REVIEW

Ischaemic stroke in young adults: a global perspective

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ABSTRACT

Ischaemic 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 aetiologies. 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 ischaemic 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 ischaemic strokes occur worldwide each year, of which more than half occurs in low- and middle-income countries.[1] Although the incidence of ischaemic stroke increases with age, an estimated 10% to 20% of these events occur in young people aged 18 to 50 years. This disorder is a major cause of long-term disability and has profound effect on quality of life of patients and caregivers.[2] In contrast to stroke in older adults, the incidence of ischaemic stroke among young adults is rising globally.[3–6]

Ischaemic 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.[1 7 8] Understanding the epidemiology of ischaemic 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 geographical differences in the causes of ischaemic 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 aetiology 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 ischaemic stroke in young adults, emphasising the differences in epidemiology (incidence and prevalence) regarding geography, ethnicity/race and sex. Furthermore, we will review the more traditional vascular risk factors and geographical 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 MedicalSubject Headings) were used in multiple combinations: 'ischemic stroke, young adults, incidence, global, epidemiology, infection, sex differences, race, ethnicity, risk factors, diabetes, hypertension, obesity, dyslipidaemia, physical inactivity, smoking, alcohol consumption, air pollution, causes, dissection, moyamoya, HIV, Chagas, sickle cell disease, neurocysticercosis'. Other rare causes of ischaemic 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 (see online supplementary appendix 1 for a more extensive overview of the search strategy and study selection). 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 AETIOLOGY FROM A GLOBAL PERSPECTIVE

Geographical differences

Incidence of young ischaemic stroke differs considerably worldwide and is generally higher in developing countries than in industrialised countries (figure 1).[1] Published incidence of young stroke varies from 5 to 15 per 100 000 person-years in many European studies to 20 per 100 000 person-years in most Northern-American, Australian and Asian studies and up to 40 per 100 000 person-years in some African countries and Iran.[7 9–11] 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

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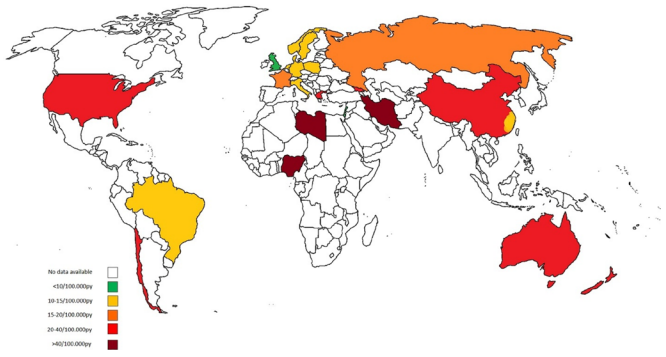

Figure 1 Global differences in incidence of stroke in young adults.[5–7 10–13 84–87] Figure legend: Years of represented incidence rates vary, as do lower (18 or 20) and upper age limits (45-55) in different countries.

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.[3 6 12–14] Aetiological differences by geography have been reported.

Moyamoya disease is a rare, non-atherosclerotic arteriopathy characterised by progressive stenosis of the internal carotid arteries, ultimately leading to occlusion.[15] 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.[15] The highest prevalence is found in Asian countries with 10.5 per 100 000 persons in Japan[16] and 16.1 per 100 000 persons in Korea[17] to 3.92 per 100 000 persons in China.[18] 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),[16] South Korea (2.3 per 100 000 population)[17] and China (0.43 per 100 000 population),[18] while the incidence in Washington and California (0.086 per 100 000 population) is much lower.[19] Exact prevalence and incidence of moyamoya disease in other regions is lacking.

Sickle cell disease is a genetic haematological disorder, caused by the sickle mutation on the haemoglobin gene. The most severe form is homozygous haemoglobin S (HbSS), which is associated with ischaemic stroke.[20] In the USA, the rate of ischaemic stroke in sickle cell disease increased with age and was 740 per 100 000 person years in middle-aged (35 to 64 years) category, which is three-fold higher than in peers.[21] The less severe form is the heterozygous sickle cell trait.[20] 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 ischaemic stroke among African-Americans suggesting that also other mechanisms may contribute.[22] The global distribution of sickle cell disease varies widely.[23] Africa accounts for 75%, followed by Southeast 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.[23]

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 cardioembolic stroke in high-prevalence areas such as Africa, the Middle East and Southeast Asia.[24]

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 cardioembolic stroke. Prevalence of rheumatic heart disease in young ischaemic patients varies from 1.8% to 2.0% in Europe and Northern America to 3.4% to 23.2% in Asia.[25] 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).[26] It can be effectively treated with benznidazole and nifurtimox.[26]

Other infections are also associated with a high risk of ischaemic stroke, including HIV, neurocysticercosis and tuberculosis. HIV has a high prevalence in sub-Saharan Africa with over two-thirds of the world's population.[27 28] 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 ischaemic strokes and stroke patients with HIV often had a coagulopathy and more severe stroke compared with young adults with stroke without HIV.[27] 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[29] and women.[30] Possible mechanisms of stroke in HIV-patients are changes in coagulation state, cardioembolism, HIV-associated vasculitis, HIV-associated vasculopathies and mycotic aneurysms.[31]

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.[32] 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.[32 33] Tuberculosis is associated with increased risk of ischaemic stroke that results from vasculitis or intimal proliferation causing thrombosis.[34] Stroke in tuberculosis occurs in 15% to 57% of patients with tuberculosis meningitis, especially in severe cases. In India, in young stroke patients in up to 8% of patients tuberculosis was the cause.[34] The incidence rates of tuberculosis vary among countries with highest rates in Africa and Asia.[28 34]

The most frequent solitary rare cause of ischaemic stroke in young adults is arterial dissection, which causes up to 15% of all young strokes.[35 36] 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.[37 38]

Racial and ethnic differences

Racial and ethnic variation in incidence and prognosis of stroke in the young are reported.[3 39–43] 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).[39 41]

The disparity in incidence rates between blacks and whites in the USA is highest between the third and fourth decade of age.[40] For both blacks and whites an increasing incidence of stroke in young adults is described over time.[3] In the USA, the length of hospital stay was found longest in Hispanics compared with blacks and whites. In blacks, the hospital stay was longer than in whites.[39 42] This can partially be explained by the higher frequency of medical complications (eg, pneumonia, deep venous thrombosis or urinary tract infections) among Afro-Americans compared with Caucasian-Americans.[42] Afro-Americans were more likely to be discharged to a rehabilitation facility, skilled nursing facility or a long-term-care hospital compared with Caucasian-Americans.[42] Also, mortality was found to be higher in blacks compared with whites. Hispanics have a lower early mortality risk.[39 41] An international multicentre study evaluated young stroke patients from prospective databases of North America, Europe and Asia and described differences in hospitalisation, functional outcome and mortality.[43] This study found that Asians (median National Institute of Health Stroke Scale (NIHSS) score of 8 (IQR: 5 to 14)) had significantly higher stroke severity at admission than blacks (median NIHSS score of 7 (IQR: 3 to 12)) and whites (median NIHSS score of 3 (IQR: 1 to 9) ($p<0.001$)).[43] In addition, early mortality was found to be lower in Asians compared with blacks and whites.[43] 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 ischaemic 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.[44]

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.[6 35 45 46] In contrast, the incidence rates were similar between both sexes in France (18 to 55 years),[13] and in Spain, the incidence was higher among men (18 to 54 years).[47] In Chinese adults (aged 20 to 49 years), there were no statistically differences in the age-standardised prevalence of ischaemic stroke between men and women.[48] 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,[45 49] whereas there is a higher increase of stroke incidence in men >35 years.[49] Regarding outcome after stroke, higher mortality-rates and a higher risk for recurrent vascular events were found in men compared with women.[50]

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 autoimmune disorders among women. According to the Trial of ORG 10 172 in Acute Stroke Treatment criteria, male predominance is mostly found in large artery disease and small vessel disease, whereas female predominance was found in other determined aetiology.[51] Smoking and diabetes mellitus type 1 were associated with ischaemic stroke in both men and women. The associations with ischaemic stroke and 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-densitylipoprotein cholesterol were significant only among men in a recent Finnish study.[52] (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.[53]

VASCULAR RISK FACTORS FROM GLOBAL PERSPECTIVE

While the prevalence of certain risk factors is declining in the general population (eg, smoking), the prevalence of the modifiable vascular risk factors (including hypertension, smoking, dyslipidaemia, diabetes and obesity) is increasing among young stroke patients (figure 2).[3 4 35 54] Young stroke patients have approximately twice as many risk factors compared with their peers.[54] Furthermore, the prevalence of having multiple risk factors is increasing.[36 54 55] The risk of future vascular events increases equally with the number of risk factors.[56] The increase in vascular risk factors seems to be more pronounced in the population aged 35 years and older than in the younger population.[3 6 35 57] 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[52] and the other with controls surveyed over telephone.[53] 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.[52–54] These continents are included in large cohort studies

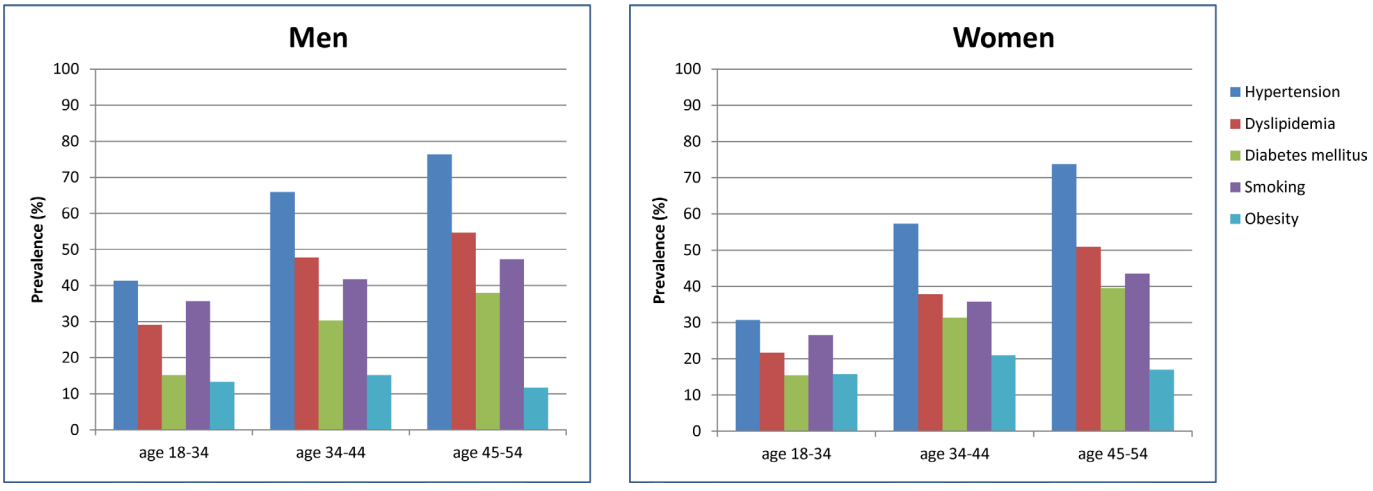

Figure 2 Prevalence of traditional vascular risk factors in young patients stratified by age and sex. Data adapted from Rolfs *et al.*

Table 1 Modifiable risk factors and their risk of ischaemic stroke

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

*Data adapted from Kivioja *et al*[52]
†Data adapted from Aigner *et al*[53]
PAR, population attributable risk.

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.[58–60] 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 ischaemic stroke patients is uncertain, as these studies did not investigate ischaemic stroke, stratified by age 18 to 50 years (ie, 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 ischaemic stroke nor continent specific.[58–60]

Hypertension

Approximately 35% of young ischaemic stroke patients were diagnosed with hypertension.[13 35 46 53] 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%).[8] The Stroke in Young Fabry Patients (SIFAP) study showed that hypertension was the most important individual risk factor for ischaemic 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).[52 53] Lower risks were found in a Finnish young stroke study with a PAR of 12.2% (95% CI 5.9 to 17.4) and OR of 1.43 (95% CI 1.17 to 1.75).[52] 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%).[61]

Diabetes

Diabetes mellitus is found in up to 10% of young stroke patients.[13 35 46 53] The PAR for diabetes mellitus in young adults is 4.8% (95% CI 2.9 to 6.7) and diabetes mellitus is associated with higher risk of stroke (OR=1.9; 95% CI 1.5 to 2.3).[53] More disturbingly, the incidence of type 2 diabetes in young adults is increasing.[35] Global differences are seen in the prevalence of diabetes. The top three countries with the highest prevalence include India, China and the USA.[62] The PAR for diabetes mellitus was highest in Southeast Asia (28.6%) and lowest in Western Europe, North-America and Australia (3.5%).[8] 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%).[63 64] 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.[63] Although there are no differences in the prevalence of diabetes type 2 between men and women,[65] the risk of stroke is found higher in women (HR 2.8; 95% CI 2.4 to 3.4) than in men (HR 2.2; 95% CI 1.8 to 2.5).[66]

There is also geographical variation in the diabetes subtypes attributed to ischaemic 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),[67] with a 4.6% prevalence among young patients with ischaemic stroke,[52] and is lowest in China and Venezuela (0.1 per 100 000 person years).[67] Adjusted OR for type 1 diabetes in Finland was 6.7 (95% CI 3.2 to 14.3), which was almost three-fold higher than for type 2 diabetes (OR=2.8, 95% CI 1.7 to 4.6). Notably, the association of type 1 diabetes was stronger for women than for men.[52]

Dyslipidaemia

About 50% to 60% of young stroke patients have dyslipidaemia, which is slightly more common in men than in women.[35 46] The prevalence of lipid disorders in young adults increases.[54] Dyslipidaemia is more often found in patients with large artery disease or small vessel disease, and is less common in ischaemic stroke caused by cardiac embolism.[55] Dyslipidaemia in young adults is not significantly associated with the risk of all-cause stroke (PAR of −2.1%; 95% CI −6.7 to 2.6 and OR=0.9; 95% CI 0.8 to 1.1).[53] This might be explained by the many other causes of stroke in young adults, for which dyslipidaemia might not be a risk factor. Contrary, in stroke due to large artery disease or small vessel disease, dyslipidaemia 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 dyslipidaemia is found not to be a significant contributor to the risk of early-onset ischaemic stroke might be that most studies defined dyslipidaemia as either a high low-densitylipoprotein cholesterol or low high-densitylipoprotein 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 apolipoprotein B (ApoB)/apolipoprotein A-I (ApoA-I) (ApoB/ApoA-I) ratio was highly associated with ischaemic stroke (OR=4.03; 95% CI 1.62 to 10.03).[68] 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.[69]

The general global prevalence of dyslipidaemia 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.[70] Data from Florida, showed a higher prevalence of dyslipidaemia in whites than in Hispanics and blacks (21.0% vs 17.1% and 17%, respectively; p<0.0001).[39]

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 to 2 years).[35 46] Smoking contributes to stroke in young adults (PAR of 19.9%; 95% CI 14.8 to 23.9 and OR 1.78; 95% CI 1.50 to 2.11).[52] In addition, over the last decade smoking is more frequently seen in

Table 2 Key global differences and gaps regarding epidemiology, risk factors and aetiology of stroke in young adults

	Important findings	Missing evidence
Global	► Incidence of young stroke is rising ► Prevalence of the modifiable vascular risk factors among young stroke patients is rising	► PAR studies specific in young stroke patients
North-America	► Highest prevalence (61.1%) of obesity (not young stroke specific)[78 79]Higher incidence of stroke among young blacks and Hispanics (11/100 000 py) compared with whites (7/100 000 py)[39 41] ► Higher young stroke mortality in blacks than in whites[39 41]	► Uncertain incidence of moyamoya disease
South and Central America	► Low prevalence of diabetes type 1 (not young stroke specific)[67] ► Infectious causes of stroke including neurocysticercosis prevalent[33] ► Lowest prevalence of hypertension globally together with North-America (35%)[61]	► Missing information about risk factors (including PAR studies)
Europe	► Increasing incidence over the last decade in many countries[6] ► Extracranial artery dissections more common than intracranial dissections compared with Asia[37 38] ► Highest prevalence of dyslipidaemia (54%)[70]	► 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 (46%)[61] ► Highest prevalence (75%) of sickle cell disease[23] ► Young adults with ischaemic stroke often have HIV in sub-Saharan Africa[27] ► Lowest prevalence of dyslipidaemia globally with 22.6%[70]	► Unknown incidence in >90% of countries. ► No information about specific causes like dissection
Asia	► Highest incidence of moyamoya disease (16.1/100 000 py Korea, 10.5/100 000 py Japan)[16 17] ► Intracranial artery dissections more common than extracranial dissections[37 38] ► Higher stroke severity (NIHSS 8) in Asians compared with blacks and whites (NIHSS 7 and 3)[43] ► PAR of hypertension for stroke in general globally highest with 54.8%[8]	► Unknown incidence of stroke in young adults for many Asian countries
Australia	► Relatively high incidence of stroke in young adults with 20-30/100 000 py compared with other developed countries[7] ► Young Aboriginal people have higher incidence of ischaemic stroke compared with non-Aboriginals[44]	► Few specific continent-specific causes

PAR, population attributable risks; py, person-years.

young adults.[54 55] A stronger dose-response relationship between smoking and the risk of ischaemic stroke is found for both men and women at young age compared with older adults.[71 72] 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.[59] The prevalence of daily smoking was higher in men (25%; 95% CI 24.2 to 25.7) than in women (5.4%; 95% CI 5.1 to 5.7).[73] A higher prevalence of smoking was found in countries located mainly in Central and Eastern Europe and South Asia.[73] For women, significantly higher prevalence was mainly found in counties in Western and Central Europe.[73] Furthermore, higher prevalence of smoking (30.6% vs 18.5%) was found in whites compared with blacks.[39]

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.[35] 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.[74] 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%).[65] Waist circumference predicts the risk of developing metabolic syndrome, a condition associated with an increased risk of cardiovascular disease and diabetes mellitus type 2.[75] A high childhood BMI was associated with an increased risk of ischaemic 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.[76] Obesity in young adults was associated with a higher risk of stroke (PAR of 6.9% (95% CI 0.0 to 13.8 and OR 1.2; 95% CI 1.5 to 2.3).[53] 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.[76 77] 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 with Africa (26.9%), Western Pacific (25.4%) and Southeast Asia (13.7%),[78 79] and obesity is more often seen in woman than in men.[78 80] Hospitalisation 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).[39]

Physical inactivity is associated with obesity and worse cardiovascular risk profile, increasing the risk of stroke (PAR 59.8; 95% CI 56.2 to 63.4 and OR 5.9; 95% CI 5.1 to 6.7).[53] Among teenagers, lower physical activity is seen in girls than in boys.[78]

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 to 20.5 and OR=2.2; 95% CI 1.9 to 2.5) in European countries.[53] In all continents, alcohol consumption was associated with an increased risk of ischaemic stroke in general (though not assessed for young adults specifically).[59] 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 with low-income countries. Furthermore, episodic heavy alcohol consumption is higher among men compared with women.[59]

Air pollution

Air pollution is an emerging global risk factor for stroke. Rapid economic development leads to major changes to air quality due increased energy demands, urbanisation, transportation and

widespread industrialisation.[81] 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).[8] Geographical differences are also seen in stroke-related mortality due to 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%.[82] 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 to 1.20) compared with patients >65 years (OR=1.00; 95% CI 0.96 to 1.03). Higher risk was found in patients living within 75 m from a main road (OR=1.26; 95% CI 1.04 to 1.51)).[83] 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 ischaemic 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 (ie, industrialisation and urbanisation 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-specific and country-specific risk factors. The important epidemiological differences and differences in exposure of risk factors stretch the need for region-specific programmes 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 programmes can be developed, more extensive research in a well-defined young stroke population is needed with larger numbers and well-defined risk factors. Characterising the regional differences with regard to epidemiology and aetiology is currently not possible, 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 ischaemic stroke in young adults.

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Appendix 1: Flowchart of search strategy and study selection