Stroke in Young Adults: Epidemiology, Causes, and Consequences

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Objectives

- To discuss the epidemiology of stroke in young adults
- To describe the causes of stroke
- To describe the impact on recurrent stroke, quality of life and access to services

Stroke Rates Rising in Younger People

By NICHOLAS BAKALAR
NOVEMBER 29, 2016

Stroke rates have been declining in older people over the past 20 years — but have sharply increased in those under 55.

Researchers at Rutgers University used data from the New Jersey Department of Health on more than 227,000 hospitalizations for stroke from 1995 through 2014, calculating incidence by age over five-year periods. The findings appeared in the Journal of the American Heart Association.

Compared with the 1995-99 period, the rate of stroke in 2010-14 increased by 147 percent in people 35 to 39, by 101 percent in people 40 to 44, by 68 percent in those 45 to 49, and by 23 percent in the 50 to 54 group.

Stroke is still far more common in older people. But the rate decreased by 11 percent in those 55 to 59, by 22 percent in the 60 to 64 group, and by 18 percent in people 65 to 69.

The reasons are unclear, but the lead author, Joel N. Swerdel, now an epidemiologist with Janssen Pharmaceuticals, said that increasing obesity and diabetes in younger people are probably involved.

"For a person 30 to 50, the good news is you ain't dead yet," he said. "With behavioral changes, changing diet, increasing exercise, there's still hope for you. Behavioral change is hard, but this study is an early warning sign."

Stroke in the Young

- Accounts for 10% to 15% of all stroke

- Incidence rates: 2005 GCNKSS study, age 20-54 years
  - whites, 48 per 100,000; blacks, 128 per 100,000
  - ischemic (69%), ICH (17%), SAH (10%), unknown (5%)

- Case Fatality: FUTURE study, age 18-50 yrs

  30-day fatality 4.5%; one-year mortality for survivors 1.2% for TIA, 2.4% for ischemic stroke, and 2.9% for ICH.

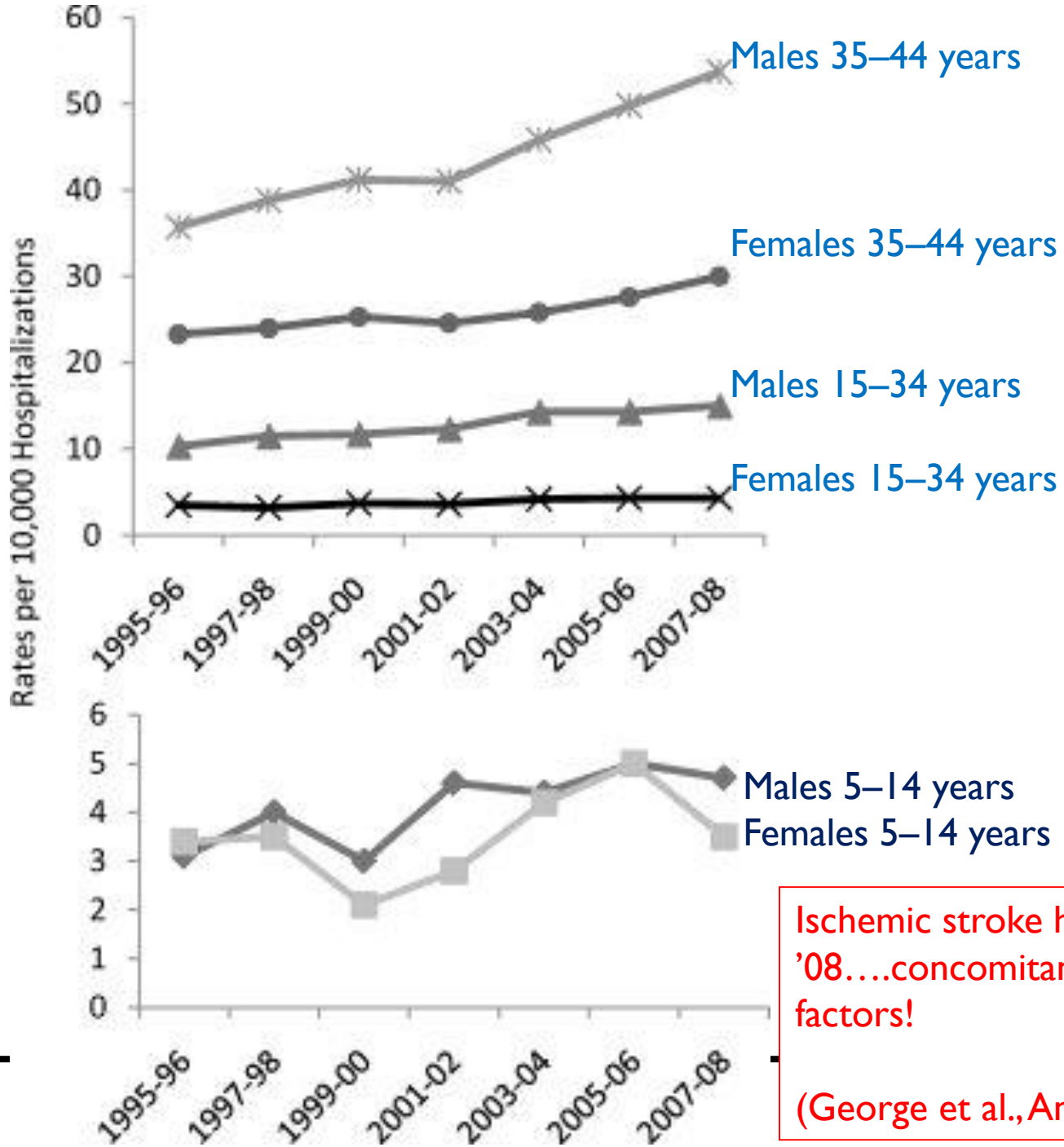
  After 9 years, 32% had modified Rankin score >2

Trends in Stroke Hospitalizations and Associated Risk Factors among Children and Young Adults, 1995–2008

Mary G. George, MD, MSPH, Xin Tong, MPH, Elena V. Kuklina, MD, PhD, and Darwin R. Labarthe, MD, PhD

Objective: The aim of this study was to determine acute stroke hospitalization rates for children and young adults and the prevalence of stroke risk factors among children and young adults hospitalized for acute stroke.
Methods: The study population consisted of 1995–2008 hospitalizations from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project. Subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke hospitalizations were identified by the primary International Classification of Diseases, 9th ed, Clinical Modification (ICD-9-CM) code. Seven consecutive 2-year time intervals were selected. Three age groups were utilized: 5 to 14 years, 15 to 34 years, and 35 to 44 years. Stroke risk factors and comorbidities among those hospitalized with acute stroke were identified by secondary ICD-9-CM codes.
Results: During the period of study, the prevalence of hospitalizations of acute ischemic stroke increased among all age and gender groups except females aged 5 to 14 years. Females aged 15 to 34 years and males and females aged 35 to 44 years showed a decrease in the prevalence of hospitalizations for subarachnoid hemorrhage, whereas females aged 5 to 14 years showed increases for subarachnoid hemorrhage. Hypertension, diabetes, obesity, lipid disorders, and tobacco use were among the most common coexisting conditions, and their prevalence increased from 1995 to 2008 among adolescents and young adults (aged 15–44 years) hospitalized with acute ischemic stroke.
Interpretation: Increases in the prevalence of ischemic stroke hospitalizations and coexisting traditional stroke risk factors and health risk behaviors were identified among acute ischemic stroke hospitalizations in young adults. Our results from national surveillance data accentuate the need for public health initiatives to reduce risk factors for stroke among adolescents and young adults.

ANN NEUROL 2011;70:713–721

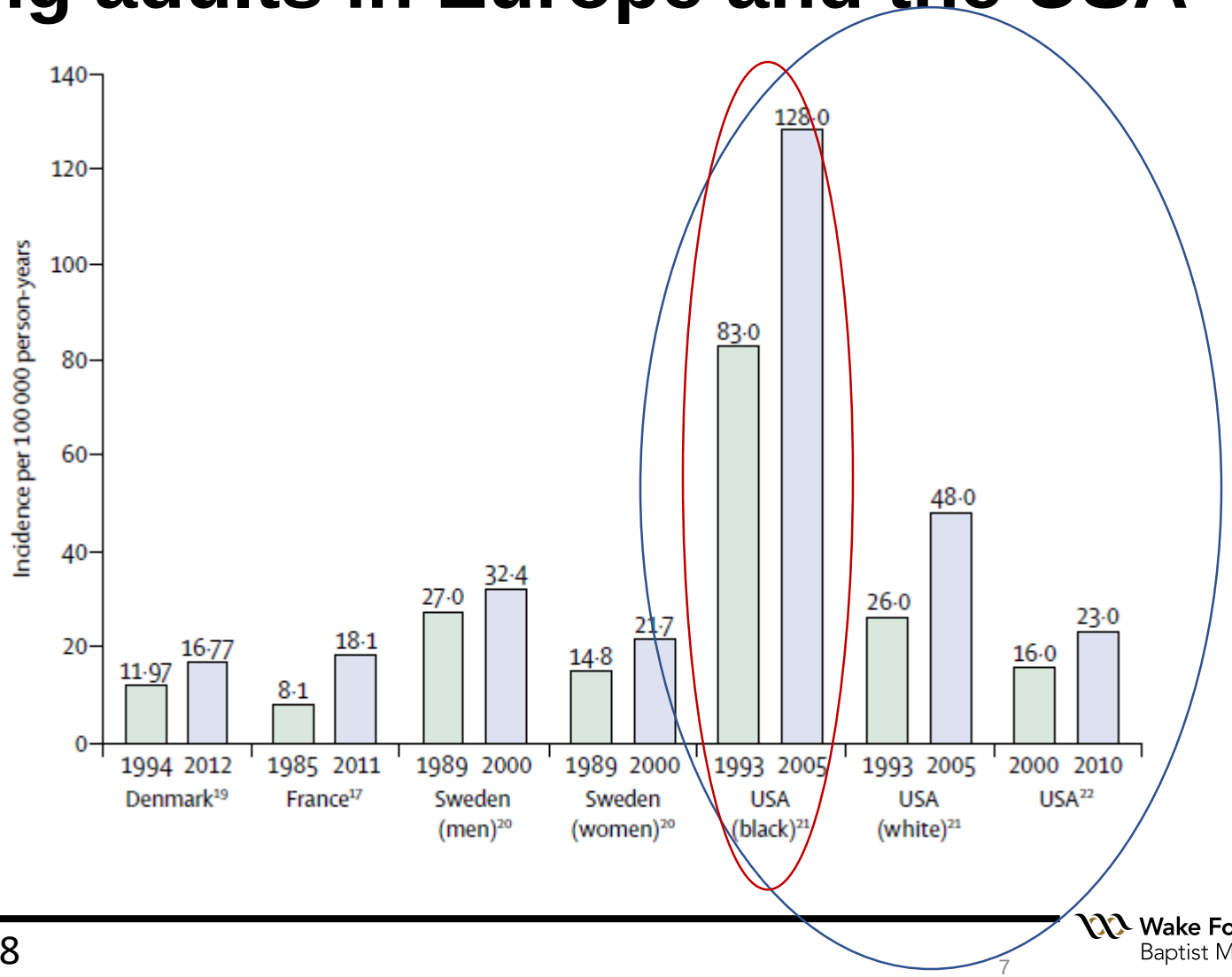


Ischemic stroke hospitalization rates, '95-'08….concomitant increase in vascular risk factors!

(George et al., Ann Neurol 2011)

Increasing incidence of stroke in young adults in Europe and the USA

Highest increase in American Blacks (40%)



Ekker et al. Lancet Neurol 2018

Age at stroke

Temporal trends in stroke incidence in a large, biracial population

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ABSTRACT

Objectives: We describe temporal trends in stroke incidence stratified by age from our population-based stroke epidemiology study. We hypothesized that stroke incidence in younger adults (age 20–54) increased over time, most notably between 1999 and 2005.

Methods: The Greater Cincinnati/Northern Kentucky region includes an estimated population of 1.3 million. Strokes were ascertained in the population between July 1, 1993, and June 30, 1994, and in calendar years 1999 and 2005. Age-, race-, and gender-specific incidence rates with 95% confidence intervals were calculated assuming a Poisson distribution. We tested for differences in age trends over time using a mixed-model approach, with appropriate link functions.

Results: The mean age at stroke significantly decreased from 71.2 years in 1993/1994 to 69.2 years in 2005 ($p < 0.0001$). The proportion of all strokes under age 55 increased from 12.9% in 1993/1994 to 18.6% in 2005. Regression modeling showed a significant change over time ($p = 0.002$), characterized as a shift to younger strokes in 2005 compared with earlier study periods. Stroke incidence rates in those 20–54 years of age were significantly increased in both black and white patients in 2005 compared to earlier periods.

Conclusions: We found trends toward increasing stroke incidence at younger ages. This is of great public health significance because strokes in younger patients carry the potential for greater lifetime burden of disability and because some potential contributors identified for this trend are modifiable. *Neurology*® 2012;79:1781–1787

Analysis of 1008 Consecutive Patients Aged 15 to 49 With First-Ever Ischemic Stroke

The Helsinki Young Stroke Registry

Jukka Putaala, MD; Antti J. Metso, MD, PhD; Tiina M. Metso, MD; Nina Konkola, MD; Yvonn Kraemer, MD; Elena Haapaniemi, MD, PhD; Markku Kaste, MD, PhD; Turgut Tatlisumak, MD, PhD

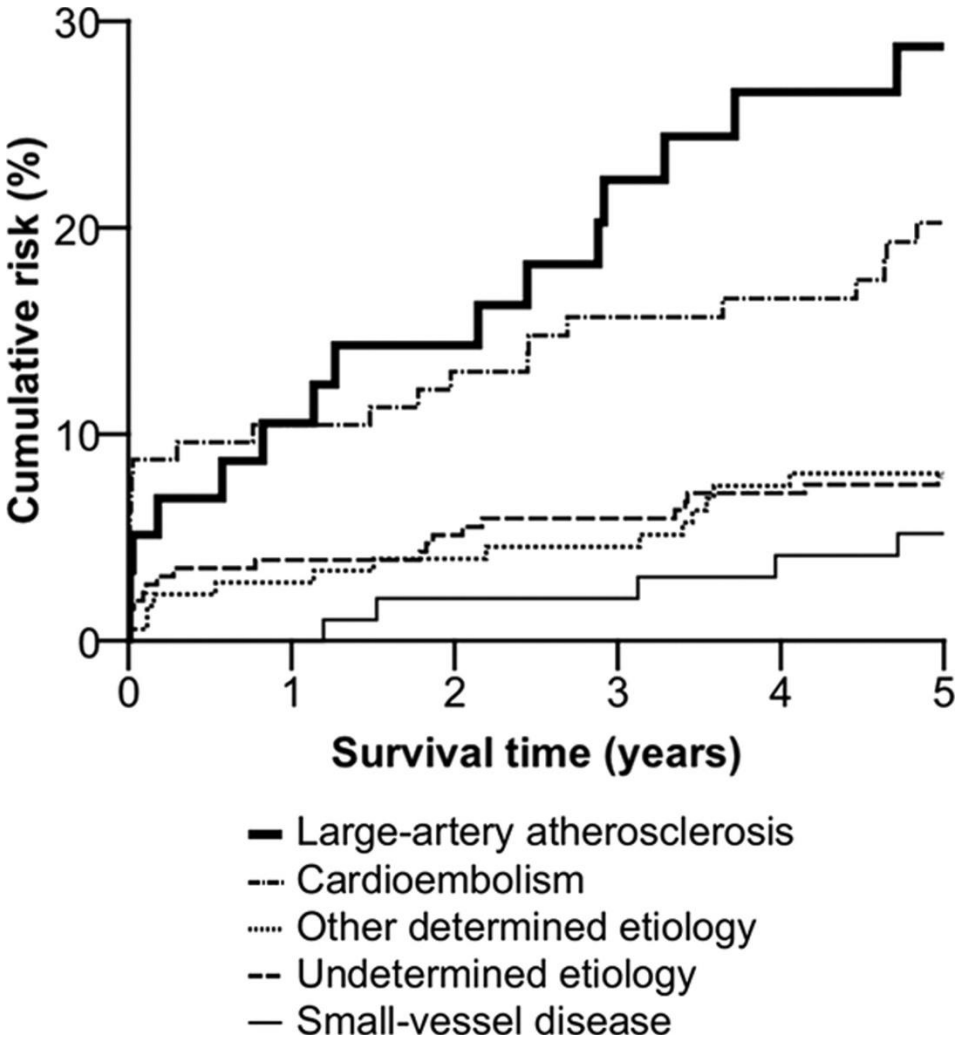
Background and Purpose—To analyze trends in occurrence, risk factors, etiology, and neuroimaging features of ischemic stroke in young adults in a large cohort.

Methods—We evaluated all 1008 consecutive ischemic stroke patients aged 15 to 49 admitted to Helsinki University Central Hospital, 1994 to 2007. Etiology was classified by Trial of Org 10172 in Acute Stroke Treatment criteria. Comparisons were done between groups stratified by gender and age.

Results—Estimated annual occurrence was 10.8/100 000 (range 8.4 to 13.0), increasing exponentially with aging. Of our 628 male and 380 female (ratio 1.7:1) patients, females were preponderant among those <30, whereas male dominance rapidly increased around age of 44. The most frequent risk factors were dyslipidemia (60%), smoking (44%), and hypertension (39%). Males and patients >44 clearly had more risk factors. Cardioembolism (20%) and cervicocerebral artery dissection (15%) were the most frequent etiologic subgroups. Proportions of large-artery atherosclerosis (8%) and small-vessel disease (14%) began to enlarge at age 35, whereas frequency of undetermined etiology (33%) decreased along aging. Posterior circulation infarcts were more common among patients <45 years of age. Left hemisphere infarcts were more frequent in general. There were 235 (23%) patients with multiple and 126 (13%) with silent infarcts, and 55 (5%) patients had leukoaraiosis.

Conclusions—The frequency of ischemic stroke increases sharply at age 40. Etiology and risk factors start resembling those seen in the elderly in early midlife but causes defined in younger patients still are frequent in those aged 45 to 49. Subclinical infarcts were surprisingly common in the young. (***Stroke*. 2009;40:1195-1203.**)

Figure 2. Kaplan-Meier estimates depicting cumulative 5-year mortality risks stratified by etiologic subgroups (log rank P<0.001).



Putaala J et al. Stroke 2009;40:2698-2703

Causes of Stroke in Young Adults (TOAST)

- Large-vessel atherosclerosis (2%-11%)
- Small-vessel disease (7%-14%)
- Cardiac embolism (20%-47%)
- Other determined etiology (20%-34%)
- Multiple etiologies (2%-3%)

- Note: more than 150 identified causes of early onset ischemic stroke exist

Epidemiology, aetiology, and management of ischaemic stroke in young adults

Merel S Ekker, Esther M Boot*, Aneesh B Singhal, Kay Sin Tan, Stephanie Debette, Anil M Tuladhar, Frank-Erik de Leeuw*

- Large artery atherosclerosis
  - Atherosclerotic arteriopathy
- Cardioembolism
  - Atrial fibrillation, cardiac tumors, cardiomyopathy, endocarditis, PFO or atrial septum defect
- Small vessel disease
  - Genetic cerebral small vessel disease, CADASIL
  - Sporadic cerebral small vessel disease

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- Stroke of other determined cause
  - Antiphospholipid syndrome (women:men = 5:1)
  - Autoimmune diseases, i.e. systemic lupus erythematosus (women:men = 9:1)
  - Cervical artery dissection (carotid > vertebral in Europeans; mean age 44 y)
  - Fabry disease (mean age in men 39.8 y; women 45.7 y) clinical features: acroparesthesia, hypohidrosis, angiokeratoma, chronic kidney disease, cardiomyopathy

Epidemiology, aetiology, and management of ischaemic stroke in young adults

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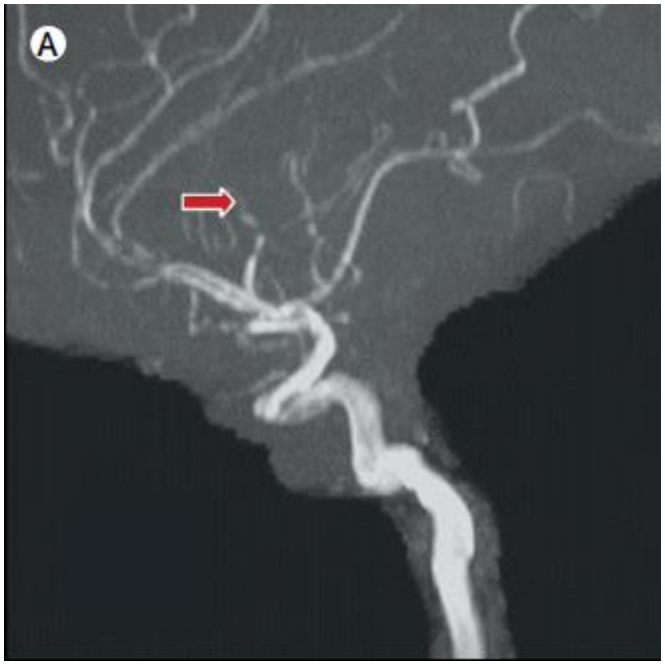
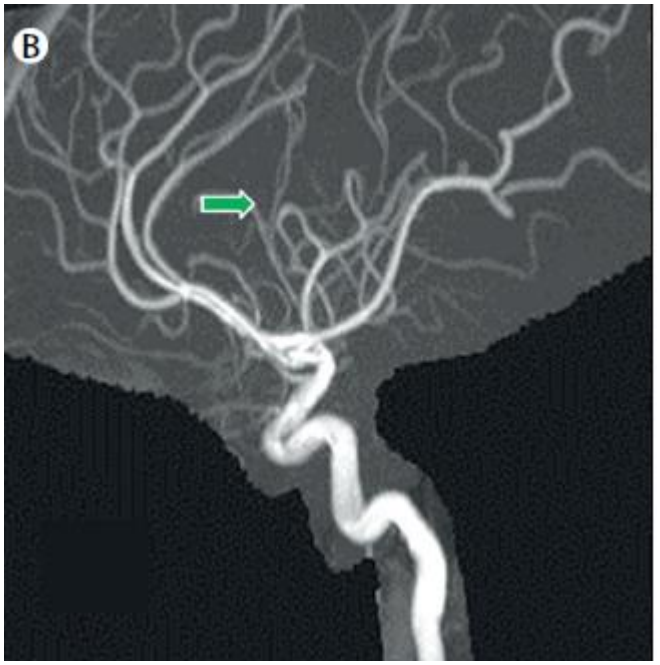
- Factor II deficiency, Factor V Leiden, Protein C or S deficiency
- Illicit drug use
- Intracranial dissection
- Malignancy
- Mitochondrial disorders (MELAS)
- Moyamoya disease
- Post-radiation
- Reversible Cerebral Vasoconstriction Syndrome
- Vasculitis

Arterial imaging: vasculitis or RCVS?





RCVS due to cannabis use in a 41 yo woman with acute severe headache during a bowel movement, followed by recurrent thunderclap headaches

Epidemiology, aetiology, and management of ischaemic stroke in young adults

Merel S Ekker, Esther M Boot*, Aneesh B Singhal, Kay Sin Tan, Stephanie Debette, Anil M Tuladhar, Frank-Erik de Leeuw*

- Stroke of undetermined cause
  - Often younger than 35
  - No cause or attributable risk factor identified after thorough investigations (transesophageal echocardiogram, digital subtraction angiography, hypercoagulable workup)
  - Treat with long-term antiplatelet therapy

Misdiagnosis of acute stroke in young adults

N=57 (age 16-50, 2001-2006)

Misdiagnosis: N=8 (14%)

4 men and 4 women; mean age, 38 years

All 8 initially seen at non-Primary Stroke Centers

Seven initially discharged from the ED

Predictors

- Age <35y (p = 0.05)
- Posterior circulation stroke (P = 0.006)

Early use of **MRI** improves diagnostic accuracy

→ Increasing need for "young stroke awareness“

→ Lost opportunity for thrombolysis

Kuruvilla, et al. J Stroke Cerebrovasc Dis 2011;20:523-7

Clinical Clues

Headache

- Above the eye (carotid artery dissection)
- Recurrent worst-ever headaches (RCVS)
- Chronic headache (CADASIL, CNS vasculitis, Moyamoya)

Stereotyped transient ischemic attacks

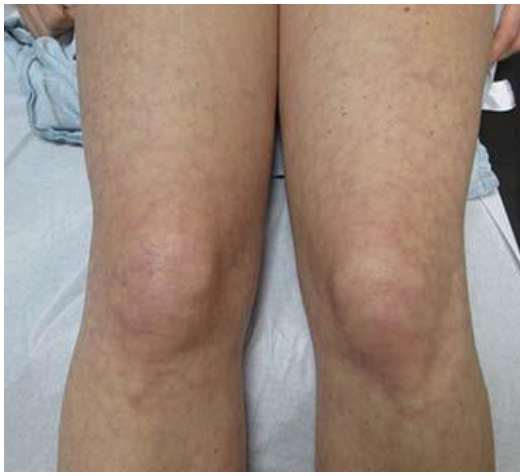
- Fixed arterial stenosis e.g. Moyamoya, premature atherosclerosis, focal arteritis

Clinical setting

- Infection e.g. TB, HIV, Zoster
- Exposure to illicit drugs, vasoconstrictive drugs, pregnancy, chemotherapy (RCVS)
- XRT (radiation associated carotid stenosis)

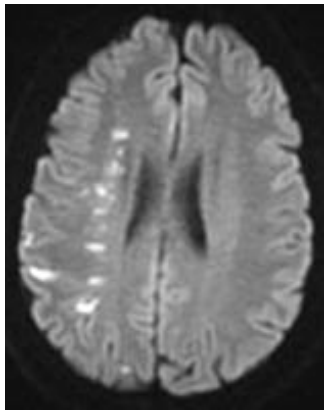
Clinical Clues

- Systemic Examination
  - Arterial pulse: temporal (TA), radial (Takayasu)
  - Skin lesions (Syphilis, neurofibroma, livedo reticularis—Sneddon's syndrome)
  - Rheumatological conditions (SLE, Wegener's)
  - Connective tissue (Marfan's, Ehler Danlos Syndrome)
- Neurological Examination
  - Multifocal brain and spine deficits (vasculitis)
  - Peripheral nerve involvement (Zoster, HIV)
- Eye examination
  - Premature atherosclerosis, Moyamoya, other rare conditions



Laboratory and Imaging Clues

- Blood tests
  - Abnormal toxicology screen
  - Abnormal Rheumatological tests
- Abnormal cerebrospinal fluid examination results
- Brain Imaging: Lesion Patterns
  - string of pearls (MCA stenosis)
  - disseminated infarcts (vasculitis)
  - watershed infarcts with PRES (RCVS)
  - ext capsule and anterior temporal lobe (CADASIL)



Cardiac myxoma on transthoracic echocardiogram in 34 yo woman with basilar thrombosis

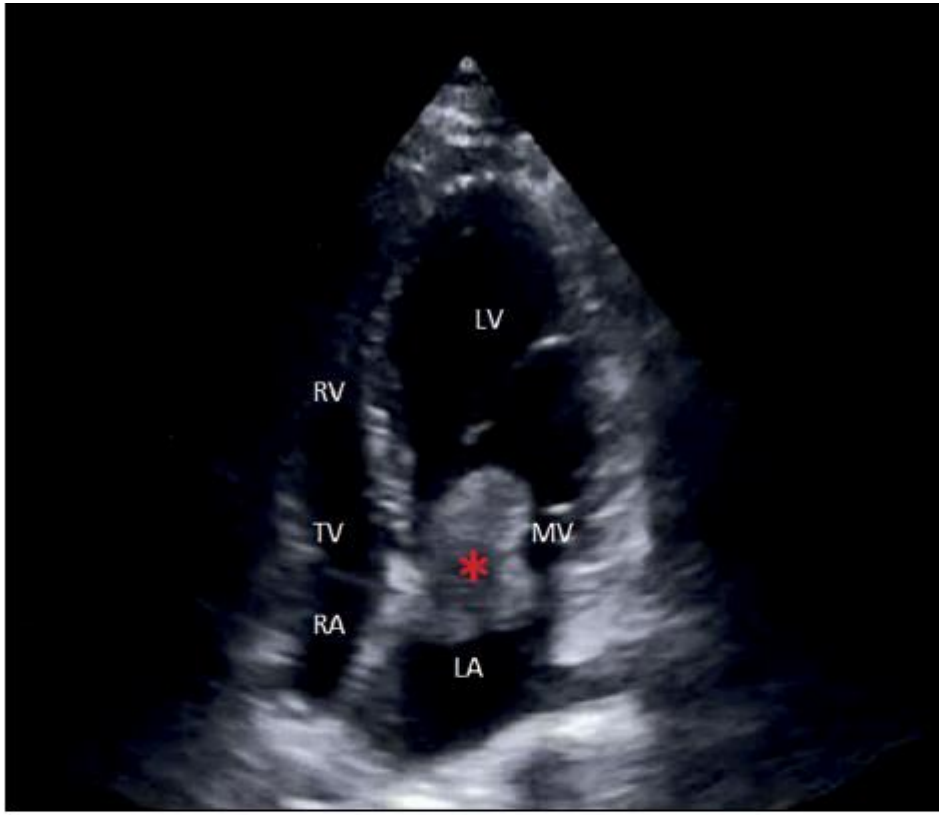


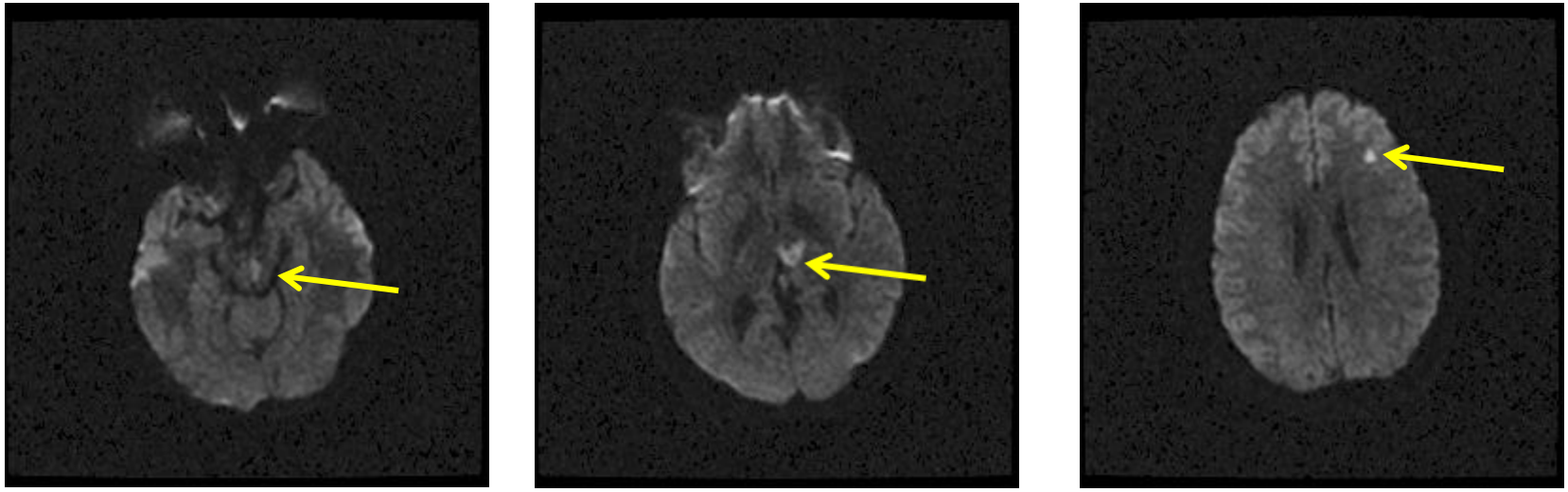
Figure 2: **Basilar thrombosis due to cardiac myxoma**
A 34 year old woman complained of headache, nausea, and vomiting before losing her consciousness during a bus ride. Neurological examination showed a Glasgow Coma Scale Score of 9 out of 15, with deviation of the head to the left and pinpoint pupils, 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 ischaemic lesions in several arterial territories (the left and right cerebellum; the right lateral pons), indicative of a cardioembolic 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. RV=right ventricle. LV=left ventricle. TV=tricuspid valve. MV=mitral valve. RA=right atrium. LA=left atrium.

Ekker et al.
Lancet
Neurol 2018

Case 1

- 35 yo woman, PMHx Pre-eclampsia and vaginal delivery, 3 weeks post-partum
- Acute onset slurred speech and right sided weakness at 20:25 pm. Initial NIHSS 17. CT/CTA showed no acute intracranial hemorrhage and no acute vessel cut-off.
- BP 122/86
- tPA infusion began at 22:38
- Magnesium started for possible post-partum preeclampsia.

Case 1 Stroke workup: MRI and TTE



- MRI brain: multifocal acute/subacute infarcts, different vascular territories
- TTE: Severely dilated left and right ventricle, LVEF 15-20%, and a left ventricular thrombus

Peripartum cardiomyopathy

- Definition:
  - Development of symptomatic heart failure in the last month of pregnancy or within 5 months of delivery
  - Absence of identifiable cause of heart failure
  - Absence of preexisting heart disease prior to the last month of pregnancy
  - Left ventricular systolic dysfunction(EF < 45% and/or fractional shortening <30% on TTE

Peripartum cardiomyopathy

- U.S. 1/1000 to 1/4000 pregnancies
- Nigeria and Haiti: 1/100 to 1/300 pregnancies
- Prognosis: Mortality is 5-15% (higher in Africa)
- 4% of heart transplants performed in U.S.
- Recovery of EF to normal => 50% but high recurrence with subsequent pregnancies
- Pathophysiology: Prolactin (pituitary) and VEGF receptors (placenta) are implicated
    - Association with preeclampsia

Approach to Treatment

- Antiplatelets e.g. aspirin
- Anticoagulants (dissection)
- Steroids, immunosuppressive agents (arteritis)
- Statins (premature atherosclerosis)
- Permissive hypertension to boost perfusion ?
- Treatment of infection, malignancy
- Surgical options: intracranial stenting, balloon angioplasty, revascularization for moya moya

Preventing recurrence after ischemic stroke at young age

Table 3. Prognostic IPSYS Score for the Calculation of the Probability of Recurrent Thrombotic Events After Ischemic Stroke at Young Age

	HR (*P* Value)	β-Coefficient	Score Points
Cumulative risk factor index*	1.21 (0.020)	0.192	0.2
History of MA	1.87 (0.011)	0.626	0.6
Family history of stroke	1.63 (0.003)	0.489	0.5
Circulating antiphospholipid antibodies	2.39 (<0.001)	0.869	0.9
Medication discontinuation†	3.33 (<0.001)	1.202	1.2

HR indicates hazard ratio; and MA, migraine with aura;

*Values ranging from 0 to 0.8 (presence/absence of arterial hypertension, diabetes mellitus, smoking, or hypercholesterolemia).

†Antiplatelets or antihypertensive agents.

Pezzini, et al. Circulation 2014;129:1668-1676

Italian Project on Stroke in Young Adults Study:

-1,867 patients with first-ever ischemic stroke at 18 to 45 yrs followed for 10 years

-**Cumulative risk** of IS, TIA, MI or other arterial events was **14.7%**

-14.0% for brain ischemia

Long-term outcome after stroke/TIA in the young: FUTURE study

	mRS > 2		iADL < 8	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Ischemic stroke[a]	0.8 (0.4–1.6)	0.537	0.6 (0.3–1.1)	0.099
Female sex	2.7 (1.5–5.0)	0.001	2.0 (1.2–3.4)	0.013
Age at baseline	1.0 (1.0–1.1)	0.026	1.0 (1.0–1.1)	0.118
NIHSS at admission (per point increase)	1.2 (1.1–1.2)	<0.001	1.2 (1.1–1.3)	<0.001
Incident stroke	5.7 (2.9–11.2)	<0.001	5.0 (2.6–9.6)	<0.001
Incident cardiovascular disease[b]	1.1 (0.5–2.4)	0.863	1.0 (0.5–2.2)	0.984
Duration of follow-up (years)	1.0 (1.0–1.1)	0.212	1.0 (1.0–1.0)	0.432

[a] TIA patients serve as the reference group

[b] Incident cardiovascular disease: incident cardiac disease and/or peripheral artery disease

Synhaeve, et al. J Neurol 206;264:1099-1105

	Risk factors
Anxiety[110]	Lower educational level, history of depression, unemployment, and alcohol consumption
Central post-stroke pain[111]	Severe infarctions with haemorrhagic transformation
Cognitive impairment[112,113]	Supratentorial infarction
Depression[110]	Lower educational level and unemployment
Mortality[10,34]	Older age (40–50 years), male sex, history of cardioembolic stroke, and coexisting cause of stroke
Post-stroke epilepsy[114]	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[115]	Post-stroke depressive symptoms, anxiety, and recurrent cerebrovascular events
Recurrent stroke[12,34]	Older age (40–50 years), male sex, history of cardiovascular risk factors, atherothrombotic stroke, cardioembolic stroke, and lacunar stroke
Risk of suicide attempts[116,117]	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[118]	Depression and use of angiotensin-converting-enzyme inhibitors
Unemployment[3,119]	Higher NIHSS at admission, a longer duration of follow-up, female sex, self-employment before stroke, and lower occupational status

NIHSS=National Institutes of Health Stroke Scale.

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

Ekker et al. Lancet Neurol 2018

Long-term increased risk of unemployment after young stroke

A long-term follow-up study

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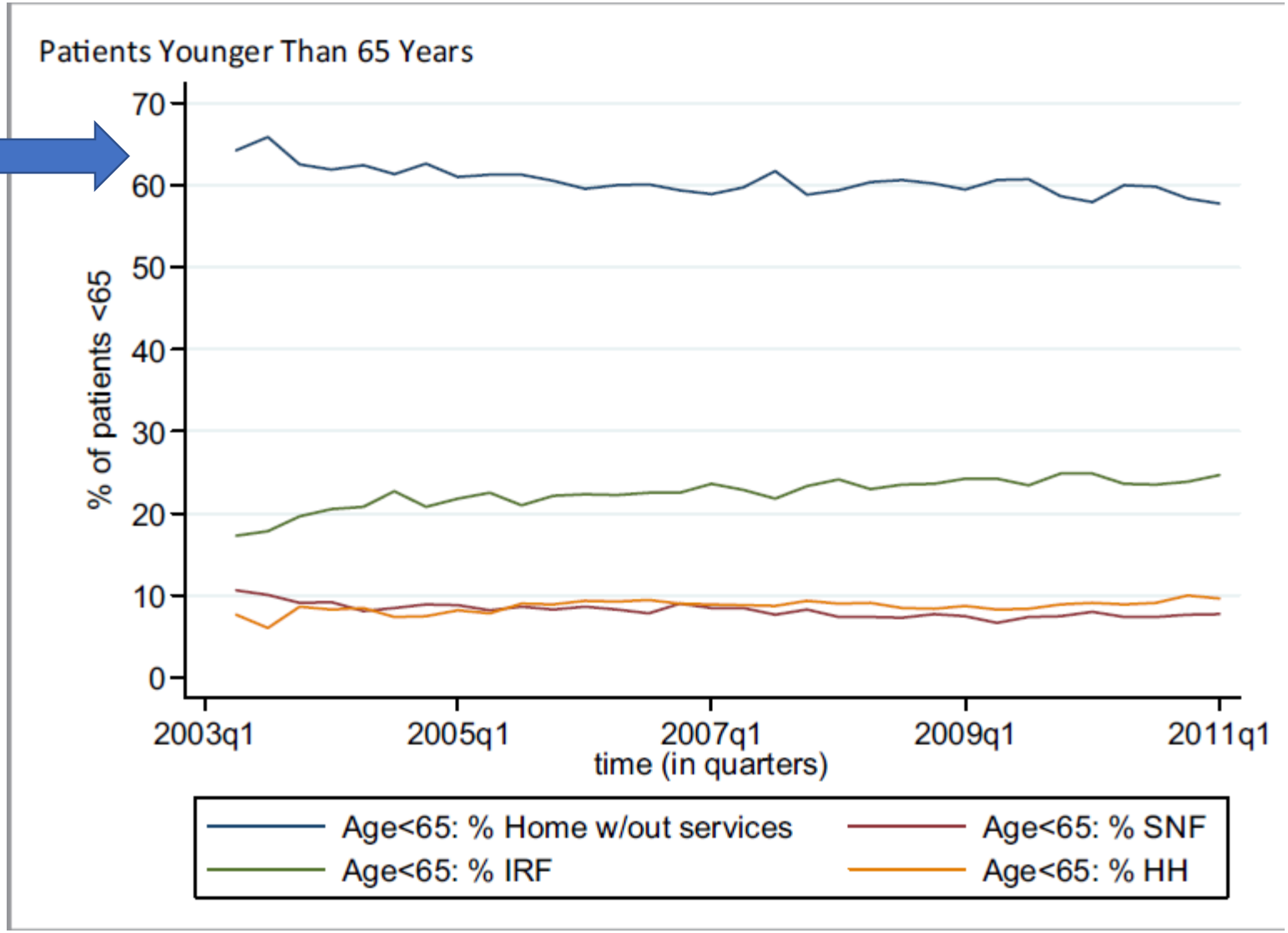
ABSTRACT

Objective: To investigate the prevalence, excess risk, and risk factors of unemployment in patients after a TIA, ischemic stroke, or intracerebral hemorrhage at ages 18 through 50 years, compared with nationwide controls.

Methods: We performed a hospital-based cohort study among 694 patients, aged 18–50 years, with a first-ever TIA, ischemic stroke, or intracerebral hemorrhage. After a mean follow-up duration of 8.1 (SD 7.7) years, we used logistic regression analysis to calculate odds ratio (OR) with 95% confidence interval (CI) for being unemployed as a young stroke patient, compared with the Dutch population of vocational age (n = 7,803,000), with subsequent assessment of risk factors of unemployment.

Results: Young stroke patients had a higher risk of being unemployed than their peers in the Dutch population: women OR 2.3 (1.8–2.9), men OR 3.2 (2.5–4.0). A higher NIH Stroke Scale score at admission (OR 1.1 [95% CI 1.0–1.1]) and a longer follow-up duration (middle tertile OR 2.8 [95% CI 1.7–4.7], upper tertile OR 3.4 [95% CI 1.9–6.1]) were associated with a higher risk of being unemployed.

Conclusion: Young stroke patients had a 2–3 times higher risk of unemployment after 8 years of follow-up. Return-to-work programs should be developed, adjusted, and evaluated in order to diminish the negative effects that unemployment can have on patients' life satisfaction and to limit the socioeconomic consequences. *Neurology*® 2014;83:1132–1138



Prvu Better, JAHA 2015

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Take Home Messages

- Stroke in young adults is increasing worldwide
- The causes of stroke in the young are more diverse and often lead to more diagnostic tests and a wider differential diagnosis list
- The risk of recurrence can be quantified
- Stroke can impact lifespan, employment, disability, quality of life, and the development of other comorbidities

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