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Risk factors and their impact on carotid intima-media thickness in young and middle-aged ischemic stroke patients and controls: The Norwegian Stroke in the Young Study

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Abstract

Background: Vascular morbidity and mortality due to cardiovascular disease (CVD) are high after ischemic stroke at a young age. Data on carotid intima-media thickness (cIMT) as marker of atherosclerosis are scarce for young stroke populations. In this prospective case–control study, we examined cIMT, the burden of vascular risk factors (RF) and their associations among young and middle-aged ischemic stroke patients and controls. We aimed to detect clinical and sub-clinical arterial disease.

Methods: This study was conducted in 150 patients aged 15–60 years and 84 controls free of CVD. We related RF to ultrasonographic B-mode cIMT-measurements obtained from 12 standardized multiangle measurements in the common carotid artery (CCA), carotid bifurcation (BIF) and internal carotid artery (ICA).

Results: RF burden was higher among patients than among controls (p < 0.001). In multivariate analyses of all 234 participants, increased cIMT was associated with age in each carotid segment. Incident stroke was associated with increased ICA-IMT. ICA-IMT increase was associated with a family history of CVD among patients aged 15–44 years, and with RF at mid-age. The overall cIMT difference between patients and controls was 12% for CCA, 17% for BIF and 29% for ICA. Further, increased CCA-IMT was associated with male sex and hypertension. Increased BIF-IMT was associated with dyslipidemia, coronary heart disease and smoking. Increased ICA-IMT was associated with dyslipidemia and stroke.

Conclusions: Ischemic stroke is associated with increased ICA-IMT, related to a family history of CVD among patients aged <45 years, and to increasing RF burden with increasing age. Preventive strategies and aggressive RF treatment are indicated to avoid future cardiovascular events.

Trial registration: NOR-SYS is registered in ClinicalTrials.gov (NCT01597453).

Keywords: Young stroke, Ischemic stroke, Risk factors, Carotid intima-media thickness, Atherosclerosis, Ultrasound

Background

High rates of recurrent stroke, vascular morbidity and mortality due to cardiovascular disease (CVD) [1-3] clarify the need to detect and treat vascular risk factors and incipient atherosclerosis at early stages. Carotid intima-media thickness (cIMT) is a surrogate marker of atherosclerosis [4,5], and ultrasound screening a valuable tool for cardiovascular risk prediction [6,7]. Nevertheless, cIMT data obtained from young stroke populations are scarce. We aimed to assess the prevalence of clinical and subclinical carotid artery atherosclerosis and the impact of vascular risk factors (RF) among young ischemic stroke patients compared to CVD-free controls in a case–control study.

Methods

The Norwegian Stroke in the Young Study (NOR-SYS) is a prospective three-generation study with longitudinal

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follow-up design. NOR-SYS combines medical history and RF ascertainment by standardized questionnaires with clinical, laboratory, neuroradiological, cardiological and complex ultrasonographic data [8]. This analysis contains data from 150 patients and 84 controls included in NOR-SYS between September 2010 and June 2012.

Approvals, registrations and consents

NOR-SYS is conducted according to the Declaration of Helsinki, approved by the Regional Committee for Medical and Health Research Ethics, Western-Norway (2010/74), and registered in ClinicalTrials.gov (NCT01597453). Written informed consent was obtained from all participants or their legal representatives.

Subject selection

Patients aged 15–60 years with documented acute ischemic stroke and residency in Hordaland county, Norway, were

included. Two patients refused study participation. Seven patients were excluded; three due to incomplete neurosonographic data set, and four non-Caucasian patients. Patients' partners served as controls due to their function as reference persons for joint offspring in future analyses. Of 123 available partners, 63 (70.8%) females and 21 (61.8%) males participated. Seven controls with prior cardiovascular events were excluded from statistical analysis.

Risk factors

Medical history of prior stroke, coronary heart disease (CHD: myocardial infarction, angina pectoris) and peripheral artery disease (PAD) was defined if diagnosed before admission or revealed during hospitalization for the qualifying stroke. Family history of CVD (stroke, CHD and/or PAD) was considered positive if reported for parents and/or siblings. Hypertension and diabetes mellitus were defined by diagnosis and/or treatment before

Table 1 Patient and control characteristics

	N	All	15-44 y	45-60 y	Females	Males	Age (p)	Sex (p)
Patients	**N**	**150(100)***	**45(30)***	**105(70)***	**49(32.7)***	**101(67.3)***		
Age (mean)	150	48.5	35.8	54.0	46.3	49.6	<0.001	0.075
Prior stroke	150	13(8.7)	1(2.2)	12(11.4)	6(12.2)	7(6.9)	0.017	0.325
CHD	150	15(10.0)	1(2.2)	14(13.3)	4(8.2)	11(10.9)	0.006	0.589
PAD	150	8(5.3)	1(2.2)	7(6.7)	2(4.1)	6(5.9)	0.181	0.617
Family CVD	150	78(52.0)	9(20.0)	69(65.7)	29(59.2)	49(48.5)	<0.001	0.222
Diabetes	150	16(10.7)	2(4.4)	14(13.3)	7(14.3)	9(8.9)	0.053	0.357
Hypertension	150	101(67.3)	23(51.1)	78(74.3)	30(61.2)	71(70.3)	0.009	0.282
Dyslipidemia	150	114(76.0)	27(60.0)	87(82.9)	36(73.5)	78(77.2)	0.007	0.623
Smoking	150	104(69.3)	23(51.1)	81(77.1)	28(57.1)	76(75.2)	0.003	0.033
BMI > 25	144	99(68.8)	28(62.2)	71(67.6)	30(61.2)	69(68.3)	0.941	0.542
Alcohol	141							
None		9(6.4)	5(11.1)	4(3.8)	4(8.2)	5(5.0)	0.173	0.476
Low		119(84.4)	37(82.2)	82(78.1)	41(83.7)	78(77.2)	0.947	0.252
High		13(9.2)	2(4.4)	11(10.5)	1(2.0)	12(11.9)	0.137	0.011
Controls	**N**	**84(100)***	**21(25)***	**63(75)***	**63(75)***	**21(25)***		
Age (mean)	84	49.3	36.6	53.5	48.8	50.6	<0.001	0.453
Family CVD	84	49(58.3)	9(42.9)	40(63.5)	35(55.6)	14(66.7)	0.112	0.372
Diabetes	84	9(10.7)	1(4.8)	8(12.7)	5(7.9)	4(19.0)	0.218	0.249
Hypertension	84	16(19.0)	3(14.3)	13(20.6)	7(11.1)	9(42.9)	0.502	0.012
Dyslipidemia	84	12(14.3)	1(4.8)	11(17.5)	8(12.7)	4(19.0)	0.066	0.52
Smoking	84	57(67.9)	12(57.1)	45(71.4)	40(63.5)	17(81.0)	0.26	0.11
BMI > 25	80	45(56.3)	11(52.4)	34(54.0)	31(49.2)	14(66.7)	0.872	0.147
Alcohol	81							
None		4(4.9)	0(0.0)	4(6.3)	3(4.8)	1(4.8)	0.045	0.989
Low		74(91.4)	20(95.2)	54(85.7)	56(88.9)	18(85.7)	0.399	0.817
High		3(3.7)	1(4.8)	2(3.2)	2(3.2)	1(4.8)	0.79	0.757

Data presented as number (percentage) or mean. *Percentage of total population. y = years; CHD = Coronary heart disease; PAD = Peripheral artery disease; CVD = Cardiovascular disease; BMI = Body mass index.

hospital admission, or when revealed and treated during hospitalization for the qualifying stroke (blood pressure >140/90 mmHg; HbA1c >6.4%). Dyslipidemia was defined as prior statin use, or when revealed during hospitalization (total cholesterol >5.0 mmol/L and/or low-density lipoprotein (LDL) >3.0 mmol/L and/or high-density lipoprotein (HDL) <1,0 mmol/L and/or triglycerides >2.5 mmol/L). Smoking was categorized as never-smoking or previous/current smoking. Alcohol consumption was categorized as never used/low (0–12 units/week) or high (>12 units/week). Body-mass index (BMI) was dichotomized as normal or >25. RF burden was defined as the number of RFs present (0–10).

Neurosonology and Duplex/Doppler ultrasound examinations

Extracranial high-resolution sonography of the carotid arteries was performed with Philips iU22 and 9–3 MHz linear array transducer. Two patients were examined at the intensive care unit with a portable Phillips CX50 ultrasound system and 12–3 MHz linear array transducer (both systems Philips Medical Systems, Bothell, WA, USA). Patients and controls were examined by two sonographers (AF, UWA), which both are trained and certified for the NOR-SYS duplex sonography research protocol in collaboration with the Vascular Imaging Centre, University Medical Centre, Utrecht, The Netherlands.

Data reliability tests

Reproducibility testing of cIMT measurements within (intra-observer) and between (inter-observer) sonographers of the research group, and between ultrasound equipment (inter-equipment) was performed applying both ultrasound systems. The intra-observer correlation of sonographers was 0.78-0.98 (mean absolute cIMT difference 0.02-0.08 mm). The inter-observer correlation of sonographers was 0.83-0.93 (mean absolute cIMT difference 0.04-0.11 mm). The inter-equipment correlation for iU22/CX50 was 0.94 (mean absolute cIMT difference 0.04 mm). These results correlate with previously published studies [9-12].

cIMT-measurements

The methods of the cIMT measurements were previously described [8]. In total 12 far-wall cIMT measurements in the common carotid artery (CCA), the carotid bifurcation (BIF) and the internal carotid artery (ICA) were performed in each participant in the end-diastolic phase of the cardiac cycle, and mean cIMT values were acquired using Philips QLAB® (Philips Medical Systems, Bothell, WA, USA). In case of intra-segmental irregularities or plaques, maximum IMT or plaque thickness were measured additionally. Maximum segmental IMT values were used in statistical analysis. IMT values were defined as normal when <0.8 mm, as suspect for arterial disease when 0.8-0.99 mm [13,14], and as pathological when ≥1.0 mm [15,16]. Plaques were defined as focal IMT measurements >1.5 mm [17].

Statistical analyses

To allow for comparison to other studies [18-20], and in order to assess the influence of age and sex on IMT, our study population was grouped according to age (younger, 15–44 years; middle-aged, 45–60 years) and sex. Statistical analysis was performed using R version 3.0.0, and data
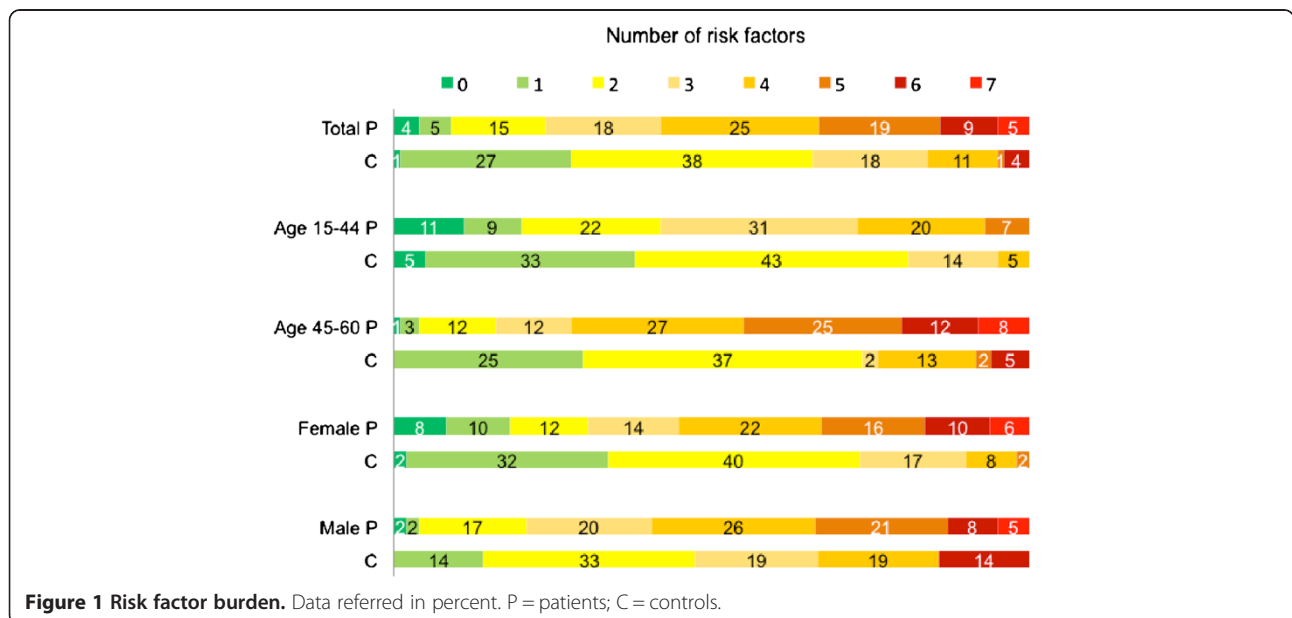

Figure 1 Risk factor burden. Data referred in percent. P = patients; C = controls.

Table 2 Relative change in IMT between patients and controls and mean IMT values

	NA	Total	15-44 y	45-60 y	Females	Males	Age (p)	Sex (p)
CCA								
Relative change		12 (4–22)	3 (−9-15)	19 (8–30)	4 (−6-15)	6 (−9-23)		
Mean IMT patients	1	0.85	0.63	0.94	0.75	0.89	<0.001	0.003
Mean IMT controls	0	0.73	0.61	0.77	0.7	0.82	<0.001	0.008
BIF								
Relative change		17 (2–34)	11 (−9-36)	23 (7–43)	9 (−9-31)	8 (−16-38)		
Mean IMT patients	11	1.34	0.84	1.54	1.23	1.39	<0.001	0.079
Mean IMT controls	2	1.12	0.7	1.26	1.04	1.34	<0.001	0.067
ICA								
Relative change		29 (12–49)	20 (−2-46)	35 (15–58)	28 (7–53)	1 (−23-31)		
Mean IMT patients	30	0.97	0.63	1.1	0.9	1.0	<0.001	0.312
Mean IMT controls	14	0.73	0.47	0.83	0.64	1.06	<0.001	0.021

Data sorted by carotid segment, age group, and sex. Relative change presented in % (CI); IMT presented in mm. CCA = Common carotid artery; BIF = Carotid bifurcation; ICA = Internal carotid artery; NA = Not available.

were formatted in STATA version 12.1. A t-test was applied when testing for differences between groups. The unadjusted analysis was conducted applying a univariate linear regression. Because each individual had two measurements per segment (right/left), a random intercept approach was used, utilizing the R-function lmer() from the lme4 package. Dependent variables (cIMT) were skewed towards low values, and a base 10 log transform was applied to meet the assumptions of a linear regression. Hence, the relative change (RC) in cIMT per unit change in the independent variables (typically 0 or 1) could be obtained. Adjusted analyses were carried out accordingly, and multivariate logistic regression was applied. Simulations were used to determine the power to detect differences between controls and patients for RC ranging from 1.00 to 1.50 across each carotid segment. Fisher's exact test (based on simulations when appropriate) was applied when comparing tables or rows within tables.

Results
Population demographics are given in Table 1. Of patients, 30.0% were aged 15–44 at study inclusion, and 32.7% were female. Of 84 controls, 25.0% were aged 15–44 at study inclusion, and 75.0% were female.

Risk factors
Patients had a higher RF burden than controls in analysis of the entire study population (p < 0.001) and in subgroup analyses (age 15–44: p = 0.027; age 45–60: p < 0.001; females: p < 0.001; males: p = 0.021), visualized in Figure 1.

Table 3 Statistical significance for IMT increase in patients compared to controls

	Total	15-44 y	45-60 y	Females	Males
CCA					
Relative change (unadjusted)	**0.005**	0.669	**<0.001**	0.404	0.465
Mean IMT (t-test)	**<0.001**	0.501	**<0.001**	0.151	0.161
IMT distribution (Fisher's exact test)	**0.018**	0.383	**0.003**	0.418	0.906
BIF					
Relative change (unadjusted)	**0.024**	0.299	**0.005**	0.344	0.544
Mean IMT (t-test)	**0.006**	**0.030**	**0.005**	0.108	0.760
IMT distribution (Fisher's exact test)	0.111	0.447	**0.010**	0.202	**0.027**
ICA					
Relative change (unadjusted)	**<0.001**	0.079	**<0.001**	**0.008**	0.947
Mean IMT (t-test)	**<0.001**	**0.003**	**0.001**	**0.004**	0.741
IMT distribution (Fisher's exact test)	**<0.001**	**0.005**	**<0.001**	**0.003**	0.155

Data presented as p-values, sorted by carotid segment, age group, and sex. Statistical significance presented in boldface. CCA = Common carotid artery; BIF = Carotid bifurcation; ICA = Internal carotid artery. Boldface represents statistical significant differences between patients and controls, mainly within the total population and among middle-aged participants, and as well among the young population and females in the ICA segment.
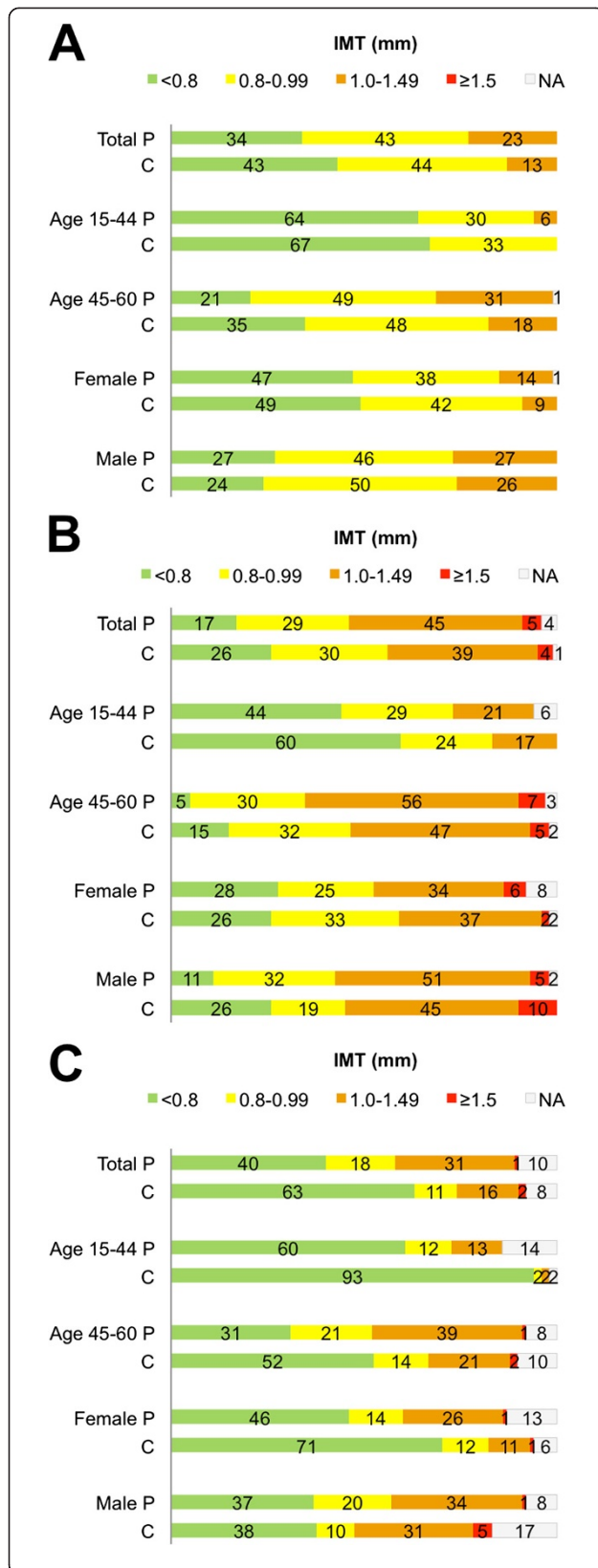
Figure 2 Segmental cIMT distribution in common carotid artery, carotid bifurcation and Internal carotid artery. Data referred in percent. **A** = Common carotid artery; **B** = Carotid bifurcation; **C** = Internal carotid artery; P = patients; C = controls.

Hypertension and dyslipidemia were more frequently present among patients. Prior stroke, CHD, family history of CVD, hypertension, dyslipidemia and smoking were less prevalent among young than among middle-aged patients, and smoking and high alcohol consumption were more common among male than among female patients.

Carotid Intima-media thickness (cIMT)

Values of mean IMT and RC are presented in Table 2 and significance of all tests applied is shown in Table 3. Mean IMT values were in all subgroups of patients and controls lowest in CCA and highest in BIF, and lower in young than in middle-aged participants. Sex-related differences were inconsistent. Mean values <0.8 mm were mostly restricted to the young population and to controls. Mean values ≥1.0 mm were found in BIF in all patient and control subgroups but the young, and in ICA in middle-aged patients and male patients and controls. Mean values ≥1.5 mm were solely found in middle-aged patients.

The RC between patients and controls was in all subgroups but males most distinct in ICA (20-35%). Only middle-aged patients showed IMT increase compared to controls in CCA (19%) and BIF (23%). Statistical simulation suggested the need of RC > 12% for CCA, RC > 22% for BIF, and RC > 25% for ICA to detect cIMT-differences ≥80% between patients and controls, which matches our results fairly well.

Details on categorized segmental cIMT distribution are shown in Figure 2 and Table 3. IMT distribution was higher than that of controls in all patient subgroups but males in ICA. IMT distribution was further higher among middle-aged patients in CCA, and among middle-aged and male patients in BIF.

Impact of risk factors on cIMT

Table 4 shows analysis of all participants (n = 234). Associations between RF and IMT increase varied in the different carotid segments, and across age and sex subgroups. With one exception (ICA in middle-aged participants), IMT increase was associated with age in all carotid segments among all subgroups. On the other hand, ICA in males was the only carotid segment in any subgroup, where patients' RF had a stronger impact on IMT increase than controls' (p = 0.038).

Discussion

Our study presents cIMT data obtained from young and middle-aged patients after acute ischemic stroke. Previous studies on multisegmental RF-cIMT associations related to

Table 4 Associations between vascular risk factors and segmental carotid IMT increase

Participant group	Segment	Risk factor associations
Entire study population (n = 234)	CCA:	Age (p < 0.001); male sex (p = 0.023); hypertension (p < 0.001)
	BIF:	Age (p < 0.001); dyslipidemia (p = 0.018); CHD (p = 0.017); smoking (p = 0.012)
	ICA:	Age (p < 0.001); dyslipidemia (p = 0.025); prior stroke (p = 0.009)
Age 15–44 years (n = 66)	CCA:	Age (p = 0.001); hypertension (p = 0.008)
	BIF:	Age (p < 0.001); hypertension (p = 0.009)
	ICA:	Age (p = 0.002); family history of CVD (p = 0.039)
Age 45–60 years (n = 168)	CCA:	Age (p = 0.05); male sex (p = 0.037); hypertension (p = 0.016)
	BIF:	Age (p = 0.022); dyslipidemia (p = 0.033); smoking (p = 0.016)
	ICA:	Dyslipidemia (p = 0.022); prior stroke (p = 0.037)
Females (n = 112)	CCA:	Age (p < 0.001); hypertension (p = 0.031)
	BIF:	Age (p < 0.001); hypertension (p = 0.049)
	ICA:	Age (p < 0.001)
Males (n = 122)	CCA:	Age (p < 0.001); hypertension (p = 0.012)
	BIF:	Age (p < 0.001); dyslipidemia (p = 0.003); CHD (p = 0.031)
	ICA:	Age (p < 0.001); dyslipidemia (p = 0.006), PAD (p = 0.028), prior stroke (p = 0.004)

CCA = Common carotid artery; BIF = Carotid bifurcation; ICA = Internal carotid artery.

incident stroke did either not include participants <45 years [21,22], or did not provide acute phase cIMT data [23]. By combination of three statistical methods, we identified increased ICA-IMT as distinctly associated with incident stroke not only among middle-aged adults, as others described before [21], but also among young adults aged 15–44 years. Patients aged 15–44 showed a surprising 20% ICA-IMT increase compared to controls. Only a family history of CVD was found to be associated with increased ICA-IMT in the younger subgroup, which may reflect a genetic predisposition [24].

Female patients represent the best-controlled subgroup in this study. We found an unexpected ICA-IMT increase of 28% compared to female controls. The increase was surprisingly high compared to a 4% increase in CCA-IMT, and a 9% increase in BIF-IMT. In comparison, we found rather low and constant segmental differences (1-8%) from controls in male patients, though their control group was less representative. The only factor related to ICA-IMT increase in females was age. Our results may reflect hormonal influences on the development of atherosclerosis [25-27]. ICA-IMT among male patients did not differ from controls'. However, male controls are insufficiently represented, what implies limitations for the interpretation of comparing results among males.

Our study shows a higher RF burden among patients, but also a high prevalence of RF among presumably healthy controls. Other studies have reported increasing risk of vascular events [28] and higher mortality proportional to RF burden [28-30], and recommended early preventive treatment. Our data strongly support broad preventive initiatives in families at risk.

We found an increasing RF burden with age, and the three most frequent RF were dyslipidemia (76%), smoking (69%) and hypertension (67%). This is in accordance with other studies [19,31]. Our RF rates among patients are, however, higher than previously reported [31], as e.g. cholesterol levels among the Norwegian population remain high despite improvement during the last decades [32]. Our data further support that cIMT depends on age, sex and cardiovascular risk [15,33-36]. We found pronounced cIMT increase in middle-aged patients, which is in line with a recent young stroke study demonstrating substantial clinical and subclinical atherosclerosis [20].

The major strengths of NOR-SYS are the inclusion of CVD-free controls and the standardized ultrasound protocol. However, our study has limitations. The size of patient subgroups varies as a consequence of stringent stratification of our patient population. Accordingly, controls (the patients' partners) are unequally represented. Due to overall low case numbers, RF associations are in parts calculated with small sample sizes, which may have affected our results. Further, our data may be valid only for Caucasians, and may be influenced by the high risk profile of our population.

We did not account for multiple testing. However, as we performed approximately 100 tests, Bonferroni correction (BC) would yield a corrected significance level of about 0.05/100 = 0.0005, rounded to p < 0.001 in our study. Hence, associations with p < 0.001 would survive a BC. BC further reduces the number of type I errors at the cost of increasing the number of type II errors, and p-values above 0.0005 may still be indicative of an association.

Conclusions

Stroke is associated with increased ICA-IMT already at a young age, related to a family history of CVD among the youngest patients and related to RF burden increasing with age. Also in CVD-free controls, RFs and subclinical atherosclerosis are prevalent. Our data suggest that vascular screening reveals established clinical and sub-clinical arterial disease requiring broad and aggressive treatment in order to prevent progressing CVD.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AF designed the study, carried out the ultrasound examinations and data aquisition, participated in statistical analysis and data interpretation, and drafted the manuscript. ØAH participated in the design of the study, performed statistical analysis and data interpretation and drafted the manuscript. HN contributed with acquisition of data and critical revision of the manuscript for intellectual content. LT contributed with acquisition of data and critical revision of the manuscript for intellectual content and helped to draft the manuscript. UWA contributed to study design, data aquisition, statistical analysis and data interpretation, critical revision of the manuscript for intellectual content and drafted the manuscript. All authors read and approved the final manuscript.

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