

The Relationship of Hypertension and Diabetes Mellitus with Ischemic Stroke

Sari Dianita Purnama^{1,2*}, Roselina Panghiyangani², Lenie Marlinae², Husaini², Meitria Syahadatina Noor²

¹Sultan Suriansyah Regional Hospital, Banjarmasin, Indonesia

²Master of Public Health Study Program, Faculty of Medicine and Health Sciences, Universitas Lambung Mangkurat, Banjarbaru, Indonesia

Correspondence Email: purnamasaridianita@gmail.com

ABSTRACT

Ischemic stroke is a common cause of disabilities among adults around the world and the second reason of death around the world after the first one, ischemic heart disease, the prevalence keeps rising after years. Some of the most common risk factors are hypertension, diabetes mellitus, heart disease, smoking, alcohol consumption, and high blood lipid levels that affect the blood viscosity and the blood clot. This research aims to study some of ischemic stroke's risk factors which are hypertension and diabetes mellitus. This research is an observational retrospective study with effect size that can be found by secondary using search engines such as Google Scholar, Science Direct, PubMed, etc. The data filtered only for the last 5 years old journal, case-control study, and logistic regression analysis. From the 180 articles, found 14 worth articles about hypertension and diabetes mellitus with stroke ischemic and analyzed using JASP app. The result is hypertension related with ischemic stroke by p-value 0.0003 and mean effect size 4.32 (95% CI 1.97-9.49), then diabetes mellitus also related with ischemic stroke by p-value 0,00001 and mean effect size 2.99 (95% CI 2.28-3.92). Hypertension and diabetes mellitus statistically related with ischemic stroke by meta-analysis.

Keywords: Ischemic stroke, hypertension, diabetes mellitus

INTRODUCTION

Non-communicable diseases are currently the largest cause of morbidity and mortality in the world and the number is increasing all the time. This will continue to develop into a problem that has an impact on increasing state spending on health so that one of the keys to achieving the sustainable development goals (SDGs) is to prevent non-communicable diseases and their complications. In general, non-communicable diseases have several risk factors that can be prevented such as unhealthy eating patterns, lack of physical activity, alcohol, and smoking, to the final complications that occur. However, it has not been widely studied that the main cause of this non-communicable disease comes from environmental health problems, either direct exposure, air, chemicals, radiation, and even occupational risks. According to WHO, 8.2 million people out of 12.6 million deaths due to the environment are caused by non-communicable diseases with the first rank being occupied by stroke as many as 2.5 million people.¹

The risk factor for stroke itself is basically any event that causes blood flow to the brain to be disrupted. Most of these risk factors are modifiable risk factors where hypertension, smoking, alcohol use, drugs, lack of physical activity, diabetes mellitus, and increased blood lipids are interrelated.²

Many general environmental factors that clinically influence the incidence of hypertension, so it is recommended to be more vigilant and it is hoped that the hypertension guidelines will consider hypertension management from an environmental perspective.³

Diabetes mellitus on the other hand has increased a large socioeconomic and health burden on the world, where it has been stated that the increase in diabetes occurs due to the interaction between environmental risks, biological risks, and behavioral risks.⁴

The environment plays a role in the etiopathology of diabetes mellitus such as obesity, exposure to chemicals, drugs, and organic pollutants. Therefore, the increase in non-communicable diseases, especially stroke

from an environmental perspective, is something that cannot be ignored.⁵ In addition, because ischemic stroke is a common cause of permanent disability in adults worldwide and this illustrates how important it is to understand and manage ischemic stroke.⁶ Based on research and development center, The Indonesia Ministry of Health in 2014 stated that stroke is the first rank of the ten highest causes of death in Indonesia.⁷

In addition to Indonesia, the prevalence of stroke in the world also shows data that ranks the second most common cause of death after ischemic heart disease. This does not even include stroke, which is thought to be largely undiagnosed, with the most popular risk factors being hypertension and diabetes mellitus.⁸

In addition to having a direct effect, hypertension can also be a source of weak blood vessel walls and the formation of atherosclerosis which ultimately facilitates the accumulation of fat which in the future will lead to coronary heart disease and also ends up being ischemic in the brain.⁹

The second most common risk factor after hypertension is diabetes mellitus, which contributes twice the chance of ischemic stroke and is included as a modifiable risk factor related to lifestyle.¹⁰ Briefly, the incidence of diabetes mellitus causes thickening of the walls of blood vessels so that blood vessels narrow and complicate the smooth flow of blood, resulting in infarction of brain cells.¹¹

Several studies in Indonesia have conducted direct patient analysis to see the contribution of these two risk factors to the increasing prevalence of ischemic stroke. Letelay's research (2019) regarding the

relationship between stroke and diabetes mellitus states that diabetes mellitus has a significant effect on ischemic stroke,¹¹ In addition, Ghani (2016) also analyzed both risk factors for hypertension and diabetes mellitus which obtained the same results, namely a significant risk factor for ischemic stroke. However, both of these studies have drawbacks, namely the diagnosis is made only by physical examination without supporting radiological data and only in outpatients so it can be biased by the incidence of TIA (Transient Ischemic Acute) which is a momentary mild ischemic event that occurs less than 24 hours without leaving sequelae.¹² Another study from Risnawati (2014) states that hypertension is the main risk factor followed by diabetes mellitus with the incidence of ischemic stroke.⁹ The difference occurred in the Irdelia study (2014) where hypertension remained at the highest risk but in the same study the number of people with diabetes was less than stroke without diabetes.¹³

Based on the explanation of the importance of ischemic stroke prevention and the results of several studies above, it is necessary to conduct a meta-analysis of the relationship between hypertension and diabetes mellitus with the incidence of ischemic stroke.

METHOD

The research design used is a meta-analysis, which combines various similar scientific studies to get a research conclusion. The stages that will be carried out include Planning, Conducting, and Reporting by adapting the PECOT (Population, Exposure, Comparison, Outcomes, Time) article strategy.

Table 1. Article Determination Strategy with PECOT

Criteria	Determinant
Population	Ischemic stroke patients hospitalized
Exposure	The relationship between the incidence of ischemic stroke with hypertension and diabetes mellitus
Ratio	The ischemic stroke case group and the control group are people who are declared neurologically healthy without complaints related to ischemic stroke or other neurological diseases
Result	There is a relationship between hypertension and diabetes mellitus with the incidence of ischemic stroke
Time	January 2016 until 2021

The data used is secondary data obtained from previous studies obtained from

books and primary reports or results contained in scientific publication articles or international journals and national journals found on GoogleScholar, ScienceDirect, Pubmed, and Research Gate search portals.

Selection Criteria are based on:

1. Updating Data Sources are articles published in 2016-2021 which can be accessed in full in pdf format. The language used is Indonesian or English with the population being hospitalized patients with a diagnosis of ischemic stroke and the article discusses the relationship between risk factors for the incidence of ischemic stroke with at least one variable of hypertension, diabetes mellitus, or both.
2. Case-control study and statistical analysis used is logistic regression.
3. Type of intervention with the theme of the relationship between the incidence of ischemic stroke with hypertension and or diabetes mellitus. The actions taken on the patient are standard actions and supporting examinations without any special intervention that will affect the final results of the study.

The measurement results in this article are the relationship between the incidence of ischemic stroke with hypertension and diabetes mellitus which were analyzed using a meta-analysis application, namely JASP with a benchmark for the final result of tilapia on the forest plot, namely $p: 0,05$, which means that the two variables are related or $p: > 0,05$ which means the two variables are not related.

Article searches are carried out using search engines, namely GoogleScholar, ScienceDirect, PubMed, and ResearchGate. The keywords used in the journal collection were ischemic stroke, ischemic hypertension stroke, diabetes ischemic stroke, ischemic diabetes mellitus stroke.

RESULT AND DISCUSSION

Critical appraisal is the process of evaluating a research article carefully and systematically in order to determine whether it is worthwhile. Research articles that are carried out carefully and systematically to determine if the articles used are feasible based on reliability, validity, and clinical practice, in other words to determine whether the article is suitable for use or not in the meta-analysis. following are the results.

Table 2. Critical Appraisal

No	Article Name (Year)	Location	Number of Research Subjects (people)	Duffy's criteria	PECOT Criteria	Disadvantages	Pros
1.	Diabetes Mellitus as A Risk Factor for Ischemic Stroke: A Case Control Stud Singh (2019) (14)	India	378	Meets the criteria	Feasible	A Small number of research subjects	Research methods and conclusions are well-presented
2.	Dominant Modifiable Risk Factors For Stroke in Ghana and Nigeria (SIREN): A Case Control Study Owalabi (2018) (15)	Nigeria	2,860	Meets criteria	Feasible	Too many variables taken in one subject group	A large number of research subjects
3.	Risk Factors for Early-Onset Ischemic Stroke: A Case-Control Study Kivioja (2018) (16)	Finlandia	2,364	Meets the criteria	Feasible	Too many variables were taken in one subject group	The number of research subjects is large
4.	Stroke Among Young West Africans: Evidence From The SIREN (Stroke Investigative Research and Educational Network) Large Multisite Case-Control Study	Nigeria	4,236	Meets the criterion	Feasible	Less than optimal supporting examination so that there is a risk of bias with other differential diagnoses	The number of research subjects is large

No	Article Name (Year)	Location	Number of Research Subjects (people)	Duffy's criteria	PECOT Criteria	Disadvantages	Pros
Sarfo (2018) (17)							
5.	Post Hypertension and Stroke: A Case Control Study	Indonesia	264	Meets the criterion	Eligible	The number of research subjects is small	Research conducted in Indonesia
Imanda (2019) (18)							
6.	Association of Paroxysmal Supraventricular Tachycardia with Ischemic Stroke: A National Case-Control Study	Taiwan	36,528	Meets the criteria	Decent	There are too many variables so there is a risk that the results will be biased towards other variables.	The number of research subjects is large
Chiang (2017) (19)							
7.	HIV, Antiretroviral Treatment, Hypertension, and Stroke in Malawian Adults, A Case-Control Study	Malawi	725	Meets the criteria	Decent	In the explanation the author focuses on ischemic stroke but the table description still includes hemorrhagic stroke	The number of research subjects is large
Benjamin (2016) (20)							
8.	Relationship Between Factor V Leiden Gene Variant and Risk of Ischemic Stroke: A Case-Control Study	India	500	Meets the criteria	Decent	There is no description of the genetic examination process related to variables	The number of research subjects is large
Kumar (2017) (21)							
9.	Association Between Heavy Metals and Rare Earth Elements with Acute Ischemic Stroke: A Case-Control Study Conducted in the Canary Island (Spain)	Spanyol	175	Meets the criteria	Decent	The number of research subjects is small	The research is well-explained and complete
Medina-Estevez (2020) (22)							
10.	Association Between Carotid Bulb Diaphragm and Ischemic Stroke in Young Afro-Caribbean Patients: A Population-Based Case-Control Study	Prancis	86	Meets the criteria	Decent	The number of research subjects is small	The presentation is simple and easy to understand
Joux (2016) (23)							
11.	Association of Apolipoprotein E Gene Polymorphism with Lipid Profile and Ischemic Stroke Risk	Indonesia	60	Meets the criteria	Decent	The number of research subjects is small	The presentation is simple and easy to understand,

No	Article Name (Year)	Location	Number of Research Subjects (people)	Duffy's criteria	PECOT Criteria	Disadvantages	Pros
	in Type 2 Diabetes Mellitus Patients Maratni (2021) (24)						and the research was conducted in Indonesia.
12	Association Between lncRNA ANRIL Genetic Variants with The Susceptibility to Ischemic Stroke: Form A Case-Control Study to Meta-Analysis Wang (2021) (25)	Cina	1,119	Meets the criteria	Decent	This journal analyzes two types of research in one journal so there is a risk of misinterpreting the results if without confirmation or just glancing at it	The number of research subjects is large
13	Faktor Risiko yang Mempengaruhi Terjadinya Stroke Non Hemoragik pada Pasien di RS Charitas dan RS Myria Palembang Hardika (2020) (26)	Indonesia	150	Meets the criteria	Decent	Small number of research subjects	The presentation is simple and easy to understand, and the research was conducted in Indonesia.
14	COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke Belani (2020) (27)	New York	123	Meets the criteria	Eligible	Small number of research subjects	The research was conducted during the pandemic with the latest conditions and backgrounds

Based on the conclusions from Table 2 above, through the critical appraisal process, it can be stated that the 14 articles used for meta-analysis research are articles that are feasible and meet all the expected criteria.

Based on the article selection process, 180 articles related to ischemic stroke were obtained through a GoogleScholar, ResearchGate, and ScienceDirect. Through various inclusion and exclusion processes, articles that are not full text, case control, not hospitalized, and not using logistic regression analysis will be removed leaving a total of 14 articles.

Based on all the results of these studies, for the incidence of hypertension there are 13 articles which show 11 research results stating that hypertension and the incidence of ischemic stroke are significantly related, but 2 other studies show results are not significantly related the article includes 11 international articles and 2 national articles.

Diabetes mellitus has 12 articles related to the incidence of ischemic stroke with a comparison of 8 articles stating a significant

relationship between the two while the other 4 articles stated that there was no significant relationship between diabetes mellitus and ischemic stroke. A total of 11 articles are international articles and 1 article from a national journal.

The research locations in all articles are very varied, covering Indonesia itself as many as 3 articles, India 2 articles, Nigeria 2 articles, Finland 1 article, Taiwan 1 article, China 1 article, Malawi 1 article, Spain and France 1 article each, and New York 1 article. According to Wang (2021) the influence of ethnicity is very large because different genetic conditions and related to blood vessel resistance cause the hypertension group in Wang's research group in Asia to have no significant effect compared to previous studies in Europe which showed a significant effect. However, the same group still exerted an association between diabetes mellitus and ischemic stroke.²⁸

Race also has a quite different effect when compared between white, African-American, Hispanic, and Asian groups with ischemic stroke incidence, so that in the South

Asian group ischemic stroke is most common compared to other races with ischemic stroke due to embolic type.

The next aspect that looks varied is the number of research subjects, some research subjects only numbered in the tens and others even more than 30,000. The number of research subjects that are more is an advantage and conversely the number of research subjects that are less is a drawback of the study. As in one of the studies on black and white ethnicity and gender with the incidence of ischemic stroke, the research subjects amounted to 25,789 people, it was stated that

the study provides advantages in terms of numbers because it can more deeply observe the variations of ischemic stroke that arise while also providing more opportunities. the results of the adjudication of doctors about the incidence of ischemic stroke and the classification of stroke itself.²⁹

Forest plot analysis showed an overall p value of <0.00001 and a pooled odds ratio of 2.99 (2.28-3.92) with all effects being positive. It was concluded that diabetes mellitus gave a 2.99 times higher risk of triggering ischemic stroke.

Table 3. Comparison of Research Results of The Two Variables Causing Ischemic Stroke

Research variable	Heterogeneity Test	Result	Average of Effect Size
Hypertension	I ² : 99% (very high)	p-value: 0.0003	4.32 (1.97-9.49)
Diabetes mellitus	I ² : 84% (very high)	p-value : <0.00001	2.99 (2.28 – 3.92)

The two variables above give the same heterogeneity test results, namely very high heterogeneity, several things that might cause this to happen are the number of research subjects which is quite varied, there are articles with more than 1,000 research subjects and other articles in the same group only 60 people. In addition, another influential cause is ethnicity. Wang (2021) with his research that also looked at the genetic code to assess the vulnerability of blood vessels of research subjects stated that ethnic Asians tend to be more prone to ischemic stroke than Europeans due to the enzymes and genetic code of their blood vessels. So that ethnic differences mean differences in ischemic stroke response.²⁸

Relationship between Hypertension and Ischemic Stroke

The first variable in the study that has been analyzed is hypertension and its relationship with the incidence of ischemic stroke. After the researcher entered the data, the results of the heterogeneity test of the collected data were heterogeneous data with a p value <0.001 with a research variation value (I²) of 99%. The results of calculations from all articles related to hypertension with the incidence of ischemic stroke, both heterogeneity tests and meta-analysis statistical tests can be seen from the forest plot in picture 1. below which includes 13 articles.

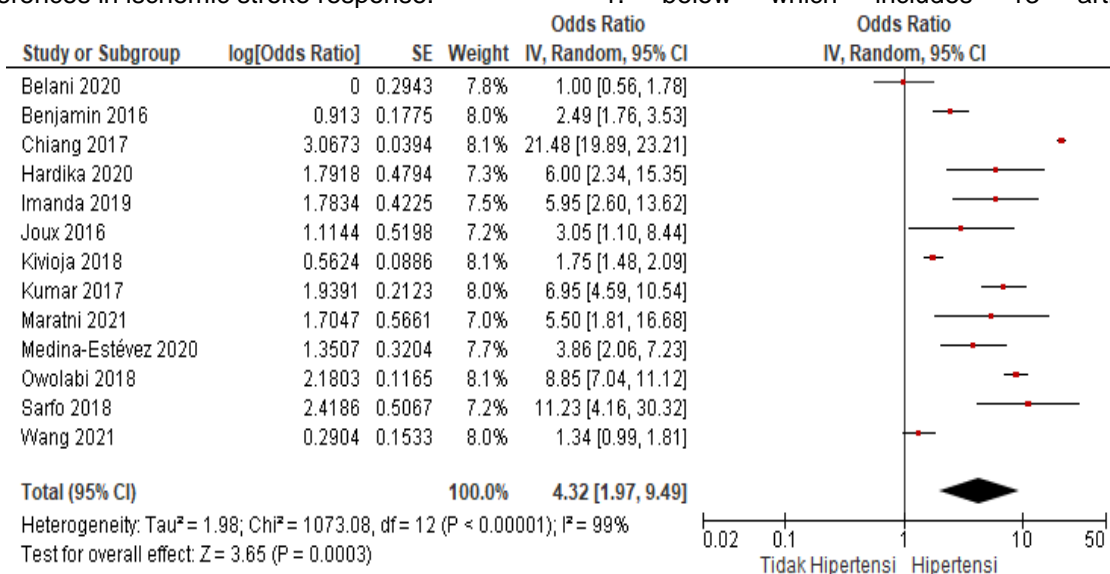


Figure 1. Forest Plot Relationship of Hypertension with Ischemic Stroke Incidence (n=13)

Based on a total of 13 articles that describe the relationship between these two variables, 11 of them have a statistically significant relationship and have a large difference in the number of research subjects between one research group and another (the highest number is 36,528 people and the least is 60 people) so as to give the results of the heterogeneity test. with a very high that is 99%.

A total of 11 articles provided results in accordance with a literature review related to the incidence of hypertension and ischemic stroke. The long-term damage process caused by hypertension can change the anatomy of blood vessels to become weaker and lead to the formation of thrombus which in the future poses the risk of becoming a blockage in any vessel throughout the body. The brain needs a lot of intake through the bloodstream, small obstacles in the brain can cause symptoms of TIA (Transient ischemic attack), namely a momentary stroke (<24 hours) and a larger thrombus will give more permanent symptoms, namely ischemic stroke with persistent sequelae.

In addition to all studies that provide related results, there are also two articles that conclude that hypertension and ischemic stroke are not significantly related. The first study of Wang (2021) who conducted a study in China was precisely all patients treated in Chinese teaching hospitals. Through several inclusion criteria, there were 567 case groups with ischemic stroke and 552 control groups without ischemic stroke with a p-value of 0.058. The study was in the process of collecting research subjects, conducting several exclusions in patients with transient ischemic acute stroke, namely stroke-like events that only occurred 24 hours or less, brain trauma, brain malformations, tumors, accompanying chronic

infectious diseases, autoimmune diseases and vascular diseases. peripheral blood and focuses on risk factors for hypertension and ischemic stroke associated genetic variants so. The genetic variant of lncRNA ANRIL itself by Wang (2021) is recognized to be more closely related to disorders of large blood vessels than small vessels. This is what then excludes several potential subjects and causes the results obtained to be unrelated.²⁸

Based on a total of 12 articles that describe the relationship between diabetes mellitus and ischemic stroke, 8 of them have a significant relationship and the difference in research subjects is large, overseas locations also provide very high heterogeneity test results, namely 82%. According to Wang (2021), who has conducted research on the relationship between diabetes mellitus and ischemic stroke in the Chinese community, ethnicity is very influential due to differences in genetic variants related to vascular susceptibility of Asians compared to Europeans in the incidence of ischemic stroke.²⁸

Relationship between Diabetes Mellitus and Ischemic Stroke Kejadian

The second research variable that has been analyzed is diabetes mellitus and the relationship with the incidence of ischemic stroke. After the researchers entered the data, the results of the heterogeneity test of the collected data were heterogeneous data with a p value of <0,00001 with a study variation value (I²) of 84%. The results of the calculation of all articles related to diabetes mellitus with the incidence of ischemic stroke, both heterogeneity tests and p-values from the meta-analysis statistical test can be seen from the forest plot below which includes 12 articles.

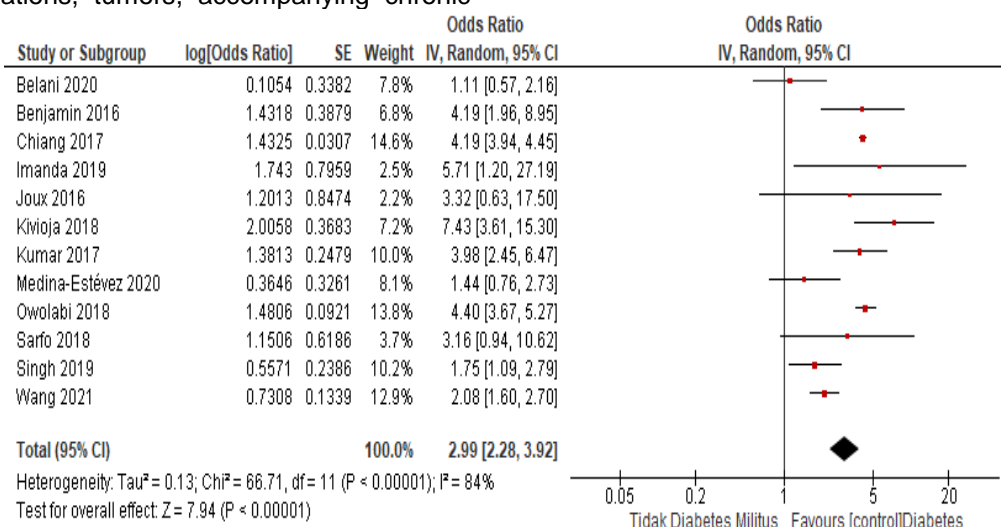


Figure 2. Forest Plot Relationship of Diabetes Mellitus with Ischemic Stroke Incidence (n=12)

Based on a total of 12 articles that describe the relationship between diabetes mellitus and ischemic stroke, 8 of them have a significant relationship and the difference in research subjects is large, overseas locations also provide very high heterogeneity test results, namely 82%. According to Wang (2021), who has conducted research on the relationship between diabetes mellitus and ischemic stroke in the Chinese community, ethnicity is very influential due to differences in genetic variants related to vascular susceptibility of Asians compared to Europeans in the incidence of ischemic stroke.²⁸

The p-value obtained from statistical analysis was 0.02, which means that diabetes mellitus was significantly associated with ischemic stroke. The results of the p value obtained for the variable diabetes mellitus <0.0001 which means there is a relationship between diabetes mellitus and ischemic stroke.

Another study is from Wang (2021) who conducted a study in China to be exact on all patients treated in Chinese teaching hospitals. Through several inclusion criteria, there were 567 case groups with ischemic stroke and 552 control groups without ischemic stroke with a p value of 0.000 which means that diabetes mellitus with ischemic stroke has a significant effect.²⁸

Diabetes mellitus is a disorder in which there is an increase in blood sugar because the pancreas, the organ that produces insulin for blood sugar metabolism, is damaged. Damage occurs due to various long-term processes such as smoking, unhealthy diet, and genetics. Diabetes mellitus can independently increase the incidence of stroke significantly because the process of damage to blood vessels by high blood glucose results in a more severe oxidation process, besides causing more thrombus to appear, it also triggers thinning of the blood vessels.³⁰

Several other studies have also reported that respiratory tract infections increase the short-term risk of ischemic stroke where bacterial and viral infections can pose a risk of embolism or thrombus. This infectious condition also makes patients tend to increase their response to the inflammatory process which results in an increase in d-dimer and c-reactive protein which causes hypercoagulation.³¹

CONCLUSION

From this meta-analysis study, it can be concluded that the incidence of ischemic stroke is a condition that greatly affects the community both individually and the whole of society in general, even this condition always increases over time. The most common risk factors

associated with ischemic stroke are hypertension and diabetes mellitus. Even the majority of studies that have been analyzed show a significant relationship between hypertension and diabetes mellitus with the incidence of ischemic stroke.

This meta-analysis study also shows that hypertension and diabetes mellitus are risk factors that are statistically significant, although some of the studies also show that these two risk factors have no significant effect.

REFERENCES

1. WHO. Preventing Noncommunicable Disease (NCDs) by Reducing Environmental Risk Factors. Departement of Public Health, Environmental and Social Determinants of Health WHO. Geneva., 2017.
2. Kuriakose, D., Xiao, Z. Pathophysiology and Treatment of Stroke : Present Status and Future Perspectives. International Journal of Molecular Sciences 2020; 21(20): 7609.
3. Brook, RD., Weder, AB, Rajagopalan, S. "Environmental Hypertensionology" The Effects of Environmental Factors on Blood Pressure in Clinical Practice and Research. The Journal of Clinical Hypertension. 2011; 13(11): 836-41.
4. Dendup T, et al. Environmental Risk Factors for Developing Type 2 Diabetes Mellitus: A Systematic Review. Int. J. Environ. Res. Public Health 2018; 15(1): 78.
5. Raman, PG. Chapter 9: Environmental Factors in Causation of Diabetes Mellitus. Intech Open. Indore, 2016.
6. Chehaibi, K., Trabelsi, I., Mahdouani, K and Slimane, MN. Correlation of Oxidative Stress Parameters and Inflammatory Markers in Ischemic Stroke Patients. Journal of Stroke and Cerebrovascular Diseases 2016; 25(11): 2585-93.
7. Permanasari and Julianti. Pola Konsumsi dan Gaya Hidup Kaitannya dengan Kejadian Penyakit Kardiovaskular di Indonesia. Penelitian Gizi dan Makanan 2018; 41(2): 113-23.
8. Virani, SS., Alonso, A., Benjamin, EJ., Bittencourt, MS., Callaway, CW., Carson, AP., et al. AHA Statistical Update, Heart Disease and Stroke Statistics – 2020 Update. Circulation 2020; 141:e139-e596.
9. Risnawati. Faktor Risiko Penyakit Stroke Di Rumah Sakit Umum Provinsi Sulawesi Tenggara Tahun 2009. Terapeutik Jurnal 2014; 1(2); 45-53.
10. Tamburian, AG., Ratag, BT and Nelwan,

- JE. Hubungan antara Hipertensi, Diabetes Melitus, dan Hiperkolesterolemia dengan Kejadian Stroke Iskemik. *Journal of Public Health and Community Medicine* 2020; 1(1): 27-33.
11. Letelay, ANA., Huwae, LBS and Kailola, NE. Hubungan Diabetes Mellitus Tipe II dengan Kejadian Stroke pada Pasien Stroke di Poliklinik Saraf RSUD dr. M. Haulussy Ambon. *Molucca Medica* 2019; 12(1): 1-10.
 12. Ghani, L., Mihardja, LK and Delima. Faktor Risiko Dominan Penderita Stroke di Indonesia, Dominant Risk Factors of Stroke In Indonesia. *Buletin Penelitian Kesehatan* 2016; 44(1): 49-58.
 13. Irdelia, RR. Profil Faktor Risiko Yang Dapat Dimodifikasi Pada Kasus Stroke Berulang di RSUD Arifin Achmad Provinsi Riau. *Jom FK* 2014; 1(2): 1-15.
 14. Singh SK, Semwal J, Shikha D, Singh Y, Bansal D, Bhattacharya S. Diabetes Mellitus as A Risk Factor for Ischemic Stroke: A Case Control Study. *Int J Community Med Public Health*. 2019;6(4):1554–7.
 15. Owalabi MO, Sarfo F, Akinyemi R, Gebregziabher M, Akpa O, Akpalu A, et al. Dominant Modifiable Risk Factors For Stroke in Ghana and Nigeria (SIREN): A Case Control Study. *Lancet Glob Health*. 2018;6:e436–46.
 16. Kivioja R, Pietilla A, Martinez-Majander N, Gordin D, Havulinna AS, Salomaa V, et al. Risk Factors for Early-Onset Ischemic Stroke: A Case-Control Study. *J Am Heart Assoc*. 2018;7:1–21.
 17. Sarfo FS, Ovbiagele B, Gebregziabher M, Wahab K, Akinyemi R, Akpalu A, et al. Stroke Among Young West Africans: Evidence From The SIREN (Stroke Investigative Research and Educational Network) Large Multisite Case-Control Study. *StrokeAHA*. 2018;49:1116–22.
 18. Imanda A, Martini S, Artanti KD. Post Hypertension and Stroke: A Case Control Study. *Kesmas Natl Public Health J*. 13(4):164–8.
 19. Chiang J, Kao H, Kao Y. Association of Paroxysmal Supraventricular Tachycardia with Ischemic Stroke: A National Case-Control Study. *J Stroke Cerebrovasc Dis*. 2017;26(7):1493–9.
 20. Benjamin LA, Corbett EL, Connor MD, Mzinganjira H, Kampondeni S, Choko A, et al. HIV, Antiretroviral Treatment, Hypertension, and Stroke in Malawian Adults, A Case-Control Study. *Neurology*. 2016;86:324–33.
 21. Kumar A, Misra S, Saqar R, Kumar P, Yadav AK, Talwar P, et al. Relationship Between Factor V Leiden Gene Variant and Risk of Ischemic Stroke: A Case-Control Study. *Ann Indian Acad Neurol*. 2017;20(3):284–8.
 22. Medina-Estevez F, Zumbado M, Luzardo OP, Rodriguez-Hernandez A, Boada LD, Fernandez-Fuertes F, et al. Association Between Heavy Metals and Rare Earth Elements with Acute Ischemic Stroke: A Case-Control Study Conducted in the Canary Island (Spain). *Toxics*. 2020;8(66):1–14.
 23. Joux J, Boulanger M, Jeannin S, Chausson N, Hennequin J, Molinie V, et al. Association Between Carotid Bulb Diaphragm and Ischemic Stroke in Young Afro-Caribbean Patients: A Population-Based Case-Control Study. *StrokeAHA*. 2016;47:2641–4.
 24. Maratni NPT, Saraswati MR, Dewi NNA, Yasa S, Widyadharma E, Putra K, et al. Association of Apolipoprotein E Gene Polymorphism with Lipid Profile and Ischemic Stroke Risk in Type 2 Diabetes Mellitus Patients. *J Nutr Metab*. 2021;2021(5527736):1–7.
 25. Wang Q, Zhao J, Chang H, Liu X, Zhu R. Association Between lncRNA ANRIL Genetic Variants with The Susceptibility to Ischemic Stroke: Form A Case-Control Study to Meta-Analysis. *Medicine*. 2021;100(11):1–9.
 26. Hardika BD, Yuwono M, Zulkarnain HM. Faktor Risiko yang Mempengaruhi Terjadinya Stroke Non Hemoragik pada Pasien di RS Charitas dan RS Myria Palembang. *J Akad Baiturrahim Jambi*. 2020;9(2):268–74.
 27. Belani P, Schefflein J, Kihira S, Rigney B, Delman BN, Mahmoudi K, et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. *Am J Neuroradiol*. 2020;41(8):1361–4.
 28. Wang, Q., Zhao, J., Chang, H., Liu, X and Zhu, R. Association Between lncRNA ANRIL Genetic Variants with The Susceptibility to Ischemic Stroke : Form A Case-Control Study to Meta-Analysis. *Medicine* 2021; 100(11): 1-9.
 29. Howard, VJ., Madsen, TE., Kleindorfer, DO., Judd, SE., Rhodes, JD., Soliman, ZS., Kissela, BM., Safford, MM., Moy, CS., McClure, LA., Howard, G and Cushman, M. Sex and Race Differences in the Association of Incident Ischemic Stroke with Risk Factors. *JAMA Neurology* 2019; 76(2): 179-86.
 30. Mobula LM, et al. Predictors of glycemic

control in type-2 diabetes mellitus: Evidence from a multicenter study in Ghana. [Translational Metabolic Syndrome Research](#) 2018; 1: 1-8.

31. Belani P, et al. Covid-19 is an independent risk factor for acute ischemic stroke. *American journal of neuroradiology* 2020; 41(8): 1361-4.