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The Growing Problem of Stroke among Young Adults

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Abstract

Although overall stroke incidence has been declining in developed countries, there is evidence that stroke in the young is increasing. Increasing incidence may be particularly pronounced among minorities in whom historically a higher burden of stroke has been reported. Compared with older adults, time spent with disability is longer for those affected at younger ages, and new data suggests that among 30-day young adult stroke survivors, increased mortality persists for as long as 20 years. Stroke in young adults is often missed by less experienced clinicians due to its unexpectedness, leading to lost opportunities for intervention. The causes and risk factors for stroke in the young are often rare or undetermined, but young adults with stroke also have a high burden of traditional cardiovascular risk factors, including hypertension, diabetes, obesity, and substance abuse. Disseminating awareness and promoting research on young adult stroke are steps towards reducing the burden of stroke.

Keywords

Young adult; Stroke; Risk factors; Mortality; Prevention

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Introduction

Cardiovascular disease prevention efforts to reduce hyperlipidemia, hypertension, and smoking have contributed to the decline in stroke incidence in developed countries [1–4]. Despite these improvements, a high burden of disability and death from cardiovascular disease and stroke remains [5••]. There is evidence, in particular, that stroke in young adults is increasing [6•]. While there is no uniform definition of "young stroke," strokes occurring in those after adolescence and before the age of 50 are typically considered as occurring in young adults. We reviewed the literature published since 2011 to identify new reports regarding incidence, risk factors, and outcomes of stroke in the young. In addition to summarizing the literature (Table 1), we discuss general limitations in the data and implications for recognition and management of stroke in young adults.

Incidence Trends

Age Differences

Stroke incidence increases with age. Recent analyses of temporal trends in stroke incidence from long-term observational studies, however, provide evidence that incidence among younger adults is increasing. In a retrospective analysis of the population-based Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), the proportion of incident stroke occurring among 20–54 year-olds increased at each of 3 1-year time intervals over 13 years: from 12.9 % in 1993/1994, to 13.3 % in 1999, and to 18.6 % in 2005 [6•]. In the US Nationwide Inpatient Sample among patients 14–44 years old ischemic stroke admissions increased from 1995–2008. From 1995–1996 to 2007–2008, per 10,000 hospitalizations, an admitting diagnosis of ischemic stroke increased from 3.2 (SE 0.4) to 4.2 (SE 0.6) among children 5–14 years old; from 5.0 (SE 0.2) to 6.5 (SE 0.2) among patients 15–34 years old; and from 28.2 (SE 0.6) to 38.6 (SE 0.9) among young adults 35–44 years old [7•]. In New Jersey, childhood stroke incidence increased in 2007 after a nadir in 1999, from approximately 0.8 to 1.2 per 100,000 children [8].

Other data do not support an increase in stroke rates outside the US. Stroke incidence and mortality decreased from 1995 to 2005–2006, in Joinville, Brazil, among adults <75 years, including young adults [relative incidence 0.59 (0.42–0.84)] [4]. In The Netherlands, there was a rapid decline in ischemic stroke mortality after 2000 for all age-sex categories, except for young men where the decline was less rapid [9].

An important limitation in these analyses of stroke incidence trends relates to changes in diagnostic imaging. Stroke diagnosis and etiologic classification have historically been clinically based. With the adoption and widespread implementation of magnetic resonance imaging (MRI), stroke definitions have changed. The revised definition for ischemic stroke requires the presence of clinical symptoms of a stroke and evidence of tissue ischemia [10••]. MRI is much more sensitive than CT for ischemic changes, and so it is likely that many patients currently diagnosed with small infarcts on MRI would have been missed in the era limited to CT. In the GCNKSS, 18 % of patients received an MRI in 1993/1994, 27 % in 1999, and 58 % in 2005, and the proportion receiving MRI varied by age, with younger patients more likely to receive MRI in 2005. Changes in stroke incidence may thus

be strongly influenced by the evolution of diagnostic technology. Future study in other populations is needed to corroborate these findings and elucidate whether changing trends are a US or global phenomenon.

Sex Differences

Sex differences in stroke incidence vary by age with increasing male predominance at older ages. In IBERICTUS, a study of stroke and transient ischemic attack incidence in Spain, for example, stroke incidence in 2006 was approximately equal for men and women 18–34 years old but was more than twice as high for men compared with women aged 45–54 years. Among 18–24 year olds the incidence rate was, per 100,000 persons, 2.6 for men, and 2.7 for women; among 25–34 years olds 12 for men and 12 for women; among 35–44 year olds 50 for men and 29 for women; and among 45–54 year olds 110 for men and 39 for women [11]. The European 15 Cities Young Ischemic Stroke Registry reported higher stroke incidence among women compared with men at 18–34 years with a reverse trend at 35–49 years [12].

Racial Disparities

Increasing stroke incidence in the young may be especially marked among minorities. Racial disparities in stroke incidence among young adults have been found in a number of cohorts, including in the United States [13–16]. The GCNKSS stroke incidence was consistently higher in blacks than in whites in 1993/1994, 1999, and 2005. The incidence rates for first-ever stroke per 100,000 population increased among those 20–54 years, from 1993/1994 to 2005, from 26 (95 % CI 22–31) to 48 (95 % CI 42–53) in whites, and from 83 (95 % CI 64–101) to 128 (95 % CI 106–149) in blacks [6•].

Outcomes

Morbidity

The prognosis among young stroke patients tends to be better than among older patients. In a registry from a single tertiary stroke center in Boston participating in the Get with the Guidelines- Stroke program, 81 % of young adult patients (18–45 years) had a good outcome based on a modified Rankin score (mRS) of 0–2 at hospital discharge [17•]. In the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), functional independence (mRS 0–2) among 18–50 year olds was 72.1 % compared with 54.5 % among 51–80 year olds [$OR_{adjusted}$ 1.61 (95 % confidence interval 1.43–1.80)]. Predictors of functional independence at 3 months were younger age, lower baseline systolic blood pressure, and no previous stroke [18]. In the Helsinki Young Stroke Registry, predictors of an unfavorable 3-month outcome (mRS 2–6) were greater age, higher NIHSS, large volume stroke, bilateral strokes, and internal carotid artery dissection [19].

From another perspective, the long -term burden of disability after stroke is high among young adults. Indirect costs are estimated to be more than 6 times higher for adults <65 years compared with adults ≥65 years due to the higher lifetime earnings value [1]. In a subcohort (n =697) of the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study, 11.3 % of young adults with a first-

ever TIA, ischemic stroke, or intracranial hemorrhage (ICH) developed epilepsy during a mean follow-up of 9.1 years. Ongoing seizures were seen in 5.6 % and the risk of seizures was higher if the initial seizure was later, if there was a stroke compared with a TIA, and for higher NIHSS [20].

Mortality

Short-term mortality after a stroke increases with age. In the IBERICTUS study, the annual mortality rate after a first-ever stroke or TIA, per 100,000 population, was 5.1 for 35–44 year-olds and 8.7 for 45–54 year olds [11]. After thrombolysis, 3-month mortality in SITS-ISTR was 4.9 % in young adults (18–50 years) compared with 14.4 % in older adults (51–80 years) [$OR_{adjusted}$ 0.49 (95 % CI 0.40–0.60)] [18].

Despite relatively low early mortality, the risk of death after a young adult stroke may not taper with time. Among 30-day stroke survivors, the FUTURE cohort found a higher 20-year mortality rate compared with expected mortality in the under-lying population. The standardized mortality ratio was 2.6 (95 % CI 1.8–3.7) for TIA, 3.9 (95 % CI 3.2–4.7) for ischemic stroke, and 3.9 (95 % CI 1.9–7.2) for ICH [21•]. The data showed a U-shaped mortality curve reflecting a high mortality in the first year following a TIA or ischemic stroke and a second high risk period at ~5–6 years. This could be due to a failure to adequately address the original causes of the first stroke or to lifestyle risk factors that remain uncontrolled with aging [22]. Mortality was more pronounced among young adults in some populations. The Northern Sweden, MONICA Stroke Registry (1985–2005) showed that young age was associated with reduced survival among diabetic stroke patients [23].

Mortality differences by sex may vary by the time period from the index stroke. Regarding in-hospital mortality, in the IBERICTUS stroke study, there was no sex difference. Among 35- to 44-year-olds, 6 % (95 % CI 0–12.8) of men and 3.4 % (95 % CI 0–10.2) of women died, and among 45–54 year olds 7.3 % (95 % CI 2.2–12.3) of men and 12.8 % (95 % CI 1.6–24.1) of women died [11]. Regarding long-term mortality, the FUTURE cohort's 20-year mortality data showed higher mortality for men (33.7 %, 95 % CI 26.1–41.3) than women (19.8 %, 95 % CI 13.8–25.9) [21•].

Predictors of Poor Outcome

Predictors of mortality and a poor functional outcome among young adult stroke survivors may differ from predictors in older stroke patients. Predictors of 3-month mortality among 18–50 year olds in SITS-ISTR were baseline serum glucose, male sex, higher NIHSS score, early CT signs, and atrial fibrillation [18]. An indicator of kidney disease, low estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2), and to a lesser extent, high eGFR (>125 mL/min/1.73 m^2), an indicator of early kidney disease, both predicted long-term mortality in the Helsinki Young Stroke Registry [24]. High HDL cholesterol also predicted a favorable outcome in this registry [19]. On the other hand, in the Vienna Stroke Registry traditional stroke risk factors were associated with long-term mortality among adults >50, but were not associated with mortality in adults <50 years [25].

Stroke Etiologies and Risk Factors (Table 2)

Stroke etiologies may differ among young compared with older adults. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) categorization of ischemic stroke is the most widely used system. Five categories convey an etiologic classification: (1) large-artery atherosclerosis (LAA), (2) cardioembolism (CE), (3) small-vessel occlusion (lacune), (4) stroke of other determined etiology (for example, arterial dissection or vasculitis), and (5) stroke of undetermined etiology [26].

Traditional Etiologies

In addition to other determined and undetermined etiologies, traditional stroke etiologies (ie, cardioembolic, atherosclerotic, and lacunar) are increasingly recognized in the young. Investigators from both US and international cohorts have reported more frequent traditional classifications compared with other determined and undetermined etiologies [17•, 18]. A high proportion of traditional classifications among young adults may be due to a similarly high prevalence of traditional stroke risk factors, such as hypertension, diabetes, smoking, obesity, and dyslipidemia. In the SITS-ISTR registry current smoking was twice as common in participants 18–50 years (42.7 %) than in participants 51–80 years (22.8 %) [18]. The high prevalence of traditional risk factors is apparent even among adolescents. A cardiovascular health study of US adolescents (NHANES 2005–2010) showed that approximately one-third of those 12–19 years had a body mass index ≥85th percentile, and had tried smoking in the previous 30 days. Blood pressure ≥90th percentile was seen in 22 % of males and 10 % of females. Only 44 % of females and 67 % of males had at least 60 minutes per week of moderate activity, and <1 % of the sample was consuming a healthy diet according to dietary recommendations [27].

Traditional stroke risk factors are also increasingly recognized among children with stroke. Hypertension was a predisposing condition in 10 %–11 % of children with ischemic stroke in New Jersey (1994–2007) [8]. In the US Nationwide Inpatient Sample, among adolescents and young adults (15–44 years), the prevalence of hypertension, diabetes, obesity, lipid disorders, and tobacco use increased from 1995–1996 to 2007–2008 [7•].

Echoing stroke incidence differences by age, sex and race, a higher prevalence of risk factors has been reported in higher risk demographic subgroups. The prevalence of traditional ischemic stroke risk factors increased with age in the Stroke in Young Fabry Patients cohort [28]. Men were more likely to have a history of dyslipidemia, coronary heart disease, and smoking, compared with women, in the 15 Cities Young Stroke Study [12]. Young adult men were also more likely than women to have dyslipidemia in the MGH Get with the Guidelines-Stroke database [17•]. High risk alcohol consumption [>5 alcoholic drinks/day (ie, >50–70 g pure alcohol/d) at least once per month within the previous year] was more frequent in men, but women were more often physically inactive and had a higher proportion of abdominal obesity (73 % vs 64 %) in the Stroke in Young Fabry Patients cohort [28].

Racial disparities in stroke incidence are thought to be due largely to a high prevalence of risk factors. In the GCNKSS, abuse of substances (tobacco, alcohol, or illegal drugs) was more frequently reported in blacks compared with whites (61 % vs 51 %) [29]. In NHANES,

minority adolescents were more commonly overweight or obese, and reported lesser amounts of physical activity [27].

The proportion of young adults with traditional stroke risk factors may be expanding with time. The trend for increasing stroke incidence among young adults seen in the GCNKSS was related to a similar increase in the prevalence of stroke risk factors. From 1993 to 2005 coronary heart disease increased from 2.5 % to 12.0 % [6•]. The US has seen a rise in the prevalence of obesity and diabetes across the population. Based on the high prevalence of overweight US adolescents in 2000, the prevalence of obese 35-years-olds is projected to increase substantially over the next 3 decades, with an estimated 100, 000 excess cases of coronary heart disease due to obesity [30]. Internationally, obesity nearly doubled between 1980 and 2008 [31]. The prevalence of overweight among children (2–19 years) in the US increased between 1976–1980 and 1988–1994, and between 1988–1994 and 1999–2000, and among boys between 1999–2000 and 2009–2010 [32, 33]. The prevalence of obesity in the US may have stabilized, according to NHANES data, but the estimates remain rather high and the population at risk continues to increase [34]. Where obesity is defined as a BMI greater than or equal to the 95th-percentile standardized by age and sex, in NHANES (2007–2008) the prevalence was 32.2 % among men, 35.5 % among women, and 16.9 % among children (2–19 years) [35, 36].

Obesity is a strong predictor of type 2 diabetes. In the Framingham Heart Study, compared with the 1970s, the likelihood of diabetes in the 1980s was 1.40 (0.89–2.22) and in the 1990s was 2.05 (1.33–3.14) [37]. The US Behavioral Risk Factor Surveillance System in 2001 found that compared with the year 2000, the prevalence of diabetes increased by 8.2 % in 2001 [38].

Other Determined and Undetermined Etiologies

Compared with older adults, young adults are more likely to have a stroke of other determined etiology or an undetermined etiology. In the South Korean Yonsei Stroke Registry, among adults with a stroke of other determined etiology, the mean age was 20 years lower (mean ± SD, 46.6±16.2) than the mean age for CE, LAA, lacunar stroke, and stroke of undetermined etiology [39]. In a correspondence about the Cerrahpasa Stroke Registry from Istanbul, Turkey, the mean age of patients with an undetermined etiology was also lower (59.6+13.2) than among patients with any other stroke etiology(63.0+13.4 years; P <0.001) [40].

Stroke due to other determined etiology encompasses what are sometimes considered rare causes of stroke, though in young adults they are not rare. This includes arterial dissection, other arteriopathies, inherited hypercoagulable traits, acquired hypercoagulable states, migraine, and illicit drug use. Other arteriopathies includes moyamoya disease, fibromuscular dysplasia (FMD), cerebral angiitis, postpartum angiopathy, radiation arteriopathy, and thrombosed vascular malformation. While a discussion of all these causes of stroke is beyond the scope of this review, comments about some of the most important of these entities follows.

Arterial Dissection

Arterial dissection may account for 10 %–25 % of ischemic stroke in young adults [41–43]. Dissection can occur intracranially, or extracranially in the carotid or vertebral arteries. There is increasing data that spontaneous cervical artery dissection (sCAD) is associated with more diffuse arterial changes than only in the artery affected. In one study, superficial temporal artery biopsy in all 14 young adults (31–62 years) with sCAD showed pathologic adventitial and medial vacuolar degeneration with capillary neoangiogenesis and erythrocyte extravasation compared with only 1 who had similar pathologic changes of 9 control subjects [44]. Among patients with a connective tissue disorder, the extent of vertebral artery tortuosity was linearly associated with a younger age at arterial dissection [45]. Vascular complications were common in the US national FMD registry (n =447): 19 % had a TIA or stroke, 20 % had a history of arterial dissection, and 17 % had aneurysm(s) [46].

Moyamoya Disease

Moyamoya disease is a progressive condition with stenosis of the supraclinoid internal carotid arteries with compensatory development of small vessel collateral vasculature, and often the involvement of proximal branches of the internal carotid arteries. When Moyamoya disease occurs with a recognized associated condition (such as neurofibromatosis type 1 or sickle cell anemia), the condition is referred to as Moyamoya syndrome [47]. Bimodal peaks in Moyamoya disease incidence have been found in Asian populations. Among Chinese patients (n =802) surgically treated for Moyamoya disease at one institution, the incidence of symptomatic moyamoya disease peaked at 5–9 years and again at 25–44 years [48].

Hypercoagulable Traits

Hypercoagulable states associated with stroke may be either inherited or acquired. A meta-analysis of inherited hypercoagulable traits in studies on pediatric stroke showed a higher likelihood for protein C deficiency [OR 8.76 (4.53–16.96)]; antithrombin III deficiency [OR 7.06(2.44–22.42)]; antiphospholipid antibodies [OR 6.95(3.67–13.14)]; elevated lipoprotein(a) [OR 6.27(4.52–8.69)]; factor V Leiden [OR 3.26 (2.59–4.10)]; protein S deficiency [OR 3.20(1.22–8.40)]; factor II G20210A mutation [OR 2.43(1.67–3.51)]; and MTHFR C677T mutation [OR 1.58(1.20–2.08)], among children with stroke compared with healthy children [49•]. One single center registry found abnormalities on a hypercoagulable panel in 15.9 % of 189 young adult participants who underwent testing [17•]. The Genetics of Early Onset Stroke (GEOS) case-control study in adults (15–49 years) found a similar frequency of the factor V Leiden between ischemic stroke patients [3.6 % (2.5–5.1)] and non-stroke controls [3.8 % (2.7–5.2)] [50]. A hypercoagulable state is present in late pregnancy and postpartum, and may contribute to the increased peripartum risk of stroke, though precisely how this occurs remains unknown.

Migraine

The 2-fold increased risk of ischemic stroke among those who experience migraines seems to be related to the presence of an aura [51]. The mechanism of this association remains unclear [52]. A migraine transformed into an ischemic stroke is rare. A meta-analysis of

cardiovascular disease-related mortality among patients with any form of migraine did not find an increased risk. This meta-analysis was limited by high hetero-geneity between studies [53].

Substance Abuse

Sympathomimetic drugs such as amphetamine, cocaine, and crack may contribute to ischemia through hypertensive, platelet aggregation, and other vascular effects. Compared with non-cocaine related ischemic stroke patients, patients with cocaine-related ischemic stroke from 3 academic hospitals were on average 10 years younger; were more likely to have cardiac arrhythmias (25.0 % vs 8.6 %), including sinus bradycardia (n =6), sinus tachycardia (n =1), supraventricular tachycardia (n =1), and atrial fibrillation (n =1); and had similar discharge and 3-month disability [54]. The MGH registry for young adults, Vienna Stroke Registry and GNKCSS reported illicit drug use in 7 %–19.8 % of participants [6•, 17•, 25]. From 1993 to 2005 in GNKCSS, reported use of illegal drugs increased from 3.8 % to 19.8 % [29].

Hormonal Contraceptives

Hormonal contraceptive use may increase the risks of arterial and venous thrombosis. Among the Danish female population (1995–2009) the relative risk of thrombotic stroke was higher among users of low-dose estrogen–progestin oral contraceptives with different progestins (range RR 1.3–2.3), a vaginal ring [RR 2.5 (1.4–4.4)], and transdermal patch [RR 3.2(0.8–12.6)], compared with non-users [55•]. Despite this increased relative risk of stroke, there were few strokes and on an individual level, the overall risk was low. Increased events attributable to hormonal contraception was only 1–2 per 10,000 [56].

Possible Cardioembolic Mechanism, Including Patent Foramen Ovale

Cardioembolic stroke may be due to an inherited or acquired cardiomyopathy, developmental valvular abnormalities, a neo-plasm such as fibroelastoma or a patent foramen ovale (PFO). In the MGH registry, 17 % of young adults had a cardioembolic stroke associated with a PFO [17•]. Recent evidence from a multi-center collaborative effort, the Risk of Paradoxical Embolism (RoPE) project, also suggests that certain neuroimaging features of stroke are associated with the presence of a PFO. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were unapparent, smaller, or deep strokes, and those accompanied by chronic infarcts [57•]. In addition, the RoPE project provides evidence that a simple scoring system can be used to identify those patients with unexplained stroke in whom a PFO is most likely to be found. Variables negatively associated with a PFO in patients with unexplained stroke included age, diabetes, hypertension, smoking, prior stroke or TIA, and absence of a cortical stroke on neuroimaging. The 10-point RoPE score includes a point for each of the 5 non-age factors and 1 point for roughly each full decade over age 18 (up to 5 points). The prevalence of PFO increased from 23 % in those with score 0–3 to 73 % in those with 9–10 points. The risk of recurrent stroke, however, is lowest in those who are most likely to have PFOs: 2-year recurrence rates decreased from 20 % in the lowest RoPE score stratum to 2 % in the highest [58•].

Recently completed randomized clinical trials continue to show no definitive evidence of benefit for closure of PFO over medical therapy for secondary stroke prevention. RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Standard of Care Treatment), and the PC trial (Clinical Trial Comparing Percutaneous closure of PFO Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) were published in 2013. RESPECT randomized patients (18–60 years) with a cryptogenic stroke and a PFO to closure or medical therapy [59•]. After an average follow-up of 2.6 years there were a total of 25 recurrent strokes with a 51 % risk reduction in the closure group with similar adverse event rate, but the difference was not statistically significant [HR with closure 0.49 (95 % CI, 0.22–1.11)]. The study may have been underpowered. The PC trial included a wider age range (pediatric-<60 years) and a broader definition for a thrombotic event: ischemic stroke, TIA, or peripheral thromboembolism. After an average of 4.1 years, 18 patients had an outcome event with a hazard ratio of 0.63(95 % CI 0.24–1.62) for closure vs medical therapy. Again, this trial may have been underpowered [60•]. Further studies are ongoing.

Venous Thrombosis

Cerebral venous thrombosis (CVT) is a relatively rare cause of stroke, but occurs more often among young adults. In the ISCVT (International Study on Cerebral Venous and Dural Sinuses Thrombosis) adult registry, the mean age was 37 years. Risk factors such as pregnancy, oral contraceptives, and thrombophilia overlap with rare causes of arterial stroke. The diagnosis can be elusive because the most common presenting symptoms are nonspecific: headache, papilledema, and seizure. In ISCVT hemiparesis was a presenting sign in only one third of patients [61]. An algorithm for the management of suspected CVT is available in a recent AHA/ASA scientific statement [62].

Thrombolysis in Young Adults

Thrombolysis may be more safely implemented in the younger adult. In the MGH registry, from 2005–2010, 29 young adult participants received thrombolysis. Of these, 55 % had good outcome (mRS 0–2) at hospital discharge and none developed symptomatic brain hemorrhage [17•]. In SITS-ISTR symptomatic intracerebral hemorrhage occurred in 0.6 % of 18–50 year-olds and 1.9 % of 51–80 year-olds [18].

Importance of Recognizing Stroke and its Risk Factors in the Young

Health-related quality of life may be reduced among long-term young stroke survivors. After a mean follow-up of 6 years, Norwegian young adults (15–49 years) with ischemic stroke reported lower physical functioning, general health, and social functioning on a Short-Form General Health Survey, compared with age-matched healthy controls [63]. Timely diagnosis of stroke in young adults is challenged by the infrequent occurrence of stroke and the not infrequent presence of competing causes of neurologic symptoms in young adults. At one institution, over a 5-year period, 47 % of patients with a missed cerebellar infarction were <50 years old [64]. Age <35 years was a predictor for acute stroke misdiagnosis in another hospital series [65].

Stroke awareness can improve diagnostic accuracy and implementation of acute stroke treatment. At one institution, among participants (16–50 years) in their Young Stroke registry, initial presentation to a hospital without neurology residents was associated with an approximately 3 times higher likelihood of stroke misdiagnosis compared with presentation to a hospital with neurology residents, and the likelihood of receiving acute stroke treatment was similarly more than 3 times higher for presentation to a hospital with, compared with or without, neurology residents [66].

Early education can favorably impact stroke risk factors, such as blood pressure and low-density lipoprotein cholesterol values, and early markers of atherosclerotic disease in children and adolescents [67, 68]. In the Finnish prospective Special Turku Coronary Risk Factor Intervention Project for Children study, children were randomized to receive biannual dietary counseling from randomization at 7 months of age through 20 years of age. Adolescents in the standard medical care arm had fewer ideal cardiovascular health metrics compared with the intervention arm at 15, 17, and 19 years of age. Fewer ideal cardiovascular health metrics (≤3) was associated with a nearly 2-fold increased risk of high aortic intima-media thickness (>85th percentile) [1.78 (95 % CI 1.31–2.43)], a marker of atherosclerosis [69].

Strengths and Limitations

Data on stroke in young adults only rarely comes from large established stroke cohorts. Data from only 2 of the cohorts reported here are population-based [6•, 11]. The remaining 7 are registry cohorts or patient series, and these are by design not representative of a population. Enrollment in series is by the initiative of investigators and subject to variability in enrollment practice between sites. Five of these cohorts are hospital based registries subject to referral and ascertainment biases [12, 17•, 18, 21•, 25]. Two cohorts originated from a single university tertiary care center [17•, 21•]. Data from such cohorts should only be generalized with caution. Findings from European cohorts with primarily Caucasian participants similarly may not be applicable to other ethnically diverse populations.

Stroke classification/etiology is determined by a clinician’s synthesis of the relevant and available data. Classifications are unlikely to be fully objective, and the cause remains difficult to determine with certainty in most cases. An incomplete evaluation would impose even further difficulty assigning an etiology and incomplete evaluations are expected in a voluntary registry and with a retrospective medical record review. Prospective cohorts with long study intervals will have an additional information bias related to changes in the availability and accuracy of diagnostic testing over the course of a study period.

Self-reported variables such as smoking, excessive alcohol intake and illicit drug use are subject to recall and reporter biases. The functional outcome data that was available for 3 studies was generated from hospital records and based on modified Rankin scores [17•, 18, 19]. In 2 of these studies a good functional outcome was an mRS of 0–2, where 2 refers to a slight handicap, and in the third study a poor functional outcome was an mRS of 2–6. A patient with a mRS of 2 is able to perform activities of daily living but is limited in his/her ability to carry out all former activities. The 5-point scale may oversimplify outcome and

does not account for perceived changes in quality of life. The inconsistency even in the interpretation of this simple scale in the 3 studies cited here further highlights the subjectivity in the definition of a good functional outcome.

Conclusions

The identification of demographic, racial and lifestyle risk factors for young stroke incidence, morbidity, and mortality are steps towards improving health in the young adult population. Many prevalent risk factors are modifiable through lifestyle changes and/or medical therapy. Organizations have begun to disseminate awareness and encourage research in this area. The 2020 Impact Goals of the AHA Strategic Planning Task Force has a new broad perspective on stroke prevention with early implementation of heart healthy behavior [70]. The American Academy of Neurology (AAN) has established a Young Adult Stroke Awareness and Education Fund. Continued study of incidence trends, racial disparities, risk factors, and treatment will result in improved clinical care. Many of the young stroke cohorts discussed here are ongoing studies. This includes the Genetics of Early Onset Stroke (GEOS) Study, a part of the Gene Environment Association Studies initiative (GENEVA). The goal of GEOS is to identify genes and explore gene-environment interactions as risk factors for young adult ischemic stroke. Continued attention and research should facilitate public education, improved access to preventative care, and ultimately, the prevention of young adult stroke.

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2020 Impact Goals: “to improve cardiovascular health and reduce cardiovascular diseases and stroke by 20% in all Americans”.

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Table 1

Summary of study cohorts

Study	Cohort	Region	Study period	Full cohort (*n* =)	Young adult age range	Young adults (*n* =)	Stroke subtypes
Rutten-Jacobs et al. [21•]	FUTURE (Follow-up of transient ischemic attack and stroke patients and unelucidated risk factor evaluation)	Netherlands	1/1980–- 11/2010	959	18–50	959	IS, TIA, ICH
Diaz-Guzman et al. [11]	Spanish IBERICTUS study	Spain	2006	2700	>17–54	256	IS, TIA, ICH, undetermined
Putaala et al. [12]	15 Cities Young Stroke study	Europe	1988–2010	3944	15–49	3944	IS
Putaala et al. [24]	Helsinki Young Stroke Registry	Finland	1/1994–5/2007	1008	15–49	958	IS
Toni et al. [18]	SITS-ISTR (safe implementation of thrombolysis in stroke-international stroke thrombolysis register)	international	2002–2010	27,671	18–50	3246	Acute IS + thrombolysis
Ji et al. [17•]	Get with the guidelines-stroke (database at Mass General hospital)	Boston, USA	2005–2010	2643	18–45	215	IS, TIA
Greisenegger et al. [25]	Vienna Stroke Registry	Austria	10/1998 -–2/2001	661	18 <50	249	IS, TIA
Kissela et al. [6•]	Greater Cincinnati/Northern Kentucky Stroke study (GCNKSS)	USA	1993–94 1999, 2005	1942, 2034, 1916	20–54	227, 303, 393	IS, ICH, SAH
von Sarnowski et al. [28]	Stroke in Young Fabry Patients cohort	Europe	4/2007–1/2010	4467	18–55	4467	IS, TIA

ICH intracerebral hemorrhage, *IS* ischemic stroke, *SAH* subarachnoid hemorrhage, *TIA* transient ischemic attack

Table 2

Stroke classifications and risk factors by cohort

	FUTURE (21•]	Helsinki Young Stroke Registry [24]	SITS-ISTR [18]	Get with the Guidelines-Stroke (MGH) [17•]	Vienna Stroke Registry [25][a]	15 Cities Young Stroke Study [12]	GCNKSS[b] [6•, 29]	Stroke in Young Fabry Patients cohort [28]
TOAST etiology (%)								
LAA	12.4 (+15.0 likely LAA)	7.5	23.2	2.0	8.8	-	-	-
CE	11.4	20.6	22.3	47.0	18.5	-	-	-
lacune	12.7	13.6	10.4	7.0	14.5	-	-	-
Other	17.7	26.3	14.5	34.0	9.2	-	-	-
Undetermined	28.1	32.0	17.1	8.0 (1 % incomplete evaluation)	43.0	-	-	-
Risk factor (%)								
HTN	28.0	38.4	27.1	20.0	35.0	35.9	52.2	46.6
DLD	-	59.5	20.6	38.0	28.0	45.8	18.2	34.9
DM	6.6	6.1	5.8	11.0	11.0	8.0	19.6	10.3
smoking	57.3	44.7	42.7	34.0	60.0	48.7	52.0	55.5
obesity	-	10.4	-	-	-	-	43.8	22.3
Excess alcohol	7.6	14.5	-	-	12.0	-	15.0	33.0
Illicit drug use	-	-	-	12.0	7.0	-	19.8	-
physical inactivity	-	-	-	-	-	-	-	48.2
PFO	-	-	-	17.0	-	-	-	-
AF	1.5	4.4	4.6	-	2.0	3.7	-	2.4
migraine	-	-	-	-	22.0	-	-	26.5

-=not available

TOAST subtypes *AF* atrial fibrillation, *CE* cardioembolism, *DLD* dyslipidemia, *DM* diabetes mellitus, *LAA* large-artery atherosclerosis, *Lacune* small-vessel occlusion, *Other* stroke of other determined etiology, *Undetermined* stroke of undetermined etiology

Risk factors *HTN* hypertension, *PFO* patent foramen ovale

[a]Combined for participants deceased and alive

[b]2005 estimates