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INFLUENCE OF DIABETES MELLITUS ON THE INCIDENT OF STROKE: META-ANALYSIS

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ABSTRACT
Blood vessel disorders can occur due to the narrowing and hardening of the artery walls, which is called atherosclerotic plaque. Stroke is a serious health problem because of the high mortality and morbidity rates and its impact can cause chronic disability and occurs not only in elderly people but also in young people. This study aims to estimate and analyze the effect of diabetes mellitus on the incidence of stroke. This research is a systematic review and meta-analysis research using the PRISMA diagram. Article searches were carried out based on the PICO Model eligibility criteria. P= DM patient; I= Diabetes mellitus; C= Normal blood sugar; O= Stroke. The articles used come from Google Scholar. With keywords including "Diabetes mellitus" AND "Normal blood sugar" AND "Stroke" AND "adjusted Odds Ratio". Articles were analyzed using the PRISMA diagram and the Review Manager 5.3 application. 5 articles (2016-2022) with a randomized controlled trial study design will be used as a source for meta-analysis of the effect of diabetes mellitus on the incidence of stroke. Shows that people with diabetes mellitus increase the likelihood of stroke. Patients suffering from diabetes mellitus increase the likelihood of stroke by 2.41 times compared to those with normal blood sugar. (aOR= 2.41; 95% CI= 1.71 to 3.39; p=0.0001), and statistically significant. The forest plot also shows high heterogeneity of effect estimates between studies (I2 = 73%). The funnel plot shows that there is publication bias which tends to exaggerate the true effect (overestimate). Meta-analysis of 5 studies cross-sectional concluded that people with diabetes mellitus increase the likelihood of stroke.

Keywords: diabetes mellitus; stroke; sufferers

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder caused by the pancreas not producing enough insulin or the body not being able to use the insulin it produces effectively. As a result, there is an increase in glucose concentration in the blood (Zhao et al., 2021; Indarto et al., 2023; Widiyanto et al., 2022). Blood vessel disorders can occur due to the narrowing and hardening of the artery walls, which is called atherosclerotic plaque. If this condition continues it can cause a stroke. Stroke is a serious health problem because of the high mortality and morbidity rates and its impact can cause chronic disability and occurs not only in elderly people but also in young people. Stroke is also the main cause of disability for sufferers of this disease (Kezerle et al., 2022). A stroke is defined as an interruption in the blood supply to the brain, usually due to a blockage caused by a blood clot (Sarfo et al., 2022). This disrupts the supply of oxygen and nutrients to the brain, causing damage to brain

tissue. A stroke is also believed to be an acute disturbance of nerve function caused by a sudden disruption of cerebral blood circulation, the symptoms and signs of which are related to localized disturbances (Isaman et al., 2021)

According to WHO (World Health Organization), 15 million people suffer from stroke worldwide every year. Of this number, 5 million people, including 4,444 people died and 5 million others experienced permanent disability (Zaki et al., 2020). Based on the results of Riskesdas (2018), the incidence of stroke in Indonesia increased from 7% in 2013 to 10.9% in 2018. Looking at current trends, it is estimated that it will continue to increase until reaching 23.3 million people will die in 2030 (Ariva et al., 2022). Stroke is a very dangerous disease because it can cause disability and even death. To reduce the increase in the incidence of stroke, prevention efforts are needed related to the risk factors that cause these events (Mohammad, 2020). There are two risk factors for stroke: controllable risk factors and uncontrollable risk factors. One risk factor that cannot be controlled is gender. One risk factor that can be controlled is hyperglycemia (Al-Eithan et al., 2011).

Several other studies have been conducted to determine the effect of diabetes on stroke rates (Gudi et al., 2019) suggesting that people with a history of diabetes are 2.7 times more likely to develop the disease than people without a history of diabetes. Other research conducted by(Zhao et al., 2021), found that diabetes increased the risk of stroke by 1.9 times compared to people without a history of diabetes. Based on the background above and several similar previous research findings regarding the influence of diabetes mellitus on the incidence of stroke. So researchers are interested in conducting research using a systematic review and meta-analysis which can summarize several results of primary studies or previous research with a systematic search to combine the results and get more precise estimates to draw new conclusions. This study aims to estimate and analyze the effect of diabetes mellitus on the incidence of stroke.

METHOD

This research is a systematic review and meta-analysis research using the PRISMA diagram. The publications utilized in this study were found between 2016 and 2022 in a number of databases, including Google Scholar, Pubmed, and Science Direct. 1022 identified articles screened and inclusion were carried out based on the PICO Model eligibility criteria and 5 articles included in meta-analysis. P= DM patient; I= Diabetes mellitus; C= Normal blood sugar; O= Stroke. The articles used come from the database, namely: Google Scholar. With keywords including "Diabetes mellitus" AND "Normal blood sugar" AND "Stroke" AND "adjusted Odds Ratio".

Articles were analyzed using the PRISMA diagram and the Review Manager 5.3 application.

Meta-analysis is carried out in the following 5 steps:

1) Formulate PICO format research questions (Population, Intervention, Comparison, and Outcome).
2) Search for primary study articles from various electronic and non-electronic databases such as PubMed and Google Scholar.
3) Carrying out screening determines inclusion and exclusion criteria and carries out critical assessments.
4) Extract primary study results data and synthesize effect estimates using the Revman application.
5) Interpret the results and conclude.

RESULTS

Search for articles in this research through databases including PubMed and Google Scholar. With keywords including: "Diabetes mellitus" AND "Normal blood sugar" AND "Stroke" AND "adjusted Odds Ratio". The review process for related articles can be seen in the PRISMA flow diagram in Figure 1. Research related to the effectiveness of honey in healing wounds consists of 5 articles. The initial search process yielded 390 articles, after the process of deleting published articles 174 articles were obtained with 100 of them meeting the requirements for further research. A full-text review was carried out as many as 5 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis. It can be seen in Figure 2 that research articles come from 5 of the Asian continents (Iran, Lebanon, Arabia, Ghana, China).

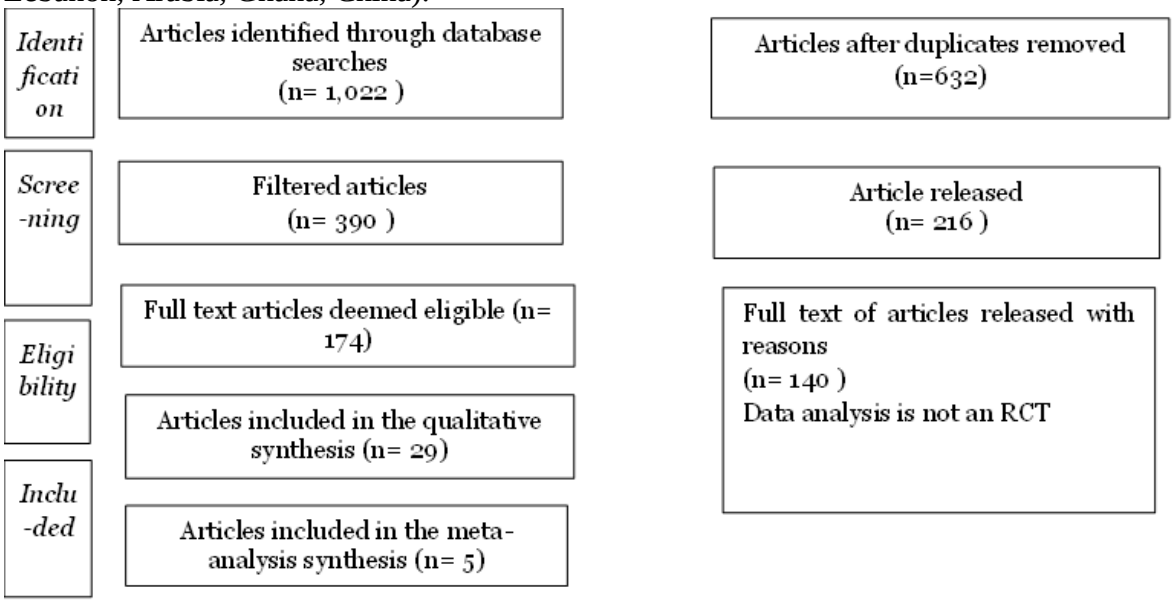

Figure 1. PRISMA Flow Diagram of the influence of diabetes mellitus on the incidence of stroke

Figure 2. Regional map of the influence of diabetes mellitus on the incidence of stroke

Table 1. Results of quality assessment of aOR studies on the influence of diabetes mellitus on the incidence of stroke

Author (Year)	Question Criteria							Total
	1	2	3	4	5	6	7	
Khodabandehlou et al. 2016	7	4	4	4	4	4	2	29
El-Hajj et al. (2019)	8	4	4	4	4	4	2	30
Mohammed (2020)	8	4	4	4	4	4	2	30
Sarfo et al. (2022)	7	4	4	4	4	4	2	29
Zhang et al. (2017)	8	4	4	4	4	4	2	30

Answer score Description:

1. If there is a conflict of interest, give a value of "0".
2. If there is no conflict of interest, give a value of "2".
3. If in doubt, rate "1".

Description of question criteria:

1. Formulation of research questions in the acronym PICO
   a. Is the population in the primary study the same as the population in the PICO meta-analysis?
   b. Is the operational definition of exposure/intervention in the primary study the same as the definition intended in the meta-analysis?
   c. Is the comparison used in the primary study the same as that planned in the meta-analysis?
   d. Are the outcome variables examined in the primary study the same as those planned in the meta-analysis?
2. Methods for Selecting Research Subjects
   a. Is the sample selected from the population so that the sample represents the population?
   b. Was the allocation of subjects into experimental and control groups carried out by randomization?
3. Methods for measuring comparison (intervention) and outcome variables (outcome)
   a. Are the exposure/intervention and outcome variables measured with the same instruments (measuring tools) in all primary studies?
   b. If the variable is measured on a categorical scale, are the cutoffs or categories used the same across primary studies?
4. Design-related bias
   a. Was double-blinding carried out, that is, the research subjects and research assistants who helped measure the outcome variables did not know the intervention status of the research subjects?
   b. Is there a possibility of "Loss-to Follow-up Bias"? What have primary studies done to prevent or overcome such bias?
5. Methods for controlling confusion
   a. Is there any ambiguity in the results/conclusions of primary studies?
   b. Have primary study researchers used appropriate methods to control the influence of confounding?
6. Statistical analysis methods
   a. Are outcome data compared between the experimental group and the control group after the intervention?
   b. Was all data analyzed according to randomization results or only data from subjects who met the research protocol?
7. Conflict of interest
   a. Is there a conflict of interest with the research sponsor?
   (UNS Public Health, 2023)

After assessing the quality of the research, a total of 5 articles with a cross-sectional study design were obtained which will be used as a source for meta-analysis of the influence of diabetes mellitus on the incidence of stroke. The articles were then extracted and summarized according to the research PICO. Table 2, a description of primary research on the influence of diabetes mellitus on the incidence of stroke, which carried out a meta-analysis of 5 articles with varying research locations, namely from Iran, Lebanon, Arabia, Ghana, and China. Similarities were found in these studies, namely a cross-sectional research design, the

research subjects were diabetes mellitus patients, and the intervention was diabetes mellitus with normal blood sugar. In this study there were also differences in the number of samples, the smallest was 144, and the largest was 4,100.

Table 2.
Description of primary studies on the influence of diabetes mellitus on the incidence of stroke included in the meta-analysis

Author (Year)	Country	Sample	P	I	C	O
Khodabandehlou et al. 2016	Iran	144	DM patient	Diabetes mellitus	Normal blood sugar	Strokes
El-Hajj et al. (2019)	Lebanon	300	DM patient	Diabetes mellitus	Normal blood sugar	Strokes
Mohammed (2020)	Saudi Arabia	194	DM patient	Diabetes mellitus	Normal blood sugar	Strokes
Sarfo et al. (2022)	Ghana	2,431	DM patient	Diabetes mellitus	Normal blood sugar	Strokes
Zhang et al. (2017)	China	4,100	DM patient	Diabetes mellitus	Normal blood sugar	Strokes

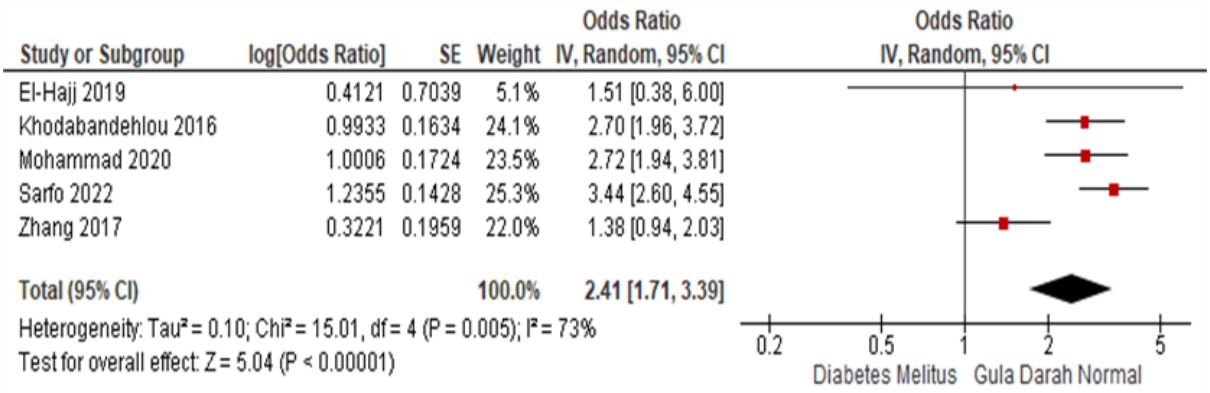

Figure 3. Forest plot of the influence of diabetes mellitus on the incidence of stroke

Forest Plots Figure 3. Shows that people with diabetes mellitus have an increased likelihood of stroke. Patients suffering from diabetes mellitus increase the likelihood of stroke by 2.41 times compared to those with normal blood sugar. (aOR= 2.41; 95% CI= 1.71 to 3.39; p=0.0001), and statistically significant.

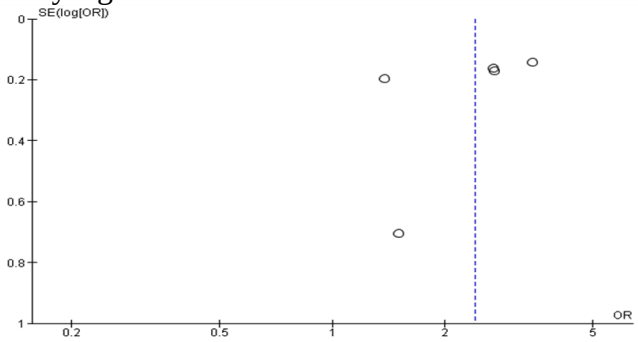

Figure 4. Funnel plot of the influence of diabetes mellitus on the incidence of stroke

Funnel plotsin Figure 4. Shows the unequal distribution of effect estimates between studies to the right and left of the vertical line of average estimates. The image above shows the existence of publication bias (overestimate). The plot on the left has 2 plots with a standard error between 0 and 0.7, and the plot on the right has 3 plots with a standard error between 0 and 0.2.

DISCUSSION

The influence of diabetes mellitus on the incidence of stroke

In diabetics, increased blood fat levels greatly increase the risk of heart disease and stroke. Diabetes accelerates the occurrence of atherosclerosis in both small and large blood vessels throughout the blood vessels, including the blood vessels of the brain and heart (Chehaibi et al., 2014). High blood glucose levels in stroke will expand the area of infarction or dead cells due to the formation of lactic acid due to glucose metabolism carried out anaerobically or with little oxygen which damages brain tissue (Tsivgoulis et al., 2019). One of the causes of diabetes mellitus to become a stroke is the process of atherosclerosis. Patients with proven cerebral atherosclerosis are diabetics (Mohammad, 2020). The occurrence of hyperglycemia causes damage to the walls of large blood vessels and peripheral blood vessels, besides that it will also increase platelet aggregates, both of which can cause atherosclerosis (Kurnianto & Pramukarso, 2019). Hyperglycemia can also increase blood viscosity which will then cause an increase in blood pressure or hypertension and result in ischemic stroke (Kang et al., 2019). The macroangiopathic process is considered very relevant to stroke and there is also evidence of the involvement of the macroangiopathic process which is characterized by the occurrence of lacunar strokes in diabetes mellitus sufferers (Oyarce-calderón, 2023).

In the opinion of researchers, diabetes mellitus is a condition where a person's hyperglycemia increases due to a deficiency in insulin secretion (Hong et al., 2019). Hyperglycemia causes damage to the walls of large blood vessels and peripheral blood vessels, besides that it will also increase platelet aggregates, both of which can cause atherosclerosis and stroke due to blockages in the brain stem due to the atherosclerosis process (Zhu et al., 2019). Stroke is a functional brain disorder in the form of death of neurological nerve cells due to disruption of blood flow in one part of the brain. Specifically, this occurs due to stopping blood flow to the brain due to blockage or bleeding (Han et al., 2020). A person who has a stroke will lose the function of part of the brain because the dead brain cells can no longer function to control parts of the body. This disorder can appear suddenly within a few seconds or within a few hours with symptoms or signs according to the part of the brain that is disturbed (Lim et al., 2020). Diabetes mellitus is a metabolic disorder syndrome with inappropriate hyperglycemia as a result of a deficiency in insulin secretion or reduced biological effectiveness of insulin or both and is a degenerative disease whose incidence rate is quite high (Marso et al., 2010). Diabetes mellitus increases the risk of stroke because excess glucose in the blood causes vasculopathy, making one more prone to hypertension and atherosclerosis. Additionally, diabetes increases the risk of blood clots, which can lead to heart attacks and strokes (Pitt et al., 2022).

CONCLUSION

This meta-analysis research was conducted using 5 articles originating from Iran, Lebanon, Arabia, Ghana, and China. All of the research was carried out with a cross-sectional design. The total sample was 7,169 diabetes mellitus sufferers. Forest plots show that people with diabetes mellitus increase the likelihood of stroke. Patients suffering from diabetes mellitus increase the likelihood of stroke by 2.41 times compared to those with normal blood sugar. (aOR= 2.41; 95% CI= 1.71 to 3.39; p=0.0001), and statistically significant. The forest plot also shows high heterogeneity of effect estimates between studies (I2 = 73%). The funnel plot shows that there is publication bias which tends to exaggerate the true effect (overestimate).

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