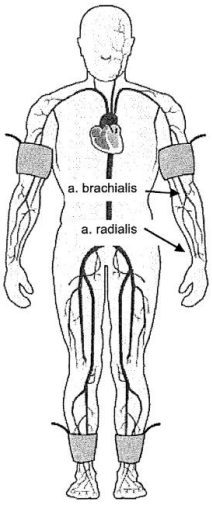
Appendix 2 Ankle-arm index

Pasient

Ankel-arm-indeks (AAI)

Haukeland Universitetssjukehus
Nevrologisk avdeling

dato:



Pasienten skal ligge horisontalt med ankler/overarmer i hjertehøyde.
Pasienten skal hvile i 5-10 minutter før målingen.
Blodtrykk måles i armer og ankler med vanlig arm-mansjett.

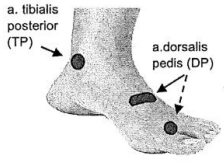
Ultralydgel legges på huden over målepunktet
Dopplerproben holdes i 45-60° vinkel mot huden.
Finn arterielt pulssignal (dopplersignal).
Mansjetten inflateres til over det punkt hvor dopplersignalet forsvinner
hvis signalet ikke forsvinner ved 250 mmHg, kan det skyldes
inkompressible arterier (diabetes), ødem eller for smal mansjett.
Mansjetten deflateres langsomt.
Systolisk BT tilsvarer trykket når jevne dopplersignaler opptrer igjen.
Mål trykket minst to ganger, noter det høyeste trykket.

Arm

BT måles i a. radialis, eventuelt i a. brachialis.

Ankel

BT måles i a. dorsalis pedis (DP), eventuelt mellom 1. og 2. tå.
Ikke komprimer arterien med trykk, hold eventuelt i kabelen.
BT måles deretter på samme måte i a. tibialis posterior (TP).



	høyre		venstre
a. radialis			
a. dorsalis pedis			
a. tibialis post			
	AAI høyre		**AAI venstre**
Høyeste ankeltrykk (DP eller TP)		=		=	
Høyeste armtrykk (hø eller ve)					

Tolkning av AAI

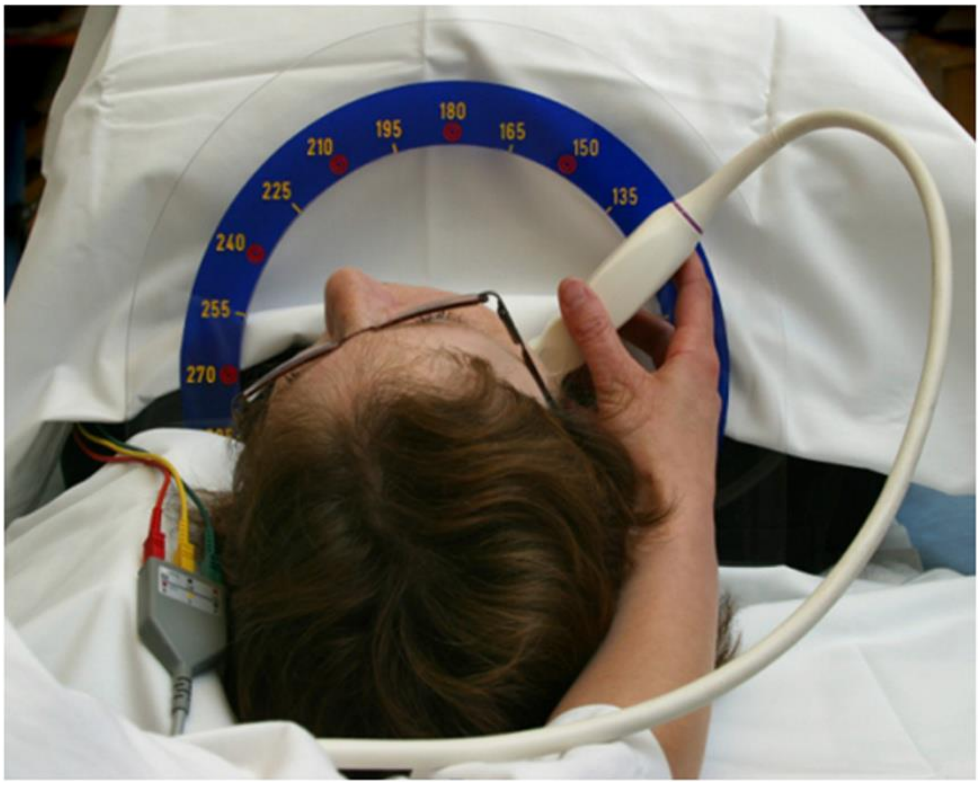
>1,3	sannsynlig inkompressible arterier (ikke pålitelig måling)
0,9 - 1,3	normalt
0,7 - 0,9	mild arteriesykdom
0,4 - 0,7	moderat arteriesykdom
<0,4	uttalt arteriesykdom. Ankeltrykk <50 mmHg er forenlig med kritisk iskemi

Adaptert etter skjema fra www.plavix.no

Skj.nr. 202.3633

L.Thomassen juli 2008

Appendix 3 Meijer's Carotid Arc®



Adapted from Waje-Andreassen.[291] With permission from the publisher.

Appendix 4 Ultrasound protocol at inclusion of patients and partners from 2010-2015

Family number	Patient	Partner
First Name		
Filecode		
IMT (max / mean)		
R CCA 180		
R CCA 150		
R CCA 120		
R CCA 90		
R BIF		
R ICA		
L CCA 180		
L CCA 210		
L CCA 240		
L CCA 270		
L BIF		
L ICA		
EPITRANS 1		
EPITRANS 2		
EPITRANS 3		
AORTA LONGITUDINEL (v/d)		
AORTA TRANSVERSE (d)		
MIDL ABDOMEN		
L ABDOMEN		
R ABDOMEN		
SUBCUTANEOUS		
L CFA		
L SFA		
R CFA		
R SFA		

Success under 70% was remarked if the mean value was calculated from less than about 70 point-to-point measurements of one cm artery segment

Abbreviations: IMT = intima-media thickness; R = right; L = left; CCA = common carotid artery; BIF = carotid bifurcature; ICA = internal carotid artery; CFA = common femoral artery; SFA = superficial femoral artery

Papers I-III

II

Original Research Article

EUROPEAN STROKE JOURNAL

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Prevalence of atherosclerosis and association with 5-year outcome: The Norwegian Stroke in the Young Study

Beenish Nawaz[1,2], Annette Fromm[2], Halvor Øygarden[3,4], Geir E Eide[5,6], Sahrai Saeed[7], Rudy Meijer[8], Michiel L Bots[8], Kristin M Sand[9,10], Lars Thomassen[2], Halvor Næss[2,11] and Ulrike Waje-Andreassen[2]

Abstract

Objectives: We studied the prevalence of atherosclerosis among ischaemic stroke patients ≤60 years and controls at the time of the index stroke, and its association with occurrence of new cardiovascular events (CVEs) and mortality at a 5-year follow-up.

Methods: Prevalent atherosclerosis was assessed for 385 patients and 260 controls in seven vascular areas by electrocardiogram (ECG), ankle–arm index (AAI) and measurement of right and left carotid and femoral intima-media thickness (cIMT and fIMT) and abdominal aorta plaques (AAP). Clinical end-points were any new CVE (stroke, angina, myocardial infarction or peripheral arterial disease) or death from any cause at 5-year follow-up. All results were sex- and age-adjusted; logistic regression and Cox proportional hazards models were applied.

Results: Young patients ≤49 years had prevalent atherosclerosis in 1/2 of males and 1/3 of females. Compared with controls, young female patients showed significantly higher prevalent atherosclerosis, $p = 0.024$. Ischaemic ECG and mean cIMT were higher in young and middle-aged female patients ($p = 0.044$, $p = 0.020$, $p = 0.023$ and $p < 0.001$, respectively). Mean fIMT was higher in middle-aged female patients ($p < 0.001$). Cardiovascular events were associated with ischaemic ECG; AAI ≤0.9, fIMT ≥0.9 mm and increased number of areas with atherosclerosis (NAA) among patients, and with AAP, cIMT ≥0.9 mm, fIMT ≥0.9 mm and NAA among controls. Mortality was associated with higher age, ischaemic ECG and NAA among patients, and cIMT ≥0.9 mm among controls.

Conclusion: Atherosclerosis is highly prevalent even in young stroke patients. Some areas and increasing NAA are associated with CVEs and death.

Keywords

Young ischaemic stroke, atherosclerosis, carotid intima-media thickness, femoral intima-media thickness, ankle–arm index, abdominal aorta plaques, cardiovascular events, mortality, long-term outcome, Trial of Org 10172 in Acute Stroke Treatment (TOAST)

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[1]Department of Clinical Medicine 1, University of Bergen, Bergen, Norway
[2]Department of Neurology, Haukeland University Hospital, Bergen, Norway
[3]Department of Neurology, Sørlandet Hospital, Kristiansand, Norway
[4]Department of Health and Nursing Sciences, Univeristy of Agder, Kristiansand, Norway
[5]Centre of Clinical Research, Haukeland University Hospital, Bergen, Norway
[6]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[7]Department of Cardiology, Haukeland University Hospital, Bergen, Norway
[8]Julius Center of Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[9]Department of Medicine, Sørlandet Hospital, Flekkefjord, Norway
[10]The Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[11]SESAM, Centre for Age-related Medicine, Stavanger University Hospital, Stavanger, Norway

Corresponding author:
Beenish Nawaz, Centre of Neurovascular Diseases, Department of Neurology, Haukeland University Hospital, Jonas Lies vei 65, Bergen N-5021, Norway.
Email: beenish.nawaz@helse-bergen.no

Introduction

The 15 cities young stroke study showed smoking, dyslipidemia and hypertension as the three most frequent risk factors (RF) for cardiovascular events (CVEs), without regional differences in Europe.[1] Several European long-term young stroke studies have shown high rates of recurrent CVEs, such as ischaemic stroke (IS), angina, myocardial infarction (MI), peripheral arterial disease (PAD) and mortality mainly due to coronary atherosclerosis (CA).[2,3] Autopsy studies have also shown high prevalence of CA, predominantly in young healthy male populations.[4,5]

The 15 cities study found 39.6% stroke of undetermined cause (SUC) and 9.3% large-artery atherosclerosis (LAA) based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, requiring ≥50% artery stenosis.[6]

Combining knowledge of the high rates of recurrent CVEs and mortality in young stroke patients,[7] worst prognosis for patients with atherosclerosis,[8] high rates of cryptogenic stroke among young patients,[9] and knowledge showing that plaque instability is more important than the degree of stenosis for coronary and cerebral CVEs,[10,11] we wanted to investigate the extent of atherosclerosis in young stroke patients. Staging of arterial vascular areas, with a more scrutineous detection of atherosclerosis, became a main pillar for the Norwegian Stroke in the Young Study (NOR-SYS). Our hypothesis is that atherosclerosis is far more present among young and middle-aged patients than the TOAST definition of atherosclerosis with at least 50% stenosis[12] is able to show, and arterial staging is the first step to understand the extent of established artery wall disease. The aims of this study are the detailed presentation of seven predefined vascular areas at study inclusion, and their association with new CVEs and mortality at 5-year follow-up.

Methods

Participants

From 1st September 2010 to 31st December 2015, 385 stroke patients aged 15–60 years, and 260 partners, serving as controls aged 21–69 years, were included. NOR-SYS design and ultrasound protocol,[13] and methods and results of inclusion have been published.[14] Verified acute ischaemic stroke diagnosis was done by magnetic resonance imaging (MRI) in 98.5% among patients or by computed tomography (CT) alone in case of contraindications. The majority of stroke patients were admitted within a few days after symptom onset (Table 1). However, in some cases, inclusion in NOR-SYS was delayed, often when patients got the stroke at other sites in Norway or abroad.

Baseline procedures

A 12-lead electrocardiogram (ECG) was verified by a cardiologist to identify signs of acute or previous myocardial ischaemia. Detailed information about the NOR-SYS ultrasound protocol has been published before.[13] In brief, ankle–arm index (AAI) ≤0.9 indicated PAD. High quality measurements of mean carotid intima-media thickness (cIMT) and femoral intima-media thickness (fIMT) were obtained at predefined segments from the common carotid artery, carotid bifurcation, internal carotid artery, common femoral artery and superficial femoral artery. In the analyses, the maximum of any mean IMT segment value was used, and plaques were included in the IMT measurements. Mean IMT values ≥0.9 mm were considered pathological,[15] and mean IMT values ≥1.5 mm were defined as atherosclerosis.[16] The abdominal aorta was assessed by ultrasound for detection of abdominal aorta plaques (AAP).

Table 1. Overview over time of admission to our hospital from acute stroke symptom onset and inclusion into the Norwegian Stroke in the Young Study.

Time of admission	Patients, *n* (%)
<24 h (h)	256 (66.5)
≥24 h to <72 h	59 (15.3)
≥72 h to <1 week	21 (5.4)
≥1 week to <1 month	27 (7.0)
≥1 month	22 (5.7)

Longest time delay appeared mainly due to first admission to other hospitals in Norway or abroad.

Prevalent atherosclerosis

Atherosclerosis was defined prevalent at seven chosen areas by the following: presence of ischaemic ECG signs; AAI ≤0.9; right and left mean cIMT and fIMT ≥1.5 mm, respectively, and presence of AAP. Presence of atherosclerosis on each vascular area was assigned a value of 1. Atherosclerosis was defined as number of affected vascular areas 0–7.

Stroke classification

Stroke aetiology was classified according to TOAST criteria, independent from the results of the ultrasound research protocol.

Follow-up data

Patients and controls visited our outpatient clinic from 1st September 2015 to 31st December 2020 for a 5-year follow-up. Primary end-points were occurrence of any new CVE (ischaemic or haemorrhagic stroke; angina or MI; and PAD), and death of any cause. Study participants were interviewed about occurrence of any CVE during the follow-up period, and new CVEs were verified by medical records for those who attended the follow-up. ECG were

performed. For mortality analysis, we chose the date of 31st August 2020. In Norway, mortality data appears in medical records, connected to each citizen's 11-digit personal identification number.

Ethical considerations

The study complies with the Declaration of Helsinki and is approved by the Regional Ethics Committee (REK-Vest 2010/74). Written consent is present for all study participants. The Regional Ethics Committee did not allow to follow dropouts apart from the dead–alive state and causes of death.

Statistics

The mean and standard deviation (SD) were used for descriptive statistics. Study participants were dichotomised into young (≤49 years) and middle-aged (≥50 years). Analyses were adjusted by age and sex. To avoid systematic bias, univariate comparisons of vascular areas between patients and controls were done within the four sex and age strata using the unpaired t-test and the Fisher's exact test. For the unadjusted comparison of all patients to their controls, McNemar's test of symmetry was used. Mean cIMT and fIMT values were compared between patients and controls by relative change (RC). The number of vascular areas affected by atherosclerosis was compared between TOAST subgroups using the Kruskal–Wallis rank test. To adjust for confounding and matching, logistic regression and Cox models were used to estimate the risk of new CVE and mortality, with respect to age, sex and vascular areas. The results were reported as odds ratios (OR) and hazard ratios (HR) with a 95% confidence interval (CI). Two-sided p-values ≤0.05 were considered significant. All statistical analyses were performed in Stata SE 16.0.

Results

Study population

At inclusion, patients had a mean age of 49.5 years, and controls had a mean age of 50.3 years (Table 2). The majority of patients were males (68.6%), and the majority of controls were females (70.0%). Young age ≤49 years were present for 39.5% of patients and 39.2% of controls.

Clinical and ultrasonographic findings

Compared to controls, young aged and middle-aged female patients had higher prevalence of ischaemic ECG ($p = 0.044$ and $p = 0.020$) and higher mean cIMT ($p = 0.023$ and $p < 0.001$), as shown in Tables 2 and 3. Mean fIMT was higher in middle-aged female patients ($p < 0.001$). Abdominal aorta plaques presence and pathological AAI did not differ in any comparisons between patients and controls. The prevalence of atherosclerosis among male patients and controls did not differ for clinical and ultrasonographic variables.

Eight (5.1%) of 157 patients with fIMT ≥0.9 mm in their right femoral artery (FA) had previously performed percutaneous coronary intervention (PCI) with access from their right FA.

Missing data

Ultrasonography was not performed in two patients due to terminal unconsciousness at admission and morbid obesity causing insufficient imaging quality, respectively. Main reasons for other missing data (Table 3) were arterial occlusion due to atherosclerosis or dissection, bad imaging quality, air (AAP) or anatomical reasons. Good quality measurements of at least 70% segmental analysis for cIMT and fIMT were averagely achieved in 96.7%.

Prevalence of atherosclerosis

The prevalence of atherosclerosis was higher in young female patients (32.7% vs 14.3%, $p = 0.024$) compared with young female controls (Figure 1). The prevalence did not differ between patients and controls among young male patients (49.4% vs 32.0%, $p = 0.167$), middle-aged male patients (77.6% vs 78.6%, $p = 1.000$) and middle-aged female patients (62.7% vs 52.5%, $p = 0.229$). The prevalence was higher in middle-aged patients than in younger patients (male 77.6% vs 49.4%, $p < 0.001$, female 62.7% vs 32.7%, $p = 0.026$) and higher in male patients than in female patients (67.4% vs 48.0%, $p = 0.014$). Maximum number of affected vascular areas were six among patients and five among controls.

Stroke classification

LAA was found among 28 (7.3%) of patients according to the TOAST classification (Table 4). Atherosclerosis was present among all of the patients in LAA group, and least present by 34.4% among patients of stroke with other determined cause (SOC) ($p < 0.001$), Figure 2. In the SUC group ≤49 years, 71.4% of males and 37.5% of females had prevalent atherosclerosis.

Follow-up data

The average duration of our outpatient clinical follow-up was 5.3 years for all participants. There were 323 (83.9%) patients and 219 (84.2%) controls participating in the 5-year follow-up. Three patients had telephone interviews. During follow-up, 44 patients (13.7%) and 9

Table 2. Baseline characteristics of patients and controls at inclusion and at 5-year follow-up.

		NA *n*	All	Male ≤49 years	Male ≥50 years	Female ≤49 years	Female ≥50 years
At inclusion							
Patients, *n* (%)	P		385 (100.0)	94 (35.6)	170 (64.4)	58 (47.9)	63 (52.1)
Controls, *n* (%)	C		260 (100.0)	28 (35.9)	50 (64.1)	74 (40.7)	108 (59.3)
Age (y), *mean (SD)*	P	0	49.5 (9.8)	40.5 (8.2)	55.9 (3.0)	38.4 (8.9)	55.8 (2.9)
	C	0	50.3 (8.6)	42.0 (6.7)	57.5 (4.9)	41.7 (6.6)	55.0 (3.2)
Unpaired T-test, p[a]			**0.001***	0.312	**0.028**	**0.019**	0.102
Ischaemic ECG, *n* (%)	P	0	40 (10.4)	9 (9.6)	17 (10.0)	6 (10.3)	8 (12.7)
	C	4	7 (2.7)	1 (3.6)	2 (4.1)	1 (1.4)	3 (2.8)
Fisher's exact test, *p*			**0.002****	0.450	0.259	**0.044**	**0.020**
AAI ≤0.9, *n (%)*	P	23	17 (4.7)	2 (2.3)	9 (5.7)	2 (3.6)	4 (6.8)
	C	5	7 (2.7)	1 (3.7)	3 (6.3)	1 (1.4)	2 (1.9)
Fisher's exact test, *p*			1.000**	0.559	1.000	0.577	0.188
AAP, *n (%)*	P	39	162 (46.8)	29 (33.0)	90 (58.8)	13 (25.0)	30 (56.6)
	C	13	87 (35.2)	5 (18.5)	29 (61.7)	9 (12.7)	44 (43.1)
Fisher's exact test, *p*			**0.002****	0.158	0.865	0.097	0.129
At 5-year follow-up							
Patients, *n* (%)	P	62	323 (83.9)	82 (36.1)	145 (63.9)	47 (49.0)	49 (51.0)
Controls, *n* (%)	C	41	219 (84.2)	21 (35.6)	38 (64.4)	64 (40.0)	96 (60.0)
Deceased, *n* (%)	P	0	21 (5.5)	1 (1.1)	13 (7.6)	2 (3.4)	5 (7.9)
	C	0	9 (3.5)	0 (0.0)	5 (10.0)	1 (1.4)	3 (2.8)
Fisher's exact test, *p*			0.524**	1.000	0.560	0.582	0.146
Any CVE, *n* (%)	P	2	44 (13.7)	10 (12.3)	22 (15.3)	7 (14.9)	5 (10.2)
	C	0	9 (4.1)	1 (4.8)	2 (5.3)	0 (0.0)	6 (6.3)
Fisher's exact test, *p*			**0.001****	0.451	0.172	**0.002**	0.509
Stroke[b], *n* (%)	P	2	26 (8.1)	7 (8.6)	10 (6.9)	6 (12.8)	3 (6.3)
	C	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fisher's exact test, *p*			**< 0.001****	0.340	0.218	**0.005**	**0.037**
Angina and/or MI, *n* (%)	P	2	16 (5.0)	5 (6.1)	8 (5.6)	2 (4.3)	1 (2.04)
	C	0	8 (3.6)	1 (4.8)	2 (5.1)	0 (0.0)	5 (5.2)
Fisher's exact test, *p*			**0.002****	1.000	1.000	0.177	0.664
PAD, *n* (%)	P	1	11 (3.4)	1 (1.2)	8 (5.6)	1 (2.1)	1 (2.1)
	C	0	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Fisher's exact test, *p*			0.07**	1.000	0.363	0.423	1.000

Abbreviations: NA: not available, missing data; *n*: number of subjects; y: years; P: patients; C: controls; SD: standard deviation; ECG: electrocardiogram; AAI: ankle–arm index; AAP: abdominal aorta plaques; MI: myocardial infarction; PAD: peripheral artery disease.
*Paired T-test; ** Exact McNemar's test of symmetry.
[a]*p*-values are comparisons between patients and controls.
[b]Stroke included haemorrhagic and ischaemic stroke. Two patients had haemorrhagic stroke.

controls (4.1%) experienced any CVE ($p = 0.001$), and occurrence of CVE was higher in young female patients than controls ($p = 0.002$). In total, 21 (5.5%) patients and 9 (3.5%) controls died ($p = 0.524$). No difference was found after adjustment for age and sex. Seven patients died within 1 month after hospital admission due to malign oedema (4), basilarisocclusion (2) and subarachnoidal haemorrhage (1). Regarding 14 patients who died after the first month after hospital admission, and within 31th August 2020, when dead–alive state was checked, the causes of deaths were recurrent stroke (1), coronary heart disease (1), lung embolism (1), cancer (4), infection (3), dementia (1) and unknown cause (3). The causes of death among controls were cancer (4), infection (1), respiratory failure after lung transplant (1) and unknown cause (3).

CVEs and mortality

Adjusted for sex and age, occurrence of CVEs was associated with ischaemic ECG (OR 3.48; $p = 0.005$), AAI ≤0.9 (OR 5.15; $p = 0.004$), fIMT ≥0.9 mm (OR 2.48; $p = 0.019$) and increased number of areas with atherosclerosis (NAA) (OR 1.31; $p = 0.025$) among patients, and with presence of AAP (OR 7.41; $p = 0.023$), cIMT ≥0.9 mm (OR 11.17; $p = 0.042$), fIMT ≥0.9 mm (OR 9.69; $p = 0.010$) and increased NAA (OR 1.81; $p = 0.014$) among controls (Table 5). Adjusted

Table 3. Ultrasound protocol on mean IMT[a] from carotid and femoral arteries of patients and controls.

		NA *n*	All	Male ≤49 years	Male ≥50 years	Female ≤49 years	Female ≥50 years
Patients, *n* (%)			385 (100.0)	94 (35.6)	170 (64.4)	58 (47.9)	63 (52.1)
Controls, *n* (%)			260 (100.0)	28 (36.4)	50 (64.1)	74 (40.4)	108 (59.3)
Carotid arteries, cIMT							
Relative change % (95% CI)			22 (13, 31)	6 (−16, 30)	10 (−8, 28)	17 (2, 32)	31 (16, 46)
Mean cIMT (SD)	P	2	1.35 (0.90)	1.02 (0.57)	1.60 (0.94)	0.90 (0.55)	1.59 (1.13)
	C	1	1.05 (0.52)	0.95 (0.37)	1.44 (0.71)	0.74 (0.17)	1.10 (0.47)
Unpaired t-test, *p*			**<0.001****	0.578	0.278	**0.023**	**<0.001**
CCA							
Relative change % (95% CI)			10 (5, 15)	2 (−10, 13)	2 (−8, 11)	2 (−4, 8)	15 (6, 24)
Mean CCA-IMT (SD)	P	2	0.84 (0.29)	0.74 (0.21)	0.94 (0.30)	0.64 (0.14)	0.90 (0.34)
	C	1	0.75 (0.21)	0.73 (0.14)	0.92 (0.27)	0.62 (0.09)	0.77 (0.19)
Unpaired t-test, *p*			**<0.001****	0.777	0.758	0.485	**0.001**
BIF							
Relative % change, 95% CI			18 (10, 26)	1 (−18, 20)	8 (−9, 24)	12 (−14, 25)	26 (11, 42)
Mean BIF-IMT (SD)	P	3	1.19 (0.73)	0.90 (0.38)	1.41 (0.75)	0.79 (0.40)	1.42 (0.96)
	C	1	0.98 (0.46)	0.90 (0.35)	1.30 (0.54)	0.70 (0.17)	1.04 (0.46)
Unpaired t-test, *p*			**<0.001****	0.945	0.345	0.079	**<0.001**
ICA							
Relative % change, 95% CI			25 (14,−35)	9 (−18, 36)	12 (−12, 35)	18 (1, 36)	35 (17, 53)
ICA-IMT (SD)	P	9	1.00 (0.79)	0.81 (0.56)	1.15 (0.85)	0.70 (0.51)	1.17 (0.99)
	C	3	0.75 (0.44)	0.73 (0.26)	1.02 (0.73)	0.57 (0.15)	0.77 (0.37)
Unpaired t-test, *p*			**<0.001****	0.506	0.329	**0.042**	**<0.001**
Femoral arteries, fIMT							
Relative % change, 95% CI			31 (21, 42)	28 (−5, 60)	14 (−6, 34)	15 (−6, 37)	31 (13, 49)
Mean fIMT (SD)	P	7	1.42 (1.08)	1.13 (0.92)	1.82 (1.19)	0.75 (0.51)	1.42 (0.96)
	C	1	0.98 (0.76)	0.82 (0.47)	1.57 (0.99)	0.64 (0.44)	0.97 (0.73)
Unpaired t-test, *p*			**<0.001****	0.095	0.176	0.164	**<0.001**
CFA							
Relative % change, 95% CI			31 (20, 42)	26 (−6, 58)	14 (−6, 34)	15 (7, 37)	31 (13, 49)
Mean CFA-IMT (SD)	P	7	1.41 (1.08)	1.11 (0.90)	1.81 (1.19)	0.75 (0.51)	1.41 (0.96)
	C	1	0.97 (0.77)	0.82 (0.47)	1.56 (0.99)	0.64 (0.44)	0.97 (0.73)
Unpaired t-test, *p*			**<0.001****	0.115	0.170	0.169	**0.001**
SFA							
Relative % change, 95% CI			20 (10, 30)	15 (−11, 41)	17 (−8, 43)	12 (2, 22)	10 (−1, 21)
Mean SFA-IMT (SD)	P	8	0.60 (0.47)	0.56 (0.37)	0.70 (0.62)	0.47 (0.18)	0.54 (0.13)
	C	2	0.48 (0.19)	0.47 (0.13)	0.58 (0.22)	0.42 (0.07)	0.49 (0.22)
Unpaired t-test, *p*			**<0.001****	0.254	0.184	**0.014**	0.072

Abbreviations: NA: not available, missing data; *n*: number of subjects; y: years; cIMT/fIMT/IMT: carotid/femoral intima-media thickness; CI: confidence interval; SD: standard deviation; P: patients; C: controls; CCA: common carotid artery; BIF: carotid bifurcature; ICA: internal carotid artery; CFA: common femoral artery; SFA: superficial femoral artery.

**Paired t-test.

[a]Mean IMT measurements units were millimetres, and were obtained bilaterally from 1 cm segment at four standardised angles for CCA using Meijer's Carotid Arc[©] and at one angle for BIF, ICA, CFA and SFA. Among several measurements at any segmental level, the maximal IMT value was used.

for all variables, we did not find any significant results with occurrence of CVEs. No interactions were found between sex, age and vascular areas. Adjusted for sex and age, mortality was associated with higher age (HR 1.08; $p = 0.036$), ischaemic ECG (HR 3.51; $p = 0.009$) and increased NAA (HR 1.36; $p = 0.047$) among patients, and with cIMT ≥0.9 mm (HR 8.26; $p = 0.013$) among controls (Table 6). Adjusted for all variables, mortality was associated with increased NAA (HR 1.98; $p = 0.047$) among patients, and with cIMT ≥0.9 mm (HR 8.51; $p = 0.014$) among controls.

Discussion

Prevalent atherosclerosis

To our knowledge, this is the first study of young and middle-aged acute IS patients and controls which has described the

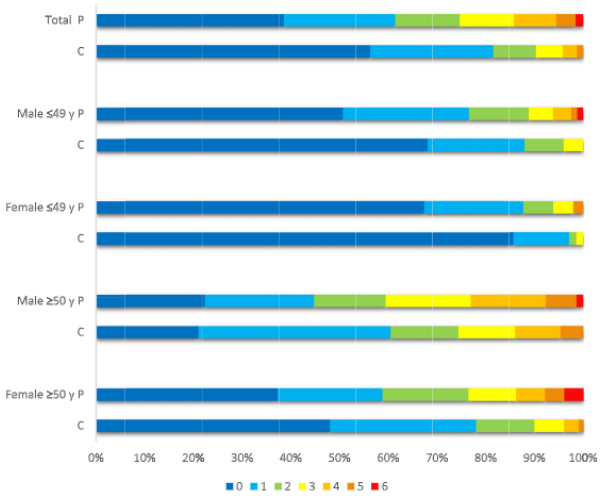

Figure 1. Prevalence of atherosclerosis at different vascular areas[a] among 324 stroke patients and 238 controls. Abbreviations: P: patients; C: controls; y: years. (a) Atherosclerosis was evaluated in seven vascular areas by electrocardiogram, ankle–arm index and by ultrasonography of abdominal aorta and right and left carotid and femoral arteries for intima-media thickness (IMT) measurements. Among several measurements at any segmental level, the maximum IMT value was used.

Table 4. Stroke subtypes according to TOAST classification in young stroke patients related to gender and age group.

		Men		Women			
Stroke subtypes, *n* (%)	All *n* = 385	≤49 years *n* = 94	≥50 years *n* = 170	≤49 years *n* = 58	≥50 years *n*= 63	*p*-value sex	*p*-value age group
LAA	28 (7.3)	2 (2.1)	17 (10.0)	4 (6.9)	5 (7.9)		
CE	100 (26.0)	36 (38.3)	40 (23.3)	17 (29.3)	7 (11.1)		
SAO	73 (19.0)	17 (18.1)	29 (17.1)	6 (10.3)	21 (33.3)	0.385	<0.001
SOC	41 (10.6)	16 (17.0)	10 (5.9)	11 (19.0)	4 (6.3)		
SUC	143 (37.1)	23 (24.5)	74 (43.5)	20 (34.5)	26 (41.3)		

Abbreviations: TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA: large-artery atherosclerosis; CE: cardiac embolism; SAO: small artery occlusion; SOC: stroke of other determined cause; SUC: stroke of undetermined cause; *p*-value: from Chi-square test.

state of the arteries at different vascular areas, regardless of the cause of stroke. The overall result is that atherosclerosis is prevalent even in young patients and controls, and middle-aged males are most affected, confirming established knowledge. Detailed assessment demonstrated atherosclerosis in half of young male patients and one third of young female patients. Young patients had numerically more atherosclerosis than controls had, but there was a statistical difference only between young female patients and controls.

Our findings are in line with other studies showing that clinical CVEs are only 'the tip of the iceberg',[17] and that subclinical and clinical atherosclerosis starts in early life, and increases with age, particularly in males.[2] The Aragon Workers' Health Study assessed 1423 males, aged 40–59 years, for coronary artery calcium score and carotid and femoral plaques, and reported subclinical atherosclerosis in 72% of participants.[18] Hormonal influences are assumed to contribute to the delayed development of atherosclerosis in females.[19]

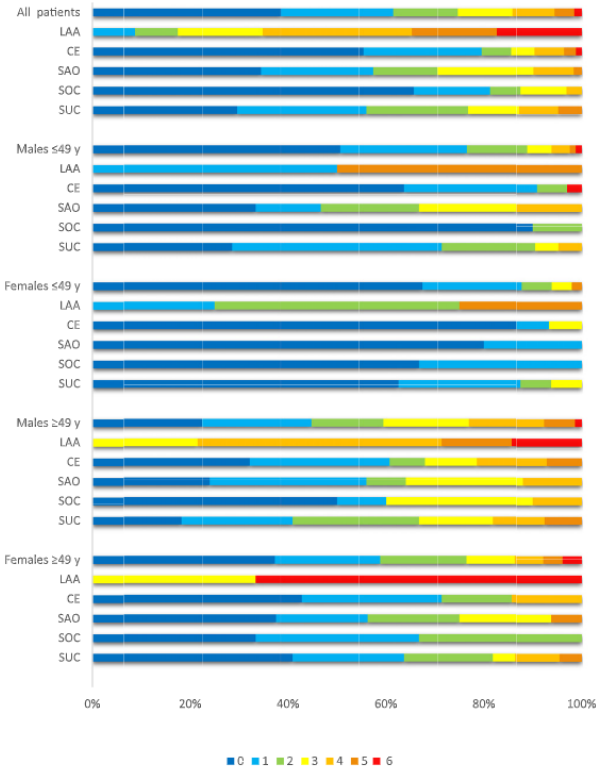

Figure 2. Prevalence of atherosclerosis at different vascular areas[a] among 324 stroke patients related to TOAST classification. Abbreviations: TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA: large-artery atherosclerosis; CE: cardiac embolism; SAO: small artery occlusion; SOC: stroke of other determined cause; SUC: stroke of undetermined cause; y: years. (a) Atherosclerosis was evaluated in seven vascular areas by electrocardiogram, ankle–arm index and by ultrasonography of abdominal aorta and right and left carotid and femoral arteries for intima-media thickness (IMT) measurements. Among several measurements at any segmental level, the maximum IMT value was used.

Surrogate markers for atherosclerosis

Since atherosclerosis is regarded as a risk factor for CVEs and mortality, various non-invasive surrogate markers for atherosclerosis have been identified.[20] We found that all of the investigated vascular areas were associated with CVEs in patients as well as controls. We found that increased fIMT was common vascular area among patients and controls that predicted CVEs. Previous studies have associated fIMT with extent of coronary atherosclerosis[21] and carotid atherosclerosis,[22] and regarded fIMT as a surrogate marker for atherosclerosis.[23] Kocygit et al. followed 215 subjects (mean age 54.85 years) for a median of 24 months and found that femoral plaques were independent predictors for

Table 5. Results from logistic regression of any new cardiovascular event within 5-year follow-up of 323 patients and 219 controls.

Groups / Variables	*n*	Adjusted for sex and age			Adjusted for all variables		
		OR	95% CI	*p*-value	OR	95% CI	*p*-value
Patients						*n* = 273	
Male sex	321	0.93	(0.45, 1.92)	0.851	1.30	(0.55, 3.08)	0.544
Age at inclusion (y)	321	1.03	(0.99, 1.07)	0.125	1.02	(0.97, 1.07)	0.486
Ischaemic ECG	321	3.48	(1.45, 8.33)	**0.005**	2.28	(0.61, 8.44)	0.218
AAI ≤0.9	309	5.15	(1.68, 15.84)	**0.004**	3.29	(0.79, 13.71)	0.103
AAP	288	1.45	(0.70, 3.02)	0.318	0.96	(0.33, 2.80)	0.947
cIMT ≥0.9 mm	321	1.82	(0.80, 4.14)	0.155	0.92	(0.36, 2.39)	0.869
fIMT ≥0.9 mm	317	2.48	(1.16, 5.30)	**0.019**	2.22	(0.79, 6.20)	0.129
NAA[a]	260	1.31	(0.00, 0.32)	**0.025**	1.09	(0.73, 1.63)	0.685
Controls						***n* = 197**	
Male sex	219	0.82	(0.19, 3.49)	0.789	1.80	(0.37, 8.71)	0.465
Age at inclusion (y)	219	1.05	(0.95, 1.16)	0.311	0.95	(0.84, 1.09)	0.473
Ischaemic ECG	210	0.00	—	—	0.00	—	—
AAI ≤0.9	216	3.81	(0.36, 40.05)	0.265	2.07	(0.09, 47.96)	0.650
AAP	208	7.41	(1.32, 41.59)	**0.023**	3.37	(0.39, 29.21)	0.270
cIMT ≥0.9 mm	218	11.17	(0.00, 6.30)	**0.042**	5.53	(0.48, 63.30)	0.169
fIMT ≥0.9 mm	218	9.69	(1.71, 55.03)	**0.010**	4.16	(0.62, 27.97)	0.143
NAA[a]	202	1.81	(1.13, 2.91)	**0.014**	1.05	(0.48, 2.33)	0.898

Abbreviations: n: number of subjects; OR: odds ratio; CI: confidence interval; y: years; ECG: electrocardiogram; AAI: ankle–arm index; AAP: abdominal aorta plaque; cIMT/fIMT: carotid/femoral intima-media thickness.
[a]NAA = number of vascular areas with atherosclerosis, indicating whether there is increasing trend with increasing NAA.

Table 6. Results of Cox regression of mortality risk within 5-year follow-up of 385 patients and 260 controls.

Groups / Variables	*n*	Adjusted for sex and age			Adjusted for all variables		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Patients						*n* = 323	
Male sex	383	1.24	(0.50, 3.09)	0.642	1.51	(0.47, 4.84)	0.487
Age at inclusion (y)	383	1.08	(1.00, 1.15)	**0.036**	1.09	(0.99, 1.19)	0.081
Ischaemic ECG	383	3.51	(1.36, 9.07)	**0.009**	1.52	(0.33, 7.04)	0.596
AAI ≤0.9	360	2.90	(0.64, 13.09)	0.165	0.77	(0.12, 5.13)	0.786
AAP	345	1.08	(0.41, 2.81)	0.880	0.35	(0.06, 1.94)	0.231
cIMT ≥0.9 mm	381	0.59	(0.23, 1.52)	0.271	0.36	(0.08, 1.56)	0.171
fIMT ≥0.9 mm	376	0.85	(0.33, 2.19)	0.734	0.59	(0.11, 3.10)	0.533
NAA[a]	310	1.36	(1.00, 1.84)	**0.047**	1.98	(1.01, 3.86)	**0.047**
Controls						***n* = 219**	
Male sex	239	2.84	(0.61, 13.21)	0.183	3.42	(0.73, 16.02)	0.119
Age at inclusion (y)	239	1.07	(0.98, 1.16)	0.132	1.01	(0.92, 1.12)	0.776
Ischaemic ECG	235	3.36	(0.44, 25.98)	0.245	2.67	(0.23, 31.55)	0.436
AAI ≤0.9	235	0.00	(0,–)	1.000	0.00	—	—
AAP	227	0.98	(0.30, 3.20)	0.972	0.76	(0.12, 4.88)	0.776
cIMT ≥0.9 mm	238	8.26	(1.57, 43.41)	**0.013**	8.51	(1.55, 46.72)	**0.014**
fIMT ≥0.9 mm	238	1.09	(0.32, 3.74)	0.886	0.60	(0.13, 2.74)	0.507
NAA[a]	219	1.14	(0.71, 1.83)	0.578	1.13	(0.48, 2.69)	0.776

Abbreviations: n: number of subjects; HR: hazards ratio; CI: confidence interval; y: years; ECG: electrocardiogram; AAI: ankle–arm index; AAP: abdominal aorta plaque; cIMT/fIMT: carotid/femoral intima-media thickness.
[a]NAA: number of vascular areas with atherosclerosis, indicating whether there is increasing trend with increasing NAA.

CVEs.[24] Giannoukas et al. reported that fIMT separately or in combination with cIMT was related to cardiovascular disease.[25]

CIMT and AAI are well-established surrogate markers for subclinical atherosclerosis and strong predictors of future CVEs and mortality.[20,26,27] In the ARIC (Atherosclerosis risk in communities) study, cIMT predicted CVEs or death in participants recruited from four communities in the United States.[27] A meta-analysis has shown that increased cIMT by 0.10 mm is associated with an increased risk of 18% for stroke and 15% for myocardial infarction.[26] Our study confirms that cIMT predicts increased risk of CVEs and mortality among controls and that AAI is strongly related to CVE among patients.

Another important finding in our study is that ischaemic ECG predicts CVEs and mortality among patients, regardless of age and sex. Also, Bacquer et al. reported that major abnormalities in ECG are strongly associated with CVE and mortality in both sexes.[28] Furthermore, ECG findings revealing silent ischaemia has been a powerful and independent predictor for cardiac mortality in another study.[29]

Regarding AAP, we found a positive association with CVEs among controls. Li et al. reported higher prevalence of AAP in patients with coronary artery disease (CAD), compared to those without CAD.[30] In the Rotterdam study, AAP, measured by X-ray in 6389 subjects, was associated with MI.[31]

Stroke classification by TOAST

The TOAST classification is most widely used by date, but there is the problem of the big group of up to 33–40% of young stroke patients with SUC,[6,32] and this is in line with our results.

Strengths and limitations

The major strength of NOR-SYS is the population-based design with inclusion of consecutive acute IS patients and comprehensive vascular work-up based on a standardised protocol. The number of unobtainable IMT measurements was low. We used mean IMT measurements, which provide information on cardiovascular risk even in absence of plaques.[33] PCI of the FA is associated with haematoma, intimal dissection or arterial occlusion.[34] However, in our study, only few patients with increased fIMT on the right side had undergone PCI.

An important study limitation was inequality of sex group sizes, with a high number of male patients and relatively low number of male controls. Our controls were partners of included patients, selected as such to improve the three-generation design of NOR-SYS, and also including joint offspring. We expected higher risk factor matching between patients and partners compared with controls selected by random.[35] We chose not to include intracranial arterial pathology analysis due to uncertainties in defining the cause and degree of stenosis by common imaging methods.[36] Another limitation was the low number of outcome events, especially numbers of deaths.

Conclusion

Atherosclerosis is highly prevalent in our study population, being found in half of the young male patients and one third of the young female patients ≤49 years. Comprehensive investigation reveals a far higher prevalence of atherosclerosis than found by TOAST criteria.

In oncology, staging of tumours has for decades been the first step to tailor individual treatment. Staging arteries of young stroke patients should be performed, accordingly. This would contribute to potential early individual-tailored secondary prophylaxis, and selection of patients to targeted and reasonable treatment, and future more targeted genetic diagnostics in order to search for why we do find serious early arterial disease (LAA) in some patients, while other patients are protected from development of atherosclerosis despite of a high number of risk factors. Ultrasound images of good quality were used in this study as teaching tool to explain interested patients the findings and importance of life-style changes, and to take and continue medication that we evaluate necessary for secondary prevention. Randomised future studies could show if this could contribute significantly to reach important treatment goals.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

Ethical approval for this study was obtained from the Regional Committee for Medical and Health Research Ethics, western Norway (REK-VEST 2010/74).

Informed consent

Written informed consent was obtained from all subjects before the study.

Trial registration

The study was registered in ClinicalTrials.gov NCT01597453

Guarantor

UWA

Contributorship

UWA conceived the study, and gained the ethical approval. Protocol development was done by UWA, and RM and MB were also involved in the ultrasound protocol. Data collection was done by BN, AF, HØ, KMS and UWA. Data interpretation of electrocardiograms were done by SS. TOAST classification of stroke was done by HN. BN did literature search and wrote the first draft of the manuscript. Statistical analysis was done by BN and GEE. All authors reviewed and edited the manuscript, and approved the final version.

ORCID iD

Beenish Nawaz https://orcid.org/0000-0002-4055-9744

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Vascular risk factors and staging of atherosclerosis in patients and controls: The Norwegian Stroke in the Young Study

Beenish Nawaz[1,2], Annette Fromm[2], Halvor Øygarden[3,4], Geir Egil Eide[5,6], Sahrai Saeed[7], Rudy Meijer[8], Michiel L Bots[8], Kristin Modalsli Sand[9,10], Lars Thomassen[2], Halvor Næss[1,2] and Ulrike Waje-Andreassen[2]

Abstract

Objectives: We studied the prevalence of vascular risk factors (RFs) among 385 ischaemic stroke patients ≤60 years and 260 controls, and their association with atherosclerosis in seven vascular areas.

Methods: History of cardiovascular events (CVE), hypertension, diabetes mellitus (DM), dyslipidaemia, pack-years of smoking (PYS), alcohol, and physical inactivity were noted. Blood pressure, body mass index (BMI), waist-hip ratio (WHR), lipid profile, epicardial adipose tissue (EAT), visceral abdominal adipose tissue (VAT), and subcutaneous abdominal adipose tissue were measured. Numeric staging of atherosclerosis was done by standardized examination of seven vascular areas by right and left carotid and femoral intima-media thickness, electrocardiogram, abdominal aorta plaques, and the ankle-arm index. All results were age and sex-adjusted. Poisson regression analysis was applied.

Results: At age ≤49 years at least one RF was present in 95.6% patients versus 90.0% controls. Compared to controls, male patients and middle-aged female patients showed no significant differences. Young female patients compared to young female controls had a higher burden of RFs (94.3% vs 88.6%, $p = 0.049$). Poisson regression analysis combined for patients and controls, adjusted for age and sex, showed numeric staging of atherosclerosis associated with age, prior CVE, hypertension, DM, dyslipidaemia, PYS, alcohol, BMI, WHR, EAT, VAT, and an increased number of risk factors. Adjusted for all risk factors, numeric staging of atherosclerosis was associated with increasing age, hypertension, DM, PYS, and BMI.

Conclusion: Vascular risk factors are highly prevalent in young- and middle-aged patients and controls, and are predictors of established atherosclerosis at study inclusion. Focus on main modifiable vascular RFs in primary prevention, and early and aggressive secondary treatment of patients are necessary to reduce further progression of atherosclerosis.

Keywords

Young ischaemic stroke, vascular risk factors, fat measurements, EAT, VAT, SAT, staging of atherosclerosis

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[1]Department of Clinical Medicine 1, University of Bergen, Bergen, Norway
[2]Department of Neurology, Haukeland University Hospital, Bergen, Norway
[3]Department of Neurology, Sørlandet Hospital, Kristiansand, Norway
[4]Department of Health and Nursing Sciences, University of Agder, Kristiansand, Norway
[5]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway
[6]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[7]Department of Cardiology, Haukeland University Hospital, Bergen, Norway
[8]Julius Center of Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[9]Department of Medicine, Sørlandet Hospital, Flekkefjord, Norway
[10]The Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway

Corresponding author:
Beenish Nawaz, Centre of Neurovascular Diseases, Department of Neurology, Haukeland University Hospital, Jonas Lies vei 65, Bergen 5021, Norway.
Email: beenish.nawaz@helse-bergen.no

Introduction

According to TOAST,[1] the internationally widely applied classification of causes of stroke, we found large artery atherosclerosis due to 50% arterial stenosis prevalent among our patients in 7.3%, and cryptogenic stroke prevalent in 37.1%.[2] We found total prevalent atherosclerosis among 61.4% of our stroke patients, and even our patients ≤49 years with cryptogenic stroke had total prevalent atherosclerosis among 71.4% males and 37.5% females.[2] Young stroke patients are at substantial risk for new cardiovascular events (CVE) and death, particularly due to atherosclerosis leading to coronary artery disease (CAD), mostly attributable to modifiable risk factors (RFs).[3,4] The number of RFs is associated with increased risk for CVE and mortality,[5] and the RF burden is high throughout Europe.[6]

Carotid and coronary arteries, the abdominal aorta, and femoral arteries are particularly susceptible areas for atherosclerosis. Many previous studies have related localized atherosclerosis at one single vascular area to vascular RFs,[7–10] and to CVE and mortality.[9,11,12] However, young stroke studies on atherosclerosis at multiple vascular areas are scarce. A previous study of 212 patients without known cardiovascular disease (CVD) showed high presence of subclinical atherosclerosis in carotid, femoral and coronary areas, but a weak concordance between the different vascular territories, and suggested that all three vascular areas should be investigated.[13] Post-mortem studies of subjects indicated that atherosclerosis developed simultaneously in cerebrovascular, coronary and peripheral arteries, and a weak positive correlation was found between femoral and coronary atherosclerosis,[14,15] whereas clinical studies of patients showed a strong positive correlation between femoral atherosclerosis and the severity of CAD.[16,17] Numerous studies also reported a modest relation between carotid intima-media thickness and CAD, which probably reflects variability in the atherosclerotic process between different vascular areas.[18]

Analog to oncological staging of tumors, we performed numerical staging of atherosclerosis, and related the findings to vascular risk factors among patients with ischaemic stroke and their partners as controls as part of a three-generation research program. Due to the fact that CVD dominates causes of hospital admission and mortality in Norway,[19,20] as in other industrialized countries,[21,22] inclusion of controls was wanted as previous studies have shown that atherosclerosis starts early in life, and has a high prevalence at a subclinical level.[23–25] Based on our previous findings of prevalence of atherosclerosis, showing only a significant difference for young female patients compared to young female controls,[2] our hypothesis was that a high number of risk factors are prevalent in both groups, but even more among patients, and we aimed to identify the predictors of severity of atherosclerosis.

Methods

Study population

NOR-SYS 3-generation design and ultrasound protocol, methods and results of inclusion have been published.[26,27] In total, 152 young (≤49 years) and 233 middle-aged (50–60 years) acute ischaemic stroke patients and 260 partners/ex-partners, serving as controls, were included from 2010 to 2015. Supplemental Figure 1 shows a chart with inclusion and exclusion criteria and methods used for patients and controls.

Consents and ethics

The study complies with the Declaration of Helsinki, is approved by the Regional Ethics Committee (REK-Vest 2010/74), and registered in ClinicalTrials.gov (NCT01597453). Written consent is present for all study participants.

Risk factor definitions

Vascular RFs included prior CVE, hypertension, diabetes mellitus (DM), dyslipidaemia, pack-years of smoking (PYS), alcohol, physical inactivity, body mass index (BMI), waist-hip ratio (WHR), epicardial adipose tissue (EAT), visceral abdominal adipose tissue (VAT), and subcutaneous abdominal adipose tissue (SAT).

Prior CVEs including stroke, CAD, and peripheral artery disease (PAD) were verified in hospital records. CAD included cases of myocardial infarction and/or verified CAD by percutaneous coronary intervention (PCI). Angina pectoris or non-obstructive CAD were not included. Uncertain information about previous stroke was substantiated by information from cerebral magnetic resonance imaging. Hypertension, DM, and dyslipidaemia were defined as known when treated by lifestyle changes and/or by medication before admission, or when diagnosed during hospitalization. Hypertension was diagnosed if blood pressure was >140/90 mmHg in two separate measurements in both arms after 15–30 min rest in a supine position following the ultrasound examination. In patients only, DM and dyslipidaemia were diagnosed by blood tests as HbA1c >6.4%, total cholesterol >5.0 mmol/L, low-density lipoprotein >3.0 mmol/L, high density lipoprotein <1.0 mmol/L, and/or triglycerides >2.5 mmol/L. In controls, an unknown history of dyslipidaemia was categorized as normal. Smoking was categorized as never-smoking, ex-smoking when stopped at least 1 year ago, and current smoking, and pack-years of smoking (PYS) were calculated as number of cigarette packs (20 cig/pack) per day multiplied by number of years smoking. Alcohol consumption was categorized as increased if ≥12 units/week. Physical inactivity was defined as activity of light, moderate or vigorous intensity of less than 60 min/week. BMI was categorized as increased if ≥25 kg/m^2. Increased WHR was defined for females

(≥0.85) and males (≥0.90).[28] Our methods for ultrasonographic measurements of EAT, VAT, and SAT have been published.[26] EAT thickness with a cut-off value of 0.5 cm was used to identify individuals at higher cardiovascular risk.[29] Cut-off values for ultrasonographic abdominal fat measurements are not yet established. Thus, we based our sex-specific high VAT and SAT definitions on 90th percentile cut-points from normal weight referent sample, as a similar method was used in the Framingham heart study.[30] The referent sample in our study consisted of 133 men and 99 women with normal BMI, and our cut-offs of VAT and SAT were 9.6 and 3.5 cm in men and 8.3 and 4.2 cm in women, respectively. The total risk factor burden (RFB) was assessed as number of RFs present (0–12).

Staging of atherosclerosis

Staging of atherosclerosis among patients and controls, was defined by the number of affected vascular areas from 0 to 7, based on right and left mean carotid and femoral intima-media thickness ≥1.5 mm respectively, ischemic electrocardiogram (ECG), presence of abdominal aorta plaques and ankle-arm index ≤0.9. For carotid intima-media measurements (IMT), we used the maximum value of a total of 12 standardized artery segments at the far wall; 4 of the distal common carotid artery, 1 of the carotid bifurcation, and 1 of the proximal internal carotid artery, measured on the right and the left side. Plaques were included, and defined as focal IMT ≥1.5 mm. For femoral IMT measurements, we used the maximum value of a total of four standardized artery segments at the far wall of the common femoral artery and the superficial femoral artery on the right and the left side. Any artery segment was measured over a distance of 1 cm, resulting in a mean value of about 100 possible point-to point measurements, calculated by Philips Q-Lab software® (Advanced Ultrasound Quantification, Philips Ultrasound, Bothell, WA, USA). Detailed procedures of our ultrasound protocol have been published.[26] We chose not to include intracranial arterial pathology analysis due to uncertainties in defining the cause and degree of stenosis by common imaging methods.[31]

Statistics

The mean and standard deviation (SD) were used for descriptive statistics, all adjusted by age and sex. Univariate comparisons of RFs between patients and controls were done within the four age and sex strata using unpaired *t*-test and the Fisher's exact test. For unadjusted comparison of all patients to their individual partners/ex-partners, McNemar's test of symmetry was used. In the Poisson regression analysis, we related possible risk factors to the results of numeric staging of atherosclerosis for patients and controls separately as our controls consisted of patients' partners and ex-partners (Table 2). However, as predictors of severity of atherosclerosis, we combined both groups in Table 3. To adjust for confounding, Poisson regression analysis was done with respect to age, sex, and all RFs. Interactions were tested for association of risk factors on atherosclerosis between patients and controls. Results were reported as incidence rate ratios (IRR) with 95% confidence intervals (CI). Two-sided *p*-values ≤0.05 were considered significant. All statistical analyses were performed in Stata SE 17.0.

Results

Study population

At inclusion, patients had a mean age of 49.5 (range 15–60) years and controls had a mean age of 50.3 (range 21–69) years (Table 1). The majority of patients were males (68.6%), and the majority of controls were females (70.0%). Young age ≤49 years was present for 39.5% of patients and 39.2% of controls.

Reported risk factors, clinical, and ultrasonographic findings among young study participants ≤49 years

Compared to controls, young male patients had higher prevalence of hypertension (48.9% vs 17.9%; $p=0.004$), and young female patients had higher prevalence of prior CVE (8.6% vs 0.0%; $p=0.015$) (Table 1).

Obesity (BMI ≥25.0 kg/m^2 64.7%, increased WHR 58.9%, increased EAT 51.3%), dyslipidaemia (63.2%), smoking (60.5%), and hypertension (42.8%) were the most frequent vascular RFs among young stroke patients (Supplemental Table 1). Regarding sex differences, young male patients had more prevalent hypertension (48.9% vs 32.8%, $p=0.050$), and higher alcohol intake (12.9% vs 1.8%, $p=0.018$) than young female patients. Prevalence of all RFs was increased among middle-aged patients, except from alcohol intake, physical inactivity, BMI, and SAT (Supplemental Table 1).

The most common RFs among couples were smoking and physical inactivity (Supplemental Table 2).

Missing data

WHR was not obtained for 26 stroke patients, mainly due to their disability. Among them, 18 patients had increased BMI. Ultrasonographic measurements were not obtained for two patients due to unconsciousness at admission, and morbid obesity causing insufficient imaging quality, respectively. Some EAT, VAT, and SAT had missing segments due to bad imaging quality. Due to missing information of some risk factors and vascular areas, the RFB was assessed in 346 patients and 250 controls, and atherosclerotic staging was performed in 324 patients and 238 controls. The Poisson regression analysis was possible to perform for 307 (94.8%) of 324 patients, and 232 (97.5%) of 238 controls.

Table 1. Baseline characteristics of 385 acute ischemic stroke patients and 260 controls.

Variables		NA, *n*	All	Male ⩽49 years	Male ⩾50 years	Female ⩽49 years	Female ⩾50 years
Categories							
Patients, *n* (%)	P	0	385 (100.0)	94 (24.4)	170 (44.2)	58 (15.1)	63 (16.4)
Controls, *n* (%)	C	0	260 (100.0)	28 (10.8)	50 (19.2)	74 (28.5)	108 (41.5)
Age (years), mean (SD)	P	0	49.5 (9.8)	40.5 (8.2)	55.9 (3.0)	38.4 (8.9)	55.8 (2.9)
	C	0	50.3 (8.6)	42.0 (6.7)	57.5 (4.9)	41.7 (6.6)	55.0 (3.2)
Unpaired *T*-test, *p*[a]			**0.001***	0.312	**0.028**	**0.019**	0.102
Prior CVE, *n* (%)	P	0	49 (12.7)	8 (8.5)	27 (15.9)	5 (8.6)	9 (14.3)
	C	0	18 (6.9)	3 (10.7)	8 (16.0)	0 (0.0)	7 (6.5)
Fisher's exact test, *p*			0.121**	0.715	1.000	**0.015**	0.107
Prior stroke[b], *n* (%)	P	0	27 (7.0)	7 (7.4)	10 (5.9)	2 (3.4)	8 (12.7)
	C	0	8 (3.1)	0 (0.0)	6 (12.0)	0 (0.0)	2 (1.9)
Fisher's exact test, *p*			0.263**	0.199	0.210	0.191	**0.006**
Prior CHD, *n* (%)	P	0	25 (6.5)	3 (3.2)	16 (9.4)	3 (5.2)	3 (4.8)
	C	0	8 (3.1)	3 (10.7)	2 (4.0)	0 (0.0)	3 (2.8)
Fisher's exact, *p*			0.119**	0.136	0.377	0.082	0.671
Prior PAD, *n* (%)	P	0	4 (1.0)	0 (0.0)	4 (2.4)	0 (0.0)	0 (0.0)
	C	0	4 (1.5)	0 (0.0)	1 (2.0)	0 (0.0)	3 (2.8)
Fisher's exact, *p*			1.000**	–	1.000	–	0.298
Hypertension[c], *n* (%)	P	0	238 (61.8)	46 (48.9)	125 (73.5)	19 (32.8)	48 (76.2)
	C	1	89 (34.4)	5 (17.9)	31 (62.0)	13 (17.6)	40 (37.4)
Fisher's exact, *p*			<**0.001****	**0.004**	0.156	0.065	<**0.001**
Diabetes mellitus[d], *n* (%)	P	0	44 (11.4)	6 (6.4)	28 (16.5)	5 (8.6)	5 (7.9)
	C	0	15 (5.8)	1 (3.6)	6 (12.0)	2 (2.7)	6 (5.6)
Fisher's exact, *p*			0.071**	1.000	0.512	0.239	0.536
Dyslipidaemia[e], *n* (%)	P	0	293 (76.1)	61 (64.9)	145 (85.3)	35 (60.3)	52 (82.5)
	C	0	34 (13.1)	3 (10.7)	11 (22.0)	3 (4.1)	17 (15.7)
Fisher's exact, *p*			<0.001**	<0.001	<0.001	<0.001	<0.001
Smoking[f], *n* (%)	P	0	268 (69.6)	59 (62.8)	130 (76.5)	33 (56.9)	46 (73.0)
	C	1	169 (65.3)	17 (60.7)	37 (74.0)	41 (56.2)	74 (68.5)
Fisher's exact, *p*			0.313**	1.000	0.710	1.000	0.605
Alcohol[g], *n* (%)	P	4	38 (10.0)	12 (12.9)	22 (13.1)	1 (1.8)	3 (4.8)
	C	2	8 (3.1)	2 (7.1)	3 (6.0)	1 (1.4)	2 (1.9)
Fisher's exact, *p*			0.007**	0.516	0.211	1.000	0.359
Physical inactivity[h], *n* (%)	P	0	71 (18.4)	21 (22.3)	33 (19.4)	7 (12.1)	10 (15.9)
	C	0	28 (10.8)	4 (14.3)	8 (16.0)	10 (13.5)	6 (5.6)
Fisher's exact, *p*			0.134	0.432	0.683	1.000	**0.031**
BMI ⩾25 kg/m^2, *n* (%)	P	3	254 (66.5)	66 (70.2)	123 (72.8)	31 (55.4)	34 (54.0)
	C	4	152 (59.4)	20 (74.1)	32 (64.0)	45 (61.6)	55 (51.9)
Fisher's exact, *p*			**0.028****	0.811	0.288	0.477	0.874
Increased WHR[i], *n* (%)	P	26	254 (70.8)	56 (64.4)	131 (82.9)	27 (50.0)	40 (66.7)
	C	5	130 (51.0)	13 (48.1)	40 (81.6)	28 (38.9)	49 (45.8)
Fisher's exact, *p*			<**0.001****	0.176	0.831	0.276	**0.010**
EAT mean in cm (SD)	P	13	0.63 (0.23)	0.58 (0.20)	0.67 (0.24)	0.54 (0.16)	0.68 (0.28)
	C	1	0.59 (0.20)	0.54 (0.24)	0.59 (0.17)	0.54 (0.22)	0.65 (0.19)
Unpaired *T*-test, p			**0.004***	0.367	**0.022**	0.956	0.329
VAT mean in cm (SD)	P	9	9.40 (2.49)	9.44 (2.17)	10.3 (2.39)	7.6 (2.20)	8.66 (2.38)
	C	1	8.02 (2.43)	8.64 (2.59)	9.78 (2.42)	7.18 (2.35)	7.62 (2.00)
Unpaired *T*-test, *p*			<**0.001***	0.118	0.217	0.297	**0.003**
SAT mean in cm (SD)	P	9	3.25 (1.33)	3.15 (1.35)	2.95 (1.10)	3.71 (1.63)	3.81 (1.27)
	C	1	3.40 (1.24)	3.25 (1.18)	2.92 (1.15)	3.59 (1.35)	3.54 (1.17)
Unpaired *T*-test, *p*			0.120*	0.704	0.888	0.650	0.165

NA: not available; *n*: number of observations; P: patients; C: controls; SD: standard deviation; CVE: cardiovascular events; CHD: coronary heart disease; PAD: peripheral artery disease; BMI: body mass index; WHR: waist-hip ratio; EAT: epicardial adipose tissue; cm: centimetre; VAT/SAT: visceral/subcutaneous abdominal adipose tissue.

[a]p-Values are comparisons between patients and controls, and significant p-values are given in bold.

[b]Two patients and one control had haemorrhagic stroke.

[c]Hypertension was defined as known, or diagnosed if blood pressure >140/90 mmHg.

[d]Diabetes mellitus was defined as known among patients and controls, or diagnosed by HbA1c >6.5% among patients only.

[e]Dyslipidaemia was defined as known among patients and controls, or diagnosed by blood tests among patients only.

[f]Smoking included ex-smokers and active smokers.

[g]Alcohol intake is defined as ⩾12 units/week.

[h]Physical inactivity is defined as activity less than 60 min/week.

[i]Increased WHR is defined as ⩾0.85 in females and ⩾0.90 in male.

Table 2. Poisson regression of possible associated risk factors with the number of areas[a] with atherosclerosis among 324 patients and 238 controls.

Group	*n*	Adjusted for age and sex			Adjusted for all variables		
Variables		IRR	95% CI	*p*-Value	IRR	95% CI	*p*-Value
Patients						*n* = 307	
Age per 10 years	324	1.93	(1.68, 2.22)	<**0.001**	1.60	(1.36, 1.89)	<**0.001**
Sex (male)	324	1.36	(1.10, 1.69)	**0.005**	1.24	(0.95, 1.61)	0.118
Prior CVE[b]	324	1.63	(1.30, 2.06)	<**0.001**	1.23	(0.91, 1.67)	0.181
Hypertension	324	1.67	(1.34, 2.09)	<**0.001**	1.30	(0.98, 1.73)	0.071[‡]
Diabetes mellitus	324	1.50	(1.15, 1.94)	**0.002**	1.44	(1.03, 2.02)	**0.034**
Dyslipidaemia	324	1.40	(1.08, 1.81)	**0.012**	1.19	(0.87, 1.61)	0.274
Pack-years of smoking[c]	324	1.02	(1.02, 1.03)	<**0.001**	1.02	(1.02, 1.03)	<**0.001**
Increased alcohol intake[d]	321	1.49	(1.15, 1.92)	**0.002**	1.17	(0.85, 1.60)	0.329
Physical inactivity[e]	324	1.46	(1.18, 1.81)	<**0.001**	1.17	(0.87, 1.59)	0.299
BMI ⩾25 kg/m^2	324	1.39	(1.13, 1.72)	**0.002**	1.14	(0.82, 1.60)	0.438
Increased WHR[f]	312	1.24	(0.98, 1.57)	0.070	0.74	(0.52, 1.06)	0.104
EAT (cm)	322	2.22	(1.55, 3.16)	<**0.001**	1.41	(0.94, 2.11)	0.101[‡]
VAT (cm)	324	1.06	(1.02, 1.11)	**0.004**	1.01	(0.95, 1.07)	0.697
SAT (cm)	324	1.03	(0.95, 1.18)	0.463	1.04	(0.94, 1.15)	0.451
Number of risk factors	307	1.17	(1.12, 1.22)	<**0.001**	1.04	(0.89, 1.21)	0.624
Controls						*n* = 232	
Age at inclusion (years)	238	2.22	(1.79, 2.76)	<**0.001**	1.36	(1.03, 2.29)	<**0.001**
Sex (male)	238	1.59	(1.17, 2.15)	**0.003**	1.43	(0.99, 2.04)	0.054
Prior CVE[b]	238	1.86	(1.26, 2.74)	**0.002**	1.49	(0.83, 2.64)	0.177
Hypertension	238	1.33	(0.98, 1.81)	0.067	1.17	(0.75, 1.83)	0.491
Diabetes mellitus	238	1.21	(0.65, 1.94)	0.680	1.02	(0.50, 2.09)	0.953
Dyslipidaemia	238	1.13	(0.78, 1.64)	0.510	0.88	(0.52, 1.50)	0.641
Pack-years of smoking[c]	238	1.03	(1.02, 1.04)	<**0.001**	1.04	(1.02, 1.05)	<**0.001**
Increased alcohol intake[d]	237	1.00	(0.52, 1.92)	0.997	0.20	(0.07, 0.53)	**0.001**
Physical inactivity[e]	238	1.61	(1.10, 2.36)	**0.013**	1.00	(0.58, 1.73)	0.997
BMI ⩾25 kg/m^2	237	1.52	(1.12, 2.07)	**0.008**	0.92	(0.54, 1.56)	0.751
Increased WHR[f]	235	1.60	(1.16, 2.21)	**0.004**	1.21	(0.75, 1.94)	0.430
EAT (cm)	237	2.42	(1.20, 4.90)	**0.014**	1.44	(0.54, 3.87)	0.465
VAT (cm)	238	1.07	(1.01, 1.14)	**0.024**	0.94	(0.84, 1.04)	0.218
SAT (cm)	238	1.12	(0.98, 1.27)	0.087	1.06	(0.88, 1.28)	0.517
Number of risk factors	232	1.14	(1.07, 1.21)	<**0.001**	1.10	(0.80, 1.41)	0.675

n: number of observations; IRR: incidence rate ratio; CI: confidence interval; CVE: cardiovascular events; BMI: body mass index; WHR: waist-hip ratio; EAT: epicardial adipose tissue; cm: centimetre; VAT/SAT: visceral/subcutaneous abdominal adipose tissue.
Significant *p*-values are given in bold. The final regression analysis with adjustment of all variables was also performed after removal of the variable "number of risk factors" among 307 patients and 232 controls. This was performed as the actual final regression analysis included the risk factors twice – firstly as individual risk factors and secondly in the variable "number of risk factors."
[‡]Risk factor which then became significant.
[a]Seven vascular areas were assessed for atherosclerosis by electrocardiogram, ankle-arm index, right and left carotid and femoral intima-media thickness and abdominal aorta plaques.
[b]CVE included stroke, coronary artery disease or peripheral artery disease.
[c]Pack-years of smoking was calculated as number of cigarette packs (20 cig/pack) per day multiplied by number of years smoking.
[d]Increased alcohol intake is defined as >12 units/week.
[e]Physical inactivity was defined as activity less than 60 min/week.
[f]Increased WHR is defined as ⩾0.85 in females and ⩾0.90 in males.

Total risk factor burden

The RFB was higher in young female patients compared to young female controls (94.3% vs 88.6%, $p=0.049$). Among subgroup analysis of middle-aged females, young males, and middle-aged males, there were no significant differences between patients and controls (100.0% vs 97.2%, $p=0.689$; 96.4% vs 92.3%, $p=0.590$; and 100.0% vs 97.9%, $p=0.240$, respectively), as presented in Figure 1. The RFB was higher in middle-aged male patients than in young male patients (100.0% vs 96.4%, $p<0.001$) and in middle-aged female patients than in young female patients (100.0% vs 94.3%, $p=0.016$). There were no sex

Table 3. Poisson regression of possible associated risk factors with the number of areas[a] with atherosclerosis among 562 study participants (324 patients and 238 controls).

Group	*n*	Adjusted for age, sex, and group			Adjusted for all variables		
Variables		IRR	95% CI	*p*-Value	IRR	95% CI	*p*-Value
Patients and controls						*n* = 423	
Group (patient vs control)	503	0.88	(0.74, 1.05)	0.151	1.09	(0.85, 1.38)	0.502
Age per 10 years	503	1.82	(1.63, 2.03)	<**0.001***	1.50	(1.31, 1.72)	<**0.001***
Sex (male)	503	0.92	(0.78, 1.09)	0.329*	0.81	(0.66, 1.01)	0.057[f]*
Prior CVE[b]	503	1.54	(1.25, 1.91)	<**0.001***	1.14	(0.86, 1.51)	0.352*
Hypertension	502	1.41	(1.19, 1.67)	<**0.001***	1.34	(1.04, 1.71)	**0.022***
Diabetes mellitus	503	1.53	(1.22, 1.93)	<**0.001**	1.51	(1.12, 2.03)	**0.007**
Dyslipidaemia	503	1.36	(1.10, 1.67)	**0.004**	1.07	(0.83, 1.38)	0.595
Pack-years of smoking[c]	502	1.02	(1.02, 1.02)	<**0.001***	1.02	(1.02, 1.03)	<**0.001***
Increased alcohol intake[d]	498	1.35	(1.74, 1.92)	**0.022***	1.11	(0.82, 1.50)	0.515*
Physical inactivity[e]	503	1.22	(1.00, 1.49)	0.053*	0.99	(0.75, 1.31)	0.947*
BMI ⩾25 kg/m^2	501	1.57	(1.32, 1.86)	<**0.001**	1.49	(1.12, 1.98)	**0.006**
Increased WHR[f]	491	1.41	(1.18, 1.69)	<**0.001**	0.97	(0.73, 1.30)	0.854
EAT (cm)	500	1.70	(1.23, 2.35)	**0.001***	1.17	(0.78, 1.75)	0.453*
VAT (cm)	503	1.06	(1.03, 1.10)	**0.001***	0.97	(0.92, 1.03)	0.345*
SAT (cm)	503	1.05	(0.99, 1.12)	0.115	1.02	(0.94, 1.12)	0.591*
Number of risk factors	423	1.16	(1.12, 1.21)	<**0.001***	1.03	(0.90, 1.38)	0.700*

n: number of observations; IRR: incidence rate ratio; CI: confidence interval; CVE: cardiovascular events; BMI: body mass index; WHR: waist hip ratio; EAT: epicardial adipose tissue; cm: centimetre; VAT/SAT: visceral/subcutaneous abdominal adipose tissue.
Significant *p*-values are given in bold. The final regression analysis with adjustment of all variables was also performed after removal of the variable "number of risk factors" 481 study participants. This was performed as the actual final regression analysis included the risk factors twice – firstly as individual risk factors and secondly in the variable "number of risk factors."
[f]Risk factor which then became significant.
*Interactions were tested for association of risk factors to atherosclerosis among patients and controls.
[a]Seven vascular areas were assessed for atherosclerosis by electrocardiogram, ankle-arm index, right and left carotid and femoral intima-media thickness and abdominal aorta plaques.
[b]CVE included stroke, coronary artery disease or peripheral artery disease.
[c]Pack-years of smoking were calculated as number of cigarette packs (20 cig/pack) per day multiplied by number of years smoking.
[d]Increased alcohol intake was defined as >12 units/week.
[e]Physical inactivity was defined as activity less than 60 min/week.
[f]Increased WHR was defined as ⩾0.85 in females and ⩾0.90 in males.

differences in the RFB among stroke patients (males 98.7% vs females 97.3% $p = 0.267$).

Risk of atherosclerosis

Poisson regression analysis, separate for patients and controls, adjusted for age and sex in Table 2 showed that age, sex, prior CVE, hypertension, DM, dyslipidaemia, PYS, alcohol, physical inactivity, BMI, EAT, VAT, and an increased number of RFs were associated with numeric staging of atherosclerosis among patients, and age, sex, prior CVE, PYS, physical inactivity, BMI, WHR, EAT, VAT, and an increased number of RFs were associated with numeric staging of atherosclerosis among controls. Adjusted for all risk factors, numeric staging of atherosclerosis was associated with age, DM, and PYS among patients and age, PYS, and alcohol among controls.

The Poisson regression analysis combined for patients and controls, adjusted for age, sex, and group (patients vs controls) in Table 3, showed that age, prior CVE, hypertension, DM, dyslipidaemia, PYS, alcohol, BMI, WHR, EAT, VAT, and an increased number of RFs were associated with numeric staging of atherosclerosis. After adjustment for all risk factors, age, hypertension, DM, PYS, and BMI were associated with numeric staging of atherosclerosis.

The association of several risk factors with staging of atherosclerosis differed between patients and controls when interactions were applied (Table 3).

Discussion

To our knowledge, our study of young and middle-aged ischaemic stroke patients and controls is the first one to identify predictors of numeric staging of atherosclerosis by detailed ultrasound diagnostics of carotid- and femoral arteries, the abdominal aorta and leg arteries, and by evaluation of ischaemic ECG signs. Previous studies have only assessed the impact of vascular risk factors restricted to one or two vascular areas, most commonly to carotid IMT, or to carotid and femoral IMT.[7,8,10,25]

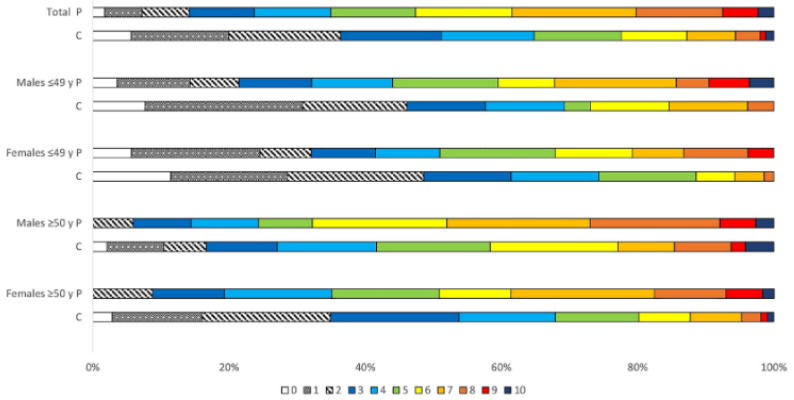

Figure 1. Total burden of risk factors[a] among 346 patients and 250 controls.
[a]Risk factors included prior cardiovascular events, hypertension, diabetes mellitus, dyslipidaemia, smoking, alcohol intake, physical inactivity, body mass index, waist-hip ratio, epicardial adipose tissue, visceral abdominal adipose tissue, and subcutaneous abdominal adipose tissue. P: patients; C: controls; y: years.

We found that obesity, smoking, dyslipidaemia, and hypertension were the most frequent modifiable RFs among young stroke patients without sex differences, as also found in several European studies of young stroke.[6,32–34] Notably, the risk factor burden in this study, and prevalence of atherosclerosis in our previous study was found equally high among young and middle-aged male patients and controls, and among middle-aged female patients and controls.[2] A retrospective case-control study of patients ≤40 years with premature CAD, and gender-matched controls reported dyslipidaemia, smoking, hypertension and obesity as more significantly associated in patients as compared to controls.[35]

In our final combined regression analysis, strongest risk factors related to numeric staging of atherosclerosis were age, hypertension, diabetes mellitus, smoking and increased BMI. The Bogalusa Heart Study showed that hypertension, dyslipidaemia, smoking, BMI, and an increased number of RFs were related to the extent of atherosclerosis in the aorta and coronary arteries in even younger individuals aged 2-39 years, who died due to trauma.[36] Obesity, often defined as BMI ≥30 kg/m^2 in literature, associated with young stroke was found weak or absent when adjusted for vascular RFs in other studies.[37,38] By contrast, one study found that increased BMI in childhood and adolescence was associated with young stroke.[39] As BMI reflects body size rather than fat distribution,[40] WHR seems more strongly associated with risk of stroke, rather than BMI.[41] We found also atherosclerotic staging associated with increased WHR, but after adjustment for all variables, the finding became non-significant. Among stroke patients, WHR showed a positive trend. As majority of missing WHR had increased BMI, we might have underestimated its association with atherosclerosis in our study. In a meta-analysis of 58 prospective studies, 1 SD increase in BMI and WHR was associated with higher risk for CAD and ischaemic stroke for study participants aged 40-59 years, whereas the hazard ratio (HR) attenuated for older subjects (≥70 years).[42] The association between WHR and ischaemic stroke was stronger than that of BMI and ischaemic stroke (HR 1.25 vs 1.20) adjusted for age, sex and smoking.[42]

EAT and VAT were associated with increased numeric staging of atherosclerosis among our study-participants, but turned non-significant after adjustment for all variables. By contrast, other studies have found EAT and VAT to be predictors of CVD.[43–45] SAT was not associated with atherosclerosis in any performed analysis, and we therefore did not evaluate SAT as risk factor for atherosclerosis. The Framingham Heart Study reported stronger associations of VAT with metabolic risk factors than with SAT.[46]

Physical inactivity was also significantly associated with increased numeric staging of atherosclerosis in the regression analysis done separately for patients and controls. Physical inactivity has been associated with obesity and worse cardiovascular profile, increasing the risk of ischaemic stroke (OR 5.9),[37] and the fact that obesity

provides an increased risk for earlier development of hypertension and diabetes mellitus.[47]

Finally, we found high risk factor matching regarding physical inactivity and smoking between patients and their partners as controls, indicating that couples share some habits as noted in genetic studies.[48]

Our study confirmed high prevalence of vascular risk factors and atherosclerosis among young and middle-aged stroke patients and controls, indicating necessity of both primary and secondary intervention in a population where CVEs are most common causes of death and hospital admissions.[19–21] The primary goal may be achieved by educating individuals for a healthy lifestyle, and initiation of early treatment of asymptomatic individuals who are at high risk. As young stroke patients are at high risk for new CVE and earlier mortality, mainly due to atherosclerosis,[2,23] they should be aimed at for aggressive secondary treatment of modifiable RFs.

Strengths and limitations

Strengths of the present study are the population-based design, standardized diagnostic work-up of multiple RFs, and a comprehensive ultrasound protocol permitting numeric staging of atherosclerosis. Limitations are due to the necessity of age and sex matched analysis, which reduced the number of participants in each group, and thereby probably reduced the ability for reporting "statistically significant" results. But our findings seem to be in line with previous studies for stroke patients and young trauma victims, showing high prevalence of atherosclerosis related to vascular risk factors.[6,32,34,36]

We assessed only the prevalence of RFs, not the duration or severity that would be more actual for long-term data to show RFs change after treatment intervention, and its effects on atherosclerosis. Uncertainty about history of dyslipidaemia and diabetes mellitus was substantiated by blood tests among patients but not among controls, which resulted in an expected underestimation of its prevalence among controls. Dyslipidemia was not found significant in the final Poisson regression analysis, but was very frequent among patients, and we regard dyslipidemia as an important risk factor.

Conclusion

This study expanded the knowledge about present atherosclerosis among young and middle-aged ischaemic stroke patients and controls by targeted individual artery wall diagnostics. We found a high burden of vascular RFs in both groups. No significant differences in the burden of risk factors among young and middle-aged males and middle-aged females emphasize the need for early primary prevention including health education, and early treatment of modifiable risk factors to avoid further progression of atherosclerosis. Main modifiable risk factors were hypertension, diabetes mellitus, pack-years of smoking, and a high BMI. We regard also dyslipidaemia as a well-known vascular risk factor, although we could not find this in our study.

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Declaration of conflicting interests

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Informed consent

Written informed consent was obtained from all subjects before the study.

Ethical approval

Ethical approval for this study was obtained from the Regional Committee for Medical and Health Research Ethics, Western Norway (REK-VEST 2010/74).

Guarantor

UWA.

Author contributions

UWA conceived the study and gained the ethical approval. Protocol development was done by UWA, and RM and MB were also involved in the ultrasound protocol. Data collection was done by BN, AF, HØ, KMS, and UWA. Data interpretation of electrocardiograms were done by SS. BN did literature search and wrote the first draft of the manuscript. Statistical analysis was done by BN and GEE. All authors reviewed and edited the manuscript, and approved the final version.

Disclosure

This study is an academic study without any funding from companies or other sources with financial interests. The authors and co-authors declare no disclosures related to this article.

Trial registration

The study was registered in ClinicalTrials.gov NCT01597453.

ORCID iD

Beenish Nawaz https://orcid.org/0000-0002-4055-9744

Supplemental material

Supplemental material for this article is available online.

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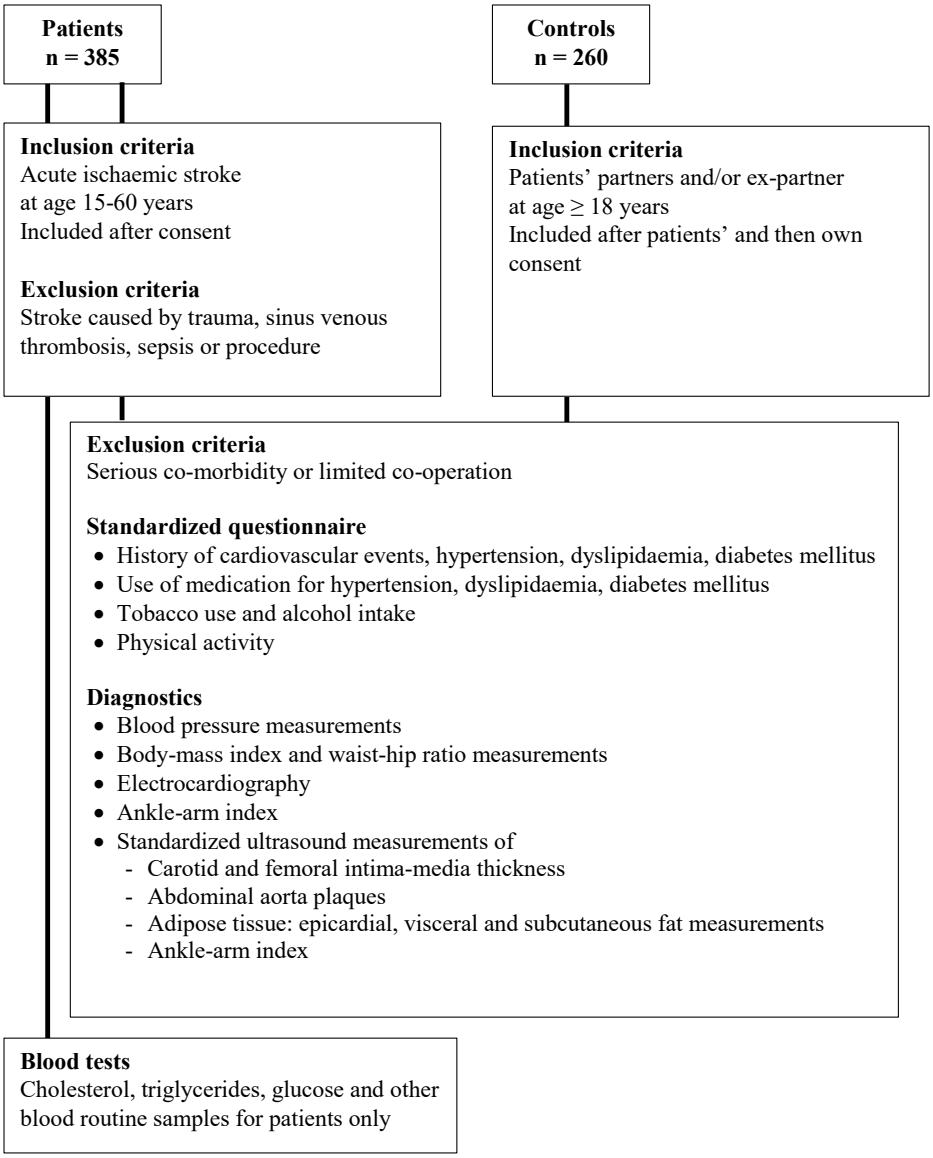
Supplementary material for Paper III

Supplementary Figure 1: Flow chart about inclusion- and exclusion criteria, and methods applied for patients and controls included into the Norwegian Stroke in the Young Study from 2010 – 2015



Supplementary Table 1 Prevalence of risk factors among young and middle-aged stroke patients in the Norwegian Stroke in the Young Study

Risk factors	Young aged ≤49 years					Middle-aged ≥50 years					
	NA, *n*	All, *n* (%) 152 (39.5)	Male, n (%) 94 (61.8)	Female, n (%) 58 (38.2)	P-Value Sex *	NA, *n*	All n (%) 233 (60.5)	Male, n (%) 170 (73.0)	Female, n (%) 63 (27.0)	P-value Sex *	P-value* Age group
Prior CVE[a)]	0	13 (8.6)	8 (61.5)	5 (38.5)	0.981	0	36 (15.4)	27 (75.0)	9 (25.0)	0.765	**0.047**
Hypertension[b)]	0	65 (42.8)	46 (70.8)	19 (29.2)	**0.050**	0	173 (74.2)	125 (72.3)	48 (27.7)	0.680	**<0.001**
Diabetes mellitus[c)]	0	11 (7.2)	6 (54.5)	5 (45.5)	0.605	0	33 (14.2)	28 (84.8)	5 (15.2)	0.097	**0.037**
Dyslipidaemia[d)]	0	96 (63.2)	61 (63.5)	35 (36.5)	0.572	0	197 (84.5)	145 (73.6)	52 (82.5)	0.605	**<0.001**
Smoking[e)]	0	92 (60.5)	59 (64.1)	33 (35.9)	0.472	0	176 (75.5)	130 (76.5)	46 (26.4)	0.586	**0.002**
Alcohol[f)]	2	13 (8.7)	12 (92.3)	1 (7.7)	**0.018**	2	25 (10.8)	22 (88.0)	3 (12.0)	0.069	0.493
Physical inactivity[g)]	0	28 (18.4)	21 (75.0)	7 (25.0)	0.113	0	43 (18.5)	33 (76.7)	10 (23.3)	0.536	0.993
BMI ≥25 kg/m^2	2	97 (64.7)	66 (68.0)	31 (32.0)	0.066	1	157 (67.7)	123 (78.3)	34 (21.7)	**0.006**	0.543
Increased WHR[h)]	11	83 (58.9)	56 (64.9)	27 (32.5)	0.092	15	171 (78.4)	131 (76.6)	40 (23.4)	**0.009**	**<0.001**
Increased EAT[i)]	2	77 (51.3)	50 (54.3)	27 (35.1)	0.352	11	152 (68.5)	112 (68.7)	40 (67.8)	0.897	**0.001**
Increased VAT[j)]	4	64 (43.2)	42 (65.6)	22 (34.4)	0.448	5	130 (57.0)	95 (73.1)	35 (26.9)	0.947	**0.009**
Increased SAT[j)]	5	50 (34.0)	29 (58.0)	21 (42.0)	0.484	4	77 (33.6)	51 (66.2)	26 (33.8)	0.105	0.938
Total RFB[k)]	15	131 (95.6)	84 (61.3)	53 (38.7)	0.544	24	209 (100.0)	152 (72.7)	57 (27.3)	0.486	**<0.001**

Abbreviations: NA = not available*; n* = number of patients, CVE = cardiovascular events; BMI = body-mass index; WHR = waist-hip ratio; EAT = epicardial adipose tissue; VAT = visceral abdominal adipose tissue; SAT = subcutaneous abdominal adipose tissue; RFB = risk factor burden

a) Prior CVE included stroke, coronary artery disease or peripheral artery disease; b) Hypertension was defined as known or diagnosed if blood pressure >140/90 mmHg; c) Diabetes mellitus was defined as known among patients and controls, or diagnosed by HbA1c >6.5% among patients only; d) Dyslipidaemia was defined as known among patients and controls, or diagnosed by blood tests among patients only; e). Smoking included ex-smokers and active smokers; f) Alcohol consumption is defined as ≥12 units/week; g) Physical inactivity was defined as activity less than 60 minutes/week; h) Increased WHR was defined as ≥0.85 in females and ≥0.9 in men; i). Increased EAT is defined as >0.5 cm; j). Increased VAT and SAT are based on 90th percentile of sex-specific cut points from normal weight referent sample; k) number of risk factors present ≥1.

*Chi-square test.

Supplementary Table 2 Similar risk factors in 257 couples* in the Norwegian Stroke in the Young Study

	Risk factors in 385 patients, *n* (%)	Risk factors in 260 controls, *n* (%)	NA, *n*	Prevalent risk factors in 257 couples, *n* (%)
Prior CVE[a)]	49 (12.7)	18 (6.9)	0	5 (1.9)
Hypertension[b)]	238 (61.8)	89 (34.4)	1	63 (24.6)
Diabetes mellitus[c)]	44 (11.4)	15 (5.8)	0	3 (1.2)
Dyslipidaemia[d)]	293 (76.1)	34 (13.1)	0	26 (10.1)
Smoking[e)]	268 (69.6)	169 (65.3)	1	141 (55.1)
Alcohol[f)]	38 (10.0)	8 (3.1)	4	3 (1.2)
Physical inactivity[g)]	71 (18.4)	28 (10.8)	0	191 (74.3)
BMI ≥25 kg/m^2	254 (66.5)	152 (59.4)	6	107 (42.6)
Increased WHR[h)]	254 (70.8)	130 (51.0)	25	95 (40.9)
Increased EAT[i)]	229 (61.6)	147 (56.8)	6	106 (42.2)
Increased VAT[j)]	194 (51.6)	77 (29.7)	4	44 (17.4)
Increased SAT[j)]	127 (33.8)	72 (27.8)	5	27 (10.7)

Abbreviations: NA = missing couples; CVE = cardiovascular event; BMI = body-mass index; WHR = waist-hip ratio; EAT = epicardial adipose tissue; VAT = visceral abdominal adipose tissue; SAT = subcutaneous abdominal adipose tissue.

*There were 257 couples in total out of 385 patients and 260 controls, where 16 patients had two partners included (ex-partner/ partner) and three patients were excluded retrospectively but their partners remained in the study.

a) Prior CVE included stroke, coronary artery disease or peripheral artery disease; b) Hypertension was defined as known or diagnosed if blood pressure >140/90 mmHg; c) Diabetes mellitus was defined as known among patients and controls, or diagnosed by HbA1c >6.5% among patients only; d) Dyslipidaemia was defined as known among patients and controls, or diagnosed by blood tests among patients only; e) Smoking included ex-smokers and active smokers; f) Alcohol consumption is defined as ≥12 units/week; g) Physical inactivity was defined as activity less than 60 minutes/week; h) Increased WHR was defined as ≥0.85 in females and ≥0.9 in men; i). Increased EAT is defined as >0.5 cm; j). Increased VAT and SAT are based on 90th percentile of sex-specific cut points from normal weight referent sample.

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