stroke in the young

FROM EPIDEMIOLOGY TO PROGNOSIS

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Voor mijn ouders

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GENERAL INTRODUCTION

Stroke is defined as an acute neurological deficit, caused by a sudden occlusion of a cerebral artery (ischemic stroke, or transient ischemic attack (TIA) if symptoms last less than 24 hours) or by rupture of a cerebral artery (intracerebral hemorrhage; ICH). An estimated 10% of all strokes occur in young adults (18 to 50 years), which amounts to about two million young adults who are affected by stroke worldwide every year.[1-3] Stroke at young age affects individuals often at crossroads in their lives, with active social lives, families to take care of and decisive career steps to make. It not only affects lives shortly after stroke, but usually for the rest of their lives. To provide reliable information regarding their long-term prognosis and counselling on treatment, insight in the epidemiology, risk factors and causes of stroke at young age is of utmost importance.

The epidemiology of stroke in young adults

Despite improvement in primary and secondary prevention as well as treatment of cardiovascular disease over the last decade, an increase in the incidence of stroke in young adults has been described. This is in contrast with the decrease in incidence observed in the elderly.[4-11] This rise in incidence might partly be explained by improved stroke detection due to more advanced neuroimaging techniques.[12, 13] Other possible explanations are the increased prevalence of modifiable traditional risk factors already at young age[4, 7] and increased illicit and recreational drug use.[14] Looking into differences between the incidence of stroke between men and women and age-strata can be helpful to provide leads for (new) potential causes.

Investigating the cause of ischemic stroke and TIA at a young age is important, though often poses challenges. First, many other, often rare, causes and risk factors are associated with stroke at a young age, including arterial dissections, coagulation disorders, illicit drug use, pregnancy and the puerperium and patent foramen ovale (PFO), which often require specific additional investigations and treatment.[12] Still, despite an extensive diagnostic work-up, in around 30% of young adults with stroke according to the currently widely used TOAST and ASCOD classification systems, no clear cause of stroke is found. However, a limitation of these classification systems is that they were designed to classify causes of stroke in all ages, often in patients aged over 65 years, with the main categories being large- and small vessel disease, and atrial fibrillation as cardio-embolic source. The rare causes seen in young adults are merged in one ''other'' category, although underlying pathophysiological mechanisms of these causes vary extensively. In contrast to the TOAST and ASCOD classification, the International Pediatric Stroke Study (IPSS) developed an extensive risk factor classification specifically for children and adolescents, which recognizes more rare and some supposed risk

factors and causes in pathophysiological subcategories. Many of the risk factors in this classification can also be found in young adults aged 18 to 50 years. Though this approach has not often been employed it might be helpful in finding possible risk factors in strokes previously classified as ''cryptogenic'' (without a known cause).

Another approach is investigating the presence of trigger factors in a young patient with a stroke. Trigger factors are brief moments of exposure to toxins, exercise or infection, causing a short-lasting increase in blood pressure or prothrombotic state. Trigger factors may provide clues for underlying pathophysiological mechanisms as it is likely that in these young patients trigger factors may convert risk factors into causes. The large number of unknown causes or potential risk factors for which the causal relationship is uncertain is an important knowledge gap. Determination of the risk factors and potential new causes of stroke is a first step that will allow for studies investigating more individualized treatment and prognosis for young individuals with stroke.

Worldwide differences in stroke in young adults

Other leads to new insights in risk factors of young stroke may come from global differences in the epidemiology of young stroke around the world. Besides ethnic and racial variation, the incidence of stroke in young adults shows major regional differences, varying from 5-10 per 100,000 person-years in many European countries to over 100 per 100,000 person-years in Africa.[15-17] These differences in stroke incidence at young age might reflect yet unidentified regional variation in burden of risk factors and causes of stroke. Many infectious diseases, such as HIV, that that are common causes of stroke in developing countries are rarely seen in developed countries. In addition, some ethnicities have a high(er) predisposition to certain risk factors and causes than others, for example hypertension in Black patients and diabetes and moyamoya in Asian individuals.[15, 18, 19] Apart from regional, ethnic and racial differences, economic inequality may also play a role, which may influence not only the incidence due to risk factor profile and causes of stroke, but also patients' prognosis.[20, 21] Careful investigation of global differences may lead to better understanding of stroke in young adults.

Long-term perspective on stroke in young adults

Information on incidence, risk factors and etiology is essential to provide individual patients with an adequate long-term prognosis. Compared to older stroke patients, prognosis in terms of mortality is considered to be good, however, comparisons would be much more meaningful if they were made with healthy individuals of the same age. In addition, young adults who survived their initial stroke, still have a long life-expectancy and face many uncertainties about their future. To reduce the risk of recurrence, they are often prescribed antithrombotic medication for the rest of their lives. However, as

young patients were highly underrepresented or excluded in secondary prevention trials on stroke, with only limited follow-up up to one year, it is unknown if the benefits of lifelong antithrombotic medication outweigh the side effects, such as serious bleeding complications.[22-27] Information on long-term mortality, risk of recurrence and effects of secondary prevention in young adults is very sparse.

Aim of the thesis and study design

The aim of this thesis was to investigate the incidence, risk factors and etiology, trigger factors and long-term prognosis in young adults with stroke aged 18 to 50 years, both in the Netherlands and worldwide.

The studies reported in this thesis are based on data from the Statistics Netherlands, the Observational Dutch Young Symptomatic StrokE studY (ODYSSEY), the Global Outcome Assessment Life-long after stroke in young adults" (GOAL) initiative and the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study.[2, 28, 29]

OUTLINE OF THIS THESIS

In **chapter 2** the rationale and design of the GOAL initiative are described. The GOAL initiative was set up to collect individual patient data from hospital-based young stroke cohorts in 29 countries with the aim to investigate the risk factors, etiology and outcome in young individuals with stroke as an individual patient data meta-analysis. In **part II**, an overview of epidemiological studies on incidence, etiology and management of ischemic stroke in young adults are reported (**chapter 3**) as well as the incidence of stroke overall in the Netherlands from 1998 to 2010 using data of the Statistics Netherlands (**chapter 4**). In **chapter 5**, I investigated risk factors and causes of ischemic stroke in the ODYSSEY cohort using different classification systems, including a pediatric risk factor system (International Pediatric Stroke Society; IPSS) (**chapter 5**). Furthermore, we evaluated the association between trigger factors and stroke in young adults in the ODYSSEY cohort (**chapter 6**). The ODYSSEY study is a Dutch multicenter prospective cohort study on the risk factors and prognosis of 1492 patients aged 18 to 50 years with a first-ever ischemic stroke or ICH, in 17 centers in the Netherlands, between May 2013 and February 2021. In **part III**, I first review global differences of ischemic stroke in incidence, etiology and risk factors including racial and ethnic differences (**chapter 7**). By using the GOAL-initiative data, a meta-analysis of different risk factors, etiology and outcome in 29 countries worldwide was performed (**chapter 8**). In **Part IV**, the long-term prognosis including mortality in the Netherlands was evaluated with data of the Statistics Netherlands (**chapter 9**). In addition, the very long-term risk of recurrence and bleeding events in the FUTURE study is described (**chapter 10**). The FUTURE study comprises of 1005 consecutively included patients aged 18 to 50 years with a first-ever TIA, ischemic stroke, or ICH, admitted to the Radboud University Medical Centre Nijmegen between 1980 and 2010. Patients underwent extensive follow-up assessments between 2009 and 2012 and were approached again between 2014 and 2015 for occurrence of vascular events. All available patient files for patients with a stroke after 1995 were checked in 2020 and 2021 for information on antithrombotic medication, bleeding complications and recurrent vascular events.

The final part of this thesis (**part VI**) includes a summary (**chapter 11** in English; **chapter 13** in Dutch) and general discussion of the main results with implications and recommendations for clinical practice and future research (**chapter 12**).

Chapter 2

The GOAL initiative: study protocol and rationale

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Global Outcome Assessment Life-long after stroke in young adults initiative; The GOAL initiative: Study protocol and rationale of a multicentre retrospective individual patient data meta-analysis.

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ABSTRACT

Introduction: Worldwide, 2 million patients aged 18-50 years suffer a stroke each year, and this number is increasing. Knowledge about global distribution of risk factors and etiologies, and information about prognosis and optimal secondary prevention in young stroke patients is limited. This limits evidence-based treatment and hampers the provision of appropriate information regarding the causes of stroke, risk factors, and prognosis of young stroke patients.

Methods and Analysis: The Global Outcome Assessment Life-long after stroke in young adults (GOAL) initiative aims to perform a global individual patient data meta-analysis with existing data from young stroke cohorts worldwide. All patients aged 18-50 years with ischemic stroke or intracerebral hemorrhage will be included. Outcomes will be the distribution of stroke etiology and (vascular) risk factors, functional outcome after stroke, risk of recurrent vascular events and death and finally the use of secondary prevention. Subgroup analyses will be made based on age, gender, etiology, ethnicity and climate of residence.

Ethics and Dissemination: Ethical approval for the GOAL initiative has already been obtained from the Medical Review Ethics Committee region Arnhem-Nijmegen. Additionally and when necessary, approval will also be obtained from national or local institutional review boards in the participating centers. When needed, a standardized data transfer agreement shall be provided for participating centers. We plan dissemination of our results in peer-reviewed international scientific journals and through conference presentations. We expect that the results of this unique study will lead to better understanding of worldwide differences in risk factors, causes and outcome of young stroke patients.

BACKGROUND

Worldwide, two million patients aged 18-50 years suffer a stroke each year.[30, 31] Due to physical, cognitive and emotional post-stroke consequences faced by individual patients after stroke that often occur early in life, our societies face high socio-economic costs.[30-32] The absolute number of young patients who live with the consequences of stroke is expected to increase rapidly due to a rising incidence in ischemic stroke and increasing long term survival.[30, 31]

Patients with stroke at young age comprise a heterogeneous group with many different underlying causes. Furthermore, the etiology remains unknown in one third of all young stroke patients.[33] Information regarding causative risk factors and etiology and about long-term prognosis including the risk of recurrence or death, the potential of recovery and the range of sequelae is scarce and mainly based on smaller studies.[34] Most previous studies of young patients with ischemic stroke comprised less than 1000 patients, with even smaller numbers in etiologic subgroups. Studies regarding young patients with intracerebral hemorrhage are even smaller. In addition, only few studies have taken ethnicity, geographical region and climate of residence into account.[30-32] Finally, the optimal secondary prevention strategy for young stroke patients is poorly defined as numbers of young patients are low in randomized trials on secondary prevention.[35] As a consequence, guidelines on secondary prevention or counseling after stroke do not provide specific information for individual young patients.

Information regarding specific subgroups of young ischemic stroke patients and larger numbers of young intracerebral hemorrhage patients are long awaited and can be helpful in treating and counseling individual patients. Recent reviews have stressed the importance of initiating large collaborative studies in order to develop reliable prognostic models based on clinical and demographic features, diagnostics, and genetics and establish stroke guidelines specifically for patients at young age.[12, 35, 36]

We therefore launched the "Global Outcome Assessment Life-long after stroke in young adults" (GOAL) initiative to collect individual patient data worldwide, with the aim of performing an individual patient data meta-analysis. The GOAL initiative aims to investigate the etiology, risk factors, functional outcome, risk of recurrent vascular events and death after stroke on young age with special emphasis on ethnic and regional variation.

METHODS

Study objective

The GOAL-initiative aims to collect individual patient data from young-stroke cohorts that included consecutive patients. We aim to perform an individual patient data meta-analysis to assess etiology, risk factors, functional outcome and prognosis in patients aged 18 up to and including 50 (18-50) years with an ischemic stroke or intracerebral hemorrhage (ICH).

Specific study questions

1. *What are the risk factors for stroke at young age?*
2. *What are the causes of stroke in young patients aged 18-50 years?*
3. *What is the functional outcome after stroke in patients aged 18-50 years?*
4. *What is the cumulative risk of recurrent vascular events and of death in young stroke patients?*
5. *What are the differences in risk factors and causes of stroke, case fatality and prognosis between patients with different clinical (e.g. stroke subtype) and demographic characteristics (e.g. age, sex, ethnicity, and climate)?*

Patient eligibility

The following inclusion criteria apply:

1. Ischemic stroke or intracerebral hemorrhage, according to the definition of the WHO [37]
2. Age 18-50 years
3. Available individual patient data including at least one of the following variables of interest: risk factors (as defined in Table 2), or cause of stroke, or functional outcome, or follow-up data regarding recurrent events and death.

Exclusion criteria were:

1. Traumatic intracerebral hematoma
2. Intracerebral hemorrhage or ischemic stroke due to intracerebral malignancy
3. Subarachnoid hemorrhage
4. Cerebral venous thrombosis with or without brain ischemia/cerebral hemorrhage
5. Any iatrogenic stroke as a result of surgery or any other medical interventions
6. Retinal infarction

Definition of stroke

Stroke is defined as a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks or myoclonus, with no other cause, and symptoms persisting for more than 24 hours.[37] Stroke will be further divided into intracerebral hemorrhage and ischemic stroke based on neuro-imaging. Hemorrhagic transformation of an ischemic stroke will be classified as an ischemic stroke.

Study design

The GOAL initiative is an international multicenter consortium in which individual patient data will be collected from young stroke cohorts. The relevant cohort studies were identified through a systematic search of PubMed using the following Mesh Major Topics: 'Young Adult', 'Stroke', 'Risk Factors', 'Stroke/etiology', 'Prognosis', and 'Secondary Prevention'. References of relevant studies were examined to detect other potential cohorts of interest (Appendix 2). Prospective and retrospective, as well as hospital-based and population-based cohorts were considered eligible for enrollment if the patients would meet our inclusion criteria. The principal investigators were contacted and informed about the study with the request to participate. Furthermore, when participants indicated they knew of other cohorts or collaborators that might be interested in participating, we contacted these centers. A specific website for potential participants was developed to provide more information about the aims of the project (www.goalinitiative.org). An overview of the participating centers is listed in Table 1 and Figure 1. Analyses and results on baseline variables will be conducted and published before March 2020. Furthermore, the GOAL study strives to be as inclusive as possible. Therefore we have set an ongoing open invitation for all researchers in the field who are interested in participating. We do this with the aim of setting up a worldwide young stroke consortium with an ongoing data collection and data analyses on a broad range of aspects of young stroke. Therefore, we cannot indicate a precise time period for conducting all GOAL-related studies.

Table 1. Overview of participating cohorts in alphabetical order

Country	Population	Study period	IS patients
Australia	Hospital-based multicenter	2006-2010	306
Australia	Hospital-based multicenter	2006-2018	N.A.
Austria	Hospital-based	2008-2017	334
Belgium (BeFas & MiFas)	Hospital-based multicenter	2007-2008	447
Brazil	Hospital-based	2008-2012	135
Canada -*Toronto Sunnybrook Health Sciences Centre*	Hospital based multicenter		118
Canada -*Toronto University Health Network*	Hospital-based	2011-2018	350*
Costa-Rica	Hospital-based	2012-2018	166
Estonia	Hospital-based multicenter	2003-2012	*
Finland (HYSR)	Hospital-based	1994-2007	1004
Finland	Hospital-based	2000-2010	N.A.
France	Hospital-based	2006-2010	291
Germany	Hospital-based	2007-2012 2017-2018	80
India	Hospital-based	1988-1997	206
Israel	Hospital-based multicenter	2007-2017	326
Italy (IPSYS)	Hospital-based multicenter	2000-2013	2147
Japan (FSR)	Hospital-based Multicenter	2009-2018	*
Malaysia	Hospital-based		177
Mexico -*Mexico-City*	Hospital-based	1990-2017	1383
Mexico -*Guadalajara*	Hospital-based	2017-ongoing	15
Mongolia	Hospital-based Multicenter	2012-2017	*
Nigeria / Ghana (SIREN-study)	Hospital-based Multicenter		245
the Netherlands (FUTURE-study)	Hospital-based	1980-2010	451
New-Zealand	Hospital-based	2004-2009	128
Norway (NOR-SYS)	Hospital-based	2010-2015	149

ICH patients	Design	Patient selection	Stroke definition
N.A.	Retrospective	Consecutive	WHO
100*	Retrospective	Consecutive	Radiological
21	Retrospective	Consecutive	Radiological
49	Prospective and Retrospective	Consecutive	WHO
N.A.	Retrospective	Consecutive	WHO
16	Prospective	Consecutive	WHO
*	Prospective and retrospective	Consecutive	WHO
47	Prospective and retrospective	Consecutive	WHO
*	Retrospective	Consecutive	WHO
N.A.	Retrospective	Consecutive	WHO (modified)
330*	Retrospective	Consecutive	Radiological
N.A.	Prospective	Consecutive	Radiological
N.A.	Prospective and retrospective	Consecutive	Radiological
23	Prospective	Consecutive	WHO
N.A.	Prospective and retrospective	Consecutive	WHO
N.A.	Prospective	Consecutive	Radiological
*	Prospective and Retrospective	Consecutive	WHO
N.A.	Retrospective	Consecutive	Radiological
566*	Prospective	Consecutive	Radiological
N.A.	Retrospective and prospective	Consecutive	Radiological
*	Retrospective	Consecutive	WHO
270	Case-control	Consecutive	Radiological
69	Retrospective	Consecutive	WHO
N.A.	Retrospective	Consecutive	WHO
N.A.	Prospective	Consecutive	Radiological

Table 1. Continued

Country	Population	Study period	IS patients
Portugal	Hospital-based	2009-2018	164
Republic of Korea (SKY-study)	Hospital-based multicenter	2014-2016	166
South-Africa	Hospital-based	2003-2016	88
Sweden	Hospital-based	1998-2007	502
Switzerland -*Bern* (SYSS)	Hospital-based multicenter	2008-2012	399
Switzerland - *Luzern*	Hospital-based	2016-2018	57*
Taiwan	Hospital-based	1997-2001	590
Turkey	Hospital-based	2017-ongoing	102
United Kingdom-*Chertsey*	Hospital-based	2015-2018	100*
United Kingdom- *Stockton on Tees*	Hospital-based	2013-2018	180*
USA - *Baltimore-Washington region*	Hospital-based multicenter	1992-2008	889
USA - *Tampa*	Hospital-based		381
United Arab Emirates	Hospital-based	2015-2018	174*

Numbers of patients are the result of present received data. Definite numbers could differ from the numbers stated in this table as some cohorts/registers are still ongoing and will be providing additional data concerning newly included patients. *Data not yet received.
Abbreviations: IS, ischemic stroke; ICH, intracerebral hemorrhage; radiological, radiologically confirmed stroke; N.A., not applicable; BeFaS, Belgian Fabry Study; MiFaS, Middelheim Fabry

Data collection and storage

Participating centers will be requested to transfer their anonymized coded data electronically, according to current laws and legislation concerning research conduct at each participating research center, to the GOAL-research team of the department of Neurology, Radboudumc, Nijmegen. Co-authors that met the ICMJE criteria are listed as authors. Other contributors can be found in Appendix 1. Each participating center will provide their data by using an encrypted excel sheet containing pre-specified variables of interest. The key linking anonymized data to individual patients will remain at the participating centers. All received data will be entered in a uniform database in IBM SPSS Statistics 22 and stored on secured servers at the coordinating study center, and will only be accessible to designated researchers working under the supervision of the study coordinator. All data will be processed, stored, and destroyed after end of the study according to European Union General Data Protection Regulation.

ICH patients	Design	Patient selection	Stroke definition
N.A.	Prospective and Retrospective	Consecutive	Radiological
N.A.	Prospective	Consecutive	Radiological
N.A.	Retrospective	Consecutive	WHO
N.A.	Prospective	Consecutive	WHO
N.A.	Prospective	Consecutive	Radiological
	Retrospective	Consecutive	Radiological
N.A.	Retrospective	Consecutive	Radiological
6	Retrospective	Consecutive	WHO
20*	Retrospective	Consecutive	WHO/Radiological
15*	Prospective and retrospective	Consecutive	WHO/ Radiological
N.A.	Retrospective	Not consecutive	WHO
30	Prospective and Retrospective	Consecutive	WHO
79*	Retrospective	Consecutive	WHO

Study; HYSR, Helsinki Young Stroke Registry; IPSYS, Italian project on Stroke in Young Adults; FSR, Fukuoka Stroke Registry; SIREN, Stroke Investigative Research and Educational Network; FUTURE, Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation study; NOR-SYS, Norwegian Stroke in the Young Study; SKY-study, Stroke in Korean Young adults study; SYSS, Swiss Young Stroke Study.

The data will be verified, before entering the data in the uniform database, on data completeness and missing data. In cases of missing data or inconsistencies with published articles, the GOAL research team will contact the study investigators to resolve these issues. Data will be stored for at least 15 years. The study will be conducted following the principles of the Declaration of Helsinki (version 60, 19 October 2013) and in accordance with the Law for Human Research. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study protocol. When necessary, national or local institutional review boards reviewed the study protocol and approved data transfer.

Patient and public involvement

Still, information about the etiology and prognosis is uncertain for many young stroke patients. For both young stroke patients and many clinicians treating this patient group, the study questions as described earlier are very relevant and have high priority.

Figure 1. Map with participating countries (April 2019)

No patients were involved in the design, recruitment or conduction of the study. Study results will be published in peer-reviewed journals and be communicated to country specific young stroke communities by participating authors.

Sample size and power calculation

Based on our literature search and consequently estimated available patient data, we aim to include at least 10,000 patients, as this size will allow assessing causes of, risk factors for and prognosis of stroke at young age in meaningful subgroups.

Baseline variables

Data for each individual patient is collected from the hospital at index-stroke. Baseline data will include demographic characteristics, medical history including medication used on admission, and data of diagnostic work-up within 1 month after the index-stroke (Table 2).

In addition, the season of the index-event and climate of the country or region of origin will be registered. The climate will be classified according to the Köppen-Geiger climate classification system [38], and the season of index-stroke according to the date of admission (Table 3).

The severity of stroke is assessed with the National Institutes of Health Stroke Scale score (NIHSS)[39], and the functional performance with modified Ranking Scale (mRS)[40] right after a stroke. The mRS will also be assessed during follow up, preferably at 3 months and when available also later during follow-up.

Secondary prevention at admission is categorized as antihypertensive medication, HMG-CoA reductase inhibitors (statins) or other cholesterol lowering medication, platelet aggregation inhibitors (antiplatelets), oral anticoagulants (vitamin K antagonists or direct oral anticoagulants). Death will be analyzed based on occurrence within 30 days (case fatality) or thereafter.

Table 2. Definitions of baseline demographics and risk factors

Variable or risk factor	Definition
Sex	Male/Female
Age	18-50 years
Ethnicity	• Caucasian • Black • Hispanic • Asian • Aboriginal • Maori • Pacific Islander • Other
Prior stroke or transient ischemic attack (TIA)	Stroke prior to the index stroke is defined according to the same criteria as the index-stroke; a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks or myoclonus, with no other than vascular cause, with symptoms persisting for more than 24 hours.[37] Stroke will be further divided into intracerebral hemorrhage and ischemic stroke based on neuro-imaging. Hemorrhagic transformation of an ischemic stroke will be classified as an ischemic stroke. TIA is defined as a history of an episode of focal cerebral dysfunction lasting <24 hours without evidence of corresponding ischemic lesion in earlier or present imaging studies.
Hypertension	A history of hypertension was defined as its presence either in the patients' medical history, or when identified during admission for the index event after the acute phase within the first month after stroke. Hypertension was defined as the use of antihypertensive medication and/or systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater.

Table 2. Continued

Variable or risk factor	Definition
Diabetes mellitus (DM)	A history of DM was defined as its presence either in the patients' medical history, or when identified during admission for the index event. Diabetes was defined as the use of diabetic medication and/or a fasting (defined as no caloric intake for at least 8 hours) plasma glucose >7 mmol/L and/or 2-h PG ≥ 11.1 mmol/L during OGTT and/or HbA1C ≥ 6.5% (48 mmol/mol) and/or symptoms of hyperglycemia or hyperglycemic crisis and a random glucose >11.1 mmol/L [41].
Dyslipidemia	A history of dyslipidemia was defined as its presence either in the patients' medical history, or when identified during admission for the index event. Dyslipidemia was defined as use of statins and/or cholesterol level ≥5.0 mmol/L (193 mg/dL) and/or low-density lipoprotein level ≥3.0 mmol/L (116 mg/dL) and/or high-density lipoprotein level <1.0 mmol/L (39 mg/dL) and/or triglyceride level ≥ 1.7 mmol/L (150mg/dL).
Atrial fibrillation (AF)	A history of AF (chronic/paroxysmal) was defined as its presence either in the patients' medical history, or when identified during admission for the index event. Atrial fibrillation will be defined as diagnosis based on ECG-findings.
Patent foramen ovale (PFO)	A presence of PFO was defined based on documentation in medical records, or when identified during hospitalization for the index event. PFO will be defined as PFO with or without atrial septum aneurysm, as identified on TTE or TEE with or without contrast.
Coronary artery disease (CAD)	CAD included myocardial infarction and/or angina pectoris. A history of myocardial infarction or angina pectoris was defined as its presence either in the patients' medical history, or when identified during admission for the index event.
Heart failure	A history of heart failure was defined as its presence either in the patients' medical history, or when identified during admission for the index event. Heart failure was defined as ejection fraction <55%, reported on echocardiogram.
Peripheral artery disease (PAD)	A history of PAD was defined as its presence either in the patients' medical history, or when identified during admission for the index event.

Table 2. Continued

Variable or risk factor	Definition
Obesity	Obesity was defined as a body mass index greater than 30 kg/m^2, measured during admission for the index event or when reported by the patient.
Migraine	A history of migraine was defined as its presence either in the patients' medical history or when identified during hospitalization for the index event. Migraine was defined according to the International Headache Society criteria. [42]
Hormone replacement therapy	Use of oral or non-oral hormone replacement therapy at admission for the index event.
Oral contraceptives	Use of oral contraceptive pills at time of stroke onset.
Recent or acute infection	Signs or laboratory findings indicative of infection at admission or reported symptoms of any infectious disease during the month prior to stroke, or as concluded by institution of cohort.
Ever smoking	Any current or former smoker.
Heavy drinking	Heavy drinking was defined as the consumption of more than 21 units a week for men and 14 units a week for women, identified at admission for the index event.
Illicit recent drug use	Within the month prior to stroke.
Family history of stroke	History of ischemic/hemorrhagic stroke or TIA in a first-degree relative.
Index-stroke related to pregnancy	• No • Yes, pregnant at time of stroke • Yes, stroke <6 weeks post-partum • Yes, stroke <1 year after pregnancy
Pregnancy-related complications during any pregnancy	• Gestational diabetes • Hypertension • Pre-eclampsia • HELLP syndrome

Abbreviations: 2-h PG, 2-hours post glucose; OGTT, oral glucose tolerance test; HbA1c, glycosylated hemoglobin, type A1c; PFO, patent foramen ovale; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; HELLP syndrome, hemolysis elevated liver enzymes and low platelets syndrome.

Table 3. Classification of climates and seasons

Climate of country of origin / city of study-hospital	**Köppen-Geiger climate classification system:**
	A (Tropical)
	• f (rainforest)
	• m (monsoon)
	• w (savanna)
	B (Arid)
	• W (desert)
	• S (steppe)
	  • h (hot)
	  • k (cold)
	C (Temperate)
	• s (dry summer)
	• w (dry winter)
	• f (without dry season)
	  • a (hot summer
	  • b (warm summer)
	  • c (cold summer)
	D (Continental)
	• s (dry summer)
	• w (dry winter)
	• f (without dry season)
	  • a (hot summer
	  • b (warm summer)
	  • c (cold summer)
	E (Polar)
	• T (tundra)
	• F (frost)

Season of index-stroke	Northern hemisphere countries (Austria, Belgium, Canada, Estonia, Finland, France, Germany, Ghana, India, Israel, Italy, Japan, Mexico, Mongolia, The Netherlands, Nigeria, Norway, Portugal, Republic of Korea, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, USA, United Arab Emirates): • Spring: March-May • Summer: June-August • Fall: September-November • Winter: December-February Southern hemisphere countries (Australia, Brazil, Costa Rica, New-Zealand, South Africa): • Spring: September-November • Summer: December-February • Fall: March-May • Winter: June-August Equatorial countries: Malaysia

Abbreviations: N.A., not applicable.

Outcomes at baseline

Outcomes will include: cause of stroke, both individually assessed and according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[43] for ischemic stroke and SMASH-U[44] for ICH, stratified for age, sex, ethnicity, and climate. Other outcomes will include frequency and distribution of vascular risk factors, stroke severity at baseline by using the NIHSS, functional neurological outcome at baseline by using the mRS, case fatality and the use of secondary prevention at baseline. Considering that not all patients have had an imaging-confirmed stroke, subgroup analyses will be done in patients with and without imaging-confirmed stroke when analyzing the abovementioned outcomes.

Risk factors

Cardiovascular risk factors include conventional risk factors, as described according to the 2014 guidelines of the American Stroke Association[45]: hypertension, diabetes, atrial fibrillation (AF), dyslipidemia and cigarette smoking. Additionally, we will include the following other vascular risk factors and diseases: a history of cardiovascular diseases, patent foramen ovale, heavy drinking, illicit recent drug use, obesity, hormone replacement therapy and recent or acute infection. Previous cardiovascular diseases will include prior stroke or TIA, ischemic heart disease, heart failure and peripheral artery disease (PAD). Table 2 summarizes the collected vascular risk factors and their definitions/operationalization.

Causes

Ischemic stroke - Causes of stroke are defined according to the TOAST classification.[43] Causes of stroke defined according to Causative Classification System of ischemic stroke (CCS) [46] and ASCO classification [47] will, when available, also be collected. The participating centers will also be requested to state, if known, the precise cause of the stroke (e.g. dissection, vasculitis, hematological disorder, cardiac condition).

Intracerebral hemorrhage - Location of ICH (lobar/deep, supra-/infratentorial) will be collected. Also the ICH volume, calculated by using the ABC/2 method from the axial computed tomography images [48], will be collected. The cause of intracerebral hemorrhage will be preferably be defined according to the SMASH-U[44]. Etiology as defined by the H-ATOMIC classification will, when available, also be collected.[44] The precise cause of ICH (as possibly identified with neuroimaging of the intracranial vasculature) will also be requested.

Outcome during follow-up

Follow-up evaluation of use of secondary prevention, recurrence of vascular events and death has been collected differently across the various studies; either in person, by telephone interviews with patients or relatives, by collecting hospital/general practitioner medical records or discharge diagnosis ICD codes.

The following cardiovascular risk factors will be collected at follow-up, whenever available, according to the same definitions described at baseline and in Table 2: hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, obesity, AF, heavy drinking, and illicit drug use.

Functional performance will be assessed with the mRS score and data on the use of secondary prevention medication will be collected from the medical records files.

Outcomes will include recurrent vascular events and all-cause death. Recurrent vascular events are defined as occurrence of any of the following events: transient ischemic attack (TIA, defined as in Table 2), ischemic stroke and ICH (defined similarly as baseline events) and other vascular ischemic events, when available. Other vascular ischemic events of interest include angina pectoris,, myocardial infarction (defined by symptoms of cardiac ischemia with electrocardiographic changes corresponding to myocardial necrosis with or without cardiac biomarker elevation or pathologic evidence of infarction according to the universal definition of myocardial infarction[49]), peripheral artery disease including revascularization procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy, or other peripheral arterial revascularization procedures). All outcomes had to be confirmed by physicians from the appropriate specialty through medical records, or through the appropriate ICD code.

Statistical analysis

We aim to perform statistical analyses with IBM SPSS Statistics or R (most recent versions). A p-value of <0.05 with correction for multiple testing when appropriate will be considered statistically significant, and/or a 95% confidence interval not containing 1. Sub-analysis to identify differences in demographic characteristics including gender, age, ethnicity, pregnancy-related stroke, climate and season at time of admission will be performed.

Differences between groups will be compared using ANOVA-test, student T-test for continuous variables and χ^2 test for categorical variables. Univariate multivariable logistic regression analysis will be performed to determine risk factors and potential trigger factors. In case of missing data at baseline, and if considered necessary,

multiple imputation will be used. The cumulative risk of death and vascular events will be calculated with Kaplan-Meier survival analysis. Differences in survival between different subgroups will be assessed using Log-Rank tests. In the analysis for vascular events, patients who have died or were lost to follow-up, will be censored from the last available follow-up. We will use Cox regression models to obtain hazard ratios (HRs) and their corresponding 95% confidence intervals to calculate the risk of death and recurrent vascular events between different etiologies and demographic characteristics while adjusting for confounders. Only patients for whom follow-up data is available will be included for these separate analyses.

Strengths & Limitations

- By combining existing individual datasets, the GOAL initiative will be the largest study on young patients with stroke ever, with more than 10,000 patients already included.
- Sufficient statistical power due to large individual data set for sub analysis on stroke subtypes, gender, ethnicity, climate.
- Risk of misclassification and missing data due to the use of existing data gathered with varying protocols and cohorts.
- Variability in diagnostic work-up and non-obligatory imaging-based confirmation of stroke due to long inclusion period and varying cohorts.
- Mainly hospital-based cohorts are included, risking inclusion bias.

DISCUSSION

The GOAL initiative aims to investigate the causes and risk factors of ischemic stroke and ICH in young patients, aged 18 to 50 years, to determine functional outcome, and the risk of new or recurrence of vascular events, and to study variation according to etiological subgroups, geographical region, continent, and ethnicity. The most important strength of our study is the participation of to date 30 stroke centers throughout the world, from 29 different countries across all continents (Figure 1). By combining existing individual datasets, the GOAL initiative will be the largest study on young patients with stroke ever, with more than 10,000 patients already included. This large set of individual patient data provides sufficient statistical power to not only reliably quantify the differences in risk factors and etiology of stroke between men and women, different age groups, ethnic subgroups and possibly search for differences between climates of residence, but also assess the risk of recurrent vascular events.

The study also has its limitations. There will be a risk of misclassification of etiology, risk factors and events of interest during follow-up, as we will make use of already existing data that have been collected according to various local protocols that will not be completely identical. We will harmonize variables across studies as much as possible. There may also be a risk of missing data, as we have included studies that were designed prior to the GOAL initiative, and therefore did not include all variables of interest. Furthermore, our study will cover a long time period in which data collection took place. This may lead to variability in the diagnostic work-up and differences in brain imaging protocols due to adjusted guidelines and improvements in imaging techniques. For instance, not all patients will have undergone complete cardiac examination (e.g. both transthoracic and transesophageal echocardiography, prolonged ECG), which may lead to an underestimation of the frequency of cardio-embolic strokes. Moreover, included cohorts are mainly hospital-based. In addition, not all cohorts will have had the same inclusion criteria, which may lead to an underestimation of case fatality. Finally, imaging-based confirmation of the stroke was neither mandatory nor available in all cohorts, although very few patients were diagnosed with stroke based on clinical symptoms alone, and all patients included were identified and treated as strokes by their main physicians.

In conclusion, the GOAL initiative will include data of at least 10,000 patients with a stroke at young age from six continents, providing sufficient patient numbers to allow for individual patient data meta-analysis. The size of this study will allow for detailed description of the global distribution of causes and risk factors, and for the quantification of the cumulative risk of outcomes.

The GOAL initiative explicitly reaches out to other researchers and aims to become a platform that facilitates future collaborative research in the area of stroke at young age. We envision enriching the cohort with genetic and imaging data and long-term outcomes.

Part II

Incidence, risk factors and
etiology of stroke in young adults

Chapter 3

Epidemiology, etiology, and management of ischemic stroke in young adults

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ABSTRACT

Epidemiological evidence suggests that the incidence of ischemic stroke in young adults (18-50 years) has increased substantially. These patients have a long life expectancy after stroke, and the costs of long-term care pose huge challenges to health-care systems. Although the current recommendations for treatment of young and old (>50 years) patients with stroke are similar, the optimal management of young adult patients with stroke is unknown. They are usually not included in trials, and specific sub analyses limited to young adult patients with stroke are usually not done, owing to lower incidence of stroke and lower prevalence of vascular risk factors in young adults. Progress has been made in identifying patients with a considerable risk of stroke occurrence, such as those with patent foramen ovale. Future prevention studies might result in a decrease in the incidence of stroke and its sequelae in young adults. The development of guidelines specifically devoted to the management of stroke in young adults will be an important step in achieving this aim.

INTRODUCTION

Worldwide, more than two million young adults have an ischemic stroke yearly.[3, 17] Stroke in young adults has a considerable socioeconomic impact because of high health-care costs and loss of labor productivity.[3, 50] In contrast with the decreasing incidence of stroke in older adults, epidemiological studies consistently report an increasing incidence *and* proportion of young stroke patients within the total stroke population (one in ten strokes concerns a young adult).[3] This incidence emphasizes the need for rapid identification of new risk factors and elucidation of the mode of action of traditional vascular risk factors, such as hypertension, smoking, and obesity, to reverse this trend.[13, 51-53]

Investigations into the cause of ischemic stroke at a young age often pose challenges. By contrast to stroke in older patients, many different, often rare causes and risk factors are associated with stroke at a young age, including illicit drug use, pregnancy, arterial dissections, and patent foramen ovale (PFO), which require specific additional investigations and treatment.[12] Furthermore, prognosis after stroke differs in patients with a life expectancy of decades, in comparison with older patients.[34, 54] Recommendations for the clinical approach and management of young stroke are scarce in published guidelines of the American Heart and Stroke Association and Royal College of Phycians.[45, 51-53]

Although, a formal operationalization of "young" is absent, most studies defined it as between 18 to 50 years of age, which will be used in this review.[33, 55] However, studies do not use a uniform cut-off, with lower age limits varying between 15 and 18 years and upper age limits of 45 to 65 years.[17, 56, 57]

In this Review, we cover evidence in epidemiology and provide insight on traditional risk factors with increasing prevalence in young adults with stroke. We also discuss diagnosis and management of specific causes of stroke in young adults according to TOAST criteria[58], long-term prognosis, and future perspectives in the diagnosis and management of stroke in young adults.

EPIDEMIOLOGY

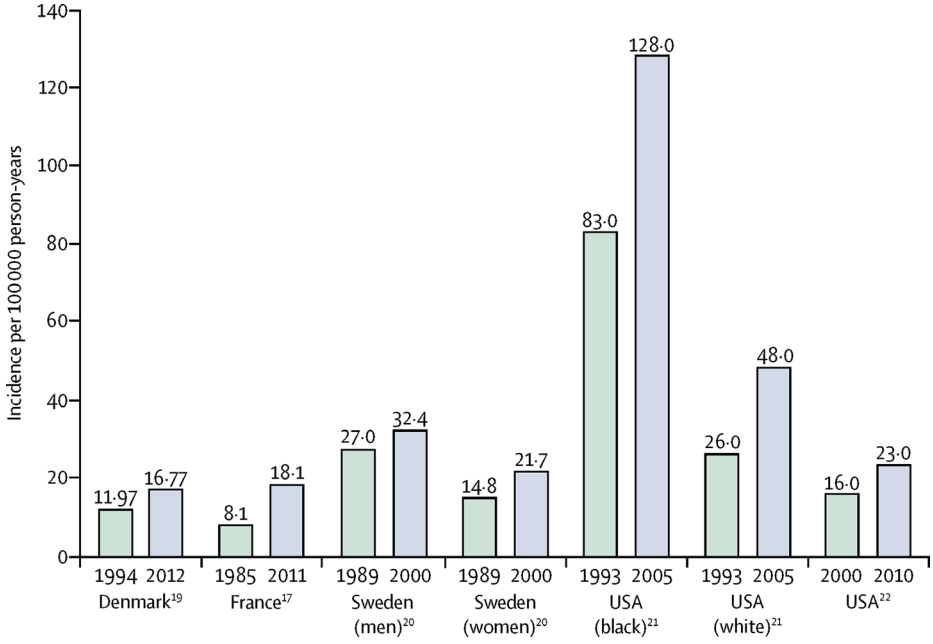
The incidence of ischemic stroke in young adults varies considerably between countries, ranging from 7-8 to more than 100 per 100,000 person-years in Sub-Saharan Africa.[3, 9, 17, 33, 59] This variability can be explained by differences in methods, such as variation in the definition of stroke in young adults, in terms of age and stroke subtype, and by geographical differences in climate, air pollution, genetics, ethnicity, prevalence of comorbid disease, cardiovascular risk profile, and socioeconomic circumstances.[12, 33, 59]

Worldwide, an increase of up to 40% in the incidence of stroke in young adults has been reported over the past decades (Figure 1).[9, 17, 33] Possible explanations for the rising incidence include better stroke detection due to advanced neuroimaging techniques, particularly diffusion-weighted MRI,[12, 13] increased prevalence of modifiable traditional risk factors[4, 7] and increased illicit and recreational drug use.[14]

Gender-specific risk factors, such as pregnancy and puerperium, use of oral contraceptives, and higher incidence of autoimmune disorders (e.g. antiphospholipid syndrome[12]), might explain a higher incidence observed among women than men (especially those younger than 30 years of age).[5, 7] However, other studies have found no difference or an increased risk among men, possibly because patients aged between 50 years and 65 years were included.[9, 10]

Other unidentified risk factors might exist, as the proportion of cryptogenic stroke is greater in young adults compared with older patients and has remained unchanged over past decade.[17] The call for global collaboration has been heeded,[12] with the recently started Global outcome after stroke at young age (GOAL) initiative and the SECRETO study (NCT01934725) which will help characterize these possible unidentified risk factors and their global distribution.

Figure 1. The increasing incidence of stroke in young adults



DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF RISK FACTORS AND CAUSES OF STROKE

As in every stroke patient, being young or old, the most common approach is to start with acute, symptomatic treatment (if possible), followed by a diagnostic process to find the underlying cause and secondary prevention.

Management in the acute stage - e.g. treatment with intravenous thrombolysis, intra-arterial thrombectomy (extended towards 24 hours after symptom onset, based on imaging criteria,)[60, 61] and admission to a specialized stroke unit, is similar in young adults and old patients with stroke. Intravenous thrombolysis is proven safe and more beneficial in young adults with lower mortality and morbidity than in older patients.[62, 63] Thrombectomy in young adults seems to have fewer complications than in older patients,[64] with emerging evidence of safe stent placement in an occluded extracranial internal carotid artery before thrombectomy in young adults with a proximal intracranial occlusion; although data are scarce.[65, 66] In case of neurological deterioration due to malignant middle-cerebral infarction early (within 48 hours of neurological deterioration) decompressive craniectomy should be considered, because it lowers mortality risk and improves functional outcome (number-needed-to-treat for young adults is two).[67]

Young patients are usually underrepresented in randomized controlled trials investigating the effect of secondary prevention. This underrepresentation unfortunate, since the prevalence of traditional vascular risk factors is increasing[68] and young adults with stroke are at higher risk of recurrent stroke and mortality than their healthy peers, especially those with stroke due to large artery disease or due to cardio-embolism.[54, 69] Because guidelines are not specific to young adults with stroke,[51-53] recommendations for secondary prevention are extrapolated from older patients with stroke (often atherosclerotic), including long-term antiplatelet therapy after almost any cause of stroke. Exceptions exist for cervical artery dissection, after which therapy can be stopped after 6 months, and for a cardio-embolic cause, for which oral anticoagulants are indicated.[45, 53, 70] As the management of young adult patients with stroke and old patients with stroke is similar overall, we will specifically address the diagnostic and therapeutic management of those risk factors and causes of stroke associated with important developments (e.g. new procedures or therapies) or overrepresented in young adults with stroke (Table 1).

Vascular risk factors

Modifiable, also known as traditional, risk factors are prevalent in young adults, with an absolute increase in the prevalence of hypertension (4-11%), hypercholesterolemia (12-21%), diabetes mellitus (4-7%), smoking (5-16%) and obesity (4-9%) over the past decade.[68] The population-based attributable risks of smoking, waist-to-hip ratio, alcohol, and psychosocial factors are slightly higher in young adults with stroke compared with old patients.[84] However in one study, population-attributable risk of most traditional risk factors (hypertension, diabetes mellitus, coronary heart disease, smoking, heavy episodic alcohol consumption, low physical activity, and high BMI) were increased with age.[85] For some traditional risk factors (hypertension, diabetes mellitus, smoking, and alcohol consumption), this risk was greater in young men than in young women and, for others (low physical activity and high BMI), it was greater in young women.[85] These traditional risk factors combined accounted for almost 80% of all ischemic strokes in young adults.[85] Obesity is becoming one of the largest global health epidemics and an increasing BMI is already seen in children and adolescents,[86, 87] putting them at risk for cardiovascular complications, including stroke at young age.[87] These alarming trends warrant improved primary prevention including life style adjustments such as dietary advice, smoking cessation, increased physical activity,[68] and better identification and treatment of these risk factors.

Migraine

The role of migraine in stroke is still controversial. A meta-analysis has shown an increased risk for ischemic stroke in patients with migraine with aura.[88] In addition, a Danish population study with more than 15,000 patients with migraine reported, that migraine, irrespective of aura, leads to an increased risk of ischemic stroke.[89] However, a recent Swedish population twin study in 53404 patients with migraine showed no statistically significant increased risk for migraine and a slightly increased risk for migraine with aura (gender-adjusted hazard ratio (HR) 1.27 (95% CI 1.00-1.62)), which disappeared after adjustment for confounders.[90] These conflicting findings, corroborated by the large statistical heterogeneity found in the meta-analysis,[88] might depend on differences in the ascertainment of migraine (structured interview in the Swedish study and retrospective chart review in the Danish study).[89, 90] Future studies are needed to clarify whether migraine is a risk factor for stroke.

Table 1. Stroke causes and risk factors (arranged according to TOAST classification) in young adults with clinical and diagnostic features

	Patient characteristics	Clinical features
Large artery atherosclerosis		
Atherosclerotic arteriopathy*	Age range: often 40-49 years; sex: both; ethnicity: all	History of cardiovascular disease and presence of traditional risk factors (e.g., smoking, obesity, hypercholesterolemia, diabetes)
Cardio-embolism		
Atrial fibrillation and other arrhythmias	Age range: often than 35 years; sex: both; ethnicity: all	History of palpitations and multifocal neurological symptoms (cranial nerve palsies, hemiparesis, aphasia, apraxia, etc.)
Cardiac tumors	Age range: all; sex: both; ethnicity: all	Multifocal neurological symptoms
Cardiomyopathy	Age range: all, but depends on type of cardiomyopathy; sex: men more than women; ethnicity: all, but depends on type of cardiomyopathy	Multifocal neurological symptoms
Endocarditis with or without valve vegetations	Age range: all; sex: both; ethnicity: all	Fever (fluctuating), spondylodiscitis, abscess in other organs and peripheral stigmata (e.g., splinter hemorrhage), and heart murmur at auscultation
PFO or atrial septum defect	Age range: higher risk in patients aged 18-29 years compared with 30-39 or 40-49 years, and in patients aged 30-39 compared with 40-49 (RoPE score of ≥7); sex: both; ethnicity: all	Onset after Valsalva maneuver, forced immobility or prolonged travelling, history of pulmonary embolism or deep venous thrombosis, or hypercoagulability, and absence of traditional risk factors
Small vessel disease		
Genetic cerebral small-vessel disease, CADASIL	Mean age: 49 years (range of 20-70 years); sex: both; ethnicity: not reported	Migraine with (atypical) aura, psychiatric symptoms (e.g., depressive symptoms, apathy), progressive cognitive impairment (e.g., executive functions), and family history of CADASIL
Sporadic cerebral small-vessel disease	Age range: often older (>35 years); sex: both; ethnicity: all	Hypertension and other cardiovascular risk factors

	Diagnostic features	Treatment
	Duplex or angiography or transcranial Doppler: stenosis of large vessels at typical sites (e.g., carotid bifurcation, carotid siphon, middle cerebral artery)	Long-term antiplatelet therapy; carotid endarterectomy: ipsilateral carotid stenosis >50%; management of conventional risk factors, such as lipid lowering drugs, antihypertensives, antidiabetics[45, 53]
	ECG: atrial fibrillation; CT or MRI: multiple infarctions in different arterial territories	Anticoagulants[45, 53]
	Echocardiography: tumor, mostly in left atrium or apex	Surgery[71]
	Echocardiography: ventricular dilatation or hypertrophy, ventricular apical aneurysm	Anticoagulants[45]
	Echocardiography: abscess, prosthetic valve dehiscence, valvular regurgitation, valvular vegetation	Surgery should be performed without any delay in case of heart failure, uncontrolled infection, abscess, or persistent high embolic risk (except in coma or cerebral hemorrhage)[72]
	Echocardiography (TEE more sensitive than TTE): right-left shunt at Valsalva maneuver; transcranial Doppler bubble test: right-left shunt	Antiplatelet therapy; PFO closure in patients with a high risk of recurrent PFO-related stroke[73] (based on RoPE score and additional PFO characteristics, such as degree of shunting and ASA); NNT=38, NNH=29
	MRI: white matter hyperintensities in the anterior temporal pole or external capsule, lacunes; genetic testing: *NOTCH3* mutation	Long-term antiplatelet therapy[74]
	CT or MRI: leukoaraiosis, white matter hyperintensities, lacunes, microbleeds	Long-term antiplatelet therapy; treatment of risk factors (e.g., antihypertensive medications)[45, 53]

Table 1. Continued

	Patient characteristics	Clinical features
Stroke of other determined cause		
Antiphospholipid syndrome	Age range: all; sex: women more than men (5:1); ethnicity: all	History of arterial or venous thrombosis and history of pregnancy complications (e.g., ≥3 miscarriages, intrauterine death, premature birth due to high blood pressure, pre-eclampsia, HELLP syndrome or placenta failure)
Autoimmune diseases (e.g., systemic lupus erythematosus)	Age range: all; sex: women:men 9:1; ethnicity: more common in non-white individuals	Headache or migraine, mood disturbances or cognitive impairment, epilepsy, peripheral neuropathies, systemic involvement (e.g., arthritis, arthralgias, malar rash, oral ulcers, Raynaud's phenomenon, pulmonal involvement, proteinuria, glomerulonephritis, pericarditis, and endocarditis)
Cervical artery dissection	Mean age: 44 years (SD 9.7 years); sex: both; ethnicity: all, CeAD more common than vertebral artery dissection in European patients, the opposite is found in Asian patients	Cervical pain and headache, (minor) head or cervical trauma, Horner's syndrome and cranial nerve palsy, and tinnitus
Fabry disease	Mean age: men 39.8 years (SD 11.9 years), women 45.7 years (SD 14.8 years); sex: both; ethnicity: not reported	Acroparesthesia, hypohidrosis, angiokeratoma, chronic kidney disease, and cardiomyopathy
Factor II deficiency	Mean age: 41.1 years; sex: both; ethnicity: more common in white individuals and African Americans, less common in Australia and east Asia	History (family) of venous thrombosis
Factor V Leiden, Protein C or S deficiency	Age range: all; sex: both; ethnicity: more common in white American and African American individuals, less common in Australia and East-Asia individuals	Deep venous thrombosis and (family) history of pulmonary embolism

	Diagnostic features	Treatment
	Laboratory: positive antiphospholipid antibodies (lupus anticoagulants, beta-2 glycoprotein, and anticardiolipin antibodies) at two different timepoints with at least a 12-week interval	Vitamin K antagonist alone or in combination with antiplatelet therapy[45]
	Laboratory: positive ANA, ANCA, inflammatory parameters (CRP and ESR), positive lupus anticoagulant, IgG and IgM) anticardiolipin, IgG and IgM anti-beta2-glycoprotein; CT or MRI: asymmetrical subcortical and periventricular white matter lesions, focal white matter hyperintensities, infarcts, hemorrhages, cerebral venous sinus thrombosis	Treatment of the autoimmune disorder; long-term antiplatelet treatment; anticoagulants in case of antiphospholipid syndrome in combination with systemic lupus erythematosus[75]
	CT or magnetic resonance angiography (MRI/A with fat saturated T1 sequence is recommended imaging mode): long, irregular stenosis (starting >2cm above the bifurcation for carotid CeAD), an occlusion or a dissecting aneurysm, typically associated with an intramural hematoma, and less often a double lumen or intimal flap	Short-term antiplatelet therapy 6-12 months;[45] long-term antiplatelet therapy if residual arterial abnormalities are present at 6-12 months[76]
	MRI: non-specific findings might include confluent white matter hyperintensities in basal ganglia, thalamus, and pons, and basilar dolichoectasia	Enzyme replacement therapy with alpha-galactosidase[77]
	Laboratory: prothrombin *G20210A* mutation	Anticoagulants; avoid oral contraceptives in women, because of higher risk of stroke[45]
	Laboratory: Factor V Leiden mutations, low protein C or S concentrations	Anticoagulants; avoid oral contraceptives in women, because of higher risk of stroke[45]

Table 1. Continued

	Patient characteristics	Clinical features
Illicit drug use	Age range: all, but depends on type of drug; sex: both; ethnicity: all	Injection marks and history of drug use
Intracranial dissection	Mean age: 50 (40-49 years); sex: both, predominance of men in Asian people; ethnicity: all, but more common in Asian individuals	Headache
Malignancy	Age range: all, but depends on type of malignancy; sex: both, but depends on type of malignancy; ethnicity: all	History of malignancy, and non-specific symptoms, including severe fatigue without other cause, unintended weight loss, and night sweats
Mitochondrial disorders (MELAS)	Mean age of onset: 32.2 years (SD 10.0 years); sex: both; ethnicity: not reported	Seizures, recurrent headaches, anorexia, recurrent vomiting, myopathies with exercise intolerance, and family history (maternal)
Moyamoya disease	Mean age: two age peaks at 5 years and 40 years; Sex: women:men 1.8:1; ethnicity: more common in East-Asian individuals	Migraine or epilepsy, and multiple TIAs, stress-induced limb shaking TIA, ischemic stroke, or intracerebral hemorrhage
Post-radiation	Age range: all; sex: all; ethnicity: all	History of radiation of cervical spine, neck, or head
Reversible cerebral vasoconstriction syndrome	Mean age: 42 years (range of 10-76 years); sex: women:men 3:1; Ethnicity: all	Recurrent thunderclap headaches lasting 1-3 h with or without focal neurological symptoms or seizures
Vasculitis	Age range: all; sex: both; ethnicity: all	Headache, behavioral and cognitive symptoms, encephalopathy, seizures, fever, weight loss, rash, visual problems, and other organ involvement (e.g., lungs, skin, joints)

	Diagnostic features	Treatment
	Laboratory: detection of metabolites in urine	No specific treatment recommended
	Angiography: intramural hematoma, intimal flap, and double lumen, but these might be difficult to detect given the small size of intracranial arteries; CT or MRI: ischemic stroke or subarachnoid hemorrhage	Antiplatelet therapy; endovascular or surgical treatment in case of further embolic events or progressive increase in aneurysm size[78]
	Not specific	No specific treatment recommended, but most patients will receive antiplatelet therapy
	CT: multiple infarcts, basal ganglia calcification, atrophy; MRI: chronic and acute infarcts which are typically not restricted to an arterial territory	Arginine therapy for stroke-like episodes[79]
	Angiography: distal internal carotid artery narrowing with collateral formation (so-called puff of smoke sign)	Long-term antiplatelet therapy; revascularization surgery[80]
	Angiography: distal internal carotid artery narrowing with or without development with collaterals	Long-term antiplatelet therapy
	Angiography: segmental narrowing of branches of cerebral arteries (string of beads)	Eliminate precipitating factors (e.g., illicit drug use, medication); blood pressure control to avoid hypertension and hypotension; nimodipine for headache[81]
	Laboratory: raised erythrocyte sedimentation rate or of CRP; CSF: mild pleocytosis, usually with protein elevation; contrast enhanced CT or MRI: multiple (bilateral) infarctions, at various stages, usually affecting different vascular territories, meningeal enhancement; angiography: focal or multifocal segmental narrowing of branches of cerebral arteries or occlusions (PACNS: affecting medium and small blood vessels; Takayasu's arteritis: affecting large blood vessels, including major aortic branches)	Prednisone 1 mg/kg per day and cyclophosphamide (2 mg/kg per day or 0.75 g/m^2 per month for 6 months); infliximab shows favorable responses in neurosarcoidosis[82]

Table 1. Continued

	Patient characteristics	Clinical features
Stroke of undetermined cause		
Cryptogenic stroke	Age range: often younger (<35 years), but can be seen in all ages; sex: both; ethnicity: all	No cause or attributable risk factor identified after thorough investigations

*Other cerebral arteriopathies are listed in Supplementary Table 1.
Abbreviations: CeAD, cervical artery dissection; CRP, C-reactive protein; PACNS, primary angiitis of the CNS; TIA, transient ischemic attack; ECG, electrocardiogram; PFO, patent foramen ovale; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; ASA, atrial septum aneurysm; RoPE, Risk of Paradoxical Embolism; NNT, number needed to treat;

Malignancy

Malignancy is increasingly recognized as a risk factor for stroke in young adults. The large Teenage and Young Cancer Survivor study,[91] involving a cohort of 178,962 patients aged 15-39 years, showed a 48% higher than expected incidence of ischemic stroke after a malignancy. This outcome was explained because of the toxic effects of chemotherapy and radiotherapy.[91] Recommendations to prevent the development of stroke after cancer or how to counsel patients are not available.[51, 52] Given the large proportion of strokes without an apparent cause in young adults, underlying (often occult) malignancies as a risk factor for stroke have been investigated. Of 1002 young adults with stroke in Finland, 77 (8%) patients were found to have a malignancy, of which 39 (4%) were diagnosed with malignancy pre-stroke; for the other 38 (4%), the median time from stroke to post-stroke cancer was 6.7 (IQR 2.7-10.9) years.[55, 92] Several pathophysiological explanations for the link between malignancy and stroke have been proposed, including hypercoagulable state, direct tumor effects (e.g. vessel compression or tumor embolism), marantic endocarditis, or accelerated atherosclerosis.[93] No information about standard screening for occult malignancy at young age is given in current guidelines for stroke.[51, 52] Implementation of screening for an occult malignancy should be further investigated, with cost-effectiveness as an important outcome.

Illicit and recreational drug use

Illicit and recreational drug use has risen tremendously in the past decade. An estimated 5% of all individuals aged 15-64 years use recreational drugs at least once a year.[14] Evidence suggests that drugs previously believed to be innocuous in terms of risk of cardiovascular disease, such as cannabis, opioids, and so-called designer drugs, like ecstasy and lysergic acid diethylamide, are now more frequently associated with stroke, although with a lower incidence than cocaine.[14] The possible pathophysiological mechanisms depend

	Diagnostic features	Treatment
	Not specific	Long-term antiplatelet therapy[83]

NNH, number needed to harm; CADASIL, cerebral autosomal dominant angiopathy with subcortical infarctions and leukoencephalopathy; HELLP, hemolysis, elevated liver enzymes, and low platelets; SLE, systemic lupus erythematosus; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ESR, erythrocyte sedimentation rate; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.

on the drug itself and the mode and administration of the drug use - e.g. embolism of endocarditis from intravenous use.[4, 12, 14] A relatively higher proportion of ischemic stroke has been reported after inhalation than other routes of drug administration.[94] Causes of stroke attributable to cocaine and amphetamine use include cerebral vasospasm, cardiac arrhythmias, cardiomyopathy, accelerated atherosclerosis and vasculitis.[14] Other studies show direct toxic effects on cerebral vessels.[12, 14] Thorough history taking and urine, saliva and blood testing can reveal illicit drug use.

Pregnancy and the puerperium

Pregnancy and the puerperium, especially from the third trimester to six weeks postpartum,[95] are associated with an increased risk of ischemic stroke,[96, 97] although the absolute risk of pregnancy-related stroke is low and varies worldwide, with an incidence of 12.2 per 100,000 pregnancies (95% CI 6.7-22.2).[95-97] Causes of stroke specific to pregnancy include peripartum cardiomyopathy, postpartum cerebral angiopathy (part of the spectrum of reversible cerebral vasoconstriction syndromes (RCVSs), amniotic fluid embolism, or hypertensive disorders of pregnancy (e.g. eclampsia).[97] However, often, the cause of stroke remains uncertain and is possibly related to the physiological hypercoagulable state in the third trimester.

The diagnostic approach in pregnant women differs from non-pregnant patients, owing to the need for careful balancing the risks and benefits for pregnant women and their unborn children. MRI is the preferred choice of imaging, with time-of-flight sequences without contrast agent to visualize arteries.[98] If MRI is not available or contraindicated, low-radiation-dose CT-scans are a valid alternative.[97] Intravenous thrombolysis can be considered in pregnant woman with moderate-to-severe ischemic stroke,[99] and mechanical thrombectomy alone can be justified in case of large vessel occlusion.[97]

Aspirin, instead of clopidogrel, can be given during pregnancy and the lactation period as secondary prevention.[97, 100] Vitamin K antagonists cross the placenta and are teratogenic,[97, 100] and data on the effects of direct-acting anticoagulants (e.g. dabigatran, rivaroxaban, and apixaban) are scarce.[97, 100] If oral anticoagulation is needed, low-molecular weight heparins are preferred over unfractioned heparin,[97, 100] and are safe, since they do not cross the placenta.[97, 100]

An important knowledge gap exists regarding the clinical management of women who wish to conceive, or are pregnant, with a history of previous stroke, which has been investigated in only a few studies, involving only several hundred post-stroke pregnancies in total. Based on these studies, current clinical insight is that future pregnancy is not contraindicated in young adult women with a previous stroke. To carefully address contributing factors to stroke (e.g. coagulation disorders such as the antiphospholipid syndrome) or a PFO that might become symptomatic because of higher risk of venous thromboembolism during pregnancy, women with a previous stroke should be counselled in a multidisciplinary setting. The higher number of pregnancy-related complications in young adult women after stroke compared with the general population (miscarriages 35.2% vs. 13.5%, fetal death 6.2% vs. 0.9%, HELLP syndrome 9.0% vs. 0.5% and preterm delivery 9.0% vs. 1.4%),[101] suggests that stroke and pregnancy complications have shared mechanisms. Another study confirmed the higher (not significant) risk of pregnancy-related complications in women with ischemic stroke compared with stroke-free mothers.[102] More research, with larger sample sizes, is needed to improve management and reduce pregnancy-related complications.

Genetic risk factors

Monogenic (Mendelian) disorders are responsible for up to 7% of all strokes in young adults (Supplementary Table 2).[7, 103, 104] A large proportion of known monogenic strokes is mediated by cerebral small vessel disease (SVD).[105-107] A genetic cause of small-vessel disease should be suspected when (recurrent) lacunar infarctions occur with accompanying severe, confluent white matter hyperintensities without any vascular risk factors. As clinical and radiological signs and symptoms are often not specific to any single underlying genetic cause, exploring a panel of genetic causes of small-vessel disease can be the fastest way to diagnose genetic small-vessel disease.[108, 109]

Although rare, underlying metabolic disorders, such as Fabry disease, might also be associated with stroke in young adults. For example, the Stroke in Young Fabry Patients study[57] identified 27 (0,5%) Fabry patients among 5023 patients with cerebrovascular disease. Thus, routine genetic testing for Fabry disease in young adults with stroke is not required yet.

Next generation sequencing studies have suggested that potentially deleterious mutations in genes causing monogenic stroke may be more frequent than previously suspected.[110, 111] However, systematic screening for such mutations is not yet required in the absence of a suggestive clinical presentation (e.g. burning feet syndrome or angiokeratomas).

In most cases genetic risk factors contribute to the risk of stroke as part of a multifactorial predisposition, in which individual genetic variations are responsible for modest increases in risk; therefore routine genetic testing has not been warranted yet.[111]

For example, a common genetic variant in an intron of the *PHACTR1* gene was associated with a modest increase in risk for cervical artery dissection and fibromuscular dysplasia in the first genome-wide association studies (GWAS) involving these conditions.[78, 112, 113] A large international collaborative genome wide association studies (GWAS)[114] identified common risk variants and genes associated with monogenic causes of stroke (e.g. COL41A) and provided crucial insight into the biological pathways underlying stroke. GWAS restricted to young adults with stroke are still in their infancy, just one genome-wide association signal has been identified, near HABP2,[115] which encodes a serine protease that regulates coagulation, fibrinolysis, and inflammatory pathways and is expressed in high concentration in young adults with stroke. Studies with larger sample sizes are ongoing to confirm and expand this finding.

Cardiac embolism

Several studies showed a reduced risk of recurrent strokes in patients with cryptogenic stroke and patent foramen ovale (PFO) who underwent PFO closure combined with antiplatelet therapy compared with patients with antiplatelet therapy only (number-needed-to-treat was 38, during a mean follow-up duration of 4.1 years[73]),[116-118] although the risk of device complications, atrial fibrillation and venous thrombosis increased transiently.[116-118] Together with a 25% prevalence of PFO in a stroke-free population, this relatively high number-needed-to-treat highlights the need to better understand in whom PFO is causally related to stroke. Clinical features that increase the risk of stroke due to PFO include predisposition to venous thrombosis (such as hypercoagulable states, immobility, and pregnancy), presence of an atrial septum aneurysm, and absence of atherosclerosis or associated risk factors.[119] PFO screening can be done with transthoracic (with contrast)(TTE) or transesophageal echocardiogram (TEE), which are safe to use in pregnant women.[120] The Risk of Paradoxical Embolism (RoPE) score, can be used to predict the probability of stroke-related PFO.[116, 121] A younger age, absence of vascular risk factors, and a cortical

stroke yield a higher RoPE score that is associated with a greater probability of a stroke-related PFO.[121] A high RoPE score was also associated with lower short-term risk of recurrent strokes,[120] possibly because those with a low RoPE score are patients with a high burden of vascular risk factors and an associated high risk of recurrent score. PFO closure should be considered in patients with cryptogenic stroke with a high risk of recurrent PFO-related stroke (based on RoPE score >7[121] *and* additional PFO characteristics, such as degree of shunting and atrial septum aneurysm).

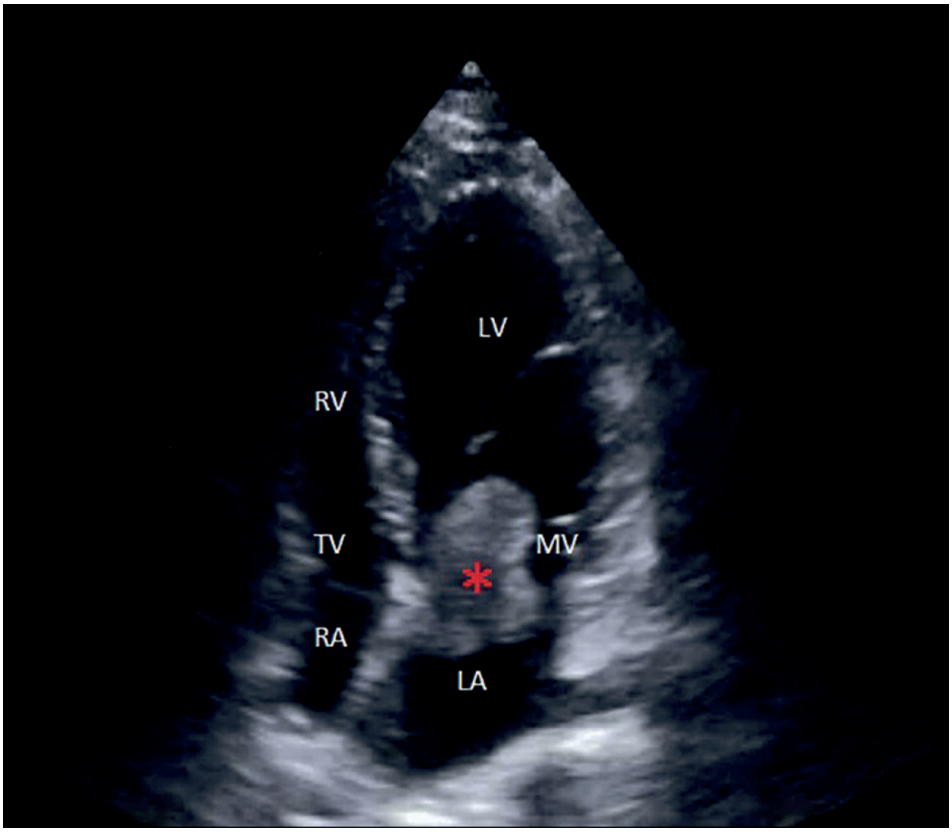
Other cardiac abnormalities, including cardiomyopathy and cardiac tumors (Figure 2) can also be identified with echocardiography (Table 1) and, although rare, patients might benefit from acute treatment.[7, 12] Several studies have also shown both the feasibility and diagnostic value of cardiac CT or MRI after an ischemic stroke,[122, 123] to evaluate left atrial thrombus, PFO, atrial septal aneurysm, aortic atheroma and coronary artery disease.[122] Although these diagnostics avoid the discomfort and complications (injuries of the gastrointestinal tract and infections) associated with TTE and TEE, they have not been recommended in initial investigations.[75]

Atrial fibrillation can be diagnosed by electrocardiogram (ECG); however, it can be missed because of its paroxysmal occurrence.[124] Other ECG patterns (mostly those associated with atrial pathology), including P-wave abnormalities, are associated with ischemic stroke in young adults.[125, 126]

New technologies for detection of subclinical atrial fibrillation, such as external ambulatory recorders for prolonged cardiac monitoring, are rapidly evolving.[45] However, arrhythmias have a much lower incidence in young adults (3%) than in elderly (16%) patients with cryptogenic stroke, even after 3 years of continues monitoring with an inserted loop recorder.[124,127]

Prolonged monitoring has not been recommended for young adults, apart from those with evidence of atrial pathology.[119]

Figure 2. Basilar thrombosis due to cardiac myxoma



Abbreviations: RV, right ventricle; LV, left ventricle; TV, tricuspid valve; MV, mitral valve; RA, right atrium; LA, left atrium.

A 34-year-old woman complained of headache, nausea, and vomiting before losing her consciousness during a bus ride. Neurological examination showed a Glasgow Coma Scale Score of 9 out of 15, with deviation of the head to the left and pinpoint pupils, bilateral hyperreflexia, and pathological reflexes. CT angiography revealed an occluded basilar artery. The patient was treated with intravenous thrombolysis followed by intra-arterial thrombectomy. MRI done 3 days later showed multiple ischemic lesions in several arterial territories (the left and right cerebellum; the right lateral pons), indicative of a cardio-embolic source. Transthoracic echocardiogram showed an echolucent structure in the left atrium (indicated by the red asterisk), which was pathologically confirmed to be myxoma. At follow-up 2 weeks after surgery, her symptoms improved remarkably, and she had no neurological deficits or symptoms, apart from a mild headache.

Cervical artery dissection

Cervical artery dissection is the cause of about 20% of strokes in young adults, with a mean age at presentation of 44 years (SD 9.7 years).[7, 78] The pathophysiology of cervical artery dissection is incompletely understood. Hypertension, migraine (especially without aura), cervical trauma, and recent infection (particularly intracranial or systemic infections) are risk factors for cervical artery dissection, whereas hypercholesterolemia and overweight appear protective.[76, 128] In the acute stage, intravenous thrombolysis is not contraindicated in ischemic stroke caused by cervical artery dissection, except for the rare instances in which cervical artery dissection occurs as an extension of an aortic dissection.[129, 130] The rate of recurrent or de-novo cerebral ischemia and recurrent cervical artery dissection after treatment initiation was reported to be low (approximately 2% at 3 months).[70, 131] However, a single tertiary center study[132] showed that 22 (9.2%) of 238 patients with acute cervical artery dissection had a recurrent cervical artery dissection within the first month and 17 (7%) of 238 patients after the first month. With regards to the choice of antithrombotic therapy in the first months following the stroke event, a randomized trial comparing antiplatelets and oral anticoagulants found no difference in stroke recurrence, which could well be explained by a type II error.[70] These findings should be interpreted with caution, because 26 (about 10%) of 250 patients did not have a stroke or transient ischemic attack as presenting symptom of their dissection, and dissection could not be confirmed after central review of imaging in 52 (20%) patients. The results of an ongoing trial comparing antiplatelets and oral anticoagulants for patients with cervical artery dissection, with silent infarcts on brain MRI combined with incident clinical strokes as a composite outcome, are awaited (NCT02046460).

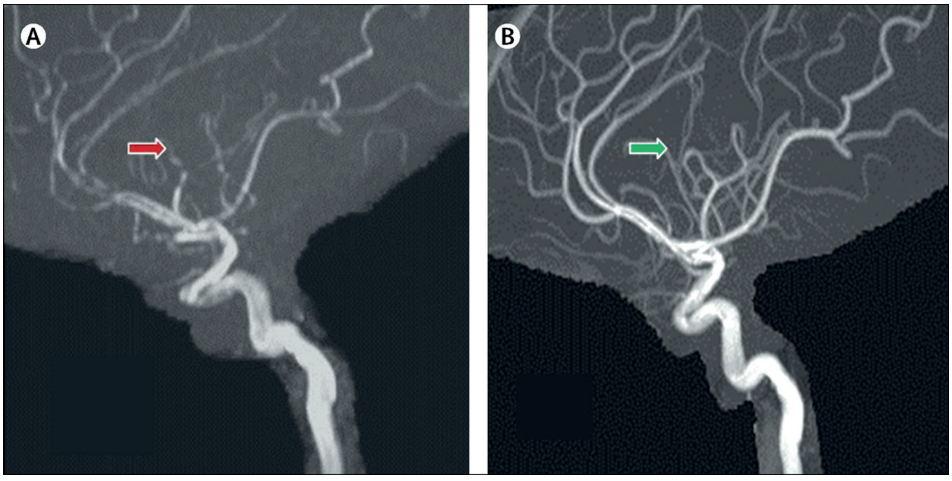
Reversible cerebral vasoconstriction syndrome (RCVS)

With a peak age of 42 years, RCVS, which is known to cause ischemic stroke in less than 5% of all patients, is an increasingly recognized condition with relevance to young adults with stroke.[7, 12, 81] RCVS remains underdiagnosed because of its reversible aspect, but should rank highly in differential diagnoses when stroke symptoms are preceded by acute, thunderclap headache (mimicking that of an aneurismal subarachnoid hemorrhage) (Figure 3).[7, 12, 81] It can occur after pregnancy,[36] and after use of vasoactive or illicit drugs (e.g. cocaine, amphetamines) and is more common in patients with cervical artery dissection.[133] Although evidence for a role of vasoconstriction in the pathophysiology of RCVS is available, further understanding is hampered by a typical 2 week interval between the stroke and its presumed cause (vasoconstriction on CT or magnetic resonance angiography).[81, 133] RCVS is radiologically characterized by diffuse segmental constriction of cerebral arteries that resolve spontaneously within 3 months.[81, 133] Blood, CSF diagnostic measurements, and MRI are usually normal, although RCVS can be accompanied by subarachnoid hemorrhage,

usually at the convexity.[81] Although glucocorticoids were previously considered benign and often administered while primary angiitis of the CNS was being excluded, a retrospective study with 159 RCVS patients and 47 patients with primary angiitis of the CNS indicated that glucocorticoids are harmful in patients with RCVS.[134] Moreover, RCVS and primary angiitis of the CNS can now be distinguished upon clinical presentation based on criteria with high specificity,[134] so glucocorticoids are not indicated for RCVS.[135]

Treatment is mostly symptomatic, with analgesics and nimodipine to reduce the intensity and frequency of thunderclap headache, although these drugs have no proven effect on vasoconstriction and the possible complications (e.g., ischemic stroke and subarachnoid hemorrhage).[81, 136] Blood pressure should be controlled following American College of Cardiology and American Heart Association guidelines,[137] while avoiding hypertension, which can theoretically induce progression of vasoconstriction and hypotension, because of the risk of hypoperfusion and ischemic stroke. Antiplatelet therapy has not been recommended.

Figure 3. Reversible cerebral vasoconstriction syndrome associated with cannabis use



(A) A 41-year-old woman with chronic cannabis use of unknown duration developed acute severe headache during a bowel movement. The headache subsided in 20 min. 3 days later, during a spicy meal, she developed another severe thunderclap headache. Neurological examination, CT scan, and CSF were normal. After 1 week, she had five thunderclap headaches episodes. Although MRI done 10 days after the first episode of headache was normal without parenchymal lesions or subarachnoid hemorrhage, MR angiography showed segmental multifocal vasoconstriction of the circle of Willis arteries and their branches (red

arrow) suggestive of reversible cerebral vasoconstriction syndrome. (B) Serological tests for vasculitis were negative. The patient was treated with analgesics. Follow-up MRI and magnetic resonance angiography after 3 weeks showed resolution of cerebral angiographic abnormalities (green arrow).

Embolic stroke of undetermined source

The concept of embolic stroke of undetermined source (ESUS) was devised to identify a subgroup of patients with cryptogenic ischemic stroke with radiological evidence of territorial infarcts, thought to be caused by cardiac emboli, in the absence of an arteriopathy and without definite proof of a cardio-embolic source.[138] Care should be taken with this concept in clinical practice as, although now defined as one construct, ESUS still reflects a plethora of underlying embolic sources that are unlikely to benefit from the same therapeutic strategy.[139]

An estimated 9-25% of young stroke patients meet the criteria for ESUS.[140, 141] This high variation might be explained by the fact that studies were retrospective (with ESUS criteria not existing at the start of the studies) or differed in their ascertainment of a cardio-embolic source.[139]

It has been argued that anticoagulants could be superior to platelet inhibition in the prevention of recurrent stroke in patients with ESUS. NAVIGATE ESUS,[142] a randomized, controlled trial of 7213 patients with ESUS, compared the safety and efficacy of rivaroxaban with aspirin and found no difference in prevention of recurrent stroke (158 [4.7%] for rivaroxaban vs 156 [4.7%] for aspirin), with a higher major bleeding risk in rivaroxaban users (62 [1.8%] vs 23 [0.7%]).[142] For now, young adults with ESUS should be treated with antiplatelets, although only 1716 (24%) of the 7213 individuals in the study population were less than 60 years old.[142, 143] Two randomized, controlled trials are currently ongoing (RE-SPECT ESUS [NCT02239120] and ATTICUS [NCT02427126]).

LONG-TERM SEQUELAE

Counselling of young adult patients and their families on the effects of stroke should ideally be multidisciplinary and should occur during admission and rehabilitation, addressing possible long-term medical and psychosocial consequences. Prognosis of stroke in young adult patients and associated risk factors are outlined in Table 2.

The 20 year cumulative mortality after stroke in young adults (30%) is up to four times higher than in healthy age-matched individuals.[54, 69] The 20 year cumulative mortality after stroke in young adults (30%) is up to four times higher than in healthy age-matched individuals.[55, 69] Thus, in high-risk patients, lifestyle changes and therapy compliance need to be emphasized during counselling.

A Dutch prospective study[144] in 537 young adults with ischemic stroke reported a cumulative risk for post-stroke epilepsy of 12.7% after 9.8 years of follow-up. Patients with post-stroke epilepsy also had a poorer functional outcome on both the modified ranking scale (mRS) and the Instrumental Activities of Daily Living (iADL) scale (27.5% vs 9.8% for mRS>2; 27.8% vs 12.6% for iADL<8) than those without.[144] The SeLECT score is a prognostic model consisting of several stroke-related parameters, like severity and location of stroke, that was designed to quantify the risk of late seizures in patients after stroke. It can be used to counsel patients, although it should be interpreted with caution, as the study did not include young adults with stroke.[145] Depending on the preferences of patients, treatment can include antiepileptic drugs, although no formal evidence, in the form of randomized, controlled trials, for this approach in young adult patients exists.[146]

A substantial proportion of young adults with stroke (>50%) perform worse on a wide range of cognitive domains, even 11 years after stroke.[147] A substantial proportion of young adults with stroke (>50%) perform worse on a wide range of cognitive domains, even 11 years after stroke.[148] Young adult patients seem to have better cognitive prognosis than elderly patients; however, given that they have a long life ahead and the effect on daily life, cognitive functioning should be monitored in clinical practice. 41% of young adults with stroke have fatigue, which is twice as many as in healthy, age-matched individuals.[149] Patients with post-stroke fatigue more often have a poor functional outcome (mRS>2: 13% vs 1%; iADL<8: 15% vs 1%) and impairment of speed of information processing (34% vs 6%) compared with healthy, age-matched controls.[149] A randomized, controlled phase 2 trial of 36 patients (mean age 63 years, SD 15) with post-stroke fatigue found a significant decrease in fatigue and improvement in quality of life after 6 weeks of daily modafinil therapy.[150] More

research with long-term modafinil therapy is needed to implement this treatment in clinical practice. Exercise therapy in combination with cognitive therapy seems to reduce post-stroke fatigue;[151] however, evidence is scarce, and further studies are warranted.

The prevalence of depressive symptoms was found to be almost three times higher in young adults with stroke than in healthy, age-matched controls in one study (17% vs 6%).[152] Young adult patients with stroke had a prevalence of anxiety around two times higher than controls (23% vs 12%).[152] The high prevalence of anxiety was related with a poor functional outcome,[152] and could also lead to avoidance of daily activities. Patients after stroke have a more than two times greater risk of suicidal ideation and a three to six times greater risk of suicide attempts than healthy controls.[153,154] As patients do not always spontaneously report these thoughts, proactively asking for these thoughts creates an opportunity to refer them to a psychologist or a psychiatrist.

A cohort study of 104 young ischemic stroke patients reported sexual dysfunction in 30 patients (29%) 1-year after stroke.[155] Multiple factors can aggravate sexual dysfunction—e.g., type of lesion, medications (including ACE inhibitors), depression, and anxiety.[155] Given the high prevalence of sexual dysfunction and its effect on quality of life, this issue should be discussed during follow-up and consultation with a urologist concerning treatment should be offered.

Central post-stroke pain occurred in 49 (6%) of 824 young adults with stroke, which also reduces their quality of life.[156] Severe infarctions with hemorrhagic transformation are more likely to be associated with central post-stroke pain.[156] Suitable treatment (e.g., neuropathic pain medication) should be offered, if needed.

A Dutch study[50] found that 202 (29.1%) of 694 young adults with stroke were unemployed, even 8 years after stroke, which is comparable to a Danish study that found unemployment in 3322 (33%) of 9930 patients 2 years after stroke.[157] An occupational therapist should ideally join the multidisciplinary team, to inform patients and their relatives of labor reintegration and legal issues regarding social security.

Table 2. Prognosis and associated risk factors in young adults with stroke

	Risk factors
Anxiety[152]	Lower educational level, history of depression, unemployment, and alcohol consumption
Central post-stroke pain[156]	Severe infarctions with hemorrhagic transformation
Cognitive impairment[147, 148]	Supratentorial infarction
Depression[152]	Lower educational level and unemployment
Mortality[54, 69]	Older age (40-50 years), male sex, history of cardio-embolic stroke, and coexisting cause of stroke
Post-stroke epilepsy[144]	Severity of stroke, history of stroke caused by large-artery atherosclerosis, early seizures (within 7 days of stroke), cortical involvement, and territory of middle cerebral artery involvement
Post-stroke fatigue[149]	Post-stroke depressive symptoms, anxiety, and recurrent cerebrovascular events
Recurrent stroke[55, 69]	Older age (40-50 years), male sex, history of cardiovascular risk factors, atherothrombotic stroke, cardio-embolic stroke, and lacunar stroke
Risk of suicide attempts[153, 154]	Male sex, living alone at stroke onset, low income, lower educational level, severe stroke (being drowsy or unconscious on hospital admission), and post-stroke depression
Sexual dysfunction[155]	Depression and use of angiotensin-converting-enzyme inhibitors
Unemployment[50, 157]	Higher NIHSS at admission, a longer duration of follow-up, female sex, self-employment before stroke, and lower occupational status

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

CONCLUSIONS AND FUTURE DIRECTIONS

Stroke at a young age is a societal challenge with a rising incidence. It has lifelong consequences for people at a crucial juncture in their lives, with an accompanying socioeconomic burden.[3, 50, 157] Stroke at a young age is a societal challenge with a rising incidence. It has lifelong consequences for people at a crucial juncture in their lives, with an accompanying socioeconomic burden.[14, 68] These trends warrant better prevention and, since over a third of cases remain cryptogenic,[12, 103] further identification of new risk factors is needed. Much progress has been made in the management of specific causes of stroke in young adults, such as closure of PFO in high-risk patients.[116-118] Owing to their age and long life-expectancy, counselling of young adults with stroke regarding their post-stroke sequelae differs from older patients with stroke (e.g., future pregnancy considerations and unemployment) and should, therefore, be multidisciplinary.

Future research should provide more insight into the biological pathways underlying stroke. For example, the nature of extracranial and intracranial arteriopathies that cause 10-20% of all strokes in young adults (depending on the definition of arteriopathies)[12, 158] cannot be properly visualized with conventional imaging techniques, because they visualize the arterial lumen rather than the pathology of the vessel wall itself (e.g., arterial dissection, atherosclerotic arteriopathy, and vasculitis).[159] Furthermore, high-throughput genotyping technologies will generate more knowledge on stroke mechanisms, by identifying new stroke risk loci and genes implicated in monogenic small-vessel disease, like COL4A1.[114] These future advances hold the promise of accelerating the development of innovative drugs and novel treatment strategies.[111]

Although many differences in risk factors and causes exist between young and old patients with stroke, they are not often translated into distinct secondary prevention management, owing to an absence of secondary prevention studies exclusively done in young adults. Future research should, therefore, include secondary prevention trials specifically in this population.

Development of reliable prognostic models, based on clinical, radiological, or genetic profiles, will enable personalization of counselling and treatment of patients who might benefit most from specific treatment or patients with a poor prognosis. Meta-analysis of individual patient data is one of the preferred approaches to build these models. Global efforts to evaluate variation in risk factors, etiology, and prognosis, with participating centers from every continent are currently being deployed in the GOAL-initiative. The development of guidelines specifically devoted to young adults with stroke is long awaited.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Cerebral Arteriopathies

1.	Premature atherosclerosis
2.	Carotid and vertebral artery dissection
3.	Reversible cerebral vasoconstriction syndromes (RCVS)
4.	Moyamoya disease
5.	Vasculitis *(e.g. primary angiitis of the CNS, giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, scleroderma, systemic lupus erythematosus, Behcet's disease, Churg-Strauss syndrome, Kohlmeier-Degos disease, Eale's disease, Spatz-Lindenberg disease, vasculitic cerebral amyloid angiopathy; acute posterior multifocal placoid pigment epitheliopathy (APMPPE))*
6.	Infectious arteritis *(e.g. tuberculosis, syphilis, cysticercosis, herpes zoster, bacterial meningitis)*
7.	Genetic / Inherited / Developmental
	a. Sickle cell disease from hemoglobin beta-chain gene mutations
	b. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; NOTCH-3 mutation)
	c. CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; HTRA-1 mutation)
	d. Fabry disease (a-GalA mutations resulting in α-galactosidase A enzyme deficiency)
	e. COL4A1 mutation
	f. ADA2 mutation
	g. Ehlers-Danlos syndrome (COL3A1 mutations affecting type III collagen)
	h. Marfan syndrome (FBN1 (fibrillin 1) mutations)
	i. HERNS (hereditary endotheliopathy with retinopathy, nephropathy, and stroke; TREX-1 mutations)
	j. FHM (familial hemiplegic migraine; CACNA1A mutations that affect the alpha1A subunit of voltage-gated calcium channels in neurons
	k. MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; mitochondrial tRNA (Leu) A3243G mutations
	l. Homocystinuria (multiple genes can be affected)
	m. Pseudoxanthoma elasticum (ABCC6 or ATP-binding cassette C6 mutations)
	n. Fibromuscular dysplasia
	o. Dolichoectasia (probable dysfunction of matrix metalloproteinases or MMPs)
	p. Neurofibromatosis type 1 (autosomal dominant NF1 gene mutations)
	q. Osteogenesis imperfecta (mutations in the COL1A1 and COL1A2 genes that encode type I procollagen)

Supplementary Table 2. Monogenic causes of ischemic stroke

Disease	Gene	Inheritance mode	Other clinical features (main)
Monogenic diseases causing large artery and small vessel ischemic stroke			
Sickel cell disease	*HBB*	autosomal recessive	more seldom intracerebral hemorrhage, vaso-occlusive or painful crisis, retinopathy, chronic leg ulcers, increased susceptibility to infection, anemia
Homocystinuria	*CBS* *	autosomal recessive *	thromboembolism, mental retardation, ectopia lentis, skeletal abnormalities
Fabry disease	*GLA*	X-linked	acroparesthesia, hypohidrosis, angiokeratoma, chronic kidney disease, cardiomyopathy
PXE	*ABCC6*	autosomal recessive	peau d'orange lesions, ocular complications, hypertension, peripheral artery disease, coronary artery disease, gastrointestinal bleeding
Monogenic diseases causing small vessel ischemic stroke			
CADASIL	*NOTCH3*	autosomal dominant	migraine with aura, mood disturbance, progressive cognitive impairment
CARASIL	*HTRA1*	autosomal recessive	alopecia, dementia, gait disturbance, low back pain, mood disturbance
Other	*HTRA1*	autosomal dominant	cognitive decline (later onset than CARASIL)
RVCL	*TREX1*	autosomal dominant	visual loss, dementia, seizures, headache, personality disorders
PADMAL	3'UTR of *COL4A1* ǂ	autosomal dominant	progressive imbalance, cognitive impairment
CARASAL	*CTSA* §	autosomal dominant	Intracerebral hemorrhage, cognitive impairment, therapy-resistant hypertension

Supplementary Table 2. Continued

Disease	Gene	Inheritance mode	Other clinical features (main)
Monogenic diseases causing ischemic stroke of other etiologies			
vascular EDS	*COL3A1*	autosomal dominant	dissection and rupture of arteries, rupture or hollow organs, easy bruising, thin skin with visible veins
Marfan syndrome	*FBN1* *	autosomal dominant	aortic root dilatation and dissection, ectopia lentis, marfanoid habitus, dural ectasia, pneumothorax
Monogenic mitochondrial disorders			
MELAS	*tRNA Leu*	maternal inheritance	seizures, recurrent headaches, anorexia, recurrent vomiting, myopathy with exercise intolerance

Only monogenic diseases for which stroke is one of the main clinical manifestations are presented. Inherited cardiopathies (e.g. familial atrial fibrillation), vascular malformations (such as familial cavernomas) or genetic coagulopathies are not included in this table. * most frequent form ; ǂ affects a binding site of miR-29 microRNA; [§] reported in two families only.
Abbreviations: CAA, Cerebral Amyloid Angiopathy; CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CARASIL, Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; COL4A1, Collagen 4A1; EDS, Ehlers-Danlos syndrome; MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; PADMAL, Pontine Autosomal Dominant Microangiopathy with Leukoencephalopathy; PXE, Pseudoxanthoma Elasticum; RVCL, Retinal vasculopathy and cerebral leukodystrophy.

Chapter 4

Trends of stroke incidence in the young

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Stroke-incidence in young adults according to age, subtype, sex, and time-trends.

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ABSTRACT

Objective: To investigate incidence of stroke and its subtypes in young adults, according to sex and age, and to study trends over time.

Methods: We established a nationwide cohort through linkage of national registries (hospital discharge-, cause of death-, and population-register) with patients aged 18-50 years and those ≥ 50 with first-ever ischemic stroke, intracerebral hemorrhage or unspecified stroke, using ICD-9/-10 codes between 1998 and 2010 in the Netherlands. Outcomes were yearly incidence of stroke stratified by age-, sex-, stroke-subtype, its changes over time, and comparison of incidence in patients 18-50 to patients ≥ 50.

Results: We identified 15,257 patients (53% women; mean age 41.8). Incidence increased exponentially with age (R^2=0.99) and was higher for women than men, most prominently in the youngest patients (18-44). The relative proportion of ischemic stroke increased with age (18-24: 38.3%; 44-49: 56.5%), whereas the relative proportion of intracerebral hemorrhage decreased (18-24: 34.0%; 44-49: 18.3%). Incidence of any stroke in young adults increased (1998: 14.0/ 100,000 person-years: 2010: 17.2; +23%; p<0.001), driven by an increase in those aged over 35 and ischemic stroke incidence (46%), whereas incidence decreased in those ≥ 50 (329.1 to 292.2; -11%; p=0.009).

Conclusions: Incidence of any stroke in the young increases with age in patients over 35, is higher in women than men aged 18-44 and has increased by 23% in one decade, through an increase in ischemic stroke. Incidence of intracerebral hemorrhage is comparable for women and men and remained stable over time.

INTRODUCTION

An estimated 10-15% of all first-ever strokes occur in people aged 18 to 50 years.[4, 13] With a yearly stroke incidence of 15 million people worldwide, at least 1.5 million young adults are affected every year.[160] The consequences of stroke in the young are substantial and, due to their long survival after stroke, long-lasting. Sequelae of stroke in the young have specific implications in relation to their age, as young patients are often at cross-roads in their lives with young families, demanding careers, and social interactions that may remain impaired for decades to come. In addition, the social-economic burden of stroke in the young is high, considering the number of productive life years lost.[17, 161]

Despite improvement in the prevention and treatment of cardiovascular disease, recent studies have suggested an increase in the incidence of stroke in young adults, which is in contrast with the decrease in incidence observed in the elderly.[4-11] However, there are still several uncertainties. Due to low patient numbers it is unknown whether the suggested increase in incidence is present across all age strata for both men and women. In addition, most previous studies were (single) hospital based (with the possibility of selection bias) or occurred in countries where not all patients with stroke were likely to be seen by a neurologist, were limited to either ischemic stroke, intracerebral hemorrhage, or did not specify a stroke subtype, and included also subarachnoid hemorrhage. The studies also had varying lower and upper age limits to define young adults, did not always adjust for the total number of individuals within the general population when reporting the (change of) incidence and did not compare results with time-trend in incidence of stroke in patients over 50 years of age to determine whether observed time-trends were age-specific.

We therefore investigated age- and sex-specific incidence, and incidence trends over time of first-ever ischemic stroke and intracerebral hemorrhage among young adults in the Netherlands.

METHODS

Patients

Through linkage of the Dutch Hospital Discharge Register (HDR) and Population Register all Dutch patients with a hospitalization for first-ever stroke (either ischemic stroke, intracerebral hemorrhage or stroke not otherwise specified) were identified between 1998 and 2010, using ICD-9 codes for stroke (International Classification of Diseases). We also utilized the Cause of Death Register with the Population Register to identify all Dutch persons who died from a first-ever stroke outside of the hospital between 1998 and 2010, using ICD-10 codes for stroke (Table 1). The index event was operationalized through selecting the first admission for stroke from 01-01-1998 onwards, since we were unable to identify possible previous strokes before this date. We excluded patients with subarachnoid hemorrhage or cerebral venous sinus thrombosis.

The validity of ICD-codes for identifying patients with ischemic stroke and intracerebral hemorrhage has been demonstrated for stroke patients of all ages [162, 163], but not for young adults specifically. At young age, some stroke mimics like for example migraine and seizures may occur more frequently than in the elderly.[164] Therefore we assessed the validity of the ICD codes for 569 patients with a stroke at young age (301 with an ischemic stroke, 183 patients with intracerebral hemorrhage and 85 with an unspecified stroke), hospitalized between January 1998 and May 2017 in two academic and one large non-academic teaching hospital. We chose to analyze all data that was available to us of patients that had complete files including neuro imaging (n=569), therefore not restricting the validation period to our study period, to sample as many young stroke patients as possible to provide a more reliable validation analysis. We compared all ICD-9 or ICD-10 codes logged as discharge codes in the local hospital administration with the main diagnosis (including findings on neuroimaging) in the medical files. Ischemic stroke was correctly diagnosed through registered ICD-codes in 90.4% of cases, intracerebral hemorrhage in 86.3%, and unspecified stroke in 87.1% of all cases, comparable to the validity in the general stroke population. Of the 74 unspecified strokes, 67 (90.5%) were ischemic strokes and 7 were intracerebral hemorrhages (9.5%) (Table 2). [162, 163]

The HDR contains records of all individual hospital admissions of the participating Dutch hospitals, including information about primary diagnosis (four-digit ICD-9 codes) as well as date of birth, sex and numeric part of the postal code. Using these personal identifiers, we linked the HDR admission records containing the selected ICD-9 codes for stroke with the Population Register to link multiple hospital admissions of one

person. Approximately 85% of the Dutch population can be identified through a unique combination of their date of birth, sex and postal code.[165] These registers and linkage procedures have been previously described in detail.[165-167]

In addition, we identified patients who were not admitted to the hospital because they died outside the hospital either primarily or secondarily from first-ever stroke through the cause of death register using ICD-10 codes (Table 1).

From 2005 onwards fewer hospitals participated in the HDR, leading to an increasing number of missing records. In 2005 1.1% of records were missing, whereas between 2006 and 2010 the percentage of missing records varied between 10.5 and 14.0%. The estimated number of actual strokes by Statistics Netherlands is listed in the Supplementary Material 1, as well as an overview of contributing centers, and a table concerning the regional coverage of the HDR from 2006 to 2010 (Supplementary Table 1-3).

Case definition

Any stroke was defined as a first-ever hospitalization for ischemic stroke, intracerebral hemorrhage or unspecified stroke (either ischemic or hemorrhagic, but not specified as such) or out-of-hospital death due to first-ever stroke. We defined young adults as those aged between 18 to 50 years old at the time of stroke and the reference group as those aged ≥50 years.

Data analysis

We calculated the crude age-, sex-, and stroke subtype- specific incidence per 100,000 person-years for each consecutive year from 1998 to 2010. For this, we used the age-, sex- and year- specific population estimates from Statistics Netherlands.[168]

We assessed age-specific differences in stroke incidence between men and women by calculating incidence rate ratio's (IRR) including 95% confidence intervals based on Poisson distribution.

We also calculated the relative proportions of stroke subtypes in young adults according to age- and sex-strata and under the age of 50 in the stroke population and compared differences herein by chi-squared test of proportions.

Finally, we calculated the 13-year relative change in incidence for each age- and sex-subgroup by using the following formula: (incidence 2010 - incidence 1998)/incidence 1998, and tested for significant trends in incidence rates over time by linear regression, by age- and sex-subgroup for individuals 18-50 years and those ≥ 50 years.

Table 1. Overview of used ICD-9 and ICD-10 codes

ICD-9	
Any stroke	
431	Intracerebral hemorrhage
433	Occlusion and stenosis of pre-cerebral arteries with/without cerebral infarction
434	Occlusion of cerebral arteries with/without cerebral infarction
436	Stroke, unspecified as hemorrhagic or infarction
Intracerebral hemorrhage	
431	Intracerebral hemorrhage
Ischemic stroke	
433	Occlusion and stenosis of pre-cerebral arteries with/without cerebral infarction
434	Occlusion of cerebral arteries with/without cerebral infarction
Unspecified stroke	
436	Stroke, unspecified as hemorrhagic or infarction
ICD-10	
Any stroke	
I61	Intracerebral hemorrhage
I63	Cerebral infarction
I64	Stroke, unspecified as hemorrhagic or infarction
Intracerebral hemorrhage	
I61	Intracerebral hemorrhage
Ischemic stroke	
I63	Cerebral infarction
Unspecified stroke	
I64	Stroke, unspecified as hemorrhagic or infarction

Abbreviations: ICD, International Classification of Diseases.

We used SPSS Software version 22, R version 3.2.2 (*Package rateratio.test*), MedCalc statistical software 2018 and Microsoft Office Excel 2007.

Data Availability

All data used for analysis are presented in the tables and supplementary tables. Data will be shared after ethics approval if requested by other investigators for purposes of replicating the results.

Standard protocol approvals

This study was performed according to the guidelines of the local research ethics committees.

Table 2. Results of validation procedure

Ischemic stroke	Intracerebral hemorrhage	Unspecified stroke
Total N		
301	183	85
Correct diagnosis, N (%)		
272 (90.4%)	158 (86.3%)	74 (87.1%)
Incorrect diagnoses N (%)		
29 (9.4%)	25 (13.7%)	11 (12.9%)
5 (1.7%) - conversion	4 (2.2%) - traumatic ICH	4 (4.7%) - conversion
4 (1.3%) - vestibulopathy	10 (5.5%) - PMH	3 (3.5%) - neoplasm
3 (1.0%) - TIA[a]	3 (1.6%) - SAH	2 (2.4%) - TIA
3 (1.0%) - ICH[b]	8 (4.4%) - ischemic stroke	1 (1.2%) - traumatic ICH
3 (1.0%) - SAH[c]		1(1.2%) - CADASIL[g]
2 (0.7%) - neoplasm		
2 (0.7%) - encephalitis / meningitis		
1 (0.3%) - migraine with aura		
1 (0.3%) - HaNDL syndrome[d]		
1 (0.3%) - SUSAC syndrome		
1 (0.3%) - subdural hematoma		
1 (0.3%) - MS[e]		
1 (0.3%) - PMH[f]		
1 (0.3%) - traumatic ICH		

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; HaNDL syndrome, headache and neurologic deficit with CSF lymphocytosis; ICH, intracerebral hemorrhage; MS, multiple sclerosis; PMH, perimesencephalic hemorrhage; SAH, subarachnoid hemorrhage.

RESULTS

We identified 15,257 cases of first-ever stroke in adults aged 18 to 50 years old, between 1998 and 2010. Of these 8444 (55.3%) were ischemic stroke, 3077 (20.2%) were intracerebral hemorrhage, and 3736 (24.5%) were unspecified stroke. 53% of all strokes occurred in women. Mean age at first-ever any stroke was 41.4 (SD 7.0) years for women and 42.3 (SD 6.5) years for men. Less than 1% of cases were out-of-hospital deaths.

Sex-specific variation in age at first-ever stroke

The incidence of first-ever any stroke in young adults increased exponentially with age in both sexes (R^2=0.98 in men and R^2=0.99 in women, R^2 is a measure of how close data-points fit a regression line, which in this case indicates an exponential increase). In all age-strata the incidence in women was higher than in men, except in those aged 44-49 years (Table 3). The IRR of women compared to men declined with age from 1.93 (95% CI 1.62-2.31) in 18-24 year olds to 1.06 (95% CI 1.01-1.11) in 45-49 year olds for any stroke. No age-related decline was found for intracerebral hemorrhage (Table 4).

Sex-specific distribution of stroke subtypes in the different age-strata

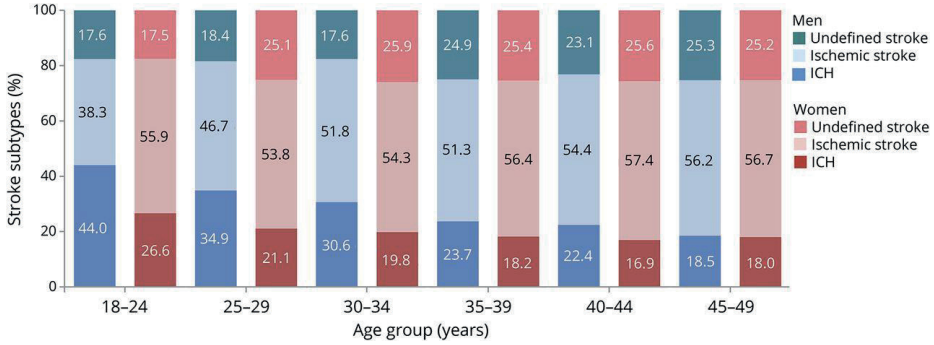
The proportion of ischemic stroke in the different age groups was significantly different for those aged 18-24 years old, 38.3% in men and 55.9% in women (p<0.001), and those aged 35-39 years old, 51.3% in men and 56.4% in women (p=0.018), but not for the other age-strata. In men, the relative percentage of intracerebral hemorrhage was significantly higher than that in women in the same age-category in younger age-strata, namely 44.0% in men and 26.6% in women aged 18-24 years old (p<0.001) and 34.9% versus 21.1% in those aged 25-29 years old (p<0.001). Similarly results were seen for the age-strata 30-34 years olds (p<0.001), 35-39 years old (p=0.002), 40-44 years olds (p<0.001). There was no significant difference in the relative percentage of intracerebral hemorrhage for men and women aged 45-49 years old, 18.5% in men and 18.0% in women (p=0.591). The percentage of unspecified stroke was significantly different in those aged 30-34 years old, 17.6% in men and 25.9% in women (p<0.001) (Figure 1).

Sex- and age-specific time trends in the incidence of any stroke

Any stroke incidence among young adults increased from 14.0 per 100,000 person-years in 1998 to 17.2 per 100,000 person-years in 2010, resulting in a relative change of 23% (p<0.001). This increase was present across all age strata over 35 years old, but not in patients aged 18-34 years (Table 3, Figure 2A). The increase of any stroke incidence was observed both in men (23% increase; p<0.001) and in women (17% increase; p<0.001), and most prominently in those aged 44 to 49 years. In contrast, in patients aged 50 years or older, the incidence of first-ever any stroke declined from 329.1 per 100,000

person-years in 1998 to 292.2 per 100,000 person-years in 2010, a relative decrease of 11% (p=0.009; Table 3). The proportion of strokes in young adults of the total number of strokes across all ages increased significantly over time from 13.3% in 1998 to 15.5% in 2010 (p<0.001).

Figure 1: Sex- and age-specific distribution of stroke subtypes



Abbreviations: ICH, Intracerebral hemorrhage.

Sex-specific time trends of incidence by stroke subtype

In young adults, the incidence of ischemic stroke increased by 46% from 7.4 in 1998 to 10.8 per 100,000 person-years in 2010 (p<0.001). In women, the incidence of ischemic stroke increased from 8.9 in 1998 to 12.1 per 100,000 person-years in 2010, a relative change of 37% (p<0.001) and in men from 6.0 to 9.5 per 100,000 person-years, a relative change of 60% (p<0.001) (Table 5, Figure 2B).

The incidence of intracerebral hemorrhage and of unspecified stroke remained stable over the course of 13 years (Table 5, Figure 2C and 2D), without any sex differences.

Table 3. Sex-specific incidence of any stroke from 1998-2010

	Incidence per 100,000 person-years[a]						
Age in years (y)	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
18-49 y	13.99	14.00	14.51	14.76	15.26	15.80	16.64
men	12.13	12.70	13.49	13.01	13.67	15.48	16.06
women	15.93	15.34	15.56	16.56	16.89	16.12	17.24
Any ages	105.39	105.11	103.12	104.15	110.75	111.84	115.81
men	104.96	104.21	101.24	102.80	109.80	110.35	116.33
women	105.81	105.99	104.96	105.48	111.68	113.30	115.31
18-24 y	2.36	2.31	2.92	2.69	2.31	2.52	2.51
men	2.18	1.76	1.92	2.80	2.20	2.48	2.19
women	2.54	2.87	3.94	2.58	2.42	2.56	2.85
25-29 y	4.40	3.97	3.66	5.09	4.57	3.88	4.76
men	2.32	2.72	2.19	3.37	3.52	2.31	3.15
women	6.56	5.26	5.16	6.85	5.64	5.47	6.38
30-34 y	7.29	5.87	7.61	7.44	8.37	7.10	7.90
men	6.08	4.92	6.70	4.91	6.73	6.55	6.48
women	8.56	6.87	8.56	10.06	10.07	7.67	9.34
35-39 y	10.90	12.73	12.55	10.92	11.96	11.93	14.20
men	7.56	12.13	10.15	8.86	10.17	11.69	13.88
women	14.35	13.35	15.03	13.06	13.82	12.17	14.54
40-44 y	23.79	22.87	23.47	21.61	22.91	23.99	25.44
men	22.81	19.85	22.46	18.38	19.95	24.62	23.35
women	24.79	25.96	24.50	24.94	25.95	23.34	27.58
45-49 y	39.57	40.34	40.11	43.84	43.45	46.74	45.30
men	35.95	38.75	41.02	42.89	41.51	46.44	47.58
women	43.33	41.98	39.17	44.83	45.43	47.04	42.97
≥ 50 y	329.08	322.92	311.66	311.36	328.18	327.11	334.03
men	355.07	344.92	327.83	329.52	347.61	341.94	355.33
women	307.02	304.13	297.75	295.67	311.29	314.14	315.31

[a] Incidence per 100,000 person-years calculated with Dutch population estimates.

[b] Change = (Incidence 2010 - Incidence 1998) / Incidence 1998.

[c] Time trends tested by linear regression.

2005	2006	2007	2008	2009	2010	Change[b]	Time trend[c]
17.60	16.73	16.81	16.61	17.07	17.24	0.23	**p<0.001**
16.10	15.71	15.99	14.52	16.72	15.64	0.29	**p=0.001**
19.14	17.77	17.64	18.74	17.43	18.86	0.18	**p<0.001**
117.37	108.50	103.22	102.33	109.64	111.27	0.06	p=0.450
117.62	109.40	102.97	101.12	109.30	111.37	0.06	p=0.359
117.12	107.61	103.46	103.50	109.97	111.17	0.05	p=0.581
2.43	2.36	2.72	2.77	2.28	3.29	0.40	p=0.232
1.60	2.47	2.18	1.87	2.11	2.21	0.01	p=0.919
3.28	2.24	3.29	3.70	2.46	4.41	0.73	p=0.251
5.14	5.04	4.75	4.34	3.53	4.20	-0.05	p=0.949
3.82	4.22	3.43	2.42	2.41	3.98	0.71	p=0.207
6.47	5.86	6.07	6.28	4.66	4.43	-0.32	p=0.245
8.73	9.33	7.77	6.83	6.35	7.20	-0.01	p=0.808
8.69	6.04	6.74	5.85	3.96	5.99	-0.01	p=0.880
8.77	12.64	8.80	7.80	8.73	8.42	-0.02	p=0.699
14.31	12.69	14.20	12.71	13.50	13.21	0.21	**p=0.029**
13.63	11.93	11.77	9.98	14.02	11.84	0.57	p=0.060
15.00	13.47	16.68	15.47	12.99	14.59	0.02	p=0.403
25.69	24.87	25.12	25.33	25.63	23.75	0.00	**p=0.023**
23.39	23.11	26.22	21.66	26.54	21.35	-0.06	p=0.126
28.06	26.68	23.99	29.10	24.69	26.21	0.06	p=0.314
48.68	44.66	43.70	44.37	47.19	47.73	0.21	**p=0.003**
44.75	44.78	42.74	42.15	46.65	44.76	0.24	**p=0.014**
52.67	44.54	44.67	46.63	47.74	50.75	0.17	**p=0.019**
333.01	302.36	281.91	275.17	291.66	292.20	-0.11	**p=0.009**
353.71	322.11	295.46	286.80	303.84	306.66	-0.14	**p=0.006**
314.75	284.87	269.85	264.79	280.73	279.18	-0.09	**p=0.014**

Table 4: Sex- and age-specific incidence of stroke subtypes

	Male incidence[a] (N)	py[b] at risk	Female incidence[a] (N)
Any stroke			
18-24 y	2.15 (193)	8974907	3.02 (263)
25-29 y	3.03 (212)	6985800	5.78 (398)
30-34 y	6.15 (483)	7859303	8.94 (687)
35-39 y	11.34 (966)	8515778	14.19 (1175)
40-44 y	22.63 (1888)	8342998	25.85 (2102)
45-49 y	43.14 (3385)	7846997	45.62 (3505)
Ischemic stroke			
18-24 y	0.82 (74)	8974907	1.69 (147)
25-29 y	1.42 (99)	6985800	3.11 (214)
30-34 y	3.18 (250)	7859303	4.87 (374)
35-39 y	5.82 (496)	8515778	8.00 (662)
40-44 y	12.32 (1028)	8342998	14.84 (1207)
45-49 y	24.26 (1904)	7846997	25.89 (1989)
Intracerebral hemorrhage			
18-24 y	0.95 (85)	8974907	0.80 (70)
25-29 y	1.06 (74)	6985800	1.22 (84)
30-34 y	1.88 (148)	7859303	1.76 (135)
35-39 y	2.69 (229)	8515778	2.60 (215)
40-44 y	5.07 (423)	8342998	4.38 (356)
45-49 y	7.98 (626)	7846997	8.23 (632)
Unspecified stroke			
18-24 y	0.38 (34)	8974907	0.53 (46)
25-29 y	0.56 (39)	6985800	1.45 (100)
30-34 y	1.08 (85)	7859303	2.32 (178)
35-39 y	2.83 (241)	8515778	3.60 (298)
40-44 y	5.24 (437)	8342998	6.63 (539)
45-49 y	10.90 (855)	7846997	11.51 (884)

[a] Incidence per 100,000 person-years calculated with Dutch population estimates.

[b] Person years at risk over 13 years (1998-2010).

[c] IRR, incidence rate ratio; CI, confidence interval.

py[b] at risk	IRR (95% CI)[c] of women compared to men	p-value
8722640	1.93 (1.62-2.31)	**p<0,001**
6882795	1.91 (1.61-2.26)	**p<0,001**
7680769	1.46 (1.29-1.63)	**p<0,001**
8280089	1.25 (1.15-1.36)	**p<0,001**
8131226	1.14 (1.07-1.22)	**p<0,001**
7683179	1.06 (1.01-1.11)	**p=0.021**
8722640	2.04 (1.54-2.74)	**p<0,001**
6882795	2.19 (1.72-2.81)	**p<0,001**
7680769	1.53 (1.30-1.80)	**p<0,001**
8280089	1.37 (1.22-1.31)	**p<0,001**
8131226	1.20 (1.11-1.31)	**p<0,001**
7683179	1.07 (1.00-1.14)	**p=0.045**
8722640	0.85 (0.61-1.18)	p=0.343
6882795	1.15 (0.83-1.60)	p=0.418
7680769	0.93 (0.73-1.19)	p=0.603
8280089	0.97 (0.80-1.17)	p=0.748
8131226	0.86 (0.75-1.00)	**p=0.045**
7683179	1.03 (0.92-1.15)	p=0.061
8722640	1.39 (0.87-2.22)	p=0.174
6882795	2.60 (1.78-3.87)	**p<0,001**
7680769	2.14 (1.65-2.81)	**p<0,001**
8280089	1.27 (1.07-1.51)	**p=0.006**
8131226	1.27 (1.11-1.44)	**p<0,001**
7683179	1.06 (0.96-1.16)	p=0.266

Table 5. Sex-specific incidence of stroke subtypes in young adults (<50 years) from 1998-2010

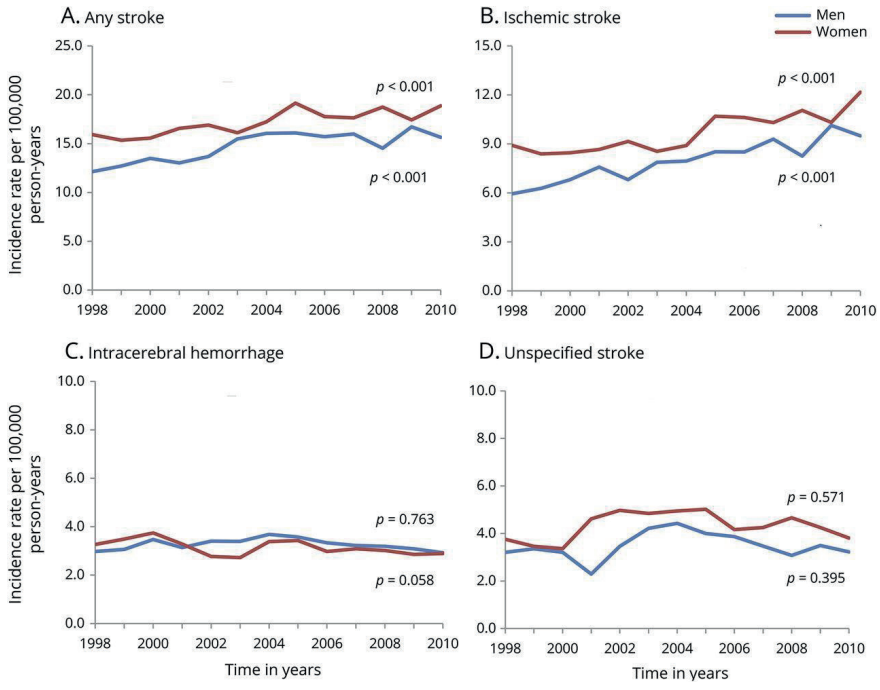
	Incidence per 100,000 person-years[a]					
Stroke subtype	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**
Ischemic stroke	7.40	7.32	7.62	8.11	7.96	8.21
Men	5.95	6.29	6.81	7.59	6.81	7.87
Women	8.91	8.39	8.46	8.66	9.15	8.55
Intracerebral hemorrhage	3.12	3.27	3.60	3.21	3.09	3.06
Men	2.97	3.06	3.47	3.14	3.40	3.39
Women	3.27	3.49	3.74	3.28	2.77	2.72
Unspecified stroke	3.48	3.41	3.28	3.44	4.20	4.53
Men	3.21	3.35	3.21	2.29	3.46	4.22
Women	3.75	3.46	3.36	4.61	4.97	4.85

[a] Incidence per 100,000 person-years calculated with Dutch population estimates.

[b] Change = (Incidence 2010 - Incidence 1998) / Incidence 1998.

[c] Time trend tested by linear regression.

Figure 2. Time trends in incidence of stroke and stroke subtypes in young adults from 1998 to 2010



Incidence per 100,000 person-years calculated with Dutch population estimates [18]

P-values calculated *by linear regression*

2004	2005	2006	2007	2008	2009	2010	Change (%)[b]	Time trend[c]
8.42	9.60	9.55	9.80	9.64	10.23	10.82	46.22	**p<0.001**
7.95	8.52	8.51	9.29	8.25	10.13	9.49	59.50	**p<0.001**
8.91	10.70	10.62	10.31	11.06	10.32	12.16	36.48	**p<0.001**
3.54	3.50	3.16	3.16	3.10	2.97	2.91	-6.73	p=0.143
3.68	3.57	3.33	3.23	3.19	3.08	2.92	-1.68	p=0.763
3.39	3.43	2.98	3.08	3.02	2.85	2.89	-11.62	p=0.058
4.68	4.51	4.02	3.86	3.87	3.87	3.52	1.15	p=0.384
4.43	4.00	3.87	3.47	3.08	3.50	3.23	0.62	p=0.571
4.94	5.02	4.17	4.25	4.66	4.25	3.81	1.60	p=0.395

DISCUSSION

This study shows that in young adults the risk of stroke increased exponentially with age, with women more often affected than men in all age strata. The relative distribution of stroke-subtypes was similar in women in all age-strata with ischemic stroke occurring two to three times more frequently than intracerebral hemorrhage. In men the proportion of intracerebral hemorrhages was relatively high in younger age-strata, and declining with increasing age. In young adults, the incidence of ischemic stroke but not of intracerebral hemorrhage and unspecified stroke increased by almost 50% between 1998 and 2010, while the incidence of stroke in older patients decreased by 11%.

We found a relatively high increase of 46% in the incidence of ischemic stroke over a 13-year period among young adults, where previous studies reported percentages varying from 4.7% to 74%.[4, 9, 68, 169-171] Differences may be explained by variation in the definition of patient groups (due to inclusion of different ICD-codes) and the chosen lower- and upper age-limits that ranged from as low as 15 to as high as 60 years.[4-11] In our study the increase in stroke incidence was limited to ischemic stroke; incidence was stable for those with an intracerebral hemorrhage and for those younger than 35 years old at their first event. In contrast, others found a clear increase in incidence in those younger than 30 years old. This might be partially explained by smaller patient numbers, hospital based settings, or a broader definition of stroke also including subarachnoid hemorrhage, TIA, other cerebrovascular disorders and sequelae of stroke (ICD-9 codes 430-438).[5] Incidences and rates of increase may also vary in different parts of the world because of differences in genetic profile and occurrence and control of (cardiovascular) risk factors.[4, 9, 170]

There are several possible factors that may contribute to the increased incidence of stroke in young adults over the past two decades. First, we may diagnose stroke more often because of the improvement and accessibility of neuroimaging and the development of stroke sensitive techniques, such as diffusion weighted MR imaging, that allow for rapid and reliable detection of acute infarcts. This explanation is supported by studies that showed an increased incidence of stroke in young adults that coincided with the increased use of MRI during their study period, in particular in young adults who more often had MRI in later years of these studies.[4, 161] However, if the application of MRI would have had a large influence in our study, we would have expected an increase in incidence across all young stroke age-strata, and perhaps even more in the youngest age-strata. In contrast, we found a significant increase of stroke incidence only in those ***over*** 35 years old. Therefore, the implementation of MRI seems to only partially explain the increase in incidence of ischemic stroke. A second explanation is an increased prevalence of traditional vascular risk factors already among children

and young adults that could lead to atherosclerosis early in life and subsequently to stroke.[5, 34] The effects of these risk factors are likely to become more prominent with aging, which is supported by findings of a higher prevalence of vascular risk factors in patients aged 45-49 years compared to younger participants in The Helsinki Young Stroke Registry and compatible with the increase in incidence in patients over 35 years.[3, 172] Third, other risk factors may have gained importance over the last decade, including illicit drug use. In the Netherlands, the number of young adults who used illicit drugs before their ischemic stroke has been reported to increase from 3.8% in 1993 to 19.8% in 2005.[173-175] The increase in incidence is unlikely attributable to a shift from outpatient to clinical work-up, because according to protocols during our study period nearly all young patients with neurological deficits would have been referred to a neurologist by general practioners in the Netherlands. Furthermore, the ICD codes used include both outpatient and inpatient diagnosis of a stroke. If the increase would be due to increased hospitalization, we would have expected the increase to occur across all age-strata.

We do not see an increase in incidence for intracerebral hemorrhage, that was already detectable with CT in contrast with ischemic stroke that is now more easily diagnosed with help of MRI-DWI. Also intracerebral hemorrhage has a different etiology and is particularly in young patients often due to structural vessel abnormalities, that are less likely to be influenced by the increasing prevalence of modifiable, tradiational risk factors like obesity and hypercholesterolemia, that do play an important role in the pathogenesis of ischemic strokes.

We found clear sex-differences in both the overall occurrence and age-related increase in the incidence of stroke in young adults, women being more often affected than men in all age strata. Previous studies have yielded conflicting results, some showing no difference or only in a specific age group, others showing a higher incidence in men, yet again possibly explained by differences in study design, age limits and stroke definition.[3, 5, 6, 8-11, 176] Differences in prevalence of (women-specific) risk factors between men and women may also contribute to the varying incidences for men and women in the different study populations.[3, 5, 6, 8-11, 176]

A possible explanation for the excess risk of stroke in young women may be found in risk-factors that are more prevalent in women, such as migraine with aura, auto-immune disorders like the anti-phospholipids syndrome or systemic lupus erythematosus (SLE), or women-specific such as pregnancy or the use of oral anti-conception, especially in combination with smoking.[36, 161, 177] Because the prevalence of these women-specific risk factors is very low and the exact effect size of their role in incidence unclear, other, yet unknown hormonal factors or genetic differences may also contribute.

Strengths of our study include the large sample size of the cohort, the fact that it was nation-wide, and included patients over a period of more than a decade. The large sample enabled us to perform age-, sex- and stroke subtype specific subgroup analyses. In addition, we were able to investigate the changes of incidence of stroke in young adults over a 13-year period. Finally, we created a cohort of well-defined stroke subtypes, whereas many previous studies were more heterogeneous with the inclusion of transient ischemic attack (TIA), subarachnoid hemorrhage (SAH), unspecified intracranial hemorrhage, several other cerebrovascular diseases and even sequelae of cerebrovascular disorders. We excluded SAH and unspecified intracranial hemorrhage based on their distinct underlying etiologies. Finally, we validated the ICD-codes for young stroke patients specifically.

Our study also has some limitations. First, we could not further specify stroke etiology, e.g. with TOAST classification, or look at underlying causes of intracerebral hemorrhage. Additionally, there was a substantial number of strokes in our cohort classified as unspecified, meaning that the stroke could either be ischemic or hemorrhagic.[58] Through our validation of the ICD-codes in young stroke patients in several Dutch medical centers, we found 90.5% of unspecified stroke were in fact ischemic strokes and 9.5% were intracerebral hemorrhages (Table 2). Therefore, it is most likely that the vast majority of these unspecified strokes were in fact ischemic strokes and could be added to this group for trend-analysis. However we chose to analyze the groups separately, thereby safeguarding the purity of the data. Furthermore, the incidence of unspecified stroke did not increase, whereas the incidence of ischemic stroke increased, which may be explained by a more reliable differentiation between ischemic stroke and intracerebral hemorrhage through the implementation of improved imaging techniques, such as the (DWI) MRI, leaving less strokes being classified as unspecified.

Second, we may have overestimated the total number of first-ever strokes because we had no information on strokes prior to 1998 and therefore may have misclassified some recurrent strokes as first-ever strokes. As the risk of recurrent stroke decreases by the number of years of event free survival after the first-ever stroke, the chance of misclassification of a recurrent stroke as first-ever stroke becomes increasingly less likely over time, particularly for the later years of our study.[178, 179] Third, because fewer hospitals contributed to the HDR register from 2006 onwards, the data is less reliable for estimating nationwide incidence after 2005. As a consequence, the rate of the increase of the incidence of stroke between 1998 and 2010 may have been underestimated. However, since there is no reason to assume these 'missing records' are not missing at random, this will most likely have led to underestimation of the

observed temporal trends of stroke incidence between 2006 and 2010 and does not affect subgroup-analyses for specific age-strata or sex comparisons performed within each year. Stroke care is provided throughout the Netherlands, so it is unlikely that when some centers no longer provide their discharge data this would lead to a specific loss of intracerebral hemorrhage diagnoses or ischemic stroke diagnoses. Finally, we may have missed non-fatal strokes for which patients were not admitted to a hospital. This may have led to underestimation of the incidence estimates but is unlikely to affect subgroup-analyses and time-trends.

If the observed rise in incidence of ischemic stroke in young adults continues, the estimated number of strokes in young adults will have nearly doubled by 2020 in comparison to 2000. This will have large socio-economic consequences. We urgently need to identify the main factors that have led to the increased incidence with a view to counter this worrisome trend. Further investigations of trigger factors, women-specific risk factors and genetic causes may shed further light on the cause of stroke in the young.[180] The continuing increase of stroke in young adults asks for immediate public health strategies, including programs for better awareness of risk factors for vascular disease, already among young adults. This study shows a steep increase in the incidence of ischemic stroke in young adults over time, especially in those aged 35 to 50 years and with a higher incidence in women than in men. The pronounced female predominance in stroke incidence among young adults warrants specific attention to this group.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Estimated number of actual strokes according to Statistics Netherlands

	2006[a]	2007	2008	2009	2010
Estimated 'actual' total of all stroke admissions in HDR	25,066	24,456	24,736	25,625	26,538
Number of 'actual' supplied records of all stroke admissions in HDR	22,568	21,479	21,245	22,450	22,885
Number of 'missing records' for all stroke admissions	2498	2977	3491	3175	3653
Percentage completeness of all stroke records	90.03%	87.83%	85.89%	87.61%	86.23%

[a] Percentages of supplied admissions only available from 2006 onwards

Supplementary Table 2. HDR Coverage from 1998 to 2010

			Coverage of hospital admissions in HDR from supplying centers*:							
	Coverage of hospital admissions in HDR from supplying centers	Coverage of hospital admissions in HDR after linkage to PR[a]	Academic hospitals (N complete / N total)	% of complete records[b]	General hospitals (N complete / N total)	% of complete records[b]	Specialist medical centers (N complete / N total)	% of complete records[b]	Teaching general hospitals (N complete / N total)	% of complete records[b]
1998	98.41%	84.1%	7 / 8		88 / 89		7 / 9		14 / 15	
1999	98.78%	84.2%	8 / 8		87 / 89		7 / 8		15 / 15	
2000	98.54%	84.4%	8 / 8		80 / 86		5 / 7		15 / 15	
2001	98.59%	84.5%	8 / 8		79 / 81		5 / 6		16 / 16	
2002	99.00%	84.6%	7 / 8		75 / 77		5 / 6		18 / 18	
2003	98.94%	84.7%	7 / 8		69 / 71		5 / 6		17 / 19	
2004	98.50%	84.8%	8 / 8		69 / 71		4 / 5		17 / 19	
2005	96.20%	85.2%	7 / 8		61 / 69		2 / 3		18 / 19	
2006	89.02%	85.3%	6 / 7	89.4%	50 / 55	85.0%	2 / 3	85.1%	17 / 18	98.9%
2007	87.54%	85.4%	6 / 7	92.5%	48 / 49	81.7%	2 / 3	75.4%	21 / 23	94.8%
2008	87.55%	85.4%	8 / 8	100%	42 / 44	80.9%	1 / 2	41.1%	19 / 22	94.3%
2009	86.79%	85.6%	7 / 8	95.2%	42 / 44	80.8%	1 / 2	42.4%	16 / 21	93.4%
2010	85.62%	85.6%	6 / 8	84.9%	38 / 43	83.7%	1 / 2	44.5%	17 / 21	90.0%

[a] Percentage of all hospital admissions in the HDR that can be linked to the PR through basic personal identifiers such as sex, date of birth and zip-code to facilitate analyses on a person-level instead of on admission-level.

[b] Percentages of supplied admissions only available from 2006 onwards

Supplementary Table 3. Regional coverage of HDR from 2006 to 2010

Dutch provinces	2006 [a]	2007	2008	2009	2010
Drenthe	74.84%	76.39%	77.10%	76.73%	77.49%
Flevoland	100%	100%	100%	78.69%	47.41%
Friesland	83.06%	100%	99.17%	100%	100%
Gelderland	95.02%	95.21%	91.03%	96.28%	96.44%
Groningen	90.77%	90.32%	91.06%	91.24%	100%
Limburg	100%	100%	100%	91.74%	90.46%
Noord-Brabant	82.92%	84.44%	79.61%	78.02%	69.05%
Noord-Holland	82.95%	81.41%	90.28%	88.87%	86.53%
Overijssel	85.89%	74.70%	73.98%	72.32%	75.78%
Utrecht	98.95%	99.01%	99.07%	99.11%	99.16%
Zeeland	100%	85.79%	67.40%	65.08%	55.29%
Zuid-Holland	91.67%	86.71%	86.93%	87.43%	89.15%

[a] Percentages of supplied admissions only available from 2006 onwards

Chapter 5

Risk factors and etiology of ischemic stroke in 1322 young adults

Revisions for *Stroke*:

Ekker MS, Verhoeven JI, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers PJAM, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, de Kort PLM, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Zonneveld TP, Kerkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, Klijn CJM, Tuladhar AM, de Leeuw FE.

Risk factors and etiology of ischemic stroke in 1322 young adults.

ABSTRACT

Objectives: To identify risk factors and leads for (new) causes of cryptogenic ischemic stroke in young adults using the pediatric classification system from the International Pediatric Stroke Study (IPSS) in patients with cryptogenic stroke according to current classification systems (Trial of Org 10172 in Acute Stroke Treatment (TOAST) and atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection (ASCOD)).

Methods: Multicenter prospective cohort study in 17 hospitals in the Netherlands, consisting of 1322 patients aged 18-49 years with first-ever, imaging confirmed, ischemic stroke, between 2013 and 2021. Main outcome was distribution of risk factors according to IPSS classification in patients with cryptogenic and non-cryptogenic stroke according to the TOAST and ASCOD classification.

Results: The median age was 44.2 years, and 697 (52.7%) were men. Of these 1322 patients, 333 (25.2%) had a cryptogenic stroke according to the TOAST classification. Additional classification using the ASCOD criteria reduced the number patients with cryptogenic stroke from 333 to 260 (19.7%). When risk factors according to the IPSS were taken into account, the number of patients with no potential cause or risk factor for stroke reduced to 10 (0.8%).

Interpretation: Among young adults aged 18-49 years with a cryptogenic ischemic stroke according to the TOAST classification, risk factors for stroke are highly prevalent. Using a pediatric classification system provides new leads for the etiology in cryptogenic stroke, and could potentially lead to more tailored treatment for young individuals with stroke.

INTRODUCTION

An estimated 10-15% of all strokes occur in young adults (18-49 years), resulting in about two million young adults who are affected by stroke worldwide every year, with incidence increasing over the past decade.[1, 3, 181] Stroke at young age comes with high socio-economic costs and patients encounter lifelong consequences.[3, 50] Rapid identification of causes and risk factors of ischemic stroke in young adults is key to optimize treatment and prevent recurrence. Still, in up to one third of all cases with ischemic stroke at young age, no clear cause is identified after thorough clinical work-up and the use of stroke classification schemes such as the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and the ASCOD classification (atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection).[7, 12, 43, 182]

However, these classifications have been developed for ischemic stroke patients often older than 65 years. They have gradually been implemented in clinical practice of patients with stroke at younger ages, without any formal evaluation and validation in this specific domain. This may result in unjustified classification of patients with a cryptogenic stroke, while in fact causes or risk factors for stroke are present that are *not* recognized as such within the conventional developed classification schemes. In addition, the currently used classifications lump patients with diverse and rare causes and underlying pathophysiological mechanisms into one "other determined" category, thereby ignoring the possible different long-term prognosis of stroke depending by the different causes.

In contrast to the classification schemes used in adults, the classification developed for childhood- and adolescent stroke by the International Pediatric Stroke Study (IPSS) designates not one single cause of stroke. The IPSS allows multiple risk factor categories that are not mutually exclusive and recognizes age-specific presumed risk factors and etiologies that are not included in the TOAST and ASCOD.[183] Although a risk factor is not necessarily synonymous with a cause, rapid identification of risk factors is an important step to initiate treatment and counseling of patients.

We therefore investigated the causes and risk factors of stroke in young adults in a prospective cohort study of young patients with imaging proven ischemic stroke according to the TOAST, ASCOD and IPSS criteria to search for clues that help find potential causes in cryptogenic stroke.

METHODS

This study is part of the Observational Dutch Young Symptomatic StrokE studY (ODYSSEY), a Dutch multicenter prospective cohort study in 17 centers on the risk factors and prognosis of patients with a first-ever ischemic stroke or intracerebral hemorrhage (ICH) aged 18-49 years. Details of the study have been described previously.[29] For this study, we included patients with ischemic stroke and TIA. Patients were included consecutively between May 2013 until end of inclusion in February 2021.

In short, our study comprises consecutive patients aged 18-49 years with first-ever symptomatic ischemic stroke with radiological evidence of cerebral ischemia. Patients with transient symptoms (<24 hours) all had diffusion weighted imaging positive lesions (DWI+) on MRI and as such were included as (minor) stroke according to the tissue based definition.[184]

Baseline data collection

Information on (vascular) risk factors, stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) on admission and modified Ranking scale (mRS) at discharge, treatment in the acute phase and at discharge were systematically collected as were results of neuroimaging, laboratory and cardiac diagnostic tests. Case-fatality was defined as death within the first 30 days after stroke. In addition, patients completed a standardized structured questionnaire on level of education, marital status, employment and additional potential risk factors such as illicit drug use.

Risk factors and causes of stroke

Patient's medical files, including risk factors and the cause of ischemic stroke, were systematically assessed for all patients by one of four raters (ME, JV, MS or EB) according to the modified TOAST criteria, (including a subdivision into high-risk and medium-risk sources of cardio-embolism and in large artery atherosclerosis and likely atherothrombotic disease)[185, 186] (further referred to as TOAST), ASCOD criteria[182], and modified IPSS criteria (referred to as IPSS)[183] (Supplementary Table 1). In case of doubt or disagreement of a risk factor of cause, a consensus meeting was held with a vascular neurologist (FEdL). The adjudicated causes and risk factors for stroke according to the TOAST, ASCOD and IPSS classification were reviewed by two separate raters in the first 100 patients with an inter-rater agreement of 98%.

Statistical analyses

We reported categorical variables as numbers and frequencies unless otherwise stated. Continuous variables were reported as median and interquartile range (IQR). Age- and sex-specific analyses for etiology and risk factors were performed by predefined age-groups: 18-25, 26-30, 31-35, 36-40, 41-45, and 46-49 years.

Categorical variables were compared through Pearson's Chi-squared or Fisher's Exact tests, whichever was appropriate. Continuous variables were compared by Student's t test or Mann Whitney U test and the Kruskal-Wallis test was used for comparing median age, NIHSS and mRS between men and women and between stroke subtypes.

For all analyses two-sided p-values of <0.05 were considered statistically significant. Data were analyzed using SPSS Software version 22 (IBM), R version 3.6.2 (R Project for Statistical Computing) and Microsoft Office Excel 2007.

Ethical approval

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). Informed consent was obtained for all patients. Additional approval was obtained for Inclusion of patients that died within the first 30 days after stroke without informed consent for those who had been unable to provide informed consent.

Data availability

The raw and anonymized data used in this study can be shared upon and after permission of our Institutional Review Board. Written proposals can be addressed to the corresponding author and will be assessed by ODYSSEY investigators for appropriateness of use, and a data sharing agreement in accordance with Dutch regulations will be put in place before data are shared.

RESULTS

Demographics

1223 (92.5%) patients had an ischemic stroke with symptoms lasting longer than 24 hours, 99 (7.5%) with symptoms less than 24 hours. Median age was 44.2 years (IQR 38.4-47.5), 697 were men (52.7%), and 38 (2.9%) patients died within the first 30 days (case fatality) (Table 1). Work-up was according to clinical practice and local protocols for young patients with stroke including neuro-imaging for all patients: 1114 (84.3%) patients underwent CT, 1160 (87.7%) underwent MRI, 953 (72.1%) both CT and MRI, 96.0% had imaging of the carotid arteries (658 (49.8%) CTA, 627 (47.4%) MRA, 517 (39.1%) an ultrasound of the carotids). An ECG was made in 1279 patients (96.7%), 1131 patients had a least 24 hours of cardiac rhythm monitoring (85.5%), 1071 patients (81.0%) had a transthoracic echocardiography (TTE) and 249 patients (18.8%) underwent a transesophageal echocardiography (TEE). Of the 213 patients (16.1%) that did not receive any cardiac ultrasound, 31 patients (2.3%) had no clear cause for their stroke. The other 182 patients (13.8%) without cardiac ultrasound had a clear other cause of stroke, deeming cardiac ultrasound unnecessary for the etiologic diagnosis. Laboratory diagnostics for antiphospholipid syndrome[187] was performed in >70% of all patients.

Table 1. Baseline characteristics

	Overall
18-49 years, N (%)	1322 (100)
Median age, years (IQR)	44.2 (38.4-47.5)
Age groups, N (%)	
18-25 years	75 (5.7)
26-30 years	72 (5.4)
31-35 years	110 (8.3)
36-40 years	186 (14.1)
41-45 years	380 (28.7)
46-49 years	499 (37.7)
Men, N (%)	697 (52.7)
Median NIHSS at admission, median (range)	3.0 (0-42)
Median NIHSS at discharge (range)	1.0 (0-42)
Median mRS at discharge (IQR)	2.0 (1.0-3.0)
Case fatality, N (%)	38 (2.9)

Table 1. Continued

	Overall
Territorial stroke, N (%)	1035 (78.3)
Lacunar stroke, N (%)	287 (21.7)
Localization	
Left hemisphere, N (%)	588 (44.5)
Right hemisphere, N (%)	589 (44.5)
Bilateral, N (%)	145 (11.0)
Acute interventions, N (%)	
Intravenous thrombolysis	241 (18.2)
Intra-arterial thrombectomy	34 (2.6)
Both	88 (6.7)
Hypertension	499 (37.7)
Smoking	657 (49.6)
Excessive alcohol consumption	92 (7.0)
Dyslipidemia	864 (65.4)
Diabetes mellitus	138 (10.4)
Positive family history cardiovascular disease <60yrs	386 (29.2)
BMI 25 to 30	369 (27.9)
BMI 30 to 35	187 (14.1)
BMI > 35	81 (6.1)
Large artery atherosclerosis	59 (4.5)
Likely atherothrombotic	172 (13.0)
Small vessel disease	166 (12.5)
Cardio-embolic	226 (17.1)
Other determined cause	287 (21.7)
Multiple causes	79 (6.0)
Cryptogenic	333 (25.2)

Definitions of vascular risk factors: arterial hypertension: treated or known blood pressure before stroke >140/90 mm Hg or hypertensive retinopathy; current smoking or smoking stopped within the last 6 months; excessive alcohol use: use of more than 200 grams of alcohol/week; dyslipidemia: treated or known low-density lipoprotein before the stroke >160 mg/dl or 4.1 mmol/l and/or high-density lipoprotein <1.0 mmol/L; diabetes mellitus: treated or known blood fasting glucose >7 mmol/l or HbA1c > 48 mmol/L.
Abbreviations: IQR, interquartile range; NIHSS, The National Institutes of Health Stroke Scale; mRS, modified Ranking Scale; BMI, Body mass index.

Etiology according to modified TOAST criteria, stratified by age and sex

Large artery atherosclerosis was identified as the cause of stroke in 59 (4.5%) patients, likely atherothrombotic stroke in 172 (13.0%), small vessel disease in 166 (12.5%), and cardio-embolic stroke in 226 (17.1%) patients (Supplementary Table 2). Other determined cause of stroke was present in 287 (21.7%) patients (Table 2) and multiple causes in 79 (6.0%) patients (Supplementary Table 3). In 333 (25.2%) patients, the stroke had an undetermined cause and was classified as cryptogenic. Patients with a cryptogenic stroke were younger (median age of 43.3 years, IQR 36.2-46.7), than those with non-cryptogenic stroke (median age 44.6, IQR 39.1-47.6, p=0.001). Cause of stroke according to the TOAST classification differed between age-groups (Figure 1, Supplementary Table 4).

Table 2. Other determined causes of stroke (within TOAST other determined and multiple causes category)

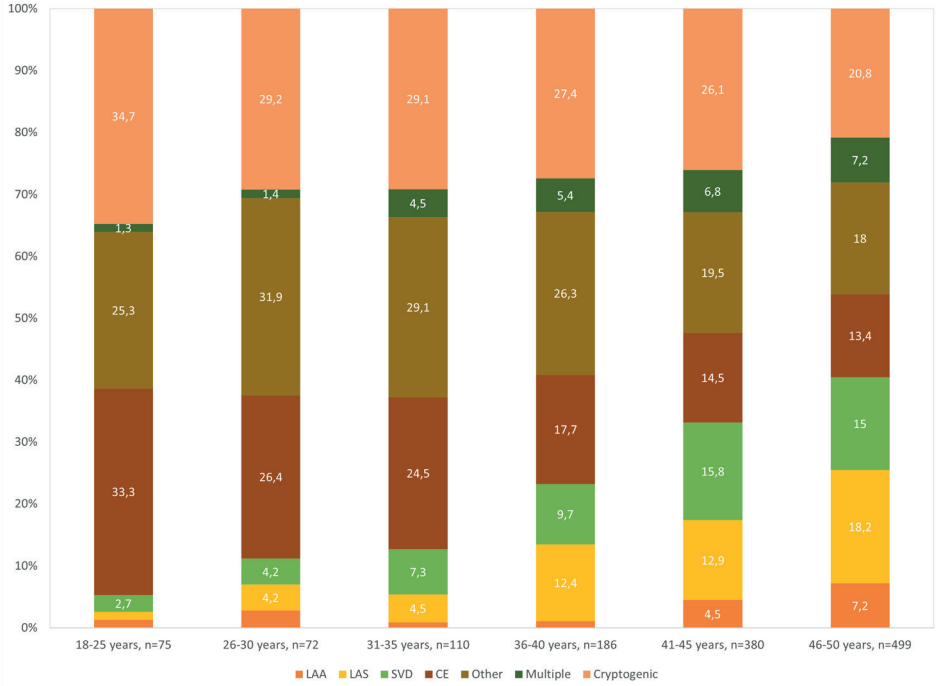
Cause of stroke*	Number of patients	Comments
Carotid artery dissection	92	
Vertebral artery dissection	64	Including basilar top dissection (1)
Antiphospholipid syndrome	50	APS in combination with increased factor VIII activity (1)
Illicit drug use	16	Cocaine (9), cocaine + XTC + cannabis (2), cocaine + methadone (1), cocaine + cannabis (1), amphetamine (1), amphetamine + ketamine (1), cocaine induced vasculitis (1)
Hyperhomocysteinemia	12	
Pregnancy/puerperium	9	
Active malignancy	7	Cervical cancer (1), metastatic paraganglioma (1), metastatic anal carcinoma (1), metastatic pancreatic carcinoma (1), thyroid carcinoma (1), colon carcinoma (1), metastatic non-small-cell lung carcinoma (1)
Moyamoya	6	
Radiotherapy induced vasculopathy	6	
Migrainous stroke	6	
Hematological (thrombocytosis)	5	positive JAK2 mutation (1), thrombocytosis, anemia and leukocytosis (1), essential thrombocytosis (1), TTP (2)
Systemic lupus erythematosus and SLE-like disease	4	SLE-like disease (1)

Table 2. Continued

Cause of stroke*	Number of patients	Comments
Iatrogenic	4	during placement of device in carotid (study) (1), cardio-thoracic surgery for aorta rupture (1), for type A dissection (1), during endovascular treatment of ACOM aneurysm (1)
PACNS	3	
Reversible vasoconstriction syndrome	4	
Sneddon syndrome	3	
HIV-associated	3	
Acute systemic infection preceding stroke	3	Bacterial empyema with reactive vasculitis of middle cerebral artery (1), herpes zoster (1), varicella zoster (1)
Neurological infection	3	Neurosarcoidosis (1), neuroborreliosis (1), neurolues (1)
Other rare causes	3	Exophytic thrombus in brachiocephalic trunc (1), thrombus brachiocephalic artery (1), aneurysm carotid artery with mural plaque (1)
Polycythemia vera >800	2	
MELAS	2	
Takayasu arteritis	2	
Intracranial dissection	2	
Hypotension	2	suicide attempt with blood pressure lowering medication (1), blood pressure lowering in hypertensive crisis (1)
Inadequate oral coagulation therapy	2	Low INR (1.9) in Wegener's disease on oral coagulation therapy (1), forgotten doses of rivaroxaban in patient with history of a pulmonary embolism (1)

*: Definitions and cut-off values can be found in Supplementary Table 1.
Single cases were found for homozygous factor V Leiden, sickle cell disease, fibromuscular dysplasia, toxic induced stroke due to cisplatin induced thrombosis, hemolytic anemia as paraneoplastic phenomenon, migraine with aura in combination with oral contraceptive use, PFO and lung embolus, a fat embolus after femur fracture and a congenital predisposition disorder.
Abbreviations: APS, antiphospholipid syndrome; XTC, ecstasy; TTP, thrombotic thrombocytopenic purpura; SLE, systemic lupus erythematosus; ACOM, anterior communicating artery; PACNS, primary angiitis of the central nervous system; HIV, human immunodeficiency viruses; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; INR, international normalized ratio.

Figure 1. TOAST etiology distribution among different age-groups



Significant differences between age groups and the percentages of the smallest groups that are not shown in the figure are shown in Supplementary Table 4.

Abbreviations: LAA, Large artery atherosclerosis; LAS, likely atherothrombotic stroke; SVD, small vessel disease; CE, cardio-embolic stroke; Other, Other determined cause of stroke.

ASCOD classification

Of the 333 patients with a cryptogenic stroke according to the TOAST classification, 73 could be assigned to one of the ASCOD categories (Supplementary Table 5). The 260 patients in whom the stroke remained cryptogenic were younger (median age 43.1 years; IQR 36.4-46.5) than the 1062 patients classified otherwise according to TOAST and ASCOD (median age 44.6; IQR 39.0-47.6; p<0.001).

IPSS classification

Distribution of risk factors according to the IPSS is shown in Table 3 for the whole cohort and for patients with a cryptogenic stroke according to the TOAST criteria. Of 333 patients 18 (5.4%) reported illicit drug use in the year before stroke. Coagulation abnormalities were found in 85 of 333 patients (25.5%). Given that the risk factors migraine, oral contraceptive use and smoking in the IPSS are known for their increased risk of stroke in interaction[89, 188], these were investigated: Migraine was present in 92 of the 333 patients (27.6%), of whom 34 women (18.9%) also used oral contraceptives. 122 of the 333 patients with a cryptogenic stroke according to the TOAST criteria (36.6%) were smokers, of whom 31 women (17.3%) used oral contraceptives. 13 women (7.3%) used both oral contraceptives, had migraine and were smokers.

In 10 patients of the 333 patients with cryptogenic stroke according to the TOAST criteria (3.0%) not a single IPSS risk factor could be identified (Table 3). The group of 10 patients without any IPSS risk factor consisted of five men and five women (median age 42.3 years; 36.6-45.8). Eight patients had an ischemic stroke with symptoms lasting >24 hours, two had symptoms lasting <24 hours.

Differences between the IPSS classification in cryptogenic and non-cryptogenic strokes according to TOAST classification

In comparison with patients with a non-cryptogenic stroke according to TOAST, patients with a cryptogenic stroke less often had arteriopathies (4.5% versus 35.6%) and cardiac conditions (6.6% versus 32.4%), more often had a prothrombotic state (44.7% versus 38.3%) and a chronic systemic condition (9.0% versus 4.3%, Table 3). Risk factors for early atherosclerosis were highly prevalent in both groups (90.1% versus 91.8%).

Table 3. IPSS risk factor categories for all patients, cryptogenic patients according to TOAST and all non-cryptogenic patients according to TOAST criteria

IPSS risk factor categories	Total cohort	TOAST cryptogenic	TOAST non-cryptogenic
	N=1322 (%)	N=333 (%)	N=989 (%)
Arteriopathy	367 (27.8)	15 (4.5)	352 (35.6)
Arterial dissection	163 (12.3)	0 (0.0)	163 (16.5)
Carotid artery stenosis (<50%)	77 (5.8)	4 (1.2)	73 (7.4)
Arteriopathy, otherwise	65 (4.9)	8[‖] (2.4)	57 (5.8)
Carotid artery stenosis (>50%)	35 (2.6)	0 (0.0)	35 (3.5)
Focal arterial stenosis	24 (1.8)	4 (1.2)	20 (2.0
Moyamoya	6 (0.5)	0 (0.0)	6 (0.6)
Radiotherapy induced vasculopathy	6 (0.5)	0 (0.0)	6 (0.6)
RCVS	4 (0.3)	0 (0.0)	4 (0.4)
PACNS	3 (0.2)	0 (0.0)	3 (0.3)
Takayasu	2 (0.2)	0 (0.0)	2 (0.2)
Sickle cell arteriopathy	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac condition	342 (25.9)	22 (6.6)	320[#] (32.4)
Patent foramen ovale (PFO)	196 (14.8)	6[**] (1.8)	190 (19.2)
Cardiac condition otherwise	68 (5.1)	14[‖] (4.2)	54 (5.5)
Atrial fibrillation	33 (2.5)	0 (0.0)	33 (3.3)
Atrial septal aneurysm	26 (2.0)	2[**] (0.6)	24 (2.4)
Hypokinetic segment of left ventricle	17 (1.3)	1 (0.3)	16 (1.6)
Mitral valve insufficiency	14 (1.1)	1 (0.3)	13 (1.3)
Dilated cardiomyopathy	14 (1.1)	0 (0.0)	14 (1.4)
Congestive heart failure	12 (0.9)	0 (0.0)	12 (1.2)
Akinetic segment of left ventricle	10 (0.8)	0 (0.0)	10 (1.0)
Myocardial infarction <4 weeks	10 (0.8)	0 (0.0)	10 (1.0)
Mechanical valve prothesis	8 (0.6)	0 (0.0)	8 (0.8)
Left ventricle thrombus	10 (0.8)	0 (0.0)	10 (1.0)
Infectious endocarditis	7 (0.5)	0 (0.0)	7 (0.7)
Atrial myxoma	6 (0.5)	0 (0.0)	6 (0.6)
Atrial flutter	5 (0.4)	0 (0.0)	5 (0.5)
Aortic valve insufficiency	4 (0.3)	0 (0.0)	4 (0.4)
Cardiac intervention <72 hours	4 (0.3)	0 (0.0)	4 (0.4)
Left atrial thrombus	3 (0.2)	0 (0.0)	3 (0.3)
Aortic valve stenosis	3 (0.2)	1 (0.3)	2 (0.2)
Mitral valve stenosis	2 (0.2)	0 (0.0)	2 (0.2)
Myocardial infarction (1-6months)	2 (0.2)	0 (0.0)	2 (0.2)
Non-infectious endocarditis	2 (0.2)	0 (0.0)	2 (0.2)

Table 3. Continued

IPSS risk factor categories	Total cohort	TOAST cryptogenic	TOAST non-cryptogenic
	N=1322 (%)	N=333 (%)	N=989 (%)
Chronic systemic conditions	206 (15.6)	48 (14.4)	158 (16.0)
Other chronic systemic condition	72 (5.4)	30‖ (9.0)	42 (4.3)
Illicit drug use*	68 (5.1)	18 (5.4)	50 (5.1)
Auto-immune disorders	44 (3.3)	11 (3.3)	33 (3.3)
Solid extracranial tumor	12 (0.9)	0 (0.0)	12 (1.2)
Hematological malignancy	6 (0.5)	1 (0.3)	5 (0.5)
Fibromuscular dysplasia	3 (0.2)	1‖ (0.3)	2 (0.2)
Ehlers Danlos syndrome	3 (0.2)	0 (0.0)	3 (0.3)
MELAS	2 (0.2)	0 (0.0)	2 (0.2)
Prothrombotic state‡	528 (39.9)	149 (44.7)	379 (38.3)
Oral contraceptive use	298 (22.5)	99 (29.7)	199 (20.1)
Hyperhomocysteinemia	121 (9.2)	25 (7.5)	96 (9.7)
Mild hyperhomocysteinemia <40 µmol/l	102 (7.7)	24‖ (7.2)	78 (7.9)
Antiphospholipid antibodies			
Increased factor VIII activity	63 (4.8)	2 (0.6)	61 (6.2)
Antithrombin deficiency	49 (3.7)	14 (4.2)	35 (3.5)
Other acquired	43 (3.3)	16 (4.8)	27 (2.7)
Factor V Leiden mutation‡	36 (2.7)	11‖ (3.3)	25 (2.5)
Prothrombin mutation§	33 (2.5)	14 (4.2)	19 (1.9)
Other genetic	18 (1.4)	8 (2.4)	10 (1.0)
Protein C deficiency	8 (0.6)	3 (0.9)	5 (0.5)
Protein S deficiency	14 (1.1)	3 (0.9)	11 (1.1)
Diffuse intravasal coagulation	7 (0.5)	3 (0.9)	4 (0.4)
	2 (0.2)	0 (0.0)	2 (0.2)
Acute systemic conditions	21 (1.6)	4 (1.2)	17 (1.7)
Other acute systemic condition	16 (1.2)	3‖ (0.9)	13 (1.3)
<72 hours after surgery	4 (0.3)	0 (0.0)	4 (0.4)
Hypotension	1 (0.1)	0 (0.0)	1 (0.1)
Need of vasopression	1 (0.1)	0 (0.0)	1 (0.1)
Chronic head/neck condition	374 (28.3)	95 (28.5)	279 (28.2)
Migraine	348 (26.3)	92 (27.6)	256 (25.9)
Head/neck tumor otherwise	12 (0.9)	0 (0.0)	12 (1.2)
VP drain	8 (0.6)	1 (0.3)	7 (0.7)
Brain tumor or metastasis	7 (0.5)	0 (0.0)	7 (0.7)
Intracranial AVM	4 (0.3)	3 (0.9)	1 (0.1)
Cerebral aneurysm	4 (0.3)	0 (0.0)	4 (0.4)

Table 3. Continued

IPSS risk factor categories	Total cohort	TOAST cryptogenic	TOAST non-cryptogenic
	N=1322 (%)	N=333 (%)	N=989 (%)
Acute head/neck condition	25 (1.9)	2 (0.6)	23 (2.3)
Trauma <3 months	13 (0.1)	2 (0.6)	11 (1.1)
Other acute head/neck injury	10 (0.8)	0 (0.0)	10 (1.0)
Meningitis <4 weeks	1 (0.1)	0 (0.0)	1 (0.1)
Head/neck surgery <72 hours	1 (0.1)	0 (0.0)	1 (0.1)
Pregnancy related	15 (1.1)	4 (1.2)	11 (1.1)
Pregnant	7 (0.5)	3 (0.9)	4 (0.4)
Postpartum <6 weeks	7 (0.5)	0 (0.0)	7 (0.7)
Risk factor for early atherosclerosis	1208 (91.4)	300 (90.1)	908 (91.8)
Dyslipidemia	864 (65.4)	186 (55.9)	678 (68.6)
Cigarette smoking in last year	657 (49.7)	122 (36.6)	535 (54.1)
Hypertension	499 (37.7)	70 (21.0)	429 (43.3)
Family History positive <60 years	386 (29.2)	94 (28.2)	292 (29.5)
BMI 25-30	369 (27.9)	101 (30.3)	268 (27.1)
BMI 30-35	187 (14.1)	37 (11.1)	150 (15.2)
Diabetes mellitus	138 (10.4)	10 (3.0)	128 (12.9)
Excessive alcohol consumption	92 (7.0)	19 (5.7)	73 (7.4)
BMI > 35	81 (6.1)	12 (3.6)	69 (7.0)
No IPSS risk factors	10 (0.8)	10 (3.0)	0 (0.0)

*: Use of soft- and/or hard drugs on regular basis.

†: When use of oral contraceptives is counted as a chronic systemic condition instead of a prothrombotic state, numbers are as follows (chronic systemic condition versus prothrombotic state): Total cohort: 467 (35.3%) versus 315 (23.8%), TOAST cryptogenic 137 (41.1%) versus 80 (24.0%).

‡: Only 2 patients had a homozygous Factor V Leiden mutation.

§: All prothrombin mutations were heterozygous.

‖: Not considered as causal by the treating physician and rater.

#: Patients with both TOAST cardio-embolic stroke and multiple causes.

**: Very small PFO's or atrial septum aneurysm without PFO, not considered the cause of stroke.

Abbreviations: IPSS, International Pediatric Stroke Society; TOAST, Trial of Org 10172 in Acute Stroke Treatment; RCVS, reversible vasoconstriction syndrome; PACNS, Primary Angiitis of the Central Nervous System; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; VP, ventriculoperitoneal; AVM, arteriovenous malformation; BMI, body mass index.

DISCUSSION

We found that 25.2% of young patients with an ischemic stroke had a cryptogenic stroke according to the modified TOAST and 19.7% when further classified according to ASCOD criteria. Only 0.8% of 1322 patients had a cryptogenic stroke without any potential risk factors when applying the IPSS classification.

Using the TOAST classification, we found a lower percentage of patients with a cryptogenic stroke than most European cohort studies.[12, 56] This might be due to both our systematic approach and to differences in time period between studies, since radiological, cardiac and laboratory testing have become more extensive over the last decade resulting in more identifiable causes. Both the TOAST and ASCOD classification, though often applied in young patients with stroke, were not designed to classify stroke in the young. This might explain why 46.9% of all strokes are classified as 'other determined- and cryptogenic strokes'. Although the ASCOD classification separates patients with an arterial dissection from the 'other determined causes', other categories are similar to the TOAST classification. As such ASCOD has limited added value in clinical practice to identify additional causes of stroke. Current classification systems developed for stroke patients in general (often > 65 years) seem therefore inadequate to classify stroke etiology and risk factors in young adults.

Evaluating patients with the IPSS classification can broaden the view of clinicians on potential risk factors, or factors that by interaction or combined presence can play a role, such as oral contraceptive use, migraine and smoking.[89, 188] The IPSS may shed light on (new) mechanisms that potentially lead to stroke in young adults, by subdividing risk factors in many different categories, based on a presumed pathophysiological mechanism. In contrast, the TOAST and ASCOD only have separate categories for large and small vessel disease, cardio-embolism and dissection (ASCOD).

Although we found a potential risk factor in many patients according to the IPSS classification, this is not synonymous with causality. Classical concepts about the cause of a disease include "an event, condition, or characteristic that plays an essential role in producing an occurrence of the disease", "and multiple component causes can act in combinations to produce different sufficient causes for a disease".[189] In addition, strength of association, consistency, specificity, temporality, biological plausibility of a risk factor and the occurrence of stroke support causality.[189] For many of the risk factors included in the IPSS, causality remains to be demonstrated. However, this also holds true for some of the causes in the TOAST and ASCOD systems (for example mild hyperhomocysteinemia). Searching for risk factors in the large group of young adults with cryptogenic stroke

using a risk factor system designed for children and adolescents can provide leads for new causes and potential treatable targets. Evaluating causality of certain common yet presumed risk factors in young adults with stroke would be an important area of future research,[190] and to further proof causality, evaluation of the long-term prognosis for patients with different presumed risk factors is key, as is comparison of the prevalence of some presumed risk factors in the general population. Examples we found in this study are the high number of young adults with coagulation abnormalities with or without a PFO[191] in both the cryptogenic and non-cryptogenic category. Also, cannabis is frequently used among young adults, often with concomitant use of alcohol and other substances, but it is rarely considered the cause of stroke. Meanwhile, a study in the United States showed a rising trend in hospital admissions for cardiovascular events in young adults due to cannabis use without concomitant use of other substances.[192] However, studies on differences in the prevalence of these coagulation abnormalities between patients and the healthy population, as well as studies on the long-term effects and causality of cannabis on cardiovascular outcomes are scarce.[193]

Our study has several strengths. First, this study is a large, prospective cohort study investigating stroke in young adults in the last decade. Patients were therefore analyzed and treated according to the latest guidelines including MRI an extensive cardiac work-up. The large number of patients allowed for detailed subgroup analysis between men and women, different age-groups, stroke subtype and different etiologies. Second, stroke misclassification was not present as all strokes and TIA's were confirmed on neuroimaging and checked independent from the treating physicians. Third, information was gathered in both a detailed and structured manner and verified by two from a pool of four investigators. Risk factor and etiology designation was done systematically by four raters, checked by one another afterwards in 100 cases and overall discussed to reduce the inter-rater variability. Fourth, the study has a nation-wide character, with consecutive patients from both academic and non-academic hospitals in different regions of the Netherlands. By also including patients who visited outpatient clinics (TIA's and minor strokes) and patients who died within the first 30-days of stroke (very severe) selection bias was limited. In addition, this provides a good reflection of the stroke population of young adults and increases the generalizability of our results to other European countries.

Limitations

Our study also has limitations. First, there were no demands on diagnostic work-up for hospitals that participated in the ODYSSEY study, therefore 2.3% of our patients without a cause of stroke did not receive a cardiac ultrasound, potentially leading to overestimation of the number of cryptogenic strokes. Second, all 17 participating centers included consecutive patients, although this was not always possible, for example

during the COVID period (March 2020-February 2021). However, these were most likely missing at-random. Third, besides the standardized questionnaires, all patient's files were checked for all the risk factors in the IPSS, however on some risk factors such as illicit drug use, amount of alcohol consumption and cigarette smoking, patient's answers could possibly have not been honest in both the questionnaire as well as in medical history taking with their treating physician, leading to an underestimation of some of these risk factors. In contrast, attribution bias might have played a role, since all patients with stroke have been seen by a neurologist, and the professional tendency to attribute stroke to a cause. Therefore, over reporting of risk factors by patients might have occurred.

CONCLUSIONS

Current stroke classification systems developed for stroke in general (often in patients over 65 years) cannot identify the cause of stroke in many patients, leaving a large group of cryptogenic strokes in young adults <50 years of age. Many additional potential risk factors for stroke can be found using a risk factor classification system designed for children and adolescents, providing leads for (new) causes, although further research should elaborate on the actual causality of some of these factors and the prevalence in the general population. Whether a more extensive modified pediatric risk factor classification can serve as a steppingstone for a new classification scheme which may aid in the development of tailored diagnostic work-up and treatment for young patients with stroke needs to be further evaluated.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Overview of classification systems and definitions used for this study

TOAST classification		
Large vessel atherosclerosis		
1a. Atherothrombotic	Atherothrombotic stroke Patients with (1) an ipsilateral internal carotid stenosis >50% (in NASCET criteria), or (2) an ipsilateral stenosis >50% of another intra/extracranial artery, or (3) mobile thrombus in the aortic arch	
1b. Likely atherothrombotic	Likely atherothrombotic stroke Patients with no evidence of atherothrombotic stroke as defined in 1a with (1) an ipsilateral internal carotid stenosis <50%, or (2) an ipsilateral stenosis <50% of another intra/extracranial artery, or (3) aortic arch plaques >4 mm in thickness without a mobile component, or (4) a history of myocardial infarction or coronary revascularization, (5) a history of documented peripheral arterial disease, or (6) at least two risk factors for atherosclerotic disease: arterial hypertension (treated or known blood pressure before stroke >140/90 mm Hg or hypertensive retinopathy), diabetes mellitus (treated or known blood fasting glucose >7 mmol/l), current smoking (or smoking stopped within the last 6 months), high cholesterol (treated or known low-density lipoprotein before the stroke >160 mg/dl or 4,1 mmol/l)	
Small vessel disease	Patients with a small deep infarct measuring <15 mm on MRI (or CT) in the territory corresponding to symptoms, in a patient presenting a clinical syndrome compatible with a small deep infarct	
Cardio-embolic	Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism	
	High risk sources	**Medium risk sources**
	Mechanical prosthetic valve	Mitral valve prolapse
	Mitral stenosis with atrial fibrillation	Mitral annulus calcification
	Atrial fibrillation	Mitral stenosis without atrial fibrillation
	Left atrial/atrial appendage thrombus	Left atrial turbulence (smoke)
	Sick sinus syndrome	Atrial septal aneurysm
	Recent myocardial infarction (<4 weeks)	Patent foramen ovale
	Left ventricular thrombus	Atrial flutter
	Dilated cardiomyopathy	Lone atrial fibrillation
	Akinetic left ventricular segment	Bioprosthetic cardiac valve
	Atrial myxoma	Nonbacterial thrombotic endocarditis
	Infective endocarditis	Congestive heart failure
		Hypokinetic left ventricular segment
		Myocardial infarction (>4 weeks, <6 months)

Supplementary Table 1. Continued

Other determined cause	Causes as shown in Table 3
Multiple causes	Patients with two or more etiologies defined in 1-4
Undetermined etiology / cryptogenic	Patients who did not meet criteria for the groups as defined above, maybe with incidental findings or with undetermined etiology, but incomplete evaluation.

ASCOD classification

A: Causality grades for atherothrombosis	
A1 (potentially causal)	Atherothrombotic stroke defined as: (1) ipsilateral atherosclerotic stenosis between 50 and 99% in an intra- or extracranial artery supplying the ischemic field; or (2) ipsilateral atherosclerotic stenosis <50% in an intra- or extracranial artery with an endoluminal thrombus supplying the ischemic field; or (3) mobile thrombus in the aortic arch; or (4) ipsilateral arterial occlusion in an intra- or extracranial artery with evidence of underlying atherosclerotic plaque supplying the ischemic field
A2 (causal link is uncertain)	(1) ipsilateral atherosclerotic stenosis 30-50% in an intra- or extracranial artery supplying the ischemic field; or (2) aortic plaque ≥4 mm without mobile lesion
A3 (causal link is unlikely, but disease is present)	(1) plaque (stenosis <30%) in an intra- or extracranial artery, ipsilateral to the infarct area; (2) aortic plaque <4 mm without mobile thrombus; (3) stenosis (any degree) or occlusion in a cerebral artery not supplying the infarct area (e.g. contralateral side or opposite circulation); (4) history of myocardial infarction, coronary revascularization or peripheral arterial disease; (5) ipsi- or bilateral atherosclerotic stenosis 50-99% with bihemispheric MR-DWI lesion
A0 (atherosclerosis not detected)	Ruling out atherosclerosis: (1) extracranial arterial stenosis: one or several of the following diagnostic tests are performed and are negative: US-Duplex, CTA, MRA, XRA, or autopsy; (2) intracranial arterial stenosis: one or several of the following diagnostic tests are performed and are negative: US-TCD, MRA, CTA, XRA, or autopsy; (3) aortic arch atheroma: TEE with specific assessment of the aortic arch (when the probe is pulled back at the end of the cardiac examination, turn the probe counter clockwise and take time to watch the aortic arch) or specific aortic arch assessment with CTA

Supplementary Table 1. Continued

A9 (incomplete workup)	US-Duplex, US-TCD or CTA, or MRA, or XRA or autopsy not performed. [A minimum workup is extra- and intracranial assessment of cerebral arteries - maximum workup also includes transesophageal assessment of the aortic arch (or a default CTA of the aortic arch)]
S: Causality grades for small-vessel disease	
S1 (potentially causal)	Combination of: (1) lacunar infarction: small deep infarct <15 mm (in perforator branch territory) on MRI-DWI (or a default CT) in an area corresponding to the symptoms and at least one of the three following criteria: (2) one or several small deep older infarct(s) of lacunar type in other territories, *and/or* (3) severe (confluent - Fazekas III) leukoaraiosis, or microbleeds, or severe dilatation of perivascular spaces ('état criblé'); (4) repeated, recent (<1 month), TIAs attributable to the same territory as the index infarct
S2 (causal link is uncertain)	(1) only one, recent, lacunar infarction and no other abnormality on MRI (or CT) *or* (2) clinical syndrome suggestive of a deep branch artery stroke, without ischemic lesion in the appropriate area seen on MRI or CT (main clinical syndrome suggesting a deep branch artery - lacunar - stroke: pure hemiparesis, pure hemisensory loss, ataxic hemiparesis, dysarthria-clumsy hand syndrome, unilateral sensorimotor deficit, others: hemichorea, hemiballism, pure dysarthria, etc.)
S3 (causal link is unlikely, but disease is present)	Severe (confluent - Fazekas III) leukoaraiosis visible on MRI and/or CT scan, and/or microbleeds visible on T2*-weighted MRI, and/or severe dilatation of perivascular spaces (visible on T2-weighted MRI), and/or one or several old, small deep infarcts of lacunar type
S0 (small vessel disease not detected)	Ruling out small-vessel disease stroke: negative MRI (T2, FLAIR, GRE, DWI) and no appropriate clinical syndrome suggestive of a deep branch artery stroke
S9 (incomplete workup)	MRI (or CT) not performed

Supplementary Table 1. Continued

C: Causality grades for cardiac pathology	
C1 (potentially causal)	Cardiogenic stroke defined as acute, or recent and older bihemispheric or supra- and infratentorial territorial or cortical ischemic lesions and signs of systemic embolism with detection of at least one of the following potential causes: (1) mitral stenosis (surface <1.5 cm 2); (2) mechanical valve; (3) myocardial infarction within 4 weeks preceding the cerebral infarction; (4) mural thrombus in the left cavities; (5) aneurysm of the left ventricle; (6) history or presence of documented atrial fibrillation - whether paroxysmal (>60 s), persistent or permanent - or flutter, with or without left atrial thrombus or spontaneous echo; (7) atrial disease (tachycardia-bradycardia syndrome); (8) dilated or hypertrophic cardiomyopathies; (9) left ventricle ejection fraction <35%; (10) endocarditis; (11) intracardiac mass; (12) PFO *and* thrombus in situ; (13) PFO *and* concomitant pulmonary embolism or proximal DVT preceding the index cerebral infarction;
C2 (causal link is uncertain)	Regardless of stroke pattern: (1) PFO + atrial septal aneurysm; (2) PFO and pulmonary embolism or proximal DTV concomitant but NOT preceding the index cerebral infarction; (3) intracardiac spontaneous echo-contrast; (4) apical akinesia of the left ventricle and decreased ejection fraction (but >35%); (5) history of myocardial infarction or palpitation and multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation); (6) no direct cardiac source identified, but multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation) and/or evidence of systemic emboli: renal or splenic or mesenteric infarction (on CT, MRI or autopsy) or embolism in peripheral artery supplying arm or leg
C3 (causal link is unlikely, but the disease is present)	One of the following abnormalities present in isolation: PFO, ASA, strands, mitral annulus calcification, calcification aortic valve, nonapical akinesia of the left ventricle, transient atrial fibrillation <60 s, atrial hyperexcitability

Supplementary Table 1. Continued

C0 (cardiac pathology not detected or not suspected)	Ruling out a cardiac source of embolism: minimum is negative ECG and examination by a cardiologist; maximum is negative ECG/telemetry/24-hour Holter ECG/long-term ECG recording (implantable device, transtelephonic ECG, loop recorder) and negative TEE for atrium, valves and septal abnormalities, negative TTE for PFO and assessment of left ventricle, negative cardiac CT/MRI, negative abdominal CT/MRI (search for old or simultaneous subdiaphragmatic visceral infarction)
C9 (incomplete workup)	Minimum is ECG and examination by a trained cardiologist in the absence of cardiac imaging
O: Causality grades for other causes	
O1 (potentially causal)	(1) dolichoectasia with complicated aneurysm; (2) polycythemia vera or thrombocythemia >800,000/mm 3; (3) systemic lupus; (4) disseminated intravascular coagulation; (5) antiphospholipid antibody syndrome (including >100 GPL units or lupus anticoagulant); (6) Fabry's disease; (7) coexisting meningitis; (8) sickle cell disease; (9) ruptured intracranial aneurysm with or without vasospasm of the artery supplying the infarcted area; (10) severe hyperhomocysteinemia; (11) Horton's disease; (12) other cerebral inflammatory or infectious angiitis; (13) moyamoya disease, etc.
O2 (causal link is uncertain)	(1) saccular aneurysm (with a suspicion of embolism from it) (2) coincidental migraine attack with neurological deficit lasting >60 min in patients with history of migraine aura
O3 (causal link is unlikely but the disease is present)	(1) arteriovenous malformation; (2) thrombocythosis <800,000/mm 3 ; (3) antiphospholipid antibody <100 GPL units; (4) homocysteinemia <40 µmol/l; (5) malignoma with associated hypercoagulation (high D-dimer levels), deep vein thrombosis or pulmonary embolism and/or recent chemotherapy
O0 (no other cause detected)	Ruling out other causes: negative: cerebrospinal fluid, complete hemostasis, cerebral arterial imaging, family history of inherited disease, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), hematologic tests (platelet, leucocytes, and eosinophilic counts, hematocrit), specific tests according to the suspected disease (e.g. genetic test, retinal angiography for Susac syndrome)

Supplementary Table 1. Continued

O9 (incomplete workup)	Unable to reasonably exclude other causes based on best available diagnostic tests and stroke-specific history
D: Causality grades for dissection	
D1 (potentially causal)	(1) arterial dissection by direct demonstration (evidence of mural hematoma: hypersignal on FAT-saturated MRI or at autopsy or on TOF-MRA or CT on axial sections showing both enlargement of the arterial wall by the hematoma with narrowing of the lumen or on echography showing an hypoechoic arterial wall with narrowing of the lumen and sudden enlargement of the carotid or vertebral (V2) artery diameter; (2) arterial dissection by indirect demonstration or by less sensitive or less specific diagnostic test (only long arterial stenosis beyond the carotid bifurcation or in V2, V3 or V4 without demonstration of arterial wall hematoma: on X-ray angiography, and/or echography and/or CTA and/or MRA) or unequivocal US with recanalization during follow-up
D2 (causal link is uncertain)	(1) arterial dissection by weak evidence (suggestive clinical history, e.g., painful Horner's syndrome or past history of arterial dissection); (2) imaging evidence of fibromuscular dysplasia of a cerebral artery supplying the ischemic field
D3 (causal link is unlikely but disease is present)	(1) kinking or dolichoectasia without complicated aneurysm or plicature; (2) fibromuscular dysplasia on arteries not supplying the ischemic field
D0 (no dissection detected or suspected)	Ruling out dissection: negative FAT-saturated MRI of suspected artery or good quality, normal X-ray angiography (too early FAT-saturated MRI performed within 3 days of symptom onset can be falsely negative and then should be repeated). If there is no clinical suspicion of dissection, the patient can be classified D0 provided good-quality extra- or intracranial cerebral artery and cardiac evaluations have been performed
D9 (incomplete workup)	In patients aged less than 60 years and with no evidence of A1, A2, S1, C1, or O1 category: no FAT-saturated MRI performed on the extra- or intracranial artery supplying the ischemic field or no X-ray angiography performed (all performed within 15 days of symptom onset)

Supplementary Table 1. Continued

Modified IPSS classification	
Arteriopathy	Focal cerebral arteriopathy
	Moyamoya
	Arterial dissection
	CADASIL
	Radiotherapy induced vasculopathy
	Reversible vasoconstriction syndrome
	Giant cell arteritis
	Takayasu arteritis
	Primairy angiitis of the nervous system
	Significant carotid stenosis (>50%)
	Non-significant carotid stenosis (<50%)
	Vasculitis
	Sickle cell arteriopathy
	Post varicella arteriopathy
	Other
	Unspecified arteriopathy
Cardiac disorders	Congenital heart disease
	Acquired heart disease
	Mechanical valve prothesis
	Mitral valve stenosis
	Mitral valve insufficiency
	Atrial fibrillation
	Sick sinus syndrome
	Recent myocardial infarction (<4 weeks)
	Myocardial infarct (>4 weeks-6months)
	Isolated PFO
	Atrial septal aneurysm
	Dilated cardiomyopathy
	Thrombus in left ventricle
	Thrombus in left atrium
	Akinetic segment left ventricle
	Hypokinetic segment left ventricle
	Biological valve prothesis
	<72 hours after cardiac surgery
	Previous cardiac surgery
	Arrhythmia otherwise
	Infectious endocarditis
	Non-bacterial endocarditis
	Aortic valve stenosis
	Aortic valve insufficiency
	Other

Supplementary Table 1. Continued

Chronic systemic condition	Fabry's disease Fibromuscular dysplasia Ehlers Danlos Sickle cell disease Genetic condition (except CADASIL and genetic coagulation disorders) Auto-immune condition Hematological malignancy Solid extracranial tumor MELAS Illicit drug use (soft- and/or hard drugs on regular base) Other
Prothrombotic state	Factor V Leiden Prothrombin mutation Protein S deficiency Protein C deficiency Antithrombin deficiency Increased factor VIII activity Hyperhomocysteinemia Antiphospholipid syndrome Diffuse intravasal coagulation Use of oral contraceptives Other genetic coagulation disorder Other acquired coagulation disorder (HIT, TTP)
Acute systemic condition	<72 hours after surgery Hypotension at time of event (<90mmHg systole/60 diastole) Sepsis (according to SOFA criteria) Shock (need of vasopressive agents for a MAP >65 and serum lactate >2 mmol/l) Other
Chronic head/ neck condition	Migraine Brain tumor or metastasis VP drain Cerebral aneurysm Intracranial AVM Other head/neck tumor Other head/neck condition
Acute head/neck condition	Trauma head/neck <3 months Tonsillar abces <4 weeks Meningitis <4 weeks Head/neck surgery <72 hours Other
Pregnancy related	During pregnancy During puerperium (<6 weeks after delivery)

Supplementary Table 1. Continued

Risk factors for early atherosclerosis	Hypertension (systolic >140 and/or diastolic >90 24hrs after event) Smoking (at least 1 cigarette in the past year) Alcohol misuse (>200g of alcohol/week =20 units) Dyslipidemia (total cholesterol >5.0 mmol/l and/or LDL>3.0 and/or HDL<1.0) Diabetes mellitus (sober glucose > 7.0 twice or Hba1c > 48mmol/l) BMI > 25 Family history positive (1 degree family member with cardiovascular disease <60 years)

Supplementary Table 2. Sources of cardio-embolism in patients with a cardio-embolic stroke

	Number of patients
High risk sources of cardio-embolism	
Atrial fibrillation	25
Multiple high-risk sources	17
Dilated cardiomyopathy	11
Myxoma	6
Mechanic valve prothesis	5
Infectious endocarditis	5
Myocardial infarction <4 weeks	4
Left ventricle thrombus	4
Left atrial thrombus	2
Akinetic segment of left ventricle	2
Mitral valve stenosis with AF	2
Sick sinus syndrome	1
Medium risk sources of cardio-embolism	
Patent foramen ovale alone	158
Multiple medium risk sources	24*
Hypokinetic segment of left ventricle	7
Mitral valve insufficiency	6
Congestive heart failure	5
Atrial septum aneurysm	3
Non-infectious endocarditis	2
Atrial flutter	2

*18 patients had a PFO in combination with an atrial septum aneurysm
Abbreviations: AF, atrial fibrillation; PFO, patent foramen ovale.

Supplementary Table 3. Distribution of 79 patients with multiple causes among TOAST categories

	LAA	LAS	SVD	CE	Other	Unknown
LAA	x	0	0	2	5	0
LAS	0	x	2	20	17	0
SVD	0	2	x	5	6	0
CE	2	20	5	x	16	0
Other	5	17	6	16	x	4
Unknown	0	0	0	0	4	x

Abbreviations: LAA, Large artery atherosclerosis; LAS, likely atherothrombotic stroke; SVD, small vessel disease; CE, cardio-embolic stroke; Other, Other determined cause of stroke.

Supplementary Table 4. TOAST etiology distribution among different age-groups

	LAA	LAS	SVD
18-50 years median age (IQR)	46.6 years (4.2)	46.3 years (5.9)	45.5 years (5.3)
18-25 years (n=75, (%))	1 (1.3)	1 (1.3)	2 (2.7)
26-30 years (n=72, (%))	2 (2.8)	3 (4.2)	3 (4.2)
31-35 years (n=110, (%))	1 (0.9)	5 (4.5)a	8 (7.3)
36-40 years (n=186, (%))	2 (1.1)	23 (12.4)[a,c]	18 (9.7)[a]
41-45 years (n=380, (%))	17 (4.5)[c]	49 (12.9)[a,b]	60 (15.8)[a,b,c]
46-49 years (n=499, (%))	36 (7.2)[c,d]	91 (18.2)[b,c,d]	75 (15.0)[b,c]

a: Significant compared to age group 18-25
b: Significant compared to age group 26-30
c: Significant compared to age group 31-35
d: Significant compared to age group 36-40
e: Significant compared to age group 41-45

CE	Other	Multiple	Cryptogenic
42.3 years (12.7)	42.2 years (11.4)	45.3 years (6.9)	43.3 years (10.4)
25 (33.3)	19 (25.3)	1 (1.3)	26 (34.7)
19 (26.4)	23 (31.9)	1 (1.4)	21 (29.2)
27 (24.5)	32 (29.1)	5 (4.5)	32 (29.1)
33 (17.7)[a]	49 (26.3)	10 (5.4)	51 (27.4)
55 (14.5) [a,b,c]	74 (19.5)[b,c]	26 (6.8)	99 (26.1)
67 (13.4)[b,c]	90 (18.0)[b,c,d]	36 (7.2)	104 (20.8)[a]

Abbreviations: LAA, Large artery atherosclerosis; LAS, likely atherothrombotic stroke; SVD, small vessel disease; CE, cardio-embolic stroke; Other, Other determined cause of stroke.

Supplementary Table 5. Distribution of patients along ASCOD categories. (A) All 1322 patients and (B) 73 of 333 patients with cryptogenic stroke according to TOAST that fall into one of the ASCOD categories

A	N (%)		N (%)	
A0	883 (66.8)	**S0**	925 (70.0)	**C0**
A1	72 (5.4)	**S1**	87 (6.6)	**C1**
A2	31 (2.3)	**S2**	92 (7.0)	**C2**
A3	114 (8.6)	**S3**	59 (4.5)	**C3**
A9	222 (16.8)	**S9**	159 (12.0)	**C9**
Total	1322 (100)	**Total**	1322 (100)	**Total**
B	N (%)		N (%)	
A0	47 (64.4)	**S0**	50 (68.5)	**C0**
A1	1 (1.4)	**S1**	0 (0.0)	**C1**
A2	3 (4.1)	**S2**	2 (2.7)	**C2**
A3	12 (16.4)	**S3**	13 (17.8)	**C3**
A9	10 (13.7)	**S9**	7 (9.6)	**C9**
Total	73 (100)	**Total**	73 (100)	**Total**

A: 194 patients had a zero for all categories, which means after evaluation no cause was identified. Of the patients with a 9 (incomplete work-up) in one or more of the categories, 163 patients had no other possible cause (A-S-C-O-D with 1, 2 or 3) in one of the other categories. Only 2 patients had an incomplete work-up (9) for all five subcategories.

N (%)		N (%)		N (%)
797 (60.3)	**O0**	851 (64.4)	**D0**	847 (64.1)
97 (7.3)	**O1**	127 (9.6)	**D1**	165 (12.5)
33 (2.5)	**O2**	21 (1.6)	**D2**	3 (0.2)
183 (13.8)	**O3**	135 (10.2)	**D3**	1 (0.1)
212 (16.0)	**O9**	188 (14.2)	**D9**	306 (231)
1322 (100)	**Total**	1322 (100)	**Total**	1322 (100)
N (%)		N (%)		N (%)
56 (76.5)	**O0**	30 (41.1)	**D0**	56 (76.7)
0 (0.0)	**O1**	1 (1.4)	**D1**	0 (0.0)
1 (1.4)	**O2**	3 (4.1)	**D2**	1 (1.4)
8 (11.0)	**O3**	35 (47.9)	**D3**	1 (1.4)
8 (11.0)	**O9**	4 (5.5)	**D9**	15 (20.5)
73 (100)	**Total**	73 (100)	**Total**	73 (100)

B: The causal link was believed to be very uncertain in the patients with A1 and O1, who were therefore classified as having a cryptogenic stroke according to the TOAST classification by 4 raters

Chapter 6

Trigger factors for stroke in young adults

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Trigger factors for stroke in young adults: a case-crossover study.

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ABSTRACT

Background and Objectives: Causes of stroke in young adults differ from those in the elderly, and in a larger percentage no cause can be determined. To gain more insight in the etiology of (cryptogenic) stroke in the young, we investigated whether trigger factors, such as short-lasting exposure to toxins or infection, may play a role.

Methods: Patients aged 18-49 years with a first-ever ischemic stroke or intracerebral hemorrhage (ICH) in 17 participating centers in the Netherlands completed a questionnaire about exposure to nine potential trigger factors in hazard periods and on a regular yearly basis. A case-crossover design was used to assess relative risks (RR) with 95% confidence intervals (95% CI) by the Mantel-Haenszel case-crossover method, for any stroke (ischemic stroke and ICH combined) and for different etiologic subgroups of ischemic stroke.

Results: 1146 patients completed the questionnaire (1043 patients with an ischemic stroke, 103 with an ICH, median age 44.0 years, 52.6% men). For any stroke an increased risk emerged within one hour of cola consumption (RR 2.0, 95% CI 1.5-2.8) and vigorous physical exercise (RR 2.6, 95% CI 2.2-3.0), within two hours after sexual activity (RR 2.4, 95% CI 1.6-3.5), within 4 hours after illicit drug use (RR 2.8, 95% CI 1.7-4.9) and within 24 hours after fever or flu-like disease (RR 14.1, 95% CI 10.5-31.2; RR 13.9, 95% CI 8.9-21.9). Four trigger factors increased the risk of other determined and cryptogenic ischemic stroke, three that of cardio-embolic stroke, two that of large vessel atherosclerosis and likely atherothrombotic stroke combined and stroke with multiple causes, none that of stroke due to small vessel disease.

Discussion: We identified cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever- and flu-like disease as potential trigger factors for stroke in the young, and found differences in type and number of trigger factors associated with different etiologic subgroups of ischemic stroke. These findings might help in better understanding the pathophysiological mechanisms of (cryptogenic) stroke in the young.

INTRODUCTION

Stroke affects approximately 2 million young individuals (18-49 years) each year.[1-3] Stroke in young adults differs from stroke in the elderly.[194] The incidence of stroke in the young is rising, whereas it is decreasing in the older population. In addition, the cause of an ischemic stroke in the young remains undetermined in around 30% of the cases, making a causal treatment and the provision of adequate long-term prognosis difficult in these patients.[1, 195-197] Intracerebral hemorrhage (ICH) at young age also differs from the older population as it more often has a macrovascular cause (e.g. an arteriovenous malformation, AVM), and a higher percentage of patients in whom the cause is unknown.[198-202]

Therefore, it is likely that in young patients with stroke other risk factors or factors that may convert risk factors into causes play a role. Trigger factors such as exposure to toxins, caffeine, sexual activity, physical exercise or infection, have been hypothesized to create a (short-lasting) prothrombotic state or cause an increase in blood pressure that may predispose to stroke.[203-204, 205] Trigger factors differ from risk factors as risk factors are believed to be the start of a causal chain, accumulating to a cause of stroke, whereas trigger factors cause a short-term risk subsequent to the trigger. Several trigger factors have been identified for subarachnoid hemorrhage (SAH), ischemic stroke and ICH.[203, 204, 206-208]

For young patients specifically, the role of these trigger factors has never been investigated. We therefore investigated whether potential trigger factors (alcohol consumption, cigarette smoking, coffee and cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever and flu-like disease) may be associated with stroke in young adults. We further hypothesized that differences exist in the strength of association between the various trigger factors per stroke subtype (ischemic stroke and ICH), per ischemic stroke etiology by TOAST classification and per ICH etiology, since their underlying mechanisms are different. In addition, we hypothesized that trigger factors are associated with an increased risk of cryptogenic stroke.

METHODS

We performed a case-crossover study as part of the Observational Dutch Young Symptomatic StrokE studY (ODYSSEY), a Dutch multicenter prospective cohort study on the risk factors and prognosis of patients aged 18-49 years with a first-ever ischemic stroke or ICH. Details of the ODYSSEY study have been described previously.[29] In short, our study comprises consecutive patients aged 18-49 years with first-ever symptomatic ischemic stroke with radiological evidence of cerebral ischemia and with first-ever ICH. Patients with transient symptoms (duration of symptoms less than 24 hours) all had diffusion weighted imaging positive lesions (DWI+) on MRI and as such were included as (minor) stroke according to the tissue based definition.[184] Exclusion criteria were a traumatic ICH, SAH, ICH due to ruptured aneurysm, ICH in a known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis or a history of a clinically symptomatic transient ischemic attack (TIA), ischemic stroke or ICH.

Baseline data collection

We systematically collected information including stroke characteristics and severity (National Institutes of Health Stroke Scale, NIHSS), acute treatment, diagnostic laboratory- and cardiac tests, (vascular) risk factors, causes of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, modified ranking scale (mRS) at admission and discharge and medication at discharge.

All patients completed a standardized structured questionnaire on level of education, marital status, employment, risk factors and acute potential trigger factors including exposure and/or consumption within and outside predefined hazard periods. To minimize recall bias, patients were requested to complete the questionnaire as soon as possible after stroke, with or without assistance of their treating physicians or their family and/or acquaintance.

Trigger factors

Trigger factors included alcohol consumption, cigarette smoking, caffein-containing coffee consumption, caffein-containing cola consumption, vigorous physical exercise, sexual activity, use of illicit drugs (cocaine, heroin, methadone, amphetamine, ecstasy and d-lysergic acid diethylamide (LSD) were considered hard drugs, cannabis products and mushrooms containing psilocin considered soft drugs)[209, 210] and fever or flu-like disease, based on previous studies.[203, 204, 206, 211-213] Exposure to a trigger factor in a predefined hazard period supposedly leads to a short-term increased risk compared to control hours of non-exposure. Questions were trigger factor specific, and patients were asked about their average exposure to each potential trigger factor in the previous

year (usual frequency of exposure), time between onset of stroke and the last exposure and exposure during a predefined hazard period. Hazard periods were predefined for all individual trigger factors, based on the estimated duration-effect and previous literature, and were one hour for alcohol consumption, cigarette smoking, coffee consumption, cola consumption and vigorous physical exercise, two hours for sexual activity, four hours for illicit drug use and 24 hours for fever and flu-like disease. These hazard periods were then compared to a patient's usual frequency of exposure to these triggers. For cigarette smoking, vigorous physical exercise, sexual activity and fever or flu-like symptoms patients were only asked if they were exposed in the hazard period (yes/no). For alcohol consumption, coffee consumption, cola consumption and illicit drugs use, patients were also asked for the exact time interval between last exposure and stroke onset.[203, 204, 206, 211, 214] To be able to compare our findings with some of the existing literature on trigger factors for ischemic stroke in an older population that used a hazard period of two hours[204], we also assessed a two hour hazard period for alcohol consumption, coffee consumption, cola consumption and illicit drug use (Supplementary Table 1). Illicit drug use was examined both combined and by subcategory (type of drugs, soft drugs versus hard drugs).[209, 210]

Vigorous physical exercise (umbrella term) was examined separately for different grades of physical exercise. Each type of physical exercise was converted to a metabolic equivalent task [MET] by calculation the ratio of the work metabolic rate to the resting metabolic rate. One MET is equivalent to the resting metabolic rate, e.g. sitting quietly, and results in burning 1 kcal/kg/hour. As an example, a patient with a weight of 70 kg performing a 1 MET activity (sitting) for 1 hour will use 70 kcal. We analyzed the following subcategories of vigorous physical exercise ([MET] ≥6): heavy exercise [MET]=6, severe exercise [MET]=7 and, extreme exercise [MET]=8, as well as the combination of these three types of exercise, classified as vigorous physical exercise ([MET] ≥6). In addition, we assessed habitual exercisers (>500 [MET] minutes per week) versus rare exercisers (<500 [MET] minutes per week).[211, 215] MET minutes were calculated by the number of minutes X the MET activity level, e.g. 83.3 minutes of a MET 6 activity account for 500 MET minutes per week.

Data analyses

We examined exposure to the various potential trigger factors using a case-crossover design, suitable for studying the effect of trigger factors within a hazard period compared to a control period.[204, 205, 216] As each patient serves as its own control, confounding for chronic risk factors and subject characteristics will be minimized. Using the Mantel-Haenszel case-crossover method, a relative risk (RR) with 95% confidence interval (CI) was calculated for each potential trigger factor for any stroke (ischemic stroke and ICH

combined) and for ischemic stroke and ICH separately, by calculating the ratio of the exposure in the hazard period and the expected yearly exposure frequency based on a patients weekly or daily average frequency.[205] RR's should be interpreted as relative risks for a short-term period (trigger factors) and not as cumulative risks for the long-term. P-values were obtained by performing a conditional logistic regression analysis, which were adjusted for multiple comparisons using a Holm-Bonferroni post-hoc analysis. All patients with certain unreliable answers were excluded (e.g. certain inconsistent answers, unmistakable untrue answers), before performing the analyses.

Population attributable fractions (PAF), which indicates the fraction of a certain disease in a population that is attributable to exposure to a particular factor, were calculated for the trigger factors for which the RR remained significant after the Holm-Bonferroni test.[203, 217] The PAF can be used as an assessment tool for the health impact of exposure in a (study) population. It is calculated based on the RR and prevalence of exposure. The prevalence of exposure (p_e) is calculated as: mean number of exposures per year/ number of hazard periods per year. The PAF is then calculated through the following formula: pe((RR−1)/(pe(RR−1)+1)).[203, 217]

To minimize potential recall bias or bias introduced by potential unreliable data, we performed two sensitivity analyses. First, all patients who completed the questionnaire later than 30 days after stroke onset based on the completed questionnaire or inclusion date, were excluded, after which analyses were performed again. Second, we converted the usual frequency for all trigger factors (except for fever- and flu-like disease) to a 16 hours day, assuming most exposure to trigger factors to take place during waking hours and not during an average of 8 hours of sleep.[203, 205, 211]

To explore possible different mechanisms of trigger factors and unveil potential mechanisms of cryptogenic strokes specifically, we stratified our analysis for cause of stroke according to the TOAST classification. For intracerebral hemorrhage we investigated patients with a macrovascular underlying cause and all 'other' causes separately.

Data were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Data were analyzed using SPSS Software version 22 (IBM), R version 3.6.2 (R Project for Statistical Computing) and Microsoft Office Excel 2007.

Standard Protocol Approvals, Registrations, and Patient Consents

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). All patients signed informed consent.

Data availability

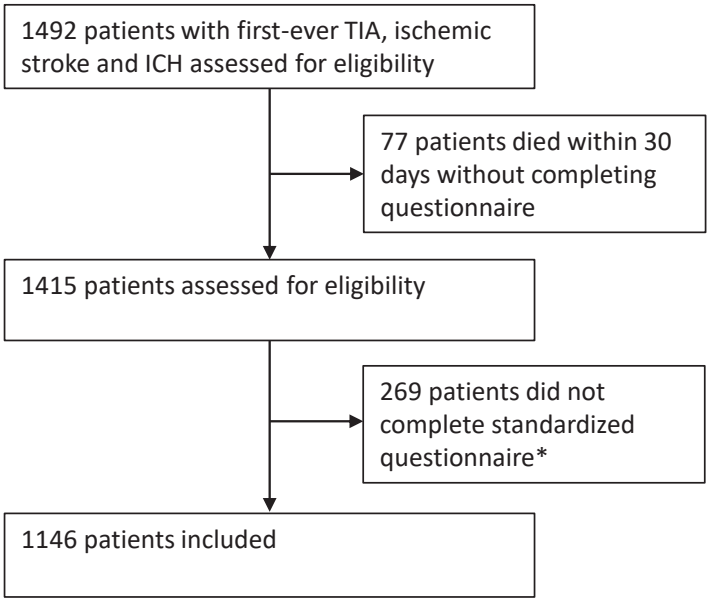
The raw and anonymized data used in this study can be made available to other researchers upon request. Written proposals can be addressed to the corresponding author and will be assessed by the ODYSSEY investigators for appropriateness of use, and a data-sharing agreement in accordance with Dutch regulations will be put in place before data are shared.

RESULTS

Baseline results

Of 1492 patients who participated in the ODYSSEY study, 1146 patients (76.8%) completed the trigger factor questionnaire (Figure 1). Ischemic stroke was found in 1043 patients (91.0%), ICH in 103 (9.0%). The median age was 44.0 years (Interquartile range, IQR, 37.8-47.4 years) and 603 patients were men (52.6%). Of all 1043 ischemic stroke patients, 80 patients (7.7%) had transient symptoms (duration less than 24 hours). Baseline characteristics of the included patients are shown in Table 1. The median duration between stroke onset and inclusion was 7 days (IQR 3-29 days). The median duration between stroke onset and completing the standardized questionnaire was 9 days (IQR 3-33 days).

Figure 1. Patient selection



*Patients that (1) had a very incomplete questionnaire, (2) refused to fill in the standardized questionnaire, (3) were unable to complete the questionnaire due to severe aphasia or cognitive impairment, or (4) had too large an interval between stroke onset and inclusion to reliably recall information requested in the questionnaire.

Trigger factors for any stroke

For any stroke (ischemic stroke and ICH combined), an increased risk emerged within one hour of cola consumption (RR 2.0, 95% CI 1.5-2.8) and vigorous physical exercise (RR 2.6, 95% CI 2.2-3.0), within two hours after sexual activity (RR 2.4, 95% CI 1.6-3.5),

within 4 hours after illicit drug use (RR 2.8, 95% CI 1.7-4.9) and within 24 hours after fever or flu-like disease (RR 14.1, 95% CI 10.5-31.2; RR 13.9, 95% CI 8.9-21.9; Table 2). No increased risk was found after exposure of alcohol or coffee consumption. Cigarette smoking decreased the risk of any stroke within one hour. Regular exercisers showed a lower relative risk (RR 1.6, 95% CI 1.3-1.9) than the group who did not exercise regularly (RR 10.2, 95% CI 7.9-13.1) (Table 2). The analysis of subcategories of illicit drug use did not show a significant difference in the risk of developing stroke after the use soft or hard drugs (Table 2).

When patient who completed the questionnaire later than 30 days after stroke onset (sensitivity analysis 1) or who had unreliable answers (sensitivity analysis 2), results remained similar. When we reduced the maximum duration of exposure to 16 hours per day, RR's for all trigger factors were lower (Table 3).

PAF's are summarized in Table 4. We found the highest PAF for vigorous physical exercise (12.4%) and the lowest for illicit drug use (0.3%).

Trigger factors stratified by ischemic stroke or ICH

Vigorous physical exercise and sexual activity increased the risk for both ischemic stroke and ICH during the hazard period, whereas cola consumption, illicit drug use, fever or flu-like disease only increased the risk for ischemic stroke (Table 4).

Trigger factors for different causes of ischemic stroke

We found four trigger factors for cryptogenic stroke, vigorous physical exercise (RR 3.2, 95% CI 2.3-4.3) (including the subcategories of heavy exercise (RR 3.7, 95% CI 2.7-5.1), severe exercise (RR 3.3, 95% CI 1.9-5.7) and extreme exercise (RR 3.2, 95% CI 1.7-6.2)), illicit drug use (RR 4.0, 95% CI 1.7-9.7), fever (RR 7.9, 95% CI 2.5-25.5) and flu-like disease (RR 10.4, 95% CI 3.9-28.1, Table 5 and Supplementary Figure 1). For large artery disease and likely atherothrombotic stroke combined we found only fever and flu-like disease to be trigger factors. No trigger factors were found for stroke due to small vessel disease. Three trigger factors (vigorous physical exercise, including the subcategories of heavy exercise, severe exercise and extreme exercise, fever and flu-like disease) showed an increased RR for developing a cardio-embolic stroke. Four trigger factors (cola consumption, vigorous physical exercise including the subcategories of heavy exercise, severe exercise, extreme exercise, fever and flu-like disease) were found to increase the risk for a stroke with other determined cause. Two trigger factors (vigorous physical exercise, including the subcategories of heavy exercise, severe exercise and extreme exercise, and fever) were found to increase the risk for stroke due to multiple causes.

Table 1. Baseline characteristics

	Overall
Demographics	
18-49 years, N (%)	1146 (100)
Median age (IQR)	44.0 (37.8-47.4)
Men, N (%)	603 (52.6)
Stroke characteristics	
Median NIHSS at admission, median (range)	1.0 (0-42)
Vascular risk factors, frequency (%)	
Smoking	549 (47.9)
Hypertension	437 (38.1)
Diabetes mellitus	107 (9.3)
Hypercholesterolemia	718 (62.7)
Alcohol	78 (6.7)
BMI > 25	555 (48.4)
TOAST classification, frequency (%)	
Large artery atherosclerosis	41 (3.6)
Likely atherothrombotic stroke	131 (12.5)
Small vessel disease	133 (12.7)
Cardio-embolic	180 (17.2)
Other determined cause	225 (21.6)
Multiple causes	65 (6.2)
Cryptogenic	268 (25.7)
ICH etiology	
Hypertensive	n.a.
AVM	n.a.
Cavernoma	n.a.
Other causes*	n.a.
Unknown	n.a.
ICH localization, frequency (%)	
Lobar	n.a.
Basal ganglia	n.a.
Thalamus	n.a.
Cerebellar	n.a.
Brainstem	n.a.

Duration of symptoms

* Other causes were: dural arteriovenous fistula (2), coagulopathy due to coagulation disorder (2), illicit drug use (cocaine) (1), Posterior Reversible Encephalopathy Syndrome (PRES) (1), vasculitis (1), diffuse intravasal coagulation during pregnancy (1), multiple venous emboli in patient with Eisenmenger syndrome (1),

	Ischemic stroke #<24 hours	Ischemic stroke #> 24 hours	ICH
	80 (7.0)	963 (84.0)	103 (9.0)
	43.3 (36.6-46.3)	44.2 (38.4-47.6)	43.1 (34.5-46.7)
	45 (56.3)	501 (52.0)	57 (55.3)
	0.0 (0-8)	3.0 (0-42)	2.0 (0-20)
	29 (36.3)	492 (51.1)	28 (27.2)
	22 (27.5)	364 (37.8)	51 (49.5)
	4 (5.0)	100 (10.4)	3 (2.9)
	47 (58.8)	645 (67.0)	26 (25.2)
	6 (7.5)	68 (7.1)	3 (2.9)
	29 (36.3)	488 (50.7)	38 (36.9)
	5 (6.3)	36 (3.7)	n.a.
	5 (6.3)	126 (13.1)	n.a.
	6 (7.5)	127 (13.2)	n.a.
	19 (23.8)	161 (16.7)	n.a.
	17(21.3)	208 (21.6)	n.a.
	6 (7.6)	59 (6.1)	n.a.
	22 (27.5)	246 (25.5)	n.a.
	n.a.	n.a.	40 (38.8)
	n.a.	n.a.	13 (12.6)
	n.a.	n.a.	10 (9.7)
	n.a.	n.a.	15 (14.6)
	n.a.	n.a.	25 (24.3)
	n.a.	n.a.	34 (33.0)
	n.a.	n.a.	38 (27.2)
	n.a.	n.a.	6 (5.8)
	n.a.	n.a.	8 (7.8)
	n.a.	n.a.	13 (12.6)

predisposition disorder of right hemisphere with mental retardation (1) Abbreviations: n.a., not applicable; ICH, intracerebral hemorrhage; IQR, interquartile range; NIHSS, The National Institutes of Health Stroke Scale; AVM, arteriovenous malformation.

Table 2. Relative Risk with 95% confidence intervals for trigger factors for any stroke

Trigger factor	Patients exposed in previous year	Patients exposed in hazard period	Patients not included (not exposed[a], missing data[b])	RR (95% CI)
Alcohol consumption	411	24	735 (444, 291)	1.3 (0.9-2.0)
Cigarette smoking	356	182	790 (670, 120)	0.6 (0.5-0.6)
Coffee consumption	659	118	487 (267, 220)	1.0 (0.8-1.2)
Cola consumption	346	39	800 (443, 357)	2.0 (1.5-2.8)[c]
Vigorous physical exercise [MET≥6]	804	186	342 (334, 8)	2.6 (2.2-3.0)[c]
• Regular	384	109	762 (757, 5)	1.6 (1.3-1.9)[c]
• Irregular	420	77	726 (723, 3)	10.2 (7.9-13.1)[c]
Heavy exercise [MET=6]	767	144	368 (358, 10)	2.9 (2.4-3.4)[c]
Severe exercise [MET=7]	476	54	670 (655, 15)	2.6 (2.0-3.5)[c]
Extreme exercise [MET=8]	257	38	889 (884, 5)	4.5 (3.2-6.4)[c]
Sexual activity	641	26	505 (498, 7)	2.3 (1.5-3.4)[c]
Illicit drug use	69	16	1077 (995, 82)	2.8 (1.7-4.9)[c]
• Soft drugs only	19	4	1127 (1102, 25)	2.1 (0.7-6.48)
• Hard drugs only	15	3	1131 (1128, 3)	5.9 (1.5-22.9)
• Hard drugs +/- soft drugs	35	9	1093 (1111, 18)	2.7 (1.4-5.5)
Fever	279	19	867 (861, 6)	14.1 (8.5-23.5)[c]
Flu-like disease	407	20	739 (736, 3)	13.9 (8.9-21.9)[c]

[a]: Patients who were not exposed in the previous year.

[b]: Lack of necessary data per trigger factor, e.g. due to patients that did not answer specific questions about their usual frequency.

[c]: RR and 95% CI remained significant after correction for multiple hypothesis testing by Holm Bonferroni.

[d]: Regular (habitual) exercisers (>500 [MET] minutes per week, irregular (rare) exercisers (<500 [MET] minutes per week

Abbreviations: RR, relative risk; CI, confidence interval; [MET], metabolic equivalent of task.

Table 3. Relative Risk with 95% confidence intervals for two sensitivity analyses on trigger factors for any stroke

Trigger factor	RR (95% CI)	Patients excluded (>30 day interval)	RR (95% CI) Sensitivity 1[a]	RR (95% CI) Sensitivity 2[b]
Alcohol consumption	1.3 (0.9-2.0)	117	1.2 (0.8-2.0)	0.9 (0.6-1.3)
Cigarette smoking	0.6 (0.5-0.6)	67	0.6 (0.5-0.7)	[c]
Coffee consumption	1.0 (0.8-1.2)	170	0.9 (0.7-1.2)	0.6 (0.5-0.7)
Cola consumption	2.0 (1.5-2.8)[d]	77	1.8 (1.2-2.6)[d]	1.3 (0.9-1.8)
Vigorous physical exercise [MET≥6]	2.6 (2.2-3.0)[d]	224	2.6 (2.1-3.1)[d]	1.6 (1.4-1.8)[d]
Heavy exercise [MET=6]	2.9 (2.4-3.4)[d]	214	2.7 (2.1-3.3)[d]	1.8 (1.5-2.1)[d]
Severe exercise [MET=7]	2.6 (2.0-3.5)[d]	145	2.6 (1.9-3.6)[d]	1.7 (1.3-1.2)[d]
Extreme exercise [MET=8]	4.5 (3.2-6.4)[d]	75	4.8 (3.2-7.2)[d]	2.9 (2.0-4.0)[d]
Sexual activity	2.4 (1.6-3.5)[d]	178	2.8 (1.8-4.3)[d]	1.5 (1.0-2.2)
Illicit drug use	2.8 (1.7-4.9)[d]	12	3.7 (2.1-6.8)[d]	1.8 (1.1-3.0)
Fever	14.1 (8.5-23.5)[d]	68	18.1 (10.5-31.2)[d]	-
Flu-like disease	13.9 (8.9-21.9)[d]	112	18.4 (11.6-29.3)[d]	-

[a]: Exclusion of patients that completed the questionnaire >30 days after onset of stroke.
[b]: Usual frequency was calculated with 16 hour awake time and 8 hours of sleep, assuming exposure to all trigger factors except fever and flu-like disease more likely to be during waking hours.
[c]: No reliable RR with 95% CI could be calculated due to the very high usual frequency that exceeded the number of hours a year necessary to calculate a usual frequency.
[d]: RR and 95% CI remained significant after correction for multiple hypothesis testing by Holm Bonferroni.
Abbreviations: RR, relative risk; CI, confidence interval; [MET], metabolic equivalent of task.

Table 4. Relative Risk with 95% confidence intervals for trigger factors stratified by ischemic stroke and intracerebral hemorrhage

	Ischemic stroke		
Trigger factor	**Patients exposed in previous year**	**Patients exposed in hazard period**	**Patients not included (not exposed, missing data[a])**
Alcohol consumption	374	20	669 (407, 262)
Cigarette smoking	335	174	708 (593, 115)
Coffee consumption	606	108	437 (236, 201)
Cola consumption	321	35	437 (400, 37)
Vigorous physical exercise [MET≥6]	732	167	311 (311, 0)
Heavy exercise [MET=6]	699	132	344 (325, 19)
Severe exercise[MET=7]	445	50	598 (586, 12)
Extreme exercise[MET=8]	238	32	805 (801, 4)
Sexual activity	586	20	457 (451, 6)
Illicit drug use	67	15	976 (903, 73)
Fever	257	18	786 (780, 6)
Flu-like disease	372	20	671 (633, 38)

[a]: Data could be missing due to patients that did not answer specific questions about their usual frequency.
[b]: RR and 95% CI remained significant after correction for multiple hypothesis testing by Holm Bonferroni.

Trigger factors for causes of intracerebral hemorrhage

Table 6 shows the results for the macrovascular causes and 'other causes' in ICH. In the macrovascular category heavy exercise (RR 19.2, 95% CI 3.8-97.7) and extreme exercise (RR 83.2, 95% CI 5.2-1336.3) were trigger factors. For the category with all 'other causes', cola consumption, vigorous exercise, severe exercise, extreme exercise and sexual activity appeared to increase the risk of developing an ICH after exposure. Due to a small sample size, RR's could not be calculated in the 'macrovascular' group for the trigger factors cola consumption, severe exercise, illicit drug use, fever nor for flu-like disease in both the 'macrovascular' and 'other' groups.

	Intracerebral hemorrhage			
RR (95% CI)	**Patients exposed in previous year**	**Patients exposed in hazard period**	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**
1.2 (0.8-1.9)	37	4	66 (66, 0)	3.4 (1.2-9.5)
0.6 (0.5-0.6)	21	8	82 (77, 5)	0.6 (0.5-0.7)
1.0 (0.8-1.2)	53	10	50 (31, 19)	1.1 (0.5-2.2)
1.9 (1.4-2.7)[b]	25	4	78 (43, 35)	4.1 (1.0-16.6)
2.5 (2.1-3.0)[b]	72	19	31 (30, 1)	3.6 (2.1-6.1)[b]
2.9 (2.4-3.4)[b]	68	12	35 (33, 2)	2.8 (1.6-5.1)
2.5 (1.9-3.4)[b]	31	4	72 (69, 3)	5.8 (1.6-20.3)[b]
4.0 (2.8-5.8)[b]	19	6	84 (83, 1)	18.1 (3.9-84.6)[b]
1.9 (1.2-3.0)[b]	55	7	47 (46, 1)	5.6 (2.4-13.6)[b]
2.7 (1.6-4.7)[b]	2	1	101 (92, 9)	7.4 (0.5-118.7)
15.1 (9.0-25.5)[b]	22	1	81 (81, 0)	6.3 (0.6-62.8)
15.2 (9.7-23.8)[b]	35	0	68 (68, 0)	-[c]

[c:] Not a single patient with ICH was exposed to flu-like disease during the hazard period, therefore no RR could be calculated

Abbreviations: RR, relative risk; CI, confidence interval; [MET], metabolic equivalent of task.

Table 5. Relative Risk with 95% confidence intervals for trigger factors stratified by etiology according to TOAST classification for ischemic stroke and TIA

	Large vessel atherosclerosis + likely atherothrombotic stroke (N=172)		
Trigger factor	**Patients exposed in previous year (exposed in hazard period)**	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**
Alcohol consumption	48 (3)	124 (83, 41)	1.2 (0.4-3.8)
Cigarette smoking	77 (36)	95 (63, 32)	[b]
Coffee consumption	97 (17)	75 (32, 43)	0.9 (0.5-1.5)
Cola consumption	55 (4)	117 (55, 62)	0.9 (0.3-2.4)
Vigorous physical exercise [MET≥6]	112 (20)	60 (59, 1)	1.6 (1.0-2.6)
Heavy exercise [MET=6]	110 (17)	62 (60, 2)	1.8 (1.1-3.0)
Severe exercise [MET=7]	53 (6)	119 (117, 2)	2.1 (0.9-4.8)
Extreme exercise [MET=8]	30 (6)	142 (142, 0)	7.1 (2.5-20.2)[c]
Sexual activity	85 (5)	87 (86, 1)	2.9 (1.3-6.5)
Illicit drug use	10 (1)	162 (133, 29)	1.1 (0.2-8.1)
Fever	33 (3)	139 (138, 1)	18.8 (5.8-61.0)[c]
Flu-like disease	61 (6)	111 (111, 0)	24.8 (10.8-56.9)[c]
	Other determined stroke (N=225)		
Trigger factor	**Patients exposed (year, hazard period)**	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**
Alcohol consumption	83 (6)	142 (90, 50)	1.7 (0.8-3.6)
Cigarette smoking	65 (32)	160 (132, 28)	0.9 (0.5-1.6)
Coffee consumption	125 (21)	100 (60, 40)	0.9 (0.5-1.4)
Cola consumption	71 (14)	154 (82, 72)	4.9 (2.6-9.3)[c]
Vigorous physical exercise [MET≥6]	154 (40)	71 (70, 1)	3.4 (2.4-4.9)[c]
Heavy exercise [MET=6]	143 (26)	82 (78, 4)	3.2 (2.1-4.9)[c]
Severe exercise [MET=7]	95 (12)	130 (127, 3)	2.6 (1.5-4.4)[c]
Extreme exercise [MET=8]	48 (6)	177 (175, 2)	4.7 (2.0-10.8)[c]
Sexual activity	112 (5)	113 (101, 12)	2.4 (0.9-6.4)
Illicit drug use	14 (4)	211 (195, 16)	4.3 (1.3-14.0)
Fever	58 (4)	167 (165, 2)	13.1 (3.4-51.0)[c]
Flu-like disease	78 (4)	147 (146, 1)	15.5 (5.6-42.9)[c]

[a]: Data could be missing due to patients that did not answer specific questions about their usual frequency.
[b]: No reliable RR with 95% CI could be calculated due to the very high usual frequency that exceeded the number of hours a year necessary to calculate a usual frequency.

Small vessel disease (N=133)			**Cardio-embolic stroke** (N=180)		
Patients exposed (year, hazard period)	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**	**Patients exposed (year, hazard period)**	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**
52 (1)	81 (49, 32)	0.4 (0.1-2.5)	74 (3)	106 (61, 45)	1.0 (0.3-3.0)
51 (32)	82 (66, 16)	[b]	42 (24)	138 (130, 8)	0.9 (0.5-1.6)
79 (14)	54 (28, 26)	0.8 (0.5-1.4)	115 (21)	65 (37, 28)	1.3 (0.8-2.1)
40 (2)	93 (55, 38)	0.7 (0.2-2.3)	53 (6)	127 (68, 59)	2.8 (1.2-6.8)
88 (14)	45 (43, 2)	1.2 (0.7-2.0)	137 (32)	43 (43, 0)	2.9 (2.0-4.2)[c]
84 (11)	49 (41, 8)	1.6 (0.9-3.0)	134 (28)	46 (44, 2)	3.1 (2.1-4.5)[c]
57 (4)	76 (73, 3)	1.0 (0.4-2.5)	94 (10)	86 (86, 0)	3.6 (1.8-7.1)[c]
27 (2)	106 (105, 1)	1.9 (0.4-8.8)	49 (6)	131 (131, 0)	4.0 (1.6-10.5)[c]
78 (2)	55 (54, 1)	1.4 (0.3-5.6)	114 (4)	66 (65, 1)	2.2 (0.8-5.8)
13 (4)	120 (113, 7)	4.8 (1.4-16.5)	12 (1)	168 (161, 7)	1.0 (0.1-8.4)
25 (0)	108 (108, 0)	-	55 (6)	125 (125, 0)	29.1 (12.3-68.4)[c]
45 (1)	88 (88, 0)	7.1 (1.0-51.6)	68 (5)	112 (111, 1)	22.2 (8.8-55.8)[c]
Multiple causes (N=65)			**Cryptogenic stroke** (N=268)		
Patients exposed (year, hazard period)	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**	**Patients exposed (year, hazard period)**	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**
15 (0)	50 (29, 21)	-	102 (7)	166 (95, 71)	1.8 (0.8-4.0)
30 (18)	35 (27, 8)	0.8 (0.4-1.4)	70 (32)	198 (174, 24)	0.5 (0.4-0.8)
37 (9)	28 (18, 10)	1.2 (0.5-2.5)	154 (26)	114 (60, 54)	1.0 (0.7-1.5)
25 (3)	40 (21, 19)	1.3 (0.5-3.9)	78 (7)	190 (118, 72)	2.0 (0.9-4.4)
46 (10)	19 (18, 1)	2.8 (1.6-5.2)[c]	196 (51)	72 (70, 2)	3.2 (2.3-4.3)[c]
44 (8)	21 (20, 1)	4.6 (2.0-10.7)[c]	185 (42)	83 (81, 2)	3.7 (2.7-5.1)[c]
25 (5)	40 (40, 0)	3.8 (1.4-10.4)[c]	121 (13)	147 (143, 4)	3.3 (1.9-5.7)[c]
14 (4)	51 (51, 0)	4.6 (1.7-12.6)[c]	70 (8)	198 (197, 1)	3.2 (1.7-6.2)[c]
40 (0)	25 (25, 0)	-	147 (4)	121 (120, 1)	1.5 (0.6-4.1)
7 (0)	58 (55, 3)	-	11 (5)	257 (236, 21)	4.0 (1.7-9.7)[c]
13 (2)	52 (50, 2)	48.4 (10.2-230.3)[c]	74 (3)	194 (193, 1)	7.9 (2.5-25.5)[c]
21 (0)	44 (43, 1)	-	100 (4)	168 (168, 0)	10.4 (3.9-28.1)[c]

[c:] RR and 95% CI remained significant after correction for multiple hypothesis testing by Holm Bonferroni.
Abbreviations: RR, relative risk; CI, confidence interval; [MET], metabolic equivalent of task.

Table 6. Relative Risk with 95% confidence intervals for trigger factors stratified by etiology for intracerebral hemorrhage

	Macrovascular [a] (N=25)	
Trigger factor	**Patients exposed in previous year (exposed in hazard period)**	**Patients not included (not exposed, missing data[a])**
Alcohol consumption	12 (1)	13 (4, 9)
Cigarette smoking	2 (1)	23 (23, 0)
Coffee consumption	12 (3)	13 (7, 6)
Cola consumption	3 (0)	22 (11, 11)
Vigorous physical exercise [MET≥6]	17 (5)	8 (8, 0)
Heavy exercise [MET=6]	17 (4)	8 (8, 0)
Severe exercise [MET=7]	8 (0)	17 (17, 0)
Extreme exercise [MET=8]	3 (1)	22 (22, 0)
Sexual activity	16 (1)	9 (9, 0)
Illicit drug use	0 (0)	25 (22, 3)
Fever	3 (0)	22 (22, 0)
Flu-like disease	2 (0)	23 (23, 0)

[a]: Macrovascular causes contain patients with arteriovenous malformations (AVM), cavernous malformation and dural arteriovenous fistula.
[b:] RR and 95% CI remained significant after correction for multiple hypothesis testing by Holm Bonferroni.

	Other (N=78)		
RR (95% CI)	**Patients exposed (year, hazard period)**	**Patients not included (not exposed, missing data[a])**	**RR (95% CI)**
1.8 (0.3-12.8)	25 (3)	53 (33, 20)	4.7 (1.4-16.3)[b]
16.0 (0.0-6598.3)	19 (7)	59 (55, 4)	0.5 (0.5-0.6)
1.7 (0.5-6.0)	41 (7)	37 (24, 13)	0.9 (0.4-2.2)
-	22 (4)	56 (32, 24)	5.1 (1.2-22.0)[b]
17.6 (4.5-69.1)	55 (14)	23 (22, 1)	2.7 (1.5-5.0)[b]
19.2 (3.8-97.7)[b]	51 (8)	27 (25, 2)	2.0 (1.0-4.0)
-	23 (4)	55 (53, 2)	6.7 (1.9-24.5)[b]
83.2 (5.2-1336.3)[b]	16 (5)	62 (61, 1)	15.2 (2.7-86.0)[b]
4.1 (0.5-33.0)	39 (5)	39 (38, 1)	6.1 (2.3-16.2[b]
-	2 (1)	76 (71, 5)	7.4 (0.5-118.7)
-	19 (1)	59 (59, 0)	6.6 (0.7-67.4)
-	33 (0)	45 (45, 0)	-

Abbreviations: RR, relative risk; CI, confidence interval; [MET], metabolic equivalent of task.

DISCUSSION

We found cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever and flu-like disease as possible trigger factors for stroke overall, and for ischemic stroke in young adults, with the highest RR for fever and flu-like disease. For ICH, cola consumption, vigorous physical exercise and sexual activity were trigger factors, but not illicit drug use, fever and flu-like disease. Trigger factors differed according to etiologic groups of ischemic stroke. We identified the most (four) trigger factors for stroke with other determined cause and for cryptogenic strokes. Vigorous physical exercise showed the highest PAF.

Several plausible biological explanations exist on how trigger factors increase the risk of stroke. First, some trigger factors, such as caffeine consumption,[218, 219] certain types of drugs,[220] sexual activity[221] and vigorous physical exercise,[211] transiently increase blood pressure. An increased blood pressure may result in increased shear stress on the arterial vessel wall, potentially resulting in the disruption of the endothelial cell surface. This can consequently increase the risk of thrombotic occlusion, especially in combination with a hypercoagulable state reportedly to be induced by strenuous physical exercise.[211, 222, 223] Conversely, a sudden rise in blood pressure might trigger rupture of a vessel wall resulting in an ICH.[203, 206] Also, some drug types are known to cause vasospasms without a blood rise, which can also lead to stroke.[224]

Second, fever and flu-like disease may result in an increased stroke risk as it can lead to systemic inflammation with endothelial dysfunction, a prothrombotic condition and increased platelet activation and aggregation.[206, 214, 225, 226] Our finding of fever and flu-like disease to be trigger factors is in line with previous literature investigating trigger factors in an older population.[206, 214] Given the observation that the one year cumulative incidence of infection is much higher than the incidence of stroke at young age,[1-3, 227] future research should identify when and which environmental, genetic or other factors predispose young people to ischemic stroke. The ongoing case control SECRETO study may potentially shed light on these mechanisms.[228]

In contrast to previous studies in older populations, coffee consumption was not identified as a trigger factor for any type of stroke in our young population.[203, 206, 212] A possible explanation may be that the effect of a sudden blood pressure surge differs between old and young people, with the elderly more often having longstanding hypertension, atherosclerosis and reduced vessel wall elasticity.[229, 230]

In line with previous literature, we did not find cigarette smoking as a trigger factor, and even found a negative relative risk. The main difference we found regarding coffee consumption and cigarette smoking compared to the significant trigger factors in our study, was the high usual daily frequency of cigarette smoking and coffee consumption, versus less frequent occurrence of triggers such as (extreme) exercise, sexual activity, illicit drug use and fever or flu-like disease. To date, there is only one study that found cigarette smoking to be a trigger factor, however this was a case-control study investigating patients with a subarachnoid hemorrhage (SAH) with controls from the general population, in which SAH patients smoked much more compared to the controls. One can therefore speculate that a regular, high consumption of coffee and very frequent habituation of cigarette smoking may lead to tolerance of the hemodynamic effects of caffeine and nicotine.[231, 232]

Our study may provide etiologic clues especially for young patients with stroke without an identifiable cause. Vigorous physical exercise and the different bouts of exercise, illicit drug use, fever and flu-like disease may all result in a temporary rise in blood pressure or a prothrombotic condition.[203, 211, 214, 218-223, 225, 226] However, this study alone is not enough to validate the causality of trigger factors in young patients with cryptogenic stroke. To obtain further support for a role of trigger factors in (cryptogenic) stroke, these patients could be followed for recurrent stroke and their relationship with the earlier identified trigger factor. In addition, more objective measurements of blood pressure and other vital functions at the time of some of the trigger factors can be obtained with the use of "wearable electronic devices", e.g. smartwatches and comparable applications.[233] This would also help to look at individual differences in reaction to triggers, which could be further studied with individual measurements and blood tests before and afterwards.

Our study has several strengths. First, we add novelty to the existing literature by investigating young adults with stroke specifically, in a unique sample of over 1000 young adults with stroke, which allowed for subanalyses regarding both stroke type and etiology of ischemic stroke. Second, the case-crossover design allowed us to limit confounding by patient specific characteristics, such as age, sex, comorbidity and vascular risk factors. Third, the large sample size of our cohort, with patients prospectively included in both academic and general hospitals in the Netherlands in different regions, provides a reliable representation of a stroke population consisting of young adults. Fourth, results largely remained in sensitivity analyses, suggesting that recall bias and bias due to unreliable data did not have a large influence on our results. Fifth, due to our sample size we were able to investigate categories of specific trigger factors separately, such as grades of physical exercise, fever

and flu-like disease.[203, 204, 206] Reporting RR's stratified by the severity of physical exercise might be of additional value, since, circulating levels of catecholamines and hence platelet activation, are supposedly related to the relative intensity of physical exercise.[222]

There are also limitations that need to be addressed. Survival and selection bias might have been introduced, since patients with a more severe stroke who died before being able to complete the questionnaire, or who had too severe symptoms or cognitive deficits, were not included. This might have affected the generalizability of our results. However, it is unlikely that trigger factors influence the severity of stroke.[206] Given that trigger factors are believed to only cause a short-lasting relative risk, potentially leading to stroke, there is no pathophysiological plausible explanation that they would be related to larger emboli and thus more severe stroke, though formal evidence is lacking. Second, recall bias might have occurred, given the detailed questions that patients were asked about their activities and exposure previous to such a serious life-event as stroke, although in the sensitivity analyses this did not appear to be an important factor. Third, we had a small sample of patients with ICH, and exposure to illicit drug use. Fourth, we were not able to distinguish between different types cola consumption (e.g. regular cola, diet cola etc.). We did not gather information on caffein-containing energy drinks. Fifth, the number of missing data on the trigger factors assessed varied. On the one hand, a lot of patients have filled in ''unknown'' to one or more questions about the last exposure, usual exposure or amount of exposure to a certain trigger factor, leading to exclusion for that specific analysis. On the other hand, missing data may have been caused by incomplete answering questions because patients felt it inappropriate to reveal personal, private details. This may have led to an underestimation of some of these trigger factors, and to smaller subgroups per trigger factor which may have influenced the width of the 95% CI's.

Clinical importance

Trigger factors might not have the same effect on every individual. More insight into the personalized effect of trigger factors would provide more insight in why certain people are affected by a trigger factor, and why other people are not, possibly leading to new information into stroke mechanisms and eventually tailor-made preventive advice. One could think of several explanations for varying effects on individuals of the trigger factors that turned out relevant in our study. For example, caffeine consumption and exercise are believed to create a lower risk for individuals who are frequently exposed in comparison to those who are not.[211, 212] For illicit drug use, the individual variety of pharmacokinetic interactions could lead to a different outcome per individual. In addition, other individual characteristics or comorbidities can contribute to the role a

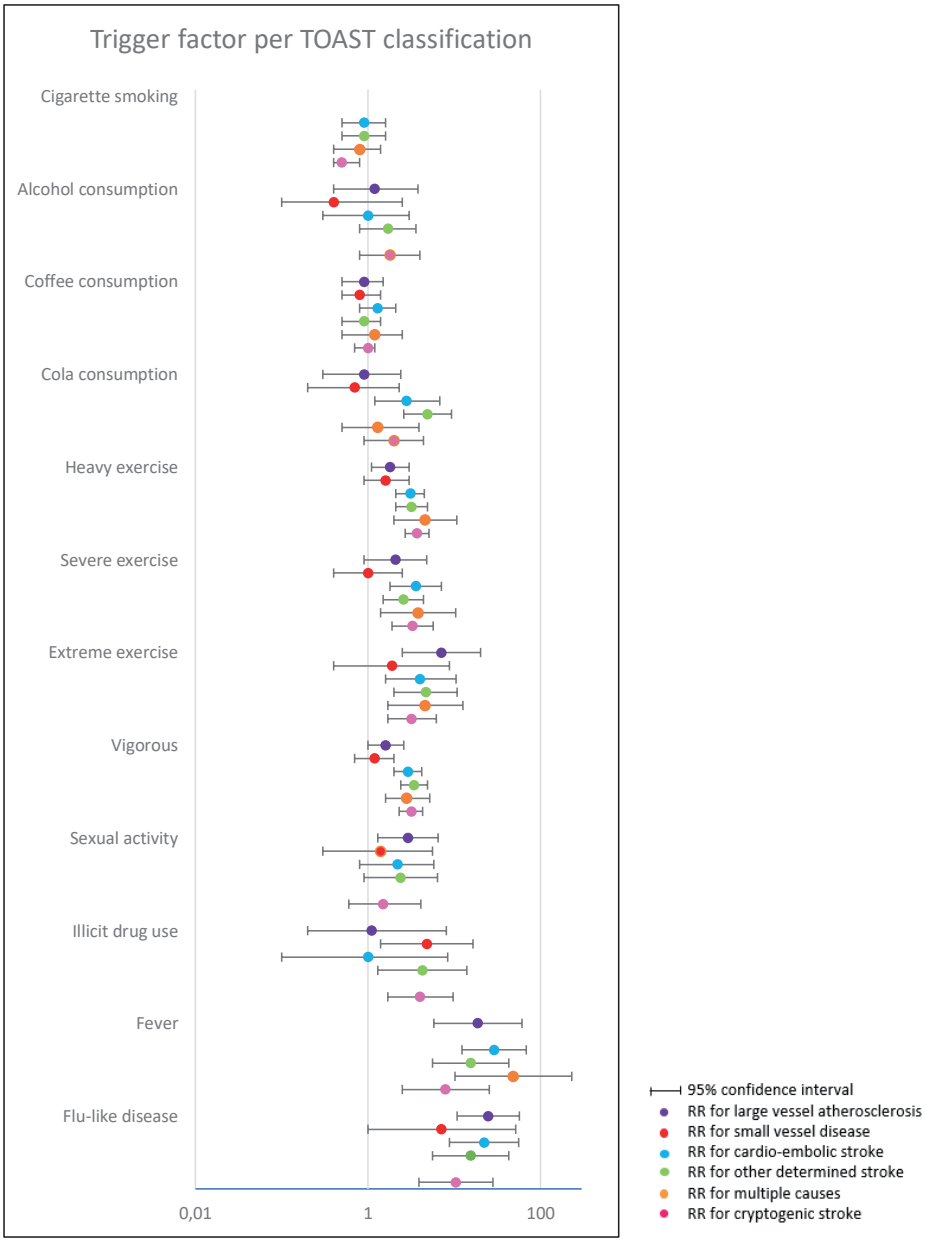
trigger factor might play. For example, while the systemic inflammatory effects of fever and flu-like disease may serve as a trigger for both ischemic stroke and ICH, some viral infections such as COVID-19, are known for the risk of venous thrombosis.[234] This will allegedly not increase the risk for arterial stroke, unless for example an individual also has a patent foramen ovale (PFO).[235]

CONCLUSIONS

To conclude, fever and flu-like disease are strongest trigger factors for stroke in young adults, followed by cola consumption, vigorous physical activity exercise, sexual activity and illicit drug use. Future research should focus on how and when trigger factors are converted into risk factors in which patients to clarify etiology in the substantial group of (cryptogenic) stroke in young patients and provide more personalized prevention.

SUPPLEMENTARY MATERIALS

Supplementary Figure 1. Relative Risk per trigger factor stratified by TOAST classification



Supplementary Table 1. Relative Risk with 95% confidence intervals for trigger factors for any stroke with a two hour hazard period

Trigger factor	Patients exposed in previous year	Patients exposed in hazard period	Patients not included (not exposed, missing data[a])	RR (95% CI)
Alcohol consumption	411	36	735 (444, 291)	1.0 (0.7-1.4)
Coffee consumption	659	170	487 (267, 220)	0.6 (0.5-0.7)
Cola consumption	346	48	800 (443, 357)	1.2 (0.9-1.6)
Illicit drug use	69	16	1077 (995, 82)	6.0 (3.5-10.5)[b]

[a]: Data could be missing due to patients that did not answer specific questions about their usual frequency or filled in "unknown".
[b]: RR and 95% CI remained significant after correction for multiple hypothesis testing by Holm-Bonferroni.
Abbreviations: RR, relative risk; CI, confidence interval.

Part III

Worldwide differences in stroke in young adults

Chapter 7

Ischemic stroke in young adults from a global perspective

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ABSTRACT

Ischemic stroke at young age is an increasing problem in both developing and developed countries due to rising incidence, high morbidity and mortality and long-term psychological, physical and social consequences. Compared with stroke in older adults, stroke in young adults is more heterogeneous due to the wide variety of possible underlying risk factors and etiologies. In this review, we will provide an overview of the global variation in the epidemiology of stroke in young adults, with special attention to differences in geography, ethnicity/race and sex, as well as traditional and novel risk factors for early-onset ischemic stroke, such as air pollution. Understanding global differences is an important prerequisite for better region-specific prevention and treatment of this devastating condition.

INTRODUCTION

More than 11 million ischemic strokes occur worldwide each year, of which more than the half occurs in low- and middle-income countries.[236] Although the incidence of ischemic stroke increases with age, an estimated 10-20% of these events occur in young people aged 18-50 years. This disorder is a major cause of long-term disability and has profound effect on quality of life of patients and caregivers.[36] In contrast to stroke in older adults, the incidence of ischemic stroke among young adults is rising globally.[1, 4, 5, 169]

Ischemic stroke in young adults affects people of all races and ethnicities, though the incidence and causes vary considerably among different countries, sex and ethnic groups. These differences can not solely be explained by resource-dependent differences in diagnostic work-up and treatment.[3, 236, 237] Understanding the epidemiology of ischemic stroke in young adults in different regions of the world is important for developing adequate region-specific preventive and management strategies to reduce the global burden of young stroke. Furthermore, an appreciation of geographic differences in the causes of ischemic stroke in young adults may also lead to a specific diagnosis in a previously cryptogenic stroke. Most current reviews of stroke in young adults provide information about the etiology and diagnostic approach written mainly from a high-income perspective and do not take global differences into account.

This review aims to provide an up-to-date synthesis of studies on the global differences of ischemic stroke in young adults, emphasizing the differences in epidemiology (incidence and prevalence) regarding geography, ethnicity/race and sex. Furthermore, we will review the more traditional vascular risk factors and geographic and racial/ethnic differences in their prevalence and strength of association with stroke.

METHODS

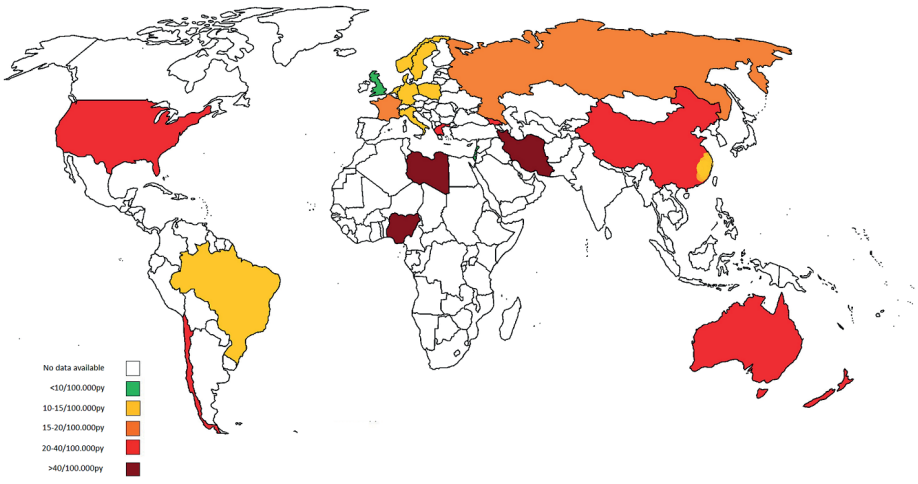
For this review, we searched in MEDLINE and WHO Database for articles published from 1 January 2008 to 1 January 2020. The following search terms (including Medical Subject Headings) were used in multiple combinations: 'ischemic stroke, young adults, incidence, global, epidemiology, infection, sex differences, race, ethnicity, risk factors, diabetes, hypertension, obesity, dyslipidemia, physical inactivity, smoking, alcohol consumption, air pollution, causes, dissection, moyamoya, HIV, Chagas, sickle cell disease, neurocysticercosis'. Other rare causes of ischemic stroke in the young were not included in this review as their global prevalence is low. The reference list of relevant articles was screened for other useful content (Supplementary Figure 1). Over 2000 abstracts were screened, all relevant studies published in English or Dutch were included. The final reference list was generated on the basis of relevance to the topics covered in this review. Being a narrative review, in case of multiple studies with the same data, the most up-to-date article was included.

EPIDEMIOLOGY AND STROKE ETIOLOGY FROM A GLOBAL PERSPECTIVE

Geographical differences

Incidence of young ischemic stroke differs considerably worldwide and is generally higher in developing countries than in industrialized countries (Figure 1).[236] Published incidence of young stroke varies from 5-15 per 100,000 person-years in many European countries to 20 per 100,000 person-years in most Northern-American, Australian and Asian studies countries and up to 40 per 100,000 person-years in some African countries and Iran.[59, 237-239] However, the exact global incidence of stroke in young adults remains a knowledge gap, data on incidence and prevalence are lacking for many African and Asian countries, as depicted in figure 1. Further methodological differences hinder proper comparisons of published incidences, which include the heterogeneity in the definition of young stroke regarding age limits used and the inclusion of other stroke subtypes. Despite these differences that do not fully seem to explain the large observed differences, a few inferences can be made. The higher incidence of stroke in young adults in low-income countries compared with high-income countries can partially be explained by differences in occurrence of risk factors and causes (see below), including the presence of rheumatic heart disease, infections such as HIV and the lesser detection and treatment of vascular risk factors due to limited resources.[1, 4, 9, 12, 170] Etiological differences by geography have been reported.

Figure 1. Global differences in incidence of stroke in young adults[1, 5, 9, 10, 12, 237-242]



*Years of represented incidence rates vary, as do lower (18 or 20) and upper age limits (45-55) in different countries.

Abbreviations: py, person-years.

Moyamoya disease is a rare, non-atherosclerotic arteriopathy characterized by progressive stenosis of the internal carotid arteries, ultimately leading to occlusion.[80] The prevalence of moyamoya disease is higher in children and young adults than those aged 50 years or over and varies widely worldwide. However, the prevalence is unknown in many non-Asian countries.[80] The highest prevalence is found in Asian countries with 10.5 per 100,000 persons in Japan[243] and 16.1 per 100,000 persons in Korea[244] to 3.92 per 100,000 persons in China[245]. While the prevalence is much lower in Western countries, exact numbers are unknown. Corresponding with the prevalence, high incidences were found in Japan (0.94 per 100,000 population)[243], South Korea (2.3 per 100,000 population)[244], and China (0.43 per 100,000 population)[245], while the incidence in Washington and California (0.086 per 100,000 population) is much lower.[246] Exact prevalence and incidence of moyamoya disease in other regions is lacking.

Sickle cell disease is a genetic hematological disorder, caused by the sickle mutation on the hemoglobin gene. The most severe form is homozygous hemoglobin S (HbSS), which is associated with ischemic stroke.[247] In the USA, the rate of ischemic stroke in sickle cell disease increased with age and was 740 per 100,000 person years in middle-aged (35-64 years) category, which is 3-fold higher than in peers.[248] The less severe form is the heterozygous sickle cell trait.[247] Although sickle cell disease is considered a monogenic disorder with stroke as one of the primary manifestations, a recent meta-analysis showed that sickle cell trait was not associated with the incidence of ischemic stroke among African Americans suggesting that also other mechanisms may contribute.[249] The global distribution of sickle cell disease varies widely[250]. Africa accounts for 75%, followed by South-East Asia with 15% of the global total of homozygote neonates per year. By comparison Europe has 1.3% and America has 4.6% of the global total of homozygote neonates per year.[250]

Preventable infectious causes of stroke are rare in developed countries but are still frequently seen in developing countries. In addition, in many developed countries due to a more complete diagnostic workup a reliable cause of stroke may be established. However, in cryptogenic strokes, a patient's travel history may not often extensively be examined, although it may be of importance in few cases. Two examples of infectious causes found in developing countries are rheumatic heart disease and Chagas disease, which should be considered as a possible cause of cardio-embolic stroke in high-prevalence areas such as Africa, the Middle East and Southeast Asia.[251] Rheumatic heart disease is caused by an abnormal immune response to untreated group A streptococcal infection causing valvular damage and consequently an increased risk for cardio-embolic stroke. Prevalence of rheumatic heart disease in young ischemic patients varies from 1.8% to 2.0% in Europe and Northern America to 3.4% to 23.2% in Asia.[252] Chagas disease is a parasitic disease caused

by a tropical protist and has an estimated prevalence of 6.6 million people, mostly in Central and South-American countries. The incidence of stroke in patients with Chagas disease is unknown, due to unawareness of the infection in many patients. Chagas disease can result in cardiomyopathy, with an associated higher risk of stroke (OR 2.10, 95% CI 1.17 to 3.78).[253] It can be effectively treated with benznidazole and nifurtimox.[253]

Other infections are also associated with a high risk of ischemic stroke, including HIV, neurocysticercosis and tuberculosis. HIV has a high prevalence in sub-Saharan Africa with over two-thirds of the world's population.[254, 255] In this specific region, stroke was commonly found to be the first manifestation of HIV infections. In a systematic review, over 90% of young adults with stroke in sub-Saharan Africa with HIV were ischemic strokes and stroke patients with HIV often had a coagulopathy and more severe stroke compared with young adults with stroke without HIV.[254] Similarly, these findings may also be found in other developing countries. After adjusting for vascular risk factors, an increased risk of stroke in HIV patients has been found in both men [256] and women.[257] Possible mechanisms of stroke in HIV-patients are changes in coagulation state, cardio-embolism, HIV-associated vasculitis, HIV-associated vasculopathies and mycotic aneurysms.[258]

Neurocysticercosis is an infectious parasitic disease caused by cerebral cysts of a tapeworm found in pigs. An inflammatory reaction surrounding cerebral cysts can induce infarcts due to narrowing and occlusion of both large and small vessels.[259] This disease is associated with local cultural practices and poor sanitation, and occurs frequently in rural areas of Latin America, in sub-Saharan Africa and in Asia.[259, 260] Tuberculosis is associated with increased risk of ischemic stroke that results from vasculitis or intimal proliferation causing thrombosis.[261] Stroke in tuberculosis occurs in 15-57% of patients with tuberculosis meningitis, especially in severe cases. In India, in young stroke patients up to 8% of patients tuberculosis was the cause.[261] The incidence rates of tuberculosis vary among countries with highest rates in Africa and Asia.[255, 261]

The most frequent solitary rare cause of ischemic stroke in young adults is arterial dissection, which causes up to 15% of all young strokes.[7, 194] Due to insufficient financial resources in developing countries, not all young stroke patients receive adequate imaging to detect an arterial dissection. In Europe, extracranial artery dissections are more common whereas in Asia intracranial dissections are more common.[76, 78]

Racial and ethnic differences

Racial and ethnic variations of incidence and prognosis of stroke in the young are reported.[4, 8, 262-265] In the USA, the stroke incidence among blacks and Hispanics (both 11 per 100,000 persons/year) was found higher than in whites (7 per 100,000 persons/

year).[8, 262] The disparity in incidence rates between blacks and whites in the USA is highest between the third and fourth decade of age.[263] For both blacks and whites an increasing incidence of stroke in young adults is described over time.[4] In the USA, the length of hospital stay was found longest in Hispanics compared to blacks and whites. In blacks, the hospital stay was longer than in whites.[262, 264] This can partially be explained by the higher medical complications (e.g., pneumonia, deep venous thrombosis or urinary tract infections)among Afro-American compared to Caucasian-American.[264] Afro-Americans were more likely to be discharged to a rehabilitation facility, skilled nursing facility or a long-term-care hospital compared to Caucasian-Americans.[264] Also, mortality was found to be higher in blacks compared to whites. Hispanics have a lower early mortality risk.[8, 262] An international multicentre study evaluated young stroke patients from prospective databases of North America, Europe, and Asia and described differences in hospitalization, functional outcome and mortality.[265] This study found that Asians (National Institute of Health Stroke Scale (NIHSS) score of 8 (median: 5-14)) had significantly higher stroke severity at admission than blacks (NIHSS score of 7 (median: 3-12)) and whites (NIHSS score of 3 (median: 1-9)) ($p<0.001$)).[265] In addition, early mortality was found to be lower in Asians compared to blacks and whites.[265] A population study in Australia reported on stroke differences between the Aboriginal and Torres Strait Islanders compared with the total Australian population. Aboriginals had an approximately double ischemic stroke incidence compared with non-Aboriginals (incidence rate ratio of 2.4, $p=0.06$). In the total group no differences were found in the crude 1-year mortality of all cause stroke.[266]

Sex differences

Conflicting results about incidence in men and women have been reported. Several studies from Europe and the USA showed a higher incidence in women under the age of 30 or 44 years.[1, 7, 56, 267] In contrast, the incidence rates were similar between both sexes in France (18-55 years),[9] and in Spain, the incidence was higher among men (18-54 years).[11] In Chinese adults (aged 20-49 years), there were no statistically differences in the age-standardized prevalence of ischemic stroke between men and women.[268] The (rate of) increasing incidence of stroke at young age differs between men and women. A higher increase of stroke in women is found than in men below the age <35 years,[177, 267] whereas there is a higher increase of stroke incidence in men >35 years.[177] Regarding outcome after stroke, higher mortality-rates and a higher risk for recurrent vascular events were found in men compared to women.[54]

These differences are in part related to the female-specific risk factors and causes, for example oral contraceptives, pregnancy and puerperium and the higher incidence of migraine and auto-immune disorders among women. According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)-criteria, male predominance is mostly

found in large artery disease and small vessel disease, whereas female predominance was found in other determined etiology.[57] Smoking, diabetes mellitus type 1 were associated with ischemic stroke in both men and women. The prevalence of risk factors for cardiovascular disease (the presence of coronary heart disease, heart failure, or peripheral arterial disease), diabetes mellitus type 2, hypertension, a positive family history and low high-density lipoprotein (HDL) cholesterol were significant only among men in a recent Finnish study.[269] (Figure 2). The population attributable risks (PARs) of hypertension, diabetes mellitus, smoking and alcohol consumption were higher in men than in women. In contrast, the PARs of physical inactivity and overweight/obesity were higher in women than in men.[85]

VASCULAR RISK FACTORS FROM GLOBAL PERSPECTIVE

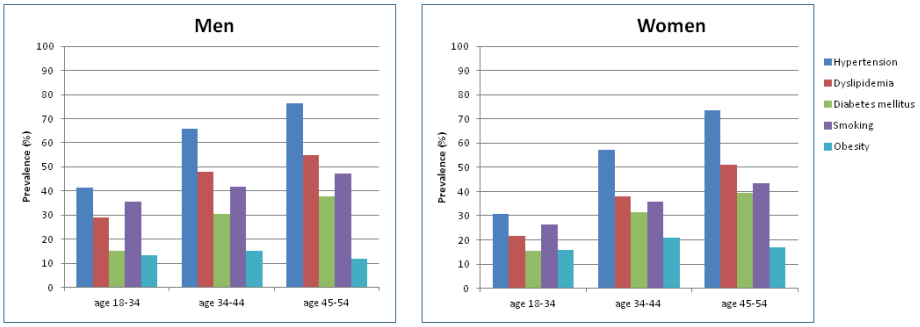
While the prevalence of certain risk factors is declining in the general population (e.g. smoking), the prevalence of the modifiable vascular risk factors (including hypertension, smoking, dyslipidemia, diabetes and obesity) is increasing among young stroke patients (Figure 2).[4, 7, 68, 169] Young stroke patients have approximately twice as many risk factors compared to their peers.[68] Furthermore, the prevalence of having multiple risk factors is increasing.[68, 194, 270] The risk of future vascular events increases equally with the number of risk factors.[271] The increase in vascular risk factors seems to be more pronounced in the population aged 35 years and older than in the younger population.[1, 4, 7, 34] Table 1 shows the strength of the associations between stroke and common vascular risk factors based on two different case-control studies, one based on a population-based prospective control sample [269] and the other with controls surveyed over telephone[85]. Both studies are performed in European countries. There remains a knowledge gap since most PAR studies for young individuals with stroke specifically lack data from South America, Asia, Africa and Australia, leaving another knowledge gap. [68, 85, 269] These continents are included in large cohort studies that have reported on the differences in risk factors from a global perspective, for example, the Global Burden Study, the INTERSTROKE study and the PURE study.[84, 272, 273] These studies show that modifiable risk factors account for a large proportion of stroke globally, while regional variation in the importance of risk factors was found. For example, in the PURE study, some modifiable risk factors, such as hypertension, have global effects, while other risk factors, including air pollution, differ by the income level of the country. Whether these findings are also applicable to young ischemic stroke patients is uncertain, as these studies did not investigate ischemic stroke, stratified by age 18 to 50 years (i.e., young stroke), specifically. In the INTERSTROKE study, only 11.8% of patients was under the age of 45 years. The INTERSTROKE study did report on differences between patients <55 and >55 years of age for some risk factors (for example, alcohol consumption, diabetes, smoking and obesity), however this was neither ischemic stroke nor continent specific.[84, 272, 273]

Hypertension

Approximately 35% of young ischemic stroke patients were diagnosed with hypertension.[7, 9, 56, 85] In the Global Burden Study, the PAR for hypertension was highest in Southeast Asia (54.8%) and lowest in Eastern and central Europe and the Middle East (40.7%).[3] The Stroke in Young Fabry Patients (SIFAP) study showed that hypertension was the most important individual risk factor for ischemic stroke, with a PAR of 25.5% (95% CI 22.1 to 28.2) and is associated with stroke in young adults (OR: 2.3; 95% CI 2.0 to 2.6).[85, 269] Lower risks were found in a Finnish young stroke study with a PAR of 12.2% (95% CI 5.9-17.4)

and OR of 1.43 (95% CI 1.17-1.75).[269] Although not young stroke specific, the WHO reports the highest prevalence of hypertension in Africa (46%), whereas the lowest prevalence was reported in North-America and South-America (35%).[274]

Figure 2. Prevalence of traditional vascular risk factors in young patients stratified by age and sex



Data adapted from Rolfs *et al.*[57]

Table 1. Modifiable risk factors and their risk of ischemic stroke
Data adapted from Kivioja *et al.*[a] and Aigner *et al.*[b 85, 269]

Risk Factor	OR (95% CI)	PAR (95% CI)
Diabetes Mellitus type 1[a]	6.72 (3.15-14.33)	3.9 (3.1-4.3)
Diabetes Mellitus type 2[a]	2.31 (1.35-3.95)	2.6 (1.2-3.4)
Hypertension[a]	1.43 (1.17-1.75)	19.9 (14.8-23.9)
Dyslipidemia[a]	0.9 (0.8-1.1)	-2.1 (-6.7-2.6)
Obesity[b]	1.2 (1.0-1.5)	6.9 (0.0-13.8)
Physical inactivity[b]	5.9 (5.1-6.7)	59.8 (56.2-63.4)
Current smoking[a]	1.81 (1.50-2.17)	15.0 (8.1-21.8)

Abbreviations: OR, odd ratios (adjusted); PAR, population attributable risk.

Diabetes

Diabetes mellitus is found in up to 10% of young stroke patients.[7, 9, 56, 85] The PAR for diabetes mellitus in young adults is 4.8% (95% CI 2.9-6.7) and diabetes mellitus is associated with higher risk of stroke (OR 1.9; 95% CI 1.5-2.3).[85] More disturbingly, the incidence of type 2 diabetes in young adults is increasing.[7] Global differences are seen in the prevalence of diabetes. The top three countries with the highest prevalence include India, China and the USA.[275] The PAR for diabetes mellitus was highest in Southeast Asia (28.6%) and lowest in Western Europe, North-America and Australia (3.5%).[3] In the

USA, racial disparities are seen with higher incidence rate of newly diagnosed diabetes for blacks and Hispanics compared with whites. The increase in incidence of newly diagnosed diabetes is highest among non-Hispanic blacks (16.3% to 20.6%) and Mexican Americans (17.5% to 20.5%).[276] The Diabetes Study of Northern Carolina reported that Pacific Islanders (18.3%), South Asians (15.9%), and Filipinos (16.1%) have the highest prevalence of diabetes among all ethnic groups.[276] Although there are no differences in the prevalence of diabetes type 2 between men and women,[278] the risk of stroke is found higher in women (hazard ratio (HR) 2.8; 95% CI 2.4-3.4) than in men (HR 2.2; 95% CI 1.8-2.5).[279]

There is also geographic variation in the diabetes subtypes attributed to ischemic stroke in young adults. Based on data from the WHO, incidence of type 1 diabetes peaks in Finland (36.5 per 100,000 person years),[280] with a 4.6% prevalence among young patients with ischemic stroke,[269] and is lowest in China and Venezuela (0.1 per 100,000 person years).[280] Adjusted OR for type 1 diabetes in Finland was 6.7 (95% CI 3.2-14.3), which was almost three-fold higher than for type 2 diabetes (OR 2.8, 95% CI 1.7-4.6). Notably, the association of type 1 diabetes was stronger for women than for men.[269]

Dyslipidemia

About 50-60% of young stroke patients have dyslipidemia, which is slightly more common in men than in women.[7, 56] The prevalence of lipid disorders in young adults increases.[68] Dyslipidemia is more often found in patients with large artery or small vessel disease, and is less common in ischemic stroke caused by cardiac embolism.[270] Dyslipidemia in young adults is not significantly associated with the risk of all-cause stroke (PAR of -2.1%; 95% CI -6.7-2.6 and OR 0.9; 95% CI 0.8-1.1).[85] This might be explained by the many other causes of stroke in young adults, for which dyslipidemia might not be a risk factor. Contrary, in stroke due to large artery disease or small vessel disease, dyslipidemia would probably attribute and increase the risk of stroke, which is found in older adults who more often have large-artery disease and small vessel disease as cause of their stroke. Another explanation why dyslipidemia is found not to be a significant contributor to the risk of stroke might be that most studies defined dyslipidemia as either a high LDL- or low HDL cholesterol, but did not investigate the association between different lipid variables and stroke. Large studies among different lipid variables and their association with stroke in young patients are scarce. A Brazilian study showed that ApoB/ApoA-I ratio was highly associated with ischemic stroke (OR 4.03; 95% CI 1.62-10.03).[281] In contrast, a Finnish study showed that there was no association between lipoprotein(a) and early atherosclerosis. However, they did not investigate the association with stroke.[282]

The general global prevalence of dyslipidemia was highest in Europe (54%), followed by the North-America (48%), Southeast Asia (29%) and Africa (22.6%), which seems related to the income level of countries.[162] Data from Florida showed a higher prevalence of dyslipidemia in whites than in Hispanics and blacks (21.0% vs. 17.1% & 17%, respectively; p<0.0001).[262]

Smoking

The proportion of smokers among young stroke patients is high, with up to 50% of them reporting themselves as smokers (defined as current smoking and smoking in the last 1-2 years).[7, 56] Smoking contributes to stroke in young adults (PAR of 19.9%; 95% CI 14.8-23.9 and OR 1.78; 95% CI 1.50-2.11).[269] In addition, over the last decade smoking is more frequently seen in young adults.[68, 270] A stronger dose-response relationship between smoking and the risk of ischemic stroke is found for both men and women at young age compared to older adults.[283, 284] In stroke patients of all ages, the highest prevalence is reported in Europe (28.7%) and in Southeast Asia (24.8%), whereas the lowest prevalence was reported in Africa (13.9%).The risk of stroke ranges with a PAR of 4.5% in Africa to a PAR of 18.0% in Western Europe, North-America, and Australia.[84] The prevalence of daily smoking was higher in men (25%; 95% CI 24.2-25.7) than in women (5.4%; 95% CI 5.1-5.7).[285] A higher prevalence of smoking was found in countries located mainly in central and Eastern Europe and South Asia.[285] For women, significantly higher prevalence was mainly found in countries in western and central Europe.[285] Furthermore, higher prevalence of smoking (30.6% vs. 18.5%) was found in whites compared with blacks.[262]

Obesity and physical inactivity

Obesity and physical inactivity are modifiable vascular risk factors that contribute to vascular pathology and might be mutually related. Obesity, often defined as a Body Mass Index (BMI) of 30 or higher, is seen in more than 10% of young individuals with stroke.[7] Other markers for obesity include waist circumference, waist-hip ratio and waist-height ratio that might be stronger associated with risk of stroke than BMI.[286] A large prospective European cohort study of Young Stroke patients, the SIFAP study, found that abdominal obesity was the most prevalent risk factor and more prevalent in women (73%) than in men (64%).[278] Waist circumference predicts the risk of developing metabolic syndrome, a condition associated with an increased risk of cardiovascular disease and diabetes mellitus type 2.[287] A high childhood BMI was associated with an increased risk of ischemic stroke at young age (<55 years). The higher the BMI, the higher the risk, but an increased risk was already seen from the 75th percentile of the BMI distribution at childhood age.[87] Obesity in young adults was associated with a higher risk of stroke (PAR of 6.9% (95% CI 0.0-13.8 and OR 1.2; 95% CI 1.5-2.3).[85] Together with the increase of stroke

in young adults, the increase of overweight and obesity, seen in both developing and developed countries over the last 30 years, is worrisome.[87, 288] Geographical differences in the prevalence of obesity in young stroke are lacking, however in general a higher prevalence is found in the USA (61.1%), Europe (54.8%) and Eastern Mediterranean (46%) compared to Africa (26.9%), Western Pacific (25.4%) and Southeast Asia (13.7%),[289, 290] and obesity is more often seen in woman than in men.[289, 291] Hospitalization rates from Florida showed that blacks were more likely diagnosed with morbid obesity than whites and Hispanics (10.9% vs. 9.2% vs. 7.8%, respectively; p<0.0001).[262]

Physical inactivity is associated with obesity and worse cardiovascular risk profile, increasing the risk of stroke (PAR 59.8; 95% CI 56.2-63.4 and OR 5.9; 95% CI 5.1-6.7).[85] Among teenagers, lower physical activity is seen in girls than in boys.[289]

Heavy episodic alcohol consumption

Heavy episodic alcohol consumption is associated with an increased risk of stroke in young adults (PAR 17.3; 95% CI 14.2-20.5 and OR 2.2; 95% CI 1.9-2.5) in European countries.[85] In all continents, alcohol consumption was associated with an increased risk of ischemic stroke in general (though not assessed for young adults specifically).[84] Multiple studies found regional differences in the association between alcohol consumption and stroke or other cardiovascular disease, explained by differences in drinking pattern and type of alcohol. The prevalence is higher in high-income countries compared to low-income countries. Furthermore, episodic heavy alcohol consumption is higher among men compared to women.[84]

Air pollution

Air pollution is an emerging global risk factor for stroke. Rapid economic development leads to major changes to air quality due to increased energy demands, urbanization, transportation and widespread industrialization.[292] The proportion of stroke burden attributable to air pollution is 29.2% globally, especially in low- and middle-income countries (33.7% vs. 10.2% in high-income countries).[3] Geographical differences are also seen in stroke-related mortality due air pollution. An explanation for this disparity is that 97% of cities in low- and middle-income countries with more than 100,000 inhabitants do not meet WHO air quality guidelines, whereas in high-income countries this is 49%.[293] Data among the association of air pollution and stroke in young adults is scarce. According to one case-crossover analysis from Israel, air pollution is associated with a higher risk of stroke in young adults (OR 1.10; 95% CI 1.02-1.20) compared to patients >65 years (OR 1.00; 95% CI 0.96-1.03). A higher risk was found in patients living within 75 meters from a main road (OR 1.26; 95% CI 1.04-1.51)).[294] Data on young adults from low-income countries are lacking.

CONCLUSION

Stroke in young adults is expected to cause an increasing public health problem in both developed and developing countries due to increasing incidence and the long-lasting consequences. Differences in geography, ethnicity and sex, and in the exposure of vascular risk factors explain in part the wide variation of incidence of ischemic stroke in young adults observed throughout the world (table 2). These differences between low-income, middle-income and high-income countries are among others related to genetic and cultural variation, availability of diagnostic and therapeutic strategies and the state of industrial era (i.e., industrialization and urbanization of a country). With a concomitant increase of vascular risk factors worldwide, focus on primary and secondary prevention should ideally start at a young age in countries of all income types with attention for continent-and country specific risk factors. The important epidemiological differences and differences in exposure of risk factors stretch the need for region-specific programs for young adults to prevent stroke and region-specific guidelines to better detect stroke at young age and to improve the treatment, which in the end will lead to better prognosis. However, before such programs can be developed, more extensive research in a well-defined young stroke population is needed with larger numbers and well-defined risk factors. A truly good comparison in global differences between epidemiology and etiology is yet impossible, mainly due to large differences in registration of strokes and available resources. Future studies should focus on large prospective worldwide collaborative studies to assess the specific causes and the role of vascular risk factors specific in young stroke patients. One such initiative is the "Global Outcome Assessment Life-long after stroke in young adults" (http://www.goalinitiative.org/) that aims to perform an individual patient data meta-analysis. These types of initiatives should eventually lead to better (region-specific) treatment and management worldwide to reduce the impact and burden of ischemic stroke in young adults.

SUPPLEMENTARY MATERIALS

Textbox. Key global differences regarding stroke in young adults

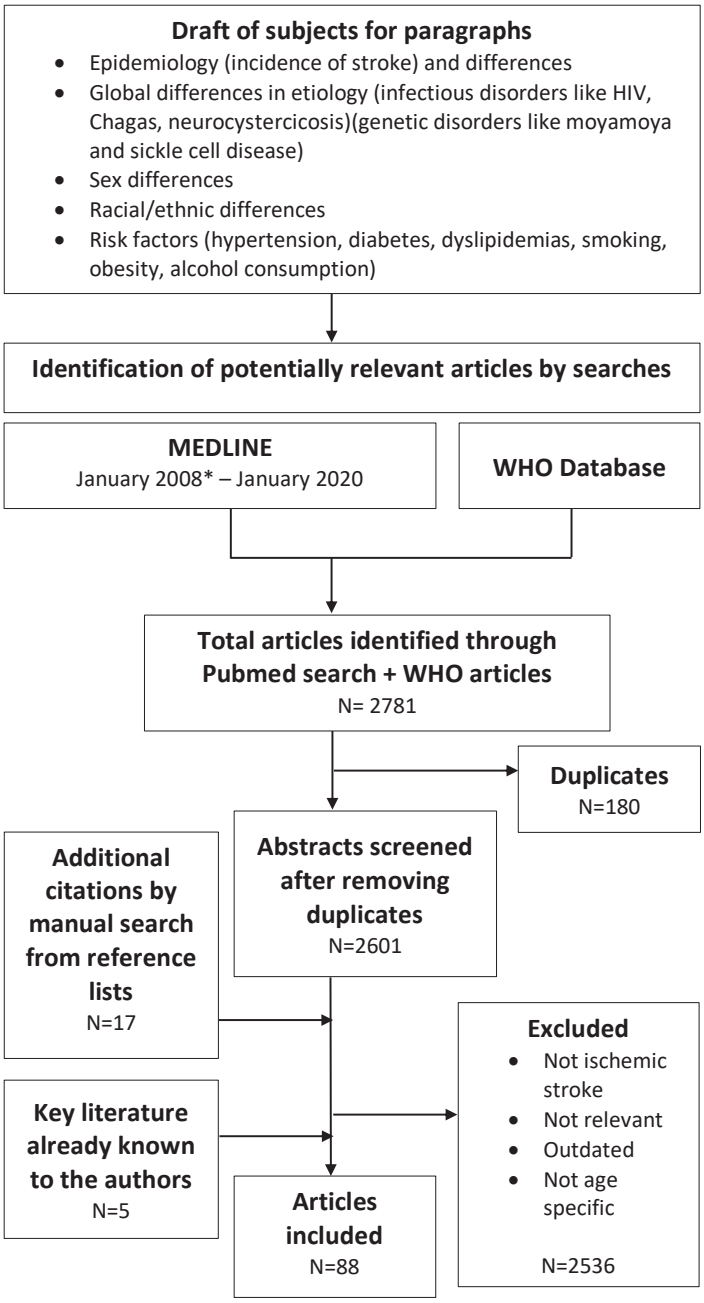
	Important findings compared to other continents	Missing evidence
In general	• Incidence of young stroke is rising • Prevalence of the modifiable vascular risk factors among young stroke patients is rising	• PAR studies in young stroke patients
North America	• Highest prevalence of obesity (not young stroke specific) with 61.1% [289, 290] • Higher incidence stroke among young blacks and Hispanics (11/100,000py) compared to whites (7/100,000/py) [8, 262] • Higher young stroke mortality in blacks than in whites [8, 262]	• Uncertain incidence of moyamoya disease
South- and Central America	• Low prevalence of diabetes type 1 (not young stroke specific) [280] • Infectious causes of stroke including neurocysticercosis prevalent [260] • Lowest prevalence of hypertension globally together with North-America (35%) [274]	• Missing information about risk factors (including PAR studies)
Europe	• Well-known incidence with an increase over the last decade in many countries [1] • Extracranial artery dissections more common than intracranial dissections [76, 78] • Highest prevalence of dyslipidemia globally with 54% [162]	• Prevalence of moyamoya disease uncertain • Few cases of patients with infectious causes
Africa	• Higher percentage of infections, rheumatic heart disease and tuberculosis causing stroke • Highest prevalence of hypertension globally with 46% [274] • Highest prevalence (75%) of sickle cell disease in the world [250] • >90% of young strokes have HIV in Sub-Saharan Africa [254] • Lowest prevalence of dyslipidemia globally with 22.6% [162]	• Unknown incidence in >90% of countries. • No information about specific causes like dissection

Textbox. Continued

	Important findings compared to other continents	Missing evidence
Asia	• Highest incidence of moyamoya disease (16.1/100,000py Korea, 10.5/100,000py Japan) [243, 244] • Intracranial artery dissections more common than extracranial dissections [76, 78] • Higher stroke severity (NIHSS 8) in Asians compared to blacks and whites (NIHSS 7 and 3) [265] • PAR of hypertension for stroke in general globally highest with 54.8% [3]	• Unknown incidence of stroke in young adults for many Asian countries
Australia	• Relatively high incidence in young adults with 20-30/100,000py compared to other developed countries [237] • Young Aboriginal people have higher incidence of ischemic stroke compared to non-Aboriginals [266]	• Few continent-specific causes

Abbreviations: py, person-years; PAR, population attributable risk; HIV, Human Immunodeficiency Virus.

Supplementary Figure 1. Search strategy



Chapter 8

Global differences in risk factors, etiology and outcome of ischemic stroke in the young

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Global Differences in Risk Factors, Etiology and Outcome of Ischemic Stroke in Young Adults: A worldwide meta-analysis: The GOAL-Initiative.

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ABSTRACT

Background and Objectives: There is a worldwide increase in the incidence of stroke in young adults, with major regional and ethnic differences. Advancing knowledge of ethnic and regional variation in causes and outcomes will be beneficial in implementation of regional healthcare services. To study the global distribution of risk factors, causes and 3-month mortality of young ischemic stroke patients, by performing a patient data meta-analysis form different cohorts worldwide.

Methods: We did a pooled analysis of individual patient data from cohort studies which included consecutive ischemic stroke patients aged 18-50 years. We studied differences in prevalence of risk factors and causes between different ethnic and racial groups, geographic regions and countries with different income levels. We investigated differences in 3-month mortality by mixed-effects multivariable logistic regression.

Results: We included 17,663 patients from 32 cohorts in 29 countries. Hypertension and diabetes were most prevalent in Blacks (hypertension, 52.1%; diabetes, 20.7%) and Asians (hypertension 46.1%, diabetes, 20.9%). Large vessel atherosclerosis and small vessel disease were more often cause of stroke in high-income countries (HICs; both $p<0.001$), whereas ''other determined stroke'' and ''undetermined stroke'' were higher in low and middle-income countries (LMICs; both $p<0.001$). Patients in LMICs were younger, had less vascular risk factors, and despite this, more often died within 3 months than those from HICs (OR 2.49; 95% CI 1.42-4.36).

Discussion: The ethnoracial and regional differences in risk factors and causes of stroke at young age provide an understanding of ethnic and racial, and regional differences in incidence of ischemic stroke. Our results also visualize the dissimilarities in outcome after stroke in young adults that exist between LMICs and HICs, which should serve as call to action to improve healthcare facilities in LMICs.

INTRODUCTION

A prominent United Nations Sustainable Development Goal is to reduce the burden of non-communicable diseases, including stroke, by one-third by 2030.[295] However, there has been a worldwide increase of up to 50% in the incidence of stroke in young adults over the last decade.[34, 36]

A stroke at young age, usually defined as aged 18-50 years, has a large personal impact during a demanding period of life. Its increasing incidence also has detrimental socioeconomic consequences worldwide, as these patients have high rates of post-stroke unemployment and a persistent increased long-term risk of death, resulting in decades of life lost.[3, 34, 296, 297]

There are major, incompletely understood regional differences in the incidence of stroke in young adults, varying between 7 per 100,000 person-years in Europe to over 100 per 100,000 persons-years in Africa.[15-17] Also, ethnic and racial disparity in incidence has been reported, with a 50% higher incidence in United States Hispanics and Black Americans than in Europeans.[15, 18] These differences in stroke incidence at young age might reflect yet unidentified regional variation in burden of risk factors and causes of stroke. Apart from regional, ethnic and racial or genetic differences, economic inequality may also play a role, which may influence not only incidence, risk factor profile and causes of stroke, but also patients' outcome. Large cohort studies among elderly stroke patients have shown a poorer prognosis in those residing in low and middle-income countries (LMICs) than those in high-income countries (HICs).[20, 21] However, it is largely unknown whether this discrepancy also applies to young patients with stroke, with often a different etiology.

To address these knowledge gaps, a global approach is needed, with detailed data from individual patients with different regional and ethnic background. We therefore set up the "**G**lobal **O**utcome **A**ssessment **L**ife-long after stroke in young adults" (GOAL) initiative, combining data from individual young patients with stroke from different cohorts worldwide. In this study, we investigated the global distribution of risk factors and causes as well as 3-month mortality in an individual patient data meta-analysis among 17,663 young ischemic stroke patients from all continents.

METHODS

Study Design and Population

The GOAL-initiative is an ongoing international multicenter initiative that collects individual patient data from hospital-based young stroke cohorts all over the world, with the aim to investigate the risk factors, etiology and outcome in young individuals with stroke. A detailed description of the GOAL-study protocol has been published previously.[2]

Relevant cohorts studies conducted from 1970 onward were identified through a systematic search of PubMed using the Mesh Major Topics: 'Young Adult', 'Stroke', 'Risk Factors', 'Stroke/etiology', 'Prognosis' and 'Secondary Prevention'. Detailed description of the search terms strategy is listed at https://doi.org/10.5061/dryad.1rn8pk0t4.

The principal investigators were contacted and informed about the GOAL-initiative with the request to participate. Furthermore, when participants indicated they knew of other cohorts or collaborators who might be interested in participating, we contacted these researchers. A specific website for potential participants was developed to provide more information about the aims of the project (www.goalinitiative.org). An overview of the selection procedure of cohorts is visualized in at https://doi.org/10.5061/dryad.1rn8pk0t4.

Prospective and retrospective, as well as hospital-based cohorts were considered eligible for enrolment if the patients would meet our selection criteria. Briefly, cohorts were eligible for inclusion if they recruited consecutive patients aged 18-50 years with a first-ever ischemic stroke. Exclusion criteria included stroke due to traumatic cerebral injury, intracerebral malignancy, cerebral venous thrombosis, iatrogenic stroke as a result of any medical intervention, or retinal infarct. A detailed overview of the inclusion and exclusion criteria are described in detail in the study protocol.[2] Ischemic stroke was defined according to the definition of the World Health Organization (WHO).[298] We performed an individual patient data meta-analysis by analyzing data from cohorts who contributed data to the GOAL-initiative until June 1st, 2020.

Standard Protocol Approvals, Registrations, and Patient Consents

Before participating, each individual center had to obtain written ethical approval form a local ethical committee for international data sharing. Participating centers were requested to pseudonymize their data before sending it by using a standardized and encrypted electronical sheet containing pre-specified variables of interest, according to the current laws and legislation concerning research conduct at each participating

center, to the GOAL-research team of the Neurology department of the Radboudumc, Nijmegen. The key linking anonymized data to individual patients remained at the participating centers. This study was conducted according to the principles of the Declaration of Helsinki (version 60, 19 October 2013) and the Dutch law for human research (WMO). Written informed consent was obtained from all participants in the prospectively collected data, no informed consent was needed for retrospective cohorts of registered patients. Ethical approval was obtained from the Medical Review Ethics Committee region Arnhem-Nijmegen. All data is processed, stored and will be destroyed after end of the study according to European Union General Data Protection Regulation.

Study Data

Study data included demographic characteristics, medical history including medication used on admission, and information on causes and risk factors of ischemic stroke based on diagnostic work-up within 1 month after stroke.

Demographics

Date of admission, date of index stroke, age, sex, and ethnic and racial subgroups including Whites (i.e. non-Hispanic White individuals), Blacks (i.e. non-Hispanic Black individuals), Hispanics (i.e. individuals who self-identified themselves as white-Hispanic or Black-Hispanic), Asians (i.e. individuals who self-identified themselves as from Asian descendants), multi-racial (i.e. individuals with two or more racial identities), other or unknown, and geographical residence were registered. Ethnic and racial identity was assigned to subjects via self-identification.

We included patients with ischemic stroke from 29 countries covering all continents except Antarctica. Europe was stratified into three regions because of previously reported regional differences in stroke incidence.[36] Countries were classified based on their income level at the start of their particular study according to the World Bank Classification in LMICs or HICs (http://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html). We grouped LMICs into one group for statistical reasons, since India was the only low-income country at the start of its study. An overview of participating cohorts is shown in Supplementary Table 1.

Risk-factors, Causes and Outcome

Detailed definitions of collected risk factors are described in the study protocol[2] and summarized in Supplementary Table 2. Risk factors included vascular risk factors, as stated by the 2014 guidelines of the American Stroke Association[45], including hypertension, diabetes, dyslipidemia, ever smoking, atrial fibrillation (AF), patent

foramen ovale (PFO), and obesity. Other risk factors collected (but not required for participation in the GOAL-initiative) included: migraine, excessive use of alcohol, and illicit drug use. Cohorts that applied a different definition for a given risk factor that could not be reclassified according to GOAL definitions were excluded from that particular sub analysis.

Cause of stroke was classified according to the Trial of Org 10172 In Acute Stroke Treatment (TOAST) criteria.[43] Outcome was the vital status assessed 3 months after index stroke.

Data quality assessment

A database was created from data of all individual patients. Cohorts were requested to send data regarding risk factors with their definition of the risk factors to ensure that only variables matching our pre-specified definitions were included included. (Supplementary Table 2). were included. All datasets underwent a standardized quality assessment for completeness and inconsistencies. In case of inconsistencies (for example when small vessel disease was considered as the cause of stroke in the presence of AF), local principal investigators were contacted for re-evaluation of their data. Patients with AF were assigned to either the subgroup 'cardio-embolism', or to 'stroke due to two or more identified causes' in presence of other causes of stroke according to the TOAST-criteria.

Data Analyses

To detect differences between increasing age and prevalence of risk factors and causes of ischemic stroke, age was categorized in six age-groups (18-25, 26-30, 31-35, 36-40, 41-45, 46-50 years). Patients were also grouped based on the number of concurrent traditional vascular risk factors (0-4), by adding up the following vascular risk factors in each patient: hypertension, diabetes, dyslipidemia, and ever smoking.[271]

First, we explored differences in mean age, sex, risk factors, causes of stroke (TOAST-subtype), and death-rates between subgroups stratified by demographic characteristics (age-group, sex, ethnic and racial groups, geographical region and socio-economic level) with Mann-Whitney test or χ^2 test when appropriate. Linear trends in frequencies of risk factors and causes according to ordinal scaled age-groups were tested with χ^2 test. All univariate group tests were corrected with Bonferroni method to adjust for multiple comparisons to ensure 5% overall Type I error rate.

Second, we studied variables associated with death within 3 months from index stroke with mixed-effects multivariable logistic regression, with study cohort set as random intercept effect to correct for intrinsic cohort heterogeneity. The independent variables of interest analyzed included demographic characteristics (sex, age, ethnic and racial groups and socio-economic level of country), stroke cause and the number of vascular risk factors. Depending on each variable under study, we constructed different models with appropriate adjustments for different covariates that are known to affect mortality, i.e. age, sex, ethnic and racial groups, cause of stroke and/or vascular risk factor score. The selection of these confounding variables was based on availability of confounders, biological plausibility, their known association with mortality, and they were often used in other studies.[20]

Patients with unreported ethnic and racial identity were classified as an independent group 'unknown' during analyses. Since data of each other variable analyzed was present in >98% of all cases, we did not impute for missing values.

All analyses were performed using R version 4.1.1 or IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY).

Data availability

Data from the GOAL-study including data supporting the findings of this study will be available from the corresponding author on request, after consent of all GOAL-participating centers and approval of local Institutional Review Boards.

RESULTS

A total of 17,663 patients (n=10,564 men; 61.2%), from 32 cohorts in 29 countries were included in this study (Table 1). The overall mean age was 40.8 years (SD 7.5), with men being older than women (41.5 SD 7.2 vs 39.7 SD 7.9 years, p<0.001). There was a male predominance across all age-strata, which increased with age (Table 1). Of patients included, 6837 (38.7%) were Asians, 5696 (32.2%) Whites, 1730 (9.8%) Hispanics and 507 (2.9%) Blacks. Most patients came from Europe (N=7265; 41.1%) and Asia (N=6775; 38.7%). 14,392 (81.5%) patients were residents from HICs (Australia, Austria, Belgium, Canada, Finland, France, Germany, Israel, Italy, Korea, Netherlands, New Zealand, Norway, Portugal, Sweden, Switzerland, Taiwan, United Arab Emirates, and the United States), whereas 3271 (18.5%) patients were from LMICs (Argentina, Brazil, Costa Rica, Estonia, India, Malaysia, Mexico, Mongolia, South Africa and Turkey). Patients residing in HICs were older than those in LMICs (41.2 SD 7.3 vs 38.8 SD 8.4, p<0.001) years.

Global Distribution of Risk Factors

Smoking was the most common risk factor (49.2%), followed by hypertension (36.6%) and dyslipidemia (31.7%; Table 2). For 16,845 (95.4%) patients, the number of concurrent vascular risk factors could be calculated, of which 12,426 (73.8%) patients had at least one vascular risk factor and 6896 (40.9%) patients had ≥2 risk factors (Supplementary Table 3). Of patients ≤30 years, 49.6% had at least one vascular risk factor. Traditional vascular risk factors (hypertension, diabetes, dyslipidemia, and smoking) were more common in men than in women and showed a higher prevalence with increasing age (all: p_{trend} <0.001; Figure 1). Women, compared to men, more often had migraine (28.1% vs 14.0%, p<0.001) and PFO (18.1% vs 12.7%, p<0.001). Migraine and PFO were also significantly more prevalent in younger patients (both: p_{trend}<0.001). Blacks and Asians had the highest prevalence of ≥2 risk factors (Supplementary Table 3). They also had the highest prevalence of hypertension (Blacks 52.1% and Asians 47.1%) and diabetes (Blacks 20.7% and Asians 20.9%), while Whites had the highest prevalence of dyslipidemia (40.4%) and PFO (24.9%). Patients from Asia, North America and Oceania showed higher frequencies of most vascular risk factors (especially obesity) compared to patients from Europe (Figure 2). The majority of vascular risk factors were significantly more prevalent in HICs compared to LMICs, particularly dyslipidemia (33.9% vs 21.7%, p<0.001, Table2).

Table 1. Demographic characteristics of total study population

	Patients	Mean age (SD)	Men	Women
Total population	17,663	40.8 (7.5)	10,683 (60.5)	6980 (39.5)
Age-group				
• 18-25	940 (5.3)	21.9 (2.2)	474 (50.4)	466 (49.6)
• 26-30	1140 (6.5)	28.3 (1.4)	576 (50.5)	564 (49.5)
• 31-35	1829 (10.4)	33.2 (1.4)	957 (52.3)	872 (47.7)
• 36-40	2997 (17.0)	38.2 (1.4)	1754 (58.5)	1243 (41.5)
• 41-45	4949 (28.0)	43.2 (1.4)	3075 (62.1)	1874 (37.9)
• 46-50	5808 (32.9	48.0 (1.4)	3847 (66.2)	1961 (33.8)
Ethnic and Racial subgroups				
• White	5696 (32.2)	39.4 (7.5)	3144 (55.2)	2552 (44.8)
• Black	507 (2.9)	41.3 (6.7)	275 (54.2)	232 (45.8)
• Hispanic	1730 (9.8)	38.1 (8.8)	864 (49.9)	866 (50.1)
• Asian	6837 (38.7)	42.7 (6.5)	4779 (69.9)	2058 (30.1)
• Multi-racial	23 (0.1)	39.4 (7.2)	10 (43.5)	13 (56.5)
• Other	137 (0.8)	38.0 (7.1)	68 (45.0)	83 (55.0)
• Unknown	2733 (15.5)	40.7 (7.9)	1553 (56.6)	1189 (43.4)
Geographic region				
• Oceania	658 (3.7)	40.1 (7.5)	376 (57.1)	282 (42.9)
• Asia	6775 (38.4)	42.7 (6.6)	4740 (70.0)	2035 (30.0)
• Africa	91 (0.5)	36.1 (8.8)	49 (53.8)	42 (46.2)
• Southern Europe	2988 (16.9)	37.9 (7.4)	1558 (52.1)	1430 (47.9)
• Central Europe	2152 (12.2)	40.7 (7.6)	1178 (54.7)	974 (45.3)
• Northern Europe	2125 (12.0)	41.4 (7.6)	1275 (60.0)	850 (40.8)
• North America	1007 (5.7)	41.8 (6.0)	578 (57.4)	429 (42.6)
• Central and South America	1867 (10.6)	37.7 (8.8)	929 (49.8)	938 (50.2)
Country income classification				
• High-income countries	14,392 (81.5)	41.2 (7.3)	8914 (61.9)	5478 (38.1)
• Low and middle-income countries	3271 (18.5)	38.8 (8.4)	1769 (54.1)	1502 (45.9)

Data are numbers (%) or mean (SD).

Table 2. Risk factors stratified by demographic characteristics

Number of patients with available data of risk factor	Hypertension (N=17,409)	Diabetes (N=17,631)	Dyslipidemia (N=17,364)	Ever smoking (N=17,328)
Patients with risk factor	6368 (36.6)	2432 (13.8)	5498 (31.7)	8525 (49.2)
Mean age (SD) of patients with present risk factor	43.6 (5.5)	44.3 (5.3)	42.8 (6.1)	41.7 (7.0)
Sex				
• Men	4294 (40.8)	1657 (15.5)	3668 (34.9)	6198 (59.0)
• Women	2074 (30.1)	75 (11.1)	1830 (26.7)	2327 (34.1)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Age-group				
• 18-25	64 (6.9)	24 (2.6)	97 (10.5)	325 (35.3)
• 26-30	137 (12.3)	35 (3.1)	183 (16.3)	435 (39.0)
• 31-35	367 (20.6)	112 (6.1)	415 (23.1)	743 (41.4)
• 36-40	914 (31.3)	307 (10.3)	904 (30.9)	1396 (47.5)
• 41-45	1955 (40.1)	693 (14.0)	1671 (34.2)	2534 (51.9)
• 46-50	2931 (50.5)	1261 (21.8)	2228 (39.0)	3092 (54.4)
p_{trend}	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Ethnic and Racial subgroups				
• White	1709 (30.2)	497 (8.7)	2254 (40.4)	2559 (45.8)
• Black	264 (52.1)	105 (20.7)	128 (25.6)	262 (52.0)
• Hispanic	397 (23.1)	190 (11.1)	247 (14.4)	840 (49.2)
• Asian	3061 (46.1)	1426 (20.9)	1948 (28.8)	3611 (52.9)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Geographic region				
• Oceania	235 (36.3)	106 (16.2)	277 (46.6)	293 (46.1)
• Asia	3038 (46.2)	1423 (21.0)	1937 (28.8)	3588 (53.1)
• Africa	20 (22.0)	11 (12.1)	16 (18.0)	29 (32.6)
• Southern Europe	777 (26.2)	213 (7.1)	880 (29.5)	1166 (39.1)
• Central Europe	669 (31.1)	138 (6.4)	849 (41.9)	1071 (50.7)
• Northern Europe	775 (36.5)	181 (8.5)	1012 (48.1)	933 (49.3)
• North America	427 (42.5)	163 (16.2)	266 (26.6)	578 (57.4)
• Central and South America	427 (23.0)	197 (10.6)	261 (14.1)	867 (47.0)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**

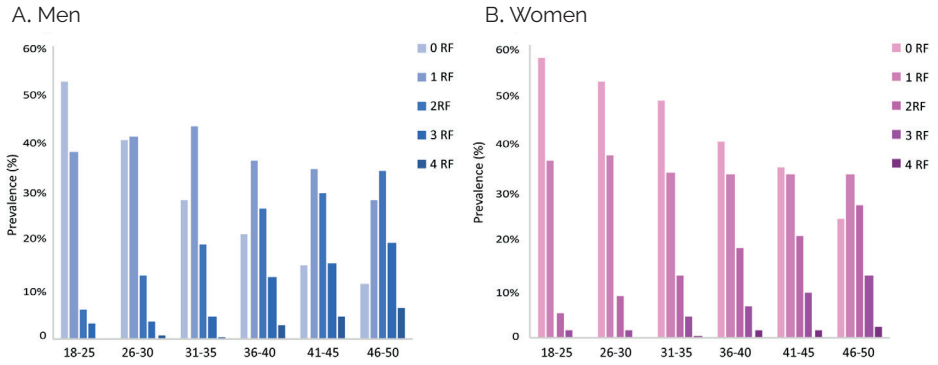
Coronary artery disease (N=16,159)	Atrial fibrillation (N=17,258)	Patent foramen ovale (N=12,024)	Obesity (N=13,217)	Migraine (N=5138)	Excessive alcohol use (N=9630)	Illicit drug use (N=5891)
759 (4.7)	691 (4.0)	1789 (14.9)	1796 (13.6)	1056 (20.6)	1030 (10.5)	254 (4.3)
43.0 (6.3)	43.5 (6.3)	38.0 (8.1)	41.9 (6.4)	37.8 (7.7)	40.6 (7.3)	38.5 (8.0)
506 (5.1)	432 (4.1)	922 (12.7)	1114 (13.4)	383 (14.0)	896 (16.7)	174 (5.2)
253 (4.0)	259 (3.8)	867 (18.1)	682 (14.0)	673 (28.1)	187 (4.4)	80 (3.1)
0.002	**0.33**	**<0.001**	**0.35**	**<0.001**	**<0.001**	**<0.001**
18 (2.1)	13 (1.4)	181 (27.2)	38 (6.1)	94 (27.2)	52 (7.8)	26 (6.9)
23 (2.2)	26 (2.3)	164 (20.1)	81 (10.5)	107 (25.2)	68 (8.3)	21 (4.3)
51 (3.1)	38 (2.1)	258 (19.8)	180 (14.6)	162 (24.6)	131 (10.9)	26 (3.8)
101 (3.7)	95 (3.3)	372 (17.8)	299 (14.4)	245 (24.0)	185 (10.1)	52 (5.0)
226 (4.9)	177 (3.7)	496 (14.2)	545 (15.7)	306 (18.5)	313 (11.3)	78 (5.2)
340 (6.4)	342 (6.0)	318 (8.7)	653 (13.0)	142 (13.7)	334 (14.3)	51 (2.9)
<0.001	**<0.001**	**<0.001**	**0.001**	**<0.001**	**<0.001**	**0.006**
174 (3.5)	184 (3.2)	1045 (24.9)	566 (19.2)	841 (20.9)	505 (9.4)	138 (6.3)
55 (11.1)	14 (2.8)	6 (1.4)	221 (44.6)	0/42	15 (4.1)	48 (10.6)
52 (3.0)	74 (4.3)	171 (13.9)	157 (9.1)	17 (19.3)	248 (16.0)	38 (2.2)
335 (4.9)	324 (4.8)	239 (4.8)	634 (9.5)	48 (18.3)	215 (17.8)	15 (1.3)
<0.001	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
48 (7.3)	43 (6.5)	110 (19.4)	153 (27.5)	0/207	79 (14.0)	59 (11.9)
330 (4.9)	323 (4.8)	231 (4.7)	637 (9.6)	45 (19.0)	206 (17.9)	17 (1.4)
1 (1.1)	0/89	0/70	8 (10.8)	0/0	13 (14.4)	2 (2.2)
35 (1.3)	92 (3.1)	742 (27.2)	59 (10.9)	558 (23.1)	255 (8.6)	13 (4.9)
92 (6.1)	45 (2.4)	324 (36.2)	99 (23.2)	159 (22.7)	97 (8.4)	6 (3.9)
72 (4.6)	85 (4.1)	179 (32.0)	292 (13.9)	252 (18.2)	148 (12.0)	28 (2.8)
128 (12.8)	26 (2.6)	25 (2.8)	387 (38.5)	25 (21.2)	20 (2.6)	82 (10.5)
53 (2.9)	77 (4.2)	178 (13.0)	161 (8.7)	17 (20.2)	265 (15.7)	47 (2.5)
<0.001	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Table 2. Continued

Number of patients with available data of risk factor	Hypertension (N=17,409)	Diabetes (N=17,631)	Dyslipidemia (N=17,364)	Ever smoking (N=17,328)
Country level of income				
High-income countries	5345 (37.2)	2054 (14.3)	4806 (33.9)	7137 (50.6)
Low and middle-income countries	1023 (33.5)	378 (11.6)	692 (21.7)	1388 (42.9)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Data are numbers (%), mean (SD), or p-values. Percentages are proportion of patients with the certain risk factor calculated based on the total patients with available data of the certain risk factor.

Figure 1. Proportions of patients with concurrent vascular risk factors, stratified by age-groups and sex



Prevalence shown for presence of zero, one, two, three or four vascular risk factors by age groups. Vascular risk factors included hypertension, dyslipidemia, diabetes and smoking.

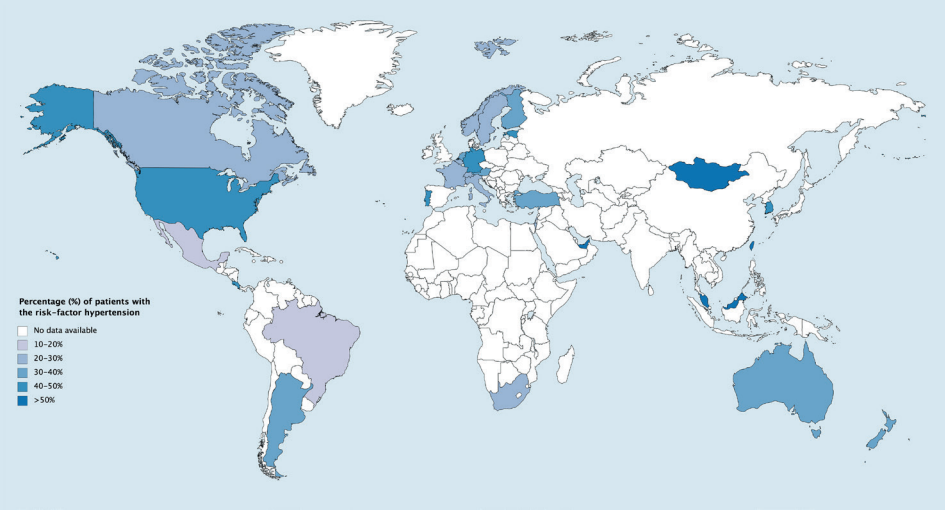
Abbreviations: RF, Risk Factor.

Coronary artery disease (N=16,159)	Atrial fibrillation (N=17,258)	Patent foramen ovale (N=12,024)	Obesity (N=13,217)	Migraine (N=5138)	Excessive alcohol use (N=9630)	Illicit drug use (N=5891)
588 (4.5)	539 (3.8)	1595 (15.4)	1494 (14.5)	987 (20.3)	739 (10.4)	190 (5.7)
171 (5.8)	152 (4.7)	195 (11.8)	302 (10.3)	69 (24.9)	344 (13.7)	64 (2.5)
<0.001	**0.02**	**<0.001**	**<0.001**	**0.08**	**<0.001**	**<0.001**

Abbreviations: SD, Standard deviation.

Figure 2. World maps visualizing geographical distribution of vascular risk factors in young stroke patients

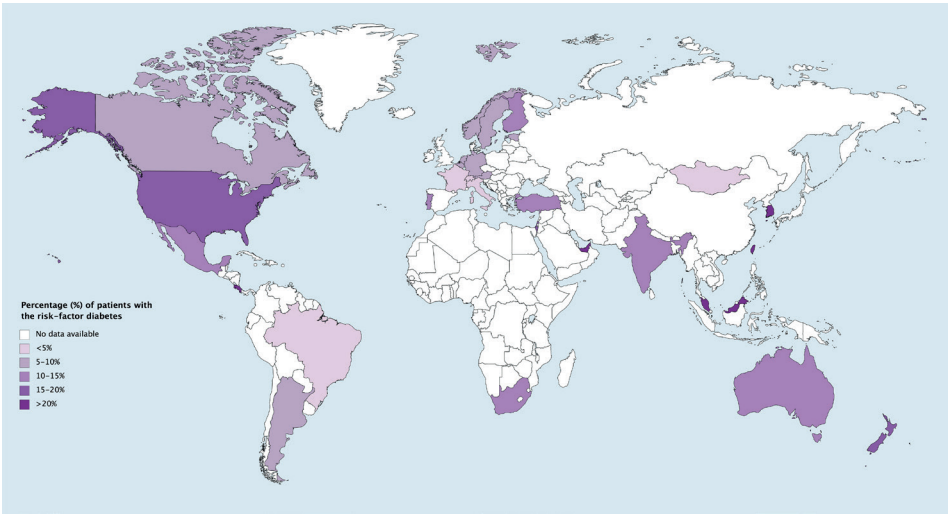
A. Hypertension;



Colors are based on proportion of particular risk factor (%).

Figure 2. Continued

B. Diabetes;



C. Dyslipidemia;

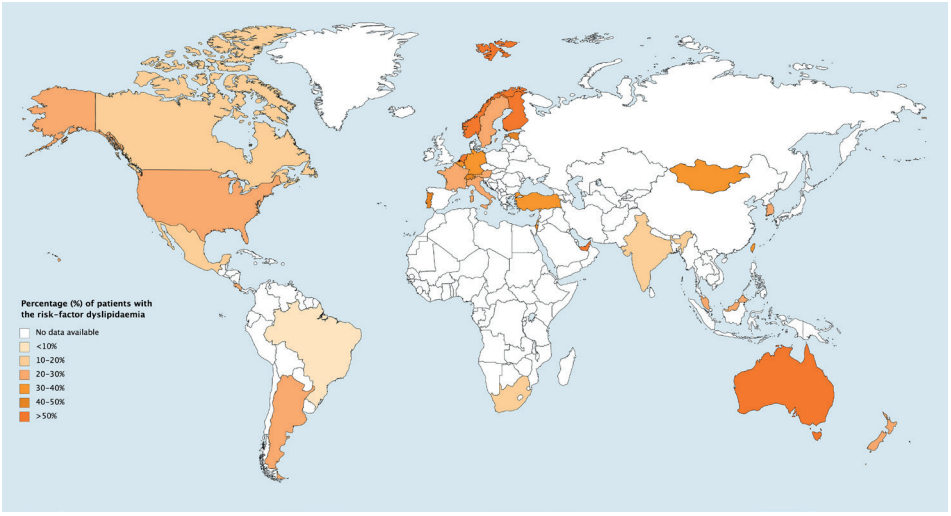
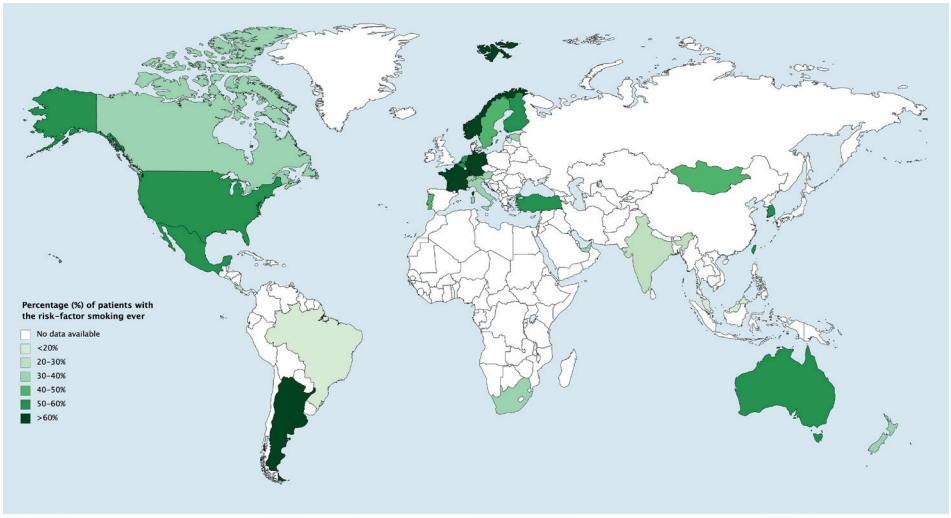
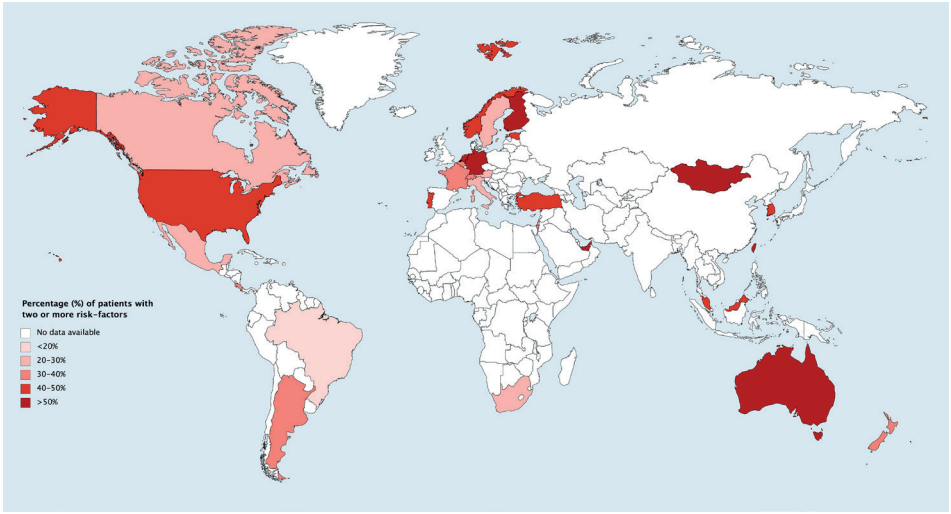


Figure 2. Continued

D. Smoking;



E. Two or more risk-factors.



Global Distribution of Causes of Stroke

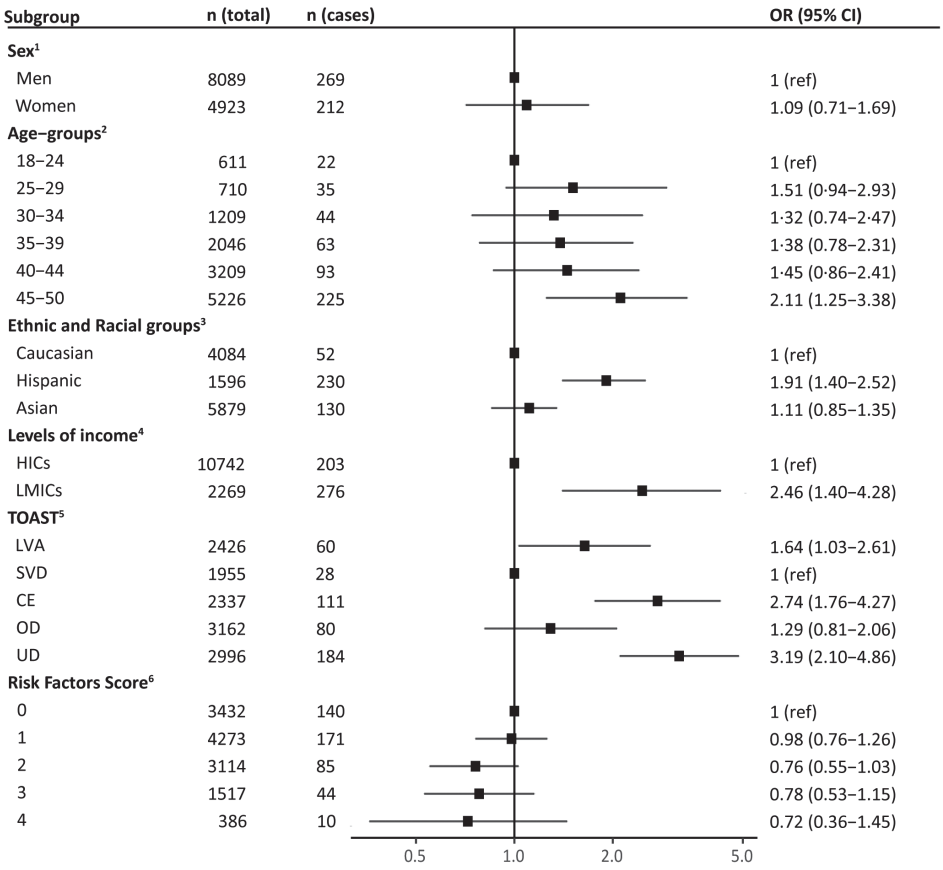
Data regarding causes of stroke was available for 16,864 (95.4%) patients. Large vessel atherosclerosis was the cause of stroke in 16.6% of cases, small vessel disease in 14.8%, cardio-embolism in 19.0%, other determined etiology in 22.7%, and undetermined etiology in 26.9% (Table 3). Large vessel atherosclerosis and small vessel disease were significantly more often the cause of stroke in men than in women (19.2% vs 12.7%, p<0.001 for large vessel atherosclerosis: 17.0% vs 11.4%, p<0.001 for small vessel disease) while cardio-embolism and other determined etiology prevailed in women (21.5% vs 17.4%, p<0.001; respectively 27.0% vs 20.0%, p<0.001). The proportions of large vessel atherosclerosis and small vessel disease as cause of stroke significantly increased with age (both: p_{trend} <0.001), whereas the proportion of cardio-embolism and other determined etiology significantly decreased with age (both: p_{trend} <0.001). Asians had at least a 3-fold higher prevalence of large vessel atherosclerosis (28.6%) compared to other ethnic and racial groups. Also, small vessel disease was most often the cause of stroke in Asians (22.0%), cardio-embolism in Whites (24.5%) and undetermined etiology among Blacks (44.0%) (Table 3). Africa, Central and South America, and Southern Europe showed the highest prevalence of stroke of other determined etiology (all: >40%). Large vessel atherosclerosis and small vessel disease were more than twice as prevalent in HICs compared to LMICs (both: p<0.001), while other determined and stroke due to an undetermined etiology were more prevalent in LMICs (both: p<0.001; Table 3).

Global differences in death at 3 months after stroke

Information on vital status at 3 months after index stroke was available for 13,012 (75.4%) patients, of which 481 (3.7%) had died; 331 (68.6%) of those died within the first month (HICs: 1.7%, LMICs: 7.7%, p<0.001). Differences in clinical characteristics between survivors and patients who died within 3 months are presented in Table 4.

In multivariable logistic regression analysis, there was no statistically significant difference in risk of death between men and women (OR 1.09; 95% CI 0.71-1.69, Figure 3). Age (years) was a significant risk factor for mortality (OR 1.02; 95% CI 1.01-1.03). Hispanic patients had a higher mortality risk than Whites (OR 1.91; 95% CI 1.40-2.52) and Asians (OR 1.81; 95% CI 1.42—2.34). Black patients were not included because of limited cases. Patients in LMICs had almost a 2.5-fold higher risk for mortality than patients residing in HICs, after adjusting for cohort heterogeneity, sex, age, and cause of stroke (OR 2.46; 95% CI 1.40-4.28). Of the deceased patients, 39.7% had a stroke of undetermined etiology (Table 4), which was strongly associated with death (OR 3.19; 95% CI 2.10-4.86), followed by cardio-embolism (OR 2.74; 95% CI 1.76-4.27) and large vessel atherosclerosis (OR 1.64; 95% CI 1.03-2.61). The number of concurrent vascular risk factors was not significantly associated with mortality (Figure 3).

Figure 3. Risk of death within 3 months after index stroke



Data are presented as n (total patients with available mortality-status), n (mortality-cases), and OR (95% CI). All models were adjusted for cohort heterogeneity by taking study cohort as random effect in the multivariable logistic regression analysis. Additionally, for each variable of interest we constructed different models with appropriate adjustments for confounders: [1]Adjusted for age, ethnicity, and TOAST-category; [2]Adjusted for sex, ethnicity, and TOAST-category; [3]Adjusted for age, sex, and TOAST-category; [4]Adjusted for age, sex, and TOAST-category; [5]Adjusted for age, sex and ethnicity; [6]Adjusted for age, sex and ethnicity.

Abbreviations: OR, Odds Ratio; HICs, High Income Countries; LMICs, Low- and Middle-Income Countries; LVA, Large Vessel Atherosclerosis; SVD, Small Vessel Disease; CE, Cardio-embolism; OD, Other Determined Etiology; UD, Undetermined Etiology.

Table 3. Causes of stroke stratified by demographic characteristics

	Total Patients	Large vessel atherosclerosis
Number of cases	16,864	2802 (16.6)
Mean Age (SD)	40.8 (7.6)	43.8 (5.8)
Sex		
• Men	10,240 (60.7)	1963 (19.2)
• Women	6624 (39.3)	839 (12.7)
p		**<0.001**
Age-group		
• 18-25	896 (5.3)	55 (6.1)
• 26-30	1104 (6.5)	86 (7.8)
• 31-35	1755 (10.4)	174 (9.9)
• 36-40	2850 (16.9)	412 (14.5)
• 41-45	4723 (28.0)	815 (17.3)
• 46-50	5536 (32.8)	1260 (22.8)
p_{trend}		**<0.001**
Ethnic and Racial subgroups		
• White	5526 (32.8)	481 (8.7)
• Black	502 (3.0)	33 (6.6)
• Hispanic	1720 (10.2)	157 (9.1)
• Asian	6622 (39.3)	1895 (28.6)
p		**<0.001**
Geographic region		
• Oceania	658 (3.9)	30 (4.6)
• Asia	6559 (38.9)	1889 (28.8)
• Africa	91 (0.6)	16 (17.6)
• Southern Europe	2897 (17.2)	228 (7.9)
• Central Europe	1959 (11.6)	250 (12.8)
• Northern Europe	1844 (10.9)	154 (8.4)
• North America	999 (5.9)	70 (7.0)
• Central and South America	1857 (11.0)	165 (8.9)
p		**<0.001**
Country level of income		
High-income countries	13,817 (81.9)	2505 (18.1)
Low and middle-income countries	3047 (18.1)	297 (9.7)
p		**<0.001**

Data are numbers (%), mean (SD), or p-values. Percentages are proportion of patients with that specific cause of stroke calculated based on the total patients with available data of the TOAST-classification.

Small vessel disease	Cardio- embolism	Other determined etiology	Undetermined etiology
2496 (14.8)	3199 (19.0)	3829 (22.7)	4538 (26.9)
43.2 (6.1)	39.8 (7.9)	37.8 (7.9)	40.8 (7.6)
1744 (17.0)	1777 (17.4)	2043 (20.0)	2712 (26.5)
752 (11.4)	1422 (21.5)	1786 (27.0)	1825 (27.6)
<0.001	**<0.001**	**<0.001**	**0.14**
41 (4.6)	225 (25.1)	344 (38.4)	231 (25.8)
51 (4.6)	241 (21.8)	411 (37.2)	315 (28.5)
126 (7.2)	368 (21.0)	608 (34.6)	479 (27.3)
339 (11.9)	604 (21.2)	761 (26.7)	734 (25.8)
744 (15.8)	882 (18.7)	1058 (22.4)	1224 (25.9)
1195 (21.6)	879 (15.9)	647 (11.7)	1555 (28.1)
<0.001	**<0.001**	**<0.001**	**0.40**
614 (11.1)	1355 (24.5)	1835 (33.2)	1241 (22.5)
93 (18.5)	89 (17.7)	66 (13.1)	221 (44.0)
128 (7.4)	343 (19.9)	605 (35.2)	487 (28.3)
1455 (22.0)	789 (11.9)	868 (13.1)	1615 (24.4)
<0.001	**<0.001**	**<0.001**	**<0.001**
76 (11.6)	163 (24.8)	153 (23.3)	236 (35.9)
1451 (22.1)	776 (11.8)	846 (12.9)	1597 (24.3)
8 (8.8)	9 (9.9)	41 (45.1)	17 (18.7)
265 (9.1)	834 (28.8)	1291 (44.6)	279 (9.6)
189 (9.6)	519 (26.5)	355 (18.1)	646 (33.0)
222 (12.0)	347 (18.8)	417 (22.6)	704 (38.2)
153 (15.3)	187 (18.7)	83 (8.3)	506 (50.7)
132 (7.1)	364 (19.6)	643 (34.6)	553 (29.8)
<0.001	**<0.001**	**<0.001**	**<0.001**
2260 (16.4)	2591 (18.8)	3004 (21.7)	3457 (25.0)
236 (7.7)	608 (20.0)	825 (27.1)	1081 (35.5)
<0.001	**0.13**	**<0.001**	**<0.001**

Abbreviations: SD, standard deviation.

Table 4. Differences in baseline characteristics between dead patients and survivors at 3 months of index stroke

	Total Patients*	Dead	Survivors	p
Total reported cases	13,012	481 (3.7)	12,531 (96.3)	
Women	4923 (37.6)	212 (44.1)	4711 (37.6)	**0.004**
Mean age (SD)	40.8 (7.6)	41.1 (8.2)	40.8 (7.6)	**0.028**
Risk Factors				
Hypertension	4654 (35.8)	149 (31.0)	4505 (36.0)	**0.025**
Diabetes	1813 (13.9)	77 (16.0)	1736 (13.9)	0.172
Dyslipidemia	4037 (31.0)	100 (20.8)	3937 (31.4)	**<0.001**
Ever/current smoking	6344 (48.8)	214 (44.5)	6130 (48.9)	0.202
Coronary artery disease	410 (2.3)	38 (7.9)	372 (3.0)	**<0.001**
Atrial fibrillation	525 (4.0)	45 (9.4)	480 (3.8)	**<0.001**
Patent foramen ovale	1454 (11.2)	18 (3.7)	1436 (11.5)	**<0.001**
Obesity	887 (6.8)	29 (6.0)	858 (6.8)	0.062
Migraine	935 (7.2)	3 (0.6)	932 (7.4)	**0.001**
Excessive alcohol use	801 (6.2)	41 (8.5)	760 (6.1)	0.890
Illicit drug use	81 (0.6)	5 (1.0)	76 (0.6)	0.474
TOAST-Classification				
Large vessel atherosclerosis	2426 (18.8)	60 (13.0)	2366 (19.1)	**0.001**
Small vessel disease	1955 (15.2)	28 (6.0)	1927 (15.5)	**<0.001**
Cardio-embolism	2337 (18.2)	111 (24.0)	2226 (17.9)	**0.001**
Other determined	3162 (24.6)	80 (17.3)	3082 (24.8)	**<0.001**
Undetermined	2996 (23.3)	184 (39.7)	2812 (22.7)	**<0.001**

Data are n (%), mean (SD), or p-values. *Total number of patients with available data on mortality status after 3 months. Percentages are proportion of patients of total patients, total survivors, or total deaths.
Abbreviations: SD, standard deviation.

DISCUSSION

We found large ethnic and racial, regional and socioeconomic differences in the prevalence of risk factors, causes of stroke, and 3-month mortality among young patients with ischemic stroke worldwide. Traditional vascular risk factors were already present in three out of four young patients, and even in 50% of patients ≤ 30 years. Furthermore, young patients with ischemic stroke living in LMICs had a 2.5 times higher 3-month mortality-risk compared to those residing in HICs, despite the fact that they were significantly younger and had less vascular risk factors.

The regional and ethnic and racial variation in prevalence of vascular risk factors coincides with the reported regional and ethnic and racial disparities in stroke incidence among young adults.[15-17] For example, North America, Asia and Oceania showed higher prevalence of most vascular risk factors than Europe and South America, which might explain their higher incidence of stroke at young age, compared to Europe.[15, 237] In addition, we observed a higher frequency of hypertension, diabetes mellitus and smoking among Blacks and Asians than in Whites; risk factors typically related with atherosclerosis of larger and smaller vessels. This is in accordance with the higher cardiovascular burden in the general population of these ethnic groups, compared with for example Whites.[84, 299, 300] Indeed, Blacks and Asians had the highest prevalence of large vessel atherosclerosis and/or small vessel disease as cause of stroke. Given the strong association between these traditional vascular risk factors and stroke occurrence, this could also partially explain the higher incidence of stroke in young patients reported in these ethnic and racial groups.[4, 15] These differences in prevalence of risk factors have a multifactorial basis and involve many factors including racial and ethnic disparities in health care access and equity, socio-economic determinants of health[301] and their accompanying lifestyle[84]. However, genetic predispositions may also play a role (for example Moyamoya disease is more often found in Asians). [24, 25] Further studies are warranted to better elucidate the link between different susceptiblities to certain vascular risk factors among individuals with different ethnic and racial subgroups.

However, non-traditional risk factors may also explain additional variation in incidence and causes of stroke at young age across different ethnic and racial groups and regions. For example, we found the highest prevalence of PFO in Whites. We consider it unlikely that ascertainment bias plays a role here, as cardiac ultrasound as part of routine examination was applied to a similar extent in the various regions (Table 2), however data regarding mode of cardiac ultrasound (transthoracic/transesophageal, with or without contrast) was not available. PFO was also more prevalent in women than men. The ethnic and racial and sex differences in PFO prevalence may contribute to the observed

differences in causes of stroke, with cardio-embolism as cause of stroke being mostly prevalent in Whites and women. These demographic differences in risk factors and causes of stroke suggest that targeted interventions to screen and manage (vascular) risk factors may have different effects on reduction of stroke incidence in different sex and ethnic groups.

We noted a male preponderance in all age-strata. Previous Western studies on young patients with ischemic stroke reported conflicting results in incidence between men and women, with higher preponderance of women in the younger age strata (<35 years).[1, 7] Possible explanations for overrepresentation of men in our sample include the accumulation of traditional vascular risk factors in men, and the inclusion of different cohorts worldwide as several Asian studies reported either no sex difference or male overrepresentation in stroke incidence at young age.[302, 303]

Patients in LMICs were younger at stroke onset than those from HICs. This may be due to exposure to different risk factors between LMICs and HICs.[3] In HICs, the prevalence of vascular risk factors is higher, whereas in LMICs environmental risks (e.g. air pollution) may play a larger role. There is growing attention for stroke occurrence attributable to environmental risk factors, which may contribute to a younger age of stroke-onset in LMICs.[3, 301] Traditional vascular risk factors are likely to become more prominent with ageing. Relatively younger age at onset has also been reported in elderly patients with other cardiovascular events, such as myocardial infarction, in LMICs.[21, 36]

There is also inequality with respect to survival after stroke at young age, with patients from LMICs having 2.5 times the risk of dying within the first 3 months after stroke compared to patients from HICs, even though they were younger and had lower burden of vascular risk factors. Possible explanations include access to and affordability of health services (early diagnosis and treatment), secondary prevention, and population educational level.[21] This interpretation is supported by observations in the INTERSTROKE study, showing less access to and availability of evidence-based acute treatments (i.e. intravenous thrombolysis) and health care services (i.e. stroke units and post-discharge rehabilitation centers) in LMICs.[20] However, limited access to health-care resources in LMICs may also result in referral bias: patients that are admitted to the hospital are likely to suffer from a more severe stroke than those who are not referred, with the accompanying higher risk of death. The increased mortality-risk among Hispanics may be explained in this way, as 98.6% of them were from LMICs. Furthermore, the higher proportion of young patients with classical vascular risk factors in HICs could be explained by better health education, earlier detection and better management strategies from acute treatment to rehabilitation compared to LMICs.[304] In contrast to

studies analyzing the long-term mortality of young patients with stroke, we did not find an association between number of risk factors and 3-month mortality. A possible explanation is that these risk factors do not lead to death within three months, but rather increase mortality-risk in the long-term.

Strengths and Limitations

Strengths of our study include the large number of patients, making it the largest study on young patients with ischemic stroke worldwide. It offers an unique opportunity to address existing knowledge gaps with respect to ethnic and racial and regional differences in stroke incidence at young age by comparing for the first-time risk factor profiles, causes and short-term outcome among young stroke patients from different ethnicities and geographic regions, including a considerable proportion of young patients from LMICs, who have been underrepresented in prior studies. Other strong elements include the standardized operationalization of data across the diverse international cohorts reducing misclassification and increasing the power of this study, inclusion of consecutive patients, and the more accurate estimations at subgroup level that arise from individual patient data meta-analyses.

This study also has limitations. First, data were collected at different time periods, during which primary and secondary preventive strategies, acute stroke treatment and etiologic work-up practices may have changed. Second, there was relatively few data from low-income countries and Africa as a continent to allow for a general conclusion. Third, we acknowledge that appointing individuals into such broad ethnic and racial categories is accompanied by some limitations. Specifically, the same ethnic and racial categories are not applied in the same way across the different geographic regions, because of differences in historical and social contexts that define ethnic and racial categories. Nevertheless, we are of the opinion that these broad groups, which are however widely used in literature, can still be of great clinical importance for demonstrating differences that can be important for clinical practice, and for health care interventions aiming on preventive strategies at subgroups at risk.

Fourth, as we used data collected according to local protocols with initially different purposes, information on certain risk factors was missing for some patients. Fifth, although we harmonized and standardized the definitions for all risk factors, differential misclassification may have occurred. For example, dyslipidemia in Western countries was often based on lipid levels or the use of statins, while in many LMICs it was primarily defined based on blood lipid level, which may result in an underestimation of the true prevalence of dyslipidemia in LMICs. Sixth, adjudicating the exact cause of stroke requires availability and access to additional investigations such as a cardiac ultrasound

or neuroimaging (MRI). It is possible that these were not equally available for patients from LMICs and those from HICs, which could also partly explain the higher prevalence of cryptogenic stroke in LMICs compared to HICs. However, we found no significant difference in prevalence of cardio-embolic stroke between HICs and LMICs (18.6% vs 20.0%), suggesting only minor misclassification of the cause of stroke. Furthermore, due to limited information on potential cardio-embolic sources (e.g. intracardiac thrombus, left ventricular ejection fraction<30%, cardiac tumors), the extent of luminal stenosis in the brain supplying arteries, and detailed topography of ischemic lesions we were not able to distinguish strokes with an embolic source of undetermined etiology (ESUS) from other strokes with an undetermined etiology. As collection of these variables was not needed to answer our initial research question, information on these variables was not systematically requested from the participating centers. Seventh, we were not able to investigate regional differences with respect to lifestyle or ambient air pollution that are increasingly recognized to play a role in stroke etiology.[3] Finally, all cohorts included in our study were hospital-based studies, potentially introducing selection bias because patients with very mild or rapidly fatal strokes might not have gone to or reached the hospital and might therefore not have been included.

Future Directions

We found regional differences in (vascular) risk factors for ischemic stroke in young adults. This raises the question whether this also translates to regional differences in outcome (e.g., recurrent stroke) after stroke and secondary prevention strategies. The current secondary prevention strategy is a more or less "one size fits all approach" without taking into account regional or ethnic background, while it is known that ethnic differences in efficacy of secondary prevention exist.[305-307] Also, future research should investigate whether improvement of access and affordability of health care facilities in LMICs will improve outcomes after stroke in younger patients, and whether this helps in tackling the current existing inequality. For example, an established evidence-based approach to improve short-term stroke outcome is the implementation of stroke units,[20] which seems readily cost-effective with feasible implementation in LMICs. This could save lives, prevent from permanent disability and loss of working capacity, decrease societal and health care costs, as well as improve the quality of life for millions of young individuals worldwide.

CONCLUSION

In conclusion, our study has shown significant differences in risk factors and causes of ischemic stroke at young age between different ethnic and racial groups and geographic regions that help in understanding ethnic and regional differences in the incidence and clustering of risk factors of ischemic stroke among young adults. These insights may be used to develop region-specific policies on stroke prevention, which could help in achieving the United Nations Sustainable Development Goals.[295] The increasing awareness for the presence of vascular risk factors already at midlife for late-life vascular disease, including the increased recognition of a role of these midlife vascular risk factors for late life cognitive decline,[308] underscores the importance of improving the health status of younger adults by managing vascular risk factors from as early as the third decade of life. Our results also visualize the inequalities in young stroke short-term mortality between LMICs and HICs and could help raise awareness of the magnitude of the problem to policy makers.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Overview of participating cohorts in alphabetical order

Country	Population	Single center or Multicenter	Number of patients (N)
Argentina	Hospital-based	Single center	91
Australia	Hospital-based	Multicenter	322
Austria	Hospital-based	Single center	363
Belgium	Hospital-based	Multicenter	448
Brazil	Hospital-based	Single center	135
Canada	Hospital based	Multicenter	118
Costa Rica	Hospital-based	Single center	166
Estonia	Hospital-based	Multicenter	424
Finland	Hospital-based	Single center	1000
France	Hospital-based	Single center	307
Germany	Hospital-based	Single center	105
India	Hospital-based	Single center	206
Israel	Hospital-based	Multicenter	321
Italy	Hospital-based	Multicenter	2147
Malaysia	Hospital-based	Single center	179
Mexico -*Mexico-City*	Hospital-based	Single center	1456
Mexico - Guadalajara	Hospital- based	Single center	19
Mongolia	Hospital-based	Single center	148
The Netherlands	Hospital-based	Single center	451
New Zealand	Hospital-based	Single center	336
Norway	Hospital-based	Single center	149
Portugal	Hospital-based	Single center	164
Republic of Korea-Hanyang University	Hospital-based	Single center	160
Republic of Korea-Seoul National University	Hospital-based	Multicenter CRCS-K	5472
South Africa	Hospital-based	Single center	91
Sweden	Hospital-based	Single center	552
Switzerland -Bern	Hospital-based	Multicenter	428

Design	Patient selection	Stroke definition	Study period
Retrospective	Consecutive	WHO	1999-2019
Retrospective	Consecutive	WHO	2006-2010
Retrospective	Consecutive	Radiologically confirmed	2008-2017
Prospective and Retrospective	Consecutive	WHO	2007-2008
Retrospective	Consecutive	WHO	2008-2012
Prospective	Consecutive	WHO	2013-2016
Prospective and retrospective	Consecutive	WHO	2012-2018
Retrospective	Consecutive	WHO	2003-2012
Retrospective	Consecutive	WHO	1994-2007
Prospective	Consecutive	Radiologically confirmed	2006-2010
Prospective and retrospective	Consecutive	Radiologically confirmed	2007-2012 2017-2019
Prospective	Consecutive	WHO	1988-1997
Prospective and retrospective	Consecutive	WHO	2007-2017
Prospective	Consecutive	Radiologically confirmed	2000-2013
Retrospective	Consecutive	Radiologically confirmed	2016-2017
Prospective	Consecutive	Radiologically confirmed	1990-2017
Retrospective and Prospective	Consecutive	Radiologically confirmed	2017- ongoing
Retrospective	Consecutive	WHO	2012-2017
Retrospective	Consecutive	WHO	1980-2010
Retrospective	Consecutive	WHO	2004-2009 2011-2016
Prospective	Consecutive	Radiologically confirmed	2010-2015
Prospective and Retrospective	Consecutive	Radiologically confirmed	2009-2018
Prospective	Consecutive	Radiologically confirmed	2014-2016
Prospective	Consecutive	Radiologically confirmed	2011-2018
Retrospective	Consecutive	WHO	2003-2016
Prospective	Consecutive	WHO	1998-2017
Prospective	Consecutive	Radiologically confirmed	2008-2012

Supplementary Table 1. Continued

Country	Population	Single center or Multicenter	Number of patients (N)
Switzerland - Luzern	Hospital- based	Single center	50
Taiwan	Hospital-based	Single center	466
Turkey	Hospital-based	Single center	100
United Arab Emirates	Hospital-based	Single center	144
USA	Hospital-based	Multicenter	889

Supplementary Table 2. Definitions of considered risk factors

Variable or risk factor	Definition
Hypertension	A history of hypertension was defined as its presence either in the patients' medical history, or when identified during admission for the index event after the acute phase within the first month after stroke. Hypertension was defined as the use of antihypertensive medication and/or systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater.
Diabetes mellitus	A history of diabetes was defined as its presence either in the patients' medical history, or when identified during admission for the index event. Diabetes was defined as the use of diabetic medication and/or a fasting (defined as no caloric intake for at least 8 hours) plasma glucose >7 mmol/L and/or 2-h PG ≥ 11.1 mmol/L during OGTT and/or HbA1C ≥ 6.5% (48 mmol/mol) and/or symptoms of hyperglycemia or hyperglycemic crisis and a random glucose >11.1 mmol/L.[32]
Dyslipidemia	A history of dyslipidemia was defined as its presence either in the patients' medical history, or when identified during admission for the index event. Dyslipidemia was defined as use of statins and/or cholesterol level ≥5.0 mmol/L (193 mg/dL) and/or low-density lipoprotein level ≥3.0 mmol/L (116 mg/dL) and/or high-density lipoprotein level <1.0 mmol/L (39 mg/dL) and/or triglyceride level ≥ 1.7 mmol/L (150mg/dL).
Atrial fibrillation (AF)	A history of AF (chronic/paroxysmal) was defined as its presence either in the patients' medical history, or when identified during admission for the index event. AF was defined as diagnosis based on ECG-findings.

Design	Patient selection	Stroke definition	Study period
Retrospective	Consecutive	Radiologically confirmed	2016-2018
Retrospective	Consecutive	Radiologically confirmed	1997-2001
Prospective and Retrospective	Consecutive	WHO	1996-ongoing
Prospective	Consecutive	WHO	2016-2018
Retrospective	Not Consecutive	WHO	1992-2008

Supplementary Table 2. Definitions of considered risk factors

Variable or risk factor	Definition
Patent foramen ovale (PFO)	A presence of PFO was defined based on documentation in medical records, or when identified during hospitalization for the index event. PFO was defined as PFO with or without atrial septum aneurysm, as identified on TTE or TEE with or without contrast.
Coronary artery disease	Coronary artery disease included myocardial infarction and/or angina pectoris. A history of myocardial infarction or angina pectoris was defined as its presence either in the patients' medical history, or when identified during admission for the index event.
Obesity	Obesity was defined as a body mass index greater than 30 kg/m^2, measured during admission for the index event or when reported by the patient.
Migraine	A history of migraine was defined as its presence either in the patients' medical history or when identified during hospitalization for the index event. Migraine was defined according to the International Headache Society criteria.[33]
Ever smoking	Any current or former smoker.
Excessive alcohol use	Heavy drinking was defined as the consumption of more than 21 units a week for men and 14 units a week for women, identified at admission for the index event.
Illicit recent drug use	Within the month prior to stroke.

Abbreviations: 2-h PG, 2-hours post glucose; OGTT, oral glucose tolerance test; HbA1c, glycosylated hemoglobin, type A1c; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram.

Supplementary Table 3. Differences in presence of concurrent risk factors, stratified by demographical characteristics and stroke etiology

	Total Patients	0 Present Risk Factor
Total reported cases	16,845	4419 (26.2)
Sex		
• Men	10,204 (60.6)	1936 (19.0)
• Women	6641 (39.4)	2483 (37.4)
Age-group		
• 18-25	894 (5.3)	491 (54.9)
• 26-30	1070 (6.4)	500 (46.7)
• 31-35	1721 (10.2)	658 (38.2)
• 36-40	2804 (16.6)	820 (29.2)
• 41-45	4748 (28.2)	1075 (22.6)
• 46-50	5608 (33.3)	875 (15.6)
Ethnic and Racial subgroups		
• White	5448 (32.3)	1559 (28.6)
• Black	499 (3.0)	109 (21.8)
• Hispanic	1700 (10.1)	599 (35.2)
• Asian	6566 (39.0)	1374 (20.9)
Geographic location		
• Oceania	578 (3.4)	126 (21.8)
• Asia	6510 (38.6)	1347 (20.7)
• Africa	88 (0.5)	47 (53.4)
• Southern Europe	2957 (17.6)	1140 (38.6)
• Central Europe	2002 (11.9)	485 (24.2)
• Northern Europe	1874 (11.1)	375 (20.0)
• North America	999 (5.9)	213 (21.3)
• Central and South America	1837 (10.9)	686 (37.3)
Country level of income		
• High-income countries	13,884 (82.4)	3443 (24.8)
• Low and middle-income countries	2961 (17.6)	976 (33.0)

1 Present Risk Factor	2 Present Risk Factors	3 Present Risk Factors	4 Present Risk Factors
5530 (34.0)	4148 (24.6)	2034 (12.1)	514 (3.1)
3470 (34.0)	2875 (28.2)	1502 (14.7)	421 (4.1)
2260 (34.0)	1273 (19.2)	532 (8.0)	93 (1.4)
333 (37.2)	49 (5.5)	21 (2.3)	0/894
422 (39.4)	116 (10.8)	28 (2.6)	4 (0.4)
670 (38.9)	278 (16.2)	106 (6.2)	9 (0.5)
988 (35.2)	652 (23.3)	283 (10.1)	61 (2.2)
1627 (34.3)	1258 (26.5)	625 (13.2)	163 (3.4)
1690 (30.1)	1795 (32.0)	971 (17.3)	277 (4.9)
1826 (33.5)	1328 (24.4)	627 (11.5)	108 (2.0)
156 (31.3)	129 (25.9)	81 (16.2)	24 (4.8)
706 (41.5)	265 (15.1)	112 (6.6)	27 (1.6)
2101 (32.0)	1831 (27.9)	946 (14.4)	314 (4.8)
188 (32.5)	164 (28.4)	80 (13.8)	20 (3.5)
2087 (32.1)	1822 (28.0)	946 (14.5)	308 (4.7)
20 (22.7)	11 (12.5)	6 (6.8)	4 (4.5)
966 (32.7)	552 (18.7)	257 (8.7)	42 (1.4)
748 (37.4)	516 (25.8)	218 (10.9)	35 (1.7)
613 (32.7)	577 (30.8)	279 (14.9)	30 (1.6)
372 (37.2)	236 (23.6)	132 (13.2)	46 (4.6)
736 (40.1)	270 (14.7)	116 (6.3)	29 (1.6)
4648 (33.5)	3579 (25.8)	1751 (12.6)	463 (3.3)
1082 (36.5)	569 (19.2)	283 (9.6)	51 (1.7)

Supplementary Table 3. Continued

	Total Patients	0 Present Risk Factor
Total reported cases	16,845	4419 (26.2)
TOAST-classification		
• Large vessel atherosclerosis	2739 (16.3)	366 (13.4)
• Small vessel disease	2450 (14.5)	262 (10.7)
• Cardio-embolism	3039 (18.0)	1086 (35.7)
• Other determined	3687 (21.9)	1438 (39.0)
• Undetermined	4199 (24.9)	1058 (25.2)

Data are n (%). Prevalence shown for presence of zero, one, two, three, or four vascular risk factors by age groups. Vascular risk factors included hypertension, dyslipidemia, diabetes and smoking.

	1 Present Risk Factor	2 Present Risk Factors	3 Present Risk Factors	4 Present Risk Factors
	5530 (34.0)	4148 (24.6)	2034 (12.1)	514 (3.1)
	785 (28.7)	887 (32.4)	532 (19.4)	169 (6.2)
	671 (27.4)	829 (33.8)	528 (21.6)	160 (6.5)
	1089 (35.8)	589 (19.4)	237 (7.8)	38 (1.3)
	1412 (38.3)	623 (16.9)	184 (5.0)	30 (0.8)
	1507 (35.9)	1060 (25.2)	474 (11.3)	100 (2.4)

Part IV

Long-term perspective on stroke in young adults

Chapter 9

Association of stroke among adults aged 18-49 years with long-term mortality

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ABSTRACT

Importance: Stroke remains the second leading cause of death worldwide. Approximately 10-15% of all strokes occur in young adults. Information on prognosis and mortality specifically in young adults is limited.

Objective: To determine short- and long-term mortality risk after stroke in young adults, according to age, sex, and stroke subtype, time trends in mortality, and causes of death.

Design, setting and participants: Registry- and population-based study in the Netherlands of 15,527 patients aged 18-49 years with first stroke between 1998 to 2010, and follow-up until January 1st, 2017. Patients and outcomes were identified through linkage of the national hospital discharge register, national cause of death register and the Dutch population register.

Exposure: First stroke occurring at age 18-49 years, documented using ICD-9 and ICD-10 codes for ischemic stroke, intracerebral hemorrhage and for stroke not otherwise specified.

Main outcomes: Primary outcome was all cause cumulative mortality in 30-day survivors at end of follow up, stratified by age, sex and stroke subtype and compared to all cause cumulative mortality in the general population.

Results: The study population included 15,527 patients with stroke (median age 44 (IQR 38-47) years; 53.3% women). At end of follow-up, a total of 3540 cumulative deaths had occurred, including 1776 deaths within 30 days after stroke and 1764 (23.2%) deaths during a median duration of follow-up of 9.3 years (IQR 5.9-13.1 years). 15-year mortality in 30-day survivors was 17.0% (95% CI 16.2-17.9). The standardized mortality rate (SMR) compared to the general population was 5.1 (95% CI 4.7-5.4) for ischemic stroke (observed mortality rate 12.0/1000 py with 95% CI: 11.2-12.9/1000 py, expected rate 2.4/1000 py, excess 9.6/1000 py), the SMR of intracerebral hemorrhage was 8.4 (95% CI 7.4-9.3; observed 18.7/1000 py with 95% CI: 16.7-21.0/1000 py, expected 2.2/1000 py, excess 16.4/1000 py).

Conclusions and relevance: Among young adults aged 18-49 years in the Netherlands who were 30-day survivors of first stroke, mortality risk compared to the general population remained elevated up to 15 years later.

KEY POINTS

Question: In young adults aged 18-49 years, what is the age and sex-specific case fatality and long-term mortality associated with stroke, and how has mortality changed over time?

Findings: In this Dutch register-based cohort-study that included 15 527 patients who in the years 1998-2010 had a first stroke at age 18-49 years, cumulative 15-year mortality among 30-day survivors was 13.27 per 1000 py compared with an expected mortality of 2.38 per 1000 py in the general population, an excess mortality of 10.89 per 1000 py.

Meaning: Mortality risk 15 years after stroke among young adults aged 18-49 years who were 30-days survivors remained elevated.

INTRODUCTION

Stroke is the second leading cause of death worldwide. In 2013, over 10 million people experienced a stroke, and over 6 million died.[309-311] Approximately 10-15% of all strokes occur in young adults aged 18-49 years.[1, 9] Information on the risk of death in this subgroup is limited.[161]

Previous studies of mortality after stroke in young adults were often small, hospital based, had limited periods of follow-up, or included patients who had their stroke between 1980 and 2000.[172, 312, 313] Over the past decades, both acute treatment and secondary prevention have improved. Because of the small number of patients younger than age 50 with stroke included in previous studies, it has not been possible to estimate mortality according to age-, sex-, and stroke subtypes.[54, 166, 312, 314-317]

This study aimed to investigate case fatality-, cumulative 1-year-, 5-year-, 10-year and 15-year mortality and trends over time of first stroke in young adults aged 18-49 years, stratified by age, sex and stroke-subtype, excess mortality after stroke compared to the general population and causes of death.

METHODS

The Medical Ethics Review Committee Arnhem/Nijmegen assessed the protocol and waived the requirement for ethical review. We performed all analyses in a secured environment of Statistics Netherlands according to the Dutch privacy legislation.

Exposure

We constructed a nationwide cohort of patients aged 18-49 years with first stroke (ischemic stroke, intracerebral hemorrhage, or stroke not otherwise specified) through linkage of the Dutch nationwide hospital registry (HDR) and Dutch population registry from January 1st 1998 to January 1st 2011 and the National Cause of Death registry (CDR) from January 1st 1998 to January 1st 2017, by using ICD-9 and -10 codes for stroke (ischemic stroke, intracerebral hemorrhage and stroke not otherwise specified; WHO International Classification of Diseases) (see Chapter 4, Table 1). We did not include transient ischemic attacks (TIA) and subarachnoid hemorrhage (SAH). Details of these registries and linkage procedures have been described previously.[165, 166, 318]

ICD-9 and ICD-10 codes for the identification of stroke has been proven to be reliable in studies of patients with stroke of all ages.[162, 163] For this study, we specifically assessed the accuracy of ICD-10 codes for young adults (aged 18-49 years old). We checked final diagnoses in medical records against the attached ICD-10 code at discharge of 569 patients admitted in two university medical centers and one large general hospital between 1995 and 2017. For ischemic stroke the ICD-code was correct in 90.4% of cases (n=301), for intracerebral hemorrhage in 86.3% (n=183), and for stroke not otherwise specified in 87.1% of cases (n=85) (see Chapter 4, Table 2).

For all individuals the Charlson-Comorbidity-Index (CCI) at the time of the index event was estimated based on previously documented hospital admissions. The CCI is a score from one to six based on 19 primary medical conditions such as congestive heart failure, diabetes, malignancies and other organ dysfunction and has previously been shown a valid tool to predict outcome.[319]

Outcomes

Primary outcome was all-cause cumulative mortality at the end of follow-up, stratified for age, sex and stroke subtype in 30-day survivors. Secondary outcomes were case fatality and cumulative 1-year, 5-year, 10-year and 15-year mortality in the 30-day survivors. Other secondary outcomes were the annual risk of death, excess mortality after stroke compared to the general population, time-trends of case fatality, 1-year and 5-year mortality in 30-day survivors after first stroke in young adults and causes of death, all

stratified by age, sex and stroke-subtype. Out of hospital deaths were identified if an ICD-10 code for stroke was registered in the CDR without previous hospitalizations in the HDR for this individual. Individuals that have emigrated have been censored. The number of hospitals participating in the HDR declined from 2005 to 2010, resulting in an increasing number of missing records, varying from 1.1% to 14%, resulting in some missing index strokes. Date and cause of death were retrieved from the CDR. In the Netherlands all deaths are recorded in the CDR by Statistics Netherlands. Cause of death was missing for 1 patient (0.05%); this patient was excluded from the analysis. Data regarding other variables, age, sex, CCI and length of stay, were complete for all patients. Follow-up after first stroke between 1998 and 2010 was defined as the time until death or the end of follow up (January 1st, 2017), whichever occurred first. Case fatality was defined as death occurring within 30 days after stroke. For survival analysis only survivors beyond these 30 days were included. Causes of death were analyzed by ICD-10 codes.

Statistical Analysis

We used Kaplan-Meier analysis to estimate the risk of death for all-cause stroke, ischemic stroke, intracerebral hemorrhage and stroke not otherwise specified for men and women separately. We calculated the number of person-years (py) at risk for each individual patient from date of stroke to the date of death or until January 1st, 2017, whichever occurred first. We censored the Kaplan-Meier curves at 16 years after the index event because thereafter the number of py at risk became too small to provide reliable estimates of mortality. We calculated 1-year-, 5-year-, 10-year and 15-year cumulative mortality by sex and stroke-subtype. Survival curves were compared between men and women using log-rank analysis.

For comparison of mortality in young adults with stroke to mortality in the general population, we used mortality data of the general Dutch population matched by sex, age and calendar year.[318] The annual risk of the observed mortality after stroke as well as the expected mortality in the general population was calculated using the formula: $1-[(1-Ic)^{(1/n)}]$ where n is the number of years after the index event and Ic is the cumulative mortality at n years, obtained by Kaplan-Meier analysis.

We calculated standardized mortality ratio's (SMRs) by dividing the observed deaths in our cohort by the expected deaths of their peers from the general population for each stroke subtype, for both sexes and for different age-categories (18-29, 30-39 and 40-49). The expected matched mortality rates were retrieved from the Worldwide Human Mortality Database (www.mortality.org).[320] The 95% CIs were calculated by assuming a Poisson distribution. Additionally, for each subgroup, we calculated an absolute excess number of deaths by taking the difference between the observed and expected deaths,

divided by the person-years at risk. Differences of the SMRs by sex and stroke subtype were evaluated by tests of interactions through univariate and multivariable linear regression modeling.

We assessed the association of age at index event, sex, CCI, and length of stay with the risk of long-term mortality, stratified for stroke subtypes, through Cox proportional hazard models, and expressed the associations as hazard ratios (HR) with 95% CIs. After univariate analysis, all four variables were entered simultaneously to obtain a multivariable model. Assumption of proportionality in the Cox regression model was evaluated graphically assessing the log(-log(Survival)) plots for all covariates. We found no indication of violating the assumption. In addition, we plotted the scaled Schoenfeld residuals against time, which confirmed proportionality. We calculated time trends in case fatality, 1-year and 5-year mortality rates in yearly average percentage change (APC) and tested change over time with linear regression analysis. We used R-squared (R^2) to assess the goodness of fit of the linear regression analyses. Time trends regarding 10-year and 15-year mortality were not calculated because we did not have a complete 10- and 15- year follow up period for all inclusion years. Also time trends were calculated for mean length of stay and tested through linear regression.

In the Netherlands, cause of death is established among all patients that die (both inside or outside the hospital) by a coroner or physician who is required by law to complete the death certificate. This death certificate is then sent to coders employed by Statistics Netherlands who assign an ICD-10 code for the primary (underlying disease) and secondary causes of death (possible complications, such as pneumonia) accordingly. Studies on the reliability of these ICD-10 codes found an intercoder-agreement of 78% and intracoder-agreement of 89%. The highest reliability was found for major causes of death (malignancy and acute myocardial infarction).[321] We categorized causes of death based on the ICD 10 codes for primary cause in 30-day survivors. (Supplementary Table 1). Proportion of causes of death were compared through chi-squared analyses. We tested for interactions between stroke subtype and different causes of death separately through using a Poisson regression model, with adjustment for sex through adding this as a covariate to a multivariable Poisson model.

Two-sided p-values of .05 were considered statistically significant. For the SMR analyses, we set the threshold for significance to a p-value of .005 after Bonferroni adjustment for ten subgroup analyses.

Data was analyzed with SPSS Software 22, R version 3.22 (Packages rateratio.test, survival, survminer), STATA version 12 and Microsoft Office Excel 2007.

RESULTS

We identified 15,257 young adults with a stroke (53.3% women, median age 44 years, IQR 38-47). 8444 (55.3%) had ischemic stroke, 3077 (20.2%) had intracerebral hemorrhage and 3736 (24.5%) had a stroke not otherwise specified. Less than 1% of strokes were out of hospital deaths, and the majority had no comorbidity (n=12,803, 83.9%) (Table 1). The median duration of follow-up was 9.3 years (IQR=5.9-13.1 y; Table 1).

Following any stroke, 1776 patients (11.6%) died in the first 30 days. Case fatality after ischemic stroke was 7.4% (n=629), 7.6% (n=291) in men, 7.4% (n=338) in women), after intracerebral hemorrhage 32.3% (29.8% (n=991) in men, 34.8% (n=519) in women), and after stroke not otherwise specified 4.2% (3.8% (n=65) in men, 4.4% (n=91) in women). This resulted in a cohort of 13,481 30-day survivors of patients with any stroke (7815 ischemic stroke, 2086 intracerebral hemorrhage and 3580 stroke not otherwise specified; Supplementary Table 4).

Cumulative mortality

At end of follow-up a total of 3540 (23.2%) patients had died. In 30-day survivors, the cumulative mortality after any stroke increased from 3.1% (95% CI, 2.8%-3.4%) after 1 year to 7.0% (95% CI 6.6-7.4) at 5 years, 11.5% (95% CI 11.0-12.1) at 10 years and 17.0% (95% CI 16.2-17.9) after 15 years (Figure 1a-d; Supplementary Table 3).

Sex-specific annual risk of death by stroke subtype

The annual risk of death of 30-day survivors was highest in the first years after stroke and then stabilized (Figure 1e-h). After ischemic stroke the risk of death after 1 year was 2.0% (95% CI 1.8-2.3) for men and 1.6% (95% CI 1.4-1.8) for women, and after 10 years decreased to an annual risk of 1.4% (95% CI 1.2-1.6) for men and 0.9% (95% CI 0.7-1.1) for women.

For intracerebral hemorrhage the annual risk of death was 4.8% (95% CI 4.4-5.1) for men and 3.9% (95% CI 3.6-4.3) for women after 1 year and after 10 years decreased to an annual risk of 1.9% (95% CI 1.7-2.1) for men and 1.4% (95% CI 1.2-1.6) for women (Figure 1e-h).

Long-term mortality in 30-day survivors of stroke compared to the general population

The standardized mortality ratio for young adults with any stroke compared to peers from the general population matched by sex, age and calendar year, was 5.6 (95% CI 5.3-5.9). The observed mortality rate was 13.3 per 1000 py (95% CI: 12.6-14.0 per 1000 py) versus an expected rate of 2.4 per 1000 py with an excess of 10.9 deaths per 1000 py. The SMR for ischemic stroke was 5.1 (95% CI 4.7-5.4) with an observed mortality rate of 12.0 per 1000 py (95% CI: 11.2-12.9 per 1000 py), and expected mortality rate of 2.4 per 1000 py and an excess of 9.6 per 1000 py. For intracerebral hemorrhage the SMR was 8.4 (95% CI 7.4-9.3; observed mortality rate 18.7 per 1000 py; 95% CI: 16.7-21.0 per 1000 py, expected rate 2.2 per 1000 py, excess of 16.5 per 1000 py). The SMR for stroke not otherwise specified was 5.2 (95% CI 4.7-5.8; observed rate 12.9; 95% CI: 11.7-14.3, expected rate 2.5, excess 10.5 per 1000 py). There were no significant differences in SMR between men and women (bivariable linear regression model, P = .74; multivariable model including stroke subtype and age groups, P = .07). Results stratified for age groups and sex are summarized in Table 2.

Figure 1. Cumulative mortality in 30-day stroke survivors, according to sex and stroke subtype, and in comparison with the general population (a-d), and annual mortality over time (e-h)

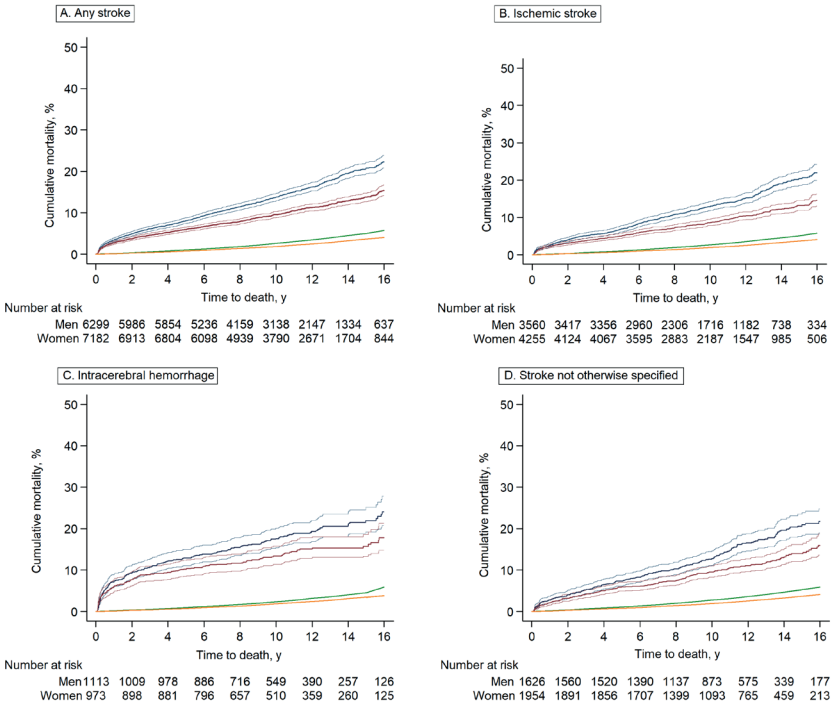

Figure 1. Continued

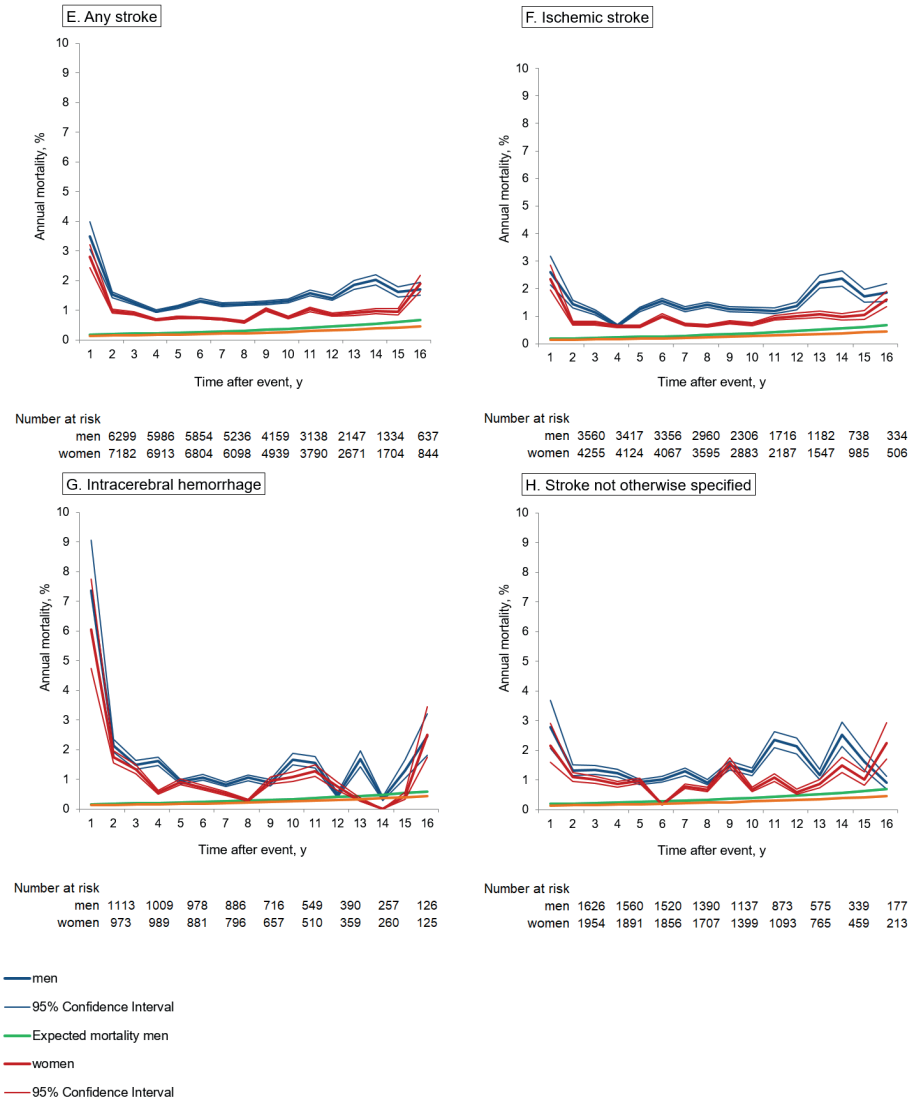

Table 1. Demographics including age, sex, comorbidity and follow-up of patients with stroke aged 18-50 years

		Any stroke			Ischemic stroke	
		Total	Men	Women	**Total**	Men
	N (%)	15,257 (100%)	7127 (46.7%)	8130 (53.3%)	8444 (100%)	3851 (45.6%)
	Mean age, y (SD[a])	41.8 (6.8)	42.3 (6.5)	41.4 (7.0)	42.0 (6.6)	42.6 (6.1)
Charlson comorbidity index[b]	**N score 0 (%)**	12,803 (83.9%)	5951 (83.5%)	6852 (84.3%)	7178 (85.0%)	3262 (84.7%)
	N score 1 (%)	1694 (11.1%)	810 (11.4%)	884 (10.8%)	879 (10.4%)	397 (10.3%)
	N score 2 (%)	574 (3.8%)	275 (3.9%)	299 (3.7%)	299 (3.5%)	152 (3.9%)
	N score >=3 (%)	186 (1.2%)	91 (1.3%)	95 (1.2%)	88 (1.0%)	40 (1.0%)
Duration of Follow up[c]	**Median Follow up, y (IQR[d])**	9.3 (5.9-13.1)	9.2 (5.8-12.9)	9.5 (6.0-13.3)	9.5 (6.3-13.2)	9.3 (6.2-12.9)
	Follow up > 5y, N (%)	12,541 (82.2%)	5789 (81.2%)	6752 (83.0%)	7355 (87.1%)	3314 (86.1%)
	Follow up > 10y, N (%)	6928 (45.4%)	3138 (44.0%)	3790 (46.6%)	3903 (46.2%)	1716 (44.6%)

[a] SD, standard deviation

[b] Charlson Comorbidity Index score ranges from 0 to 6, with higher scores indicating more comorbidity.

	Intracerebral hemorrhage			Stroke not otherwise specified		
Women	**Total**	Men	Women	**Total**	Men	Women
4593 (54.4%)	3077 (100%)	1585 (51.5%)	1492 (48.5%)	3736 (100%)	1691 (45.3%)	2045 (54.7%)
41.4 (7.0)	40.7 (7.5)	40.7 (7.5)	40.8 (7.5)	42.2 (6.4)	42.9 (6.0)	41.6 (6.7)
3916 (85.2%)	2539 (82.5%)	1307 (82.4%)	1232 (82.6%)	3086 (82.6%)	1382 (81.7%)	1704 (83.3%)
482 (10.5%)	353 (11.5%)	189 (11.9%)	164 (10.9%)	462 (12.4%)	223 (13.2%)	238 (11.6%)
147 (3.2%)	137 (4.5%)	63 (4.0%)	74 (5.0%)	138 (3.7%)	69 (4.1%)	78 (3.8%)
48 (1.0%)	48 (1.6%)	26 (1.6%)	22 (1.4%)	50 (1.3%)	25 (1.5%)	25 (1.2%)
9.7 (6.4-13.4)	6.9 (0.0-11.9)	7.1 (0.0-11.9)	6.7 (0.0-11.8)	10.3 (7.0-13.5)	10.2 (6.9-13.3)	13.7 (7.2-13.7)
4041 (88.0%)	1842 (59.9%)	969 (61.1%)	873 (58.5%)	3344 (89.5%)	1509 (89.2%)	1838 (89.9%)
2187 (47.6%)	1059 (34.4%)	549 (34.6%)	510 (34.2%)	1966 (52.6%)	873 (51.6%)	1093 (53.4%)

[c] Duration of Follow up is defined as the time, in years, between event and death or end of study, whichever occurred first in years

[d] IQR, interquartile range.

Table 2. Long-term mortality in 30-day stroke survivors compared to mortality of the general population

	Total	Patient Years (py) at risk	Observed deaths	Observed deaths per 1000 py
Any stroke	13481	102184	1356	13.27
Men	6299	46937	756	16.11
Women	7182	55247	600	10.86
18-29	928	7477	52	6.95
Men	340	2635	28	10.63
Women	588	4842	24	4.96
30-39	2951	23423	228	9.73
Men	1285	9958	128	12.85
Women	1666	13465	100	7.43
40-49	9602	71284	1076	15.09
Men	4674	34344	600	17.47
Women	4928	36939	476	12.89
Ischemic stroke	7815	58668	704	12.00
Men	3560	26228	382	14.56
Women	4255	32440	322	9.93
18-29	487	3903	26	6.66
Men	162	1247	10	8.02
Women	325	2656	16	6.02
30-39	1667	13414	100	7.45
Men	696	5510	52	9.44
Women	971	7904	48	6.07
40-49	5661	41351	578	13.98
Men	2702	19471	320	16.43
Women	2959	21880	258	11.79
Intracerebral hemorrhage	2086	15560	291	18.70
Men	1113	8158	174	21.33
Women	973	7402	117	15.81
18-29	228	1835	17	9.26
Men	109	866	11	12.70
Women	119	969	6	6.19
30-39	515	3864	72	18.63

95% Confidence interval		Expected deaths[b]	Expected deaths per 1000 py	Excess[b] per 1000 py	Standardized Mortality Rate[c] (95% CI [d])		
12.60	14.00	242.82	2.38	10.89	**5.58**	5.29	5.89
15.01	17.29	131.07	2.79	13.31	**5.77**	5.36	6.18
10.03	11.76	111.75	2.02	8.84	**5.37**	4.94	5.80
5.30	9.12	3.29	0.44	6.52	**15.83**	11.57	20.40
7.35	15.36	1.55	0.59	10.04	**18.12**	11.65	25.24
3.33	7.39	1.74	0.36	4.60	**13.79**	8.62	19.54
8.55	11.08	25.15	1.07	8.66	**9.06**	7.91	10.26
10.82	15.27	12.28	1.23	11.62	**10.42**	8.63	12.29
6.11	9.03	12.87	0.96	6.47	**7.77**	6.29	9.32
14.23	16.02	214.38	3.01	12.09	**5.02**	4.72	5.32
16.14	18.91	117.24	3.41	14.06	**5.12**	4.71	5.53
11.79	14.09	97.14	2.63	10.26	**4.90**	4.47	5.34
11.15	12.91	139.12	2.37	9.63	**5.06**	4.69	5.43
13.18	16.09	73.52	2.80	11.76	**5.20**	4.68	5.73
8.9	11.07	65.61	2.02	7.90	**4.91**	4.37	5.46
4.54	9.77	1.66	0.43	6.23	**15.62**	10.21	21.62
4.33	14.87	0.73	0.59	7.43	**13.66**	5.46	23.22
3.70	9.82	0.93	0.35	5.67	**17.15**	9.65	25.72
6.13	9.06	14.48	1.08	6.38	**6.91**	5.59	8.29
7.20	12.37	6.83	1.24	8.20	**7.61**	5.56	9.81
4.58	8.05	7.65	0.97	5.11	**6.28**	4.58	8.11
12.89	15.16	122.98	2.97	11.00	**4.70**	4.32	5.09
14.74	18.32	65.95	3.39	13.05	**4.85**	4.32	5.40
10.44	13.31	57.03	2.61	9.19	**4.52**	3.98	5.09
16.69	20.96	34.82	2.24	16.46	**8.36**	7.41	9.34
18.41	24.71	20.45	2.51	18.82	**8.51**	7.29	9.78
13.21	18.92	14.36	1.94	13.87	**8.15**	6.67	9.68
5.77	14.87	0.84	0.46	8.81	**20.35**	10.78	31.13
7.06	22.85	0.50	0.58	12.12	**21.96**	9.98	35.94
2.79	13.75	0.33	0.35	5.85	**17.94**	5.98	32.90
14.82	23.42	4.07	1.05	17.58	**17.71**	13.77	21.89

Table 2. Continued

	Total	Patient Years (py) at risk	Observed deaths	Observed deaths per 1000 py
Men	279	2042	46	22.53
Women	236	1822	26	14.27
40-49	1343	9861	202	20.49
Men	725	5250	117	22.29
Women	618	4611	85	18.44
Stroke not otherwise specified	3580	27956	361	12.91
Men	1626	12551	200	15.93
Women	1954	15405	161	10.45
18-29	213	x[e]	x	x
Men	69	x	x	x
Women	144	x	x	x
30-39	769	6145	56	9.11
Men	310	2406	30	12.47
Women	459	3739	26	6.95
40-49	2598	20072	296	14.75
Men	1247	9624	163	16.94
Women	1351	10449	133	12.73

[a] Expected deaths retrieved from mortality data of the Dutch population matched for age-, sex- and calendar year- characteristics (Human mortality database)

[b] Excess was calculated as (observed deaths - expected deaths) / py at risk expressed per 1000 py

[c] SMR is the ratio of the observed mortality rate divided by expected mortality rate, assuming the observed deaths follow a Poisson distribution

95% Confidence interval		Expected deaths[b]	Expected deaths per 1000 py	Excess[b] per 1000 py	Standardized Mortality Rate[c] (95% CI [d])		
16.93	29.98	2.40	1.18	21.35	**19.14**	13.73	24.97
9.74	20.9	1.66	0.91	13.35	**15.63**	10.22	21.65
17.87	23.48	29.91	3.03	17.45	**6.75**	5.85	7.69
18.63	26.66	17.55	3.34	18.94	**6.67**	5.47	7.92
14.93	22.76	12.37	2.68	15.75	**6.87**	5.42	8.41
11.66	14.31	68.88	2.46	10.45	**5.24**	4.70	5.79
13.89	18.28	37.10	2.96	12.98	**5.39**	4.66	6.15
8.96	12.19	31.78	2.06	8.39	**5.07**	4.31	5.85
x	x	x	x	x	**x**	x	x
x	x	x	x	x	**x**	x	x
x	x	x	x	x	**x**	x	x
7.02	11.83	6.61	1.08	8.04	**8.47**	6.35	10.74
8.74	17.79	3.05	1.27	11.20	**9.84**	6.56	13.45
4.74	10.2	3.56	0.95	6.00	**7.30**	4.77	10.11
13.17	16.51	61.49	3.06	11.68	**4.81**	4.28	5.37
14.55	19.72	33.74	3.51	13.43	**4.83**	4.09	5.57
10.75	15.07	27.75	2.66	10.07	**4.79**	4.00	5.62

[d] 95% Confidence intervals. For subgroup analyses within any stroke and the different stroke subtypes the significance threshold was set to a Bonferroni adjusted p-value of .005. P-values <.001 for all rows that have data

[e] x relates to missing data (subgroup was too small in number of patients to adequately protect privacy according to legislation regarding the use of this register-based dataset of Statistics Netherlands)

Table 3. Associated factors with mortality among 30-day stroke survivors according to stroke subtype

	Univariate analysis[a]			Multivariable analysis[b]		
	HR	**95% CI**		**HR**	**95% CI**	
Any stroke						
Age at index event, y[c]						
25-29	1.48	0.86	2.57	1.53	0.88	2.65
30-34	1.49	0.90	2.46	1.43	0.87	2.37
35-39	**2.35**	1.47	3.75	**2.26**	1.41	3.62
40-44	**2.65**	1.67	4.19	**2.54**	1.60	4.01
45-49	**3.76**	2.39	5.92	**3.36**	2.13	5.28
Sex, men[d]	**1.50**	1.37	1.65	**1.41**	1.29	1.55
Charlson Comorbidity Index[e]						
1	**2.10**	1.85	2.38	**2.07**	1.83	2.35
2	**6.48**	5.59	7.51	**5.91**	5.10	6.86
>= 3	**9.36**	7.49	11.69	**7.72**	6.17	9.65
Length of stay[f]						
3-7 days	1.09	0.92	1.30	1.19	1.00	1.41
8-14 days	1.18	0.99	1.40	**1.28**	1.08	1.53
>= 15 days	**2.17**	1.85	2.55	**2.24**	1.91	2.63
Ischemic stroke						
Age at index event, y[c]						
25-29	1.48	0.70	3.14	1.37	0.64	2.90
30-34	0.89	0.43	1.83	0.83	0.40	1.72
35-39	1.92	1.00	3.67	1.90	0.99	3.65
40-44	**2.36**	1.26	4.45	**2.24**	1.19	4.23
45-49	**3.50**	1.87	6.54	**3.13**	1.67	5.84
Sex, men[d]	**1.54**	1.35	1.75	**1.42**	1.25	1.62
Charlson Comorbidity Index[e]						
1	**2.05**	1.72	2.45	**2.02**	1.69	2.41
2	**6.29**	5.12	7.72	**5.54**	4.51	6.81
>= 3	**9.74**	7.10	13.37	**7.56**	5.50	10.40
Length of stay[f]						
3-7 days	1.19	0.93	1.53	1.29	1.00	1.65
8-14 days	1.23	0.96	1.57	**1.34**	1.04	1.72

	Univariate analysis[a]			Multivariable analysis[b]		
	HR	95% CI		HR	95% CI	
Intracerebral hemorrhage						
Age at index event, y[c]						
25-29	2.65	0.93	7.52	3.20	1.13	9.10
30-34	**3.04**	1.17	7.92	2.77	1.06	7.24
35-39	**4.46**	1.78	11.15	**3.60**	1.44	9.03
40-44	**4.36**	1.77	10.74	**4.02**	1.63	9.90
45-49	**5.09**	2.09	12.40	**4.63**	1.90	11.29
Sex, men[d]	**1.35**	1.09	1.68	**1.35**	1.09	1.68
Charlson Comorbidity Index[e]						
1	**1.66**	1.25	2.21	**1.73**	1.30	2.30
2	**8.24**	6.09	11.15	**8.26**	6.08	11.22
>= 3	**9.53**	6.06	14.98	**9.34**	5.91	14.78
Length of stay[f]						
3-7 days	1.19	0.77	1.84	1.28	0.83	1.99
8-14 days	1.23	0.82	1.86	1.27	0.84	1.92
>= 15 days	**1.99**	1.38	2.86	**2.08**	1.44	3.00
Stroke not otherwise specified						
Age at index event, y[c]						
25-29	0.67	0.18	2.48	0.72	0.19	2.69
30-34	1.73	0.60	4.99	1.67	0.58	4.84
35-39	1.98	0.72	5.48	1.73	0.62	4.77
40-44	2.20	0.81	5.98	1.95	0.72	5.30
45-49	**3.36**	1.25	9.02	2.64	0.98	7.11
Sex, men[d]	**1.47**	1.22	1.76	**1.40**	1.16	1.68
Charlson Comorbidity Index[e]						
1	**2.50**	1.98	3.14	**2.41**	1.91	3.03
2	**5.47**	4.05	7.38	**5.03**	3.72	6.79
>= 3	**7.72**	5.00	11.91	**6.32**	4.08	9.80
Length of stay[f]						
3-7 days	0.95	0.70	1.28	1.05	0.78	1.43
8-14 days	1.08	0.79	1.47	1.19	0.87	1.43

Table 3. Continued

	Univariate analysis[a]			Multivariable analysis[b]		
	HR	**95% CI**		**HR**	**95% CI**	
>= 15 days	**2.30**	1.82	2.90	**2.35**	1.86	2.96

Charlson Comorbidity Index score ranges from 0 to 6, with higher scores indicating more comorbidity.
[a] Hazard ratios (95% CI) were computed separately for age at index event, sex, Charlson Comorbidity Index and length of stay; [b] Age at index event, sex, Charlson Comorbidity Index

Table 4. Causes of death in 30-day survivors, stratified by stroke subtype and sex

	Index event:									
	Any stroke						**Ischemic stroke**			
Causes of death	**total**		**men**		**women**		**total**		**men**	
	N	%	N	%	N	%	N	%	N	%
Total	1763	100	987	100	776	100	947	100	524	100
Stroke related	267	15.1	147	14.9	120	15.5	129	13.6	72	13.7
Ischemic stroke	35	2.0	20	2.0	15	1.9	28	3.0	x	X
Intracerebral hemorrhage	49	2.8	26	2.6	23	3.0	12	1.3	x	X
Other stroke related deaths	183	10.4	101	10.2	82	10.6	89	9.4	50	9.5
Cardiac and other vascular events	302	17.1	194	19.7	108	13.9	184	19.4	113	21.6
Malignancies	577	32.7	273	27.7	304	39.2	273	28.8	127	24.2
Lung cancer	145	25.1	53	19.4	92	30.3	83	30.4	31	24.4
Brain tumor	86	14.9	56	20.5	30	9.9	29	10.6	16	12.6
Hematological malignancies	47	8.1	22	8.1	25	8.2	x	X	x	X
Breast cancer	40	6.9	X	X	x	X	22	8.1	x	X
Melanoma	28	4.9	X	x	x	X	x	X	x	X
Other forms of malignancies	232	40.2	128	46.9	103	33.9	115	42.1	71	55.9
Infections	87	4.9	50	5.1	37	4.8	52	5.5	32	6.1
Trauma	78	4.4	53	5.4	25	3.2	42	4.4	29	5.5
Miscellaneous	452	25.6	270	27.4	182	23.5	267	28.2	151	28.8

ICD codes used to define the categories of causes of death are listed in Supplementary Table 1.
[a] Blank values relate to missing data (subgroup was too small in number of patients to adequately protect privacy according to legislation regarding the use of this register-based dataset of Statistics Netherlands.

	Univariate analysis[a]			Multivariable analysis[b]		
	HR	95% CI		HR	95% CI	
>= 15 days	**2.05**	1.55	2.70	**2.10**	1.59	2.78

and length of stay were entered simultaneously in a Cox proportional hazards model; [c] Reference category for age at index event was "18-24 years"; [d] Reference category for sex was "women"; [e] Reference category for Charlson Comorbidity Index was "a score of 0"; [f] Reference category for length of stay was "0-2 days".

		Intracerebral hemorrhage						Stroke not otherwise specified					
women		**total**		**men**		**women**		**total**		**men**		**women**	
N	%	N	%	N	%	N	%	N	%	N	%	N	%
423	100	349	100	210	100	139	100	467	100	253	100	214	100
57	13.5	79	22.6	42	20.0	37	26.6	59	12.6	33	13.0	26	12.1
x	X	x	X	x	X	x	X	x	X	x	X	x	X
x	X	x	X	x	X	x	X	x	X	x	X	x	X
39	9.2	50	14.3	26	12.4	24	17.3	44	9.4	25	9.9	19	8.9
71	16.8	25	7.2	x	X	x	X	93	19.9	63	24.9	30	14.0
146	34.5	145	41.5	80	38.1	65	46.8	159	34.0	92	26.1	126	43.5
52	35.6	14	9.7	x	X	x	X	48	30.2	x	X	x	X
13	8.9	44	30.3	32	40.0	12	18.5	13	8.2	34	51.5	38	40.9
x	X	x	X	x	X	x	X	x	X	x	X	x	X
x	X	x	X	x	X	x	X	12	7.5	x	X	x	X
x	X	21	14.5	10	12.5	11	16.9	x	X	x	X	x	X
44	30.1	46	31.7	24	30.0	22	33.8	70	44.0	33	50.0	37	39.8
20	4.7	19	5.4	x	X	x	X	16	3.4	x	X	x	X
13	3.1	12	3.4	x	X	x	X	24	5.1	x	X	x	X
116	27.4	69	19.8	50	23.8	19	13.7	116	24.8	69	27.3	47	22.0

The association of age, sex, comorbidity and length of stay with the risk of death after index stroke

In univariate Cox regression analysis for any stroke age was associated with mortality during follow-up of 30-day survivors (35-39 y: HR 2.3, 95% CI 1.5-3.8, p<0.001; 40-44 y: HR 2.6, 95% CI 1.7-4.2, p<0.001; 45-49 y: HR 3.8, 95% CI 2.4-5.9, p<0.001; all compared to the reference group aged 18-24years). Age-groups 25-29 and 30-34 were not significantly associated with a higher risk of mortality. Male sex was associated with a higher risk of mortality with a HR of 1.5 (95% CI 1.4-1.6; p<0.001), as well as a CCI above 0 (CCI of 1: HR 2.1, 95% CI 1.9-2.4, p<0.001; CCI of 2 HR 6.5, 95% CI 5.6-7.5, p<0.001; CCI of 3 or higher: HR 9.4 95% CI 7.5-11.7, p<0.001). In addition, length of hospital stay longer than 14 days was associated with mortality (HR 2.2, 95% CI 1.9-2.5, p<0.001). In the multivariable Cox regression model all of the above associations remained significant. Table 3 shows HRs of the uni- and multivariable Cox regressions models specified per stroke subtype.

Time trends in case fatality, 1-year, 5-year mortality and length of stay for any stroke and for stroke subtypes

Case fatality after any stroke decreased from 15.2% (n=160) in 1998 to 6.9% (n=86) in 2010 (yearly APC -5.5%, 95% CI -13.1-2.0%; p<0.001, R^2=0.9), for ischemic stroke from 8.4% (n=47) in 1998 to 4.9% (n=38) in 2010 (yearly APC -1.3%, 95% CI -17.1-14.6%; p<0.001, R^2=0.6), for intracerebral hemorrhage from 37.9% (n=89) in 1998 to 21.1% (n=44) in 2010 (yearly APC -3.8%, 95% CI -11.9-4.4%; p<0.001, R^2=0.8) and for stroke not otherwise specified from 4.6% (n=12) in 1998 to 1.2% (n=3) in 2010 (yearly APC -0.4%, 95% CI -36.3-35.5%; p=.006, R^2=0.5).

One-year mortality in 30-day survivors after any stroke decreased from 3.7% (n=39) in 1998 to 2.3% (n=29) in 2010 (yearly APC -2.2%, 95% CI -13.0-8.6%; p=.002, R^2=0.6). In ischemic stroke, 1-year mortality decreased from 3.3% (n=18) in 1998 to 1.2% (n=9) in 2010 (yearly APC -2.8%, 95% CI -20.2-14.7%; p=.005, R^2=0.5) whereas in intracerebral hemorrhage 7.8% (n=18) in 1998 and 6.1% (n=13) in 2010; yearly APC 5.4%, 95% CI -18.6-29.4%; p=.07, R^2=0.3) and in stroke not otherwise specified 1-year mortality remained stable (3.6% (n=9) in 1998 and 2.8% (n=7) in 2010; yearly APC 24.1%, 95% CI -18.8-67.0%; p=.97, R^2=0.0).

Cumulative 5-year mortality in 30-day stroke survivors decreased significantly over time in any stroke from 8.4% (n=89) in 1998 to 5.2% (n=64) in 2010 yearly APC -3.1%, 95% CI -10.2-4.0%; p<0.001, R^2=0.8), in ischemic stroke from 8.0% (n=45) to 3.0% (n=23) (yearly APC -6.2%, 95% CI -17.2-4.8%; p<0.001, R^2=0.8), and in stroke not otherwise specified from 8.4% (n=22) to 7.2% (n=18) (yearly APC 2.8%, 95% CI -11.7-23.4%; p=.046, R^2=0.3).

Cumulative 5-year mortality remained stable in intracerebral hemorrhage (9.6% (n=23) in 1998 and 12.1% (n=25) in 2010; yearly APC 5.9%, 95% CI -13.7-19.3%; p=.98, R^2=0.0) (Supplementary Table 3).

From 1998 to 2010 length of stay after any stroke decreased significantly from a mean of 18.2days to a mean of 8.6days, resulting in a yearly decrease of -0.8 days (95% CI -0.2--1.32; p<0.001, R^2=0.4). This was also true for ischemic stroke, intracerebral hemorrhage and stroke not otherwise specified.

Causes of death

Of the 30-day survivors, a total of 1764 patients died during follow-up (13.1%), of which 267 (15.1%) were due to recurrent stroke or were stroke-related and 302 (17.1%) due to other cardiovascular diseases. The main cause of death was malignancy (N=577), 32.7%). The remaining patients (n=617) (34.9%) died as a result of infection, trauma and miscellaneous causes. The proportion of deaths attributable to malignancies was higher in the intracerebral hemorrhage group than the group with an ischemic stroke as index event (41.5% (n=145) versus 28.8% (n=273); $\chi 2$=18.9, p<0.001). The proportion of cardiovascular related deaths was higher in the ischemic stroke group than the intracerebral hemorrhage group (19.4% (n=184) versus 7.2% (n=25); $\chi 2$=28.4, p<0.001). Also, the Poisson regression model showed significant interaction between stroke subtype and malignancies, as well as cardiovascular related deaths (p<0.001), even after correcting for sex in this model (p<0.001). The different categories of causes of death stratified by stroke subtype are listed in Table 4.

DISCUSSION

Among young adults aged 18-49 years in the Netherlands with first stroke, mortality risk compared to the general population remained elevated up to 15 years later.

Major strengths of this study include the population-based setting with a large number of young patients with stroke (15 257 patients <50 years), whereas in other large studies patients were included up to 55 years (with substantially less patients <50 years). In addition, this population based setting increased the likelihood of complete ascertainment of (cause of) death, whereas referral bias has occurred in previous other studies with a hospital based setting, because the more severely affected patients are more likely to die already at home and will not be included in hospital based populations.

This study reports, to our knowledge, for the first time the risk and causes of death, cumulative mortality and annual mortality after intracerebral hemorrhage at young age in large numbers that allow for sufficient power to perform age- and sex stratified analysis. Another strength of this study is that ICD-codes for all stroke subtypes were validated in young age groups specifically.

Furthermore, due to the availability of longitudinal data in combination with the very large numbers this study was able to report on differential time trends of mortality including case-fatality after ischemic stroke and intracerebral hemorrhage. Additionally, this study reports on outcomes of patients who were treated with stroke-unit care, intravenous thrombolysis and hemicraniectomy and secondary preventive treatment, whereas earlier studies included patients that had their stroke years before the implementation of these therapies.[322-324] In addition, within this large cohort it was possible to analyze cause specific causes of death in more detail than previous studies, with information available on subtypes of malignancies. Previous studies have presented this only for patients with ischemic stroke and not for patients with intracerebral hemorrhage, and causes of death were limited to recurrent stroke, other cardiovascular disease, malignancies and other causes.

A limited number of earlier studies with a comparable duration of follow-up have shown comparable mortality rates of 4.6% (3-year) and 16% (16-year).[312-314, 317] Most previous studies on long-term mortality after stroke in young adults were hospital-based, had varying inclusion criteria or also included SAH or TIA. These disorders may have a different prognosis than ischemic stroke and intracerebral hemorrhage and may therefore bias the mortality rates after stroke. In young patients with TIA, the 1-year cumulative mortality was shown to be only 0.7% and in the years thereafter 0.2% per year. [312-314] In contrast, patients with a SAH had a 17% excess mortality compared to the

general population after 20 years of follow-up.[325] The excess long-term mortality in young adults following stroke compared to age- and sex-matched individuals in the general population may suggest that even after treatment for stroke and treatment of associated risk factors according to current standards, the risk of death of young patients with stroke remained increased compared to their population peers. From 1998 to 2017, the already low risk of death in young adults in the general population has continued to decrease, possibly because of improved treatment of other life-threatening diseases like malignancies and because of fewer traffic accidents.[326]

The observed decreasing trend observed in mortality after ischemic stroke in young adults could be partially due to improved diagnosis of ischemic stroke with better and more imaging techniques available. In this way minor and resolved syndromes can be increasingly diagnosed as stroke (by MRI), which would partially explain decreasing rates of post-stroke mortality only for ischemic stroke. This hypothesis is supported by the fact that the 1- and 5-year mortality rates of intracerebral hemorrhage do not decrease significantly over the study period, which can be readily diagnosed purely by use of a CT-scan, which was already available in the earlier years of the study period.

A previous study also found male sex as risk factor for long-term mortality.[3139] The increased risk of death in men may be due to differences in risk factors and etiology between men and women (e.g. higher prevalence of traditional vascular risk factors and more large artery disease in men[5, 7, 17]), since incidence of stroke in the study period was higher in young women.[1] When compared to the general population, no significant differences between men and women in their risk of death were found.

In Sweden, a decline in case fatality of ischemic stroke was seen in men aged 30 to 84 years, but not in women. A similar difference with significant decrease of case fatality only in men was seen in the Framingham study.[327, 328] The decrease in case-fatality of ischemic stroke this study found for both young men and women might be attributable to both the change in the organization of stroke care with better education, introduction of stroke units in the early nineties and the introduction of hemicraniectomy for space occupying infarctions,[322, 329] and the higher detection of more minor and resolved syndromes as mentioned above. The reason that case-fatality of intracerebral hemorrhage has remained stable over time, may be the limited treatment options for this type of stroke compared to ischemic stroke.[329-331]

This study explored the causes of death in young adults after stroke, which may provide evidence for possible underlying disease mechanisms. For example, a higher percentage of patients that died of malignancies and cardiovascular disease was found

compared to the general population. Malignancies were responsible for 32.7% of deaths in this cohort, where in corresponding age groups in published records of Statistics Netherlands 25.6% died from malignancy in the period 1998-2010.[93, 332] 17.1% of patients died from cardiovascular diseases, whereas in corresponding age groups from the general population this percentage was 10.6% according to Statistics Netherlands.[332] This may suggest that the underlying risk factors and causes of stroke continue to expose patients to new events throughout the rest of their lives.[54, 333] However, results of causes of death that are based on small patient numbers should be interpreted with caution.

Limitations

This study has several limitations. First, due to the registry based study design, there was an inability to control for possible confounders (e.g. stroke severity, family history, medication) and comorbidity could only be assessed with the CCI, which provides a reliable measure of someone's comorbidity, but without information about actual risk factors and underlying etiology.[319] Specifically for young patients with stroke, with a wide variety of risk factors and causes, more detailed information would have been desirable. Because the CCI is composed of comorbidities defined by a previous hospital admission before the time of index event this may underestimate the effect of comorbidity on long-term mortality when comorbidity increases between index stroke and death. Conversely, the adjustment for baseline CCI may result in overestimation when comorbidity decreases after the index stroke until death. This possible bias is expected to be very low since young adults are less likely to have major comorbidity than elderly patients.

Second, because fewer hospitals contributed to the HDR register from 2006 onwards, the incidence of stroke could have been underestimated. If these records were not missing completely at random, some bias may have been introduced into the analysis.

Third, strokes between 1998 and 2010 were defined as first if no earlier admission for stroke was registered between 1995 and 2010. A limitation of this method is that a very small proportion of incident strokes may have been misclassified as “first”, if these patients would have had a stroke before 1995.[69] However, given the 2% yearly risk of recurrent stroke 3 years after index stroke, this risk of misclassification is considered very low.[69]

Fourth, using the general population as a control group includes young adults with stroke, which could possibly bias the study toward the null. However, since only a very small proportion of the controls will have had a stroke (in the order of a few cases per thousands of controls) this is unlikely to have had a major effect on the findings.

Fifth, given that recent advances in management of ischemic stroke with mechanical thrombectomy occurred largely after the end date of the data included in this study, the risk of mortality after ischemic stroke may not entirely be generalizable to reflect contemporary management.

CONCLUSIONS

In adults aged 18-49 years who survived 30-days after stroke, long-term mortality after stroke remained increased compared to the general population up to 15 years after stroke.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. ICD codes of causes of death.

Causes of death	ICD-10 codes
All cause stroke	I60, I61, I62, I63, I64, I67, I68, I69, G45
Ischemic stroke	I63
Intracerebral hemorrhage	I61
Composite vascular	I10-I15, I20-I25, I33-I35, I38, I42, I44, I46-I51, I70-I72-I77, I80-I82, I99
Cardiac	I20-I25, I33-I35, I38, I42, I44, I46-I51
Other vascular	I10-I15, I70-I72-I77, I80-I82, I99
Other stroke-related	I60, I62, I67, I68, I69
Malignancies	C00-C97, D00-D48
Hematological malignancy	C81-C97
Breast cancer	C50, D05
Lung cancer	C34, D022
Melanoma	C43, D03
Brain tumor	C71
Other forms of cancer	C00-C97, D00-D48 except C81-C97, C50, D05, D34, D022, C43, D03 and C71
Infections	A00-A99, B00-B99, J130, J220
Trauma	S00-S99, T00-T98, V01-V99, W00-W99, X00-X99, Y00-Y98
Miscellaneous	All other

Supplementary Table 2. Demographics including age, sex, comorbidity and follow-up of stroke of 30-day survivors

			Charlson Comorbidity Index	
	N (%)	**Mean age, y (SD)**	**Score 0 (%)**	**Score 1 (%)**
Any stroke	13481 (100)	41.76 (6.8)	11282 (83.7)	1601 (11.9)
men	6299 (46.7)	42.31 (6.4)	5235 (83.1)	767 (12.2)
women	7182 (53.3)	41.28 (7.0)	6047 (84.2)	834 (11.6)
Ischemic stroke	7815 (100)	41.97 (6.6)	6653 (85.1)	844 (10.8)
men	3560 (45.6)	42.62 (6.1)	3016 (84.7)	383 (10.8)
women	4255 (54.4)	41.42 (6.9)	3637 (85.5)	461 (10.9)
Intracerebral hemorrhage	2086 (100)	40.38 (7.7)	1667 (79.9)	304 (14.6)
men	1113 (53.4)	40.53 (7.5)	891 (80.1)	165 (14.8)
women	973 (46.6)	40.21 (7.9)	776 (79.8)	139 (14.3)
Stroke not otherwise specified	3580 (100)	42.12 (6.5)	2962 (82.7)	453 (12.7)
men	1626 (45.4)	42.86 (6.0)	1328 (81.7)	219 (13.5)
women	1954 (54.6)	41.50 (6.7)	1634 (83.6)	234 (12.0)

Duration of Follow up is defined as time between event and death or end of study, whichever occurred first in years

Supplementary Table 3. Sex-specific mortality for any stroke and stroke subtypes

	N of case fatalities (%)	**Deaths at end of FU N (%)**
Any stroke	1776 (12%)	3540 (23%)
men	828 (5%)	1816 (12%)
women	948 (6%)	1724 (11%)
Ischemic stroke	629 (7%)	1576 (19%)
men	291 (3%)	815 (10%)
women	338 (4%)	761 (9%)
Intracerebral hemorrhage	991 (32%)	1340 (44%)
men	472 (15%)	682 (22%)
women	519 (17%)	658 (21%)
Stroke not otherwise specified	156 (4%)	624 (17%)
men	65 (2%)	319 (9%)
women	91 (2%)	305 (8%)

Follow-up (FU)			
Score 2 (%)	**Score >=3 (%)**	**Median FU, in years (IQR)**	**N Deaths at end of FU (%)**
455 (3.4)	143 (1.1)	10.19 (7.1-13.6)	1764 (13.1)
223 (3.5)	74 (1.2)	9.95 (6.7-13.4)	988 (15.7)
232 (3.2)	69 (1.0)	10.33 (7.3-13.8)	776 (10.8)
246 (3.1)	72 (0.9)	9.99 (7.0-13.5)	947 (12.1)
126 (3.5)	35 (1.0)	9.75 (6.8-13.3)	534 (14.7)
120 (2.8)	37 (0.9)	10.17 (7.2-13.7)	423 (9.9)
85 (4.1)	30 (1.4)	10.16 (6.7-14.0)	349 (16.7)
41 (3.7)	16 (1.4)	9.93 (6.6-13.6)	210 (18.9)
44 (4.5)	14 (1.4)	10.35 (6.9-14.3)	139 (14.3)
124 (3.5)	41 (1.1)	10.58 (7.5-13.7)	468 (13.1)
56 (3.4)	23 (1.4)	10.45 (7.3-13.7)	254 (15.6)
68 (3.5)	18 (0.9)	10.69 (7.6-13.8)	214 (11.0)

SD = standard deviation, IQR = interquartile range.
CCI score of 0 means no comorbidity, the higher the CCI score, the more comorbidity.

1 year cum. mortality % (95% CI)	**5 year cum. mortality % (95% CI)**	**10 year cum. mortality (95% CI)**
4.3 (4.0-4.7)	7.9 (7.5-8.4)	12.6 (12.0-13.3)
5.0 (4.5-5.5)	9.3 (8.6-10.1)	15.1 (14.2-16.1)
3.8 (3.3-4.2)	6.7 (6.1-7.3)	10.5 (9.7-11.3)
2.5 (2.2-2.8)	5.9 (5.4-6.4)	10.6 (9.9-11.4)
2.6 (2.1-3.2)	6.9 (6.1-7.8)	13.0 (11.8-14.2)
2.4 (2.1-2.9)	5.0 (4.4-5.7)	8.6 (7.8-9.6)
6.8 (5.8-7.9)	11.7 (10.4-13.2)	15.7 (14.1-17.4)
7.4 (6.0-9.1)	12.9 (11.1-15.1)	17.6 (15.4-20.1)
6.1 (6.0-7.8)	10.3 (8.5-12.4%)	13.4 (11.4-15.8)
2.4 (2.0-3.0)	6.6 (5.807.5)	11.0 (10.0-12.2)
2.8 (2.1-3.7)	7.4 (6.2-8.8)	12.8 (11.2-14.6)
2.1 (2.1-2.9)	5.9 (5.0-7.1)	9.6 (8.3-11.0)

Chapter 10

The long-term risk of bleeding- and ischemic events after ischemic stroke or transient ischemic attack in young adults

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ABSTRACT

Background and objectives Guidelines recommend antithrombotic medication as secondary prevention for patients with ischemic stroke or TIA at young age based on results from trials in older patients. We investigated the long-term risk of bleeding and ischemic events in young patients after ischemic stroke or TIA.

Methods We included 30-day survivors of first-ever ischemic stroke or TIA aged 18-50 years from the FUTURE study, a prospective cohort study of stroke at young age. We obtained information on recurrent ischemia based on structured data collection from 1995 until 2014 as part of the FUTURE study follow-up, complemented with information on any bleeding and ischemic events by retrospective chart review from baseline until last medical consultation or June 2020. Primary outcome was any bleeding, secondary outcome any ischemic event during follow-up. Both were stratified for sex, age, etiology, and use of antithrombotic medication at discharge. Bleeding and ischemic events were classified according to location and bleeding events also by severity.

Results We included 544 patients (56.1% women, median age of 42.2; interquartile range [IQR] 36.5-46.7 years) with a median follow-up of 9.6 (IQR 2.5-14.3) years. Ten-year cumulative risk of any bleeding event was 21.8% (95% confidence interval [CI] 17.4-26.0) and 33.9% (95% CI 28.3-37.5) of any ischemic event. Risk of bleeding was higher in women with a cumulative risk of 28.2% (95% CI 21.6-34.3) versus 13.7% (95% CI 8.2-18.9) in men ($p<0.01$), mainly due to gynecological bleeds. Female sex ($p<0.001$) and age between 40 and 49 years old ($p=0.04$) were independent predictors of bleeding.

Discussion Young patients after ischemic stroke or TIA have a substantial long-term risk of both bleeding (especially women) and ischemic events. Future studies should investigate the effects of long-term antithrombotic therapy in young patients, taking into account the risk of bleeding complications.

INTRODUCTION

Two million people, aged between 18 and 50 years, are yearly affected by stroke worldwide.[2] The incidence of stroke in young adults has been rising over the last two decades, whereas the incidence of stroke in the elderly has remained stable or decreased.[1] For these young patients long-term prognosis is particularly relevant as they still have decades to live. They remain at risk of recurrent ischemic events, for which they are prescribed antithrombotic medication for the rest of their lives, based on information from randomized clinical trials in which young patients were underrepresented.[22-27]

At the same time, the long-term use of anti-thrombotic secondary preventive medication also carries a risk of bleeding complications. However, specifically in young patients, the long-term risk of recurrent ischemia has a high interindividual variability depending on the cause of the ischemic stroke or TIA.[55, 69, 297] Despite these differences, young patients often receive antithrombotic medication according to a "one size fits all" approach.[36] In older patients with stroke, the benefits of antithrombotic medication have been shown to outweigh the side effects.[334] Whether this also holds true for young adults with ischemic stroke or TIA, and whether they should continue the antithrombotic treatment life-long, is unknown. A better understanding of the balance between these risks may lead to more individualized secondary preventive treatment options after stroke in the future.

The aim of this study was to investigate the long-term risk of bleeding events and risk of ischemic events in young adults after a first-ever ischemic stroke or TIA, stratified for age, sex, cause of stroke and use of antiplatelet therapy at discharge.

METHODS

Patients

This work is an extension of the FUTURE study (Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation), a prospective cohort study of patients with an ischemic stroke, TIA or intracerebral hemorrhage (ICH) at young age.[28] Details of the study have been described previously.[69] In short, the FUTURE study comprises 1005 consecutive patients aged 18 to 50 years with a first-ever TIA, ischemic stroke, or ICH, admitted to the Radboud University Medical Centre Nijmegen between 1980 and 2010. For this study, we included patients with first-ever ischemic stroke or TIA between 1995 and 2010, who survived at least 30 days after their index event. TIA was defined as a rapidly evolving focal neurological deficit without positive phenomena, with vascular cause only, persisting less than 24 hours. Stroke was defined as a focal neurological deficit lasting more than 24 hours. Stroke was further classified into ischemic stroke and ICH based on radiological findings.[28, 69] This time window was chosen because for patients included before 1995, the original patient medical files were no longer available. Therefore, information regarding bleeding events could not be reliably ascertained.

Baseline data collection

Information on demographics, the index event, presence of vascular risk-factors and antithrombotic medication at discharge was systematically collected at baseline.[28] Presence of vascular risk-factors was defined as the risk-factor either being present in the medical history of the patient or if the risk-factor was identified during admission for the index event. Definitions used to define the presence of vascular risk-factors have been described previously.[69] Antithrombotic medication at discharge was categorized into three groups: "no antithrombotic medication", use of "only antiplatelet therapy" and the use of "other antithrombotic medication" (e.g. vitamin K antagonist, direct oral anticoagulant monotherapy or one of the before mentioned combined with antiplatelet therapy).

Cause of the index event was classified according to the "Trial of Org 10172 in Acute Stroke Treatment" (TOAST) criteria,[58] and severity with the "National Institutes of Health Stroke Scale" (NIHSS).[335] Functional status at discharge was determined according to the "modified Rankin Scale" (mRS) and dichotomized with a mRS-score of 0-2 indicating functional independence at discharge and a mRS-score of 3-5 meaning functional dependence.

Outcomes

The primary outcome of this study was the occurrence of a first bleeding event that required a visit to the hospital (either a visit to the outpatient clinic, a visit to the emergency room or a hospital admission) during follow-up. We included spontaneous and trauma-related bleeding events as well as bleeding events secondary to surgery (defined as an unexpected and unnecessary bleeding complication for this type of surgical procedure). Bleeding events were classified in three ways. First, by severity according to the "Bleeding Academic Research Consortium" (BARC) criteria for bleeding events (Supplementary Table 1), distinguishing six levels of clinical severity ranging from BARC type 0 (no bleeding) to BARC type 5 (fatal bleeding).[336] In our study, BARC type 0 and 1 were not taken into account because they do not require a hospital visit. Minor bleeding was defined as bleeding with BARC types 2 to 3a and major bleeding was defined as bleeding with BARC types 3b to 5. Second, by type (spontaneous, surgery-related or trauma-related) and third, by location (intracranial, intraocular, pulmonary, pericardial, gastrointestinal, retroperitoneal, urogenital, soft-tissue and anemia due to bleeding of an unknown location).

Secondary outcome was the occurrence of any non-fatal or fatal ischemic event during follow-up, which was defined as a composite vascular event of recurrent stroke, TIA, myocardial infarction or peripheral artery disease (PAD), whichever occurred first. Definitions of ischemic events can be found in Supplementary Table 1. All ischemic events reported by the patients were verified by a neurologist or cardiologist.[337] There were no cases of stroke not further specified as hemorrhagic or ischemic or unexplained sudden (assumed vascular) deaths during follow-up.

Follow-up

For follow-up we employed a two staged approach. First, we obtained information on recurrent ischemia from the available follow-up data from the FUTURE study that were systematically collected in 2010 through a structured interview at the outpatient clinic and in 2014 through a structured interview by telephone. At these two time-points, only ischemic events were collected.[69, 337] Second, we complemented these data with information on any bleeding and ischemic events by retrospective chart review between date of index event and June 1st, 2020. Bleeding and ischemic events were only recorded when diagnosed by a medical specialist. Duration of follow-up was defined as the time between the index event and either the date of death or the date of last medical consultation registered in the patient medical files.

Statistical analysis

We calculated cumulative risks with 95% confidence intervals (CI) for primary and secondary outcomes using Kaplan-Meier analyses. We stratified all analyses for sex, age at index event, stroke etiology and antithrombotic medication used at discharge. We tested for group differences with single log-rank analysis for dichotomous variables and multiple comparison log-rank analysis correcting for multiple testing through the Bonferroni-Holm method for variables with more than two groups, such as stroke etiology. In the survival analyses, patients were subdivided into three age categories: 18-29, 30-39 and 40-49 years.

As sensitivity analyses, we performed the log-rank analyses for stroke etiology according to TOAST groups excluding patients using other antithrombotic medication at baseline. Similarly, we performed the log-rank analyses for the use of antithrombotic medication at discharge excluding patients with stroke or TIA due to cardio-embolism. This was done because patients with stroke or TIA due to cardio-embolism most often use other antithrombotic medication and therefore these groups overlap considerably. Of the 61 patients using "other antithrombotic medication" in our study population, 4 strokes or TIAs were due to large artery disease, 30 due to cardio-embolism, 3 to small vessel disease, 11 due to rare causes, 11 due to cryptogenic stroke and 2 due to multiple causes. Of 69 patients with stroke or TIA due to cardio-embolism, 36 used "other antithrombotic medication", 3 used no antithrombotics and 30 used "only antiplatelet therapy".

The survival plots were curtailed at 15 years because of the limited patient numbers thereafter, whereas all events were retained in the analyses. We calculated annual risks of bleeding and ischemic events using the following formula: 1-([1 - Ci]^[1/n]). Ci was the cumulative incidence of the event at n years and n was the number of years after the index event, obtained by Kaplan-Meier analysis.

We assessed possible predictors of any bleeding event and any ischemic event by Cox proportional hazards univariable analyses, expressed as hazard ratios (HR) with 95% CI. We confirmed proportionality of all assessed predictors through plotting Schoenfeld residuals against time. All predictors with a p-value of <0.2 in univariable analysis were included into a multivariable model. We assessed the predictors in the full study population as well as in the subgroup of patients using "only antiplatelet therapy" at baseline, because we hypothesized that the bleeding risk would be different in patients with "only antiplatelet therapy" compared to "other antithrombotic medication". Differences in the median follow-up duration for patients without any event, with any bleeding event, and with any ischemic event were tested with the Mann-Whitney U test to evaluate whether risk differences between the groups could be explained by differences in duration of follow-up.

Two-sided P values less than 0.05 were considered statistically significant. Data were analyzed with SPSS Software version 22 (IBM), R version 3.6.2 (packages survival, survminer; R Project for Statistical Computing) and GraphPad Prism version 5.03.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients who participated in the follow-up assessments of 2010 and 2014 of the FUTURE study signed an informed consent form.[69, 338] For this study, the Medical Review Ethics Committee region Arnhem-Nijmegen gave their approval and granted a waiver of consent to collect information in the patient files for follow-up up to 2020.

Data availability

The raw and anonymized data used in this study can be shared upon request, for analysis with individual patient data. Written proposals can be sent to the corresponding author and will be assessed by the research group and the medical ethics committee Arnhem-Nijmegen. A data sharing agreement will be put in place before any data is shared.

RESULTS

Baseline characteristics

Of the 709 patients enrolled in the FUTURE study after 1995, 544 met our inclusion criteria. The median age at the time of the index event was 42.2 (IQR 36.5-46.7) years and 305 (56.1%) were women. Of the 544 patients, 359 (66.0%) had an ischemic stroke and 185 (34.0%) a TIA. Patient characteristics are listed in Table 1. The median duration of follow-up was 9.6 (IQR 2.5-13.4) years.

Table 1. Baseline characteristics of all patients aged 18-49 years old at first-ever ischemic stroke or TIA

	Total	Men	Women	Difference[§]
Total	544 (100)	239 (43.9)	305 (56.1)	
Patient characteristics				
TIA	185 (34.0)	83 (34.7)	102 (33.4)	P=0.75
Ischemic Stroke	359 (66.0)	156 (65.3)	203 (66.6)	
Mean age at index event, SD	40.7 (7.4)	42.0 (7.0)	39.7 (7.7)	**P<0.01**
Hypertension	179 (32.9)	85 (35.6)	94 (30.8)	P=0.24
Dyslipidemia[*]	391 (71.9)	173 (72.4)	218 (71.5)	P=0.82
Diabetes mellitus	41 (7.5)	25 (10.5)	16 (5.2)	**P=0.02**
Smoking status[‡]	253 (46.5)	106 (44.4)	147 (48.2)	P=0.38
Atrial fibrillation	6 (1.1)	4 (1.7)	2 (0.7)	P=0.28
Stroke etiology: TOAST classification				
(Likely) large artery disease	108 (19.9)	52 (21.8)	56 (18.4)	P=0.32
Cardio-embolic cause	69 (12.7)	31 (13.0)	38 (12.5)	P=0.86
Small vessel disease	70 (12.9)	32 (13.4)	38 (12.5)	P=0.76
Rare causes	102 (18.8)	36 (15.1)	66 (21.6)	P=0.05
Cryptogenic	178 (32.7)	82 (34.3)	96 (31.5)	P=0.49
Multiple causes	17 (3.1)	6 (2.5)	11 (3.6)	P=0.46
Stroke severity				
NIHSS at admission	2 (0-5)	2 (0-6)	2 (0-5)	P=0.28
MRS 0-2 at discharge	455 (83.6)	199 (83.3)	256 (83.9)	P=0.85
MRS 3-5 at discharge	89 (16.4)	40 (16.7)	49 (16.1)	
Medication at discharge				
Antiplatelet therapy	430 (79.0)	184 (77.0)	246 (80.7)	P=0.29
Other antithrombotic therapy[‡]	61 (11.2)	39 (16.3)	22 (7.2)	**P<0.01**

Table 1. Continued

	Total	Men	Women	Difference§
No antithrombotic medication	49 (9.0)	15 (6.3)	34 (11.1)	P=0.05
Unknown	4 (0.7)	1 (0.4)	3 (1.0)	P=0.42
Follow-up				
Follow-up time	9.6 (2.5-13.4)	9.6 (2.3-13.8)	9.5 (2.7-13.0)	P=0.58
Follow-up duration of ≥5 years	368 (67.6)	163 (68.2)	205 (67.2)	P=0.80
Follow-up duration of ≥10 years	253 (46.5)	115 (48.1)	138 (45.2)	P=0.19

Data are n (%) or median (IQR).

* Dyslipidemia was missing in 58 cases (23 in men, 35 in women).

ǂ Smoking was missing in 12 cases (7 in men, 5 in women).

ǂ Anticoagulant or other therapy entails vitamin K antagonists, low-molecular heparin, direct anticoagulants or a combination thereof.

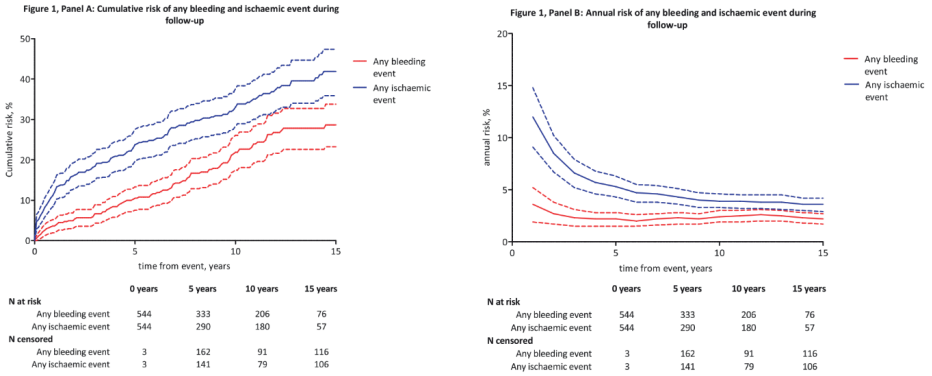
§ Categorical data was tested with chi-squared analyses and continuous data with independent t-tests.

Cumulative risk of bleeding events

During follow-up 152 bleeding events occurred in 98 patients (18.0%). Thirty-one patients (5.7%) had more than one bleeding event. Of the 152 bleeding events, 115 were minor (75.6%) and 37 (24.3%) were major bleeds (Table 2). Gynecological bleeds were the most common (N=57; 37.5%) of which 38 (25.0%) required a hospital visit. After ten years, 82 patients had at least one bleeding event (cumulative risk of 21.8% 95% CI 17.4-26.0) (Figure 1, panel A). In the first year after ischemic stroke or TIA the risk of bleeding was highest (3.6%, 95% CI 1.9-5.2). After the first year, the annual risk declined to 2.4% at ten years (95% CI 1.9-3.0) (Figure 1, panel B). The cumulative risks of any minor or major bleeding are shown in Figure 2 Panel A. The cumulative risk of any bleeding event (minor or major) increased, but not significant with age. (Figure 2, panel B). After 10 years, 59 out of 305 women (28.2%, 95% CI 21.6%-34.3%) and 23 out of 239 men (13.7%, 95% CI 8.2-18.9; p<0.01) had developed any bleeding event (Figure 2, panel C). Risk was higher for women than men, both for major (p=0.03) and minor bleeds (p<0.01). The cumulative risk of any bleeding event did not differ between ischemic stroke versus TIA as index event (p=0.13). Patients with stroke or TIA due to cardio-embolism had a significantly higher risk of bleeding during follow-up compared to patients with stroke due to large artery disease (p<0.01), small vessel disease (p=0.03), rare causes (p<0.01) and cryptogenic stroke (p<0.01). Patients using "other antithrombotic medication" had a higher cumulative risk of bleeding compared to patients using "only antiplatelet therapy" at discharge (p<0.001) (Figure 2, panel D). When excluding patients using "other antithrombotic medication" at baseline (N=61) the difference in risk of bleeding between

stroke or TIA due to cardio-embolism compared to all other groups disappeared. When excluding patients with stroke or TIA due to cardio-embolism (N=69), patients using "other antithrombotic medication" retained a higher risk of bleeding compared to patients using "only antiplatelet therapy" at discharge (p=0.03).

Figure 1. Risk of any bleeding event and ischemic event during follow-up



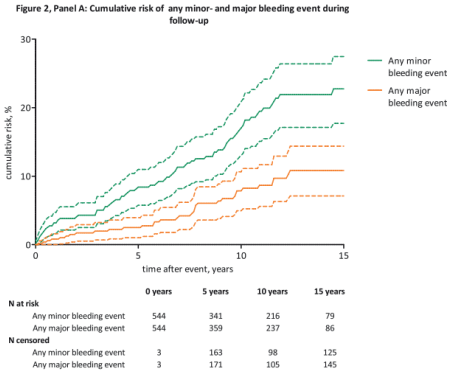
Dotted lines indicate 95% confidence intervals.

Abbreviations: N, Number at risk.

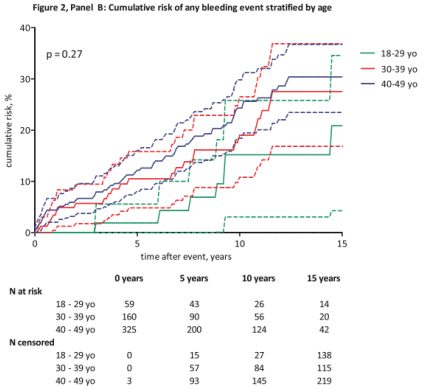
Uni- and multivariable predictors of bleeding events

Predictors (univariable) of any bleeding are listed in Supplementary Table 2 and Supplementary Table 3. In the multivariable analyses patients female sex (HR 2.6; 95% CI 1.6-4.0) and an age of 40-49 years old (HR 2.3; 95% CI 1.0-4.9) were independent predictors of any bleeding during follow-up (Supplementary Table 2). When we restricted the analysis to only antiplatelet users (N=430), female sex (HR 2.8 95% CI 1.6-5.1) remained an independent predictor, in this subgroup also stroke or TIA due to cardio-embolism was an independent risk-factor for any bleeding during follow-up compared to cryptogenic stroke (HR 2.7 95% CI 1.2-5.7) in multivariable analysis (Supplementary Table 3). Median duration of follow-up in those without an event was 7.1 (IQR 1.4-12.3) years and was significantly shorter compared to those with a bleeding event (11.6, IQR 8.9-14.1 years; p<0.001) and compared to patients with an ischemic event (11.2, IQR 6.3-14.8 years; p<0.001).

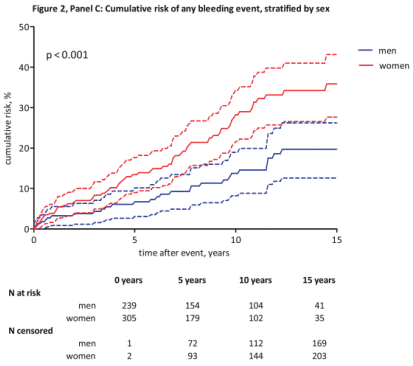
Figure 2. Cumulative risk of any bleeding stratified for minor- and major bleeding, age and sex



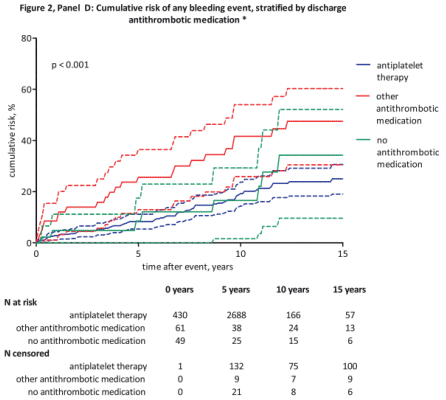
N at risk	0 years	5 years	10 years	15 years
Any minor bleeding event	544	341	216	79
Any major bleeding event	544	359	237	86
N censored				
Any minor bleeding event	3	163	98	125
Any major bleeding event	3	171	105	145



N at risk	0 years	5 years	10 years	15 years
18 - 29 yo	59	43	26	14
30 - 39 yo	160	90	56	20
40 - 49 yo	325	200	124	42
N censored				
18 - 29 yo	0	15	27	138
30 - 39 yo	0	57	84	115
40 - 49 yo	3	93	145	219



N at risk	0 years	5 years	10 years	15 years
men	239	154	104	41
women	305	179	102	35
N censored				
men	1	72	112	169
women	2	93	144	203



N at risk	0 years	5 years	10 years	15 years
antiplatelet therapy	430	2688	166	57
other antithrombotic medication	61	38	24	13
no antithrombotic medication	49	25	15	6
N censored				
antiplatelet therapy	1	132	75	100
other antithrombotic medication	0	9	7	9
no antithrombotic medication	0	21	8	6

* With pairwise comparison using log-rank analyses antiplatelet therapy was statistically significant from other antithrombotic medication (p<0.001), other pairwise comparisons between groups were not statistically significant. Dotted lines indicate 95% confidence intervals. P-values reported in the figures are according to log-rank testing.

Abbreviations: N, number.

Cumulative risk of ischemic events

During follow-up we observed 292 ischemic events in 161 (29.6%) patients. Of the 161 first ischemic events during follow-up, 62 were ischemic stroke (38.5%), 58 were TIA (36.0%), 31 were myocardial infarction (19.2%) and 10 were peripheral artery disease (6.2%) (Table 2). After ten years 128 patients had had one ischemic event (cumulative risk 33.1%, 95% CI 28.3-37.6%) (Figure 1, panel A). In the first year 57 patients already had one ischemic event (8.5%, 95% CI 6.7-10.2%), this annual risk stabilized in subsequent years at around 4% (Figure 1, panel B).

Table 2. Bleeding and ischemic events during follow-up

	All events	Women
Bleeding events		
Total of bleeding events	152	108 (71.1)
Severity*		
Minor	115 (75.7)	80 (74.0)
Type 2	101 (66.4)	72 (66.7)
Type 3A	14 (9.2)	8 (7.4)
Major	37 (24.3)	28 (25.9)
Type 3B+C	35 (23.0)	27 (25.0)
Type 5	2 (1.3)	1 (0.9)
Occurrence		
Surgery-related	20 (13.2)	12 (11.1)
Trauma-related	11 (7.2)	6 (5.6)
Spontaneous	121 (79.6)	90 (83.3)
Location		
Intracranial	9 (5.9)‡	6 (5.6)
Intraocular	5 (3.3)	4 (3.7)
Gastro-intestinal	21 (13.8)	12 (11.1)
Retroperitoneal	5 (3.3)	3 (2.8)
Pulmonary	12 (7.9)	6 (5.6)
Urogenital	71 (46.7)	68 (63.0)
Gynecological ǂ	57 (37.5)	57 (52.8)
Soft tissue	23 (15.1)	8 (7.4)
Anemia due to bleeding of unknown location	3 (2.0)	1 (0.9)
Other location	3 (2.0)	0
Ischemic events		
Total of Ischemic events	292	144
Location		
Cerebral ischemia	205 (70.2)	109 (75.7)
(Recurrent) stroke	116 (39.7)	63 (43.8)
(Recurrent) TIA	89 (30.5)	46 (31.9)
Myocardial infarction	49 (16.8)	18 (12.5)
Peripheral artery disease	38 (13.0)	17 (11.8)

Data are n (%).

* Severity according to the BARC classification (Supplementary Table 1). [17]

ǂ Gynecological bleeds represent a subgroup of urogenital bleeding events.

Men	First-ever events	Women	Men
44 (28.9)	98	69 (70.4)	29 (29.6)
35 (79.5)	70 (71.4)	49 (71.0)	21 (30.4)
29 (65.9)	64 (65.3)	45 (65.2)	19 (27.5)
6 (13.6)	6 (6.1)	4 (5.8)	2 (2.9)
9 (20.5)	28 (28.6)	20 (29.0)	8 (11.6)
8 (18.2)	26 (26.5)	19 (27.5)	7 (10.1)
1 (2.3)	2 (2.0)	1 (1.4)	1 (1.4)
8 (18.2)	12 (12.2)	6 (8.7)	6 (8.7)
5 (11.4)	7 (7.1)	3 (4.3)	4 (5.8)
31 (70.4)	79 (80.6)	60 (8.7)	19 (27.5)
3 (6.8)	7 (7.1)	4 (5.8)	3 (4.3)
1 (2.3)	4 (4.1)	3 (4.3)	1 (1.4)
9 (20.5)	11 (11.2)	6 (8.7)	5 (7.2)
2 (4.5)	4 (4.1)	2 (2.9)	2 (2.9)
6 (13.6)	7 (7.1)	4 (5.8)	3 (4.3)
3 (6.8)	47 (48.0)	46 (66.7)	1 (1.4)
0	42 (42.9)	42 (61.0)	0
15 (34.1)	15 (15.3)	4 (5.8)	11 (15.9)
2 (4.5)	1 (1.0)	0	1 (2.3)
3 (6.8)	2 (2.0)	0	2 (4.5)
148	161	86	75
96 (64.9)	120 (74.5)	66 (76.7)	54 (62.8)
53 (35.8)	62 (38.5)	36 (41.9)	26 (30.2)
43 (29.1)	58 (36.0)	30 (34.9)	28 (32.6)
31 (20.9)	31 (19.2)	15 (17.4)	16 (18.6)
21 (14.2)	10 (6.2)	5 (5.8)	5 (5.8)

ǂ Of the nine intracranial bleeding events, seven were spontaneous, one was trauma related and one was surgery related.

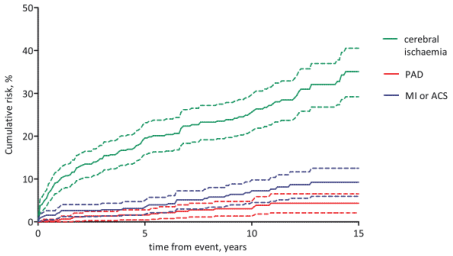
The risk of any ischemic event did not differ between age groups, sex or ischemic stroke or TIA as index event (Figure 3, panel B). The cumulative risk of any ischemic event was significantly higher for stroke or TIA due to large artery disease (p<0.01) and cardio-embolism (p<0.01) compared to cryptogenic stroke (Figure 3; panel C). According to log-rank analysis, the type of antithrombotic therapy used at discharge did not modify the risk of recurrent vascular events.

Uni- and multivariable predictors of ischemic events

Based on the univariable Cox proportional hazards model hypertension, diabetes mellitus, TOAST and types of antithrombotic medication were included in the multivariable model. Diabetes mellitus (HR 1.8, 95% CI 1.1-3.0; p=0.03), stroke or TIA due to large artery disease (HR 2.0, 95% CI 1.2-3.2; p<0.01) and cardio-embolism (HR 2.8, 95% CI 1.6-5.0; p<0.01) compared to cryptogenic stroke remained significant independent predictors of any ischemic event during follow-up. Use of "other antithrombotic medication" was related to a lower risk of ischemic events compared to no antithrombotic medication (HR 0.4, 95% CI 0.2-0.8, p=0.01) (Supplementary Table 2). When restricting the analyses to patients using "only antiplatelet therapy" at discharge (N=430) in the multivariable model, stroke due to cardio-embolism (HR 2.5, 95% CI 1.3-4.8; p=0.01) remained an independent predictor of any ischemic event. In this subgroup female sex was associated with a lower risk of recurrent ischemia (HR 0.7, 95% CI 0.5-1.0; p=0.03) (Supplementary Table 3).

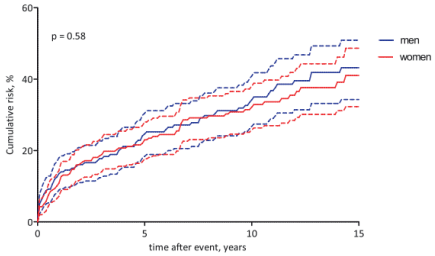
Figure 3. Cumulative risk of any ischemic event, stratified for type of ischemia, sex and etiology of index event

Figure 3, Panel A: Cumulative risk of cerebral ischaemia, cardiac ischaemia or PAD



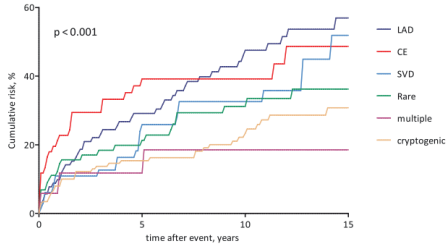
	0 years	5 years	10 years	15 years
N at risk				
cerebral ischaemia	544	305	201	65
MI or ACS	544	355	234	85
PAD	544	363	245	89
N censored				
cerebral ischaemia	3	146	84	118
MI or ACS	3	170	109	145
PAD	3	171	113	153

Figure 3, Panel B: Cumulative risk of any ischaemic event, stratified by sex



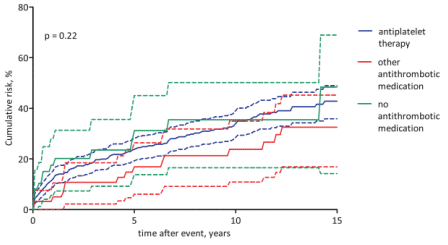
	0 years	5 years	10 years	15 years
N at risk				
men	239	127	83	32
women	305	163	97	25
N censored				
men	1	62	92	134
women	2	82	131	195

Figure 3, Panel C: Cumulative risk of any ischaemic event, stratified by TOAST categories *



	0 years	5 years	10 years	15 years
N at risk				
LAA	108	57	32	10
CE	69	30	22	1
SVD	70	39	23	6
Rare causes	102	53	30	16
Multiple causes	17	13	10	2
Cryptogenic	178	98	63	22
N censored				
LAA	1	24	36	54
CE	0	15	23	42
SVD	0	16	29	42
Rare causes	0	30	47	59
Multiple causes	0	2	4	12
Cryptogenic	2	57	84	120

Figure 3, Panel D: Cumulative risk of any ischaemic event, stratified by antithrombotic medication at discharge



	0 years	5 years	10 years	15 years
N at risk				
antiplatelet therapy	430	231	139	39
other antithrombotic therapy	61	40	30	14
no antithrombotic therapy	49	18	11	4
N censored				
antiplatelet therapy	1	110	65	87
other antithrombotic therapy	0	12	7	13
no antithrombotic therapy	0	19	6	6

* for clarity the confidence intervals were left out of panel C; LAA was significantly different from CE (p<0.01) and CE was significantly different from SVD (p=0.03), other pairwise comparisons between groups were not statistically significant. Dotted lines indicate 95% confidence intervals. P-values reported in the figures are according to log-rank testing.

Abbreviations: N, Number at risk; LAA, (likely) large artery disease; CE, cardio-embolic cause; SVD, small vessel disease.

DISCUSSION

This study shows that in patients who experienced an ischemic stroke or TIA at young age, the cumulative risk of any bleeding event is almost as high as the cumulative risk of any new ischemic event after a median follow-up of almost ten years. The risk of minor and major bleeding events was significantly higher in women than in men, which was largely driven by a high incidence of gynecological bleeds. Most bleeding events were minor. Older age (40-49 years) at the time of ischemic stroke or TIA was also an independent predictor of any bleeding event.

In our study population, two out of ten patients with ischemic stroke or TIA at young age had at least one bleeding event and around one in twenty young stroke survivors had a major bleeding event in the first ten years after their ischemic stroke or TIA. There are no previous studies focusing specifically on young patients after ischemic stroke or TIA. There have been two previous observational studies; both investigated a stroke population of all ages over 18 years old.[339, 340] In one registry based study (mean age 74.5 years, mean duration of follow-up 2 years), the risk of any bleeding was 2.6 (95% CI 2.4-2.7) per 100 person-years (py) after ischemic stroke, 2.4 (95% CI 2.3-2.5) per 100 py in single antiplatelet users.[340] This is slightly higher than we found (2.0 [95% CI 1.6-2.4] per 100 py in the overall group and 1.7 [95% CI 1.3-2.2] per 100 py in only antiplatelet users), although the definition of bleeding was the same. The difference could be due to the higher mean age in the previous study and the shorter duration of follow-up, since we have shown that the risk of bleeding is highest in the first year after stroke or TIA and declines thereafter.[341] Another observational study of patients (mean age of around 70 years old; median duration of follow-up 4.3 years) after ischemic stroke, TIA or acute myocardial infarction, showed an annual rate of any bleeding requiring medical attention of just under 2%.[339] Bleeding due to trauma or surgical procedures were excluded in this study, which may explain why the annual risk was slightly lower than the annual risk of any bleeding we found in our study population.

The increased risk of minor as well as major bleeding among women is a new finding and might be specific to young women receiving antithrombotic therapy as it was mostly due to excessive menstrual bleeding, which only occur in pre-menopausal women. Since almost all trials into antithrombotic medication as secondary prevention after stroke have excluded patients below the age of 40, this probably explains why this risk of gynecological bleeding events has not been described before.[24, 27] However, we could not compare this risk of gynecological bleeds in our population to the general population as we did not have a control group, and thus could not calculate the excess risk of gynecological bleeding events in young women after stroke or TIA. A previous

Dutch study found an annual incidence of heavy menstrual bleeding of 9.3 (95% CI 8.5-10.2) per 1000 py in pre-menopausal women at the general practitioner compared to 15.6 (95% CI 10.9-20.3) per 1000 py we found.[342] Our finding of this sex-dependent high bleeding risk underscores the need to study adverse events specifically in patients who experience a stroke at young age, instead of extrapolating findings from studies performed in the elderly. The increasing risk of any bleeding event with age, has been described previously.[339, 343] However, it is important to note that the oldest patients in our population represented the youngest patients in previous observational studies and randomized controlled trials.[25, 339, 340]

Strengths of our study were the large number of young patients with ischemic stroke or TIA considering the relative rarity of stroke at young age, the long period of follow-up and the standard way of classifying bleeding events according to the BARC criteria. All patients in the FUTURE study were seen in the Radboudumc in Nijmegen, the Netherlands. Our academic hospital serves as a tertiary referral center for a large area in the eastern part of the Netherlands. Since most patients with a stroke at young age usually are referred to a university medical center somewhere along the course of the disease, we most likely included the majority of patients in our catchment area. We therefore feel our results can be generalized to other Dutch patients with a stroke at young age, as well as to patients with a stroke at young age in other Western societies. In addition, this cohort was well phenotyped, which allowed for relevant subgroup analyses. This study also has some limitations. First, data-collection of outcomes was partly retrospective and single-center oriented. Which means that we may have missed events that took place in another hospital. We reduced this bias by limiting individual follow-up to the last moment the patient was seen in the hospital where they were followed-up after their TIA or stroke. This approach may have led to an underestimation of the number of bleeding and ischemic events.[69, 337] This underestimation may be more pronounced for bleeding events than for ischemic events because between 1995 and 2014 ischemic events were also collected prospectively through patient interviews. On the other hand, limiting the follow-up to last medical evaluation may also have led to overestimation of bleeding and ischemic events because patients without events may have visited the hospital less and therefore had a shorter follow-up. Second, during the follow-up period patients could have switched or stopped treatment following new events or as a result of changed guidelines. Therefore, we could only compare the effect of different groups of antithrombotic medication stratified at baseline and this does not allow for causal inference on antithrombotic use and the risk of bleeding events. In addition, given that mRS scores were also only collected at discharge, this may have led to an overestimation of the severity of the index event), since outcome of some patients could still have improved further as part of the natural disease course or with

therapy and rehabilitation. Third, the inclusion period was relatively long (1995-2010). Recommendations on antithrombotic therapy after TIA/ischemic stroke have changed, both during the inclusion period and during follow-up. Therefore, extrapolation of our findings towards the current young patients with stroke should be done with care.

Over the last years, there has been a growing discussion on whether routine lifelong secondary prevention in the form of antithrombotic medication is necessary in all young stroke survivors.[36] Especially in the subgroup of patients with a relatively low risk of new ischemic events, the potential benefits of life-long continuation of antiplatelet therapy may not outweigh the harms. It is important to identify groups who are on the one hand most at risk of bleeding and on the other hand most at risk of ischemia in the long run. For example, women with a cryptogenic stroke may be at a disproportionally high risk of severe bleeding compared to the low risk of recurrent ischemia. Future studies should investigate in these young patients, if and to what extent the bleeding risk is related to which kind of antithrombotic therapy. Future work should also consider the relative severity of possible bleeding events and possible recurrent ischemic events and weigh them against each other. We found most bleeding events in this study to be minor, though we did not have information on the severity of recurrent stroke. However, about one third of all 292 ischemic events during follow-up were TIAs (N= 89; 30.5%), which could also be considered "minor" events. In addition, 38 participants suffered from peripheral arterial disease (N= 38; 13.0%) and 49 individuals had a myocardial infarction (N=49; 16.8%) that can usually be managed well with either an intervention or antithrombotic/thrombolytic therapy. A future trial specifically designed for young patients with ischemic stroke or TIA with a low risk of recurrent ischemia should investigate the effect of usual anti-platelet treatment versus discontinuing antiplatelet therapy, to determine whether antiplatelet treatment can be safely ceased in these patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Definitions used for bleeding- and ischemic events

Severity of Bleeding events		
BARC type *	**Minor/Major**	**Definition**
Type 0	NA	No bleeding
Type 1	NA	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	Minor	Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3A	Minor	Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed) and/or any transfusion with overt bleeding.
Type 3B	Major	Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed) and/or cardiac tamponade and/or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) and/or bleeding requiring intravenous vasoactive agents.
Type 3C	Major	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) and/or subcategories confirmed by autopsy or imaging or lumbar puncture and/or intraocular bleed compromising vision.
Type 4 ǂ	Major	CABG-related bleeding: Perioperative intracranial bleeding within 48 hours and/or reoperation after closure of sternotomy for the purpose of controlling bleeding and/or transfusion of ≥ 5 U whole blood or packed red blood cells within a 48 hours period and/or chest tube output of ≥ 2L within a 24 hour period.
Type 5	Major	Fatal bleeding

Supplementary Table 1. Continued

Types of ischemic events	
Type	**Definition**
Stroke	A focal neurological deficit lasting more than 24 hours and subdivided into intracerebral hemorrhage and ischemic stroke based on radiological findings (same as index event)
TIA	A rapidly evolving focal neurological deficit without positive phenomena, with vascular cause only, persisting less than 24 hours (same as index event)
Myocardial infarction	Myocardial infarction defined by ischemic symptoms with corresponding electrocardiographic and cardiac biomarkers, and/or acute coronary syndrome requiring percutaneous coronary intervention, percutaneous coronary angioplasty or coronary artery bypass grafting
Peripheral artery disease	Ischemic symptoms of the extremities for which therapy (e.g. walking therapy or revascularization surgery) was implemented by a medical specialist

˙ Bleeding Academic Research Consortium Criteria.

ǂ Type 4 was not found in our study population during follow-up.

Abbreviations: NA, not applicable.

Supplementary Table 2. Predictors of any bleeding event or any ischemic event

	Risk of any bleeding event	
	Univariable analysis	
Age 40-49 yo	**1.8 (0.8-3.7)**	**0.13**
Age 30-39 yo	1.5 (0.7-3.7)	0.34
Age 18-29 yo (ref)		
Female sex	***2.1 (1.4-3.2)***	***<0.01***
Male sex (ref)		
TIA	**1.4 (0.9-2.0)**	**0.13**
Ischemic stroke (ref)		
Hypertension	***1.8 (1.2-2.7)***	***<0.01***
No hypertension (ref)		
Smoking *	0.9 (0.6-1.4)	0.64
No smoking (ref)		
Diabetes mellitus	1.2 (0.6-2.5)	0.59
No diabetes mellitus (ref)		
Dyslipidemia *	1.0 (0.6-1.7)	0.96
No dyslipidemia (ref)		
TOAST: LAD	1.1 (0.6-1.9)	0.85
TOAST: CE	***2.8 (1.6-4.8)***	***<0.01***
TOAST: SVD	1.1 (0.6-2.2)	0.72
TOAST: Rare causes	0.9 (0.5-1.8)	0.79
TOAST: multiple	2.1 (0.9-5.1)	0.85
TOAST: cryptogenic (ref)		
Antiplatelet use at discharge	0.8 (0.4-1.7)	0.54
Anticoagulant or other antithrombotic therapy at discharge	**2.0 (0.9-4.4)**	**0.09**

No antithrombotic medication at discharge (ref)
Data are hazard ratios (95% confidence interval) and p-values.

		Risk of any ischemic event			
Multivariable analysis		Univariable analysis		Multivariable analysis	
2.3 (1.0-4.9)	**0.04**	1.1 (0.7-1.7)	0.83		
1.7 (0.7-3.8)	0.21	0.8 (0.5-1.4)	0.53		
2.6 (1.6-4.0)	***<0.01***	0.9 (0.7-1.3)	0.58		
1.2 (0.8-1.9)	0.33	1.1 (0.8-1.5)	0.61		
1.5 (1.0-2.4)	*0.08*	***1.4 (1.0-1.9)***	***0.02***	*1.1 (0.8-1.6)*	*0.62*
		1.1 (0.8-1.5)	0.64		
		2.1 (1.3-3.5)	***<0.01***	***1.8 (1.1-3.0)***	***0.03***
0.8 (0.4-1.6)	0.57	***2.2 (1.4-3.4)***	***<0.01***	***2.0 (1.2-3.2)***	***<0.01***
1.3 (0.8-2.6)	*0.50*	***2.2 (1.4-3.7)***	***<0.01***	***2.8 (1.6-5.0)***	***<0.01***
0.9 (0.4-1.9)	0.86	**1.6 (0.9-2.7)**	**0.09**	1.4 (0.8-2.5)	0.20
0.8 (0.4-1.5)	0.45	**1.6 (0.9-2.4)**	**0.11**	1.6 (1.0-2.6)	0.52
1.5 (0.6-3.9)	0.38	0.7 (0.2-2.4)	0.60	0.7 (0.1-2.3)	0.52
0.7 (0.3-1.6)	0.43	0.9 (0.5-1.5)	0.66	0.7 (0.4-1.3)	0.30
1.8 (0.7-4.4)	0.19	***0.6 (0.3-1.2)***	***0.12***	***0.4 (0.2-0.8)***	***0.01***

˙ Smoking status was missing in 12 cases, dyslipidemia at baseline was missing in 58 cases, discharge medication was missing in 4 cases.

Abbreviations: CI, confidence interval; ref, reference category; yo, years old.

Supplementary Table 3. Predictors of any bleeding event in antiplatelet users at discharge

	Risk of any bleeding event		
	Univariable analysis		Multivariable analysis
Age 40-49 yo	HR 1.3 (0.5-3.0)	0.60	
Age 30-39 yo	HR 1.1 (0.4-2.7)	0.89	
Age 18-29 yo (ref)			
Female sex	**HR 2.9 (1.6-5.2)**	**<0.01**	**HR 2.8 (1.6-5.1)**
Male sex (ref)			
TIA	**HR 1.5 (0.9-2.4)**	**0.11**	HR 1.4 (0.8-2.3)
Ischemic stroke (ref)			
Hypertension	HR 1.3 (0.8-2.2)	0.27	
No hypertension (ref)			
Smoking *	HR 1.1 (0.6-1.7)	0.84	
No smoking (ref)			
Diabetes mellitus	HR 1.1 (0.5-2.5)	0.82	
No diabetes mellitus (ref)			
Dyslipidemia *	HR 1.5 (0.7-3.2)	0.27	
No dyslipidemia (ref)			
TOAST: LAD	HR 1.3 (0.6-2.5)	0.50	HR 1.4 (0.7-2.9)
TOAST: CE	**HR 3.1 (1.4-6.5)**	**<0.01**	**HR 2.7 (1.2-5.7)**
TOAST: SVD	HR 1.2 (0.5-2.8)	0.61	HR 1.3 (0.6-3.0)
TOAST: Rare causes	HR 1.2 (0.5-2.5)	0.72	HR 1.2 (0.5-2.6)
TOAST: multiple	HR 1.3 (0.6-2.5)	0.44	HR 1.8 (0.5-6.2)

TOAST: cryptogenic (ref)
Data are hazard ratios (95% confidence interval) and p-values.

		Risk of any ischemic event			
		Univariable analysis		Multivariable analysis	
		HR 1.2 (0.7-2.0)	0.62		
		HR 0.9 (0.5-1.6)	0.66		
	<0.01	**HR 0.7 (0.5-1.0)**	**0.08**	**HR 0.7 (0.5-1.0)**	**0.03**
	0.22	HR 1.1 (0.8-1.6)	0.68		
		HR 1.5 (0.1-2.2)	**0.02**	HR 1.1 (0.8-1.7)	0.54
		HR 0.9 (0.7-1.3)	0.67		
		HR 2.0 (1.2-3.3)	**<0.01**	HR 1.4 (0.8-2.5)	0.23
	0.30	**HR 2.0 (1.2-3.1)**	**<0.01**	HR 1.5 (0.9-2.6)	0.12
	0.01	**HR 2.9 (1.6-5.4)**	**<0.01**	**HR 2.5 (1.3-4.8)**	**0.01**
	0.51	**HR 1.5 (0.8-2.6)**	**0.17**	HR 1.2 (0.7-2.2)	0.54
	0.66	HR 1.3 (0.7-2.2)	0.40	HR 1.3 (0.7-2.3)	0.40
	0.36	HR 0.6 (0.1-2.4)	0.46	HR 0.5 (0.1-2.2)	0.37

N=430, number of bleeding events = 66 and number of ischemic events = 131.

˙ Smoking status was missing in 8 cases and dyslipidemia at baseline was missing in 36 cases.

Part V

Summary and
general discussion

Chapter 11

Summary

SUMMARY

Stroke is the second leading cause of death worldwide. It is often considered a disease of the elderly, yet approximately 10% of all strokes affects an individual aged 18 to 50 years. In the Netherlands, this amounts to about 1200 individuals with an ischemic stroke and 150 with an intracerebral hemorrhage (ICH) every year. When stroke strikes in young adults, they are often at crossroads in their lives, with demanding careers, families to take care of and many social interactions. In addition, they still have a long-life expectancy, during which they will have to cope with their post-stroke sequalae. This stresses the need for adequate information on the underlying risk factors and causes of their stroke, the optimal treatment and its possible side effects, and the prognosis including the risk of recurrence. Unfortunately, to date a number of knowledge gaps exist. For example, the underlying risk factors and causes remain unclear in a substantial proportion of young adults with stroke. These hampers (development of new) treatment and leaves patients with a lot of uncertainty. Finding the potential risk factors, possible trigger factors and (new) causes is therefore important.

Therefore we initiated the ODYSSEY study in 2013, a prospective cohort study in 17 centers in the Netherlands to investigate risk- and trigger factors, causes and the long-term prognosis of stroke in the young. The ODYSSEY study is the successor of the FUTURE study, that investigated stroke in young adults from 1980 to 2010 in which the very long-term consequences are currently being investigated. To find leads to (new) causes in the large group of patients with an unknown cause, and to identify differences between patients from different ethnicities from all over the world, the GOAL initiative was started in 2017. It is a joint project in which we performed an individual patient data meta-analysis with data from young patients with stroke in 29 countries. In part I of this thesis (**chapter 2**) the protocol and rationale of the GOAL initiative is described.

The studies in this thesis further describe different results of the ODYSSEY and FUTURE study, the GOAL-initiative and from studies with data from the national medical registries of the Statistics Netherlands.

Epidemiology of stroke at young age

Chapter 3 provides an overview of multiple epidemiological aspects of stroke at a young age, such as (trends in) incidence, risk factors and causes. Some actual causes and risk factors that are more common at young age than in older patients with stroke are being illustrated, such as the association between migraine and stroke, malignancies and stroke, illicit drug use, stroke during pregnancy and the puerperium, patent foramen ovale and its treatment, and genetic causes of stroke. In **chapter 4**, the incidence of

stroke in young adults in the Netherlands between 1998 and 2010 is described. A clear increase in incidence of ischemic stroke is seen, while the incidence of ICH remained stable. We also found more young women than men to get a stroke. A possible explanation for the increase in ischemic strokes may be better detection with newer MRI techniques such as diffusion weighted imaging (DWI). Alternatively, the increase may also be explained by a coinciding increase in the prevalence of traditional vascular risk factors like obesity and smoking at young age. The higher incidence of stroke in women might be explained by several women-specific risk factors or risk factors that have a higher prevalence in women. Examples are migraine with aura, pregnancy, oral contraceptive use and auto-immune disorders such as antiphospholipid syndrome.

In **chapter 5**, risk factors and causes of TIA and ischemic stroke at young age are investigated. To classify the etiology of stroke, the TOAST and ASCOD classification are widely used. Both were originally designed for the general stroke population with an average age of over 65 years. The most common causes for stroke in the elderly are large artery atherosclerosis, small vessel disease and cardio-embolic stroke (mostly atrial fibrillation), whereas these causes are often not found in young individuals with stroke. In the young, about 20-30% of all patients end up with an ''undetermined cause'', and another 20-30% with widely varying other causes that are lumped in ''other determined cause'' categories. In an attempt to limit the proportion of patients with a cryptogenic stroke, we therefore decided, to additionally use a risk factor inventory in our ODYSSEY study cohort that is often applied in children and adolescents with stroke, the International Pediatric Stroke Society (IPSS) inventory. Within the TOAST classification, 25% of all 1322 patients was classified as having a stroke with an ''undetermined cause'', which decreased to 19% after with the application of the ASCOD classification. However, in 1312 (99%) of all patients at least one potential risk factor of the IPSS could be found. These potential risk factors were mostly underlying auto-immune disorders, non-atherosclerotic arteriopathies and/or a prothrombotic state including coagulation disorders. Using this approach can be a first step in developing an etiological classification system that is more dedicated to classifying stroke in young adults. This new classification can be used in future studies investigating the prognosis of groups with young adults with comparable causes and risk factors.

Given de large group of young patients with a stroke due to an unknown cause, we decided to investigate possible trigger factors for stroke. We used the standardized questionnaires completed by patients included in the ODYSSEY study. Trigger factors are believed to cause a short-term risk of stroke subsequent to the trigger, for example by a short rise in blood pressure or transient reaction in the endothelial of arterial vessels. Cola consumption, illicit drug use, performing exercise intensively, sexual activity and

having fever or flu-like disease were identified as potential trigger factors for TIA, ischemic stroke and ICH. This was the first study to investigate trigger factors in young adults with stroke specifically, and it might provide insight in new mechanisms that lead to stroke, especially for patients for whom no cause can be found (chapter 6).

Global differences in stroke at young age

In chapter 7, an overview is provided of global differences in the incidence, risk factors including traditional vascular risk factors, etiology and mortality risk of stroke at young age, reviewing racial and ethnic variation. Our literature review shows that stroke at young age has a much higher incidence in the Middle East and Africa compared to most European countries, and that the most common risk factors and causes depend on the region of origin and ethnicity of a patient. As an example, infectious diseases such as HIV and tuberculosis are more common in low-income countries and sickle cell disease in Africa and Southeast-Asia.

In chapter 8 we compare traditional vascular risk factors such as hypertension, diabetes, hypercholesterolemia, smoking and obesity by continent and ethnic subgroup. We found that hypertension and diabetes have the highest prevalence in Black patients and Asians. In addition, stroke due to large artery disease and likely atherothrombotic stroke was more often found in high-income countries, while other causes were more often seen in low- and middle-income countries. Patients with a stroke at young age in low-income countries are younger and have less traditional vascular risk factors, and a higher mortality risk in the first three months after stroke, compared to patients in high-income countries. This might partially be explained by less access to healthcare, suboptimal secondary preventive therapy and the overall educational level of the population.

The long-term perspective after stroke at young age

In chapter 9, we describe the long-term mortality risk after stroke at young age in the Netherlands from 1998 to 2017. Of 15527 patients with stroke at young age between 1998 and 2010, 22.8% (3540) have died at the end of the study period in 2017. In the first 30 days after stroke, 11.6% of all stroke patients die. This percentage consists of 32.3% of the patients with an ICH at young age and 7.4% of the patients with an ischemic stroke at young age. The 15-year mortality of the patients that survive the first 30 days (so called 30-day survivors) remains high with 17%. The risk of mortality is five times higher after an ischemic stroke and eight times higher after an ICH, compared with age- and sex matched individuals from the general population. A large number of the 30-day survivors die of a stroke-related cause, other cardiovascular disease or of any type of cancer.

In **chapter 10** we investigated the long-term risk of a recurrent cardiovascular event and compared it with the long-term risk of any bleeding complication related to the use of antithrombotic medication that patients are prescribed after stroke. The 10-year cumulative risk of a recurrent cardiovascular event was almost 34%; the risk of any bleeding complication was around 22%. Bleeding complications were classified according to severity, ranging from minor symptoms to fatal bleeding. Most of the bleeding complications were minor, and women more often had bleeding complications than men, especially due to excessive gynecological bleeding. In patients without a clear cause for stroke it will be important to further investigate and balance the risk of bleeding complications and prevention of recurrent ischemic events due to antithrombotic medication, as they were found to have the lowest risk of recurrent events, and the highest risk of bleeding complications.

CONCLUSION

The studies in this thesis show that the number of patients with stroke at young age is increasing in the Netherlands over time, and that the risk of mortality remains high up to years after stroke, especially compared to the general population. Furthermore, in a substantial proportion of all strokes at young age, no clear cause can be found, while potential risk- and trigger factors are present by looking from a different perspective. Evaluation of patient data from different countries all over the world shows a large global variation in risk factors, etiology and outcome. The underlying explanations for these differences can help in finding leads for (new) causes and help to improve local stroke care. In addition, it is important to take a patient's ethnicity and region of origin into account in the search for risk factors and causes of stroke.

Besides the high mortality risk, there is also a high risk of recurrent cardiovascular events, despite treatment with antithrombotic medication, of which the risk of potential bleeding complications is now increasingly more recognized. Future studies should investigate new and yet unclear risk factors and causes, to improve treatment and prognosis on an individual patient level.

Chapter 12

General discussion

GENERAL DISCUSSION

Stroke is the second leading cause of death and a major cause of disability worldwide. About two million young adults are affected every year.[9, 309-311] For these young individuals, stroke has a tremendous impact on their daily life, usually for the rest of their lives. Tailored information about their prognosis from a lifespan perspective is therefore essential. Clinicians need to have up to date knowledge about the epidemiology including risk factors and etiology, and treatment of stroke in the young to be able to counsel their patients with this tailored information.

The overall aim of this thesis was to investigate in the young the incidence of stroke in the Netherlands, risk factors and etiology both in the Netherlands and worldwide and the long-term prognosis regarding mortality, recurrence and antithrombotic therapy-related bleeding complications.

The results described in this thesis are based on four different studies: a registry-based study with data from the Statistics Netherlands, the ODYSSEY-study, the GOAL-initiative and the FUTURE-study.

This chapter will focus on methodological considerations first, then discuss the main findings of the studies and end with clinical relevance of the studies in this thesis and future perspectives.

Methodological considerations

Discussion on the methodological strengths and limitations of a study, the study design, internal validity, precision and external validity are important for the interpretation of the findings of a study.

Study design

The studies in **chapter 4** and **9** are performed with data from the Dutch Hospital Discharge Register, Population Register and National Cause of Death Registry of the Statistics Netherlands. The registers were linked to construct a cohort of patients aged 18-49 years with first-ever ischemic stroke and intracerebral hemorrhage (ICH). The registry-based data allowed us to examine a large nation-wide cohort of patients over a long time period, but did not provide us with details on risk factors, etiology and treatment of stroke in individual patients. This limited the interpretation of the results with respect to understanding which type of ischemic stroke is increasing and what patient or stroke characteristics increase the risk of mortality.

The studies in chapter 5 and 6 are based on the prospective ODYSSEY study cohort. In this study we included consecutive patients with a TIA, ischemic stroke or ICH, aged 18-49 years, in 17 centers in the Netherlands. Data were collected in a structured manner, though not completely uniformly since the diagnostic work-up differed slightly between hospitals. All well-established causes for ischemic stroke were investigated for nearly all individuals. However, 2.3% of individuals with no clear cause for stroke did not receive and cardiac ultrasound and antiphospholipid testing was incomplete in 15% of the patients with cryptogenic stroke. In addition, some prothrombotic abnormalities known to cause venous thrombosis (e.g. protein S deficiency or presence of prothrombin mutations) with uncertain meaning for arterial thrombosis might not have been complete for all individuals. This might have led to less International Pediatric Stroke Society (IPSS) risk factors found than were truly present.

The study in chapter 8 is based on data collected as part of the GOAL initiative from cohorts of patients with ischemic stroke in 29 countries all over the world. By using an individual patient data meta-analysis as design for our study, more accurate estimations in subanalyses for six age-strata, number of vascular risk factors, geographic region, ethnicity and socioeconomic level were possible. Unfortunately, part of the data was collected retrospectively. In addition, only data that was available for large enough subgroups was analyzed, thereby limiting the number of variables that we could study and leaving potential valuable information unused. For example, functional outcome after 3 months (besides mortality) by modified ranking scale and stroke severity by NIHSS were missing for too many patients.

The study in chapter 10 is based on the FUTURE study, which comprises a prospective cohort of all consecutive patients with a TIA, ischemic stroke or ICH, aged 18-49 years, who visited the neurology department of the Radboudumc between 1980 and 2010. The FUTURE-study was designed as a prospective, longitudinal cohort with structured follow-up until 2014. Additional data on bleeding complications and recurrent events between 2014 and 2020 were collected retrospectively from patient's medical files. This approach may have led to an underestimation of the number of bleeding and ischemic events.

Internal validity

The internal validity is the extent to which a study can demonstrate a causal relation between two variables. The internal validity of studies can be compromised by random or systematic errors, which are subdivided in different categories: selection bias (sampling), information bias (validity of measurements) and confounding (interference of confounding variables).[344]

Selection bias

Selection bias can occur when participation depends on either the determinant or the outcome.[344]

The ODYSSEY study aimed to include all consecutive young patients with stroke in 17 centers in the Netherlands, although this was not always possible, for example during the COVID period (March 2020-February 2021). We included patients with stroke irrespective of severity. However, in some hospitals patients that died very soon were not included. This might have caused bias towards inclusion of patients with less severe stroke, which is reflected by the relatively low median NIHSS of 3 in the ODYSSEY study. The fact that we may have missed patients with severe stroke might have influenced the distribution of the etiological classification (Chapter 5), since large artery disease or high-risk cardio-embolic sources may lead to more severe strokes than for example stroke due to small vessel disease.

Similarly, in **chapter 6**, we could assess trigger factors only in survivors and in those without aphasia, leading to possible selection bias. Nevertheless, we believe this will be comparable to other prospective cohort studies and trials that also need informed consent. Regarding **chapter 6**, we believe trigger factors will unlikely have influenced the severity of stroke.[206] Given that trigger factors are believed to only cause a short-lasting relative risk, potentially leading to stroke, there is no pathophysiological plausible explanation that they would be related to larger emboli and thus more severe stroke, though formal evidence is lacking.

All cohorts included in the GOAL-initiative were hospital-based studies, potentially introducing selection bias because patients with very mild or rapidly fatal strokes might not have gone to, or reached the hospital in time. This may have influenced the outcome results and led to a false estimation of the 3-month mortality, since the mortality would most likely have been higher if more patients with rapidly fatal stroke had gone to the hospital and would have been lower with more very mild strokes. Underestimation or overestimation of the 3-month mortality may have been more pronounced in low- and middle-income countries because of or less access to healthcare.

Within the FUTURE study, patients were only included in het Radboudumc Nijmegen. Our academic hospital serves as a tertiary referral center for a large area in the eastern part of the Netherlands. Although most patients with a stroke at young age were referred to a university medical center somewhere along the course of the disease, especially at the time of the study period, selection bias may have occurred. In case of the FUTURE study, this may have caused selection towards

inclusion of patients that will more likely be referred to an academic hospital, for example patients with unknown or rare causes of stroke. Yet, the distribution of the TOAST classification in the FUTURE cohort was comparable to other cohort studies in that period.[7, 12]

Information bias (misclassification)
Information bias may occur when the determinant and/or the outcome is not measured in the right way or when their definitions are multi interpretable or vary between centers.[344] Different types of misclassification may have occurred in this thesis; misclassification of the event, misclassification of risk factors and etiology and misclassification of patients to categories used for sub analyses.

In our studies, misclassification of the event may have occurred in **chapter 4** and **9**. The use of ICD-codes to detect all incident strokes in the studies that made use of the data of Statistics Netherlands may have resulted in a false estimation of the true number of strokes in the investigated time period, caused by two problems. First, due to a coding problem (assignment of the wrong ICD code), strokes that were in fact not strokes could have been taken into account in our analyses. However, we validated ICD-codes for stroke in the young and found a high percentage (>90%) of correct ICD-code classification. Second, less hospitals participated in this form of ICD-registration after 2006, which may have resulted in an underestimation of the true number of strokes in the investigated time period. However, we assume that missing records due to hospitals that no longer participated to the ICD-registration were missing at random. Missing records will most likely have led to underestimation of the observed temporal trends of stroke incidence.

In the ODYSSEY study, it is unlikely that misclassification of the index event has occurred, since every TIA, ischemic stroke and ICH was confirmed by neuroimaging.

Misclassification of risk factors and etiology may have occurred in the patients of the GOAL initiative (**chapter 8**) as the inclusion of patients took place in very different time periods, with possible changing definitions of some risk factors over time. To minimize this risk of misclassification we standardized and harmonized the definitions of all risk factors. In addition, no specific diagnostic work-up was required, which may have led to misclassification of the cause of stroke as not all patients received all additional investigations to come to a final etiological classification.

Misclassification of patients to (incorrect) different subgroups of antithrombotic medication may have occurred in **chapter 10**. For the FUTURE study, information regarding recurrent events after 2014 and bleeding complications during follow-up

was retrieved from medical files. Patients were divided into three subgroups, namely use of 'only antiplatelet therapy', 'other antithrombotic medication including vitamin K antagonists and direct oral anticoagulants' or 'no antithrombotic medication'. Due to inconsistent reporting of antithrombotic medication after stroke (e.g. switching or (dis)continuing of medication) the medication use during follow-up could not reliably be registered. Therefore, we could only compare the effect of different groups of antithrombotic medication stratified at baseline, which may have led to misclassification when patients did no longer use the same antithrombotic medication as prescribed at baseline when a recurrent event or bleeding complication occurred. As a consequence, the true number of bleeding complications in the subgroups with 'only antiplatelet therapy' or 'other antithrombotic medication' may be slightly lower when patients stopped using their medication.

Confounding

Confounding can occur when a factor is associated with both the determinant and outcome of interest, which is not part of the causal chain but might influence the result or association found between determinant and outcome.[344]

If possible, we corrected for known confounders such as age, sex and vascular risk factors in all studies, but sometimes information on confounding was missing. For example, in our analyses regarding mortality after stroke in the Netherlands we corrected for age and sex but were not able to correct for all confounding vascular risk factors and comorbidity due to missing information in the registries used. However, we tried to limit the risk of confounding by using the Charlson-Comorbidity-Index as a rough estimate of someone's comorbidity.

Precision

Precision refers to the degree of random error in a study, which can lead to imprecise effect estimates reflected by wide confidence intervals. The precision of a study can be increased by using larger sample sizes, and by using validated outcome scales.[344]

All studies described in this thesis were based on cohorts or combinations of cohorts (GOAL) with large to very large sample sizes in an attempt to increase precision. For some analyses on trigger factors, however, the sample size of patients was too small, which might have led to imprecise or less reliable results and should therefore be interpreted with caution.

External validity

The external validity is the extent to which results of a study can be generalized to a general population.[344] The large sample of Dutch patients with stroke in the cohort constructed with data from Statistics Netherlands enabled us to perform age-, sex- and stroke subtype specific analyses for the studies on incidence and mortality, which increases the generalizability and thus the external validity of our results. Since the Dutch population consists of mostly Caucasian individuals, results can probably be generalized to most European countries, but will be less generalizable to countries with a substantial number of patients that identify themselves as Black-Americans, Hispanics or Asians.

The ODYSSEY-study ensured inclusion of patients from both non-academic and academic hospitals, from both clinical wards as well as outpatient clinics, providing a very heterogenous cohort of patients with both minor and very severe strokes, allowing for generalizability to a general stroke population in other European countries. This mean age of 44 years was comparable to other studies of stroke in young adults, as was the men/women ratio of 52.7% men versus 47.3% women.[7, 9] We found less patients with cryptogenic stroke and more patients with 'other determined' and cardio-embolic stroke compared with earlier cohort studies investigating stroke in the young. This is probably due to our systematic approach and extensive diagnostic work-up.

The baseline characteristics and stroke characteristics of the FUTURE-study were more or less comparable to other studies concerning stroke at young age in the same time period.[7, 345]

The GOAL study comprised relatively few data from low-income countries and Africa, potentially limiting generalizability towards other low-income or African countries. Furthermore, the mean age of 40.8 years we found was comparable to the median age of 42 found in the 15-cities stroke study[103] and somewhat lower than that of 46 years in the SIFAP study, that both included patients from Europe only.[57]

DISCUSSION OF MAIN FINDINGS

Incidence of stroke

This thesis shows that the incidence of ischemic stroke in young adults increased with almost 50% from 7.4 to 10.8 per 100,000 person-years in the Netherlands between 1998 and 2010, with a more or less stable incidence for ICH at young age and unspecified stroke. This increase in ischemic stroke has also been observed in Denmark and France.[5, 9] There are several explanations for this. A part of the increase may be explained by a higher detection rate of ischemic stroke due to improved detection by better access to MRI with diffusion-weighted-imaging (DWI), although this seems unlikely to explain the entire increase.[4, 161] First, the incidence did not increase in all age-strata, but only in young adults *over* 35 years old, whilst young adults are even more likely to receive a MRI than those 35 years or over. In addition, stroke-mimics such as migraine, epilepsy and TIA's that due to better imaging techniques can now be recognized as ischemic strokes and consequently increase the incidence, will most likely be present in all age-strata, or perhaps even more in the youngest. Second, a coinciding increase of the prevalence of traditional vascular risk factors and illicit drug use amongst young adults was seen, possibly leading to a higher risk of and ultimately to more ischemic strokes.[6, 68, 173-175, 192]

We also found that more young women were affected by stroke than young men. Especially in the fertile age-range, certain women-specific risk factors or risk factors that have a higher prevalence in women exist, including pregnancy and the puerperium, oral contraceptive use, migraine with aura and auto-immune disorders such as antiphospholipid syndrome or systemic lupus erythematosus (SLE). Still, yet unidentified risk factors, perhaps hormonally or genetically determined, are expected to play a role, since the absolute number of women with stroke due to these risk factors and causes is low and can therefore not explain the entire difference in incidence with men.

Risk factors and etiology of stroke in young adults

The studies in this thesis underline the importance of optimizing the classification of the etiology of stroke in the young and of investigating the causality of possible risk factors that can be found in young adults with stroke. In Chapter 5 we show that in the vast majority of young patients with stroke a (potential) cause can be found and in 99% at least one presumed risk factor for stroke is present. Many of these risk factors are not taken into account in the most commonly applied TOAST classification,[58] and as a result, only 25% of the 1322 ODYSSEY patients were classified as a cryptogenic stroke according to the TOAST criteria. With the Atherosclerosis, Small-vessel disease, Cardio-embolic, Other causes, Dissection (ASCOD) classification,[182, 346] that was developed in 2009 and adapted in 2013 to better describe overlap between diseases underlying ischemic stroke

and describe the degree of causality, still around 20% of our patients was classified as having a cryptogenic stroke. This percentage is lower than the 30-40% of cryptogenic strokes found in earlier studies[7, 12, 158], which is most likely due to both a higher detection rate of causes with the improved diagnostic work-up over the last decade and to the systematic manner of classification by a small, selected group of raters in our cohort. The approximately 25% of strokes classified as due to an 'other determined' cause was slightly higher or quite similar in comparison with earlier studies.[7, 12] Above all, it shows that by using a structured way of classifying well-phenotyped patients the number of cryptogenic strokes is lower than previously reported.[7, 12]

Overall, both the TOAST and ASCOD classification leave over 20% of young patients with stroke without an etiological diagnosis, and around 25% of patients with 'other' varying causes are grouped as one. Based on the evidence from previous studies that used these classifications to investigate prognosis, it is difficult to counsel an individual patient adequately on treatment and prognosis, given the large differences in underlying potential risk factors and pathophysiological mechanisms leading to stroke. Moreover, it emphasizes that current etiological classification systems for ischemic stroke are inaccurate in classifying almost half of the young adults with stroke.

The presumed risk factors that the IPSS mention in their risk factor inventory are based on pathophysiological mechanisms.[183]To diagnose some of the risk factors and mechanisms of the IPSS, additional or advanced diagnostics are required such as vessel wall imaging or more extensive cardiac imaging. These investigations are now performed more often in young adults especially when they have a stroke without a clear cause. With our approach, including history taking and the additional investigations as described, almost all patients could be adjudicated to one or more of the IPSS categories in our population of young adults with stroke. Awareness of the existence of a wider spectrum of possible risk factors and etiologies may be the result of using the IPSS categorization as a risk factor inventory. However, providing someone with information that presumed IPSS risk factors may have caused his/her stroke has to be done with caution, as risk factors are not necessarily causes. To further establish proof of causality of other presumed risk factors and investigate the role of interactions between risk factors, we need information on their long-term effects, on their prevalence in healthy individuals and on the effect of treatment of risk factors.

In **chapter 6**, we show that trigger factors may play a role in the pathway leading to stroke. Cola consumption, vigorous physical exercise, sexual activity and illicit drug use might serve as trigger factors for stroke when consumed or performed in the hour(s) preceding stroke, and fever- and flu-like disease in the day preceding stroke. Trigger

factors were never investigated for young adults with stroke, nor for large enough subgroups with different types of (ischemic) stroke. There was a significant difference in the number of trigger factors associated with for example ischemic stroke versus ICH and with the etiologic subtypes of ischemic stroke, which suggests differences in the pathophysiological effect of trigger factors. Possible biological explanations in how trigger factors increase the risk of stroke are by an increase in blood pressure, by systemic inflammation leading to endothelial dysfunction or by vasospasms.[16,211,224] One can speculate that in patients with a clear cause like large artery disease and small vessel disease, who often already have longer existing presence of risk factors such as hypertension and atherosclerosis, the effect of a short lasting rise in blood pressure or change in endothelial function, is less pronounced and therefore less of a potential trigger. The individual response to a trigger may be of greatest interest in the search for (new) causes and may lead to new insights into pathophysiological mechanisms and eventually treatment.

Large ethnic and racial, regional, and socioeconomic differences in the prevalence of risk factors, causes of stroke, and 3-month mortality among young patients with ischemic stroke worldwide are shown in this thesis. Traditional vascular risk factors were already present in 3 out of 4 young patients, and in 50% of patients under the age of 30 years, but differed in prevalence per ethnic and racial group, for example hypertension and diabetes were more prominent in Black individuals and Asians and dyslipidemia in Caucasians. It is important for clinicians to be aware of someone's origin, since it may influence the possible underlying risk factors and etiology of their stroke. For example, it might be worth to search more intensively and longer for hypertension as a risk factor in Black individuals, or for moyamoya in Asian individuals. Finally, being the largest study on young patients with ischemic stroke worldwide, we were able to show that there still exists great inequality when it comes to access to healthcare, stroke care and (secondary) prevention.

Long-term prognosis

The mortality risk after stroke at young age is high, especially compared to the mortality risk in the general population which was around 5 times higher after ischemic stroke and around 8 times higher after ICH. This risk remains elevated up to 15 years after stroke. The high mortality risk might reflect suboptimal treatment of a large group of patients, since even after treatment to prevent recurrent stroke and treatment of associated risk factors according to current standards, the risk of death remained increased compared to the general population. In our patients the underlying causes of death were cardiovascular disease and malignancies in 50% of the deceased, which was a lot higher than in the general population.[332] This provides clues for possible underlying disease mechanisms.

The high percentage of patients that die of (recurrent) cardiovascular disease suggests that the underlying risk factors that lead to first-ever stroke continue to expose patients to new cardiovascular disease throughout the rest of their lives.[54, 69] The high percentage of patients that died of malignancies suggests an intimate relationship between stroke and malignancies. Stroke and cancer are two of the most important causes of morbidity and mortality, and not only may they share common risk-factors leading to one and/or the other, cancer itself may also contribute to stroke.

Besides a high mortality risk, **chapter 10** shows that the risk of recurrent cardiovascular events is also high. This will partially be explained by the continuous exposure to the very same risk factors that caused death due to cardiovascular disease in chapter 9. Although screening for most of these traditional risk factors is recommended in the acute phase after stroke, risk factors that emerge afterwards may go unnoticed. In addition, while all patients are routinely treated with standard secondary preventive medication, none of the therapies was investigated in young adults with stroke, and the high number of patients with a recurrent event while using secondary prevention suggests that therapy might be suboptimal. Also, therapy compliance is not always monitored. Still, life-long prescription of secondary preventive medication means multiple decades of medication use, with corresponding costs, psychosocial consequences and risk of bleeding complications.[347] In this thesis we show that many young adults (22%) need medical attention for bleeding complications somewhere after their stroke. It seems likely that this will be an underestimation of the true number of bleeding complications, since very minor (though bothersome) bleeding events may have gone unnoticed in our study. Interestingly and not previously described in literature, we found a high percentage of young women that sought help for abnormal gynecological bleeding, sometimes leading to removal of their uterus. This finding might be partly explained by the young age of our study population, while women of older age are often menopausal when they have a stroke and receive antithrombotic medication. This raises the question if there might be a group of women who are at a disproportionally high risk of severe bleeding compared to the low risk of recurrent ischemia, for who it is uncertain if discontinuation of antithrombotic medication is safe and meaningful.

A different organization of care, perhaps with collaboration of general practitioners and nurse practitioners, might help to improve a patient's long-term prognosis. On the one hand to detect emerging risk factors and on the other hand to assess all possible therapy related complications and monitor therapy compliance. This will help clinicians in treating their patients while making an individual assessment of risks and side effects.

Clinical relevance

The increasing incidence of stroke in the young has impact on both health care and society. Not only more and more clinicians will encounter a patient with stroke at young age at some point in their career, the number of adults who have to live with the daily consequences will also increase, making accurate information regarding individualized treatment and prognosis essential. The results in this thesis underline the importance of knowing the underlying risk factors and etiology to be able to provide future patients with this personalized prognosis.

Clinicians who encounter a young adult with stroke should be aware that there are many more possible causes for stroke compared to those considered in older stroke patients. This justifies an extensive, yet structured diagnostic work-up. By doing so, risk factors in individual patients can be detected, and when possible be treated or patients can be advised to stop certain risk factors, for example smoking, illicit drug use or oral contraceptive use. Coining a stroke a ''cryptogenic stroke'' should be a diagnosis "per exclusionem" and can only be diagnosed after thorough evaluation, for which a pediatric stroke risk factor inventory can be of help. The underlying risk factors and etiology are important to decide on different treatment strategies, but also to decide on (dis)continuation of medication in the many years after stroke for the individual patient.

For both clinicians and researchers, it is important to keep in mind that current classification systems are unable to distinguish between many of the possible other causes such as for example antiphospholipid syndrome, coagulation disorders, stroke due to illicit drug use or in pregnancy. At this point in 2022, the large groups of patients with either very different ''other'' causes or with unknown causes lead to unreliable prognostic outcomes for these groups. It is impossible to make a proper comparison between a treatment effect or prognosis between patients with varying pathophysiological mechanisms or potential risk factors. For example, to compare the treatment and prognosis of patients with stroke due to a carotid dissection or stroke due to antiphospholipid syndrome would qualify for the same category in the TOAST classification, whereas both the cause and explicitly treatment and prognosis will be very different. This hampers extrapolation of the results of (earlier and future) studies which use(d) these classifications to a population of young adults with stroke, and one should be wary of that.

The use of antithrombotic medication is not without risks. Patients should be counselled about possible complications and there is a role for clinicians to actively inform patients about therapy related complications to enable shared decision making.

Based on the studies in this thesis, prognosis after stroke in young adults may not be as favorable as previously described, with some patients encountering a high case fatality and long-lasting increased risk of recurrence, risk of therapy-related complications and risk of mortality.

Finally, the high incidence and poor outcome of young patients with stroke in low- and middle-income countries is distressing. Urgent measures are needed, and we should try to gain more equality in both prevention and stroke care worldwide, for example by improving health care access, increase the number of stroke care units or lower costs of antithrombotic medication. This is in line with two of the United Nations Sustainable Development Goals, to ensure healthy lives and promote well-being for all at all ages, and to reduce inequality in and among countries.

Future directions

Future research should first continue to monitor the trends in incidence. A rising incidence of stroke that coincides with a rising prevalence of vascular risk factors warrants attention and should lead to better information campaigns and primary prevention strategies to stop this increase. Given the large, global epidemiological variation, differences in risk factors and etiology can aid in region-specific stroke prevention. Overall, there might be an important role for neurologists in creating more public awareness.

Another remaining important knowledge gap is the only partially explained high number of young women with stroke, for which it would be interesting to investigate the hormonal and genetic influence on cardiovascular disease. Likewise, an important knowledge gap lies in the large numbers of patients with cryptogenic strokes, for whom it is uncertain how many truly have no potential cause with current stroke classification systems. A new etiological classification system for young patients with stroke, which enables clinicians and researchers to classify patients by stroke mechanism is needed. This is important for future studies that investigate treatment strategies based on the etiology of stroke. A young stroke specific classification system may result in a smaller group of patients with a true cryptogenic stroke, in which further investigations can be performed to find a potential (new) cause.

Finding yet unidentified causes is another point that deserves future attention. There is increasing interest for the interplay between the coagulation system and classic vascular risk factors, other potential new causes and genetics. The ongoing Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRETO) study hopes to shed light on transient

triggers and (sub)clinical chronic risk factors, new sources for embolism, covert thrombosis and hemostasis abnormalities and complex risk-factors interactions.[228] In addition, with next-generation sequencing and RNA gene expression studies they hope to find new disease pathways in cryptogenic stroke.[228]

In addition, to provide more phenotypic details of prospectively included patients and to incorporate knowledge from recent studies including the ones described in this thesis, an extended version of the ODYSSEY study, the ODYSSEY next, was initiated. This cohort aims to provide even more insight in the risk factors, the relationship between trigger factors and the eventual mechanism that causes stroke, the etiology and prognosis of very-well phenotyped patients with stroke in the young.

The follow-up of the ODYSSEY study is currently ongoing. It focusses on the long-term prognosis including recurrent events and its association with underlying risk factors and etiology. It may also shed more light on bleeding complications, with more reliable information on the effect of using antithrombotic medication according to current guidelines, with most patients now being prescribed clopidogrel, whereas this was mostly acetylsalicylic acid in the FUTURE study. In addition, for more insight into the differences between men and women, the characteristics of pregnancy-related stroke and the two-way association between pregnancy-complications and stroke will be investigated.

With the use of advanced intracranial vessel wall imaging in the acute phase after stroke and later during follow-up, we hope to gain more insight in (transient) vessel wall pathology in young adults, which may help in deciding on (duration of) treatment.[348, 349]

Regarding the long-term prognosis, mortality remains high despite improvement in acute stroke care and secondary prevention. Almost one third died of a malignancy. With use of Statistics Netherlands and ICD codes the incidence of malignancies in a stroke population in the Netherlands during follow-up can be determined. In addition, in the near future it should be possible to link the ODYSSEY cohort to the National Cancer Registry (NCR) from the Netherlands Comprehensive Cancer Organization (IKNL) to investigate the risk of being diagnosed with cancer in the years after stroke including clinical and radiological predictors, to establish the number of patients with occult malignancy. This research may help to determine whether screening for (occult) malignancies in young adults with stroke is useful, cost-effective, leads to lower mortality and if so, what would then be the best time and way to screen.

Finally, there may be a substantial proportion of patients that do not need secondary prevention for the rest of their lives, for example those without vascular risk factors or with a temporary, transient cause of stroke. Our ongoing longitudinal study among young stroke patients with advanced vessel wall imaging may provide useful information on transient pathology (for example inflammation, dissection, reversible vasoconstriction), versus ongoing pathology and the differential risk of recurrence.[348, 350, 351] This can be helpful in identifying low-risk patients for a trial investigating the discontinuation versus continuation of platelet inhibition and the effects on recurrent vascular events and bleeding complications.

Chapter 13

Dutch Summary | Nederlandse samenvatting

DUTCH SUMMARY | NEDERLANDSE SAMENVATTING

Ongeveer 15 miljoen mensen krijgen wereldwijd jaarlijks een beroerte, het is daarbij doodsoorzaak nummer 2. Het wordt gezien als een ziekte van vooral oudere mensen, maar ruim 10% van alle beroertes betreft (jong)volwassenen tussen de 18 en 50 jaar. In Nederland komt dit neer op ongeveer 1200 herseninfarcten op jonge leeftijd en 150 hersenbloedingen per jaar. Niet alleen staan mensen die op jonge leeftijd een beroerte krijgen midden in het leven, met vaak een baan, gezin en veel sociale verplichtingen, maar ook hebben zij nog een lange levensverwachting. De behoefte aan juiste informatie over de risicofactoren en oorzaken van hun beroerte, de beste behandeling en mogelijke bijwerkingen, en de toekomst wat betreft kans op herhaling, is daarom groot. Tot op heden is er veel onduidelijk, en blijft voor een groot aantal jonge patiënten de oorzaak onduidelijk of volledig onbekend. Dit bemoeilijkt de behandeling en brengt veel onzekerheid met zich mee. Het vinden van mogelijke risico- en triggerfactoren, alsmede (nieuwe) oorzaken is daarom belangrijk.

Met dit doel werd in 2013 de ODYSSEY studie gestart, een prospectief onderzoek in 17 Nederlandse ziekenhuizen naar risicofactoren, oorzaken en lange termijn gevolgen van een TIA, herseninfarct en hersenbloeding op jonge leeftijd. De ODYSSEY studie is de opvolger van de FUTURE studie, die van 1980 tot 2010 in het Radboudumc te Nijmegen liep waarin veel onderzoek werd verricht naar de zéér lange termijn gevolgen.

Om verder mogelijk aanknopingspunten te vinden voor (nieuwe) oorzaken in de grote groep patiënten met een tot op heden onbekende oorzaak, en verschillen tussen patiënten van verschillende etnische afkomst van over de gehele wereld te onderzoeken, werd het GOAL-initiatief gestart. Een project om data van individuele patiënten in 29 landen ter wereld te analyseren.
In **deel I**, **hoofdstuk 2**, wordt beschreven hoe het GOAL-initiatief is opgezet.

De studies in dit proefschrift bevatten verschillende resultaten van de ODYSSEY en FUTURE studie, het GOAL-initiatief, alsmede onderzoek dat gedaan werd door naar data in de landelijke medische registraties van het Centraal Bureau voor Statistiek te kijken.

De epidemiologie van een beroerte op jonge leeftijd
Deel II, **hoofdstuk 3** geeft een overzicht van meerdere epidemiologische aspecten van beroertes op jonge leeftijd, zoals incidentie, riscofactoren en oorzaken. Een aantal oorzaken die meer voorkomen op jonge leeftijd dan op oudere leeftijd en actueel zijn wat betreft huidige studies en mogelijke kennishiaten worden uitgelicht. Het gaat dan

over de rol van migraine, mogelijk tot beroerte leidend drugs gebruik, maligniteiten en daardoor verandering van de bloedstolling, het krijgen van een beroerte tijdens de zwangerschap, een patent foramen ovale en de nu geadviseerde behandeling daarvoor en mogelijk aangeboren erfelijke aandoeningen die tot een beroerte kunnen leiden.

In **hoofdstuk 4** wordt de incidentie van een herseninfarct en hersenbloeding op jonge leeftijd in Nederland beschreven tussen 1998 en 2010. Er is een duidelijke toename van het jaarlijkse aantal eerste herseninfarcten op jonge leeftijd, terwijl het aantal eerste hersenbloedingen stabiel is gebleven. Ook zien we dat meer jonge vrouwen een herseninfarct krijgen dan mannen. De toename van het jaarlijkse aantal herseninfarcten kan deels verklaard worden door een toename in gebruik van meer geavanceerde diagnostiek; zoals specifieke MRI-scans waarmee herseninfarcten beter gedetecteerd kunnen worden. Verder wordt een vergelijkbare stijging van het vóórkomen van vasculaire risicofactoren, zoals overgewicht en roken, al op jonge leeftijd beschreven als mogelijke oorzaak. Een mogelijke verklaring voor het verschil tussen mannen en vrouwen is het bestaan van een aantal vrouwspecifieke, of meer in vrouwen voorkomende risicofactoren en oorzaken op jonge leeftijd. Dit zijn bijvoorbeeld migraine met aura, zwangerschap, de orale anticonceptiepil en auto-immuunziekten zoals het antifosfolipidensyndroom.

In **hoofdstuk 5** komen deze risicofactoren en oorzaken van een TIA en een herseninfarct op jonge leeftijd aan bod. Voor het classificeren van oorzaken wordt meestal de TOAST classificatie gebruikt, dan wel het iets later ontworpen ASCOD systeem. Beide systemen zijn oorspronkelijk uitgebracht voor een populatie patiënten met TIA's en herseninfarcten met een gemiddelde leeftijd boven de 65 jaar. De meest voorkomende oorzaken op die oudere leeftijd zijn atherosclerose van de grote vaten, small vessel disease en een cardiale emboliebron, waarbij voornamelijk boezemfibrilleren gevonden wordt. Deze oorzaken komen in veel mindere mate voor bij jongvolwassenen met een beroerte. Bij hen blijft, met het gebruik van de huidige classificatiesystemen, de oorzaak van de TIA of het herseninfarct in 20-30% van de patiënten onbekend, en wordt een ander groot deel van de patiënten (ongeveer 20%) met zeer uiteenlopende vastgestelde oorzaken samengevoegd in een "overige" categorie. In onze ODYSSEY populatie van 1322 patiënten hebben we daarom, na eerst geclassificeerd te hebben met de TOAST en ASCOD classificatie, een classificatie van risicofactoren toegepast die gebruikt wordt voor TIA's en herseninfarcten bij kinderen en adolescenten, de zogeheten IPSS (International Pediatric Stroke Society) inventarisatie. Met de TOAST classificatie bleef de oorzaak onbekend in 25%, wanneer hierna met ASCOD geclassificeerd werd nog 19%. Echter in 1312 (99%) van de patiënten wordt dan ten minste 1 mogelijke risicofactor of potentiële verklaring gevonden, en daarmee dus ook in de 25% of 19% die anders

als onbekend worden beschouwd. Deze factoren wezen in de richting van auto-immuunziekten, niet-atherosclerotische arteriopathieën en protrombotische oorzaken waaronder stollingsstoornissen. Het gebruik van deze IPSS methode kan een eerste benadering zijn om een classificatie systeem te ontwerpen dat meer specifiek is voor de oorzaken bij jonge mensen, wat gebruikt kan worden in toekomstige studies waarin uitkomsten van groepen patiënten met een bepaalde vergelijkbare oorzaak worden vergeleken.

Vanwege de grote groep patiënten met een onbekende oorzaak op jonge leeftijd, hebben we in **hoofdstuk 6** aan de hand van de door ODYSSEY patiënten ingevulde vragenlijsten over bepaalde gebeurtenissen vlak voorafgaand aan de beroerte gekeken naar het bestaan van mogelijke trigger-factoren. Trigger-factoren zijn mogelijk uitlokkende momenten die zorgen voor een kortdurende stijging van de bloeddruk of een ontstekingsreactie in de bloedvaten van het lichaam, waardoor een beroerte uitgelokt kan worden. Het gebruik van cola en drugs, beoefenen van intensieve sport, seksuele activiteit of het hebben van koorts of griepachtige verschijnselen bleken kortdurende trigger-factoren te zijn voor zowel het krijgen van een TIA, herseninfarct als hersenbloeding. Soortgelijk onderzoek was nog niet eerder verricht bij beroertes op jonge leeftijd en kan helpen om in de richting van nieuwe mechanismen te zoeken, zeker bij mensen waarbij tot nu toe geen duidelijke verklaring gevonden wordt.

Wereldwijde verschillen ten aanzien van beroertes op jonge leeftijd

In **deel III**, wordt in **hoofdstuk 7** een overzicht gegeven van wereldwijde verschillen in de incidentie, risicofactoren, oorzaken en overlijden op korte termijn na een beroerte op jonge leeftijd, met de nadruk op regionale, en op ras- en etniciteit gebaseerde verschillen. Onze literatuurstudie laat zien dat beroerte op jonge leeftijd veel vaker voorkomt in het Midden-Oosten en Afrika dan in de meeste Europese landen, en dat het afhankelijk is van de regio en afkomst van een patiënt wat daar veel voorkomende risicofactoren en oorzaken zijn. Zo komen infectieziekten zoals HIV en tuberculose meer voor in ontwikkelingslanden, en sikkelcelziekte in Afrika en Zuidoost-Azië. In **hoofdstuk 8** tonen we de uitgebreide verschillen in de prevalentie van onder andere traditionele vasculaire risicofactoren zoals hypertensie, diabetes, hypercholesterolemie, roken en overgewicht per continent en per etnische subgroep. Hypertensie en diabetes komen veruit het meest voor in patiënten met een donkere huidskleur en Aziaten. In landen met een gemiddeld laag tot midden inkomen worden verder meer andere oorzaken gezien, hart- en vaatziekten als oorzaak van de beroerte wordt meer in landen met een hoog inkomen gezien. Patiënten met een beroerte op jonge leeftijd in landen met gemiddeld laag tot middelhoog inkomen

zijn vaak jonger en hebben minder traditionele vasculaire risicofactoren, en hebben een groter risico om de eerste 3 maanden te overlijden dan patiënten in landen met een hoog gemiddeld inkomen. Dit kan deels te maken hebben met minder toegang tot gezondheidszorg, suboptimale secundaire preventie en het opleidingsniveau van de bevolking.

Het lange termijn perspectief na een beroerte op jonge leeftijd

In **deel IV**, **hoofdstuk 9**, beschrijven we de lange-termijn mortaliteit na een beroerte op jonge leeftijd in Nederland van 1998 tot 2017. Van 15527 patiënten met een beroerte op jonge leeftijd zijn er aan het einde van de studieperiode begin 2017 reeds 3540 overleden. In de eerste 30 dagen na een beroerte overlijdt 11.6%, waarbij dit getal voornamelijk bepaald wordt door de hoge 30-dagen sterfte na een hersenbloeding van 32.3%, en minder door de 30-dagen sterfte na een herseninfarct (7.4%). De 15-jaars mortaliteit van de patiënten die de eerste 30 dagen overleven is met 17% nog steeds hoog. Als we de sterfterisico's onder jonge patiënten vergelijken met die van gezonde leeftijdsgenoten van hetzelfde geslacht is de sterfte na een herseninfarct 5 keer hoger en na een hersenbloeding ruim 8 keer hoger dan de sterfte van gezonde leeftijdsgenoten. Een groot deel van de patiënten die na 30 dagen overlijdt heeft als doodsoorzaak een aan de beroerte gerelateerde oorzaak, een vorm van kanker of een ander cardiovasculair probleem.

In **hoofdstuk 10** wordt het risico op een recidief beroerte op de lange termijn onderzocht en vergeleken met het risico op bloedingscomplicaties door het gebruik van bloedverdunners die patiënten voorgeschreven krijgen na een beroerte. Het cumulatieve risico op opnieuw hart- en vaatziekten na 10 jaar bleek bijna 34%; het risico op een bloedingscomplicatie was in die periode bijna 22%. Bloedingscomplicaties werden in ernst geclassificeerd van licht tot dodelijk. Het merendeel van de bloedingscomplicaties was licht, en er traden meer bloedingscomplicaties op bij vrouwen, voornamelijk van gynaecologische aard. Bij mensen zonder duidelijke oorzaak van hun beroerte lijkt het belangrijk dat op basis van verder onderzoek een goede afweging gemaakt kan worden tussen risico op een recidief na het staken van de medicatie in verhouding tot het risico op bloedingscomplicaties. Dit omdat zij het laagste recidief risico lijken te hebben, maar net zo vaak bloedingscomplicaties.

CONCLUSIE

De studies in dit proefschrift laten zien dat het aantal patiënten dat op jonge leeftijd getroffen wordt door een beroerte in Nederland toeneemt over de jaren, en dat de sterfte op populatieniveau hoger is dan dat van gezonde leeftijdsgenoten. Ook blijft in een groot deel van de patiënten de oorzaak van hun beroerte onbekend, terwijl er wel potentiële risicofactoren en triggerfactoren gevonden kunnen worden door op nieuwe en andere manieren naar deze groep te kijken. Door data van patiënten uit verschillende landen in de wereld te analyseren kunnen veel verschillen in risicofactoren, oorzaken en uitkomsten gezien worden. De achterliggende redenen van deze verschillen onderzoeken kan helpen in het vinden van nieuwe oorzaken en het verbeteren van lokale zorg. Daarnaast is het belangrijk om iemands achtergrond in gedachten te houden bij het zoeken naar risicofactoren en oorzaken.

Naast de hoge sterftekans, is het risico op een recidief beroerte hoog, ondanks het gebruik van bloedverdunners waarvan het ontstaan van bloedingscomplicaties ook steeds meer wordt herkend. Toekomstige studies zullen moeten zoeken naar andere nog steeds onduidelijke risicofactoren en oorzaken, om zo de behandeling en prognose van patiënten op individueel niveau te verbeteren.

Part VI

Appendices

Appendix 1

List of main abbreviations

LIST OF MAIN ABBREVIATIONS

95% CI	95% confidence interval
ASCOD	atherosclerosis; small vessel disease; cardiac pathology; other causes; dissection
BMI	body mass index
CCI	Charlson-comorbidity-index
CDR	cause of death registry
CI	confidence interval
CT	computed tomography
DWI	diffusion-weighted imaging
e.g.	exempli gratia, "for example"
FUTURE study	Follow-up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation study
GOAL initiative	Global Outcome Assessment Life-long after stroke in young adults initiative'
HDR	hospital discharge registry
ICD	international classification of diseases
ICH	intracerebral hemorrhage
i.e.	id est, "in other words"
IRR	incidence rate ratio
IQR	interquartile range
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	national institutes of health stroke scale
ODYSSEY	Observational Dutch Young Symptomatic StrokE studY
PR	population registry
PY	person years
Radboudumc	Radboud university medical center
RCVS	reversible vasoconstriction syndrome
RR	risk ratio
SD	standard deviation
SMR	standardized mortality ratio
SVD	small vessel disease
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WHO	world health organization

Appendix 2

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Appendix 3

Research Data Management

RESEARCH DATA MANAGEMENT

All research data that are presented in this thesis were archived according to the FAIR (Findable, Accessible, Interoperable and Reusable) principles.

Data presented in **chapters 5**, **6**, **10** is based on the results of human studies completed at the Radboudumc in Nijmegen, including the ODYSSEY study and the FUTURE study. These studies were approved by the local medical ethics committee Region Arnhem-Nijmegen, Nijmegen, the Netherlands. We guaranteed the privacy of the participants by the use of individual subject codes. This code was stored separately from the study data. Data from the FUTURE study were collected between 1989 and 2010 with last follow-up in 2014. Data collection for the ODYSSEY study started in 2013, with ongoing collection of follow-up data. All clinical data are archived on a Radboudumc server. Scripts, including a description and output files from the FUTURE study are stored on Radboudumc department server (\\umcms011\neuro_onderzoek$\FUTURE). Data from the ODYSSEY study is also stored on (\\umcms011\neuro_onderzoek$\ODYSSEY). The data will be saved for 15 years.

Data presented in **chapter 4** and **9** is based on the results of registry-based research. The studies were performed according to the guidelines of the local research ethics committees. The Medical Ethical Committee waived the need for approval. After output was checked and approved from the Statistics Netherlands Server, all data used for analysis are presented in the tables and supplementary tables of these manuscripts.

Data presented in **chapter 8** is based on the results of the GOAL initiative study. Before participating, each individual center had to obtain written ethical approval form a local ethical committee for international data sharing. Participating centers were requested to pseudonymize their data before sending it, according to the current laws and legislation concerning research conduct at each participating center. The key linking anonymized data to individual patients remained at the participating centers. This study was conducted according to the principles of the Declaration of Helsinki (version 60, 19 October 2013) and the Dutch law for human research (WMO). Written informed consent was obtained from all participants in the prospectively collected data, no informed consent was needed for retrospective cohorts of registered patients. Ethical approval was obtained from the Medical Review Ethics Committee region Arnhem-Nijmegen. All data is processed, stored and will be destroyed after end of the study according to European Union General Data Protection Regulation. Data is stored on a Radboudumc server: (H:\Onderzoek\GOAL_Honours).

All data are accessible only by authorized persons and on request available from the corresponding author. The data are documented in English or Dutch, and are reusable for further research and analysis.

Appendix 4

PhD Portfolio

PHD PORTFOLIO

Abstracts accepted for oral presentations at national and international conferences

May 2022 **European Stroke Organisation Conference, Lyon, France**
Title: Trigger factors for stroke in the young.

Sept 2021 **European Stroke Organisation Conference, Online**
Title: Cryptogenic stroke, does it really exist.*

May 2019 **European Stroke Organisation Conference, Milano, Italy**
Title: Geographic differences in the etiology of stroke at young age: The Global Outcome After Stroke at young age (GOAL)-initiative.*

Sept 2018 **Wetenschappelijke vergadering neurovasculaire werkgroep, Amsterdam, the Netherlands**
Title: Update on the ODYSSEY-study

May 2018 **European Stroke Organisation Conference, Göteborg, Sweden**
Title: Risk factors of stroke in young adults from a worldwide perspective. The Global Outcome After Stroke at young age (GOAL)-initiative.

May 2017 **European Stroke Organisation Conference, Prague, Czech Republic**
Title: Rapid increase of the incidence of stroke in young adults in the Netherlands between 1998 and 2010.

**Presented by colleague due to maternity leave.*

Invited speaker at international conferences

April 2022 **ESO Focused Workshop Young Stroke 2022, Bergen, Norway**
Title: The GOAL-initiative: how to connect and organize a young stroke network.

May 2018 **European Stroke Organisation Conference, Goteborg**
Title: Long-term prognosis of stroke in the young.

Abstracts accepted for poster presentations at international conferences

Sept 2013 European Journal of Paediatric Neurology Conference, Brussel
Title: Diagnostic pitfalls in congenital myasthenic syndromes in children: clinical experience in an academic neuromuscular center.

Courses

2022:	Cursus palliatieve zorg, Nijmegen
2021:	Scientific integrity for PhD candidates, Nijmegen
2021:	Donders Writing Week, Nijmegen
2020-2022:	Leergang 4.0, Leiderschap (Be-your-own-Boss), Nijmegen
2019:	Cursus Persoonlijk Leiderschap, Berg-en-Dal
2018:	LUMC Klinische Epidemiologie, Schiermonnikoog
2018:	Pilot communicatie cursus, Nijmegen
2017:	Hand-on snijzaalcursus Neuro-anatomie, Nijmegen
2016 & 2022:	Stroke in the young meeting, Bergen, Norway
2016:	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK), Nijmegen

Teaching

2016-2021:	Supervision of research internship of medical students (J. Verhoeven, M. van Dongen, M Jacob, K. Rensink)
2017-now:	Teaching of medical master students, Radboudumc Nijmegen
2019-now:	Teaching of nurses from the neurology, neurosurgery and intensive care department Radboud Health Academy, Nijmegen

Other

2019-now:	Review activities for various journals (Stroke, European Journal of Stroke, International Journal of Stroke, European Journal of Neurology)

Appendix 5

Acknowledgments | Dankwoord

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Ik hou van jullie alle drie, nog verder dan tot de maan en terug.

Appendix 6

About the author

ABOUT THE AUTHOR

Merel Ekker was born on December 27, 1990 in Tilburg, the Netherlands. She attended the gymnasium at the Maurick College in Vught and graduated summa cum laude in 2009.

The same year she started medical school at the Radboud University Nijmegen, the Netherlands. She obtained her medical degree in September 2015 and started as a resident not in training at the Neurology department of the Radboudumc in October 2015 for six months.

In April 2016 she started combining a residency in neurology with the PhD project on epidemiology and prognosis of patients with a stroke at young age, under the supervision of Professor Frank-Erik de Leeuw and Professor Karin Klijn, resulting in this thesis. In 2024 Merel hopes to finish her residency in Neurology. Merel is married with Kees and together they have two daughters, Isa (August 2019) and Sophie (September 2021).

Appendix 7

List of publications

PUBLICATIONS IN THIS THESIS

* Shared authorship

Trigger factors for ischemic stroke in young adults. A case-crossover study.
Ekker MS, Verhoeven JI*, Rensink KR*, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers PJAM, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, de Kort PLM, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Herkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, Klijn CJM, Tuladhar AM, de Leeuw FE
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Schellekens MMI, Boot EM, Verhoeven JI, Ekker MS, van Alebeek ME, Brouwers PJAM, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, de Kort PLM, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Zonneveld TP, Herkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, de Leeuw FE, Kessels PRC, Tuladhar AM

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Appendix 8

Dissertations of the Vascular disorders of movement - The Radboud Stroke Center research group Nijmegen

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