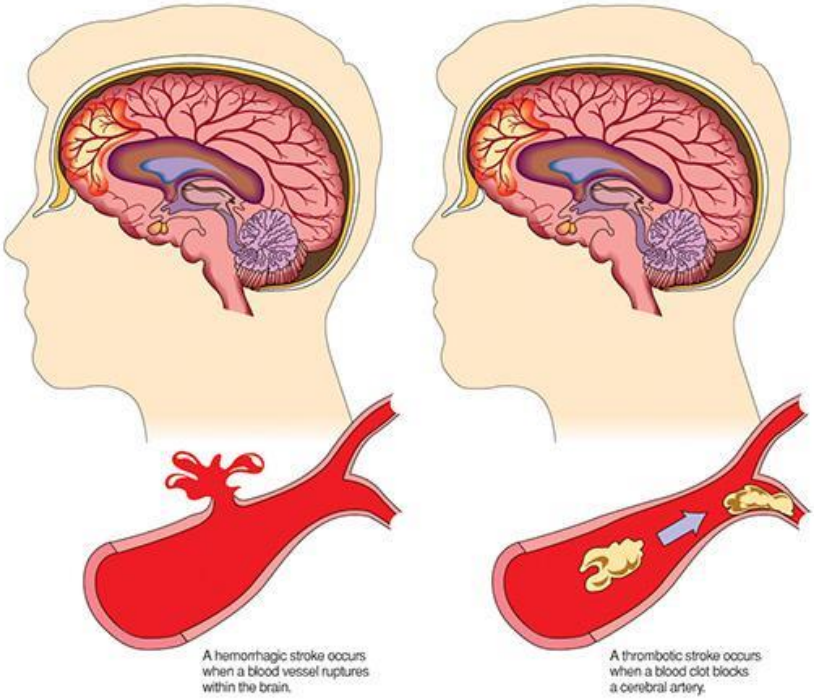
Stroke

Stroke is a brain injury caused by an interruption in blood flow to brain tissue due to a blocked or burst artery. It is also called a cerebral vascular accident (CVA) or brain attack.



A hemorrhagic stroke (left) compared to a thrombotic stroke (right).

Illustration by Hans & Cassady, Inc. © Cengage Learning®.

Description

Arterial blood carries oxygen and nutrients to all cells of the body, including the brain. When arteries are unable to carry out this function due to constriction, obstruction, or rupture, the cells nourished by those arteries die. Thus, stroke can cause brain death or significant disability, including paralysis, speech difficulties, and mental and emotional problems. More than 2,400 years ago the ancient Greek physician Hippocrates described stroke as the sudden onset of paralysis.

Types of stroke

According to the American Heart Association, there are two types of stroke: ischemic and hemorrhagic. An ischemic stroke—accounting for about 87% of all strokes—occurs when blood supply is cut off to a portion of the brain. Ischemic stroke caused by a blocked artery can cause the

Comment [1]: away from the heart, so usually O2-rich

Comment [2]: blood supply is cut off to the brain

Comment [3]: can be either thrombotic or embolic

death of two million brain cells every minute. There are two types of ischemic stroke—thrombotic or cerebral thrombosis and embolic or cerebral embolism.

Cerebral thrombosis accounts for 40–50% of all strokes. As people age, atherosclerosis or hardening of the arteries occurs through the buildup of waxy, cholesterol-laden plaque that eventually narrows the interior of the arteries. This process can occlude or shut off the blood supply. Transient ischemic attacks (TIAs), or mini-strokes, are caused by the blockage of a very small artery or arteriole or the intermittent or temporary obstruction of a larger artery. TIAs usually last only minutes and affect only small areas of brain tissue, generally without noticeable permanent effects. However, TIAs are a warning signal for a possible future thrombotic (cerebral thrombosis) stroke.

Cerebral embolism accounts for 25–30% of all strokes. An embolic stroke occurs when a blood clot moves through the circulatory system to block an artery, usually in the brain but occasionally an artery in the neck, especially the carotid artery.

Approximately 20% of strokes are hemorrhagic. Hemorrhagic strokes occur when a thin, weak spot in an artery in the brain balloons outward, producing an aneurysm that can burst, causing bleeding (hemorrhaging) in the brain. Two types of weakened arteries most often cause an hemorrhagic stroke: aneurysms and arteriovenous malformations (AVMs). The most common cause of hemorrhagic stroke is high blood pressure, what is medically called hypertension.

Risk factors

The biggest risk factor for thrombotic stroke is age, since the incidence of atherosclerosis and high blood pressure increase with age. Strokes also appear to run in families. This may be because of an inherited susceptibility toward high blood pressure and diabetes—two of the major risk factors for stroke—or because of lifestyle risk factors within families. More than 9% of adult Americans have diabetes, and studies have found that adults with diabetes were more likely to suffer ischemic stroke. The Greater Cincinnati/Northern Kentucky stroke study found higher incidences of ischemic stroke across all age groups for people with diabetes; however, the risk was much higher for African Americans before the age of 55 years and for white Americans before the age of 65 years. Higher rates of high blood pressure, diabetes, and smoking among African Americans may account for their higher stroke risk. Sickle cell disease, an inherited disorder that affects African Americans, is also a risk factor for stroke. Other stroke risk factors are:

- diets high in cholesterol or fatty foods
- smoking, which doubles the risk of ischemic stroke
- obesity
- heart disease
- TIAs or previous stroke
- oral contraceptives or hormone replacement therapy
- polycythemia—excess red blood cells
- sleep apnea

The risk factors in adults for hemorrhagic stroke are conditions that can weaken arteries supplying blood to the brain. These include high blood pressure, which can cause aneurysms, and hereditary malformations. Abuse of substances such as cocaine or amphetamines and chronic alcoholism can also weaken blood vessels and result in hemorrhagic stroke.

Risk factors for stroke in children include the following:

- congenital malformations of blood vessels or other structures in the brain
- brain infections such as encephalitis or meningitis
- head trauma

Comment [4]: bc of age-related atherosclerosis

Comment [5]: TIA (mini-strokes) are an example of cerebral thrombosis strokes

Comment [6]: when a blood clot moves the arteries and blocks part of the brain or carotid artery.. (pulmonary embolism socks DVT)

Comment [7]: most hemorrhagic strokes occur because of hypertension

Comment [8]: why so important to take care of such problems

Comment [9]: age, genetic (high BP, diabetes)

Comment [10]: would be interesting to look into why there is a higher incidence of ischemic stroke there.... future assessment or maybe original work

- blood disorders, especially sickle cell disease

The American Stroke Association reported in 2016 that, generally, for all types of strokes African Americans are most likely of all racial groups in the United States to suffer from strokes.

Comment [11]: can look into why they are more predisposed to strokes

Demographics

Stroke is the second most common cause of death worldwide, according to the World Health Organization, and the most common cause of early disability. In the United States, stroke is the fifth leading cause of death, based on statistics from the Centers for Disease Control and Prevention, and the leading cause of neurological disability, with approximately 795,000 new stroke patients annually and about three million Americans permanently disabled from stroke. Approximately 600,000 of these annual strokes are first attacks, while the rest are recurrent ones. Stroke is a leading cause of long-term disability in the country. Further, approximately 130,000 Americans die annually from stroke; accounting for one in every 20 deaths in the United States.

Comment [12]: for people who get a 2nd stroke... more dangerous

A stroke can strike anyone at any age, including fetuses in the womb. However, the risk of stroke doubles with each decade over the age of 55 years, and two-thirds of all strokes occur in people over 65, who are also seven times more likely to die from stroke. High blood pressure (also called hypertension) is the largest risk factor for stroke. Men are at higher risk for stroke than women, but more women die from stroke, probably because they tend to have strokes at an older age. Strokes in children are rare: 6.4 cases per 100,000 children (between the ages of 0 to 15 years) per year in North America, with about half of these being hemorrhagic strokes, and approximately one-third within newborns.

African Americans have almost double the incidence of stroke as white Americans, and twice as many die from stroke. Although Asian Americans have rates of stroke and stroke mortality similar to white Americans, Asians in the Far East have significantly higher rates.

Comment [13]: why asians and african americans more susceptible

A so-called stroke belt in the southeastern United States has been recognized for decades, and its high rate of stroke mortality cannot be accounted for solely by the higher percentage of African Americans or lower overall socioeconomic status. In particular, North Carolina, South Carolina, and Georgia have up to twice the stroke mortality rates as the country does as a whole.

Comment [14]: look up!!

Causes and symptoms

Causes

A thrombotic stroke is caused by a blood clot or thrombus—often resulting from atherosclerosis—blocking blood flow in the brain. Cerebral thrombosis occurs most often at night or early in the morning and is often preceded by a TIA.

Comment [15]: why does it occur more often in the night or early morning?

An embolic stroke occurs when a blood clot from elsewhere in the circulatory system breaks free and becomes lodged in an artery supplying the brain. The most common cause of cerebral embolism is atrial fibrillation, in which the upper chambers (atria) of the heart beat weakly and rapidly so that they do not empty completely. This stagnant blood may form clots that can break off and enter the circulation. Atrial fibrillation (often abbreviated Afib) is a factor in about 15% of all strokes.

Comment [16]: can lead to stagnant blood to form clots and break off

Hemorrhagic stroke can be caused by the sudden bursting of a brain aneurysm, most often from high blood pressure. Brain aneurysms are surprisingly common—affecting about 1.5% to 5% of all Americans according to the American Stroke Association—yet they rarely cause symptoms unless they burst. Hemorrhagic stroke can also occur if thin, brittle arteries break and leak blood directly

Comment [17]: bulge in the wall of a blood vessel

into the brain (intracerebral hemorrhage) or into the membranes covering the brain (subarachnoid hemorrhage). Intracerebral hemorrhages, abbreviated ICHs, represent about 10% of all strokes, whereas subarachnoid hemorrhages, or SAHs, account for about 5%. In the United States, ICH causes about 70,000 new cases annually, and poses a risk of death in 40% of the cases. In addition to depriving affected brain tissue of its blood supply, the accumulation of fluid within the skull causes excessive pressure that can quickly lead to death.
Although the underlying causes of stroke are known, the immediate trigger is not usually apparent. It can be as simple as an abrupt change in body position, a loud noise, or an unexpected event.

Symptoms

Stroke symptoms depend on the part of the brain deprived of oxygen and how large an area is affected. The left and right hemispheres of the brain control movement on the opposite sides of the body. The left hemisphere is responsible for motor control and sensory discrimination on the right side of the body, and the right hemisphere is responsible for left body movements and sensations. Thus, a stroke on one side of the brain may affect movement and/or sensation on the opposite side of the body. Since communication and speech centers are predominately located in the left hemisphere, interruption of blood supply to that area can affect the ability to speak. Right brain strokes may affect spatial perception. Right-brain stroke patients also may deny their illness, neglect the affected side of their body, and behave impulsively.
Although strokes usually occur suddenly, symptoms of thrombotic stroke are more gradual and less dramatic due to the more gradual process of occlusion. Symptoms of embolic stroke have a rapid onset, and seizures or unconsciousness may be the first sign. Other symptoms may appear in minutes, hours, or—rarely—not for several days. Major stroke symptoms include headache—in the case of hemorrhagic stroke, often described as the worst headache ever—mental confusion, vertigo, vision problems, slurring of words, or aphasia (inability to speak or comprehend speech). Hemiplegia—weakness or paralysis on one side of the body—is a frequent symptom that often occurs first in the face, with facial drooping or slackness of the facial muscles on the affected side and difficulty swallowing. Other symptoms include sudden numbness or weakness in the face, arm, or leg, especially on one side of the body, or loss of balance or coordination.
With the possible exception of TIAs, strokes are always life-threatening emergencies. Because new treatments can reduce damage if initiated immediately, every minute counts. Diagnosis and treatment should begin as soon as possible, preferably onsite or during transport to a hospital.

Comment [18]: headache, hemiplegia(drooping of the face), slurring of words, and aphasia)

Comment [19]: dependence on which side... can look into rehab of either side

Sidebar: Hide

Key Terms

Aneurysm

A blood-filled stretching of a vessel, usually an artery, that can lead to stroke.

Angiography

A procedure for visualizing blood vessels with x rays.

Anticoagulant

Antithrombotic; blood thinner; a medication that prevents coagulation or clotting of the blood; used to prevent strokes.

Antiplatelet

A drug that reduces or destroys the activity of blood-clotting platelets; used to prevent strokes.

Atherosclerosis

Thickening of arterial walls, causing narrowing of the channels and impairing blood flow.

Atrial fibrillation

A disorder in which the upper chambers (atria) of the heart do not empty completely, which is associated with a higher risk of embolic stroke.

Cerebral vascular accident (CVA)

The medical term for a stroke.

Computed tomography (CT) scan

A diagnostic technique for producing cross-sectional images of tissues such as the brain.

Comment [20]: look into the different technology that neurologists use and how it works

Deep vein thrombosis (DVT)

A clot in a deep vein, as in the leg or pelvis; a frequent complication following stroke.

Embolic stroke

Cerebral embolism; a type of ischemic stroke in which a blood clot moves through the circulatory system to block an artery in the brain or neck.

Embolus

A clot that forms in the heart and travels through the circulatory system to another part of the body

Hemorrhagic stroke

A stroke caused by a burst blood vessel in the brain.

Intracerebral hemorrhage

A type of hemorrhagic stroke caused by bleeding within the brain.

Ischemic stroke

Insufficient blood supply to a part of the brain.

Magnetic resonance imaging (MRI)

A diagnostic technique that provides cross-sectional images of organs or structures within the body.

Muscle spasticity

Painful, continuous contraction of muscles, usually in the legs and arms, which can cause tightness or stiffness in those muscles.

Plaque

A mixture of fat, cholesterol, and cellular debris that builds up in the inner lining of arteries.

Platelets

Small, irregularly shaped cellular bodies that are involved in the formation of blood clots

Subarachnoid hemorrhage

A type of hemorrhagic stroke in which arteries on the surface of the brain bleed.

Thrombolytic

Clot-buster; a medication that dissolves blood clots.

Comment [21]: look into stroke medication

Thrombotic stroke

Cerebral thrombosis; a type of ischemic stroke caused by a blood clot formed within a blood vessel in the brain.

Thrombus

A blood clot that forms inside an intact blood vessel and remains there.

Tissue plasminogen activator (tPA)

A genetically engineered form of a natural human clot-buster that is used to halt ongoing ischemic strokes.

Transient ischemic attack (TIA)

Mini-stroke; occlusion of a smaller blood vessel in the brain that produces stroke-like symptoms for a few minutes to 24 hours, but does not usually cause permanent damage.

Diagnosis

Examination

The examination has several purposes: checking the patient's airways, breathing, and circulation; identifying any neurological deficits; identifying potential cause(s) of the stroke; and identifying any coexisting conditions. The patient or a companion provides a description of the event, which is followed by a short neurological examination. The patient will be asked to answer questions and perform physical and mental tasks. The physician may use the National Institutes of Health (NIH) standardized Stroke Scale (NIHSS) to gauge the level of consciousness, visual function, movement, sensations, and speech. Other scales include the Glasgow Coma Scale, the Hunt and Hess Scale, and the Modified Rankin Scale. The emergency department physician will note symptoms and obtain a medical history with special emphasis on risk factors for stroke. The time of onset of symptoms is critical. If the patient awoke with symptoms, then the time of onset is defined as when the patient was last observed without symptoms.

Comment [22]: look into the different neurological examinations

Tests

Various blood tests may be performed to detect conditions or disorders that increase the risk of stroke. Blood testing may include a complete blood count (CBC), coagulation studies, a basic blood chemistry profile, and cardiac markers such as cardiac enzyme levels. Hyperglycemia is a common finding after acute ischemic stroke, therefore blood glucose levels will also be monitored and treated as indicated.

Procedures

Various diagnostic procedures may be performed.

- Computed tomography (CT) scans may be used first to determine the cause of the stroke and the extent of injury.
- Magnetic resonance imaging (MRI) can locate small or deep brain injuries. A major recent advance in the neuroimaging of a suspected stroke is MRI with magnetic resonance angiography (MRA) technology.
- Blood flow imaging for detecting the location and size of any blockages may be performed with ultrasound or angiography (x rays of vessels after the injection of a contrast dye). Digital subtraction angiography is valuable in determining presence and location of occlusions, stenosis, dissections, and aneurysms.
- Carotid duplex scanning is used to determine the cause of the stroke and to determine the need for surgical intervention if pronounced carotid stenosis is present.
- Transcranial Doppler ultrasonography is used to evaluate areas of the brain such as the middle cerebral artery, intracranial carotid artery, and the vertebrobasilar artery.
- An electroencephalogram (EEG) measures the brain's electrical activity.
- Echocardiography uses ultrasound to image the heart and help determine whether an embolus caused the stroke.

Comment [23]: new technology that is even better

Comment [24]: evaluate arteries

Comment [25]: use to determine embolus (Afib)

Treatment

Effective stroke treatments have become available in recent decades. Immediate treatment is aimed at preventing further damage to the brain and is dependent on determining the type of stroke. A severe stroke that results in unconsciousness or coma requires medical monitoring and support, including oxygen, possibly intubation to assure an adequate airway and facilitate breathing, and intravenous fluids and nutrition.

A clot obstructing an artery is sometimes removed by endovascular methods using catheters or by surgery. Endarterectomy is the surgical removal of fatty deposits caused by atherosclerosis from a main artery to the brain. A mesh tube called a stent may be implanted inside the artery to prevent recurrent narrowing.

Emergency treatment of hemorrhagic stroke is aimed at controlling bleeding and intracranial pressure. Medications such as aspirin (medically known as a salicylate) or warfarin (Coumadin) that increase bleeding must be discontinued immediately, and transfusions of clotting factors may be necessary. Pressure on the brain must be relieved as quickly as possible to prevent further damage. Surgery may be required to stop bleeding and/or relieve pressure. Aneurysm clipping—clamping off the weak spot in the artery to prevent it from bursting—can prevent a second hemorrhagic stroke. Endovascular treatment uses a catheter to discharge tiny wire coils into the aneurysm to plug it. Paralysis requires prevention of contractures (tightening of paralyzed limbs). This is accomplished through physiotherapy and may include the use of supportive braces for arms or hands and

Comment [26]: many interventional cardiologists do this

Comment [27]: bc they are anticoagulants

footboards. A severely ill stroke patient must be repositioned frequently to prevent complications such as pneumonia and venous or pulmonary embolism.

Drugs

Thrombolytics are drugs used to stop an ongoing ischemic stroke by dissolving the clot that is blocking blood flow to the brain. If administered intravenously within four and a half hours of symptom onset, tPA (tissue plasminogen activator), a genetically engineered form of the body's natural clot-buster, can be especially effective for improving recovery and decreasing long-term disability. However, tPA and other thrombolytics increase bleeding and carry a risk of cerebral hemorrhage and are only used for ischemic strokes.

Antithrombotics are used to treat ischemic strokes and to prevent future blood clots, since about 3% of stroke victims have a second stroke within 30 days, and one-third of recurrent strokes occur within two years. Heparin (also known as unfractionated heparin), warfarin (Coumadin), and enoxaparin (Lovenox) are the most commonly prescribed blood thinners or anticoagulants. Antiplatelet drugs decrease the activity of platelets involved in the clotting process. Aspirin is the most commonly used antiplatelet drug and should be given within 24–48 hours after the onset of an ischemic stroke to reduce the likelihood of recurrent stroke. Others include clopidogrel (Plavix), ticlopidine (Ticlid), and dipyridamole (Persantine).

A diuretic or steroid medication may be used to relieve brain swelling from hemorrhagic stroke.

Comment [28]: bc they are slow developing

Comment [29]: for other strokes can be dangerous bc bleeding.... too much

Comment [30]: primary prevention

Comment [31]: prevent strokes, but stop this medication immediately when bleeding out/ when stroke is happening

Rehabilitation

Rehabilitation from stroke is a comprehensive program for regaining as much function as possible and compensating for permanent losses. Rehabilitation is coordinated by a team of medical professionals and may be provided in an acute-care or rehabilitation hospital, long-term care facility, outpatient clinic, or at home.

Physical therapy is used to maintain and restore range of motion and strength in affected limbs and to maximize mobility, including the use of aids such as wheelchairs, braces, and canes. Muscle spasticity and contractures are common during stroke recovery. Contractures may be treated with a combination of stretching and splinting. Weakness and loss of coordination of the swallowing muscles may be treated with retraining exercises and temporary use of pureed foods. A speech-language pathologist may work on swallowing skills as well as on communication. Occupational therapy addresses self-care skills, such as feeding, bathing, and dressing, and helps the patient develop effective compensatory strategies and devices for activities of daily living. Rehabilitation may be complicated by cognitive losses, including diminished ability to understand and follow directions, as well as by depression, which affects 30–60% of stroke patients and may require antidepressants and/or psychotherapy.

A social worker may help coordinate services and ease the transition from hospital to home. However, caring for a stroke patient requires learning a new set of skills and adapting to new demands and limitations. Home caregivers may develop stress, anxiety, and depression. Caring for the caregiver is an important part of overall stroke rehabilitation. Support groups can be an important source of information, advice, and comfort.

Prognosis

Stroke survival improved significantly from the last decade of the twentieth century and into the first two decades of the twenty-first century, due to advances in emergency treatment, decreased use (primarily smoking) of tobacco products, and better control of high blood pressure and cholesterol levels. According to the National Stroke Association, approximately 10% of stroke patients recover almost completely, while 25% have minor impairments and 40% have moderate to severe problems that necessitate special care. Of that percentage of people with moderate to severe impairments, about 10% require the use of a long-term care facility such as a nursing home. Strokes are fatal in about 15% of all cases.

Prognosis depends on the patient's age, the type and location of the stroke, and time elapsed between symptom onset and initiation of treatment. Emergency treatment and comprehensive rehabilitation can significantly improve both survival and recovery. However, recurrent stroke is common: about 25% of patients who recover from a first stroke will have another within roughly five years. The risk of severe disability or death increases with each stroke, although the risk of recurrent stroke decreases with time.

Deep venous thrombosis (DVT), in which a clot forms within an immobilized limb, is one of the most common complications following stroke. Clots that break free often become lodged in an artery feeding the lungs, causing a pulmonary embolism—a common cause of death in the weeks following a stroke. Resuming activity within a day or two after the stroke, using pressure stockings, and taking anticoagulants are important preventive measures.

Stroke in children can be devastating. It ranks among the top ten causes of death in children between the ages of one and 19 years. Between 20% and 35% of newborns who survive a stroke have a second stroke. Through the age of 19 years, stroke impacts five per 100,000 children, as reported by the Children's Hemiplegia and Stroke Association. Further, more than 66% of older children who suffer strokes have cognitive deficits, seizures, behavioral problems, personality changes, and/or physical disabilities. However, the plasticity of children's immature brains may enable them to adapt to and compensate for deficits and injury better than adult stroke victims.

Comment [32]: how is neuroplasticity affected by a stroke?

Prevention

Strokes are preventable to a significant extent. Numerous studies have demonstrated that one baby aspirin per day is an excellent blood-thinning and clot-reducing measure. In addition to antiplatelet and anticoagulant therapies, blood pressure control is the single most important factor for preventing stroke. Blood pressure should be checked regularly, and consistently elevated blood pressure (systolic above 130 and diastolic above 90–100) should be treated. Cholesterol-lowering medications may also help prevent stroke. Treatment for atrial fibrillation significantly reduces the risk of stroke. Preventive anticoagulant therapy may benefit those with untreated atrial fibrillation. Cigarette smoking, along with other tobacco usage, almost doubles the risk of ischemic stroke and is associated with other risk factors for stroke. Avoiding alcohol (or at least drinking in moderation), illicit drugs (such as cocaine and methamphetamines), and secondhand tobacco smoke is also important. Alcohol in small to moderate amounts (no more than one drink a day for women and two drinks for men) has been shown to prevent ischemic stroke. Cocaine, for instance, has been proven to cause narrowing of the arteries, thus, reducing blood flow throughout the body.

Comment [33]: what type of people should take this?

Diet, including lowering sodium (salt) intake, exercise, and weight control are important for lowering blood pressure and reducing the risk of stroke. Medical studies continue to demonstrate that diets high in fruits and vegetables (particularly leafy green vegetables and cruciferous vegetables such as broccoli, cauliflower, and cabbage) can reduce the risk of ischemic stroke. Replacing meat and trans

fats (also called trans fatty acids) with fruits and vegetables further reduces stroke risk. Meta-analyses (statistics combined from multiple studies) indicate that consumption of dietary fiber is inversely related to the risk of stroke, and is most likely independent of other risk factors. A diet low in cholesterol and saturated fat may decrease plaque in the arteries, thus, reducing the chance of stroke.

Exercising regularly lowers blood pressure and increases the level of high-density lipoprotein cholesterol (LDL; what is commonly called bad cholesterol) in the body. Walking, jogging, bicycling, swimming, and other types of exercise also help to control diabetes and lessen stress—what are other risk contributors to stroke. A healthy weight is essential to reducing the risk of stroke, along with associated factors such as high blood pressure, diabetes, and cardiovascular disease.

Stroke damage may be significantly reduced by emergency treatment; thus, knowing the symptoms of stroke and seeking immediate treatment is of the utmost importance. Furthermore, people should see their doctors immediately if they experience a TIA.

Robinson, Richard, et al. "Stroke." *The Gale Encyclopedia of Medicine*, edited by Jacqueline L. Longe, 5th ed., Gale, 2015. *Health & Wellness Resource Center*, http://link.galegroup.com/apps/doc/RWAZEA593853425/HWRC?u=j043905010&sid=HWRC&xid=cba99428. Accessed 6 Sept. 2018.

Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression in later life: A systematic review and meta-analysis

Introduction

Stroke is the commonest cause of dependency in adults in the developed world [1] and also causes cognitive, physical and psychiatric disabilities. Depression is one of the most common neuropsychiatric disturbances following stroke, occurring in approximately 31% of patients during the first 5 years [2]. People with post-stroke depression experience greater impairment, including worse cognitive impairment, more substantial reductions in activities of daily living, and increased mortality [3] compared with non-depressed stroke patients. Post-stroke depression can severely impair physical rehabilitation and recovery [3].

Several risk factors for post-stroke depression have been proposed. These include gender, medical and psychiatric history [3,4], age, and social support [4] as well as factors relating to the stroke such as severity and degree of resulting disability [3]. However, evidence supporting these factors is mixed and they only explain some of the variance in post-stroke depression. Factors from earlier in life may also be important. Two recent meta-analyses [5,6] reported that low childhood cognitive ability, low childhood socioeconomic status (SES) and low education were associated with an increased risk of stroke and subclinical cerebrovascular disease on neuroimaging or at post mortem. Few studies have specifically examined the relationships between these childhood factors and post-stroke depression, but it is possible that an association exists via the relationships between early life factors and vascular disease. A previous review [7] of 10 studies found no association between education and post-stroke depression. However, this review only included papers published in English between 1995 and 2012 which directly analysed education as a risk factor, and did not perform a meta-analysis.

To address the question of whether childhood cognitive ability, SES or education affect the risk of post-stroke depression in later life, we performed a systematic review and meta-analysis of all published literature.

Comment [1]: would be interesting to look at how strokes are dealt with in underdeveloped periods

Comment [2]: so in underdeveloped countries, the development of post-stroke depression would be ever more

Comment [3]: combine the research of different studies into one... more effective

Method

The methodology of this systematic review has been described previously [5,6]. We used the PRISMA and MOOSE guidelines [8] (see S1 Table), and registered the protocol prospectively on Prospero (registration number: CRD42015016701).

Using a detailed search strategy (Appendix in S1 File) we searched PsycINFO (1806-present), MEDLINE (1966-present) and EMBASE (1980-present) for papers published until 6 April 2017 using OVID SP UI03.16.00.110. We also checked reference lists of identified papers and relevant review papers and hand searched the previous five years of *Stroke* , *Neurology* and *International Journal of Epidemiology* .

Each abstract and title were screened by one reviewer and all potentially relevant texts were independently screened by two researchers (EB or CM) for relevance. Disagreements regarding eligibility were resolved through discussion between authors.

We included studies that provided data on one or more early life factors (education, social class, IQ) in relation to a diagnosis of depression or measurement of depressive symptoms following stroke. We defined depressive symptoms as any measurement of mood using a valid scale conducted at

Comment [4]: guidelines for systematic review of meta-analysis

any time following a stroke. Valid scales included the Beck's Depression Inventory, the Montgomery Asberg Depression Rating Scale (MADRAS) and the Hamilton Depression Rating Scale (HDRS) (higher score indicates worse depression/depressive symptoms). A diagnosis of major depression according to classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) was also included. We included general intelligence (IQ) measurements performed up to age 18 and estimates of premorbid IQ using valid tools (e.g. the National Adult Reading Test (NART)). All measures of childhood education were included (duration, attainment). We included childhood SES measures such as parental occupation or education.

We excluded papers with less than 50 patients, those focusing on a particular non-stroke patient population (e.g. Multiple Sclerosis), without primary data, not reporting data on humans aged 18 or over, or abstract only publications. We considered papers in any language. We used double data extraction conducted by two researchers.

We quality assessed the included studies on six potential sources of bias [9]: representativeness of the sample to the general population, whether study attrition was reported, how education and post-stroke depression were measured, whether results were adjusted for confounders and appropriateness of the statistical analysis. We rated each of these on a 4-point scale (corresponding to unclear, no, partly, yes) with a maximum score of 24. We counted each study only once, being careful to avoid double counting where more than one paper referred to the same study.

We standardised all education results to represent a reference level of high education, based on each paper's categorisation of education in the majority of papers. Low education was defined as approximately 6-8 years (or less than high school) and high education as 9 years and above (or high school and above).

We used Review Manager V.5.3 to calculate overall odds ratios (OR) or mean differences (MD) and 95% confidence intervals using a random effects model. Where multiple statistics were reported, we used the one that maximised data available for meta-analysis. Where possible, we used the results adjusted for depression or vascular risk factors over crude results. Where necessary, we calculated odds ratios from frequency data and we analysed correlation coefficients using the package 'metacor' for R V.3.0.1. We analysed papers which reported means years of education in a separate group. We assessed heterogeneity using the I^2 statistic and publication bias with funnel plots. We further calculated 95% prediction intervals which incorporates existing heterogeneity and quantifies the likely range of associations between education and depression in similar future studies [10].

We performed post-hoc sensitivity analyses on several clinically important subgroups and factors previously reported to be associated with post-stroke depression.

Results

We identified 24,289 titles and abstracts after removal of duplicates (Fig 1), from which we identified 1,314 full text articles. The commonest reason for exclusion was no measurement of depression. 33 articles, all examining education and post stroke depression met inclusion criteria (see Table 1 for summary of included studies and Table A in S1 File for full details). One of these articles [11] also examined premorbid cognition. There were no studies examining childhood SES and post-stroke depression.

Fig 1. PRISMA flow chart of search process. [see PDF for image]

Quality assessment and publication bias

The quality of the included papers was good, with scores from 18-23/24 (median = 20). The main risk of bias was regarding sample representativeness (Figure A in S1 File).

Comment [5]: 21-question self reporting

Comment [6]: 10 question, psychiatrists look into it

Comment [7]: 17 question, most widely used clinician led

Comment [8]: education was also measured of each person/ their IQ

Comment [9]: bc of statistics

There was no evidence of publication bias among papers examining education level and depression (Figure B in S1 File). Due to the small number of studies, it was not possible to assess publication bias in papers reporting mean years of education or correlation coefficients.

Comment [10]: therefore good source

Premorbid IQ

One paper [11] (n = 205) examined premorbid IQ using the National Adult Reading Test Revised (NART-R) and post-stroke depression diagnosed using The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (37 post-stroke depression; 98 no depression). NART scores, transformed into an IQ score, were higher (better premorbid IQ) in those without depression (mean: 104.0, SD 10.1) compared to those with post-stroke depression (mean: 101.8, SD 9.8) but this difference was not statistically significant.

Education

Thirty three studies [11-43] (n = 8,377, range: 64-1,068) examined education and post-stroke depression (2,664 post-stroke depression; 5,460 no depression participants, 314 participants not classified) aged 27-85 at follow up. Education level was assessed as duration (i.e. [less than or equal to]8 years vs >8 years) in 12 studies [12,17,19,21,24,27,30,32,33,33,34,36], attainment (i.e. <High School vs [greater than or equal to]High school) in 13 studies [13-16,18-20,22,23,28,29,31,35,35] and mean years of education in 8 studies [11,37-43]. Most studies were conducted in Europe or North America (17 studies) however some were based in the Asia Pacific Region (12 studies), Africa (1 study), the Middle East (2 studies) and South America (1 study). Twenty three studies were based in hospitals, 6 were outpatient studies and 4 were population or community based studies.

Education level and depression

Of the 33 studies 8 papers [24-31] (n = 1785) reported ORs (711 with and 1074 without post-stroke depression) and 12 papers [12-23] (n = 3879) reported frequencies of presence of post-stroke depression by educational attainment or duration (1434 with and 2445 without post-stroke depression) which we used to calculate unadjusted ORs. Three of these studies [26,27,30] reported adjusted odds ratios.

Eleven studies [12,13,15,16,20,21-23,25,29,30] (n = 1,937: range = 91-329) defined post-stroke depression according to a cut off score indicating the presence of mild depressive symptoms or above. These were measured on rating scales including the Montgomery Asberg Depression Rating, Scale (MADRAS) (4 studies [15,16,20,25]; score [greater than or equal to]7), the Hamilton Depression Rating Scale (HDRS) (2 studies [21,23]; score [greater than or equal to]8 mild depressive symptoms), the Becks Depression Inventory (BDI) (2 studies [12,13]; score [greater than or equal to]10), the Geriatric Depression scale (GDS) (2 studies; Short version [29]: score >5, short version [greater than or equal to]7[30]) and a Chinese self-report depression scale (1 study [22]). Nine studies [14,17-19,24,26-28,31] (n = 3,754: range = 105-1,068) defined post-stroke depression as a clinical diagnosis of depression or moderate to severe depressive symptoms on a self-report scale. This included four studies [17-19,24] which classified participants with depression by a diagnosis of major depressive disorder (MDD) according to DSM criteria. Two studies [28,31] used the Centre for Epidemiologic Studies Depression scale (CES-D) which diagnoses a depressive episode using the DSM criteria. Three studies defined participants with moderate or severe depressive symptoms according to depression rating scales: the Hamilton Depression Rating Scale (HDRS) (score of [greater than or equal to]21, 1 study[27]); the Bengali version of the Geriatric Depression scale (GDS) (score of [greater than or equal to]21, 1 study[26]) and the Patient Health Questionnaire 8 (PHQ-8) (score [greater than or equal to]10, 1 study[14]).

Overall low education (<9 years) was associated with increased risk of post-stroke depression or depressive symptoms (OR 1.16 95% CI 1.03-1.31, p = 0.01, Fig 2). Heterogeneity between studies was moderate (I^2 58%). The 95% prediction interval was 0.98 to 1.52.

Fig 2. Forest plot comparing low vs high education and risk of depressive symptoms following stroke. OR<1: low education decreases risk post-stroke depression; OR>1 low education increases risk of post-stroke depression. Random effects model. [see PDF for image]

Sensitivity analysis

We conducted several post hoc sensitivity analyses examining education level and post-stroke depression (see Figs 3 and 4 and Figures C-J in S1 File.). Definition of post-stroke depression explained some of the between study heterogeneity (X^2 (1) = 4.47 p = 0.03). Low education was associated with increased risk of post-stroke depression defined as a score of mild and above on a depression rating scale (n = 1,937, OR 1.47 95% CI 1.10-1.97, p<0.01, 95% PI 0.47-3.00) but not major depression or severe depressive symptoms (n = 3,754 OR 1.04 95% CI 0.90-1.31, p = 0.60, 95% PI 0.69-1.51) (Fig 3).

Comment [11]: were not adjusted for age or sex

Fig 3. Sensitivity analysis comparing studies with depression defined as mild symptoms and above vs clinical depression or severe depressive symptoms only. [see PDF for image]

Fig 4. Sensitivity analysis comparing studies adjusted for age and sex vs unadjusted studies.[see PDF for image]

Low education was associated with post-stroke depression in studies which did not adjust for age and sex (18 studies, n = 4,984; OR 1.27 95% CI 1.08-1.51, p<0.01, 95% PI 0.95-2.14) but not in studies which did adjust for age and sex (2 studies, n = 711; OR 0.86 95% CI 0.50-1.48 p = 0.58, 95% PI 0.96-1.81) (Fig 4).

The risk of post-stroke depression did not differ according to the depression scale used, participants age (<65 vs [greater than or equal to]65 years), first stroke only vs recurrent or unspecified stroke, past history of depression as an exclusion criteria (yes vs no), time since stroke ([less than or equal to]6 months vs >6 months), study setting (hospital or outpatient clinic vs population-based) and country of origin (Europe or North America vs Asia Pacific region or Africa).

Exclusion of the paper [23] with the lowest quality score, or the two studies [20,25] with unclear definitions of education levels, did not significantly alter the results (OR 1.23 95% CI 1.02-1.49, p = 0.03; OR1.24, 95% CI 1.03-1.50, p = 0.02).

Mean years of education and depression

Of the 33 studies, 7 [11,37,38,40-43] (n = 1943: range = 80-469) reported mean years of education for participants with and without post-stroke depression (273 post-stroke depression and 1251 no post-stroke depression) and one study [39] reported median years of education. Post-stroke depression was diagnosed using the DSM criteria (5 studies[11,38,40-42]), and the BDI [37], the GDS [43] and the Hospital Anxiety and Depression Scale (HADS) [39] in one study each.

Participants with post-stroke depression had significantly fewer years of education than those without post-stroke depression (MD 0.68 95% CI 0.05-1.31 p = 0.03, Fig 5). None of these papers adjusted for vascular risk factors.

Fig 5. Mean years of education for those with and without post-stroke depression. Random effects model for the mean difference. Negative mean difference = lower education decreases risk of post-stroke depression and positive mean difference = higher education decreases risk of post-strokedepression. [see PDF for image]

Heterogeneity between studies was moderate (I^2 56%). The 95% prediction interval was 1.14 to 2.50. There were too few studies to conduct any sensitivity analyses.

Correlation between education and depressive symptoms

Of the 33 studies, 5 [32-36] (n = 831: range = 64-300) reported correlation coefficients for education and post-stroke depressive symptoms at age 56-70. Most studies used years of education while one [35] used educational attainment ranging from 1 (Primary school) to 7 (University degree). One study [35] provided risk factor adjusted results. Depressive symptoms were measured using the HADS in two studies [32,36], the HDRS [34], the GDS [33]and the CES-D [35] in one study each.
Overall correlation between education and depressive symptoms did not reach statistical significance (r = -0.10 95% CI -0.24-0.04, p = 0.15, Fig 6), although the effect was in the same direction as the effect of the alternative education measures above on post-stroke depression. Heterogeneity was high between studies (I^2 77.3%) but the data were too sparse for sensitivity analyses.

Fig 6. Forest plot showing correlation between education and depressive symptoms in strokepatients. Negative correlation = low education increases depressive symptoms; Positive correlation = low education decreases depressive symptoms. DS = depressive symptoms. * adjusted for sex, income, smoking, age, cognitive dysfunction and activities of daily living. DS = depressive symptoms. [see PDF for image]

Discussion

Our meta-analysis is the first comprehensive examination of all data on education and risk of post-stroke depression and suggests that longer duration of education is associated with a decreased risk of depression following stroke occurring in later life. Less versus more education was associated with a 16% relative increase in post-stroke depression. This relative risk translates to an absolute increase in post-stroke depression risk of approximately 5.9/1,000 for lower versus higher education but with wide confidence intervals and heterogeneity. Furthermore, participants with post-stroke depression had an average of 0.68 fewer years of education than those without post-stroke depression. These findings suggest important implications for predicting risk of post-depression and of recovery afterstroke. A previous review [7] reported significant associations between education and depression in only two of the studies they identified, but only included 10 papers (versus the 33 included here) and excluded studies which did not analyse education directly, which reported mean years or correlation coefficients, and did not include a comprehensive meta-analysis such as performed here.

Our sensitivity analysis showed that low education was associated with increased risk of post-stroke depressive symptoms, defined as mild symptoms and above, but not severe depressive symptoms or a clinical diagnosis of depression. Studies using a cut of score of mild depressive symptoms to define post-stroke depression also included participants with moderate to severe depressive symptoms. Therefore it is unclear whether the association between education and post-stroke depression is stronger for milder depressive symptoms or whether these differences are due to methodological differences between studies. The association between years of education and depression severity was examined in only one study [15], which found no association. However the number of participants with major depression in this study was low (n = 14) and so this should be examined in future studies with larger sample sizes.

The diagnosis of depression in stroke populations is more difficult than in those without stroke and many depression scales were not originally developed for patients with stroke. Stroke patients may suffer from symptoms such as fatigue and lack of appetite after stroke, which may lead to inflated scores on depression scales containing a somatic component (e.g. BDI, HDRS) compared to those that do not include such items (e.g. HADS, MADRAS). No studies adjusted for other common associates of post-stroke depression such as fatigue, although these factors should be considered

Comment [12]: there is a slight correlation

Comment [13]: what was the sensitivity analysis?

Comment [14]: not accounted for

Comment [15]: can look into other studies, or maybe do own study about this

Comment [16]: this can skew results bc it causes the results to be less accurate.... symptoms based on stroke itself (which everyone has)

when conducting research into post-stroke depression. Meta-analysis [44] suggests that the CES-D, HDRS and PHQ-9 are the most promising options to screen for post-stroke depression. However in our review CES-D and the HDRS were only used in three [28,31,35], four [21,23,27] studies respectively. One study [14] used the PHQ-8 which contains one less question that the PHQ-9.

We found considerable heterogeneity between studies and calculated prediction intervals in addition to confidence intervals. The prediction interval is useful in the presence of heterogeneity as it provides a range of effects that would be expected from a new study with similar characteristics to the current studies [10]. The 95% prediction interval indicates that although low education on average is associated with an increased risk of post-stroke depression, some future studies may not find an association. Specifically in a future study the expected association between education and post-stroke depression would be between 0.98 and 1.52 with 95% confidence.

Confounders were poorly addressed, either because authors reported unadjusted results or because frequency data were used to calculate unadjusted odds ratios. In those papers that did include adjustment for confounders (four studies), there was variation in the number and type used. Of particular importance are sex and age which were adjusted for in four and three studies respectively. Female sex is a risk factor for post-stroke depression [45] and in the cohorts included in this review females may be more likely to have lower levels of education. Similarly older participants may have less education and may be more vulnerable to depression due to more advanced vascular disease. Our sensitivity analysis showed that low education was associated with post-stroke depression in studies which did not adjust for age or sex but there was no association in studies which did adjust for age and sex, however this included only two studies. Inclusion of the one study [41] that did not adjust for age but did adjust for sex did not alter the results of the sensitivity analysis. Other confounders which were adjusted for include stroke severity (one study) and impairments in activities of daily living (two studies). More studies are needed to examine associations between education and post-stroke depression after adjustment for risk factors for post-stroke depression, particularly age and sex.

No studies adjusted for other early life factors or adult SES. It is likely that education is interrelated with premorbid IQ and that all factors are associated with an increased risk of stroke, but it was not possible to assess the independence of these early life risk factors on post-stroke depression from the current literature as the only paper which examined both premorbid IQ and education reported mean values for each separately. Education is also strongly associated with adult SES which is itself a risk factor for stroke and depression [46]. Previous research has suggested that education and measures of SES such as income may have independent associations with health outcomes [47]. However future studies should examine associations between education and post-stroke depression when controlling for adult SES.

While methodological differences between studies might also contribute to heterogeneity, we were not able to find any evidence that the type of depression scale used, whether set in hospital in-patient, out-patient or population-based, world region, inclusion or exclusion of prior stroke or prior history of depression or patient age accounted for the heterogeneity. Other differences between studies include the interval between stroke and post-stroke assessment which varied from within 48 hours to greater than 18 months. However, prevalence of depression after stroke has been found to be stable across studies conducted at different time points[48,49] and our sensitivity analysis showed that the effect of education and depression did not differ between before and after 6 months post stroke.

Exclusion criteria varied among studies. Seven studies excluded participants with a pre-stroke history of depression and eight studies excluded participants with a previous history of stroke, both

factors which have been identified as risk factors for post-stroke depression[7]. Our sensitivity analyses showed that studies including participants with a history of stroke or depression reported a higher effect of education on post-stroke depression risk than those that excluded such participants, but these differences were not significant. No studies adjusted for history of depression or stroke in their analysis.

The majority of the identified studies were cross sectional. Depressive symptoms may fluctuate over time and a single measurement at a relatively arbitrary point in time may only provide a snapshot of symptoms, particularly mild symptoms. A more comprehensive measure of depressive symptoms at multiple time points may offer a more precise estimate of the association between education and post-stroke depression. Although 11 of the identified studies were longitudinal only 5 reported measures of depression or depressive symptoms at multiple time points in relation to education. In two studies [37,24] low education level was associated with depression measured at baseline, 1 month [24] and 3 months [37]. Another study reported that those whose depressive symptoms worsened between baseline and 6 month follow up were less educated than those whose symptoms stayed the same [43]. However two studies [18,20] found no association between education level and depressive symptoms measured at baseline, 6 months, 12 months [18] and 36 months [20] post-stroke.

The majority of studies were from Europe or North America followed by the Asia Pacific Region. Our sensitivity analysis found no difference between studies conducted in Europe or North America compared to the Asia Pacific Region or Africa. However, we were only able to conduct sensitivity analysis on a subset of papers and social and educational disparities may vary between these world regions.

We excluded studies with less than 50 participants as results from small studies can be less reliable[50]. Therefore, although our funnel plot showed no publication bias, we may have excluded smaller non-significant studies.

Strengths and limitations of the review

Our systematic review had limitations. Resources prevented contacting authors for original data where information on education may have been collected but not reported. The sensitivity analysis was not able to account for all the heterogeneity.

Strengths of the review include a pre-specified published protocol, validated search strategy, double data extraction. We followed published guidelines and used exemplary methods on conduct of systematic reviews and meta-analyses, and established scale for quality assessment which showed an overall high level of study quality. Some sample sizes were small, however there was a reasonable total sample size for many of the analyses producing a comprehensive literature review and meta-analyses amassing data on 8,377 participants. Some analyses lacked power and we may have missed some significant associations through lack of significant data.

Implications and conclusions

The aetiology of post stroke depression is still unclear. Some researchers propose that the primary mechanism linking stroke and depression is biological in which brain damage caused by ischaemic lesions disrupt neural circuits involved in mood regulation. Others propose that depression is caused by dysfunctional psychosocial adjustment following the stroke. It is likely that post-stroke depression is of multifactorial origin and a combination of biological and psychosocial mechanisms.

There are several possible explanations for the observed relationship between education and post-stroke depression. Our previous systematic reviews [5,6] showed that low education was associated with an increased risk of stroke and subclinical cerebrovascular disease (e.g. white matter hyperintensities). It may be that low education leads to more severe stroke which in turn increases

Comment [17]: depression is difficult to measure, and can fluctuate... why results do not show a high association

Comment [18]: this answers my previous question about third-world countries

Comment [19]: two different theories....

depression. Alternatively, low education may increase imaging markers of vascular disease which increase the risk of depression and stroke since a relationship between WMH and depression is suggested [51].

Our findings show an association between lower educational attainment and increased risk of depression following stroke. However further studies are needed to confirm this and our findings should be interpreted with caution due to the substantial heterogeneity between studies, the relatively large confidence intervals around the effect sizes and the fact that many studies did not adjust for potential confounders. Health disparities have been widely discussed and emphasise the importance of addressing social inequality to improve health outcomes. Post-stroke depression is often considered a treatable complication of stroke, but antidepressants are only partially effective and, despite its high prevalence, it remains poorly recognised and undertreated and trials are ongoing. Identifying additional aspects of the mechanisms of post-stroke depression and modifiable risk factors may lead to more specific therapeutic interventions to target those most at risk and may help design future policy. Future research should examine the combined effect of education and other early life factors on post-stroke depression after adjusting for possible confounders.

Comment [20]: importance of trans-cultural healthcare as mentioned in the prev. article

Backhouse, Ellen V., et al. "Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression in later life: A systematic review and meta-analysis." *PLoS ONE*, vol. 13, no. 7, 2018, p. e0200525. *Health & Wellness Resource Center*, http://link.galegroup.com/apps/doc/A546740327/HWRC?u=j043905010&sid=HWRC&xid=1b33e1f1. Accessed 6 Sept. 2018.