Family history in young and middle-aged acute ischemic stroke patients

The Norwegian Stroke in the Young Study

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Dissertation for the degree of philosophiae doctor (PhD)

at the University of Bergen

2016

Dissertation date: 08.04.16

Year: 2016

Title: Family history in young and middle-aged acute ischemic stroke patients
The Norwegian Stroke in the Young Study

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Print: AiT Bjerch AS / University of Bergen

Scientific environment

The work constituting this thesis has been carried out at the Department of Neurology, Haukeland University Hospital. Facilities, equipment, training and support have been provided and carried out at the Department of Neurology, Haukeland University Hospital, in collaboration with and support from the Bergen Stroke Research Group.

Contents

Acknowledgements

I would like to start by giving my sincere gratitude to my main supervisor Associate Professor Ulrike Waje-Andreassen and my co-supervisor Professor Lars Thomassen. They possess a vast knowledge and experience in the field of stroke. Their unquenchable enthusiasm to increase research and expand knowledge in the field of stroke has been truly inspiring and may only be surpassed by their ability to inspire this thirst for knowledge in others. The everlasting support, encouragement and critical revisions they provide have been indispensable in the work of producing this thesis.

I am forever beholden to Professor Ole-Bjørn Tysnes, head of Department of Neurology, Haukeland University Hospital and Professor Nils Erik Gilhus, head of Department of Clinical Medicine, University of Bergen, for providing me the opportunity to carry out this thesis.

It was an exciting opportunity to be included in the extremely enthusiastic Bergen Stroke Research Group when I finished my MD. The fast paced and highly productive research environment driven by so many intellectual powerhouses got me smitten in an instant. I owe a big thank you to Professor Halvor Næss for the inspiration he has given me in stroke research, and in setting an example of unsurpassed effectivity in both clinical and academic work.

I am grateful to Dr. Annette Fromm for teaching me the know-how of NOR-SYS and neurovascular ultrasound. Your expertise and clinical skills in wielding the ultrasound probe has been an inspiration and a goal to aspire towards. I am also grateful to Dr. Kristin Modalsli Sand who has been a valuable colleague to share work and rewarding conversations with. I would like to provide thanks to Geir Egil Eide for giving valuable feedback and advice with regards to the statistical analyses and interpretations.

I am grateful for the invaluable work of administrating the NOR-SYS study carried out by Jeanette Antoniazzi and the study nurses at the Department of Neurology, Linn Elin Rødal and Toril Bjørgo.

In my research I have had the opportunity to work on conjoining fields of stroke research and in this collaborate with several brilliant researchers. I would like to mention Dr. Christopher Elnan Kvistad and Dr. Nicola Logallo who have been and continue to be invaluable in keeping the working environment joyful and playful through hectic and busy times. I would also like to thank Dr. Eivind Kolstad for valuable and exciting conversations about research, football and life in general.

My parents greatly inspire me. Your care and love for the people around you gave me the inspiration to become a doctor. I cherish your good advice and your inexhaustible love and support for me and my family. To my sister Maria and my brother Eirik, thank you for every argument, every hug, every fight, every laugh, and every tear we have shared.

To my parents-in-law Siri and Alf Ivar: Thank you for all your help and your loving care for all of us.

To the love of my life, Christine, you make me a better me. I would not be the man I am without you. Thank you for always supporting me, and thank you for being the best wife and mother I can imagine.

To my diamonds Herman, Cornelia and Carla, you make every day brighter and you have my eternal love.

List of abbreviations and acronyms

ABI	Ankle-brachial index
AHA	American Heart Association
ASA	American Stroke Association
ASCO	Acronym for a stroke etiology classification system: Atherosclerosis, Small vessel disease, Cardiac source and Other source
BIF	Carotid artery bifurcation
BP	Blood pressure
CCA	Common carotid artery
CCS	Causative Classification System
CHD	Coronary heart disease
CI	Confidence interval
cIMT	Carotid intima-media thickness
CNS	Central nervous system
CT	Computed tomography
CVD	Cardiovascular disease
DM	Diabetes mellitus
DWI	Diffusion weighted imaging
FH	Family history
FHS	Framingham Heart Study
GWAS	Genome-wide association study
HT	Hypertension
HR	Hazard ratio
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
i.e.	id est (that is)
IS	Ischemic stroke
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NOR-SYS	The Norwegian Stroke in the Young Study
OR	Odds ratio
OXVASC	Oxford Vascular Study
PAD	Peripheral artery disease
RR	Relative risk
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment classification
WHO	World Health Organization

Abstract

Cardiovascular disease (CVD), including stroke, coronary heart disease (CHD) and peripheral artery disease, is the leading cause of death and disability in the western world. CVD is influenced by genetic and lifestyle factors. Knowledge about heredity is well documented for CHD. However, the influence of a positive family history (FH) on stroke is far less documented.

The studies included in this thesis therefore aim to quantify and evaluate a detailed FH of CVD in a young ischemic stroke population with a special regard to sex differences. Further, we aimed to verify the patient reported family history by comparison with parental reports, and to find factors associated with best accuracy of the patient reported FH. In addition we aimed to analyze if a positive FH of CVD is associated with intima-media thickness (IMT) and plaque measurements, performed at standardized sites in the carotid arteries.

A total of 59% of our patients reported ischemic CVD events among their first degree family members. Females were three times more likely to report a positive FH than males and knowledge of FH was higher in relatives with a female than male linkage. Detailed knowledge on FH was better for CHD than for stroke. The FH reported from patients were in good concordance with parental reports, but with a slightly decreased accuracy from patients aged over 45 years. FH of stroke was associated with higher internal carotid IMT in young ischemic stroke patients. The association was strong for young patients, and absent in the highest age group from 50-60 years.

In conclusion, data presented in this thesis, add new information to the field of young stroke by a detailed FH of CVD and detailed ultrasound diagnostics of the carotid arteries. Thorough diagnostics after ischemic stroke and the history of ischemic CVD events in first degree family members should be basic requirements for future genetic research.

Introduction

Cardiovascular disease (CVD) is mainly composed of three disease subgroups associated by a pathophysiologic basis of atherosclerosis, namely ischemic stroke, coronary heart disease and peripheral artery disease. CVD in general and stroke in particular are traditionally considered to be diseases of the elderly. True to some extent as incidence of stroke rises exponentially with age. However, stroke in the young deserves attention. Though less frequent than stroke at higher age, stroke at a young age can be detrimental for the individual suffering stroke and may be a big burden on the patient's family. In addition, stroke entails high societal costs with respect to treatment, rehabilitation and subsequent disability.

Worryingly, the steep decline seen in incidence rates of stroke in the elderly, is absent in the young. Some reports even suggest an opposite trend, with increasing incidence of stroke in young patients. Decreasing the incidence of stroke in the young therefore requires new approaches and other methods of identifying increased risk. A part of the solution may be a better understanding of the inherited risk of stroke.

Family history (FH) is a well-known risk factor for coronary heart disease. However, the role of FH as a risk factor for ischemic stroke is less clear. Several studies have shown that a positive FH does increase the risk of ischemic stroke, whereas others have not. The FH is an inexpensive and easily accessible tool to assess the heredity of disease. However, many years of research on the topic of FH and stroke leave us with few clear answers. FH has usually been considered positive if any family member had CVD, even the studies investigating only a FH of stroke have mostly not separated ischemic from hemorrhagic stroke. Diagnostics of stroke have improved considerably during the past 25 years, and we may now analyze the FH with greater precision.

Can the family history provide a contribution to understanding ischemic stroke?

Ischemic stroke at a young age and cardiovascular disease

Definition of stroke and cerebral ischemic arterial stroke

The traditional WHO definition of stroke is "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". [1-3] However, increased use of Magnetic Resonance Imaging (MRI) made this definition imprecise, thereby prompting the work towards a global consensus on a new definition. [4] The new definition incorporates specific pathophysiologic causes of stroke and imaging. However, as the access to imaging; especially magnetic resonance imaging varies considerably around the globe; this definition has yet to be globally endorsed. [5] The definition proposed by American Heart Association/American Stroke Association (AHA/ASA) is presented in table 1.

Table 1. Definition of ischemic stroke by The American Heart Association and The American Stroke Association

Definition of CNS infarction: CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on 1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. **Definition of ischemic stroke**: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. (Note: Evidence of CNS infarction is defined above.) **Definition of silent CNS infarction**: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Adapted from Sacco RL et al., Stroke, 2013. [4] With permission of the publisher

The new definition expands on the tissue based definition of TIA by defining pathological imaging as a central part of diagnosis and allows infarctions in the entire CNS. This definition harmonizes more with the currently used definitions of coronary heart disease (CHD). [4,6] Stroke includes both hemorrhagic and ischemic stroke, but the link with atherosclerosis is strongest for ischemic stroke. Ischemic stroke and intracerebral hemorrhage co-exist under the same diagnostic umbrella of stroke mainly due to historical reasons. Before the age of cerebral imaging, when autopsy was the only diagnostic aid able to separate between cerebral ischemia and cerebral hemorrhage, the similar symptomatology of palsy and other cerebral deficits led to the compounding of both entities as "apoplexy" or stroke. However, risk factors and the mechanism of tissue damage differ. Acute and preventive treatment is profoundly different and prognosis for brain hemorrhage is in general worse than for ischemic stroke. We now have widespread excellent diagnostic possibilities, able to separate hemorrhage from infarction, and even arterial ischemic stroke from cerebral ischemic damage caused by sinus venous thrombosis. The new definition underlining and acknowledging these differences is therefore most welcome.

Definition of young stroke

A clear and definite definition of young stroke is lacking. Different age limits for the definition of young stroke have been used in prior studies. The majority of studies have considered 45 years as the upper age limit defining young patients [7-13] but differences are apparent with several studies using <50 years [14-18] and others applying even higher age limits of 55 years. [19-22] The different definitions may cause variations in reported incidence rates, distribution of stroke etiology and risk factor prevalence in the young stroke population, as these distributions vary with age. [23,24] NOR-SYS expanded the definition of "young" to account for the high life-expectancy of over 80 years in Norway, and the normal retirement age of 67 years for both sexes. The present thesis defines young stroke as stroke occurring before 45 years of age, while patients with stroke occurring between 45 and 60 years are considered middle-aged.

Cardiovascular disease

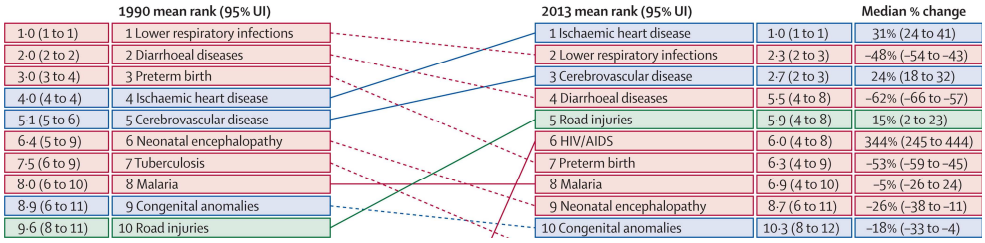
Cardiovascular diseases are diseases involving the heart and the blood vessels. The three main groups with atherosclerosis as main underlying pathophysiological mechanism are ischemic stroke, and especially CHD and peripheral artery disease (PAD). [25] The common mechanism is inflammation and development of atherosclerosis in the arteries that may lead to thromboembolic complications and ischemic damage of tissue. These three disease subgroups are considered to overlap in pathophysiology and one diagnosis carries an increased risk of the other two. [26,27] In addition, congenital heart disease, rheumatic heart disease, cardiomyopathies and cardiac arrhythmias are also considered CVDs, however caused by various different underlying mechanisms. [25] The type of tissue that is damaged and the symptomatology in ischemic stroke, CHD and PAD may differ substantially, but the final mechanism of damage for these three CVD subgroups is essentially the same with some degree of arterial occlusion leading to clinical events of ischemic tissue damage.

Epidemiology

The global burden of cardiovascular disease

Cardiovascular disease, mainly composed of cerebrovascular disease, ischemic heart disease and peripheral vascular disease, causes a large part of the total global burden of disease. An estimation of cause of death around the globe reported CVD as the cause of more than 17 million deaths in 2013. [28] Cerebrovascular disease and ischemic heart disease was the cause of more than 26% (14.6 million of 54.9 million in total) of global deaths in 2013 (Table 2). [28] Both stroke and myocardial infarction (MI) are now ranked within the top three global causes of death and years of life lost, as their relative impact have increased through recent decades (Figure 1).

Figure 1. Top 10 causes of global years of life lost in 1990 and 2013



A display of the top 10 of the 50 most frequent causes of years of life lost globally in 1990 and 2013. The change in rank is indicated by connecting lines and median change in % from 1990 to 2013 is annotated. Numbers within parenthesis are 95% Uncertainty Intervals.

From GBD 2013 Mortality and Causes of Death Collaborators, The Lancet, 2015. [28] *With permission of the publisher*

The pattern of CVD as the largest cause of years of life lost is apparent with small variations in most parts of the globe, with the exception of sub-Saharan Africa (Figure 2). The number of deaths due to CVD increased with 41% from 1990 to 2013 (Table 2).

Figure 2. Top five global causes of years of life lost in 2013

	1	2	3	4	5
Global	IHD	LRI	Stroke	Diarrhoea	Road injuries
Developed	IHD	Stroke	Lung C	Self harm	Alzheimer's
Developing	LRI	IHD	Stroke	Diarrhoea	HIV/AIDS
High-income	IHD	Lung C	Stroke	Alzheimer's	COPD
Australasia	IHD	Lung C	Stroke	Self harm	Colorectal C
Australia	IHD	Lung C	Stroke	Self harm	Alzheimer's
New Zealand	IHD	Lung C	Stroke	Colorectal C	COPD
High-income Asia Pacific	Stroke	IHD	Self harm	Lung C	LRI
Brunei	IHD	Stroke	Diabetes	Road injuries	Congenital
Japan	Stroke	IHD	LRI	Lung C	Self harm
Singapore	IHD	LRI	Stroke	Lung C	Colorectal C
South Korea	Stroke	Self harm	Lung C	Liver C	IHD
High-income North America	IHD	Lung C	Alzheimer's	COPD	Stroke
Canada	IHD	Lung C	Alzheimer's	Stroke	Self harm
USA	IHD	Lung C	COPD	Alzheimer's	Stroke
Southern Latin America	IHD	Stroke	LRI	COPD	Road injuries
Argentina	IHD	Stroke	LRI	COPD	Road injuries
Chile	IHD	Stroke	Cirrhosis	Road injuries	Self harm
Uruguay	IHD	Stroke	Lung C	Alzheimer's	COPD
Western Europe	IHD	Lung C	Stroke	Alzheimer's	Colorectal C
Andorra	IHD	Lung C	Stroke	Alzheimer's	Colorectal C
Austria	IHD	Lung C	Stroke	Alzheimer's	Self harm
Belgium	IHD	Lung C	Stroke	Self harm	COPD
Cyprus	IHD	Stroke	Lung C	Road injuries	Diabetes
Denmark	IHD	Lung C	Stroke	COPD	Colorectal C
Finland	IHD	Stroke	Alzheimer's	Lung C	Self harm
France	IHD	Lung C	Stroke	Self harm	Colorectal C
Germany	IHD	Lung C	Stroke	Alzheimer's	Colorectal C
Greece	IHD	Stroke	Lung C	Alzheimer's	COPD
Iceland	IHD	Lung C	Stroke	Alzheimer's	Self harm
Ireland	IHD	Lung C	Stroke	Self harm	COPD
Israel	IHD	Lung C	Alzheimer's	Diabetes	Stroke
Italy	IHD	Stroke	Lung C	Alzheimer's	Colorectal C
Luxembourg	IHD	Lung C	Stroke	Self harm	COPD
Malta	IHD	Stroke	Lung C	Colorectal C	Breast C
Netherlands	IHD	Lung C	Stroke	Colorectal C	COPD
Norway	IHD	Lung C	Stroke	Alzheimer's	Colorectal C
Portugal	Stroke	IHD	Lung C	LRI	Colorectal C
Spain	IHD	Lung C	Stroke	Alzheimer's	Colorectal C
Sweden	IHD	Stroke	Lung C	Colorectal C	Self harm
Switzerland	IHD	Lung C	Stroke	Alzheimer's	Self harm
UK	IHD	Lung C	Stroke	COPD	Alzheimer's
England	IHD	Lung C	Stroke	COPD	Alzheimer's
Northern Ireland	IHD	Lung C	Stroke	COPD	LRI
Scotland	IHD	Lung C	Stroke	COPD	Alzheimer's
Wales	IHD	Lung C	Stroke	Alzheimer's	COPD

The top fifteen global causes are colored. IHD=ischemic heart disease; LRI=lower respiratory infections; Congenital=congenital disorders. C=cancer. COPD=chronic obstructive pulmonary disease.

From GBD 2013 Mortality and Causes of Death Collaborators, The Lancet, 2015. [28] *With permission of the publisher*

Table 2. Global deaths caused by cardiovascular disease in 1990 and 2013

	All ages deaths (thousands)			Age-standardised death rate (per 100 000)		
	1990	2013	Median % change	1990	2013	Median % change
Cardiovascular diseases	**12 279·6 (11 776·6 to 12 764·1)**	**17 297·5 (16 520·2 to 18 071·9)**	**40·8 (36·17 to 46·36)**	**375·5 (360·5 to 389·1)**	**293·2 (280·4 to 306·1)**	**−22·0 (−24·50 to −19·07)**
Rheumatic heart disease	373·5 (302·5 to 464·6)	275·1 (222·6 to 353·9)	−26·5 (−33·64 to −17·20)	9·8 (7·9 to 12·2)	4·4 (3·5 to 5·6)	−55·4 (−59·47 to −50·11)
Ischaemic heart disease	5737·5 (5254·9 to 6148·6)	8139·9 (7322·9 to 8758·5)	41·7 (35·96 to 48·44)	177·3 (161·8 to 190·2)	137·8 (123·9 to 148·2)	−22·3 (−25·48 to −18·68)
Cerebrovascular disease	4584·8 (4162·1 to 4968·1)	6446·9 (5963·0 to 7155·2)	40·2 (34·43 to 49·56)	141·6 (128·5 to 153·9)	110·1 (101·8 to 122·2)	−22·5 (−25·56 to −17·30)
Ischaemic stroke	2182·9 (1923·3 to 2430·9)	3272·9 (2812·7 to 3592·6)	50·2 (41·02 to 59·27)	71·3 (63·0 to 79·3)	57·3 (49·3 to 62·9)	−19·6 (−24·52 to −14·97)
Haemorrhagic stroke	2401·9 (2109·4 to 2669·1)	3174·0 (2885·7 to 3719·7)	30·7 (22·23 to 49·07)	70·3 (61·2 to 77·9)	52·8 (48·0 to 62·3)	−25·9 (−30·64 to −14·73)
Hypertensive heart disease	622·1 (525·7 to 783·9)	1068·6 (849·8 to 1 242·2)	74·1 (47·34 to 93·73)	19·3 (16·4 to 24·4)	18·2 (14·5 to 21·3)	−4·5 (−18·86 to 6·41)
Cardiomyopathy and myocarditis	293·9 (243·5 to 346·3)	443·3 (370·1 to 512·0)	51·4 (37·27 to 61·45)	8·2 (6·9 to 9·6)	7·1 (6·0 to 8·3)	−12·6 (−19·98 to −7·68)
Atrial fibrillation and flutter	28·9 (26·0 to 32·4)	112·2 (97·7 to 126·7)	288·1 (246·32 to 335·03)	1·0 (0·9 to 1·1)	2·0 (1·8 to 2·3)	100·0 (77·55 to 124·90)
Aortic aneurysm	99·6 (82·4 to 118·5)	151·5 (124·2 to 180·0)	52·1 (43·75 to 60·91)	3·0 (2·5 to 3·6)	2·6 (2·1 to 3·1)	−15·3 (−20·06 to −10·50)
Peripheral vascular disease	15·9 (14·4 to 17·5)	40·5 (35·5 to 44·9)	155·3 (126·51 to 178·39)	0·5 (0·5 to 0·6)	0·7 (0·6 to 0·8)	34·1 (18·77 to 46·62)
Endocarditis	45·1 (35·6 to 58·6)	65·0 (48·6 to 79·4)	46·3 (23·88 to 65·52)	1·2 (1·0 to 1·6)	1·0 (0·8 to 1·3)	−12·7 (−25·81 to −2·80)
Other cardiovascular and circulatory diseases	478·3 (403·9 to 546·4)	554·6 (499·1 to 654·2)	15·2 (9·38 to 32·52)	13·6 (11·5 to 15·5)	9·3 (8·3 to 10·8)	−32·2 (−35·44 to −22·40)

Global deaths by cardiovascular causes in 1990 and 2013 males and females combined. Deaths in all ages are shown in thousands in the left main column and age-standardized death rates per 100 000 are shown in the right main column. Numbers within parenthesis are 95% uncertainty intervals. *From GBD 2013 Mortality and Causes of Death Collaborators, The Lancet, 2015.* [28] *With permission of the publisher*

However, this seemingly dramatic increase can to a great extent be explained by population growth and a shift in population demographics, with an ageing population in most parts of the world. By comparison, the global age-adjusted death rates due to CVD actually fell by 22% in the same period. However, large differences in improvement are seen between the developed and developing world. E.g. some high-income countries such as Denmark, Norway, South Korea, UK and Israel have seen reductions in adjusted death rates exceeding 65%. [28] The wealthy countries that experience improvement greatly exceeding the global average are contrasted by the poor countries seeing less improvement and some even seeing increased death rates due to CVD. [28] In 2012 the reported rate of death due to CVD per 100 000 Norwegian adults between 35 and 74 years were 136 in males and 53 in females, of which stroke accounted for 23 and 15 deaths, respectively, these numbers are based on ICD-codes

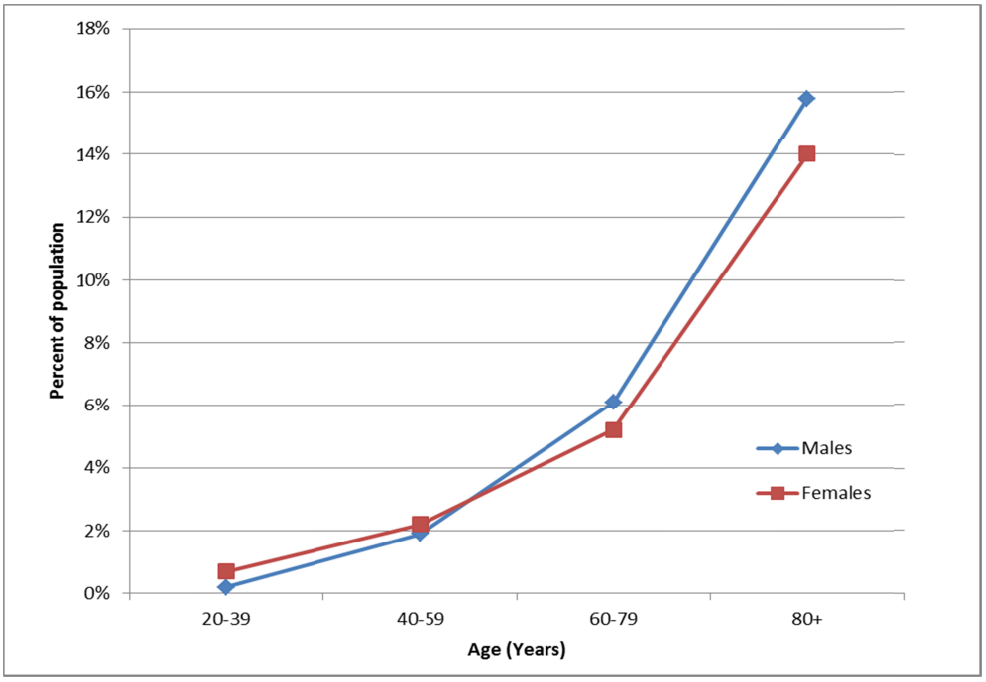
and data from WHO and national health authorities. [29] Improved and more detailed statistics from Norway will be available with reports from the Norwegian stroke registry that started collecting nation-wide data in 2013. [30] Disparities in stroke incidence between high-income and low to middle-income countries increased between 1990 and 2010 as the age-standardized incidence of stroke was decreased by 12% in high-income countries whereas a 12% increase was seen in low and middle-income countries. [31]

A normal body-mass index (BMI) is important to maintain optimal cardiovascular health and increased BMI is associated with increases risk of both ischemic stroke and coronary artery disease independently of high blood pressure, high cholesterol, and high glucose. [32] There has been an increase in BMI in most parts of the globe, contributing to increased rates of CVD. [33] Increasing BMI is also closely linked with hypertension and diabetes mellitus, and the increasing prevalence of this risk factor complex inspired a quite worrying prediction from Circulation: "The changing associations of metabolic risk factors with macroeconomic variables indicate that there will be a global pandemic of hyperglycemia and diabetes mellitus, together with high blood pressure in low-income countries, unless effective lifestyle and pharmacological interventions are implemented." [34] This prediction infers that CVD will continue to cause an increasing proportion of years of life lost (YLL) and thus the trend seen in figure 1 with CVD conquering higher places on the ranking of top 10 causes of YLL will probably continue.

Impact and costs of stroke

Stroke is a potentially devastating event, globally occurring in more than 15 million individuals each year. [35] The mortality of stroke is high with reports indicating as many as one out of three patients with stroke will die and nearly 2/3 of the survivors will suffer from severe stroke related disability. [23,35,36] Stroke is traditionally considered as a disease of the elderly and to some extent rightly so as incidence of stroke does rise exponentially with increasing age (figure 3).

Figure 3. Prevalence of ischemic stroke by age and sex in the United States from 2009 - 2012



The percentage prevalence of ischemic stroke by 20-year age-intervals is displayed in males and females. Source: The US National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Adapted from Mozaffarian D. et al., Circulation, 2015. [29] With permission of the publisher

The incidence of first ever stroke in Norway was calculated at approximately 11 000 / year in 2007. [37] The annual incidence of ischemic stroke in Western Norway was investigated in the years between 1988 and 1997 with a reported average annual incidence of 11.4 / 100 000 in the group aged 15-49 years. [38]

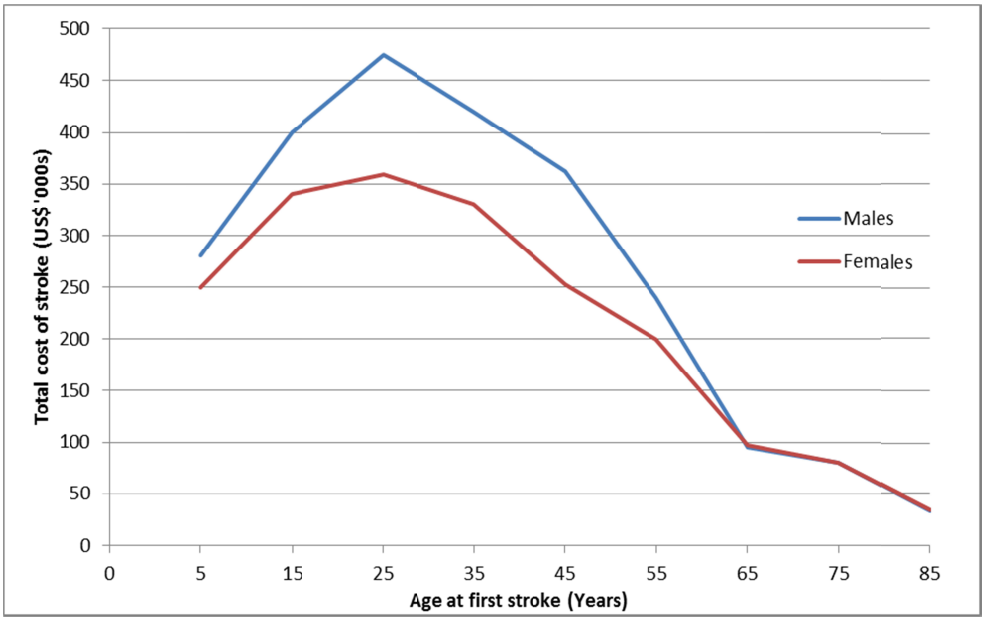
Though less frequent than stroke at higher age, stroke at young age is a serious event. Research in Hordaland in 2004/05 showed that first ever ischemic stroke patients aged < 50 years have 10x higher mortality rates than controls at mean follow up of 12 years and 27% of these young ischemic stroke patients were deceased after a follow up of 18 years. [39] In populations of predominantly European descent the incidence rates between 15-45 years are approximately 10-20 per 100 000 person-years. [40-42] Twice as high incidence rates are observed in blacks and even higher rates are reported in developing countries. [31,41,43]

The estimated direct medical cost of stroke in the US was US$ 22.8 billion in 2009. [44] Estimating the combined cost of treatment, rehabilitation, disability, subsequent need of nursing and absenteeism from work due to stroke amounted to more than € 64 billion in Europe in 2010. [45] The estimated costs of stroke in low-income and middle-income countries are considerably lower compared to high-income countries, though large variations between countries exist, from the lowest estimate of US$ 416 per stroke in Senegal up to US$ 8 424 per stroke in Nigeria. [46] The average cost of one incident stroke in Europe as a whole was estimated to € 21 000 while the yearly cost of a prevalent stroke was estimated to € 5 368 in 2010. [45] Similar estimates have been published in France [47] and Ireland [48].

A Norwegian estimate from 2007 reported costs of NOK 150 000 – 170 000 the first year after stroke and a lifetime cost of NOK 600 000 per stroke. [49] However, the authors found insufficient data to assess the cost of stroke in Norway directly and based their numbers in large part on a previous Swedish estimate. [50] The factors with the most influence on cost of stroke are age at onset, comorbidities and severity of stroke and subsequent disability. [51] The total cost of a stroke is notably higher in young patients, considering additional years of subsequent treatment, years of

disability and loss of work years must be added. [52] The decreasing total cost of stroke with increasing age is seen in figure 4.

Figure 4. Estimate of the total lifetime cost of an ischemic stroke by age of stroke onset in the United States from 1990



A display of the lifetime cost of ischemic stroke in the United States in 1990, displayed in thousands of US dollars per person by age at onset of first stroke.

Adapted from Taylor TN. et al., Stroke, 1996. [52] *With permission of the publisher*

Reducing the burden of cardiovascular disease

The reduction in age-standardized death rates due to both CVD in general and stroke in particular is mirrored by the achievement of the 2010 AHA Impact Goals for disease reduction. [53] The accomplishment of these goals included a 25 % mortality reduction for stroke and CHD, and was presumed to be caused by improvements in

both acute treatment and CVD preventive measures, combined with the implementation of public health measures to increase awareness and knowledge of disease and risk factor reduction in the public. [53] The considerable success of achieving the principal goals of 25 % mortality reduction for 2010 inspired Impact Goals for 2020 stating: "By 2020, to improve cardiovascular health of all Americans by 20 percent, while reducing deaths caused by CVD and stroke by 20 percent". [44] However, they also acknowledged that achieving the goals of reducing smoking and physical inactivity and the goal to maintain obesity and diabetes mellitus at baseline levels were harder to achieve. [53] Therefore the 2020 impact goals emphasize cardiovascular health improvement as the primary means to achieve the goals of mortality reduction. The AHA/ASA saw the need for additional focus on preventive measures and suggested new metrics were designed to aid improvement and ensure attention be paid to the most critical issues. [53] This work resulted in the identification of three medical metrics, consisting of BP, total serum cholesterol and blood glucose, and four behavioral metrics, consisting of smoking, BMI, physical activity and diet, considered as key elements in the assessment of cardiovascular health. [53] These metrics combined were coined "Life's Simple 7" and defined the areas to be measured for the 20 percent improvement in the 2020 Impact Goals. [53]

The reduction in case-fatality rates and mortality due to stroke is seen irrespective of sex, race and age groups in most studies, though some variations in rates of decline are reported. [54-56] The sustained decline in stroke mortality was coined one of the 10 great public health achievements of the 20th century in the US, and as the decline continued, it was again acknowledged as a major public health achievement in the subsequent first decade of the 21st century. [57-59] A corresponding decline in stroke mortality was seen in studies worldwide. Both from combined areas such as western Europe [60] and Great Britain [61,62] and countries such as Brazil [63], France [64,65], Australia [66], Israel [67] and Japan [68]. However, substantial differences in improvement between regions and countries of different economic status have been noted, with substantial improvement in the most developed regions and less improvement in developing regions. [28,31,69] In addition the studies performed in low-income and middle-income

countries are generally of lower methodological quality and the data regarding national disease incidence and mortality is markedly less complete. [28,31]

The improved treatment of blood pressure starting with the results of the Veterans Administration trials in the 1960s, has been awarded credit for the reduction in rate of death due to stroke. [70,71] Increased use of effective treatments alongside implementation of individual screening and public health efforts to improve lifestyle as a combined effort have proven very successful. [58] Hypertension is recognized as the treatable factor with the highest contributing factor to overall stroke risk and is together with lifestyle factors including diet, smoking, physical activity and abdominal circumference considered accountable for 82% of the population-attributable risk for ischemic stroke. [72,73] The same report estimated 90% of the population-attributable risk of stroke could be explained by a total of ten key risk factors. The biggest contributing factor to reduced stroke mortality is considered to be a reduction in the case-fatality rate. [74] The introduction of thrombolysis in acute stroke treatment is an obvious contributing factor. [75] In populations experiencing increased mortality, the increase was more attributable to an increase in case-fatality rate than increasing incidence. [74]

Time trends in stroke incidence – the age disparity

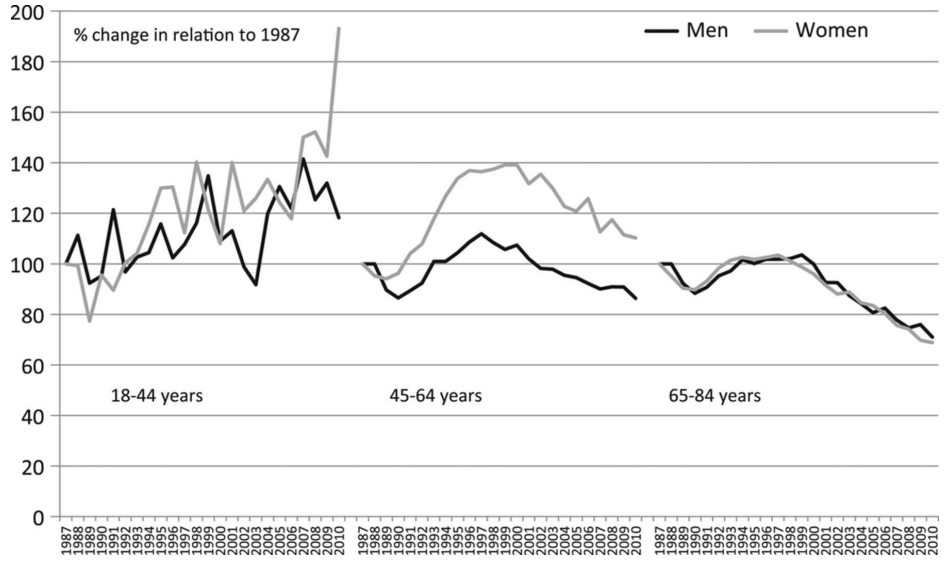
Disparities between rich and poor countries are highly apparent, and there are indications the disparities are increasing rather than decreasing. [31,73] However, disparities in the temporal progression of stroke incidence are not only apparent in economically inequivalent populations. Even though stroke incidence seems to be decreasing in total, stratification by age reveals a worrying trend among the young.

The 2010 global burden of disease study reported an increase of mean age at first stroke, but since this was caused by the demographic age shift of the entire population the authors highlighted that the stroke burden is proportionally greater in individuals younger than 75 years compared to older individuals. [31]

Incidence of both ischemic stroke and spontaneous intracerebral hemorrhage were reduced in high-income countries from 1990 to 2010. [76] A study evaluating stroke incidence in the United States from 1987 to 2011 found significant reduction in both incidence and mortality, but no reduction in incidence could be observed in individuals aged <65 years. [55] A similar disparity was observed in both Mexican Americans and non-Hispanic whites with a temporal decline in incidence in patients aged >74 years yet no reduction in incidence could be seen in patients aged 45-59 years. [77] A nationwide US study on hospitalization rates for acute stroke between 1995 and 2008 found increasing prevalence in hospitalization for ischemic stroke in the age groups 5-14 years, 15-34 years and 35-44 for both males and females, with an exception for the youngest females aged 5-14 years. [78] The Greater Cincinnati/Northern Kentucky Stroke Study showed increasing incidence of stroke in the young and in addition showed the proportion of total strokes occurring before 55 years of age increased from 12.9% to 18.6% in just one decade. [41] This was even ensued by a significant reduction in mean age at first stroke from 71.2 to 69.2 years. [41]

A Swedish study of temporal trends in ischemic stroke incidence over a period of 24 years reported increased incidences of 1.3% per year for men and 1.6% per year for women in young patients aged 18-44 years. [54] Whereas incidence decreased slightly in patients aged 45-64 years with an annual decrease of 0.4% in men and 0.6% women. The steepest declining rates were seen in the oldest patients aged 65-84 years with annual rates declining more than 3.5% as shown in Figure 5. A similar trend of diverging incidence rates in young versus older patients is seen in a Danish study of temporal trends in stroke admissions. [79] Although there are differences between males and females regarding several aspects of stroke, increasing young stroke incidence seems present in both sexes. In a study using the Swedish Hospital Discharge Register three year incidence rates of stroke in 30-65 year olds increased by 19% in men and 33% in women between 1989-1991 and 1998-2000. [80]

Figure 5. Change in incidence of ischemic stroke from 1987 to 2010 in Sweden



Relative percentage change in the incidence of ischemic stroke by sex and age group in people aged 18 to 84 years in Sweden from 1987 to 2010. Incidence of ischemic stroke in 1987 was set at 100%, and subsequent percentages are in relation to that year.

From Rosengren A. et al., Stroke, 2013.[54] With permission of the publisher

The Tromsø study reported time trends of stroke incidence and case-fatality in Northern Norway from 1977 to 2010 and found a slightly increasing incidence of ischemic stroke among young adults. [81]

Summarized, case-mortality is reduced in young and old alike. The efforts taken, predominantly in high-income countries to reduce the burden of CVD and stroke must be considered a great success with respect to the older age groups. Age-adjusted incidence and mortality of stroke have been reduced considerably among the older age groups. However, a similar reduction is not seen among the young. The reason for the diverging incidence trends of ischemic stroke in young vs. older patients is not known. There seems to be a disparity in the prevalence of risk factors and thereby risk factor acknowledgement and commencement of primary preventive ischemic

stroke treatment may be harder to achieve and less frequent among the young. The US National Health and Nutrition Examination Survey (NHANES) shows diabetes, high cholesterol and obesity measured by BMI > 30 has increased in the background population during the two latest decades. [29,82] And although active smoking decreased in the background population The Greater Cincinnati/Northern Kentucky Stroke Study showed substance abuse increased among young stroke patients in a similar time period, with a significant increase in active smokers (49 % in 1993 vs 66 % in 2005) and users of illicit drugs (3.8 % in 1993 vs 19.8 % in 2005). [83]

Etiology and risk factors

Etiology of stroke

Stroke is most commonly caused by reduced arterial blood supply leading to ischemic damage of neural tissue. Of all arterial strokes, 87% have an ischemic cause, 10% are caused by spontaneous intracranial hemorrhage (ICH) and about 3% are caused by subarachnoid hemorrhage (SAH). [29]

Ischemic stroke may be further subcategorized by the underlying cause of the ischemic damage. The most widely used etiological classification is the Trial of Org 10172 in Acute Stroke Treatment classification (TOAST). [84] TOAST contains criteria to define ischemic stroke in five categories: large-artery atherosclerosis, cardioembolism, small vessel disease, stroke of other determined cause and stroke of undetermined cause. The use of TOAST is widespread and its value is well documented, however there are inherent problems [85] with the proportion of stroke by undetermined cause being as high as 40% in some studies. [86] This has led to the creation of alternative classification systems such as the CCS [87] (Causative Classification System) and ASCO [88](Atherosclerosis, Small vessel disease, Cardiac source, Other cause) to increase the accuracy of stroke sub-classification. However, varying results on the resulting classification improvements are reported. One study reported the percentage classified with stroke of undetermined cause was reduced from 39% with TOAST to 26% with CSS, while no improvement was seen when applying the ASCO criteria. [89] Another study compared the classification results of CCS and TOAST on the same population and reported no reduction in the percentage classified with undetermined cause, but an excellent agreement between the two systems. [90] However, a large study using a database of 13 596 stroke patients reported only moderate agreement, and no improvement in the percentage of patients classified as undetermined, while observing a shift in which patients were classified with undetermined cause. [91] The reduced comparability between classification systems represents a big hurdle making interpretation and combination of results across studies difficult.

A reliable and reproducible international classification system is crucial for epidemiological and genetic studies. To date, several alternatives are available, but there is no clear consensus on the optimal classification system for the etiologic causes of ischemic stroke.

Atherosclerosis

Atherosclerosis is a complex inflammatory process in the walls of blood vessels that develops from early childhood throughout life. [92,93] However, atherosclerosis is not just a consequence of aging, though the extent of atherosclerosis in the population increases with age. Atherosclerosis is now known as a result of dynamic inflammatory processes in different stages, and is seen to have a large span in speed of development between individuals. [94] Atherosclerosis has a genetic basis, though this is not completely understood. Several genetic loci have been connected with the development of atherosclerosis and Mendelian disorders causing accelerated and premature atherosclerosis have given valuable insight in both causes and developmental stages of atherosclerosis. [95-98] The pathogenesis involves accumulation of lipoprotein particles and lipoprotein aggregates in the arterial intima at the predilection and often branching arterial sites. [99] Monocytes adhere to and migrate through the endothelium, once inside the arterial intima layer they proliferate and differentiate into macrophages and engulf modified and oxidized lipoproteins, forming foam cells. [100] Accumulations of foam cells, called fatty streaks are prevalent even at a young age and may progress or regress, depending on stimulatory and inhibitory factors. [93,101,102] Among factors promoting progression is the death of foam cells which releases cytokines that promote inflammation, recruiting more monocytes leading to a self-promoting inflammatory process. [103] If inhibitory factors are insufficient to halt the development, the fatty streak may recruit and absorb smooth muscle cells and thereby facilitate the deposition of fibrous material and evolve further into an atheroma. [103] With cells perishing, a necrotic core develops and the maturing complex atherosclerotic lesion is now called an atherosclerotic plaque. [104] Vulnerable plaques are characterized by vascularization and thin fibrous caps that are at high risk of rupture. Rupture causes immediate cascades of reactions including

platelet activation and aggregation and rapid activation of the coagulation cascade via tissue factor. [105] The formation of a thrombus may then block the artery in situ or form circulating embolic thrombi that may block arteries more distally in the arterial bed and induce ischemic damage due to reduced blood flow; thus leading to CVD events such as ischemic stroke, MI and sudden critical peripheral ischemia. [105]

Traditional risk factors for stroke in the young

The concept of risk factors for the development of CVD was introduced in the early post war years and is now a well-established term. [106] Risk factors have been a focus in research since its introduction and many of the public health achievements are due to improved recognition and treatment of risk factors. [57] Risk factors are usually defined as a trait, condition or other factor associated with an increased incidence of a disease. Many risk factors act on the development of disease and may thus be designated as causal risk factors, e.g. smoking act as a risk factor by being a causal factor for lung cancer. [107] Other risk factors may be correlated with increased incidence without causality. Age can arguably be exempt from causality as simply counting years from birth does not cause disease, but in providing knowledge of age groups at increased risk, age still adds valuable information to aid preventive intervention strategies.

Traditional modifiable vascular risk factors, their prevalence and odds ratios for stroke in the young are listed in table 3.

Table 3. Prevalence and impact of traditional modifiable risk factors in young stroke populations in Europe

Risk factor	Prevalence (%)	Odds ratio
Hypertension	19-47%	8.5
Dyslipidemia	17-60%	1.3
Diabetes mellitus	2-11%	1.6 – 11.6
Obesity	10-20%	1.7
Physical inactivity	48-67%	1.5
Smoking	34-57%	2.5 – 2.8
Low fruit and vegetable diet [a]	40-60%	1.12 – 1.35

The table is a modified excerpt of data regarding risk factors from several studies reporting prevalence and or odds ratio of risk factors in young stroke populations.

[a] Data on risk associated with fruit and vegetable consumption and stroke risk are sourced from single studies [108] [109,110] and two meta-analyses [111,112] including a broader age range.

Adapted from studies with age limit < 45 years (Varona et al. [113], Pezzini et al. [114], Ji et al. [115], Nedeltchev et al. [116]) < or ≤ 50 years (Rutten-Jacobs et al. [14], Putaala et al. [24]) and < 55 years (You et al.[117], von Sarnowski et al. [118], Rolfs et al. [119])

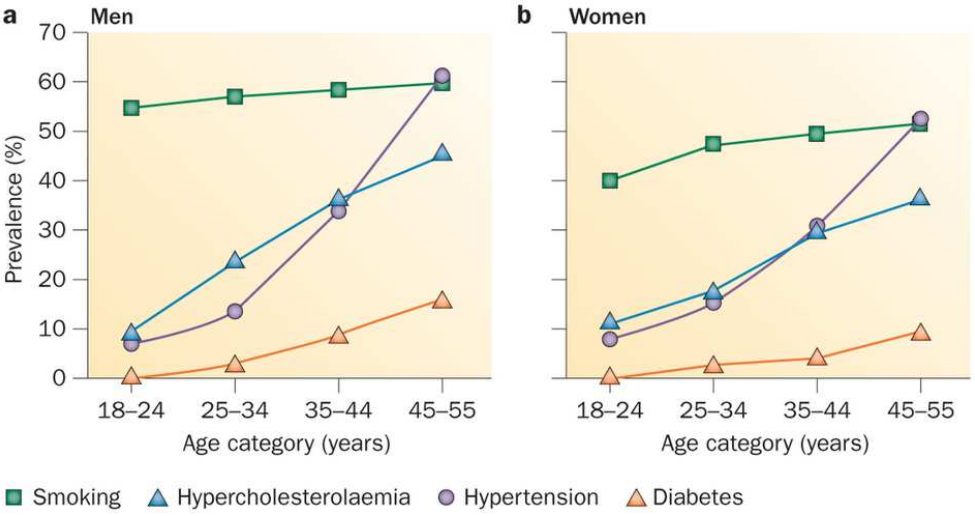
The large prevalence ranges seen in table 3 are to a large part caused by different definitions of risk factors and difference in risk factor prevalence between the geographically diverse study-populations. [73] Additionally, considering the incidence of stroke and the prevalence of most risk factors increase with age, only slight

variations in age limits defining young stroke will have a disproportionately large impact on the prevalence of risk factors as seen in figure 6. [15,23]

The presence of a dose-response relationship strengthens the evidence that a risk factor has a causal influence on a given disease, as shown for high blood pressure, dyslipidemia, diabetes mellitus, obesity, physical inactivity, tobacco exposure and diet. [44] Treatment of these seven risk factors called "Life's Simple 7" shows a dose-response relationship with regard to lowering subsequent risk of disease. [44] Presence of cardiovascular risk factors increases the risk of first time CVD and also the long term risk of recurrent events. [14,120]

Prevalence of risk factors increases with age and the increase steepens when patients exceed > 35 years of age (figure 6). [23] This pattern is seen regarding most traditional risk factors in a study comparing risk factor prevalence in patients aged ≤ 44 with patients aged 45-49 years. [15] When comparing young and middle-aged patients, no big difference is seen in the rate of smoking, but younger patients have a lower prevalence of diabetes mellitus, hypertension, dyslipidemia and atrial fibrillation. [15,24,121] Although less prevalent, the risk factors' relative impact on stroke seems to be higher in young patients, especially the impact of the risk factors hypertension and smoking. The reported ORs associated with these risk factors are 8.5 for hypertension and 2.8 for current smoking in patients of young age (≤ 45 years) compared with ORs of 3.9 and 2.2 in patients aged > 45 years, thus the effect of the risk factors seem to gradually attenuate with age. [73] This may seem a bit contradictory; the older patient will in most cases have a longer time of exposure to the respective risk factor, and one could therefore expect to see a cumulative risk increase with increased duration of exposure. However, the development of disease appears to be remarkably quicker among young patients, exemplified by the young patients exposed to risk factors experiencing ischemic events at a far younger age than average. [122] This accelerated development in presence of risk factors may be caused by an increased susceptibility to the traditional risk factors, and it is suggested this is probably caused by a genetic predisposition to a speeded disease development. [122]

Figure 6: Prevalence of four traditional vascular risk factors in young stroke patients according to age and sex, in Europe



Pooled data from the 15 Cities study, inclusion from 1988-2010,[24] FUTURE study, inclusion from 1980-2010,[14] and SIFAP1 study inclusion from 2007-2010. [118]

From Maaijwee N. et al., Nature Reviews Neurology, 2014. [23] With permission of the publisher

Rare risk factors for stroke in the young

Although traditional risk factors are quite the same in stroke patients, independent of age, [15,123] we have seen that age has a large impact on the prevalence of these risk factors (figure 6). In addition, the young have a relatively higher prevalence of "rare" risk factors and causes of stroke. [23,124] One Finnish study found cervical arterial dissection was the second most frequent cause of stroke at 15 %, [15] a subsequent European meta-analysis reported a similar high percentage of stroke caused by dissection with 12.8%. [86] With more than one out of ten young patients having stroke due to arterial dissection the term "rare" risk factor may seem inapt, and one could argue if terming dissection as a high frequency risk factor in the young would be more appropriate. Rare risk factors and etiologies, their respective strength of association and highest level of evidence are presented in table 4.

Table 4. Rare risk factors and causes of stroke in patients < 50 years

Risk factor	TOAST classification	Prevalence in young patients with stroke	Strength of association	Highest level of evidence
Migraine	Unknown cause	20-24%	Pooled effect estimate ~ 2.0	A1, association only proven for migraine with aura
Illicit drug use	Other (rare) causes	9-20%	OR 2.0 for cocaine; OR 2.3 for cannabis	A2 for cocaine, B for amphetamine, cannabis and heroin
Patent foramen ovale	Possible cardiac embolism; low-risk source	24%, up to 50% of cryptogenic stroke	HR ~ 1.5 (nonsignificant)	A2, contrasting with evidence from B-level studies
Oral contraceptives	Other (rare) cause / unknown	10-40%	Summary OR 2.1	B
Pregnancy/puerperium	Other (rare) cause / unknown	7.5% in women	Relative risk: 8.7 during puerperium, not pregnancy	A2, conflicting results

Etiology ***Non-inflammatory arteriopathies***				
Arterial dissection (cervical and or intracranial)	Other (rare) causes	10-25%	Not reported	A2
Reversible cerebral vasoconstriction syndrome	Other (rare) causes	1-5%	Not reported	B
Inflammatory arteriopathies				
Inflammatory arteritis	Other (rare) causes	3-5% (all autoimmune vasculitis combined)	Not reported	B or C, depending on the underlying autoimmune disorder
Special cardioembolic				
Cardiomyopathy	Other (rare) causes	2-3%	Not reported	A2
Prothrombotic state				
Coagulation factors	Other (rare) causes	Antiphospholipid syndrome: 10% Factor V Leiden: 3-7.5% Antithrombin III deficiency: 5-8% Protein C deficiency: 4-11% Protein S deficiency: 6% (up to 23% in occasional studies) Prothrombin mutation: 2-6%	OR 2.2 OR 1.0 Not reported Not reported Not reported Not reported	A2 for antiphospholipid syndrome, conflicting results; B for other factors, conflicting results

Adapted from Maaijwee et al, Nature reviews neurology, 2014. [23] *With permission of the publisher*

Secondary prevention and prognosis

Recommendations for secondary prevention are well documented regarding most causes of stroke. Extensive and approved guidelines are published and updated with regular intervals. [125] Contrary to stroke caused by atrial fibrillation or atherosclerosis, a primary effective preventive strategy to reduce the risk of stroke caused by or in presence of untraditional risk factors such as arterial dissection or patent foramen ovale (PFO) lack sufficient documentation. Recommendations for treatment of "rare" causes of stroke are included in the latest guidelines, but with a weaker level of recommendation and lower class of treatment effect. [125] Because of the insufficient evidence-based knowledge and the high rates of stroke by unknown cause in the young, a large proportion of young patients may get varying secondary preventive treatment. Several studies are recently published and others are underway to identify the optimal strategy for prevention of stroke in patients with arterial dissection and PFO. The Cervical Artery Dissection in Stroke Study (CADISS) study, a randomized study comparing antiplatelet and anticoagulant drugs found no difference in efficacy of preventing recurrent stroke or death. [126] This provided some answers in reply to the systematic Cochrane review problematizing the lack of data regarding treatment for cervical artery dissection. [127] A recent Cochrane review included three randomized controlled trials (RCTs) and summarized the current data comparing operative closure of PFO versus best medical therapy, finding no significant benefit of closure, but an increase in the risk of new-onset atrial fibrillation (RR 3.50, 95% CI 1.47 to 8.35). A reduction in risk for recurrent stroke was implied with the Amplatzer PFO occluder, however the HR of 0.38 (95% CI 0.14 to 1.02) did not reach statistical significance. [128] Two studies; the CryptoCard study and the Paradoxical Embolism Prevention Study in Ischemic Stroke (PEPSIS) are awaiting assessment and three more studies; Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE), Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENSE-PFO) and GORE® HELEX® Septal Occluder / GORE® Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients – (The Gore REDUCE Clinical Study) are still ongoing. An updated review is planned and expected when

additional data become available. [128] This data is highly welcomed; as several studies have failed to provide definitive answers regarding preventive treatment this underpins the need for a better understanding of the pathophysiologic and genetic background for the diverse etiologic entities in young stroke.

The ischemic event at a young age is a marker of increased mortality and morbidity. [39] A Study from western Norway found that the excess mortality in young stroke patients to a high degree were caused by vascular disease, as 47.6% of patients dead at follow up were dead due to cardiovascular disease. [39] A Dutch study found an excess long term risk of death associated with young stroke, and reported that 74% of the excess risk of death could be attributed to vascular disease. [129] One study from Tartu, Estonia even reported 5 year mortality rates as high as 29 %. [130]Although they did not report on cause of death, the authors did however comment that the mortality due to cardiovascular causes is high in the Estonian population in general, thus implying cardiovascular causes are a likely cause of many of the deaths in the young stroke population. [130]

The prevalence and degree of exposure to risk factors in addition to the etiologic stroke subtype according to TOAST both influence the subsequent risk of CVD events and mortality. [14] Patients with large-artery, small-artery and cardioembolic stroke are at higher risk of experiencing a subsequent stroke. Patients with large artery stroke suffer the highest risk of stroke, any CVD and any mortality, with a 20-year cumulative risk for any CVD of nearly 53%. [14,23] This further supports the findings of cardiovascular disease as a significant contributor to the excess mortality seen in young stroke patients. Conversely, the most favorable categories with respect to recurrent events and mortality are found to be the unknown or cryptogenic category and the “other determined” category including arterial dissections, with dissections shown to be associated with a low risk of recurrent stroke, and also the lowest risk of other recurrent events in many studies. [14,131-133]

Sex differences in stroke

The Framingham Heart Study (FHS) found a sex difference in lifetime risk of stroke among those aged 55 to 75 years, with females having five percentage points higher risk compared with males (15% vs. 20%) probably caused by the higher life-expectancy of females. [134] Males seem to have a slightly higher incidence rate overall, but the sex discrepancy seems to vary with age as shown in figure 1. [29,38] Females have higher incidence before 30 years of age while male incidence exceeds female incidence at higher ages. [15,24]A big European study on 5023 stroke patients aged 18 to 55 years found that although males dominated the population total with 59%, females outnumbered males almost 2 to 1 in the age group 18-24 years, with 65% of the total. [119] In the Greater Cincinnati/Northern Kentucky Stroke Study this pattern was also apparent with a 1.7 female to male incidence ratio in patients younger than 34 years and converging incidence ratios at higher ages. [135]

Mortality due to stroke is similar before 45 years of age, but is substantially lower in females aged 45-74.[136] The change in case fatality of stroke over time also differs between males and females, a temporal decline is evident in males, but not in females. [137] This pattern is further supported by the Heart Disease and Stroke statistics update from 2015 showing a slightly steeper decline in age-adjusted stroke mortality in males compared with females (-58.5% vs. -55.2%). [29] The absolute excess risk of death associated with vascular disease in the young stroke patients peaked at 10-15 years after stroke, and the observed peak was more pronounced in men compared to women. [129] Thus indicating vascular disease is a greater contributor to the excess long-term mortality in males compared to females. However, an Australian study evaluating sex differences in 1316 first ever strokes by a population based register found the 28 day mortality was higher in females compared with males with 32% vs 21%. [138] However, the difference in mortality was to a large degree explained by more severe strokes in female, since adjusting for this attenuated the association considerably. [138]

Some risk factors are strictly sex specific such as pregnancy, sex hormones and use of oral contraceptives while others have differing distributions between sexes. [139] The risk associated with oral contraceptives is found to be associated with ethinyl estradiol content in a dose related pattern, meaning newer generation contraceptives with low dose ethinyl estradiol (e.g. 20µg) confers a very low absolute risk increase. [140] Males more frequently have an atherosclerotic cause of ischemic stroke and develop atherosclerosis about 10 years earlier than females. [24,141]

A sex difference in the response to intravenous rTPA treatment with greater treatment response in females has been shown. [142,143] However, a corresponding sex difference regarding intra-arterial rTPA treatment has not been shown so far. [144,145]

Family history

Family history and cardiovascular disease

A positive family history (FH), prevalent among patients with CVD is considered a risk factor for CVD. [29,146-148] Several twin and sibling studies support the role of inherited factors in CVD and stroke.[149] However, clustering of CVD within families may be caused by genetic factors directly or by a related familial aggregation of risk factors such as hypertension, diabetes mellitus and obesity or behavioral factors such as smoking, alcohol consumption and or dietary and physical activity habits. [150,151] These risk factors and behavioral habits may in turn have both genetic and environmental contributors. Thus, CVD and stroke must be considered as complex traits, and the genetic contributors can increase the risk without necessarily leading to an event in all cases.

Data supporting an association between a FH of CVD and CAD is substantial.[152-156] The risk of heart attack is approximately doubled if a premature, defined as onset <55 years in fathers and <65 years in mothers, parental heart attack is reported. [146] There is evidence that increasing family history of CVD, i.e. multiple first degree relatives with CVD, confers a higher risk of own events. [157] In addition the age of parental event strongly influences the risk of events in offspring, with premature parental events conferring higher risk than events at a later stage in life. [158] A premature parental event even confers a higher risk for CAD among offspring before 55 years of age than CAD after the age of 55 in both men and women. [152] The higher risks of CAD with premature vs. late FH events and multiple family members with disease are shown in table 5.

Table 5. Odds ratios for patient risk of heart attack with different combinations of parental heart attack history

Family history	OR (95% CI)
No family history	Reference – 1.0
One parent with heart attack ≥ 50 years of age	1.67 (1.55 – 1.81)
One parent with heart attack < 50 years of age	2.36 (1.89 – 2.95)
Both parents with heart attack ≥ 50 years of age	2.90 (2.30 – 3.66)
Both parents with heart attack, one < 50 years of age	3.26 (1.72 – 6.18)
Both parents with heart attack < 50 years of age	6.56 (1.39 – 30.95)

Adapted from the INTERHEART study by Chow et.al. [158] With permission of the publisher

A British study aimed to compare the relative effects of a FH of stroke and CHD to assess the impact on proband risk of stroke compared to CHD. [159] They found the association between a FH of CHD and patient CHD was stronger than the corresponding association between a FH of stroke and patient stroke. [159] Further they reported a clustering effect for FH of CHD, meaning more family members with CHD, was associated with increasing risk for CHD, whereas no such clustering effect was obvious for a FH of stroke. [159]

Premature PAD has been shown to be strongly associated with a family history of CVD, including cerebrovascular disease, CAD and PAD. [160] The same research group later expanded on these results by showing a positive FH of CVD conferred an almost threefold increase in risk of PAD (OR 2.76), independent of other risk factors such as smoking, thereby further elucidating the strong role of FH as a risk factor for PAD. [161] A family history of PAD is associated with both increased prevalence and severity of PAD in patients. [162] Another group found an association between PAD in patients and a FH of CAD and PAD, with the strongest association for a FH of PAD. [163] A

study including patients with presumed atherosclerotic disease at one or several different arterial sites, i.e. stroke, CAD, PAD or abdominal aortic aneurysm found no increased prediction of subsequent events with a positive FH of CVD, with the exception that a paternal history of PAD was associated with subsequent PAD in patients. [164] This result indicates that high risk individuals who have already suffered a clinical CVD event may not experience increased risk prediction from a positive FH.

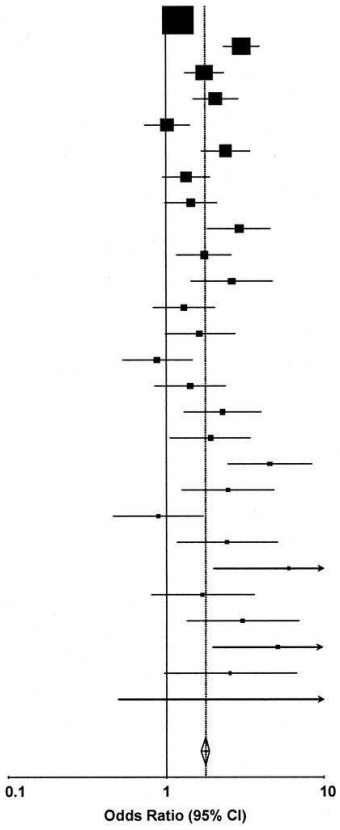
Family history and stroke

The path towards connecting a FH of CVD with increased risk of stroke with the same level of evidence as FH and CHD has been more difficult. Studies regarding FH and stroke have been hampered by a lack of diagnostic tools able to differentiate ischemic stroke from hemorrhagic stroke. Even though these tools are now widely available, studying the effect of FH on disease is contingent upon the parent generation and therefore the diagnostic tools available at the time of their diagnosis. There have been a myriad of variations in the definition of a positive FH used to analyze the effect of FH on stroke risk, from using a FH of MI [154], a combined history of stroke and or MI [165], stroke alone [166] and combining a history of fatal or non-fatal vascular events in addition to intermediate diseases such as HT and DM. [167-169] Although, FH today is acknowledged as a risk factor for stroke, there have been some contradictory results. Figure 7 shows case-control studies investigating the effect of FH on the risk of stroke. A newer case-control study found the risk of stroke and MI differed with a FH of stroke and a FH of MI, while a FH of MI was associated with both ischemic stroke and MI, a family history of stroke was not clearly associated with neither. [170] However, if multiple relatives were affected, the risk of subsequent stroke or MI in patients was increased. With reported stroke, either hemorrhagic or ischemic, in more than 40% of first degree relatives the calculated OR for stroke in probands was 6.78 (95% CI 1.15 - 40) whereas the OR for MI was 8.44 (95% CI 1.74–41). [170]

A similar variation in the reported impact of the FH on risk of stroke can be seen in cohort studies. A prospective follow up of 14371 individuals found FH of stroke an independent predictor of incident stroke. [171] However, an Atherosclerosis Risk in Communities Study (ARIC) found FH was only a predictor for subclinical stroke detected by magnetic resonance imaging (MRI) and not for clinical stroke. [172] And another study found no predictive value of a FH of stroke to predict subsequent ischemic stroke after TIA. [173] A large and systematic meta-analysis combined the cohort studies and found FH a significant risk factor for stroke (figure 7). [174]

Figure 7. Meta-analysis of case-control studies showing odds for stroke patients vs. controls to have a positive family history (FHx) of stroke (ordered by variance).

	Positive FHx / Patients		OR	95% CI
	Stroke patients	Controls		
Jerrard-Dunne et al 2003[49] ★	319 / 944	235 / 789	1.20	1.0-1.5
Toyoshima 1997[68]	142 / 251	755 / 2518	3.04	2.3-4.0
Caicoya et al 1999[35]	157 / 470	106 / 477	1.76	1.3-2.3
Spriggs et al 1990[61]	124 / 327	90 / 397	2.08	1.5-2.9
Starr et al 2001[62]	87 / 225	173 / 454	1.02	0.7-1.4
Polychronopoulos et al 2002[59] ★	168 / 351	66 / 239	2.41	1.7-3.4
Thompson et al 1989[63]	76 / 190	163 / 494	1.35	1.0-1.9
Vitullo et al 1996[64] ★	86 / 237	67 / 237	1.45	1.0-2.1
Li et al 1990[51] ★	73 / 449	28 / 449	2.92	1.8-4.6
Liao et al 1997[52]	40 / 105	790 / 3039	1.75	1.2-2.6
Matias-Guiu et al 1990[55] ★	122 / 386	15 / 100	2.62	1.5-4.7
Hu et al 1989[47]	23 / 143	1097 / 8562	1.30	0.8-2.0
Abu-Zeid et al 1977[29] ★	41 / 410	26 / 410	1.64	1.0-2.7
Herman et al 1983[45]	29 / 132	58 / 239	0.88	0.5-1.5
Kubota et al 1997[50] ★	43 / 159	33 / 159	1.42	0.8-2.4
Feigin et al 1998[38] ★	43 / 237	21 / 237	2.28	1.3-4.0
Margaglione et al 1994[53] ★	41 / 106	27 / 109	1.92	1.1-3.4
Issaeva and Mikheev 1967[48]	40 / 66	38 / 150	4.53	2.4-8.4
Graffagnino et al 1994[42] ★	35 / 85	19 / 86	2.47	1.3-4.8
Alter and Kluznik 1972[31]	32 / 80	30 / 70	0.89	0.5-1.7
Fonte et al 1993[39] ★	25 / 220	11 / 220	2.44	1.2-5.1
Gifford 1966[41]	48 / 126	4 / 43	6.00	2.0-17.8
Shintani et al 1993[60] ★	20 / 45	26 / 81	1.69	0.8-3.6
Muniz et al 1993[56]	24 / 76	10 / 76	3.05	1.3-6.9
Peng and Zhao 1999[57] ★	24 / 90	6 / 90	5.09	2.0-13.2
Heyden et al 1969[46] ★	17 / 40	9 / 40	2.55	1.0-6.7
Diaz et al 1986[37] ★	5 / 41	2 / 41	2.71	0.5-14.8
TOTAL	**1884 / 5991**	**3905 / 19806**	**1.76**	**1.7-1.9**



Significance p< 0.00001
Heterogeneity p< 0.00001

★ The case-control studies separating ischemic and hemorrhagic stroke in the proband.

Adapted from Floßmann E. et al., Stroke, 2004. [174] *With permission of the publisher*

Several studies investigating the relation between stroke and FH of stroke have grouped ischemic stroke and cerebral hemorrhage together. [170,171,173-176] A systematic review [174] on the genetic epidemiology of ischemic stroke reported that none of three initially identified twin studies, five of 19 cohort studies and 20 of 37 case-control

studies separated between ischemic and hemorrhagic stroke in the proband, and of the final included studies only 2/9 cohort studies and 15/28 case-control studies separated ischemic and hemorrhagic stroke in the proband. [174] Regarding stroke in the FH, there are even fewer attempts to separate ischemic stroke from ICH. One case control study separates a FH of SAH while grouping a FH of IS and ICH together. [167] One study by Kubota et al. [177] separates different types of stroke in the phrasing of the question regarding FH but groups them together when analyzing FH. [178] Another study by Graffagnino et al. [179] states that attempts were made to separate a FH of stroke due to infarction from a FH of stroke caused by cerebral hemorrhage, but unfortunately only provides combined FH data and no data with the two separated. [179] Neither of the two included cohort studies that specified proband stroke separated between a FH of ischemic versus hemorrhagic stroke. [172,180] Two newer studies, not included in the review, also refrained from distinguishing between a FH of ischemic and hemorrhagic stroke, one study [175] stating this was a result of the difficulty distinguishing IS from ICH by history alone. [181] However, a Framingham heart study did specify that only atherothrombotic stroke was included in the combined endpoint of several CVD events and found that a validated FH of premature CVD independently predicted CVD events among their middle-aged cohort participants. [146] In addition an Oxford Vascular study comparing the heritability of stroke between males and females did not include a known history of hemorrhagic stroke as a part of the FH. [182]

The matter of testing an association between FH and stroke is further impeded by the different etiological mechanisms causing ischemic stroke that may have differing heredity. Indeed, a Greek study found FH of stroke an independent risk factor for both hemorrhagic and ischemic stroke, and a risk factor for the two TOAST subtypes; large-artery stroke and small-artery stroke, but not for cardioembolic or undetermined stroke subtype. [166] The finding that a positive FH was more frequent among large-artery and small-artery stroke subtypes has subsequently been confirmed by a population study, [183] a case-control study [165] and a large meta-analysis. [174] And the result is consistent between ethnicities as a study with a large proportion of patients

from an ethnic minority showed similar results. [181] The risk associated with a positive FH of stroke was higher in patients presenting with large artery stroke at a young age, with a calculated OR of 4.5 in patients ≤ 55 y compared to a an OR of 1.9 in stroke patients aged ≤ 70 y. [165] This relationship was also present in small vessel stroke and was subsequently confirmed by another study showing the same pattern of association between a positive FH and young age at stroke onset. [165,183] A FH of MI is shown to increase the risk of ischemic stroke and is more frequent among patients with large-artery stroke subtype. [183] However, a recent study found no differences in rates of positive FH of stroke between stroke subtypes according to TOAST except for a lower frequency of positive FH in stroke patients with arterial dissection. [184] Another study on a patient cohort with premature CVD defined as CVD before 60 years of age, found the risk of subsequent stroke was not increased in patients with a FH of CVD or with a FH of stroke only (HR 1.0, 95%CI 0.4-2.4). [164]

The Family Heart Study showed that having one first-degree relative with a history of stroke increased the odds of stroke with 50% in both men and women. [185] The Framingham Heart Study showed a parental stroke before the age of 65 years was associated with an increased risk of stroke at any age in offspring. [186] The increased risk associated with a FH was significant regarding all stroke combined, ischemic stroke and atherothrombotic stroke both in parents and patients. [186] When adjusting for possible confounders the increased risk associated with a positive FH was slightly attenuated. [186] However, the hazard ratio for ischemic stroke was >3 times higher in patients with a parental history of ischemic stroke before 65 years of age. [186] Thus, a family history of young stroke seems to especially increase the risk of stroke at a young age.

In summary, although some conflicting results have been published, the vast majority of data acknowledges family history as a robust risk factor for stroke, especially in young patients. [174,187] Albeit the increase in risk of stroke associated with a positive FH may not be overwhelming with a 30% to 76% increase (OR 1.3 - 1.76) as estimated in a review by Flossman et al. [174]

Genetics in cardiovascular disease

Cardiovascular disease may occur sporadic or cluster within families. However, most CVD types do not follow a classic Mendelian inheritance where genotype = disease phenotype. Monogenic diseases associated with elevated risk of stroke, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Fabry disease and familial hypercholesterolemia are acknowledged. [95,149,188,189] The majority of the known monogenic conditions are considered to be quite rare, with population prevalence of less than 1 per 100 000 to 2-3 per 100 000, depending on the population studied. [189,190] Somewhat more frequent conditions, like Neurofibromatosis type 1 and familial Moyamoya disease may also cause stroke and are known to be found with higher frequencies in some populations, but the monogenic conditions combined still account for a very small proportion of total strokes worldwide.[190,191]

One approach to investigate the genetic predisposition in predominantly polygenetic disorders is the genome-wide association studies (GWAS) approach; this approach is based on using large data material to identify genetic loci associated with disease. [192] The identification of a genetic hot spot more common among diseased, e.g. stroke patients gives the opportunity for further investigation of the function of the respective gene and gene-products.[193] Several genetic markers have been identified both for stroke[194] and CAD[195] and overlap in genetic markers between the two has been shown, especially for the large artery atherosclerosis subtype of stroke. [196]

The METASTROKE collaboration was initiated to enable large meta-analyses of GWAS and did verify several previously identified genetic loci to be associated with increased risk. [192] Further, they found that all of the associated loci were subtype specific. [192] This is not surprising as stroke etiology subtypes should be considered different entities with differing pathophysiological traits resulting in ischemic stroke as the common outcome. It is therefore likely that genetic loci are mostly associated with a single underlying etiological subtype of stroke. And conversely it will be quite

unlikely to find genetic loci strongly associated with stroke as a whole in these analyses. The authors therefore added the conclusive remark that a careful identification of stroke subtypes for future research would increase the possibility of identifying the different genetic pathophysiological mechanisms responsible for disease. [193]

Heritability of the different ischemic stroke subtypes has been calculated from previously provided genome-wide data, resulting in heritability estimates of 40% for large-vessel stroke, 33% for cardioembolic stroke, 16% for small-vessel stroke, and 38% for the combined endpoint of any ischemic stroke.[150,197] Single nucleotide polymorphisms in different loci have shown association with blood pressure variability[198] and large artery stroke.[199] However the ORs associated with the non-Mendelian genetic variants are modest at best, with the highest OR of 1.39 for a mutation in the *HDAC9* gene on chromosome 7 reported in one review. [150] The risk allele frequency for this mutation was 16% and the population-attributable risks to any one of the genetic variants is likely to be small. [150] Thus, the value of genetic findings in improving cardiovascular risk prediction beyond tools incorporating family history has yet to be shown. [200] The international stroke genetics consortium has recently published two recommendation papers outlining a common standard methodology in standardizing case ascertainment, risk factor definitions, phenotyping of stroke subtype and outcome measurements across studies. [201] The second recommendation involves methods for biological sampling and storage in a biorepository to increase availability to share and conjoin data. [202] This clearly outlines that homogenization of study protocols and data collection both eases and increases comparability between studies and strengthens the reliability of results from pooled data.

Verification of the cardiovascular family history

Family history is a well proven, easily accessible and inexpensive method to obtain information about and evaluate the possible heredity of disease.

Stroke patients have by definition suffered brain damage, and in more than 80% of cases the damage is caused by ischemia.[29] These cerebral infarctions can easily be detected by MRI DWI.[203] It is known that a large proportion of patients will suffer subsequent cognitive difficulties after stroke.[204,205] Even a decade after stroke, nearly half of stroke patients score below average on cognitive performance testing, with cognitive impairments in working memory, processing speed and or attention as the most common problems.[205] The degree of cognitive impairment depends on the size and location of the infarcted area. Cognitive deficits can potentially reduce the validity of the patient-provided FH and thereby reduce its value as a tool to evaluate the heredity of stroke. The validity of a patient provided FH has been tested previously with a variety of methods, e.g. medical records and or concordance with family members.[206-211] Varying accuracy has been reported and some patient characteristics have been shown to influence the accuracy. Increasing age has been shown to reduce the accuracy, while female sex is associated with increased accuracy of FH reporting.[208] However, most of the studies testing the accuracy of FH were performed in presumably healthy cohorts, with a few exceptions assessing the accuracy of FH in patients with CAD.[212,213] However, these participants had no or minor problems of cognitive impairment compared with stroke patients. A Greek study reported they verified the FH provided by patients in a structured interview by interviewing first-degree family members the same way. [166] However, no data regarding the accuracy of the patient provided information or the additional gain of this strategy was provided.[166] One study on relatives´ clustering of disease and risk factors in stroke patients' siblings compared with the siblings of patient spouses also tested the agreement between the relatives' questionnaire and the medical history provided by their treating physician with an overall agreement of 97%.[214] To my knowledge, studies testing the accuracy of information provided by patients suffering stroke are lacking.

Carotid intima-media thickness and cardiovascular disease

Carotid intima-media thickness (cIMT)

Carotid intima-media thickness (cIMT) is an ultrasound acquired measurement of a double-line reflex pattern representing the luminal-intimal and the medial-adventitial interfaces of the carotid artery. Performed on the far wall of the carotid artery this measurement corresponds well with IMT thickness as measured on histological specimens.[215] Near wall IMT measurements suffers from the echogenicity of the adventitia masking the adventitial-medial boundary and thereby gives rise to systematic measurement error, in addition, near wall measurements are more sensitive to changes in equipment gain settings.[216,217]

Methods of measuring carotid intima-media thickness

Recommendations on use of cIMT for risk assessment and prediction are somewhat conflicting. In 2010 the AHA/American College of Cardiology (ACC) presented guidelines where cIMT was given a class IIa recommendation for CVD risk assessment in intermediate risk asymptomatic adults. [218] The European Society of Hypertension/European Society of Cardiology recommends ultrasound scanning of the carotid arteries to detect vascular hypertrophy or atherosclerosis with a Class IIa recommendation and level of evidence B. [219] An update of the Mannheim Carotid Intima-Media Thickness and Plaque Consensus from the advisory board of the "Watching the Risk" symposium, published in late 2012, stated cIMT and plaque presence are recommended for the initial detection of CHD risk in asymptomatic patients if at intermediate risk and or risk factors were present. [220] However, the 2013 guidelines recommend against the use of cIMT for risk prediction in clinical practice. [221] This has been problematized in a recent review, in which the authors point out that most medical insurers deem cIMT and plaque presence investigational and the data insufficient to justify reimbursement of CIMT measurements for CVD risk

assessment. [222] They interpret the recent AHA/ACC guideline adjustment as being in line with this insurer policy. [222]

Several studies have shown association between cIMT and future CVD events. [222] The Kuoppio Ischaemic Heart Disease study showed 11% increased risk of MI with each 0.1mm increment of cIMT. [223] In the following years several large clinical studies like the Atherosclerosis Risk In Communities study[224], the Cardiovascular Health Study[225], the Rotterdam Study[226], the Malmö Diet and Cancer Study[227] and the Carotid Atherosclerosis Progression Study[228] produced similar results showing CVD risk prediction with assessment of cIMT. However, when testing if cIMT adds additional prognostic value beyond traditional risk factor scoring, most studies have found little or no additional prognostic value. [229-231] The contradictory results regarding the value of cIMT in assessing and predicting CVD risk is further portrayed by the conflicting results from two meta-analyses. One meta-analysis published in 2007 found the relative risks of cardiovascular events were increased with 1.15 with each 0.1mm increase in cIMT. [232] A second meta-analysis published in 2012 found no meaningful addition to CVD event prediction when cIMT was added to conventional risk prediction models. [233]

The explanation for the conflicting results and the wavering recommendations regarding cIMT measurements is probably caused by heterogeneous study protocols. [222] A multitude of different cIMT measurement methods have been used in studies evaluating cIMT as a prognostic indicator. Some use only one measurement from one site, with CCA as the most common, whereas others use multiple measurements from one or several sites. Some have used the mean of one segment measurements whereas others use the mean of several IMT or the mean of maximal IMT or just the maximal IMT. In addition there is heterogeneity of whether plaque was included or actively excluded from measurements. The carotid ultrasound parameters used in studies of cIMT as a prognostic indicator of cardiovascular events, inclusion or exclusion of plaque into measurements, endpoints and the odds ratio (OR), relative risk (RR) or hazard ratio (HR) associated with IMT are presented in table 6.

Table 6. Carotid intima-media thickness (cIMT) as a prognostic indicator of cardiovascular events

Study	Carotid Ultrasound Parameters: segments, walls, side, type of analysis	Plaque	Endpoints	cIMT, RR/HR/OR (95% confidence interval)
KIHD [223]	CCA,N+F, bilateral, mean of maximal IMT	not included	MI	0.1 mm increment; RR: 2.14 (1.08–4.26)
CHS [234]	CCA and ICA, N+F, bilateral, mean of maximal IMT	included	Stroke, MI, CV death, all-cause mortality	Highest tertile, HR: 1.84 (1.54–2.20)
ARIC [224]	CCA, BIF, ICA, F, bilateral, mean IMT	included	MI, CV death	IMT ≥1.0 mm, HR, women: 5.07 (3.08–8.36); men: 1.85 (1.28–2.69)
CAPS [18]	CCA, BIF, ICA, F, bilateral, mean IMT	not specified	Stroke, MI, death	1 SD increase, HR, CCA: 1.17 (1.08–1.26); BIF: 1.14 (1.05–1.24); ICA: 1.09 (1.01–1.18)
MDCS [227]	CCA, F, right, mean IMT	included	MI, CV death	Highest tertile, HR: 1.50 (0.81–2.59)
Rotterdam Study [235]	CCA,N+F, bilateral, average of max IMT	not specified	MI	Highest quartile, HR: 1.95 (1.19–3.19)
LILAC [236]	CCA, N+F, bilateral, average IMT	not specified	All-cause mortality	0.3-mm increase, RR, left: 1.65 (1.08-2.5); right: 3.3 (1.4–7.7)
Three-City Study [237]	CCA, N+F, bilateral, mean IMT	excluded	Revascularization, MI, angina, CV death	Highest quintile, HR: 0.8 (0.5–1.2)
IMPROVE [238]	CCA, BIF, ICA, bilateral, max and mean IMT	included	Revascularization, TIA, stroke, angina, MI, heart failure, CV death	1 SD mean IMT increase, HR, CCA: 1.33 (1.18–1.50); BIF: 1.28 (1.12–1.47); ICA: 1.34 (1.18–1.51)
MESA [230]	CCA, F, right, mean of maximal IMT	excluded	Revascularization, MI, CV death	HR: 1.17 (0.95–1.45)
The Edinburgh Artery Study [239]	CCA, F, bilateral, maximal IMT	not specified	Stroke, angina, MI, PAD	IMT ≥0.9 mm, OR: 1.59 (1.07–2.37)
Framingham Offspring Study [240]	CCA, ICA, F, bilateral, mean and maximal IMT	excluded	Stroke, angina, MI, heart failure, PAD, CV death	1 SD increase, HR, mean CCA: 1.13 (1.02–1.24); max CCA: 1.21 (1.13–1.29); max ICA: 1.21 (1.13–1.29)
Charlottesville study [241]	CCA, BIF, ICA, N+F, bilateral, mean IMT	included	Revascularization, TIA, stroke, MI	Highest quartile, OR, CCA: 2.4 (0.6-9.4); BIF: 5.8 (1.3-26.6); ICA: 7.4 (0.9-61.5)
FATE [242]	CCA, right, mean IMT	excluded	Revascularization, stroke, angina, MI, CV death	1 SD increase, HR: 1.45 (1.15–1.83)

Table continues

Table 6. - continued

OSACA2 [243]	CCA, BIF, ICA, N+F, bilateral, mean of maximal IMT	included	Revascularization, stroke, MI, PAD	1 SD increase, HR: 1.57 (1.11–2.20)
Tromsø Study [244]	CCA, BIF, N+F, right, mean IMT	included	MI	Highest quartile, RR, men: 1.73 (0.98–3.06); women: 2.86 (1.07–7.65)
CCCC [245]	CCA, F, bilateral, maximal IMT	excluded	Revascularization, MI, CV death	1 SD increase, RR: 1.38 (1.12–1.70)
APSIS [246]	CCA,F, left, maximal IMT	Not specified	Revascularization, MI, CV death	IMT >1.02 mm; RR, revascularization: 1.07 (0.56–2.04); MI or CV death: 0.78 (0.36–1.70)
Cournot et al. [247]	CCA, ICA, F, bilateral	excluded	Angina, MI, CV death	IMT >0.63 mm, HR: 2.26 (1.35–3.79)

APSIS = the Angina Prognosis Study in Stockholm; ARIC = Atherosclerosis Risk in Communities (ARIC); BIF = bifurcation; CABG = coronary artery bypass graft; CAPS = Carotid Atherosclerosis Progression Study; CCA = common carotid artery; CCCC = Chin-Shan Community Cardiovascular Cohort Study; CHS = Cardiovascular Health Study; CI = confidence interval; CIMT = cardiac intima-media thickness; CV = cardiovascular; F = far wall; FATE = Firefighters and Their Endothelium study; IMT = intima-media thickness; HR = hazard ratio; ICA = internal carotid artery; IMPROVE = Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population; KIHD = Kuopio Ischemic Heart Disease Risk Factor Study; LILAC = Longitudinal Investigation for the Longevity and Aging in Hokkaido County; MDCS Malmo = Malmo Diet and Cancer Study; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; N = near wall; NOMAS = Northern Manhattan Study; OR = odds ratio; OSACA2 = Osaka Follow-up Study for Carotid Atherosclerosis; PCI = percutaneous coronary intervention; PAD = peripheral artery disease; RR = relative risk; TIA = transient ischemic attack.

Adapted from Naqvi and Lee. JACC: Cardiovascular Imaging, 2014. [222] *With permission of the publisher*

Choosing one segment and one cIMT measurement representable for all research purposes would increase homogenization of studies and improve comparability. However, studies have different objectives. Therefore the one size fits all approach would be inadequate. Measurements of IMT from different segments of the carotid artery vary in their respective associations with cardiovascular risk factors. [248-250] The

choice of segment and method of measurement have therefore been debated.[165,251,252] The Mannheim consensus concluded that measurements of cIMT should occur in a plaque free region.[220] The British Regional Heart Study found CCA-IMT showed strong association with risk factors for stroke and prevalent stroke, bifurcation IMT on the other hand was associated with CHD risk factors and with prevalent CHD. [253] Nearly 27% of variation in CCA-IMT was explained by cardiovascular risk factors whereas the corresponding numbers for the BIF-IMT and ICA-IMT were 11% and 8%, respectively. [254] Interestingly, low-density lipoprotein cholesterol was the only risk factor with a qualitatively stronger association with ICA-IMT in this material. The RADIANCE 2 study provided some evidence indicating CCA-IMT is more influenced by blood pressure than atherosclerosis.[255] In addition, stroke and CHD has been shown to be associated with varying magnitude to different carotid segments in some studies, one linking stroke to the CCA-IMT[230], and others finding CHD was best predicted by ICA-IMT[234]. A Multi-Ethnic Study of Atherosclerosis (MESA) study with 6562 participants evaluated six ultrasound metrics, including various plaque definitions and IMT measurements, and reported HRs, change in C-statistics and net reclassification improvement when IMT was added to a traditional Framingham risk stratification score. [256] All carotid ultrasound metrics were associated with incident CHD, and all but one gave significant net reclassification improvement. [256] Regarding stroke prediction, only ICA plaques encroaching ≥ 25% of lumen was associated with incident stroke and no ultrasound metric gave net reclassification improvement. A review of data regarding risk prediction found better prediction of CVD events with plaque than IMT alone. [222] This supports IMT measurements including plaque in the plaque prone segments of the bifurcation and internal carotid have improved CVD prediction when compared to measurements of common carotid IMT only. [240] Indeed, several studies looking into both IMT alone and carotid plaques comment that carotid plaques seem a better predictor for CVD than IMT alone. [222,237,244]

Limitations of the axial resolution in current ultrasound equipment make it difficult to evaluate meaningful progression of IMT in short time-frames. Most studies evaluating IMT progression have found no increased CVD prediction with

progression measurements. [257,258] Although one group used applied an approach with the maximum progression of IMT from several segments and measurements, i.e. the segment with the highest increase in IMT between two time-points, and found significant association with subsequent vascular events.[252] If cIMT is to be used for risk prediction, it may be feasible to search for and measure the maximum pathology, although this may likely result in lower reproducibility of measurements. Results indicate that a proportion of the phenotypic IMT variation is explained by genetic factors, although the reported IMT variability accounted for by genes varies drastically between studies, from 30-66% of CCA-IMT up to 75% of ICA-IMT. [259-263] IMT is associated with genetic inheritance, whereas plaques seem to be more associated with risk factors. [264] This supports ICA-IMT as an appropriate measure when investigating a genetic component in stroke. [165,261]

List of publications

Paper I: **Stroke patients' knowledge about cardiovascular family history - the Norwegian Stroke in the Young Study (NOR-SYS)**
Øygarden, H; Fromm, A; Sand, KM; Eide, GE; Thomassen, L; Naess, H; Waje-Andreassen, U
BMC Neurol. 2015 Mar 12;15:30.
doi: 10.1186/s12883-015-0276-6.

Paper II: **Can the cardiovascular family history reported by our patients be trusted? The Norwegian Stroke in the Young Study**
Øygarden, H; Fromm, A; Sand, KM; Eide, GE; Thomassen, L; Naess, H; Waje-Andreassen, U
Eur J Neurol. 2016 Jan; Volume 23, Issue 1, pages 154-159
doi: 10.1111/ene.12824

Paper III: **A family history of cardiovascular disease is associated with increased intima-media thickness in young ischemic stroke - the Norwegian Stroke in the Young Study**
Øygarden, H; Fromm, A; Sand, KM; Eide, GE; Thomassen, L; Naess, H; Waje-Andreassen, U
(Submitted)

Aims of the thesis

1. To quantify and evaluate the family history of cardiovascular disease in a young and middle-aged ischemic stroke population and analyze if demographic factors influence the reported family history. We aimed to assess and quantify a detailed family history of cardiovascular disease with a special regard to sex differences.

2. To test the validity of the patient reported family history and to investigate factors associated with reduced accuracy of patient family history reports. We aimed to test the concordance between patients' reported family history and parents' own reports.

3. To investigate the heredity of carotid intima-media thickness as a risk factor in young stroke patients. We aimed to test the association between carotid intima-media thickness and plaques at standardized sites and a family history of cardiovascular disease. We also aimed to test if the association differed between the three cardiovascular disease components; stroke, coronary heart disease and peripheral arterial disease or between the three measured carotid intima-media thickness segments; the common carotid artery, the carotid bulb and the internal carotid artery.

Subjects and methods

NOR-SYS

Norwegian Stroke in the Young Study

All subjects in NOR-SYS have been prospectively included since September 2010. Patients with documented ischemic stroke, aged ≤ 60 years were registered with anamnestic, clinical, laboratory, anthropometric and radiological data. [265] In addition to the patients, the study includes biological children aged ≥ 18 years and the patients´ partners. Former partners were invited if he or she had a common child with the patient. Current partners were invited regardless of common offspring. Information and questionnaires were provided to all living parents if patients consented to contact and deemed parents able to answer the questionnaire satisfactorily. All papers included in the thesis are based on patients and family members included in NOR-SYS.

The NOR-SYS design allows the gathering of data from three generations within the same family, including clinical, biometric and ultrasound data from two generations. The multi-generational cohort gives an opportunity to investigate ischemic arterial events in families of young and middle-aged ischemic stroke patients. The NOR-SYS cohort has a planned follow-up time of 15 years for the patient generation and 20 years for the youngest offspring generation, and will therefore enable the merging of clinical prospective cohort data with clinical data of ischemic events across generations.

NOR-SYS is approved by the local regional ethics committee and is conducted in accordance with the declaration of Helsinki. Participation in NOR-SYS is based on written informed consent from all participants or legal guardians. Patients were consecutively included throughout the inclusion period from September 1st 2010 to August 31st 2015. The inclusion criteria were: area of residence within the catchment

area of Haukeland university hospital, age between 15 and 60 years and documented primary ischemic stroke verified by cerebral imaging. Patients with stroke caused by non–arterial infarction such as SAH, ICH, sinus venous thrombosis, trauma or cerebral tumor with stroke as non-relevant co-diagnosis were excluded from participation.

Bergen NORSTROKE

Bergen NORSTROKE is a prospective registration that includes consecutive consenting patients admitted with stroke to the Department of Neurology, Haukeland University Hospital. Inclusion in Bergen NORSTROKE started February 2006. Demographics, anthropometric and clinical examination results, medical history, examination results, including radiology, cardiology, laboratory and neurosonology examinations in addition to acute and sub-acute treatment are registered on the day after admission and during hospital stay by a stroke neurologist (Halvor Næss). In addition, short-term outcome is monitored by repeated NIHSS scoring and modified Rankin scale at day seven or at earlier discharge. Bergen NORSTROKE is approved by the local regional ethics committee.

Carotid intima-media thickness

Carotid ultrasound was performed with a 9–3 MHz linear array transducer (Philips Medical Systems iU22, Bothell, WA, USA) and far wall cIMT was visualized using B-mode longitudinal plane scanning. Four patients were investigated by a mobile CX50 (Philips Medical Systems, Bothell, WA, USA) when admitted to the intensive care unit. The method for image acquisition and offline measurements of cIMT have been described in detail.[265] Insonation by ultrasonography was performed at far walls at several angles defined by Meijer's Carotid Arc® as 180, 150, 120 and 90 degrees for the right common carotid artery (CCA) and 180, 210, 240 and 270 degrees for the left common carotid artery, as used in a previous study. [250] This multi angle approach guided the insonation of the carotid bifurcation (BIF) and the internal carotid artery (ICA) to the angle with most pathology if any, and one picture frame from each segment was saved for analyses. A total of twelve picture frames with clearly

discernable far wall IMT were saved at the vessel end-diastole defined by using electrocardiogram gating. Measurements of the cIMT was analyzed offline on an Xcelera® work-station using the QLAB automated IMT measurement plug-in (Philips, Bothell, WA). A predefined area of 10mm within each picture frame was used for cIMT measurements. The positioning of this area was guided by a vertical raster superimposed on the live ultrasound image with the tip of the flow divider defined as the raster set point to guide positioning. The CCA, BIF and ICA were defined as 20-10 mm, 10-0 mm proximal and 0-10 mm distal to the tip of the flow divider, respectively. A high segment cIMT using the highest cIMT from either left or right side was calculated separately for CCA, BIF and ICA. Plaques were included in the cIMT measurements when present it the pre-defined picture frames.

Ultrasound measurements were performed by 4 sonographers (Annette Fromm, Halvor Øygarden, Kristin Modalsli Sand and Ulrike Waje-Andreassen). All sonographers underwent extensive training and acquired international certification in ultrasound examinations according to the NOR-SYS research protocol. The training and certification was performed in collaboration with the University Medical Centre of Utrecht, The Netherlands. Accreditation and certification was mandatory prior to researchers including study subjects. The reliability of measurements within and between observers and equipment has been tested and reported previously. [249]

Risk factor definitions

Diabetes mellitus, hypertension and hypercholesterolemia were considered present if diagnosed before hospital admission and treated either by lifestyle changes or medication. Blood pressure (BP) was measured in both arms using appropriate cuff size after 15-30 minutes rest in the supine position. The two measurements were used to calculate mean systolic and diastolic BP. S-glucose, s-total cholesterol, s-low density lipoprotein (LDL) and s-high density lipoprotein (HDL) cholesterol and fasting triglyceride concentrations were measured. Patients were grouped as active smoker, previous smoker if smoking stopped at least one year before the index stroke, or never smoker. The degree of tobacco exposure was defined by pack-years, i.e.

number of cigarette packs (20cig/pack) per day multiplied by number of years of active smoking. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, in hospital measurements were preferred, and if in hospital measurements were missing, anamnestic values were used. Waist-hip-ratio (WHR) was calculated by dividing waist circumference by hip circumference. Activity score was calculated from a self-reported mean weekly activity level during the last year in hours per week composed of household activities, outdoor walks and active exercise. The activity score was defined as an ordinal variable ranging from 0 – 5. Inactivity and or no physical activity of significance were defined as 0, 1 defined regular household activity and maintenance work only, 2 defined as outdoor walks 1-3h/week, 3 defined as outdoor walks exceeding 3h/week, 4 defined moderate to high intensity exercise 1-3h/week, and 5 defined moderate to high intensity exercise exceeding 3h/week. Alcohol consumption was defined as an ordinal variable with range 0-4, defined as 0-3, 4-6, 7-12, 13-20 or > 20 units consumed per week. Low fruit and vegetable diet was defined as patients eating less than three portions of either fruits or vegetables a weekly average the last year.

Family history

The FH of CVD composed of stroke, CAD and peripheral artery disease (PAD), was assessed for patients´ first-degree relatives (FDRs) and patients´ grandparents using a face-to-face, standardized, questionnaire-based patient interview. Patients were interviewed within the first few days after admission and FH was considered positive (FH+) if the patient reported ≥ 1 FDR with CVD. The patient was designated FH negative (FH-) if no family members with CVD were reported. The questionnaire template used for patient interviews and the questionnaire template mailed to participating parents are attached in the appendix.

Participation and number of subjects

Due to NOR-SYS having active patient inclusion up until August 2015 the number (n) of patients included in the papers differs. More patients are included with time passed towards the end of inclusion.

Paper I includes 292 patients enrolled in NOR-SYS from September 2010 to February 2014. Two patients did not consent to inclusion and a further two were deemed not able to consent and had no legal guardian available for proxy consent. Further 35 patients were excluded from analyses after inclusion, three were adopted and had no information regarding their biological FH and 32 were unable to answer the FH alone due to severe aphasia or coma. This resulted in 257 patients eligible for analyses in paper I.

Paper II includes 313 patients enrolled in NOR-SYS from September 2010 until August 2014. Five young stroke patients were not included due to lack of consent for participation and four were adopted as children without any knowledge of biological FH. The final number of patients and patient parents eligible for joint analyses is presented in the flow chart (figure 8).

Figure 8.

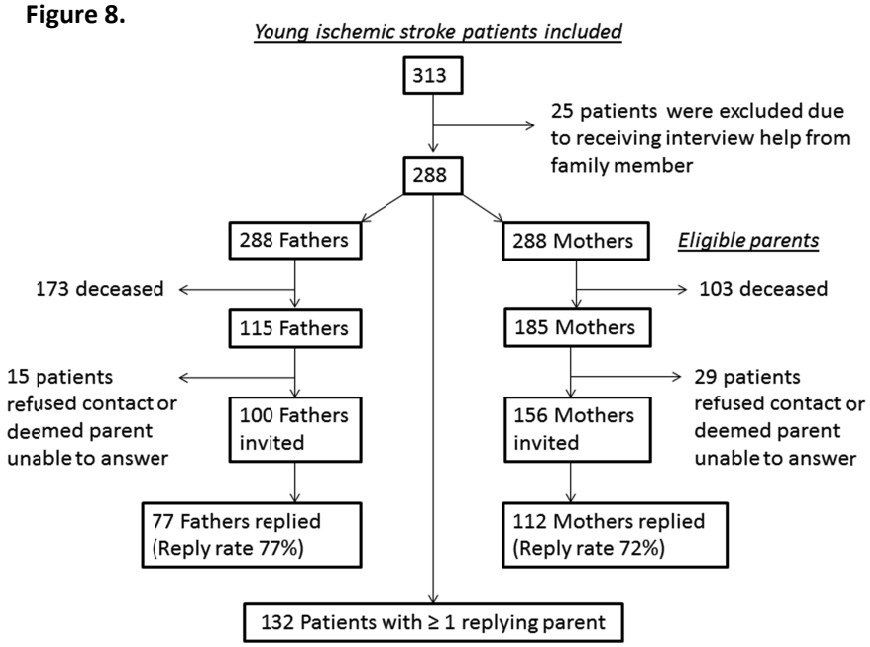


Figure showing a flow chart of patient and parent eligibility and selection for analyses in paper II.

Paper III had the final number of 391 patients included during the full five year inclusion period of NOR-SYS from September 2010 until end of August 2015 eligible for inclusion. However, three young stroke patients were excluded due to early death and lack of written consent for participation, four were adopted as children without any knowledge of biological FH and two patients were considered upon re-evaluation to not have cerebral infarctions as cause of their neurological symptoms and were therefore excluded. Paper III also includes NORSTROKE data to complement the analyses with laboratory results.

Statistical analyses

Descriptive statistics are given using the mean and standard deviations (SD) or by proportions with 95% confidence intervals (CI). Chi square test was used for categorical data. McNemar's test was used for paired proportions. Continuous and normally distributed variables were analyzed by Student's t-test, whereas non-normally distributed variables were analyzed by Wilcoxon rank-sum test. Regression analyses were performed with and without methods of variable selection, as appropriate.

In paper I, variables previously known, or suspected to influence the reporting of FH were included in the regression model.

In paper II, Spearman's correlation was used to test for correlation. Concordance between patient and parent reports was tested using kappa statistics. In addition, specificity, sensitivity, predictive values and likelihood ratios were calculated by a STATA module named 'diagt', with patient answers as the diagnostic test and parent reports as the gold standard. [266] Kappa values of 0.41–0.60 were interpreted as moderate, 0.61–0.80 as substantial and 0.81–0.99 as near perfect concordance. [267]

In paper III, the cIMT-variables were highly skewed to the right. After testing multiple methods of variable transformation, the transformation of ICA-IMT by 1/(square root of ICA-IMT) gave a distribution and residual distribution closely resembling the normal distribution and was therefore chosen as the most appropriate

conversion for linear regression analyses. Regression analyses were performed using backwards stepwise selection, removing the least significant variable in each step, to identify the variables with the highest association with cIMT. Finally, putative interactions with age and sex were added to the model and tested. Missing data-points were preferably treated by expected value imputation when possible, and robustness of the preferred imputation strategy was tested by repeating the final regression model using low, mean and high value imputation in addition to list-wise deletion and subsequently analyzing the impact of the various imputation strategies on the main results.

The level of significance was set at $P < 0.05$ for all analyses.
STATA/SE 13.1 for Windows (both StataCorp, College Station, TX, USA) was used for analyses.

Ethical considerations

All patients or legal guardians were given both oral and written information about the study purpose; the intended use of the information acquired by the interview and the investigation results and signed a written informed consent form. All participating patient parents were given written information about the study when receiving the questionnaire, and gave written informed consent to participate in the study.

NOR-SYS is approved by the Regional Ethics Committee of Western Norway, and is conducted in accordance with the Declaration of Helsinki.

Summary of included papers

Paper I:

Stroke patients' knowledge about cardiovascular family history - the Norwegian Stroke in the Young Study (NOR-SYS). Øygarden H, Fromm A, Sand KM, Eide GE, Thomassen L, Naess H, Waje-Andreassen U. *BMC Neurol 2015; 15: 30.*

Background: Family history (FH) is a risk factor for cardiovascular disease, especially coronary artery disease (CAD). The impact on risk of stroke is less clear. This study investigated young and middle-aged ischemic stroke patients' knowledge on FH of stroke, CAD, and peripheral artery disease (PAD) with a special regard to sex differences.

Methods: From September 2010 to February 2014, all ischemic stroke patients aged 15–60 years were prospectively included in the Norwegian Stroke in the Young Study (NOR-SYS). FH of stroke, CAD and PAD in offspring, siblings, parents, and grandparents was assessed using a standardized face-to-face interview. In addition to 'yes' and 'no', the optional reply 'don't know' was included to improve accuracy. McNemar's test was used to compare paired proportions, i.e. FH in male vs. female relatives. Multiple logistic regression analyses were used to test the influence of patient sex on FH reporting and to adjust for possible confounding factors.

Results: Altogether 257 patients were included. Mean age was 49.5 years and 68.1% were males. FH of cardiovascular disease was reported by 59% of patients. When asked about FH of stroke, 48 (18.7%) and 46 (17.9%) patients reported yes, whereas 17 (6.6%) and 9 (3.5%) reported 'don't know' regarding father and mother respectively. Similarly patients reported 'don't know' regarding 117 (45.5%) paternal vs. 83 (32.4%) maternal grandmothers ($p < 0.001$). Female patients reported less 'don't know' and were more likely to report a positive cardiovascular FH than males (OR: 3.4; 95% CI: 1.5 to 7.7; $p = 0.004$). Patients had more detailed knowledge about CAD than stroke in fathers ($p < 0.001$), mothers ($p < 0.001$) and siblings ($p = 0.01$).

Conclusions: Young and middle-aged stroke patients reported a high FH burden of cardiovascular disease. Females are more likely to report a positive FH than males. Detailed knowledge on FH was best for CAD. Our results suggest sex has a big impact on FH knowledge. Females have more knowledge of FH than males and knowledge is better for relatives with a female than male linkage.

Paper II:

Can the cardiovascular family history reported by our patients be trusted? The Norwegian Stroke in the Young Study. Øygarden H, Fromm A, Sand KM, Eide GE, Thomassen L, Naess H, Waje-Andreassen U. *Eur J Neurol 2016 Jan; 23 (1): 154-159*

Background and purpose: Family history (FH) is used as a marker for inherited risk. Using FH for this purpose requires the FH to reflect true disease in the family. The aim was to analyse the concordance between young and middle-aged ischaemic stroke patients' reported FH of cardiovascular disease (CVD) with their parents' own reports.

Methods: Ischaemic stroke patients aged 15–60 years and their eligible parents were interviewed using a standardized questionnaire. Information of own CVD and FH of CVD was registered. Concordance between patients and parents was tested by kappa statistics, sensitivity, specificity, predictive values and likelihood ratios. Regression analyses were performed to identify patient characteristics associated with non-concordance of replies.

Results: There was no difference in response rate between fathers and mothers ($P = 0.355$). Both parents responded in 57 cases. Concordance between patient and parent reports was good, with kappa values ranging from 0.57 to 0.7. The patient-reported FH yielded positive predictive values of 75% or above and negative predictive values of 90% or above. The positive likelihood ratios (LR+) were 10 or higher and negative likelihood ratios (LR−) were generally 0.5 or lower. Interpretation regarding peripheral arterial disease was limited due to low parental prevalence. Higher age was associated with impaired concordance between patient and parent reports (OR 1.05; 95% CI: 1.01–1.09; $P = 0.020$).

Conclusions: The FH provided by young and middle-aged stroke patients is in good concordance with parental reports. FH is an adequate proxy to assess inherited risk of CVD in young stroke patients.

Paper III:

A family history of cardiovascular disease is associated with increased intima-media thickness in young ischemic stroke - the Norwegian Stroke in the Young Study (NOR-SYS). Øygarden H, Fromm A, Sand KM, Kvistad CE, Eide GE, Thomassen L, Naess H, Waje-Andreassen U. ***(Submitted)***

Background and Purpose: Positive family history (FH+) is a risk factor for cardiovascular disease (CVD). We aimed to analyze the effect of different types of FH (stroke, coronary heart disease (CHD), peripheral artery disease (PAD) on carotid intima-media thickness (cIMT) in young ischemic stroke patients.

Methods: First-degree FH of CVD was assessed in ischemic stroke patients ≤ 60y using a standardized interview. Carotid ultrasound was performed and far wall cIMT in three carotid artery segments was registered, representing the common carotid (CCA-IMT), carotid bifurcation (BIF-IMT) and the internal carotid artery (ICA-IMT). Measurements were compared between FH+ and FH negative groups and stepwise backward regression analyses were performed to identify factors associated with increased cIMT.

Results: During the study period 382 patients were enrolled, of which 262 (68%) were males and 233 (61%) reported FH of CVD. Regression analyses adjusting for risk factors revealed age as the most important predictor of cIMT in all segments. The association between FH+ and cIMT was modified by age ($p = 0.014$) and was significant only regarding ICA-IMT. FH+ was associated with increased ICA-IMT in patients aged < 45y ($p = 0.001$), but not in patients ≥ 45y ($p = 0.083$). The association with ICA-IMT was present for a FH of stroke ($p = 0.034$), but not a FH+ of CHD or PAD

Conclusions: FH of stroke is associated with higher ICA-IMT in young ischemic stroke patients. Subtyping of cardiovascular FH is important to investigate heredity in young ischemic stroke patients.

General discussion

Demographics of the NOR-SYS cohort

Age and sex

Our young and middle-aged ischemic stroke patient cohort includes patients ranging from 15-60 years. Paper III included 382 patients presenting the following demographics. Mean age was 49.4 years. The middle-aged patients outnumber the young by 3:1 with 288 patients aged 45-60 years and 94 patients aged < 45years. The greater number of middle-aged patients is not surprising given the steep rise in incidence shown after the age of 45 years. [15,29] The cohort included 262 (69 %) males. The sex distribution varied between age-intervals as seen in table 7.

Table 7. Sex distribution across age-intervals in the young and middle-aged ischemic stroke patients included in NOR-SYS.

Age	Males	Females	Total
< 30 years	11 (4.2%)	11 (9.2%)	22 (5.8%)
30-39 years	21 (8.0%)	11 (9.2%)	32 (8.4%)
40-49 years	61 (23.3%)	36 (30.0%)	97 (25.4%)
50-60 years	169 (64.5%)	62 (51.7%)	231 (60.5%)
All patients	262 (100%)	120 (100%)	382 (100%)

The observed higher rate of female patients in those aged < 30 years and the higher proportion of males in the older age group is consistent with previous reports. [24,135,268] The observed difference in distribution of stroke between sexes that changes across

age groups is proposedly caused by increased risk of stroke caused by factors associated with pregnancy and puerperium in young females. The slightly reduced rate of female stroke among the middle-aged is suggested to be the result of a protective effect of estrogen. These theories are discussed in several review papers on sex differences in stroke that find some support from epidemiological data, as seen in figure 3, and from animal models of ischemic stroke. [136,269]

Education and work

The cohort was generally well educated. There was a slight discrepancy in level of education between FH+ and FH- patients among the young with 60 % college or university alumni in the FH- group compared with only 30% of those with a positive FH ($p = 0.017$). A study on alcohol intake and the risk of cerebral infarction in young women found the young females stroke patients were generally well-educated, they found no difference in percentage of young stroke cases having less than high-school education as compared with controls, with 14.9% vs 12.5%, respectively. [270] The recorded high level of education is comparable to national statistics on education level, where around 80 % of the young have upper secondary school or tertiary education level. [271]

Full time work or other full time occupation such as students and pupils were most common in both the young and the middle-aged with 78% of the young and 65% of the middle aged. In Hordaland County the average unemployment rate in the age-group 15-74 years was 2.3% from 2010 to 2014, and the population percentage receiving pensions or benefits have been slightly increasing from 20.8% in 2010 to 22.6% in 2014 due to an increasing number on age related pensions. [272] Thus, we see no large differences in employment status between the population average and the reported numbers in our cohort. No significant difference in working status was seen between the FH+ and the FH- in the young or middle-aged.

Anthropometric, biologic and behavioral risk factors

There were no significant differences in BMI between the young and middle-aged or the FH+ and FH- groups. When defining obesity as BMI > 30 we found that 100 (26%) patients in the cohort were obese. This is comparable with a large European study of young stroke patients showing 22.3% of patients were obese. [118] The mean waist-hip ratio was higher in middle-aged than young patients with 0.94 vs. 0.87 ($p < 0.001$) and in the FH+ compared to the FH- ($p = 0.002$) However, no difference between FH + and FH- groups was observed in age-stratified analyses. The WHO defines abdominal obesity as a waist-hip ratio above 0.9 in males and 0.85 in females and or a BMI > 30.0. [273] When applying this definition on the NOR-SYS cohort 32 (60.4%) of young males and 22 (53.7%) of the young females had abdominal obesity. In the middle-aged the corresponding numbers are 171 (81.8%) males and 52 (65.8%) females, showing abdominal obesity was more frequent in the middle-aged compared to the young ($p < 0.001$). A pattern of more abdominal obesity with increasing age has been reported, although with a converse sex related pattern with higher rates in females than males, consistent through all age groups. [118] Abdominal obesity is shown to be a substantial risk factor for stroke, and there are indications that the effect is greater in the young. [274] This may explain why we find a high proportion of abdominally obese patients among our young and middle-aged stroke patient cohort. There were no more abdominally obese patients among the FH+ when adjusting for age and sex.

BP measurements were similar between FH+ and FH- groups when adjusting for age and sex. Lipid profile was less favorable in middle aged patients and FH+ patients had higher LDL when adjusting for age and sex ($p = 0.016$).

There were no significant differences in alcohol consumption between young and middle aged or FH+ and FH- groups. Young patients had higher activity scores compared with middle-aged patients ($p < 0.001$) but no difference between FH+ and FH- groups was seen. Both active and previous smoking were more common in the middle-aged compared to the young ($p = 0.002$). Among the young, there were more

smokers among the FH+ patients, with 56 % active smokers compared to 29 % in the FH- group (p = 0.007). This increased proportion of smokers in the young FH+ group, might suggest a non-genetic clustering of smoking as a risk factor, presuming a large proportion of the affected parents were also smokers.

In summary, the middle-aged have a pronouncedly worse risk-factor profile when compared with the young. This is in concordance with a previous NOR-SYS report using a preliminary material of 150 patients [249] in addition to several other studies reporting worsening risk factor profiles with increasing age. [24,118] The large discrepancy in the proportion of FH+ patients, with a disproportionate high number of FH+ patients among the middle aged, showed that age could be an important confounding factor when analyzing potential differences between the FH+ and FH- patients.

Family history data

In the total cohort there was a significant excess of deceased fathers compared to mothers (p <0.001). Among patients < 45 years, two patients reported that both parents were deceased, 16 reported a deceased father whereas 4 reported a deceased mother (McNemars chi-square, p = 0.007). This shows that even among patients aged < 45 years, there is a significant excess of deceased fathers compared to mothers. The higher number of deceased fathers is probably caused by males being older at birth of their first child compared to females. [275] In addition males have a lower life-expectancy than females in Norway, as has also been reported from other countries. [276]

In our cohort nearly all patients had siblings, only 8 (8.5%) of the young and 18 (6.3%) of the middle-aged reported to be an only child. Among the middle-aged the FH+ had slightly more siblings than the FH- (p = 0.024). This is not surprising since a sibling is a first-degree relative included as a potential person defining a positive FH. Thus, a bigger family with more siblings will increase the statistical probability for a FH+. This underlines the importance of adjusting for family size in analyses including FH. [277] Thirty-nine (42.9%) of young patients reported they had no

children, compared with 39 (13.5%) of the middle-aged. The middle-aged had more children, but no difference in number of children was seen between the FH+ and FH- when adjusting for age and sex.

Family history of cardiovascular disease in young and middle-aged stroke patients

A FH of CVD is frequently seen in stroke patients. In paper I we found that 59% of patients reported any first-degree FH of CVD. When the FH is expanded to the second generation including grandparents, a positive FH of CVD is even more common with 79% of patients reporting a positive FH.

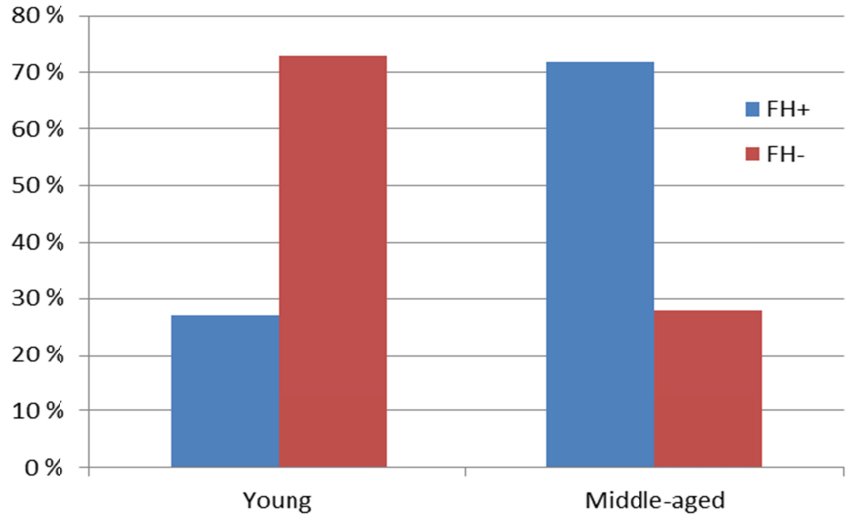
The proportion of patients with a positive FH from the complete NOR-SYS cohort presented in paper III is shown in young and middle-aged patients in figure 9. The nearly reversed proportion of FH+/FH- patients among the young vs. middle-aged shows that age has a significant influence on FH status. Middle-aged patients are more likely to report a positive FH, thus confirming the pattern of age as an influencing factor on FH that we found in paper I.

The percentages of patients reporting a first-degree FH of stroke, CAD and PAD were 34%, 41% and 6%, respectively. A FH of stroke and CAD in particular are common in patients with stroke. The percentages reported in the NOR-SYS cohort are comparable to previous European findings, a Swedish study [175] reported that 41% of patients had a FH of stroke and a SIFAP1[184] study reported that 37% of patients had a FH of stroke. The prevalence of a positive FH in these studies is quite similar, despite variations in patient age limits. NOR-SYS included patients aged 60 years and younger whereas the Swedish study had 70 years and the SIFAP1 study had 55 years as the upper age limit.

A systematic review and meta-analysis published in 2008 included 18 studies and reported the FH of stroke from both published and previously unpublished data

showing a wide variation in the frequency of positive FH between studies (table 8).[187]

Figure 9. Percentage of patients with a positive vs. a negative first degree family history of cardiovascular disease among young (15-44 years) and middle-aged (45-60 years) acute ischemic stroke patients in the complete NOR-SYS cohort



FH+: Positive first degree family history of cardiovascular disease

FH-: Negative first degree family history of cardiovascular disease

Table 8. Main study characteristics in an excerpt of studies investigating sex differences in the family history among parents (FHx) of ischemic stroke

Study (year)	Type	Setting	Country	n cases	IS only	Men, n (%)	Mean age (y)	FHx Parents, n (%)		
								All	Women	Men
Review data from Oxford studies										
OXVASC (2007) [182]	Cases	Population	UK	781	Yes	371 (48)	75	182 (23)	100 (13)	82 (22)
OCSP (1988) [268]	Cases	Population	UK	663	Yes	340 (51)	71	95 (14)	49 (15)	46 (14)
TIA-series (2005)[278]	Cases	Hospital	UK	481	Yes	312 (65)	63	90 (19)	34 (18)	56 (18)
International studies from 1971 - 2015										
Marshall (1971) [279]	Cases	Hospital	UK	201	No	146 (70)	*	28 (14)	4 (7)	24 (17)
Welin (1987) [280]	Cohort	Other	Sweden	57	No	57 (100)	*	21 (37)	NA	21 (37)
Vitullo (1996)[281]	CC	Hospital	Italy	237	Yes	157 (66)	30–69	70 (30)	31 (39)	48 (31)
Jousilahati (1997) [171]	Cohort	Population	Finland	453	No	249 (55)	25-64	47 (10)	24 (12)	23 (9)
Liao (1997) [185]	CC	Population	USA	103	No	64 (61)	62	37 (36)	15 (41)	22 (33)
Berger (1998) [282]	Cohort	Other	Germany	129	Yes	95 (73)	52	21 (16)	5 (19)	16 (17)
Caicoya (1999) [168]	CC	Population	Spain	470	No	247 (53)	71	105 (22)	47 (21)	58 (23)
Reed (2000) [283]	CC	Population	USA	83	Yes	83 (100)	72	36 (43)	NA	36 (43)
Tentschert (2003) [284]	Cases	Hospital	Austria	1564	Yes	853 (55)	69	458 (29)	224 (32)	234 (27)
Kim (2004) [277]	CC	Population	USA	49	Yes	0 (0)	36	11 (22)	11 (22)	NA
Lindgren (2005) [285]	CC	Population	Sweden	447	No	254 (57)	76	160 (36)	68 (35)	92 (36)
Lisabeth (2005) [286]	Cases	Population	USA	444	Yes	197 (44)	73	116 (26)	75 (30)	41 (21)
MacClellan (2006) [287]	CC	Population	USA	487	Yes	0	39	118 (24)	118 (24)	NA
Meschia (2006) [170]	Cases	Hospital	USA	488	Yes	276 (55)	65	167 (34)	*	*
Choi (2009) [288]	CC	Hospital	S-Korea	400	Yes	226 (56)	69	85 (21)	*	*
Siegerink (2012) [170]	CC	Hospital	Netherlands	181	Yes	0	39	22 (12)	*	*
Kastorini (2013) [289]	CC	Hospital	Greece	250	Yes	139 (56)	77	51 (31)	*	*
Thijs (2015) [184]	Cases	Hospital	Europe	4232	Yes	2509 (59)	46	1501 (36)	650 (38)	851 (34)

*: data not available; CC: Case control study; IS: ischemic stroke only (in proband) including TIA; n: number; NA: not applicable

Modified from Touzé and Rothwell, Stroke, 2008. [187] With permission of the publisher

The large variation may have several causes of varying importance. Firstly the populations studied are different. There is a large span in mean age and age range in the populations. Older patients have older parents with a higher prevalence of disease and therefore a higher frequency of positive FH. In addition, the prevalence of FH of stroke will vary with the baseline prevalence of stroke in the studied population, with a larger proportion of patients having a positive FH in populations where the baseline stroke prevalence is high. [31] Secondly, applying age limits on the parental event has a

large effect on the proportion of patients reporting a positive FH by excluding events occurring in elderly parents as defining events for a positive FH. Thirdly, a major influencing factor on the proportion of FH+ is variation in the ascertainment of FH events. Whether information was gathered from a single unsupervised questionnaire, a structured interview of the patient and or family members or from a review of medical records, can affect the frequency of FH. Even the phrasing of the questions used in an interview, and if the opportunity for doubt is included with a 'don't know / not sure' option will probably influence a patients inclination to answer positively or negatively regarding his FH.

Age and family history of cardiovascular disease

Given the steep rise in stroke incidence with age, the effect of age increasing the prevalence of FH is especially pronounced regarding the FH of stroke. The study reporting the lowest percentage; 10.4% of stroke patients with a positive FH of stroke included men and women between 25 and 64 years and enforced a 60 year old age limit on parental events. [171] The other studies range between 12% and 43% of stroke patients reporting FH+ (table 7). The studies reporting the highest percentages of FH+, such as Liao [185] (36 %) Lindgren [285] (36 %) Thijs [184] (36 %) and Reed [283] (43 %) span from 46 to 76 in mean patient age but have in common that they do not enforce age limits on the parental events.

Age is a strong risk factor for CVD. It would therefore seem logical that with increasing age, the frequency of FH+ will increase as well. Thijs et al found an age related increase in FH+ resembling this expected pattern. [184] In patients aged <25 years 32% (38/118) reported FH+, as did 32% (133/413) of patients aged 25-35 years. However, 36% (1330/3701) of patients aged 35-55 years reported FH+. A previous study on the same material shows the rate of FH+ actually stays at almost a rate of 32 % up until the age of 45 and then increases in patients aged 45-55 years, with a FH as high as 39 % (1105/2997). [119] Regression analyses confirm the association between age and a positive FH. The FH prevalence increases as patients get older than 45 years; probably this marks the age interval where the parent

generation are experiencing an age related increase in CVD incidence, as reflected by the increased FH prevalence in the patient generation. Studies including older patients, report quite similar percentages of FH irrespective the advanced age of the investigated population. The OXVASC population had a mean patient age of 75 years and reported that 31% of patients had any first degree FH of stroke. [182] Therefore the age of patients may have an effect up until a certain age, and then levels off and does not contribute to a higher FH prevalence, probably because a high proportion of patient parents are by then already deceased. This explanation seems very likely given nearly 60% of fathers and 36% mothers are deceased in our relatively young cohort.

We found increasing prevalence of FH with increasing age. This is also reported in several papers from the Sifap1 study group. [119,184] We did not systematically ascertain parent age at time of the event, and could not enforce age cut-offs defining premature parental events. We assume the Sifap1 studies do not enforce age limits on the FH, however they do not state explicitly whether they include FH events at all ages or if only premature events are included explicitly in the article reporting study methods or in any of the subsequently published studies. [118,184,290,291] Interestingly, a study enforcing an age limit of 65 years on parental events found strengthened associations between proband events and FH events and that the association is even stronger in young patients (table 9). [165] Showing the influence of FH was greater in younger patients and varied with etiologic subtype, the authors interpreted these findings saying a focus on young patients and specific etiologic subtypes would be most effective when investigating the genetic basis of stroke. [165]

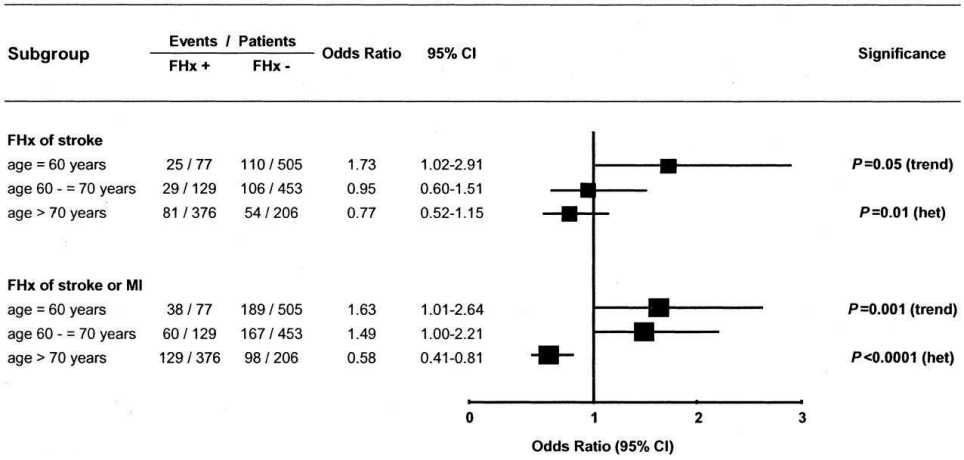
Table 9. Relationship between a positive family history of stroke ≤ 65 years and patient age of stroke for small- and large-vessel disease

Patient age at stroke onset	Small-Vessel Disease		Large-Vessel Disease	
	No. of Cases	OR (95% CI) Multivariate*	No. of Cases	OR (95% CI) Multivariate*
Stroke ≤55 y	47	3.99 (1.25–12.7)†	39	4.46 (1.03–19.3)†
Stroke ≤60 y	71	2.70 (1.18–6.18)†	78	2.55 (1.04–6.25)†
Stroke ≤65 y	117	2.69 (1.46–4.96)†	122	2.34 (1.21–4.52)†
Stroke ≤70 y	149	1.91 (1.11–3.28)†	178	1.86 (1.10–3.12)†
Stroke ≤75 y	186	1.55 (0.94–2.53)	219	1.88 (1.18–3.00)†
Stroke ≤80 y	216	1.55 (0.97–2.48)	244	1.82 (1.15–2.86)†
All strokes	232	1.49 (0.94–2.37)	262	1.67 (1.08–2.66)†
*Multivariate=adjusted for age, sex, arterial hypertension, diabetes mellitus, serum cholesterol, and smoking status.				
†P<0.05.				

From Jerrard-Dunne P. et al. Stroke, 2003.[165] With permission of the publisher

Similarly, a paper including two population based studies from the region of Oxfordshire in the United Kingdom, the OXVASC and the OCSP, found FH of stroke and FH of stroke or MI was more frequent in young compared to old patients i.e. a stronger association between FH+ and patient stroke in young patients (figure 10). [183]

Figure 10. Relationship between age of onset and family history of stroke (top) and family history of either stroke or myocardial infarction (bottom) in the Oxfordshire studies. This figure compares the odds of having family history in one age band to the odds of having family history in the combined two other age bands.



FHx +: positive family history; FHx -: negative family history

From Schulz UGR. et al. Stroke, 2004. [183] *With permission of the publisher*

Second generation family history

The knowledge of FH in grandparents is substantially reduced compared to the knowledge of parental FH. We recorded that close to half of patients answered "don't know" regarding paternal grandfathers' history of stroke and heart disease. The higher rate of "don't know" answers regarding grandparents indicates that patients know substantially less about disease in the grandparents than parents. Thus, integrating patient reported disease events in grandparents as a part of the FH seems to drastically reduce FH accuracy.

There were no apparent differences in the rate of patients answering "don't know" between stroke, heart disease and PAD in grandparents, except the rate of "don't

know" is slightly lower regarding PAD in all grandparents. However, when the knowledge of grandparental disease is further detailed with follow-up questions e.g. concerning type of stroke, type of heart disease or ordinated treatment for PAD we see the pattern of reduced knowledge for grandparents gets even more pronounced. In addition, we see a difference between the knowledge of stroke and heart disease. In the group of 13-16 % of patients responding "yes" to a specific grandparent having heart disease, only 35 % answer "don't know" regarding the type of heart disease. Whereas, as many as 75-89 % of patients answer "don't know" regarding type of stroke, even when reporting 'yes' to the prior question of stroke in the mentioned grandparent. Thus, even when patients know their grandparent has suffered a stroke, they do not know if that grandparent had an ischemic stroke, an ICH or a TIA. This may be a natural result of the diagnostics available in the grandparental generation, where diagnostic tools able to distinguish between ischemic stroke and ICH were less available than today. In addition, the introduction of thrombolytic treatment at the end of the 90-ies, and the implementation of use in Norway in 2003, resulted in public information campaigns that probably increased the public awareness of the difference between ischemic stroke and ICH. The reported rates of PAD in grandparents are low, making further analyses difficult.

Effect of sex on the family history

We found a higher OR of 2.5 for a first degree FH+ in females compared to males ($p = 0.005$), when adjusting for age, number of siblings and level of education. One possible explanation for the higher rate of positive FH in females could be that males know less about their family history than females do. The studies using databases or medical records for verification of FH bypasses this issue by not relying on the proband recollection of FH. To investigate the background for the observed discrepancy we analyzed the validity of the patient provided FH by comparing the patients' reports with the reports of their parents and found that males do not report more erroneously regarding their FH than females do. Thus it seems that females report FH+ more frequently than males, and this cannot be completely explained by

an increased rate of "don't know" in males or by false negative reporting by males, as investigated in paper I and paper II.

Data from the Oxford Vascular Study have shown similar results where probands of female sex were more likely than males to have a positive FH of stroke, with females having an OR of 1.4 to have at least one first-degree relative with stroke compared to males. [182] They further found that this disparity in FH frequency between males and females could be explained in full by an excess of stroke in female relatives, i.e. mothers and sisters. [182] The authors concluded the apparent difference in FH frequency between females and males could be caused by a greater heritability of ischemic stroke in females, caused by sex-specific genetic, epigenetic or even non-genetic mechanisms entirely. [182] This finding was subsequently confirmed by the same authors in a systematic review and meta-analysis, although the effect of sex on FH of stroke was slightly attenuated with a pooled OR of 1.15. [187]

Thijs et al found that females more often had a stroke in the maternal than paternal lineage, whereas males had slightly more stroke in the paternal lineage, albeit non-significant. [184] This finding reproduced the previously shown pattern of female-to-female stroke transmission and showed this was also the case in a young stroke population. [182,187]

We found a similar rate of FH of stroke in mothers and fathers. The reported FH of heart disease is significantly higher in fathers than mothers. The knowledge of FH depends on the sex of the patient and the sex of the relative. We observed a discrepancy regarding the knowledge of stroke in parents with 17 (6.6%) answering don't know regarding stroke in fathers (6.6%) compared to 9 (3.5%) regarding mothers ($p = 0.059$). This pattern was even more pronounced when comparing maternal and paternal grandparents, patients systematically answered "don't know" less frequent in maternal than paternal grandparents. The increased knowledge in female relatives with a link is evident also when comparing grandfathers and grandmothers of the same relation with each other. "Don't know" is answered more frequently for the male relative, regarding all diseases except CHD. A female-female

relation and even a male-female relation gives increased knowledge of the FH when compared to a male-male relation. It seems that the involvement of females on any level increases the knowledge of FH. This was also observed in a qualitative semi-structured interview based study which reported that females gave more detailed accounts of their family history with less encouragement to do so. [292] They also observed that the female link was important to facilitate the transfer of information between generations, and with the death of the mother information regarding the FH was harder to achieve. [292] Males in addition seemed to need more affected family members to deem themselves as having a positive family history. [292] Of note they also reported that some respondents with a positive family history did not perceive themselves as having increased risk due to differences between themselves and the affected family members in for example appearance or smoking habits. [292] With females having more knowledge than males, this may contribute to the observed increased FH of stroke in females as compared to males in all studies using patient provided FH. [182] This may also explain why the association was attenuated in the subsequent meta-analysis by the same authors.[187] The knowledge difference between sexes and especially sex of parents has been proposed to influence the observed maternal transmission of diabetes mellitus, as "don't know" answers were more frequent regarding fathers than mothers. [293] However, this does not exclude an additional influence of other non-genetic, genetic and or epi-genetic factors on this female-female relation, both with regards to the hereditary transmission of diabetes and stroke.

Knowledge of stroke vs. heart disease

A Canadian group surveyed cardiac inpatients and outpatients to evaluate their knowledge of risk factors and symptoms of CHD and stroke, and found that while patients had adequate knowledge of MI symptoms the knowledge of symptoms associated with acute stroke was extremely poor. [294] Defining good knowledge as knowledge of two or more symptoms, they found only 31% of the cardiac patients had good knowledge of stroke symptoms whereas 76% had good or excellent knowledge of MI symptoms. [294] This discrepancy may be influenced by the patient

population studied, as cardiac patients will be more inclined to know symptoms of cardiac disease. However, as patients with MI suffer a much higher risk of stroke than the general population and would definitely benefit from increased knowledge of stroke symptoms. [295] A telephone based survey in Australia found that 35% of the population was able to correctly identify two or more warning signs or symptoms of stroke. [296] An American study from the greater Cincinnati region found more than 40% of respondents were able to identify two or more warning signs for stroke and identified a favorable trend of increasing knowledge in the five-year period between 1995 and 2000. [297] It has been a general opinion that the public has less knowledge of their FH of stroke than their FH of CHD. A recent Norwegian study found the knowledge of stroke symptoms and risk factors in a stroke and transient ischemic attack population was unsatisfactory. [298]

A history of stroke – ischemia or bleeding

Using the index case as a source for the FH bears the possibility of recall bias. Several authors have also problematized the issue that it may be difficult to distinguish a FH of ischemic stroke from hemorrhagic stroke with this method of FH ascertainment. [124,299] A Swedish study investigated if individuals with a validated sibling history of either ischemic or hemorrhagic stroke had higher standardized incidence ratios of one or both of these stroke subtypes when compared with unaffected sibling pairs. [299] The study design separating stroke subtypes in the sibling history enabled analyzes to determine if inherited risk was subtype specific. The study showed that having an affected sibling was associated with increased risk and that the association was strictly subtype specific. [299] A sibling history of ischemic stroke was associated with ischemic stroke with an incidence ratio of 2.14 (95% CI, 1.21 to 3.74) and a sibling history of hemorrhagic stroke was associated with hemorrhagic stroke with an incidence ratio of 1.82 (95% CI, 1.21 to 2.75). [299] However, a sibling history of ischemic stroke was not associated with increased incidence of hemorrhagic stroke and a sibling history of hemorrhagic stroke was not associated with increased incidence of ischemic stroke. [299] Therefore, distinguishing between a FH of hemorrhagic stroke and ischemic stroke seems important to explore

the heredity of the stroke subtypes further. In paper I the patient reports a detailed FH of stroke, showing that discrimination between stroke subtypes in the FH represents a real problem. Patients reported a positive FH of stroke in 8 (3%) siblings, 46 (17%) mothers and 48 (19%) fathers. Answers on follow-up questions regarding the stroke subtype are displayed in table 10.

Table 10. Patients´ replies on follow-up questions regarding the subtype of stroke after having reported a positive first-degree family history of stroke, presented in paper I

Type of stroke	**Sibling (n = 8)**	**Mother (n = 46)**	**Father (n = 48)**
Cerebral bleeding	1 (12.5%)	7 (15.2%)	5 (10.4%)
Ischemic stroke	3 (37.5%)	12 (26.1%)	11 (22.9%)
Transient ischemic attack	0 (0.0%)	9 (19.6%)	8 (16.7%)
"Don't know"	4 (50.0%)	18 (39.1%)	24 (50.0%)

Our results with 10-15% percent of patients answering that the first-degree relative with stroke had a cerebral bleeding seem to correlate well with the expected proportion of cerebral hemorrhages in a population with stroke. [29] The proportions of patients reporting the first-degree relatives' stroke as ischemic were substantially lower than expected. [29] Why the patients seem to be better at reporting a FH of cerebral bleeding than a FH of ischemic stroke is not known. However, we speculate that the more dramatic clinical presentation of intracranial hemorrhage with more severe acute deficits and higher mortality or subsequent disability may increase the knowledge of this stroke subtype compared to ischemic stroke. [300]

How to get the most reliable family history

FH history is not perfect, and there are several issues that may cause concern when FH is used to study heredity or assess risk. First, family history may be obtained in different ways, the most accessible way is to ask the patient or subject about the family history. This opens the possibility for recall bias, especially if the subject was not informed about the family members' disease directly from the patient or caregiver. Receiving information from a secondary or even a tertiary source may further reduce the accuracy and quality of the FH.

To reduce the problem of information bias, one can interview close relatives, preferably the spouse, and as many first-degree family members as possible. This may verify and increase the completeness of the provided family history as much as possible.

Arguably, the FH obtained from physician-verified medical records with acknowledged diagnostic standards is the best way to assure whether the FH is correct. However, though these rigorous requirements are admirable and perhaps preferable in a research setting, they will be hard to fulfill outside of clinical family-cohort studies like the FHS. We therefore tested the FH provided by our patients against the information obtained directly from their parents via a standardized questionnaire and showed that patients´ provided FH is in high concordance with parental reports.

The use of an interview-setting to acquire FH information also allows for control and follow-up questions regarding the provided information. Misconceptions and individual interpretations of FH history and the significance of FH and impact on an individual's risk for disease have been discussed previously. [292] We encountered such misconceptions on a regular basis, and found the face to face interview setting to be of high value in identifying and correcting such misconceptions. For example, a common answer to the question "Has your mother experienced any heart disease?" was "No, my mother died from cancer". Whereas follow up questions and penetration of the family history could very well reveal that the mother had angina for 5 years

and then a MI at the age of 58. The individual's interpretation of FH should not be overlooked, and requires consideration when designing or implementing systematic FH acquisition to be used for risk assessment or for research purposes.

To combat these lay person misunderstandings and reduce the impact of FH misconceptions several approaches may be used. Standardized and structured interviews may be desirable in clinical series and research projects, but not applicable on a population basis due to the time and effort needed by qualified personnel to perform such interviews. For a population basis we propose that a web-based approach where the patient can enter and evaluate his family history and be prompted for follow-up questions may be an adequate solution. This allows the patient to gather further information from family members or physicians as the prompts can contain questions to obtain valuable information and verify the provided information e.g. age and relation to family member, follow up questions about the disease to verify the events and increase validity. In conjunction with direct links to treatment and lifestyle advice, this will enable individuals to obtain information and empower them to take appropriate action themselves or in cooperation with a physician. Even individuals designated as low or intermediate risk may benefit from being educated and informed about the heredity and risk factors for disease.

It seems that attaining a FH of CVD may not be as simple as one may presume. Although old, low-tech and well-used, new evidence suggests we have not fully charted the influence and insight a FH may give on risk for disease. Especially the previous compounding of all CVD types in one common FH may have been a fallacy. CVDs are conjoined by the shared pathophysiologic mechanism of atherosclerosis, but there may well be underlying differences we have not understood that may explain why some studies find differing heredity between the CVD disease entities. This may explain the parent PAD – patient PAD relation previously reported[163], and the parent stroke – patient stroke relation we find regarding cIMT.

Value of family history

Identifying individuals with a heritable risk of vascular events can assist in combating the worrying trend of increasing stroke incidence in young patients. This is underscored by an American study showing that although a family history of early stroke was present in only 11% of families, these families accounted for 86% of young stroke events. [301] Family history is a well acknowledged tool for risk assessment, although the additional value when added to complete risk assessment tools may be debated. The family history provides a rapid, inexpensive and easily accessible assessment of an individual's risk for CVD. Regardless of the obvious benefits, the potential of family history as a screening tool is not yet fully utilized. [302,303] Population awareness of heredity as a risk factor for CVD was reported to be unsatisfactory in a recent review, even though the population with a positive FH bears 50-60% of the premature CHD burden. [304] The perception of a positive FH may differ and is affected by the closeness of the relation, age of the relative, severity of the event, and sex and social class of the relative and respondent. [292] Thus, a common understanding between patients and health professionals of heredity and conferred risk is crucial when assessing the FH.

The knowledge of FH as a tool to improve preventive treatment has obvious benefits. Knowing of premature CVD in the family may lead to the diagnosis of familial hypercholesterolemia, and can improve the primary prevention for all family members affected by this genetic condition. Still, the benefits regarding knowledge of FH of CVD with non-Mendelian and probably polygenetic inheritance is not that clear. However, we argue that increasing the knowledge of FH as a risk factor and as a screening tool for identification of individuals at risk should be a prioritized goal. A recent study using genetic markers found increased heritability for stroke in young compared to older onset strokes. [305] The FH provides an opportunity for identification of individuals and families that suffer a high burden of the total stroke events so that preventive strategies may be undertaken in this group.[301] Increased attention on CVD prevention with an approach acknowledging both hereditary factors and risk factor identification as means to improve preventive strategies seems feasible. A total risk

evaluation that considers traditional risk factors, heredity, lifestyle factors and patient's conceptions regarding risk and preferences regarding treatment is needed to identify possible areas for intervention and choose the best non-medical or medical intervention strategy. The medical community involved in young stroke research should be especially encouraged to improve risk assessment as the individual and societal costs of young stroke are high and the potential for primary prevention may be substantial.

Family history and carotid intima-media thickness

We found that standardized cIMT- and plaque measurements were higher in young patients with a positive FH. The difference was more pronounced in the ICA (49% higher, $p < 0.001$) than the BIF (24% higher, $p = 0.002$) but not significant for the CCA. Adjusting for age and sex attenuated the coefficients associated with FH, and with this adjustment FH showed no statistical association with BIF-IMT. However, ICA-IMT was an average of 0.21mm higher in FH+ patients even when adjusting for age, and sex ($p = 0.001$). The same pattern was not evident in the middle-aged patients, and in the middle-aged we even saw higher ICA-IMT in the FH- patients. We believe that the cause for the lack of association between cIMT and FH in the middle-aged is a difference in what the FH represents and a reduced impact of genetics vs. other risk factors in the middle-aged compared with the young. [186,287,305] IMT is shown to have a stronger association with heredity than plaque. However, plaques seem to have a higher predictive power than IMT. This seems somewhat contradictory. One would expect that the risk associated with plaques in young patients is also caused by atherosclerotic processes and that a hereditary link should be present. This gap in the current knowledge requires further investigations. Initially, one can to some extent tackle this hurdle by allowing the inclusion of plaque structures in the measurement of cIMT. Although cIMT and plaque may be distinct entities, they share the anatomical location in the artery wall. Because of this shared locality, it may seem unreasonable to refrain from registering and measuring visible pathology when investigating the risk predictive power of carotid artery atherosclerotic changes.

Premature CVD has a strong heredity and we believe that a high proportion of young stroke patients have parents with premature CVD. [306] The high percentage of FH+ patients in the middle-aged is probably to a large degree caused by parental events at high age, thereby diluting the premature FH associated with a strong heredity. However, long-term studies such as the FHS that follow young people from FH+ and FH- families over a long period of time will provide us with better information about the impact of age of family member at event and different types of FH+ on risk of CVD.

Some studies and meta-analyses have found little or no net predictive benefit of adding cIMT measurements to traditional risk stratification scores. [228,233,251,257] However, there are contradicting results concerning such benefit, suggesting the benefit is dependent on what is actually measured, and where measurements are obtained. Especially inclusion or exclusion of plaques seems to be of importance. The MESA study showed that maximum IMT measurements incorporating plaques independently predicted CVD events and improved risk prediction for CHD events when added to the Framingham score in their cohort of 6562 members with a mean age of 61.1 years. [256] The ARIC study showed benefit of presence of plaques in addition to cIMT in prediction of events. [307,308] The Three-City study showed a similar result and even showed the hazard ratios increased as more sites with plaques were acknowledged. [237] A meta-analysis including 11 studies with 54 336 subjects showed that plaques were more predictive of events than was cIMT alone. [309] The value of ultrasound evaluation of the neck arteries for risk prediction is still a matter of discussion. However, it becomes more and more evident that it is more important to find the pathology i.e. plaques, than to get an easily reproducible measurement of the cIMT.

We find an association between increased ICA-IMT and a FH of stroke. It is not surprising that we find associations with measurements in the ICA, as this site is prone to plaque formation and we actively searched for and incorporated plaques in our measurement. This finding shows that heredity may serve as an additional way to identify and possibly risk stratify individuals with increased risk, possibly even

before a vascular event. We found that the young stroke population with a positive FH had increased IMT of the internal carotid artery. This gives rise to the question, could these patients have been identified before they had their stroke?

To answer if there are single or several subsets of patients that are the source of genetic association and if a specific cut-off on the arterial measurements can be applied to identify these individuals requires further research. A follow up study of these presumed high risk patients and their families to investigate if evaluation of vascular changes may identify individuals at high risk, seems feasible. Identifying changes allows the opportunity for reasonable intervention on an individual level and on a bigger scale this may help to identify groups suitable for targeted information campaigns or other societal efforts to reduce the burden of stroke in the young. We encourage further research to find and evaluate any means that may assist in identifying young individuals with increased risk, inherited or not, as this may be a feasible approach to reduce the increasing burden of stroke in the young.

Conclusions and future directions

Family history is the oldest tool to investigate heredity. This thesis, based on data from the new and prospective three-generation NOR-SYS program, brings new information on family history and heredity in young stroke.

I. We showed that a positive FH of CVD is common among young and middle-aged stroke patients. Female patients were more likely to report a positive FH than males. In addition to this we showed that knowledge of family history in the maternal lineage was higher than knowledge regarding the paternal lineage. Thus, sex of both the patient and the family member seem to influence the knowledge of FH. Patients with higher education were less likely to report a positive FH. Age was an important influencing factor on the prevalence of positive family history, with older patients more likely to report a positive FH than younger patients. We also showed that even today, with advanced diagnostic imaging available for decades, the knowledge of a FH of heart disease is significantly higher than the knowledge of a FH of stroke. With these findings we discuss the importance of taking age of patient and age of parent at parental event into consideration when acquiring the family history, and when using family history to assess heredity of CVD.

II. The patient reported family history can be trusted when acquired in a systematic standardized manner, we showed this in a young and middle-aged ischemic stroke cohort with verified brain damage, mainly by magnetic resonance diffusion weighted imaging. Increasing age of patient was the only factor that was associated with reduced concordance between patient and parent reports in our study. Whereas sex of patient, level of education, employment and living status, alcohol consumption and smoking did not have a significant effect on concordance. These results imply that FH information acquired from the patient in a standardized systematic interview can be trusted as a good, albeit not perfect account of the FH.

III. We assessed the carotid intima-media thickness (cIMT) in the young and middle-aged stroke patient cohort as a surrogate measurement of atherosclerosis. We found a significant association between the FH of CVD and the cIMT of the ICA in the young but not the middle-aged. Thus it seems a positive FH has a large impact on atherosclerosis at a young age, whereas traditional risk factors may have a larger impact in middle-aged patients. We found this relation was only present in one segment of the artery with strongest association for a FH of stroke. This indicates that a detailed FH and thorough investigations is important in future studies of heredity. Additionally we discuss the possibility that the family history may represent two slightly different aspects of disease in the two age-categories. With the young patients having more premature CVD, whereas the middle-aged patients may have more FH of CVD associated with old age.

We suggest that the involvement of several family members could be beneficial in order to obtain a valid and adequately detailed FH, including the type of and age at CVD event in first-degree family members. The limited knowledge regarding the details of the FH of stroke showed the need for educational strategies, both with a patient approach, and also as a public health effort to increase the knowledge of the FH stroke in the population.

The FH as a tool to assess heredity may very well be completely superseded and made obsolete by genetic analyses in the future. However, we are not there yet. At this point in time, I believe the FH could and should be a supplemental aid to guide and improve the design of genetic studies. These two powerful tools should be combined in a useful and synergistic manner to improve our knowledge on the heredity of complex traits such as CVD.

Source of data

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Appendix

I. Patient questionnaire regarding FH

II. Parent questionnaire regarding own disease and FH

III. Example of ultrasound measurement chart

Appendix I

NOR-SYS
Norwegian Stroke in the Young Study

Norwegian Stroke in the Young Study

Family history

Number of full siblings ☐ Number of own offspring ☐ , of whom ☐ are aged ≥18y

Who of the following family members have had stroke, heart disease or peripheral artery disease?

If unknown (or if you are adopted) tick the box: ☐ and skip to the next section regarding smoking.

Stroke?

If "Yes": What type of stroke: (multiple ticks allowed)

	Yes	No	Don't know	TIA / mini-stroke	Infarction	Bleeding	Don't know
Father	☐	☐	☐	☐	☐	☐	☐
Father´s mother	☐	☐	☐	☐	☐	☐	☐
Father´s father	☐	☐	☐	☐	☐	☐	☐
Mother	☐	☐	☐	☐	☐	☐	☐
Mother´s mother	☐	☐	☐	☐	☐	☐	☐
Mother´s father	☐	☐	☐	☐	☐	☐	☐
Own siblings	☐	☐	☐	☐	☐	☐	☐
Own children	☐	☐	☐	☐	☐	☐	☐

Heart disease?

If "Yes": What type of heart disease: (multiple ticks allowed)

	Yes	No	Don't know	Angina / Chest pain	Myocardial infarction	Heart failure / rhythm and or valve problems	Don't know
Father	☐	☐	☐	☐	☐	☐	☐
Father´s mother	☐	☐	☐	☐	☐	☐	☐
Father´s father	☐	☐	☐	☐	☐	☐	☐
Mother	☐	☐	☐	☐	☐	☐	☐
Mother´s mother	☐	☐	☐	☐	☐	☐	☐
Mother´s father	☐	☐	☐	☐	☐	☐	☐
Own siblings	☐	☐	☐	☐	☐	☐	☐
Own children	☐	☐	☐	☐	☐	☐	☐

Intermittent claudication / "Smoker's leg"?

If "Yes": What type of treatment: (multiple ticks allowed)

	Yes	No	Don't know	Exercise	Surgical revascularization	Amputation	Don't know
Father	☐	☐	☐	☐	☐	☐	☐
Father's mother	☐	☐	☐	☐	☐	☐	☐
Father's father	☐	☐	☐	☐	☐	☐	☐
Mother	☐	☐	☐	☐	☐	☐	☐
Mother's mother	☐	☐	☐	☐	☐	☐	☐
Mother's father	☐	☐	☐	☐	☐	☐	☐
Own siblings	☐	☐	☐	☐	☐	☐	☐
Own children	☐	☐	☐	☐	☐	☐	☐

Did any of the mentioned family members die before the age of 70? Yes ☐ No ☐ Don't know ☐

If yes, who died before the age of 70? _____

Was the death sudden and unexpected? Yes ☐ No ☐ Don't know ☐

Do you know the cause of death? _____

Appendix II

NOR-SYS
Norwegian Stroke in the Young Study

Norwegian Stroke in the Young Study

Own history of stroke or cardiovascular disease — *If no, please tick* ☐

Have you ever had:	Don't know	No	Yes	If examined/treated: When (year), Where (hospital)
Stroke	☐	☐	☐	
TIA / «mini-stroke»	☐	☐	☐	
Brain infarction	☐	☐	☐	
Brain bleeding	☐	☐	☐	
Neck and or brain surgery		☐	☐	
Angina, chest pain		☐	☐	
Myocardial infarction / «heart attack»		☐	☐	
Coronary angioplasty		☐	☐	
Bypass-surgery		☐	☐	
Other heart surgery		☐	☐	Why?
«Smokers leg»		☐	☐	
Surgery on arteries in the legs		☐	☐	
Aortic surgery		☐	☐	
Blood clot in the lungs		☐	☐	
Blood clot in arm/leg, swollen and blue		☐	☐	
Blood clot in arm/leg, cold and white		☐	☐	
Migraine without visual disturbance (aura)		☐	☐	
Migraine with visual disturbance (aura)		☐	☐	

Other diseases – please define: _____

If treated by a **heart specialist in private practice**, please note (approximately) what year, and the name and address of the doctor:

Yr: _____ Name _____ Addr. _____

If your **GP (general practitioner or family doctor)** has treated you for chest pain, transient visual loss, weakness in arms and or legs, or leg pain, please note (approximately) what year, and the name and address of the doctor::

Yr: _____ Name _____ Addr. _____

Family history

Has one or both of your parents had stroke, heart disease or peripheral artery disease?
If unknown (also if you are adopted) tick the box: ☐ and skip to the next section regarding smoking.

Stroke?

If "Yes": What type of stroke: (multiple ticks allowed)

	Yes	No	Don't know	TIA / mini-stroke	Infarction	Bleeding	Don't know
Father	☐	☐	☐	☐	☐	☐	☐
Mother	☐	☐	☐	☐	☐	☐	☐

Heart disease?

If "Yes": What type of heart disease: (multiple ticks allowed)

	Yes	No	Don't know	Angina / Chest pain	Myocardial infarction	Heart failure / rhythm and or valve problems	Don't know
Father	☐	☐	☐	☐	☐	☐	☐
Mother	☐	☐	☐	☐	☐	☐	☐

Peripheral artery disease / Intermittent claudication / "Smoker's leg"?

If "Yes": What type of treatment: (multiple ticks allowed)

	Yes	No	Don't know	Exercise	Surgical revascularization	Amputation	Don't know
Father	☐	☐	☐	☐	☐	☐	☐
Mother	☐	☐	☐	☐	☐	☐	☐

Appendix III

Fam.reg.nr.	Patient	Partner	Child 1	Child 2	Child 3	Child 4
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 LONG (v / d)						
AORTA TRANS (d)						
MIDL ABD						
L ABD						
R ABD						
SUBCUT						
L CFA						
L SFA						
R CFA						
R SFA						
Epitrans						
Intrabd. fat						

success under 70%

Errata

Paper I: Patients´ knowledge: This single-center study has Hordaland County as catchment area, from which all patients aged up to 60 years with suspected stroke are admitted to the stroke unit at Haukeland university hospital.
Correction/clarification: The catchment area for NOR-SYS is the area for Helse-Bergen including Voss.
This area is slightly less than the whole area of Hordaland County.

Paper I: Table 4: The numbers of patients answering "don't know" regarding grandfathers CAD and PAD have switched places in table 4 of paper I. The corrected table is attached below.

Table 4. Comparing patients answering 'don't know' regarding family history of cardiovascular disease in maternal vs. paternal family members. From the 257 patients included in the Stroke in the Young Study (NOR-SYS) in Bergen, Norway 2010-2014

Relatives	**Maternal**	**Paternal**	
CVD	**N (%)**	**N (%)**	**P***
Parent			
Stroke	9 (3.50)	17(6.61)	0.059
CAD	13 (5.06)	15 (5.84)	0.512
PAD	15 (5.84)	21 (8.17)	0.157
Grandfathers			
Stroke	98 (38.13)	125 (48.64)	0.000
CAD	97 (37.74)	115 (44.75)	0.006
PAD	81 (31.52)	97 (37.74)	0.024
Grandmothers			
Stroke	83 (32.30)	117 (45.53)	0.000
CAD	95 (36.96)	115 (44.75)	0.000
PAD	76 (29.57)	85 (33.07)	0.117

Abbreviations: CVD: Cardiovascular disease; Stroke: both ischemic events and intracranial hemorrhage; CAD: coronary artery disease; PAD: peripheral artery disease

* P-value calculated with McNemar's test.

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Øygarden et al. BMC Neurology (2015) 15:30
DOI 10.1186/s12883-015-0276-6

BMC Neurology

RESEARCH ARTICLE Open Access

Stroke patients' knowledge about cardiovascular family history - the Norwegian Stroke in the Young Study (NOR-SYS)

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Abstract

Background: Family history (FH) is a risk factor for cardiovascular disease, especially coronary artery disease (CAD). The impact on risk of stroke is less clear. This study investigated young and middle-aged ischemic stroke patients' knowledge on FH of stroke, CAD, and peripheral artery disease (PAD) with a special regard to sex differences.

Methods: From September 2010 to February 2014, all ischemic stroke patients aged 15–60 years were prospectively included in the Norwegian Stroke in the Young Study (NOR-SYS). FH of stroke, CAD and PAD in offspring, siblings, parents, and grandparents was assessed using a standardized face-to-face interview. In addition to 'yes' and 'no', the optional reply 'don't know' was included to improve accuracy. McNemar's test was used to compare paired proportions, i.e. FH in male vs. female relatives. Multiple logistic regression analyses were used to test the influence of patient sex on FH reporting and to adjust for possible confounding factors.

Results: Altogether 257 patients were included. Mean age was 49.5 years and 68.1% were males. FH of cardiovascular disease was reported by 59% of patients. When asked about FH of stroke, 48 (18.7%) and 46 (17.9%) patients reported yes, whereas 17 (6.6%) and 9 (3.5%) reported 'don't know' regarding father and mother respectively, similarly patients reported 'don't know' regarding 117 (45.5%) paternal vs. 83 (32.4%) maternal grandmothers ($p < 0.001$). Female patients reported less 'don't know' and were more likely to report a positive cardiovascular FH than males (OR: 3.4; 95% CI: 1.5 to 7.7; $p = 0.004$). Patients had more detailed knowledge about CAD than stroke in fathers ($p < 0.001$), mothers ($p < 0.001$) and siblings ($p = 0.01$).

Conclusions: Young and middle-aged stroke patients reported a high FH burden of cardiovascular disease. Females are more likely to report a positive FH than males. Detailed knowledge on FH was best for CAD. Our results suggest sex has a big impact on FH knowledge. Females have more knowledge of FH than males and knowledge is better for relatives with a female than male linkage.

Clinical trial registration: http://www.clinicaltrials.gov, unique identifier: NCT01597453.

Keywords: Young stroke, Family history, Ischemic stroke, Cardiovascular disease

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Background

Family history (FH) of cardiovascular disease (CVD) in first-degree relatives (FDRs), including stroke, coronary artery disease (CAD) and peripheral artery disease (PAD), is a risk factor for vascular disease [1,2]. The association between CAD and FH of CVD is well documented [3-6]. However, the impact on risk of ischemic stroke is less clear, although FH of CVD is a positive predictor of stroke risk [7-10]. Sibling and genetic studies support FH of CVD as a risk factor and suggest a genetic influence on ischemic stroke risk [11-13]. Females with stroke are more likely to have a positive parental history than are males, and females are also more likely to have a positive maternal than paternal history [14,15]. Why females are more likely to report a positive FH is unknown [16]. Earlier studies of FH in stroke patients seldom separate between FH of intracranial hemorrhage (ICH) and ischemic stroke, assuming that it would be difficult for patients to differentiate between these [7-9,17-19]. Few studies included a reply of 'don't know' regarding FH, and when included it was usually interpreted as negative, to avoid over-estimating the FH burden [7,9]. However, one study found that 11% answered 'don't know' regarding FH in FDRs [20]. According to Flossman et al., publications on genetic epidemiology of stroke are heterogeneous, insufficiently detailed and possibly biased [8]. Today, more detailed information about CVD and risk factors is available for patients and their family members. Diagnostic stroke imaging has improved and increased detection of stroke [21]. Repeated efforts to increase awareness of acute stroke symptoms have been implemented after the introduction of thrombolytic therapy [22]. Therefore the public should be better qualified than ever to give a precise account of their FH. As we enter the genomic era of medicine, FH still is the most accessible, inexpensive and well proven tool assessing inherited risk for disease [23].

This population-based study, performed in a well-defined region of western Norway, aims to explore what young and middle-aged ischemic stroke patients know about stroke, CAD and PAD in their families. We aimed to assess and quantify a detailed FH of CVD with a special regard to sex differences.

Methods

Ischemic stroke patients aged 15–60 years who were prospectively included in the population-based Norwegian Stroke in the Young Study (NOR-SYS) were assessed. The methods and rationale of NOR-SYS have been described in detail previously [24]. Acute cerebral infarction was documented by magnetic resonance imaging. Patients unable to provide an adequate FH due to severe stroke, aphasia or severe psychiatric illness, and patients who were adopted or had no contact with their biological family were excluded. This single-center study has Hordaland County as catchment area, from which all patients aged up to 60 years with suspected stroke are admitted to the stroke unit at Haukeland university hospital.

Patients were interviewed using a standardized questionnaire within day two or three after the diagnosis of acute ischemic stroke. The interview was done face to face to ensure the patient did not contact family members by mobile phone or in any other way during the interview; and to ensure only events recalled by the patient were registered. All registration of events was done by the interviewing doctor. To increase reproducibility of answers between study doctors, new interviewers participated as a bystander in at least 5 interviews, thereby increasing the interview similarity and minimizing differences in answer interpretation. Data regarding patient sex, age, education, number of siblings and offspring were registered in addition to a detailed disease history and family history. Patients were assigned to the educational categories, basic school, high school or college/university education. The three optional replies for the FH disease entities of stroke, heart disease and PAD/claudication were: 'yes', 'no' and 'don't know'. 'Don't know' was included to improve accuracy of reporting. The frequency of 'don't know' in FH was also analyzed to assess the effect of patient sex on reporting of FH. In addition, the frequency of 'don't know' was analyzed to assess differences in reporting of maternal vs. paternal FH. The frequency of the answer 'don't know' regarding type of heart and cerebrovascular disease in FDRs was analyzed to compare patients' knowledge on FH of heart disease with their knowledge on cerebrovascular disease. All reported non-CAD, if present without any CAD, was regarded as no CAD. FH of stroke, heart disease and PAD in FDRs; parents, siblings and biological offspring was registered. In addition, FH of all four grandparents was registered.

To explore in depth knowledge and avoid misinterpretation of disease, further questions were asked. If the patient replied 'yes' regarding FH of any of the disease entities stroke, heart disease and PAD, he was asked to specify the type of stroke or heart disease and in case of PAD he was asked to specify the prescribed treatment. When stroke was reported, the patient was asked to specify the type of stroke as a Transient Ischemic Attack (TIA)/minor stroke with quick and complete restitution, cerebral infarction, ICH or 'don't know'. When heart disease was reported, this was specified as ischemic, such as angina pectoris and myocardial infarction, as non-CAD, such as arrhythmia, valve problem and heart insufficiency or 'don't know'. If PAD/claudication was reported, the patient was asked about the applied

treatment, such as training, surgical treatment other than amputation, amputation or 'don't know'. If one answer for disease subtype was missing, the data was imputed as 'don't know'.

Statistics

Descriptive statistics are given using the mean, standard deviation (SD) and proportion with 95% confidence interval (CI). The chi square test was used for categorical data. McNemar's test was used to compare paired proportions. Continuous and normally distributed variables were analyzed by Student's *t*-test. Wilcoxon's Rank-Sum Test was used to analyze continuous variables that were not normally distributed.

We stratified the patients by sex to compare FH between males and females. FH of CVD was considered present if at least one parent, sibling or grandparent had CVD. Multiple logistic regression analyses with FH of CVD as dependent variable and age, sex, educational category and, to adjust for family size, number of siblings as independent variables were performed. The same analyses were performed using FDRs only, to ensure that the high rates of 'don't know' regarding grandparental FH did not affect the main results. The level of significance was set at 0.05. Stata 13.1 (StataCorp, College Station, TX) was used for all analyses.

Ethics

All patients or legal guardians signed a written informed consent. NOR-SYS is approved by the Regional Ethics Committee of western Norway, and the study was conducted in accordance with the Declaration of Helsinki.

Results

Demographics

Between September 2010 and February 2014, 292 stroke patients were included in NOR-SYS. Two patients did not consent, and two others were not included because of serious psychiatric illness and mental retardation. Thirty-five patients were excluded after inclusion. Three (1%) were adopted and had no contact with their biological families and 32 (10.1%) were unable to answer for themselves due to severe aphasia or coma. Participants had a mean age of 49.5 (SD = 9.3) years, 68% were male and the majority had at least a high school education (76%, Table 1). The mean number of siblings was 2.5 and 237 (92%) patients had at least one sibling. No offspring stroke, CAD or PAD were reported. There were no significant differences in demographic data by sex, however there was a trend for age ($p = 0.057$), females were slightly younger than males (47.6 years vs. 50.4 years, respectively).

Family history

About 59% of participants reported their father was deceased, while 36% reported a deceased mother ($p < 0.001$, Table 1). Two patients did not know if their fathers were alive, and data regarding deceased parents was missing in four patients. Any first-degree FH of CVD was reported by 153 (59.5%) patients. Most participants reported a first-degree FH of CAD (41%), followed by stroke (34%) and PAD (6%). Patients reported relatively low numbers of disease and high proportions of 'don't know' in grandparents for all types of CVD (Table 2).

Table 1 Demographic data of the 257 patients included in the Stroke in the Young Study (NOR-SYS) in Bergen, Norway 2010-2014

Variables	Total N = 257	Males N = 175 (68.1%)	Females N = 82 (31.9%)	P
Age in years, *mean* (*SD*)	49.5 (9.3)	50.4 (8.5)	47.6 (10.6)	0.057
Education				0.547
Basic school, n (%)	60 (23.5)	43 (24.7)	17 (21.0)	
High school, n (%)	91 (35.7)	64 (36.8)	27 (33.3)	
College/University, n (%)	104 (40.8)	67 (38.5)	37 (45.7)	
N of siblings, *mean* (*SD*)	2.5 (1.7)	2.6 (1.9)	2.2 (1.3)	0.116
N of children, *mean* (*SD*)	2.0 (1.3)	2.0 (1.4)	1.8 (1.2)	0.311
Deceased fathers, *n* (%)	149* (58.7)	103 (59.9)	46 (56.1)	0.756
Deceased mothers, *n* (%)	92† (36.4)	60 (35.1)	32 (39.0)	0.542
First-degree FH of stroke, n (%)	87 (33.9)	55 (31.4)	32 (39.0)	0.230
First-degree FH of CAD, n (%)	105 (41.0)	67 (38.3)	38 (46.9)	0.192
First-degree FH of PAD, n (%)	16 (6.2)	11 (6.3)	5 (6.1)	0.954

Abbreviations: *SD* standard deviation, *FH* family history, *First-degree FH* family history in parents, siblings or offspring, *CAD* coronary artery disease, *PAD* peripheral artery disease, *P* p-value of comparison between males and females.
*N = 254 due to missing data in 5 of patients' fathers. †N = 252 due to missing data in 4 of patients' mothers.

Table 2 Reported family history of cardiovascular disease in first-degree relatives* and grandparents of the 257 patients included in the Stroke in Young Study (NOR-SYS) in Bergen, Norway 2010–2014

Relatives	Cardiovascular disease	Yes N (%)	No N (%)	Don't know N (%)
Siblings†	Stroke	8 (3.3)	232 (95.9)	2 (0.8)
	Heart disease	36 (14.9)	202 (83.5)	4 (1.6)
	PAD	5 (2.1)	232 (95.9)	5 (2.1)
Mothers	Stroke	46 (17.1)	202 (78.6)	9 (3.5)
	Heart disease	55 (21.6)	187 (73.3)	13 (5.1)
	PAD	9 (3.5)	233 (90.7)	15 (5.8)
Fathers	Stroke	48 (18.7)	192 (74.7)	17 (6.6)
	Heart disease	101 (39.3)	141 (54.9)	15 (5.8)
	PAD	15 (5.8)	221 (86.0)	21 (8.2)
Mothers' mothers	Stroke	30 (11.7)	143 (55.9)	83 (32.4)
	Heart disease	35 (13.7)	126 (49.2)	95 (37.1)
	PAD	1 (0.4)	180 (70)	76 (29.6)
Mothers' fathers	Stroke	16 (6.2)	142 (55.5)	98 (38.3)
	Heart disease	47 (18.3)	113 (44.0)	97 (37.7)
	PAD	3 (1.2)	173 (67.3)	81 (31.5)
Fathers' mothers	Stroke	20 (7.8)	120 (46.7)	117 (45.5)
	Heart disease	21 (8.2)	121 (47.1)	115 (44.7)
	PAD	5 (1.9)	167 (65.0)	85 (33.1)
Fathers' fathers	Stroke	18 (7.0)	114 (44.4)	125 (48.6)
	Heart disease	34 (13.2)	108 (42.0)	115 (44.8)
	PAD	4 (1.6)	156 (60.7)	97 (37.7)

Abbreviations: *Stroke* both ischemic events and intracranial hemorrhage, *Heart disease* including coronary artery disease and reported non-CAD such as heart failure, rhythm and/or valve problems, *PAD* peripheral artery disease.
*No cardiovascular events were reported among offspring.
†N = 242, 242 patients had one or more siblings.

FH knowledge regarding type of CVD

Patient reports on type of CVD in FDRs are summarized in Table 3. Patients reported more CAD among fathers than among mothers ($p < 0.001$). Detailed knowledge regarding type of heart disease was high, whereas knowledge on type of parental stroke was lower. Comparing answers regarding disease type, 'don't know' type of stroke was significantly higher than 'don't know' type of heart disease for fathers ($p < 0.001$), mothers ($p < 0.01$), siblings ($p = 0.01$), and all grandparents ($p < 0.001$) except mothers' fathers ($p = 0.5$). Few patients reported a FH of PAD and the knowledge of ordinated treatment for PAD was not analyzed further.

Sex differences in FH

There was a trend of more reported FH of CVD events and less frequent reporting of 'don't know' among females compared to males (Figure 1). When analyzing FH of CVD in grandparents, females reported significantly less 'don't know' regarding heart disease in mothers' mothers ($p = 0.02$) and of stroke in fathers' mothers ($p = 0.02$). Patients reported 'Yes' or 'No' on FH of stroke in both parents in 235 (91%) cases and having knowledge of both parents' FH was most common. Patients consistently reported less 'don't know' regarding maternal FH than paternal FH (Table 4). Males reported a mean number of 1.5 (SD: 1.28) family members with CVD, whereas females reported 1.9 (SD: 1.25; $p = 0.01$). Females reported a positive FH more often than males with an OR of 3.4 (95% CI: 1.5 to 7.7; $p < 0.01$; Table 5). When analyzing a positive FH in FDRs only, females are more likely to report a positive FH with an OR of 2.5 (95% CI: 1.3 to 4.8; $p < 0.01$). In addition, increasing age was associated with a positive FH and higher educational category was associated with a negative FH.

Discussion

We observed a high rate of reported CVD in patients' parents. The reported FH of parental stroke in the present study was 33%, slightly lower than 41% reported in a Swedish study [9]. The reported 37% FH of CAD in the present study is comparable with 38% in the Swedish study [9]. The slight disparity regarding parental stroke may be explained by the lower mean age of our patients

Table 3 Comparing knowledge on type of cardiovascular disease in patients replying 'Yes' a family member suffered from stroke, heart disease and/or peripheral artery disease

	Siblings*	Mothers	Fathers	Mothers' mothers	Mothers' fathers	Fathers' mothers	Fathers' fathers
Stroke	**N = 8**	**N = 46**	**N = 48**	**N = 30†**	**N = 16**	**N = 20**	**N = 18†**
TIA (%)	0 (0.0)	9 (19.6)	8 (16.7)	4 (13.3)	3 (18.8)	2 (10.0)	0 (0.0)
Cerebral infarction (%)	3 (37.5)	12 (26.1)	11 (22.9)	2 (6.7)	4 (25)	2 (10.0)	2 (11.1)
Cerebral bleeding (%)	1 (12.5)	7 (15.2)	5 (10.4)	1 (3.3)	2 (12.5)	1 (5.0)	0 (0.0)
Don't know (%)	4 (50)	18 (39.1)	24 (50)	23 (76.7)	7 (43.8)	15 (75.0)	16 (88.9)
Heart disease	**N = 36**	**N = 55†**	**N = 101†**	**N = 35†**	**N = 47†**	**N = 21**	**N = 34†**
Angina pectoris (%)	5 (13.9)	12 (21.8)	9 (8.9)	8 (22.9)	4 (8.5)	4 (19.1)	3 (8.8)
Myocardial infarction (%)	15 (41.7)	16 (29.1)	48 (47.5)	8 (22.9)	24 (51.1)	8 (38.1)	16 (47.1)
Non-CAD (%)	12 (33.3)	21 (39.6)	25 (24.8)	7 (20)	3 (6.4)	2 (9.5)	2 (5.9)
Don't know (%)	4 (11.1)	6 (10.9)	19 (18.8)	12 (34.3)	16 (34.0)	7 (33.3)	13 (38.2)
PAD	**N = 5†**	**N = 9†**	**N = 15**	**N = 1**	**N = 3**	**N = 5**	**N = 4**
Conservative (%)	2 (40.0)	3 (33.3)	2 (13.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Revascularization surgery (%)	2 (40.0)	1 (11.1)	5 (33.3)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Amputation (%)	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)	3 (100)	2 (40.0)	1 (25.0)
Don't know (%)	1 (20.0)	5 (55.6)	6 (40)	0 (0.0)	0 (0.0)	2 (40.0)	3 (75.0)

From the 257 patients included in the Stroke in Young Study (NOR-SYS) in Bergen, Norway 2010-2014.
Abbreviations: *TIA* transient ischemic attack, *Non-CAD* non-coronary heart disease, included heart failure, rhythm and/or valve problems.
*N = 242, 242 patients had one or more siblings.
†One answer regarding type of disease was missing and was imputed as don't know.

and the methodological differences concerning the acquisition of FH, where we solely interviewed patients. The present study showed higher numbers of deceased fathers than mothers (149 vs. 92), probably caused by the higher life expectancy of females [25].

Earlier studies have observed a mother-daughter relationship in heredity of stroke [14]. Our results show that females are more likely to report a positive FH than males. Females reported a higher incidence of FH of CVD in total and had better knowledge on the type of

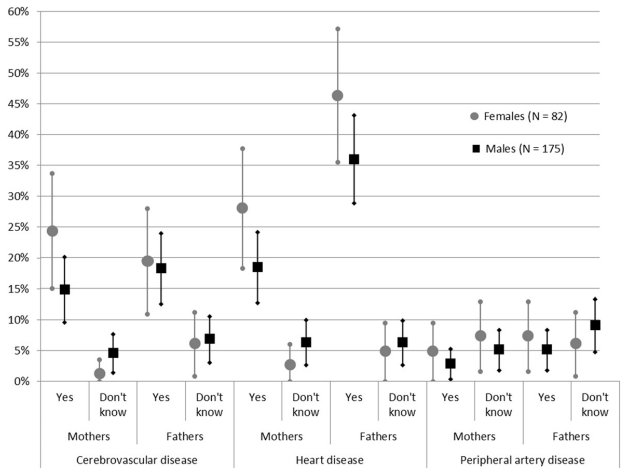

Figure 1 Reported parental history of cerebrovascular disease, coronary artery disease and peripheral artery disease from the 257 young and middle-aged ischemic stroke patients included in the Stroke in the Young Study (NOR-SYS) in Bergen, Norway 2010–2014, stratified by sex. Answers 'Yes' and 'Don't know' are displayed in percentage proportions with 95% confidence intervals of the total N, the remaining answering 'No'.

Table 4 Comparing patients answering 'don't know' regarding family history of cardiovascular disease in maternal vs. paternal family members

Relatives	Maternal	Paternal	
CVD	N (%)	N (%)	P*
Parent			
Stroke	9 (3.50)	17 (6.61)	0.059
CAD	13 (5.06)	15 (5.84)	0.512
PAD	15 (5.84)	21 (8.17)	0.157
Grandfathers			
Stroke	98 (38.13)	125 (48.64)	0.000
CAD	81 (31.52)	97 (37.74)	0.006
PAD	97 (37.74)	115 (44.75)	0.024
Grandmothers			
Stroke	83 (32.30)	117 (45.53)	0.000
CAD	95 (36.96)	115 (44.75)	0.000
PAD	76 (29.57)	85 (33.07)	0.117

From the 257 patients included in the Stroke in the Young Study (NOR-SYS) in Bergen, Norway 2010-2014.
Abbreviations: *CVD* Cardiovascular disease, *Stroke* both ischemic events and intracranial hemorrhage, *CAD* coronary artery disease, *PAD* peripheral artery disease.
*P-value calculated with McNemar's test.

CVD. In addition, both male and female patients know more about their maternal than paternal FH of CVD. Both sex of patient and maternal family linkage influence the response rate of 'don't know'; this suggests that knowledge of FH is strongly influenced by sex, possibly due to females being more involved in communication across generations in Norway. Additionally, the cultural designation of females as main family care-givers may enable them to obtain more information on FH of CVD [26].

Significant less reporting of 'don't know' regarding disease type in maternal vs. paternal grandparents supports the hypothesis that female-female communication on disease across generations increases knowledge on FH. Another possible explanation for the higher maternal FH may be that males have a higher risk of violent death at young age, before CVD manifestations occur [27]. And the higher female reporting of FH may be explained by females with ischemic stroke simply having a higher FH of CVD burden than do males. However, these hypotheses do not explain the higher maternal than paternal FH also when comparing same-sex grandparents.

The patients reporting parental stroke had difficulties differentiating between the types of stroke, 40% and 50% of patients answered 'don't know' regarding mothers' and fathers' type of stroke, respectively. The present study was conducted 20 years after the introduction of MRI and we assumed that the new diagnostic and treatment opportunities in addition to informational campaigns would have improved patients' knowledge about stroke. Our reported numbers of parental ICH in relation to total stroke numbers were comparable to the relationship found in epidemiologic studies [28]. Patients seem to clearly recall a FH of ICH, but have more problems defining an ischemic stroke in their FH. This may be due to higher mortality and often more dramatic symptoms of ICH [29]. It is reported that general knowledge on stroke is lower than knowledge on CAD, although the knowledge about stroke symptoms was not lower in newer studies [30,31]. Less reporting of 'don't know' on type of heart disease than on type of stroke regarding all FDRs in our study suggests less knowledge about stroke than CAD.

The reported FH of PAD was low in the present study; only 15 (5.8%) of patients' fathers had PAD. In a recent Dutch study including 4700 patients with a history of cerebrovascular disease, CAD, PAD or aortic abdominal aneurysm, 16% of patients had a FH of PAD, and they found that paternal PAD was a risk factor for subsequent PAD in the offspring [32]. This difference may be caused by the lower mean age of our patients, and that only patients with ischemic stroke were included in our study. However, the difference in prevalence of FH shows the importance of addressing all manifestation sites of atherosclerosis and vascular disease when evaluating FH.

The reported FH of CVD among grandparents was low. The high reporting of 'don't know' regarding grandparents' FH of CVD and the almost absent knowledge of

Table 5 Logistic regression displaying factors possibly associated with a positive family history of cardiovascular disease of the 257 patients included in the Stroke in the Young Study (NOR-SYS) in Bergen, Norway 2010-2014

Response variable:	FH of FDR			FH of FDR + grandparents		
Predictors	OR	95% CI	P	OR	95% CI	P
Sex (female)	2.50	(1.31, 4.78)	0.005	3.37	(1.48, 7.70)	0.004
Education	0.67	(0.47, 0.98)	0.038	1.20	(0.79, 1.80)	0.377
Number of siblings	1.08	(0.9, 1.27)	0.329	0.99	(0.83, 1.18)	0.922
Age of patient (years)	1.09	(1.0, 1.13)	<0.001	1.03	(0.99, 1.06)	0.116

Explanations and abbreviations: *FH* family history, *FDR* first-degree relatives, i.e. parents, siblings and offspring (no cardiovascular events were reported for offspring in this study), *OR* Odds ratio, *CI* Confidence interval, *Education* basic school, high school and college/university: Number of siblings: 1 unit increase per sibling reported.

grandparents' particular CVD type suggests this may be due to lack of knowledge on grandparental disease history and not absence of disease among grandparents. Less available medical care and less precise diagnostics may explain the lack of knowledge. In addition, the generation gap reduces information of grandparental FH.

The present study is strengthened by the homogenous and well-defined study population, and also the detailed assessment of FH including CVD subtypes and the analysis of FH from several generations. The study also has some limitations. The well-defined study population of young ischemic stroke patients makes the results not directly generalizable to the general population. In addition, the self-reported FH may not be completely correct and is dependent on family relations, the patient cognitive status at time of the interview and several other factors. We excluded patients with aphasia and patients incapable of answering themselves, but we did not assess if severity of the acute disease could influence the answers regarding FH. However, the inclusion of 'don't know' as a possible answer increases the accuracy in providing a potential answer for patients unsure of their FH.

Conclusion

In conclusion, the FH of CVD burden among young ischemic stroke patients was high. Females seem to have more knowledge on FH of CVD than do males, and knowledge on maternal FH is higher than paternal FH. Knowledge on FH of heart disease type is significantly higher than type of stroke. We recommend obtaining the FH with the patient as the primary informant, however, the involvement of other family members may increase both the completeness and accuracy of the FH and should be encouraged. More public information on FH of CVD as a risk factor is warranted to improve the general knowledge of FH in the population. Information could be directed towards males in particular. As males have less knowledge regarding own FH than females; they have the most to gain by improving their FH knowledge. Increased knowledge of own FH provides an opportunity to take action to reduce risk and may encourage patients into smoking cessation, regular exercise and adopting a healthier diet. Increased attention on FH is important for the patient and also the public in general to improve this accessible, well-proven and inexpensive tool both for risk stratification and in aiding future genetic research.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HØ participated in the design of the study, the data collection, performed the statistical analyses and drafted the manuscript. AF and KMS participated in the design of the study, the collection of data and critical revision of the manuscript. GEE participated in the statistical analyses and interpretation of results. LT and HN participated in the design of the study and critical revision of the manuscript. UWA conceived of the study, and participated in its design and coordination, the data collection and critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank Jeanette Haveland Antoniazzi and study Nurse Linn Elin Rødal for invaluable help in administering the NOR-SYS study.

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Received: 13 November 2014 Accepted: 20 February 2015
Published online: 12 March 2015

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EUROPEAN JOURNAL OF NEUROLOGY

ORIGINAL ARTICLE

Can the cardiovascular family history reported by our patients be trusted? The Norwegian Stroke in the Young Study

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Keywords:
cardiovascular disease, family history, ischaemic stroke, verification, young stroke

Received 6 May 2015
Accepted 2 July 2015

European Journal of Neurology 2016, **23:** 154–159

doi:10.1111/ene.12824

Background and purpose: Family history (FH) is used as a marker for inherited risk. Using FH for this purpose requires the FH to reflect true disease in the family. The aim was to analyse the concordance between young and middle-aged ischaemic stroke patients' reported FH of cardiovascular disease (CVD) with their parents' own reports.

Methods: Ischaemic stroke patients aged 15–60 years and their eligible parents were interviewed using a standardized questionnaire. Information of own CVD and FH of CVD was registered. Concordance between patients and parents was tested by kappa statistics, sensitivity, specificity, predictive values and likelihood ratios. Regression analyses were performed to identify patient characteristics associated with non-concordance of replies.

Results: There was no difference in response rate between fathers and mothers ($P = 0.355$). Both parents responded in 57 cases. Concordance between patient and parent reports was good, with kappa values ranging from 0.57 to 0.7. The patient-reported FH yielded positive predictive values of 75% or above and negative predictive values of 90% or higher. The positive likelihood ratios (LR+) were 10 or higher and negative likelihood ratios (LR−) were generally 0.5 or lower. Interpretation regarding peripheral arterial disease was limited due to low parental prevalence. Higher age was associated with impaired concordance between patient and parent reports (odds ratio 1.05; 95% confidence interval 1.01–1.09; $P = 0.020$).

Conclusions: The FH provided by young and middle-aged stroke patients is in good concordance with parental reports. FH is an adequate proxy to assess inherited risk of CVD in young stroke patients.

Introduction

A positive family history (FH) of cardiovascular disease (CVD) in first-degree relatives confers an increased risk of stroke and coronary artery disease (CAD) [1–7]. FH is used as a marker for inherited risk of disease both for cancer and CVD [8,9]. FH can serve as a tool in identifying individuals with high risk of developing CVD, and may aid in risk stratification and disease prevention [9–12]. FH is usually self-reported and the accuracy or validity of such self-reporting has been tested in various ways, e.g. by confirmation from medical records and by reports from patient relatives, with varying accuracy [10,13–16]. Higher age reduces accuracy, and female sex seems associated with increased accuracy of FH reporting [15]. Studies have found that under-reporting a FH of cancer is common and may be a problem when assessing FH as a risk factor [17,18]. Misreporting of FH could introduce bias and lead to misclassification of patients with inherited risk, and thereby hamper the use of FH as a tool to study the heredity of CVD [15]. The accuracy of FH has predominantly

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been tested in healthy cohorts, with a few exceptions assessing the accuracy of FH in patients with CAD [19,20]. The Norwegian Stroke in the Young Study (NOR-SYS), a prospective population-based study conducted in a well-defined region of western Norway, enrols young and middle-aged ischaemic stroke patients up to 60 years of age. The patients are interviewed regarding FH of stroke, CAD and peripheral arterial disease (PAD) [21]. NOR-SYS is designed to evaluate family patterns in the development of vascular disease using reported events, clinical examinations (e.g. by ultrasound) and genetic analyses. As this cohort consists of patients with documented cerebral infarction, a need to evaluate the accuracy of the patient-provided FH of CVD became apparent. With standardized questionnaires sent to all eligible patient parents providing self-reported disease history, the aim was to analyse the concordance between patient- and parent-reported FH.

Subjects and methods

Patients aged 15–60 years admitted to the Stroke Unit, Department of Neurology at Haukeland University Hospital, with acute ischaemic stroke since September 2010 were prospectively included in NOR-SYS. Acute cerebral infarction was confirmed by computed tomography or magnetic resonance imaging.

Patients were interviewed regarding FH of CVD using a standardized questionnaire, most within 3 days after acute ischaemic stroke was diagnosed (see Data S1). Only events recalled and reported by the patient were registered by the interviewing doctor. The interview was done face-to-face and contact with family members by mobile phone or in any other way was avoided. Only patients able to answer without assistance were included. To increase similarity and ensure reproducibility, all new interviewers participated as a bystander in at least five interviews, thereby minimizing differences amongst interviewers. The questionnaire contained detailed questions regarding the FH of stroke, CAD and PAD in mothers, fathers, siblings and all four grandparents separately. Confirmative answers prompted follow-up questions to further classify the disease. Patients were assigned to the educational categories basic school, high school and college/university education.

Patients were asked if their parents were alive and able to fill out a similar questionnaire. Based on the patient's consent a similar questionnaire was sent to the parent/parents along with a stamped return envelope. The standardized parent questionnaire recorded the parent's own clinical events of CVD, risk factors and medication, in addition to their parental FH of CVD (see Data S2).

Statistics

STATA 13.1 (StataCorp, College Station, TX, USA) was used for analyses. The chi-squared test, Wilcoxon rank-sum test or Student's t test was used to compare differences in patient and parent demographics, as appropriate. Spearman's correlation was used to test for correlation. Concordance was tested using kappa statistics. In addition, specificity, sensitivity, predictive values and likelihood ratios were calculated by a STATA module named 'diagt', with patient answers as the diagnostic test and parent reports as the gold standard [22]. Kappa values of 0.41–0.60 were interpreted as moderate, 0.61–0.80 as substantial and 0.81–0.99 as near perfect concordance [23]. Regression analyses were performed to examine if patient characteristics influenced concordance. The level of significance was set at $P < 0.05$.

Ethics

All participating patients and patients' parents gave informed written consent. The NOR-SYS protocol is approved by the Regional Ethics Committee of western Norway, and is conducted in accordance with the Declaration of Helsinki. The NOR-SYS protocol is registered at http://www.clinicaltrials.gov with the unique identifier NCT01597453.

Results

From September 2010 to August 2014, 313 acute ischaemic stroke patients were included in NOR-SYS. A flowchart for patient and parent eligibility and inclusion is presented in Fig. 1. A common reason for patients refusing the invitation of parents was parent dementia. However, causes for refusal were not asked for systematically. No differences in reply rates were seen between fathers and mothers ($P = 0.355$). The mean age of patients with both parents alive compared with one or more deceased parents was 41.55 and 53.77 years, respectively (SD 10.50 and 6.16, $P < 0.001$). The rate of parental reply was similar between patient sexes with 87 (44.67%) male and 45 (49.5%) female patients having one or more parents replying ($P = 0.402$). Spearman's correlation revealed a negative correlation between patient age and the number of parent replies ($r = -0.506$, $P < 0.001$), also present when the number of deceased parents was adjusted for in a linear regression analysis ($P < 0.001$). Both parents were alive and responded in 57

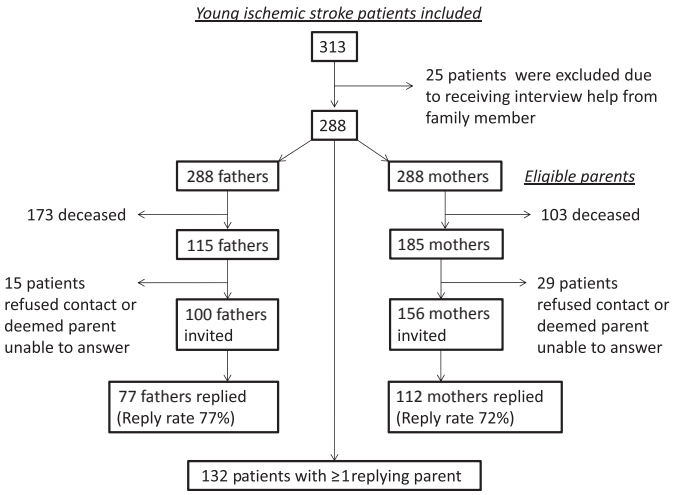

Figure 1 Flowchart of patient and parent eligibility and study inclusion.

(19.8%) cases. Table 1 shows the demographic data and presence of risk factors in the 132 patients with one or more parents replying.

Table 1 Demographic data and presence of risk factors for cardiovascular disease in 132 patients included in the Norwegian Stroke in the Young Study (NOR-SYS)

	Patients N = 132
Mean age (SD)	44.5 (11.2)
Higher education (%)	65 (49.2)
Living situation	
Alone	26 (19.7)
Partner/family member	106 (80.3)
Institution	1 (0.8)
Employment status	
Full-time job[a]	103 (78.0)
Part-time job	13 (9.8)
Stay at home parent	1 (0.8)
Unemployed	4 (3.0)
Welfare benefits[b]	11 (8.3)
Hypertension (%)	41 (31.1)
Diabetes mellitus (%)	5 (3.8)
Overweight (%)	88 (66.7)
Active smoker (%)	49 (37.1)
Alcohol units/week	
≤3 or never	83 (62.9)
4–6	29 (22.0)
7–12	11 (8.3)
≥13	9 (6.8)

Higher education, defined as completed college or university education; hypertension, defined as current treatment for hypertension; diabetes mellitus, defined as treatment for diabetes mellitus, including both medical and non-medical treatment; overweight, defined as body mass index >25 kg/m^2.[a]Also includes self-employed, full-time students and pupils; [b]including full welfare benefit recipients and partial benefit recipients if no work was registered. Six cases reporting both partial welfare benefits and part-time job were registered as part-time job.

Patient answers were in moderate to substantial concordance with parental reports, with kappa values ranging from 0.54 to 0.69 regarding stroke and CAD (Table 2). The rate of concordance was similar between parent sexes. The number of incorrect answers was lowest with regard to parental PAD and highest for parental CAD. Patient under-reporting of FH was twice as frequent as false positive FH reports. Positive predictive values were generally above 70% and negative predictive values were generally above 90%, except with regard to PAD where prevalence amongst parents was low (Table 3). Positive likelihood ratios (LR+) were around 10 or higher and negative likelihood ratios (LR−) were generally 0.5 or less. Regression analyses revealed that increasing patient age was associated with non-concordance between patient and parent reports with an odds ratio of 1.05 per year (95% confidence interval 1.01–1.09; P = 0.020; Table 4). However, neither patient sex, level of education, employment status, living status, alcohol consumption nor smoking significantly influenced concordance between patient and parent reports (Table 4).

Discussion

A high proportion of deceased parents, especially deceased fathers, was observed, probably due to longer life expectancy in females and earlier debut of CVD in males [24,25]. Stroke, CAD and PAD were reported in 53 (18%), 42 (14%) and 10 (3%) mothers, and 51 (18%), 93 (32%) and 18 (6%) fathers, respectively (data not shown). The patients had a high

Table 2 Patient versus parental answers regarding cardiovascular disease history from 132 patients and 189 parents included in the Norwegian Stroke in the Young Study (NOR-SYS)

	Patients' answers			
	No	Yes	Non-concordance (%)	Kappa (SD)
Mothers' answers				
Stroke (n = 110)				
No	92	3	9 (8.18)	0.62[a] (0.09)
Yes	6	9		
CAD (n = 107)				
No	89	2	10 (9.35)	0.57[a] (0.09)
Yes	8	8		
PAD (n = 106)				
No	100	2	6 (5.66)	−0.03 (0.09)
Yes	4	0		
Fathers' answers				
Stroke (n = 75)				
No	61	2	6 (8.00)	0.68[a] (0.11)
Yes	4	8		
CAD (n = 77)				
No	49	4	9 (12.99)	0.69[a] (0.11)
Yes	6	18		
PAD (n = 75)				
No	71	1	3 (4.00)	0.38[a] (0.11)
Yes	2	1		

CAD, coronary artery disease, defined as either myocardial infarction or angina pectoris; PAD, peripheral arterial disease, defined as intermittent claudication or initiated treatment for peripheral arterial disease. Some patients' parents did not provide answers to all disease categories as indicated by the varying number of parent replies.
[a]$P < 0.001$.

Table 4 Logistic regression analysis displaying factors associated with non-concordance between patient-reported family history of CVD and parents' own reports, from 132 patients and 189 parents included in the Norwegian Stroke in the Young Study (NOR-SYS)

	OR	95% CI	P value
Age (years)	1.05	1.01–1.09	0.020
Gender (female)	1.72	0.63–4.72	0.291
Education	0.77	0.42–1.38	0.378
Full-time job (reference)			
Part-time job	1.09	0.28–4.37	0.895
Unemployed	0.94	0.09–10.39	0.960
Living with partner (reference)			
Living with family member	1.63	0.39–6.77	0.505
Living alone	1.07	0.37–3.07	0.898
Smoking	0.75	0.44–1.26	0.272
Alcohol consumption	0.89	0.57–1.40	0.632

OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease. Full-time job also included full-time student, pupil and self-employed; part-time job included one stay at home parent; unemployed also included welfare recipients. Education, three categories: basic school, gymnasium and college/university. Living with family member, other than partner, e.g. child or parent.

burden of traditional vascular risk factors, as shown in young stroke populations in several European regions [26]. Concordance between patient and parent reports was good, especially with regard to stroke and CAD. The LR+ of 19 with regard to stroke in mothers tells us that a patient report of maternal stroke is 19 times more likely to concur with maternal reports than to be a false positive report. Correspondingly the high negative predictive values and the low LR− show that a negative patient-reported FH truly reflects no disease event amongst first-degree family members. Concordance was mostly acceptable also regarding PAD. However, interpretation was limited by the low prevalence of parental PAD. The present study shows no difference between males and females regarding non-concordance, indicating that the previously reported higher frequency of positive FH in females is not a result of more accurate FH reporting by females [27]. This supports the previous studies showing no difference in accuracy of FH reporting between males and females [15,28].

Previous studies evaluating the FH of cancer show substantial under-reporting. In probands with verified

Table 3 Accuracy of 132 patient reports of cardiovascular parental disease compared with answers from 189 parents included in the Norwegian Stroke in the Young Study (NOR-SYS)

Parent	Condition	Prevalence	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
Mother	Stroke	13.6% (15/110)	74.9 (48–91)	93.9 (89–97)	60.0 (32–84)	96.8 (91–99)	19.0 (6–62)	0.41 (0.2–0.8)
	CAD	14.8% (16/107)	79.8 (48–94)	91.8 (97–94)	50.0 (25–75)	97.8 (92–100)	22.8 (5–97)	0.51 (0.3–0.8)
	PAD	3.8% (4/106)	NA	96.1 (96–96)	NA (0–60)	98.0 (93–100)	NA	1.02 (1.0–1.1)
Father	Stroke	16.0% (12/75)	80.0 (49–94)	93.8 (87–97)	66.7 (35–90)	96.8 (89–100)	21.0 (5–87)	0.34 (0.2–0.8)
	CAD	31.2% (24/77)	81.8 (63–92)	89.1 (79–94)	75.0 (53–90)	92.5 (82–98)	9.9 (4–26)	0.27 (0.1–0.5)
	PAD	4.0% (3/75)	50.0 (7–93)	97.3 (94–99)	33.3 (1–91)	98.6 (92–100)	24.0 (2–298)	0.68 (0.3–1.5)

CAD, coronary artery disease, defined as either myocardial infarction or angina pectoris; CI, confidence interval; LR+, positive likelihood ratio is the quotient of sensitivity/(1 − specificity); LR−, negative likelihood ratio is the quotient of (1 − sensitivity)/specificity; NA, not applicable; NPV, negative predictive value is the number of true negatives/number of negative calls; PAD, peripheral arterial disease, defined as diagnosed or treated PAD; PPV, positive predictive value is the number of true positives/number of positive calls.

colorectal cancer 25% of siblings reported a negative FH of cancer [17]. Another study reported interviewee sensitivities of 50%–60% regarding cancer in first-degree relatives [18]. The present study with low rates of non-concordance shows that under-reporting is around twice as frequent as over-reporting also regarding a FH of CVD, meaning that a patient reports a false negative FH more often than a false positive. However, the under-reporting of FH of CVD varies; the NHLBI-FHS compared proband and parent reports and showed 85% sensitivity for parental CAD and substantial agreement with a kappa value of 0.76 [15]. A MONICA sub-study verifying proband reports with medical records showed sensitivities regarding myocardial infarction in first-degree relatives of around 68% with kappa values above 0.65 in both cases and controls [20]. A study on healthy undergraduates reported sensitivities of 84.2% with regard to heart attack and 100% with regard to stroke in parents. However, due to the low proband age the numbers of diseased parents was low with only one reported stroke [29]. The Framingham study reported sensitivities of 74% for heart attack <55 years and 42% for stroke <65 years [14]. The differences in methodology, with some applying age limits on parental disease and some using medical records to confirm parental events, probably cause the prevalence discrepancy and impair direct comparison with the present results. Different methods for obtaining FH and different patient characteristics probably explain the variations in accuracy. Sending questionnaires by mail [15] permits obtainment of FH information from family members or other sources, thereby increasing accuracy and concordance between patient and family reports. The previously reported association between young age and high accuracy of reporting [14] is supported by the present study. Higher patient age was associated with an incorrect FH report with an odds ratio of 1.05 per year ($P = 0.020$). CVD events at young age tend to be a more dramatic event to the family involved. These events may therefore be more vividly remembered and thereby lead to better cross-generational knowledge of FH. Lastly our cohort consists of patients with verified ischaemic stroke, which it was feared would reduce the accuracy of reporting compared to healthy individuals [2,14,15]. However, the sensitivities and kappa values in the present study are comparable with previous results, with 75% sensitivity and a kappa value of 0.69 regarding CAD in fathers.

The study is strengthened by the questionnaire-based patient interview enabling control questions and thereby increasing the accuracy of FH reports. Additional strengths are the well-defined group of young and middle-aged patients and the mandatory verification of ischaemic stroke. Our study has some limitations. Parent information was used as the gold standard for disease status. However, the contact between patients and parents after the patient's interview was not limited and therefore the possibility of joint recall bias cannot be excluded. The numbers of eligible patients and parents were modest, in part limited by the high numbers of deceased parents. The study site of one hospital and the geographical catchment area with predominantly Caucasian inhabitants limits direct generalizability beyond this population.

This study shows that a detailed FH of CVD is mostly correct when young ischaemic stroke patients are interviewed in a standardized way by trained medical professionals. Increasing age was the only demographic factor associated with reduced concordance. FH is an inexpensive and widely available tool for evaluating inherited risk; verifying it with parental reports strengthens its validity [8]. The patient FH can be used as a proxy for inherited risk of CVD in young ischaemic stroke patients.

Acknowledgements

We thank Jeanette Haveland Antoniazzi and the study nurses Linn Elin Rødal and Toril Synnøve Bjørgo for invaluable help in administering the NOR-SYS. The study was funded by the Western Norway Health Trust and the University of Bergen.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. NOR-SYS patient questionnaire regarding family history.

Data S2. NOR-SYS parent questionnaire regarding own disease- and family history.

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