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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**Available online at: <http://www.iajps.com>**Research Article****STROKE RISK FACTORS, GENETICS, AND PREVENTION**¹Dr Faisal Bin Saeed, ²Dr Shahzad Ahmad Sattar, ³Dr Zainab Haq¹MBBS, Sahiwal Medical College, Sahiwal.²MBBS, Mohi-ud-Din Islamic Medical College, Mirpur AJ and K.³Quaid e Aam Medical College, Bahawalpur.**Article Received:** March 2020**Accepted:** April 2020**Published:** May 2020**Abstract:**

Stroke is a heterogeneous syndrome. Various risk factors and treatment of stroke are dependent upon its pathogenesis, as it can be variable. Stroke has modifiable and non-modifiable risk factors. For instance, age, gender, race falls under the non-modifiable category and hypertension, diet, lifestyle, and smoking fall under the modifiable category. Moreover, inflammatory disorders, pollution, infection, and cardiac arterial disorders can also trigger stroke. Stroke is a primary manifestation of rare, hereditary disorders caused by single-gene mutation, and rare genetic polymorphism. Generally, modifiable risks are considered for stroke prevention. As changes in lifestyle, eating habits, smoking cessation, workout, and positive attitude not only minimizes the stroke factors but also play a significant role in reducing CVD and hypertension disorders. Other treatment methods include the medical assistance for hypertension and diabetes that also triggers stroke.

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INTRODUCTION:

Stroke is one of the leading causes of long-term disability in adults and 5th leading cause of death, globally. Stroke risks are likely to increase with the increase in age.^{1,2} Stroke mortality is highly linked with diabetes, obesity, and hypertension. Due to stroke, various brain issues occur like cerebrovascular disease which is associated with dementia, memory loss, gait impairment, and other functional disabilities. Stroke is also linked with depression, which leads to multiple diseases and abruptly affects overall body functioning.^{2,3}

Stroke is divided into ischemic and hemorrhagic nature. 80% of strokes are ischemic, but this ratio varies from population and area to area. Strokes can be further divided into etiologic subtypes, that elaborates the risk factors causing stroke:

atherosclerotic, cardioembolic, lacunar, dissections, specific genetic disorders, and others. Hemorrhagic and ischemic strokes have some similar and some differentiate-able risk factors; hypertension is prominent in hemorrhagic stroke, but in some cases, it can also lead to atherosclerotic disease which will ultimately turn it into an ischemic stroke as well.^{4,5} However, hyperlipidemia is an important risk factor as it can cause atherosclerosis of extracranial and intracranial blood vessels.⁶

In countries and areas, where the hypertensive burden is overwhelming, hemorrhagic stroke proportion is relatively higher than ischemic stroke. With the diet and lifestyle modifications, a prominent decline in these strokes and CVD occurrence was observed.

The table given below represents risk factors for ischemic and hemorrhagic strokes.

	Non-modifiable Risk Factors	Modifiable Risk Factors
Ischemic Stroke	Age	Hypertension
	Gender	Diet
	Race/ ethnicity	Smoking
		Physical activity
		Waist to hip ratio
		Diabetes mellitus
		Alcohol consumption
		Hyperlipidemia
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	
Hemorrhagic Stroke	Age	Hypertension
	Gender	Diet
	Race/ ethnicity	Alcohol consumption
		Physical inactivity
		Diet
		Waist to hip ratio
		Genetics*

Genetic risks are increasingly considered as potentially modifiable, either by changing the gene-environment interaction or by other means. That is why genetics is placed between both modifiable and non-modifiable categories.

Non-Modifiable Stroke Risk Factors

Age, sex, race/ethnicity, and genetics are non-modifiable risk factors for stroke. Particularly, stroke is linked with aging and its incidence rises with age and doubles up after the age of 55 years.⁷ The mean age of ischemic stroke was recorded as 69.2 years. However, recent research has shown that the prevalence of ischemic stroke has been increasing among the age group of 20 to 54 years from 1994 to onward. Stroke is sex-dependent as well, for women at a young age the risk is higher in comparison to men, and men at old age are more prone to stroke than women. The highest risks in women are basically linked with pregnancy,

postpartum state, hormonal changes, and hormonal contraceptives.⁷

When it comes to race/ ethnicity, evidence has shown that Africans have an increased risk for stroke in comparison to Americans, Asians have an increased risk ration in comparison to Europeans, and Americans have an increased risk in comparison to Europeans.⁸

Genetics is a controversial factor, as it has an overlapping location between the non-modifiable and modifiable categories. Genetic factors are,

somehow, considered modifiable through modification of gene-environment interactions.

- **Genetic Risk Factors**

Genetic mutation can impact stroke occurrence through several potential mechanisms.

1. Specific rare single-gene disorders can participate in familial syndromes that can lead to strokes like leukoencephalopathy and subcortical infarcts with cerebral autosomal dominant arteriopathy
2. Single gene disorders can develop multiple diseases and disorders like sickle cell anemia in which one manifestation can be a stroke
3. Some common variants of genetic polymorphisms like variants in 9p21 are associated with stroke risks
4. Atrial fibrillation, diabetes, and hypertension can be genetic. These also contribute to risk factors for stroke⁹

Modifiable Risk Factors

Modifiable risk factors are extremely important because, by modification, these factors can reduce the risk of stroke. It is imperative to identify and modify these factors at a very early stage to prevent any case complications.

Following are the prominent modifiable risk factors:

- **Diabetes Mellitus**

Diabetes mellitus is an independent stroke risk factor. It can double up the risk of stroke and it is the reason for 20% of the death rate in diabetic patients. The duration of diabetes defines the risk rate of stroke. According to research made at Northern Manhattan Institute, diabetes mellitus was associated with ischemic stroke and the Hazard Ratio (HR) was adjusted as 1.04/ year with a 95% Confidence Interval (CI). It was found that patients who have diabetes for 0 to 5 years and those who have it for 5 to 10 years have HR, 1.7 and 1.8, and 95% CL, respectively. Those who have diabetes for more than 10 years were found to be at greater risk for stroke with HR 3.2.

Interestingly, for reducing this modifiable factor, mere glycemic control does not help. For this behavioral modification along with medical intervention are imperative.

- **Hypertension**

The most important modifiable risk factor which has a linear, direct, strong, and continuous relationship between stroke and blood pressure is hypertension.¹² Hypertension has higher risks for hemorrhagic stroke than ischemic. Even in those people, who are not hypertensive patients, the chances of stroke still increase in them as the blood pressure increases. As the blood pressure increases with the increasing age, thereby the lifetime risk of developing hypertension also increases along with stroke risk.¹⁵ More than two-thirds of people who

are ≥ 65 years of age are hypertensive. But due to advancements in medicine and improved awareness almost 50% of hypertension is controlled globally. These patients are encouraged to change their lifestyle, diet, physical activity and attitude towards life to control their blood pressure.^{13, 14}

Studies have shown that in an individual, different blood pressure readings measured at different points are associated with the stroke risks far greater than elevated blood pressure at just one point.¹⁵ The measure of the variability of blood pressure can also be an indicator of the presence or absence of cardiovascular homeostasis in an individual. This means that not just blood pressure, but agents like calcium channel blockers are also important.^{16, 17}

- **Sedentary Lifestyle, Diet, Metabolic Syndrome**

Physical activity is the key to a healthy life. People who are physically more active, are less prone to many diseases like hypertension, obesity, CVD, and stroke in comparison to those who are inactive. Diet influences the risk of stroke and stroke-related other risk factors like diabetes mellitus, dyslipidemia, and hypertension. For example, salt intake is linked with stroke and hypertension, increased potassium intake is associated with a declined stroke risk, and increase LDL intake raises the risk for atherosclerosis and CVD. Diet rich in fruits and vegetables is sound for the body.

A large meta-analysis, including 1 million participants from different parts of the region, revealed that 77% of the BMI effect (Body Mass Index) on stroke risk was moderated by cholesterol, glucose, and blood pressure. Blood pressure alone participates as 65% in the risk of stroke.

The metabolic syndrome concept incorporates pre-hypertension, pre-diabetes, and dyslipidemia. Excess body fat, especially around the waist and abnormal cholesterol and triglyceride levels are also indicators of metabolic syndrome. This states that the body's normal metabolic activities are interrupted and this is leading towards anomalous, unwanted changes including CVD and the increased risk of stroke.

- **Dyslipidemia**

The relationship of dyslipidemia with stroke is complicated, with increase total cholesterol levels, the risk for ischemic stroke increases, but with increased density lipoprotein cholesterol, the risk for ischemic stroke declines. Total cholesterol has an inverse relation with hemorrhagic stroke, as when the former decreases the risk for later increases. Studies reveal that the use of statins in the general population, reduce the risk of total and ischemic stroke with no definite rise in the risk of hemorrhagic stroke. Patients with previous

hemorrhage, cerebral amyloid angiopathy, or small vessel disease, may have increased associated risk of intracerebral hemorrhage.

- **Alcohol Consumption and Smoking**

Stroke type defines the risks associated with alcohol consumption. A J shaped relationship is found by the researchers between stroke and alcohol consumption, ≤ 2 drinks per day in men, and ≤ 1 in women are safe from ischemic stroke, but heavy drinkers are prone to it. Hypertensive, chronic alcohol drinkers are at higher risk of hemorrhagic stroke.

Cocaine, ecstasy, amphetamines, and heroin are associated with both types of stroke. When it comes to cigarette smoking, it nearly doubles the risk of stroke. It is found that smoking contributes almost 15% of the global stroke deaths. Smoking cessation rapidly and highly reduces the stroke risk, and the risk almost disappears after 2 to 4 years of cessation.

- **Infection and Inflammation**

Just as infection and inflammation increase the risk for various cardiovascular diseases and cause mortality, similarly they are also found to be associated with stroke. In a study carried out on C-reactive protein, using a highly sensitive assay (hs-CRP) revealed that it has a consistent association with the stroke. CRP is an acute-phase protein released by the liver into the blood during inflammation that can lead to cardiovascular events. For example, monomeric CRP interconnects with other immune system agents and activate platelets and complement proteins. Each CRP has an effector and recognition face. The recognition face of CRP can bind itself with a diverse set of structural groups including nuclear autoantigens, lipoproteins, phosphocholine residues in the C-polysaccharide fraction of apoptotic cells and *Streptococcus pneumoniae*. Binding of this recognition face pinches a conformational change that initiates effector face processing by activating complement pathways. C1q and Fc receptors, some of which are present on endothelial cells binds with the effector's face when the pathway is activated. Through this process and a few others, inflammatory mediators like cytokines and CRP directly participate in stroke risks.

In atherosclerosis, plaque releases high levels of inflammatory activated macrophages and inflammatory mediators that increase the level of inflammatory markers. These markers reflect elevation in hsCRP, depicting a kind of vascular disease burden and elevated inflammation levels in the blood.

Another important aspect that elevates the stroke risks is chronic infections both bacterial and viral. Herpes simplex virus 1 and 2, *helicobacter pylori*,

chlamydia pneumoniae and cytomegalovirus are a few examples of agents causing chronic infections. As the infection increases in the body and takes a severe state, the infection burden index rises and so does the risk of all the strokes. Risk is usually due to greater immunosuppression, adverse metabolic effects, and impacts of antiretroviral drugs.

Stroke Prevention

The purpose of stroke prevention is the imperative decline in one or multiple risk factors that otherwise leads to a stroke. These factor reduction processes can be a cluster, for example, used on a population, community, or at an individual level. As in some cases, antiplatelets are used with an aim to reduce ischemic stroke risk for patients who are at an elevated risk level rather than merely reducing a factor.

Generally, three broad levels opted for stroke prevention are:

1. The most generalized and broadly opted method is primordial prevention. It deals with the healthy living standards of the specified group or community. The aim is to decrease the overall incidence of physiological stroke risk factors.
2. The second method is at the individual level known as primary prevention. It deals with the improvement of the risk factor profile in persons who have a healthy history with no stroke or transient ischemic attack signs.
3. The third one is secondary prevention. It is the most targeted and specific and is only opted when a patient has experienced a TIA or stroke.

Examples of primordial prevention include a healthy diet, weight control, increased physical activity, and healthy public interactions, smoking cessation encouragement, and a positive attitude. On the other hand, primary and secondary stroke prevention involves the individual's medical and personal lifestyle amendments, especially if they have diabetes mellitus or hypertension.

CONCLUSION:

Recent years have witnessed stupendous strides in managing stroke risk factors. Studies have shown that efforts are made not only to control the factors of hemorrhagic and ischemic stroke but also their etiologic subtypes. Research has shown that atrial fibrillation and linked atrial cardiopathies are responsible for cardioembolic stroke, lipids are associated with atherosclerotic stroke, genetic analyses can aid in understanding specific stroke categories, and mutation in genes is responsible for large and small vessel, cardioembolic and other related subtypes of stroke.

Genetics has also paved many ways out for stroke pathogenesis and better treatment for cardiovascular diseases. Evidence has shown that various medical and behavioral treatments have positive outcomes. Statin therapy, blood pressure reduction, antiplatelets, carotid revascularization, diet modification, and anticoagulants have all been proved to be very effective in the stroke fighting path.

An alternative approach is the prevention of strokes like cluster therapy or personal and secondary individual therapy. All these aspects have the potential to dramatically minimize the risks of stroke by handsomely tackling multiple factors.

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