Meta-analysis on The Effects of Hypertension, Type II Diabetes Mellitus, and Smoking on the Risk of Stroke among Asian Young Adult Population

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ABSTRACT

Background: The incidence of stroke at a young age is reported to increase. Stroke at a young age is still often found in classic risk factors that can be changed such as hypertension, dyslipidemia, and type II diabetes mellitus (type II DM). Control of the right risk factors will affect the incidence of stroke. This study aims to analyze stroke risk factors in young populations in Asia.

Subjects and Method: This study is a meta-analysis carried out using PRISMA systematic guidelines. The article is a study conducted between 2000 until 2019. The process of searching articles using a search engine database consisting of PubMed, Clinical Key, and Google Scholar using the keywords "risk factor", "stroke", "adult", "young adult ", And" Asia ". The analysis was done with the Review Manager (RevMan) software 5.3.

Results: The results showed eight articles fulfilled the criteria which contained 26,360 samples. The results showed that hypertensive young adults, type II DM, and smoking had a stroke risk at a young age of 6.6 times (OR 6.66; 95% CI 6.10 to 7.27), 3.7 times (OR 3.72; 95% CI 3.17 to 4.38), and 2.6 times (OR 2.64; CI 95% 1.77 to 3.93) higher, than those without hypertension, type II DM, and smoking, and was statistically significant.

Conclusion: hypertension, type II diabetes, and smoking are risk factors for stroke at a young age.

Keywords: young, adult, stroke, risk factor, meta-analysis

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BACKGROUND

Stroke accounts for the second highest number of deaths in the world after heart disease (WHO, 2018). Although stroke is a problem in all developed and developing countries, the burden of the disease is very serious in Asia, including in Indonesia. Based on the results of the basic health research survey (2018), compared to 2013 the prevalence of stroke in Indonesia increased from 7% to 10.9%. This is in line with the prevalence of hypertension which also increased from 25.8% to 34.1% (Riskesdas, 2018).

The incidence of stroke at a young age (less than 45 years) is reported to continue to increase (Smajlović, 2015). The average number of years lost due to disability or disability-adjusted life years due to stroke is ranked 3rd in the world (Feigin, 2017). Compared to strokes in the elderly, strokes that attack young people have a huge economic impact because they cause disability in productive age (Singhal et al., 2013). The incidence of recurrent strokes and cognitive impairment has also been reported to increase in stroke patients in young age (Maaijwee et al., 2014).

Risk factors for the cause of stroke vary widely. The increase of the age is very influential, but the incidence of stroke at a young age is still often found classic risk factors that can be changed such as hypertension, dyslipidemia, and diabetes mellitus (DM). Control of the right risk factors will affect the incidence of stroke.

Meta-analysis is analysis of the study that combines the results of existing studies and analyzes them and then draws general conclusions from the analysis that has been carried out (Liberati et al., 2009). Meta-analysis is useful for presenting the latest evidence based; one of them is to provide evidence for doctors and policy makers to assess the prognosis of risk factors possessed by a person with the disease (Haidich, 2010). Stroke at a young age can be prevented by early detection and control of known risk factors thoroughly (Sousa & Ribeiro, 2009). A study on stroke risk factors at a young age in Asia shows mixed results. The purpose of this study was to determine the incidence and analyze risk factors for stroke at a young age in Asia so that a summary of the studies that had been conducted beforehand could be known.

SUBJECTS AND METHOD

a. Study Design
This study is a meta-analysis study. It used the secondary data in the form of data from the results of previous studies. The data is sought from a systematic and comprehensive database of several indexes including; PubMed, ClinicalKey, and Google Scholar, use "young" "adult", "risk factor", "stroke" and "Asia" search keywords.

b. Inclusion Criteria
The inclusion criteria in this study were full paper articles with observational methods. Stroke diagnosis is based on physical examination and radiology using CT scans and / or MRI.

c. Study Variables
Stroke: Stroke is a clinical syndrome that develops rapidly due to focal and global brain disorders with symptoms lasting 24 hours or more. It is said that a stroke is diagnosed if a typical abnormal neurological examination is found accompanied by a radiological examination.

Hypertension: Hypertension is an increase in systolic blood pressure greater than 140 mmHg and / or diastolic greater than 90 mmHg on two measurements with an interval of five minutes in a state of adequate rest (calm).

Diabetes Melitus type II: Type II DM is an increase in blood sugar (more than 200 mg/dL) due to insulin resistance accompanied by a relative deficiency of insulin secretion.

Smoking: Smoking is the activity of sucking smoke from tobacco using pipes or cigarettes as measured by the intensity of smoking.

d. Exclusion Criteria
The exclusion criteria are patients who experience strokes more than once and / or with complications.

e. Study Instruments
The instrument used to collect the data was published articles between 2000 and 2019 whose study was conducted on the Asian continent contained in PubMed, Clinical-Key, and Google Scholar databases.

f. Data Analysis
Data analysis was carried out using Review Manager (Rev-Man) software 5.3 released by the Cochrane Collaboration. RevMan was used to calculate the adjusted Odds Ratio (aOR) as a whole

RESULTS

The data was sought from a systematic and comprehensive database of several indexes including; PubMed, Clinical Key, and Google Scholar. The results of article

search, there were 653 selected articles can be seen in Figure 1.

After a review of full text articles, articles were found that did not contain the

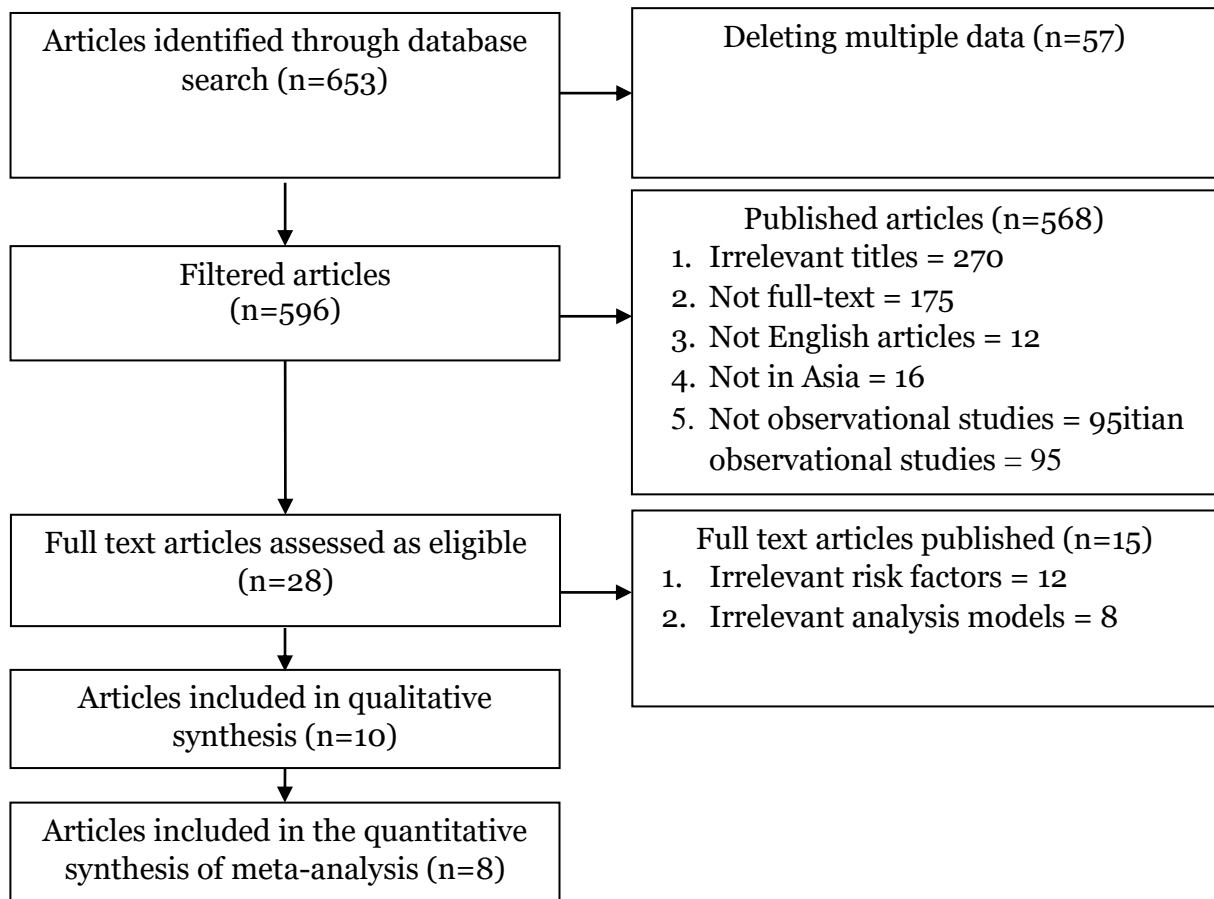risk factors studied (hypertension, type II diabetes mellitus, and smoking).

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┌─────────────────────────────┐        ┌─────────────────────────────┐
│ Articles identified through │        │ Deleting multiple data (n=57)│
│   database search (n=653)   │───────▶│                             │
└─────────────────────────────┘        └─────────────────────────────┘
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┌─────────────────────────────┐        ┌─────────────────────────────┐
│     Filtered articles       │        │ Published articles (n=568)  │
│        (n=596)              │───────▶│ 1. Irrelevant titles = 270  │
│                             │        │ 2. Not full-text = 175      │
│                             │        │ 3. Not English articles = 12│
│                             │        │ 4. Not in Asia = 16         │
│                             │        │ 5. Not observational        │
│                             │        │    studies = 95itian        │
│                             │        │    observational studies = 95│
└─────────────────────────────┘        └─────────────────────────────┘
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┌─────────────────────────────┐        ┌─────────────────────────────┐
│ Full text articles assessed │        │ Full text articles published│
│     as eligible (n=28)      │───────▶│         (n=15)              │
│                             │        │ 1. Irrelevant risk factors  │
│                             │        │    = 12                      │
│                             │        │ 2. Irrelevant analysis      │
│                             │        │    models = 8                │
└─────────────────────────────┘        └─────────────────────────────┘
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│ Articles included in        │
│ qualitative synthesis (n=10)│
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│ Articles included in the    │
│ quantitative synthesis of   │
│ meta-analysis (n=8)         │
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Figure 1. Review Process Flowchart

Articles that fulfilled the qualitative requirements were reviewed and two articles were released because they did not use multivariate analysis needed to control confounding factors. The final result of the article review process, there are 8 articles that meet the quantitative requirements for a meta-analysis of stroke risk factors at a young age. All articles obtained from the review are studies originating from the Asian continent.

The following is an overview of the research area obtained from articles that have met the requirements: China, there are three studies, Taiwan one study. One

Qatar study, two Indian studies, and one Thai study.

The results of the meta-analysis are presented in the form of a forest plot. The forest plot is a diagram that shows information from each study studied and estimates of overall results (Akobeng in Murti, 2018). In addition to the forest plot, this meta-analysis also presents a funnel plot, a diagram that illustrates the possibility of publication bias by displaying the relation between the effect size of the study and the sample size of the various studies studied. The existence of publication bias in the funnel plot can be assessed by looking at the funnel shape asymmetry, the number of

points on the right and left side compared to the standard error (Murti, 2018).

Based on the articles identified from the review results, 8 articles were qualified as sources for meta-analysis. Then the articles that have been obtained will be analyzed using RevMen 5.3 and the results will be presented in the form of a forest plot and funnel plot.

1. Hypertension

There were six articles that meet the requirements identified from the results of the review. A summary of each study is shown in Table 1.

Figure 2 shows that 6 articles reported that hypertension is a risk factor for stroke at a young age. The results obtained showed a high heterogeneity between trials (p> 0.001; I2 = 74%) so that the random effects model was used. Hyper-tension can increase 6.6 times the risk of having a stroke at a young age (OR 6.66; 95% CI 6.10 to 7.27). Figure 5 shows a

symmetrical face facing down indicating no publication bias in the study.

1. Diabetes Melitus type II

There were five articles that meet the requirements identified from the results of the review. A summary of each study is shown in Table 2.

Figure 3 shows five articles reporting that type II DM is a risk factor for stroke at a young age. The results obtained indicate high heterogeneity between trials (p> 0.001; I2 = 75%) so that the random effects model is used. Type II DM can increase 3.7 times the risk of having a stroke at a young age (OR 3.72; 95% CI 3.17 to 4.38). Figure 6 shows a symmetrical face facing down indicating that there was no publication bias in the study.

2. Smoking

There were six articles that meet the requirements identified from the results of the review. A summary of each study is shown in Table 3.

Table 1. An article summary of the source of the relationship between hypertension and the risk of stroke at a young age

Author	Year	Samples characteristics	Characteristics					Level of severity	
		Age (year)	Location	Design	Sample size	Innclusion Criteria		aOR	CI
Bi *et al.*	2002	35-45	China	*Case control*	14,248	First onset, without complications		6.64	5.96-7.40
Chiu *et al.*	2015	18-45	Taiwan	*Case-control*	10,315	First onset, without complications		7.32	6.25-8.57
Fan *et al.*	2018	18-49	China	*Cohort*	400	First onset, without complications		39.9	3.99-400.98
Khan	2007	17 − 45	Qatar	*Cohort*	40	First onset, without complications		1.34	0.29-6.19
Lipska *et al.*	2007	15-45	India	*Case control*	310	First onset, without complications		2.46	1.25-4.84
Niu *et al.*	2014	15-49	China	*Case control*	184	First onset, without complications		3.50	1.63-7.50
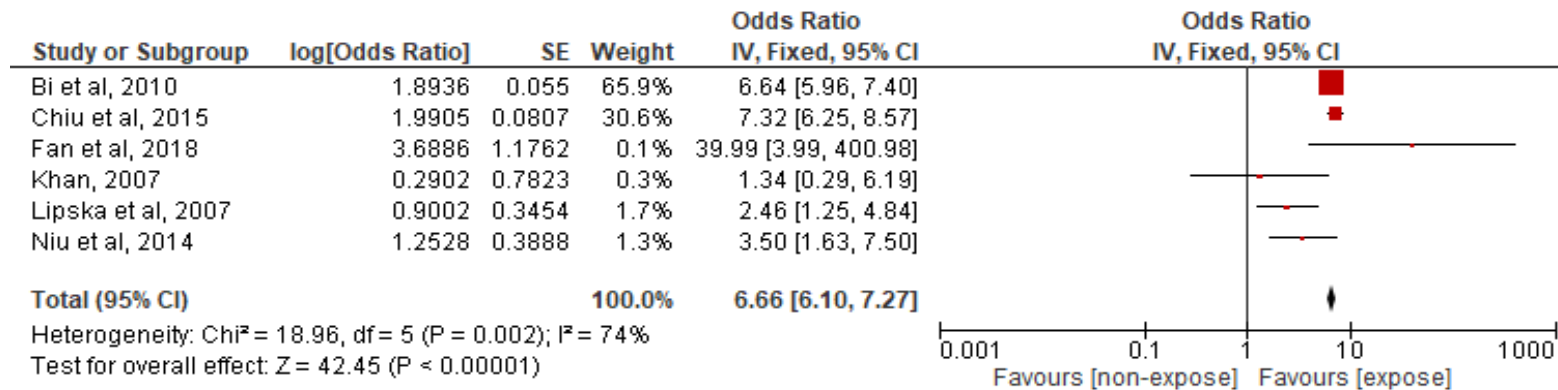
Figure 2. Meta-analysis of hypertension and risk of stroke at a young age

Table 2. Summary of articles on the source of relationship between type II DM and stroke risk at a young age

Author	Year	Samples Characteristics						Level of severity	
		Age (year)	Location	Design	Sample size	Inclusion Criteria		aOR	CI
Bi *et al.*	2002	35-45	China	*Case control*	14,248	First onset, without complications		3.01	2.37-3.82
Chiu *et al.*	2015	18-45	Taiwan	*Case control*	10,315	First onset, without complications		5.20	4.09-6.62
Fan *et al.*	2018	18-49	China	*Case control*	400	First onset, without complications		1.63	0.41-6.43
Lipska *et al.*	2007	15-45	India	*Case control*	310	First onset, without complications		2.94	0.93-9.29
Niu *et al.*	2014	15-49	China	*Case control*	184	First onset, without complications		1.70	0.80-3.61
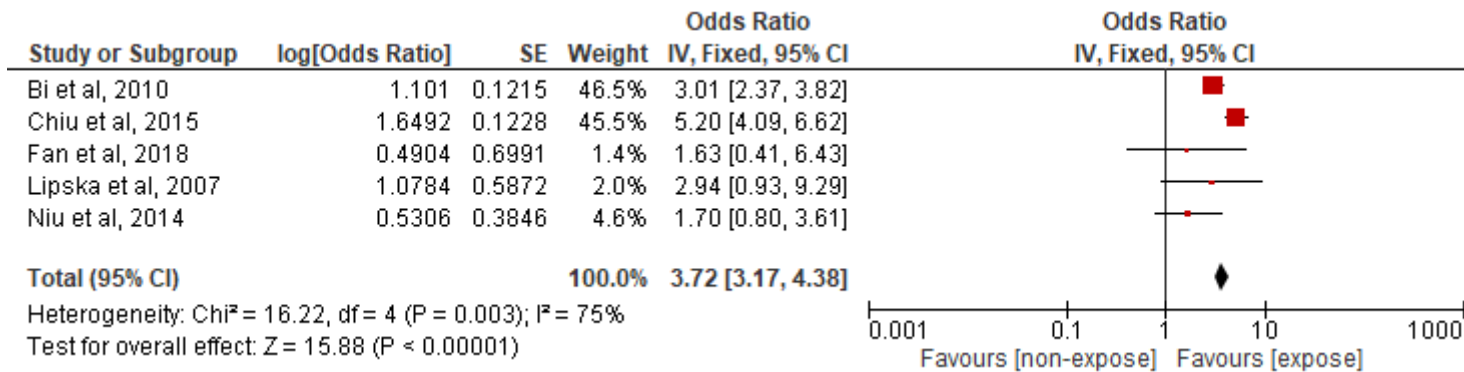
Figure 3. Meta-analysis of type II DM and risk of stroke at a young age

Table 3. Summary of articles on the relationship between smoking and risk of stroke at a young age

Author	Year	Samples Characteristics	Characteristics				Level of severity	
		Age (year)	Location	Design	Sample size	Inclusion Criteria	aOR	CI
Khan	2007	17 − 45	Qatar	*Cohort*	40	First onset, without complications	1.33	0.18- 9.46
Lipska *et al.*	2007	15-45	India	*Case control*	310	First onset, without complications	7.14	2.90- 17.54
Niu *et al.*	2014	15-49	Cina	*Case control*	184	First onset, without complications	2.6	1.2-5.8
Tiamkao *et al.*	2013	< 45	Thailand	*Case control*	782	First onset, without complications	1.03	0.37-2.83
Fan *et al.*	2018	18-49	Cina	*Case control*	400	First onset, without complications	1.840	0.47–7.09
Mishra *et al.*		< 50	India	*Case control*	45	First onset, without complications	3.00	0.97-9.30
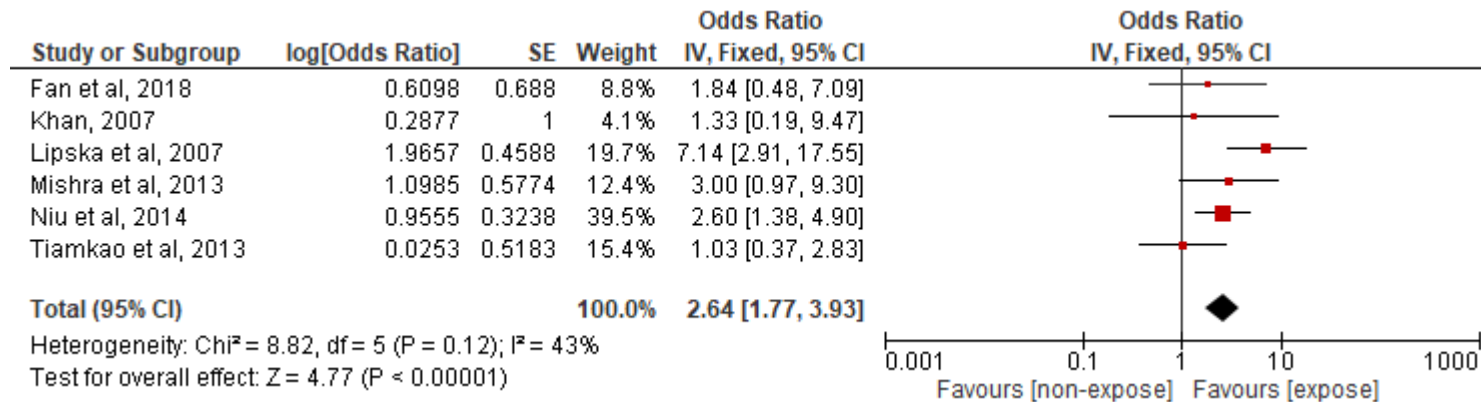
Figure 4. Meta-analysis of smoking and stroke risk at a young age
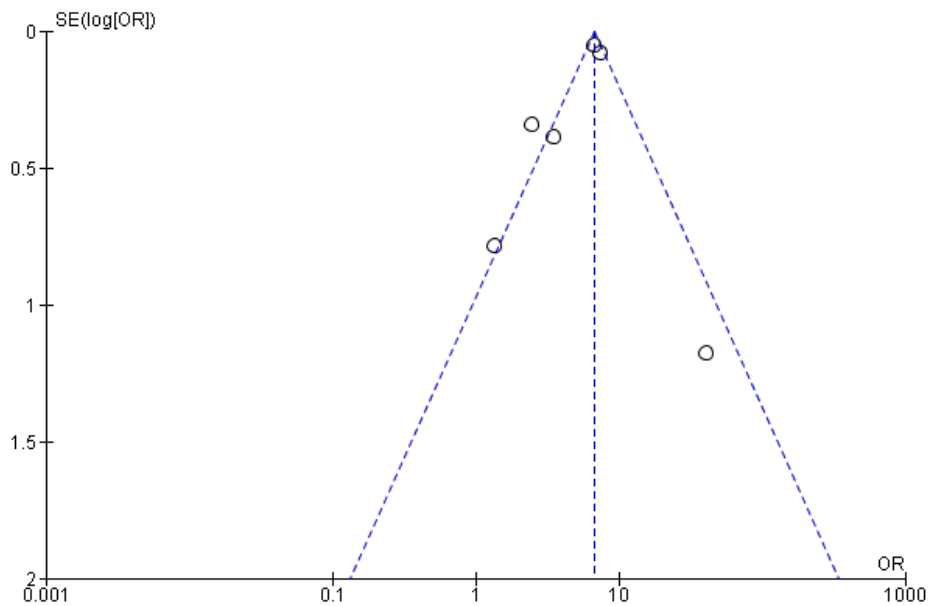
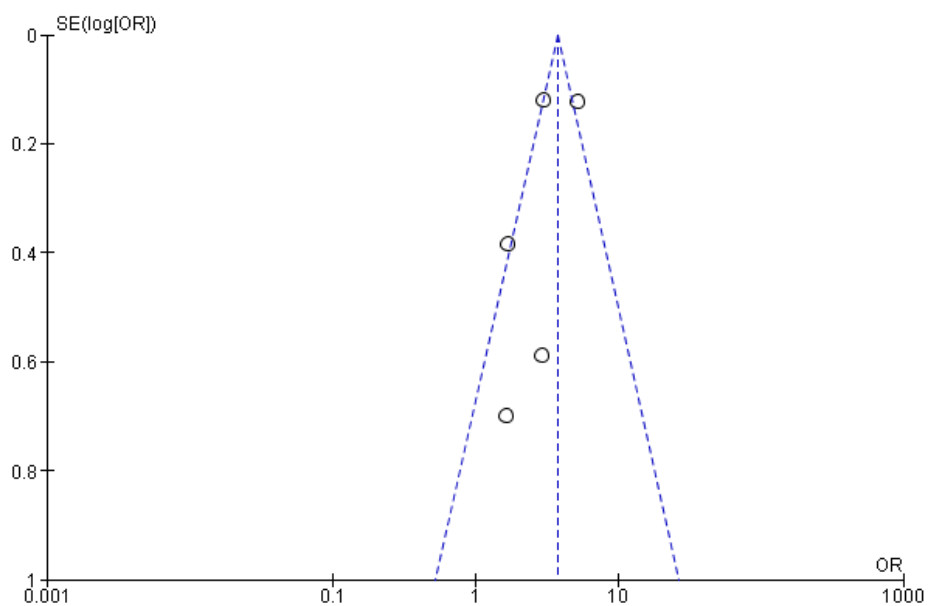**Figure 5.** *Funnel plots of hypertension and risk of stroke at a young age*

Figure 6. *Funnel plot of type II DM and risk of stroke at a young age*

Figure 4 shows that five articles reports that smoking is a risk factor for stroke at a young age. The results obtained showed a low heterogeneity between trials (p> 0.001; I2 = 43%) so that the fixed effects model was used. Smoking can increase 2.6 times the risk of having a stroke at a young age (OR 2.64; CI 95% 1.77 to 3.93). Figure 6 shows a symmetrical face facing down indicating that there was no publication bias in the study.
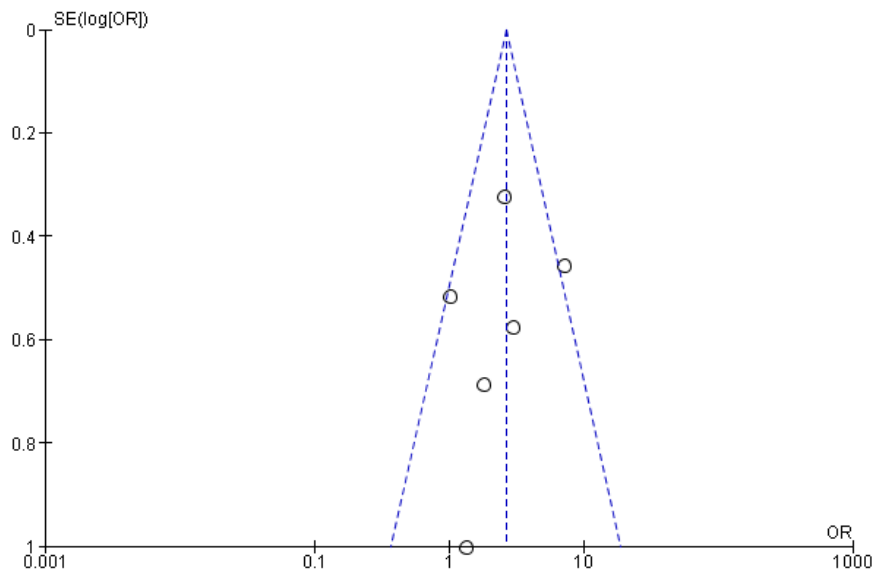
Figure 7. *Funnel smoking and risk of stroke at a young age*

DISCUSSION

Stroke at a young age was reported to have high mortality and cause an increase in DALY. The prevalence of stroke at a young age varies in each country, while its incidence continues to experience enhancement.

The incidence of stroke at a young age increases with increasing age of patients over 35 years, higher in women than men aged 18-44 years, and increasing by 23% in a decade (Ekker et al., 2019). The negative impacts caused cause the importance of known risk factors.

Risk factors for stroke at a young age are divided into biological factors and factors related to lifestyle. Some conditions also pose risks such as premature pregnancy. Various types of risk factors have been studied in the last decade. This meta-analysis contains 26,360 samples. The results of the study reinforce previous studies that smoking history, type II diabetes, and smoking are significant risk factors that influence the occurrence of stroke at a young age.

1. Hypertension

The results of the meta-analysis of six articles on hypertension and the incidence of stroke at a young age showed that hypertension was a risk factor and could increase the risk 6.6 times compared to those without hypertension (OR 6.66; 95% CI 6.10 to 7.27). These results are supported by Aigner et al. (2017) who reported hypertension to be an independent risk factor for stroke at a young age. Similarly, in the Clinical Hypertension and Vascular Disease (2016) book, it is explained that uncontrolled hypertension is a major factor in stroke in both young adults and elderly people.

The finding of hypertension is at a high young age. The Baltimore-Washington Cooperative Young Stroke study, a population-based case control study (patients aged 18-44 years), showed a positive relationship between hypertension and the risk of ischemic stroke in white and black people, both men and women (Putaala, 2016).

2. Diabetes Melitus type II

The results of the meta-analysis of five articles on type II DM and stroke at a young age showed that type II DM was a risk factor and could increase risk 3.7 times compared to those without type II DM (OR 3.72; 95% CI 3.17 to 4.38).

High levels of blood sugar in the body pathologically play a role in increasing the concentration of glycoprotein, which is the originator of vascular disease. High blood glucose levels will increase the likelihood of expanding the infarct area due to the formation of lactic acid which is an anaerobic glucose metabolism (Putaala, 2016).

3. Smoking

The results of a meta-analysis of five articles about smoking and stroke at a young age showed that smoking was a risk factor and could increase the risk 2.6 times compared to non-smokers (OR 2.64; CI 95% 1.77 to 3.93). This is in accordance with the study conducted by Shah & Cole (2010), namely the higher the frequency of smoking would increase the risk of stroke.

AUTHOR CONTRIBUTIONS

Windhy Monica is the main author who played a role in collecting and processing research data. Vitri Widyaningsih and Endang Sutisna Sulaeman examined the conceptual framework and research methodology.

CONFLICT OF INTEREST

We declare that there is no conflict of interest.

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