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Meta-Analysis

Relationship Between Smoking and Ischemic Stroke: Meta Analysis

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ABSTRACT

Background: Ischemic stroke is a non-communicable disease that has irreversible and modifiable risk factors. One of the risk factors that can be changed in preventing ischemic stroke is smoking behavior. The purpose of this study was to determine the relationship between smoking and the incidence of ischemic stroke from several previous studies.
Subjects and Method: This article was compiled with a systematic review and meta-analysis study. This study uses the PICO model as follows. Population= Patients at Risk of Ischemic Stroke, Intervention= Smoking, Comparison= Not Smoking, and Outcome= Ischemic Stroke Incidence. The articles used in this study were obtained from several databases including PubMed and ScienceDirect. This article was collected within 1 month. The keywords to search for articles were as follows: Current AND Smoking OR Tobacco OR Cigarettes AND Hypertension AND "Ischemic Stroke" OR CVA (Cerebrovascular Accident).
Results: Nine articles reviewed in this meta-analysis were from Lebanon, Mexico, Pakistan, Finland, Pakistan, United States of America, Saudi Arabia, Bangladesh, Iran. In this study, smokers had a 1.66 times risk of developing an ischemic stroke compared to nonsmokers and it was statistically significant (aOR= 1.66; 95%CI= 1.48 to 1.86; p< 0.001). People who smoked had a 1.66 times risk. experienced the incidence of isleemic stroke compared to non-smokers and was statistically significant (aOR= 1.66; 95%CI= 1.48 to 1.86; p< 0.001).
Conclusion: Smoking has a relationship with the occurrence of ischemic stroke in at-risk patients.

Keywords: smoking, hypertension, ischemic stroke.

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BACKGROUND

According to (WHO, 2016) ischemic stroke is a cerebrovascular event when there is a blockage in the blood vessels in the brain. Ischemic stroke as one of the non-communicable diseases that became the number 2 cause of death in the world in 2017 (Krishnamurthi et al., 2020). Prevention of stroke is considered less successful than treatment because the mortality-rate of stroke has decreased by 36% while the incidence has only decreased by 36% (Feigin et al., 2021). Stroke risk factors include non-modifiable factors (age, gender, race/ethnicity, and genetics) by 85% and modifiable factors (hypertension, physical activity, alcohol consumption, and smoking) by 74% (Upoyo et al., 2021; Feigin et al., 2021).

Prevention of stroke has been declared by the World Stroke Organization which recommends four primary prevention strategies for stroke, including strategies to reduce exposure to risk factors, strategies for using applications to increase motivation to prevent risky lifestyles, pharmacological strategies with blood pressure-lowering and lipid-lowering drugs, strategies for controlling risk factors. risk behavior, especially smoking behavior (Owolabi et al., 2022).

Smoking is a common thing that is done by young people, even men and women are not uncommon to smoke. Smoking is the most common form of tobacco use and all forms of tobacco are harmful. The tobacco epidemic is one of the biggest public health threats in the world, killing more than 8 million people per year worldwide. More than 7 million deaths occur in active smokers and 1.2 million in passive smokers (WHO, 2021). According to the US Office of the Surgeon General, smoking has a 24 times risk factor for causing fatal conditions and even death in hypertension and stroke (Kaplan et al., 2021).

Smoking is the strongest risk factor for stroke (Pan et al., 2019). Research Markidan et al. (2018) revealed that there was a strong dose-response relationship between the number of cigarettes smoked every day and the incidence of stroke. Therefore, in this study the researchers wanted to prove whether there is a relationship between smoking and the incidence of stroke. So that this study was appointed with the title "The Relationship Between Active Smokers and Stroke Events".

SUBJECTS AND METHOD

1. Study Design

The research design used in this study was a systematic review and meta-analysis. The articles used in this study were obtained from several databases, including PubMed and Science Direct by selecting articles published in 2012-2022 using the PRISMA flow chart guidelines. The keywords used are Current AND Smoking OR Tobacco OR Cigarettes AND Hypertension AND "Ischemic Stroke" OR CVA.

2. Inclusion Criteria

The inclusion criteria used in this study were full paper articles with case-control research methods that analyzed the relationship between smoking and ischemic stroke using the Adjusted Odd Ratio relationship measure with a 95% confidence interval.

3. Exclusion Criteria

Exclusion criteria in this study included articles published other than English and Indonesian, non-case control study designs, non-full text articles, articles published before 2012.

4. Definition Operational of Variable

Formulation of the problem in this study using PICO. The population is people with hypertension. The intervention was an active smoker, with a comparison of non-smokers and the outcome was the incidence of ischemic stroke.

Smoking is the activity of burning and smoking tobacco mixed with tar and nicotine in paper or pipes.

Ischemic stroke is a clinical sign of dysfunction or damage to brain tissue caused by a lack of blood flow to the brain, thereby interfering with the need for blood and oxygen in brain tissue (Caplan, 2000).

5. Study Instruments

Research is guided by the PRISMA flow diagram and quality assessment using the Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

In this study, data analysis was carried out using the Review Manager application (RevMan 5.3). Data were analyzed based on variations between studies by determining

the use of the fixed effects analysis model. In this study using I^2 to measure the dispersion. The results of data analysis are in the form of effect sizes from the heterogeneity of the study, which later the results of the analyzed data will be interpreted in the form of forest plots and funnel plots.

RESULTS

This study was conducted by reviewing articles from primary studies regarding the relationship between smoking and ischemic stroke using the PRISMA flow chart, as shown in Figure 1. We obtained 9 articles from 3 continents, namely, 6 studies from the Asian continent, 1 study from the European continent, 1 study in Europe. Continent of South America, and 1 study on the continent of North America. The results for several articles state smoking as a risk factor associated with the incidence of ischemic stroke. After assessing the quality of the research, 9 articles included in the quantitative meta-analysis synthesis process were analyzed using the RevMan 5.3 application.

Interpretation of the results of the meta-analysis process can be seen through the forest plot in figure 3. There was low heterogeneity between experiments (I^2= 43%). Thus, the fixed effects model was used in the data analysis on the forest plot. People who smoked had a 1.66 times risk of developing an islemic stroke in patients with hypertension than nonsmokers and were statistically significant (aOR= 1.66; 95%CI= 1.48 to 1.86; p<0.001).

In Figure 4, the smoking habit of hypertensive patients on the incidence of ischemic stroke shows a publication bias which is indicated by the asymmetry of the right and left plots where there are 3 plots on the left and 6 plots on the right which illustrates the overestimation of the effect of smoking on the incidence of ischemic stroke.

Figure 1. Map of Study Area

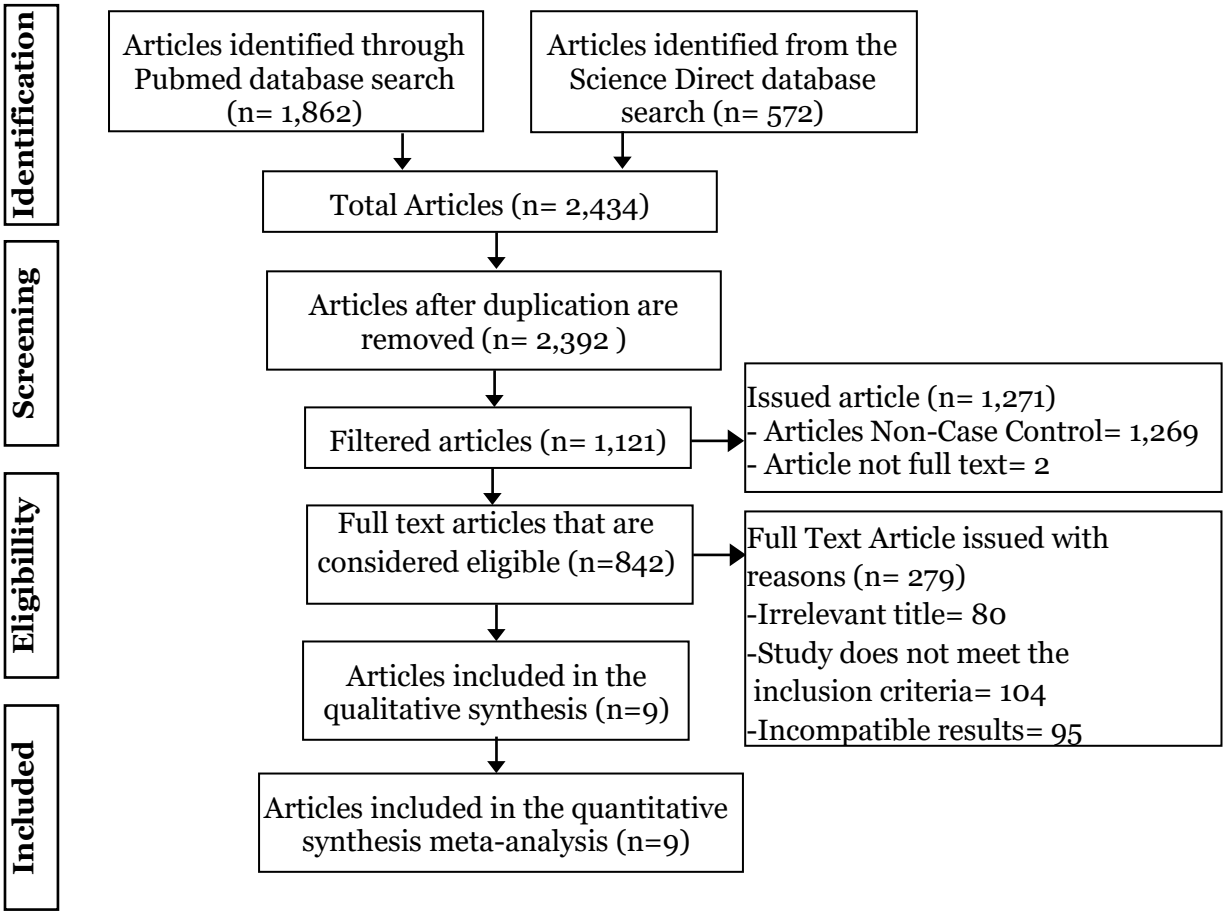

Figure 2. PRISMA Flowchart

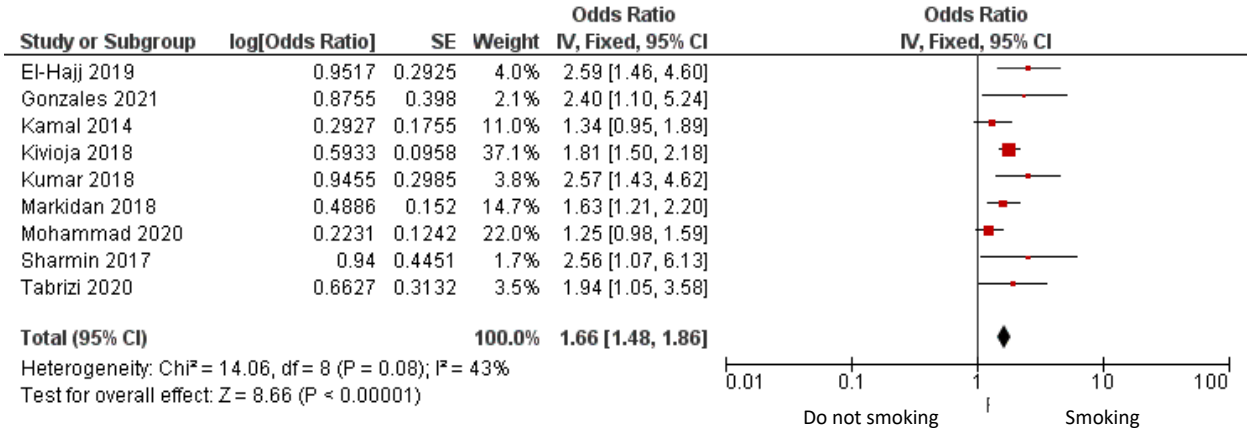

Figure 3. Forest Plot Relationship of Smoking with Ischemic Stroke Incidence

Table 1. Critical Appraisal Checklist for Case Control Studies the Relationship of Smoking to Stroke

No	Question	El-Hajj (2019)	Gonzales (2021)	Kamal (2014)	Kivioja (2018)	Kumar (2018)	Markidan (2018)	Mohammad (2020)	Sharmin (2016	Tabrizi (2020)
1.	Were the groups comparable apart from the presence of disease in cases or absence of disease in controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.	Are the cases and controls appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.	Were the same criteria used to identify	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.	cases and controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.	Is exposure measured in a standard, valid and reliable manner?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.	Was exposure measured in the same way for cases and controls?	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes
7.	Were confounding factors identified?	No	No	Yes	No	Yes	No	No	No	No
8.	What are the strategies for dealing with confounding factors?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9.	stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10.	Were results assessed in a standardized, valid and reliable manner for cases and controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. Description of the Primary Study of the Relationship of Smoking with Ischemic Stroke Incidence

Author (Year)	Country	Sample	Population	Intervention	Comparison	Outcome	aOR (95%CI)
El-Hajj (2019)	Lebanon	650	Ischemic Stroke Patients over 18 years old	Smoking Status	Do not smoke	Ischemic Stroke Incidence	2.59 (1.46 to 4.59)
Gonzales (2021)	Meksiko	408	Ischemic stroke patients aged 45 or younger	Smoke	Do not smoke	Ischemic CVD Kejadian	2.40 (1.1 to 4.5)
Kamal (2014)	Pakistan	644	Ischemic stroke patients due to atherosclerosis aged 18 years or older	Smoking with Tobacco	Do not smoke	Ischemic Stroke Due to Intra-cranial Stenosis	1.49 (1.03 to 2.16)
Kivioja (2018)	Finlandia	2364	First attack ischemic stroke patients aged 15-49 years	Cigarette	Do not smoke	First attack ischemic stroke	1.81 (1.50 to 2.17)
Kumar (2018)	Pakistan	288	Ischemic stroke patients due to hypertension at the first attack are 35 years old or older	Cigarette Smoking	Do not smoke	Incidence of Ischemic Stroke Due to Hypertension	1.25 (0.98 to 2.41)
Markidan (2018)	Amerika Serikat	1145	Men aged 15 to 49 years who are at risk of ischemic stroke	Smoking Status	Do not smoke	Risk of Ischemic Stroke	1.88 (1.44 to 2.44)
Mohammad (2020)	Saudi Arabia	194	Patients after ischemic stroke treatment	Smoking Status	Do not smoke	Ischemic Stroke Incidence	1.25 (0.98 to 2.41)
Sharmin (2016)	Bangladesh	100	Ischemic stroke patients aged 18 to 65 years	Smoking habit	Do not smoke	Incidence of ischemic stroke	2.56 (1.07 to 6.15)
(Tabrizi et al., 2020)	Iran	420	First attack ischemic stroke patient	Ciggarette Smoking	Do not smoke	First attack ischemic stroke	1.94 (1.05 to 3.58)

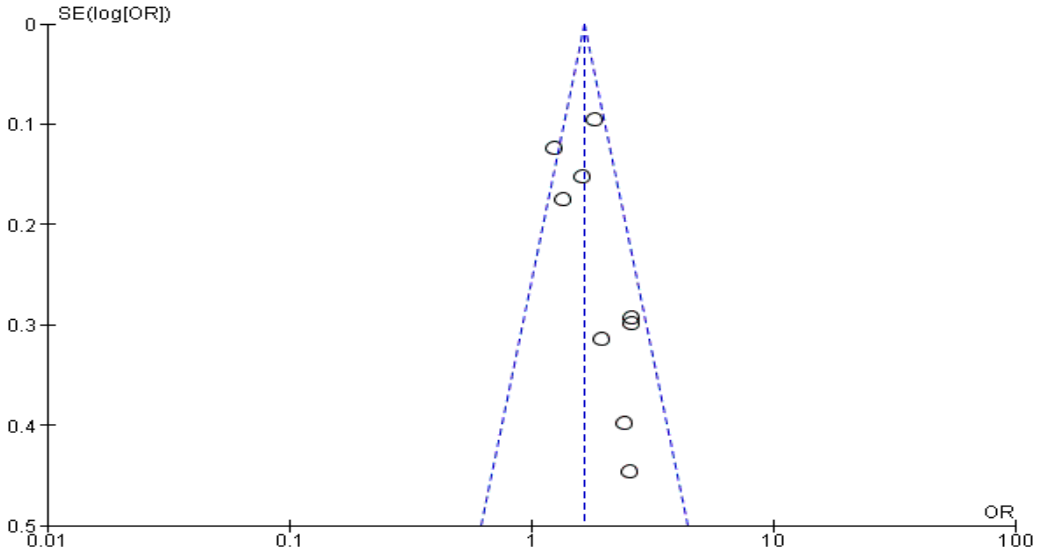

Figure 4. Funnel Plot Relationship of Smoking with Ischemic Stroke Incidence

DISCUSSION

Ischemic stroke as one of the non-communicable diseases that became the number 2 cause of death in the world in 2017 (Krishnamurthi et al., 2020). Stroke is caused by many risk factors, and one of them is smoking. The relationship between smoking and the incidence of ischemic stroke still requires further evidence, so this study was conducted with a systematic review study and meta-analysis to obtain general conclusions from various similar studies that have been carried out by previous researchers who examined the relationship of smoking to the incidence of ischemic stroke. Meta-analysis is an epidemiological study design that aims to systematically review (systematic review) and combine quantitative estimation results (meta-analysis) from a number of previous studies that answer the same research problem and can be combined (Murti, 2018). In this meta-analysis, showing a significant relationship between smoking and the incidence of ischemic stroke summarized from various research articles and obtained results (aOR= 1.66; 95%CI= 1.48 to 1.86; p<0.001) which is described in the forest plot and funnel plots.

The results of this study are supported by research by Pan et al, 2019 which found that smoking can increase the overall risk of stroke compared to not smoking. The results of the study by Markidan et al, 2018 stated that there was a strong dose-response relationship between the number of cigarettes smoked every day and the incidence of ischemic stroke.

Smoking can cause stroke in various ways. The main components in tobacco smoke are nicotine, carbon monoxide and oxidant gases that can cause stroke. Toxic substances contained in cigarette smoke can damage blood vessels, causing inflammation and endothelial cell dysfunction that causes blood to clot (Jha, 2020). According to Sharmin et al, 2016, smoking has almost double the risk of ischemic stroke in every individual. Tobacco smoke contains 7,000 chemicals. Chemicals from the lungs enter the bloodstream and cause changes and damage to blood circulation in the body (Sharmin, 2016).

Decreased function of vasodilation in blood vessels as one of the early manifestations of ischemic stroke. In humans, exposure to cigarette smoke can interfere with endothelium-dependent vasodilation in

macrovascular sites such as the coronary and brachial arteries. Nitric Oxide and free radicals are responsible for the vasodilatory function of the endothelium. Where cigarette smoke or nicotine can reduce the availability of the Nitric Oxide. Apart from being a vasoregulatory molecule, Nitric Oxide also plays a role in regulating inflammation, leukocyte adhesion, platelet activation, and thrombosis. Thus, changes in nitric oxide biosynthesis have primary and secondary effects on the initiation and promotion of atherosclerosis as well as on thrombotic events (Ambrose and Barua, 2004).

It is known that smoking has an adverse effect in the form of ischemic stroke, but the prevalence of smokers is still high. This is because countries with large populations have a high prevalence of tobacco use. The demographic forces of population growth also mean that there is no apparent progress in reducing smoking prevalence. Even countries that have had a large decline in smoking prevalence have not had progress in the last 5 years. (Reitsma et al., 2021).

There are several ways that can be done to stop smoking, namely by treatment methods, by looking for drugs that can cure addiction to cigarettes. Changes in behavior, changing without the help of drugs, just stop just like that through behavioral changes by avoiding and avoiding cigarettes and people who smoke. Positive encouragement, meaning to include the desired positive thoughts and behaviors. The three forms of therapy chosen for smoking cessation in health services according to Kleinman are included in the popular sector, because the selected health service information is only based on the advice of friends, family, or lay people and not from medical groups (Stead et al., 2013).

From this meta-analysis, it can be concluded that there is a relationship between smoking and the incidence of ischemic stroke. However, we did not find whether ex-smokers also still have a risk of stroke so that quitting smoking can eliminate the risk of stroke. We also did not analyze the number of cigarettes smoked and the duration of smoking each day to distinguish multiples of increased risk of ischemic stroke. So it is necessary to do further research.

The limitations of this study are observational data and publication bias. Several confounding variables, such as the type of cigarette used, the frequency of smoking, and other factors were less controllable. This review uses completely free electronic study database searches, so there is still the possibility of articles being excluded.

AUTHORS CONTRIBUTION

Sakinah who selects the topic, searches for and collects research data. Septyan Dwi Nugroho analyzes data and reviews research documents.

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We would like to thank the database providers PubMed and ScienceDirect. Sakinah and Septyan were the main researcher who selected topics, explored, and collected data of the study. Nindita, Dilma, Victoria, Lely played a role in analyzing data and reviewing documents of the study.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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