

Meta-Analysis the Effect of Oral Combination Contraceptive on Hypertension and Stroke

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ABSTRACT

Background: Combined oral contraceptives are a form of contraception that are considered safe and effective for some women, but this does not rule out the possibility that combined oral contraceptives contribute to adverse health effects. Several epidemiological studies have shown that oral contraceptives have adverse effects on women's health. The use of contraceptive pills containing the hormones estrogen and progesterone can cause an increase in blood pressure and also stroke if used continuously. The purpose of this study was to estimate the magnitude of the risk of using combined oral contraceptives on the incidence of hypertension and stroke with a meta-analysis study.

Subjects and Method: This was a systematic review and meta-analysis using PRISMA flowchart diagram guidelines. The article search process was carried out between 2007-2022 using 3 databases, including Google Scholar, PubMed, and Science Direct. The keywords used in the database search were "oral contraceptive" OR "contraceptive pills" OR "combined oral contraceptive" AND "hypertension" OR "blood pressure" AND "stroke" AND "women of reproductive age". The inclusion criteria for full text articles using case control observational methods, articles using English, and articles using multivariate analysis with adjusted Odds Ratio results. Articles that have met the requirements are analyzed using the RevMan 5.3 application.

Results: A total of 14 articles with case-control study designs originating from China, Ethiopia, the United States, Italy, and the Netherlands were carried out in a meta-analysis in this study. Meta-analysis of 7 articles showed that the effect of using combined oral contraceptives was to increase the incidence of hypertension 1.44 times compared to those who did not use combined oral contraceptives (aOR= 1.44; 95% CI= 1.12 to 1.84; p= 0.004). Meanwhile, 7 articles showed that the effect of using combined oral contraceptives was to increase the incidence of stroke by 2.08 times compared to those who did not use combined oral contraceptives (aOR= 2.08; 95% CI= 1.48 to 2.92; p < 0.001).

Conclusion: Combined oral contraceptives increase the risk of hypertension and stroke.

Keywords: combined oral contraceptives, hypertension, stroke, meta-analysis

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BACKGROUND

Population and family development is a planned effort that is part of a national development carried out to direct population de-

velopment and family development to create a balanced system and develop quality in all dimensions of the population (Gatiningsih and Sutrisno, 2017). The strategy carried out

by the government in order to regulate population is through the Family Planning (KB) program, namely by reducing fertility rates by providing facilities and infrastructure for contraceptive devices and drugs. At the implementation stage, the contraceptive method provided to the community is expected to provide optimal benefits and provide small side effects (BKKBN, 2015).

There are many types of contraceptives, including oral contraceptives, injections, condoms, implants, IUDs, tubectomy, and vasectomy. The pattern of choosing the type of contraception in 2020 shows that most family planning participants use hormonal contraception, namely injection and oral contraceptives, this pattern of choosing contraception occurs every year, where more participants choose to use short-term contraceptive methods compared to long-term contraceptive methods (Indonesian Ministry of Health, 2021). More than 100 million women worldwide choose to use oral contraceptives. The global average percentage of women who use oral contraceptives is quite high, namely 8.8%, even in developed countries the use of oral contraceptives can reach 15.4% (Maitre, 2013). Oral contraceptives are contraceptives that are widely accepted by women around the world. Combined oral contraceptives are a form of contraception that are considered safe and effective for some women, but this does not rule out the possibility that combined oral contraceptives contribute to very detrimental health effects (Park and Kim, 2013).

Several epidemiological studies have shown that oral contraceptives have adverse effects on women's health. For some women who do not have the disease and do not have a smoking habit, the use of oral contraceptives is safe. However, like most drugs, oral contraceptives can be associated with side effects and risks including cardiovascular

events such as venous thromboembolism (VTE), myocardial infarction, elevated blood pressure, and stroke (Rotermann et al., 2015). The use of contraceptive pills containing the hormones estrogen and progesterone can cause an increase in blood pressure (Pangaribuan and Lolong, 2015). Hypertension itself is a medical term for an increase in systolic blood pressure 140 mmHg and diastolic blood pressure 90 mmHg (Kemenkes RI, 2014). Studies on blood pressure in women show an increase in blood pressure associated with the use of oral contraceptives, 5% of women who use oral contraceptives may develop hypertension (Wang et al., 2011). Women who use hormonal contraception will experience an increase in blood pressure during the first two years of use. Increased blood pressure will increase 2-3 times after four years of using oral contraceptives (Baziad, 2014).

In addition to blood pressure, stroke is a serious health problem in various parts of the world. Over the past four decades, stroke rates in low-income countries have increased. Stroke can cause permanent disability so that it can affect the productivity of the sufferer (Johnson et al., 2016). In 2017, 15 Asian countries were included in the 50 countries with the highest death rates from stroke. Indonesia ranks first as the country with the highest average death rate due to stroke, followed by Mongolia and North Korea (WHO, 2018). The Global Burden of Disease Study (2017) estimates that stroke, which was the second leading cause of death in 2016, will remain in the same position in 2040. Stroke is an adverse and relatively serious reaction to oral contraceptives. From reporting a study that emerged after oral contraceptives were marketed said that the risk of cardiovascular events such as venous thromboembolism (VTE), myocardial infarction, increased blood pressure, and also

stroke increased among users of oral contraceptives (Wang et al., 2011).

Based on the results of various studies, the incidence of hypertension and stroke in women is still high, therefore it is necessary to do proper prevention and treatment. More comprehensive research from the results of previous primary studies on the use of oral contraceptives on the incidence of hypertension and stroke is urgently needed. The previous primary research that has been obtained by the researcher will be analyzed with a meta-analysis study design which is an epidemiological study that provides the strongest quality evidence by combining and statistically combining the results from a number of previous primary studies, if possible, to be combined. This study aims to estimate the magnitude of the risk of using combined oral contraceptives on the incidence of hypertension and stroke with a meta-analysis study.

SUBJECTS AND METHOD

1. Study Design

This research was conducted using a systematic review and meta-analysis between 2007 and 2022. Search articles using databases, including Google Scholar, Pubmed, and Science Direct. The keywords used in searching the database were “oral contraceptive” OR “contraceptive pills” OR “combined oral contraceptive” AND “hypertension” OR “blood pressure” AND “stroke” AND “women of reproductive age”.

2. Steps of Meta-Analysis

Meta-analysis is carried out through 5 steps as follows:

- 1) Formulate research questions in PICO (Population, Intervention, Comparison, and Outcome).
- 2) Searching for primary study articles from various databases including Google Scholar, PubMed, and Science Direct.

- 3) Perform screening and conduct critical quality primary studies.
- 4) Perform data extraction and enter the estimated effect of each primary study into the RevMan 5.3 application.
- 5) Interpret the results and draw conclusions.

The assessment of critical criteria is carried out by 2 independents using the Critical Appraisal Skills Program published by the 2018 Critical Appraisal Skills Program which consists of 12 questions. The questions are answered by giving a score. A score of 0 for answers was not carried out in the primary study, and a score of 1 for answers if done. The primary study is carried out if the total is at least 10. Then it is entered into the RevMan 5.3 application.

3. Inclusion Criteria

The inclusion criteria used in this study were full-text articles using a case-control design. The analysis used was multivariate with adjusted Odds Ratio (aOR).

4. Exclusion Criteria

The exclusion criteria in this study were articles published before 2007, articles that did not use English, and previous studies that used meta-analysis.

5. Operational Definition of Variable

Articles included in this study are PICO-adjusted. The search for articles was carried out by considering the eligibility criteria using the PICO model as follows: Population= family planning acceptors. Intervention= using combined oral contraceptives. Comparison= not using combined oral contraceptives. Outcome= hypertension and stroke.

Combined oral contraceptives are contraceptives in the form of pills or oral contraceptives containing the synthetic hormone estrogen and progesterone which are being used by women to prevent pregnancy.

Hypertension is a condition in which blood pressure exceeds the normal blood pressure limit of 140 mmHg and diastolic is

more than equal to 90 mmHg.

Stroke is a form of disease due to disruption of blood supply to the brain, acute neurological dysfunction caused by blood vessel disorders that arise suddenly and quickly.

6. Instrument

This study is guided by the PRISMA flow diagram and assessment of the quality of research articles using the Critical Appraisal Checklist for Case Control Study (CEB-Ma, 2014). The following are 12 questions used in the checklist, including:

1. Does this objective clearly address the research focus/ problem?
2. Is the case control research method suitable to answer the research question?
3. Are the cases representative of the designated population?
4. Are the selected controls appropriate and acceptable?
5. Are breast cancer research instruments valid and reliable?
6. Have confounding factors been taken into account?
7. Has the researcher controlled for the influence of all confounding factors?
8. Are the results applicable to your research?
9. Was the magnitude of the exposure effect assessed?
10. Was a confidence interval given for the main outcome?
11. Are the results applicable to the designated population?
12. Are the results of this study consistent with other available evidence?

5. Data Analysis

Articles are collected and processed using the Review Manager application (RevMan 5.3). Data processing is carried out by calculating the effect size and heterogeneity values to determine the combined research model and form the final results of the meta-analysis which are presented in the form of forest plots and also funnel plots.

RESULTS

The article review process was carried out using a database based on PRISMA flow-chart diagrams, which can be seen in Figure 1. The total articles obtained were 14 articles spread across 4 continents, namely Asia, Africa, America, and Europe. 7 articles in Asia, 1 article in Africa, 3 articles in America, and 3 articles in Europe, can be seen in Figure 2.

The total number of primary studies included in this meta-analysis was 14 articles from China, Ethiopia, the United States, Italy, and the Netherlands. The primary study for combined oral contraceptives on the incidence of hypertension used 7 case control studies from China, Ethiopia, the United States. Meanwhile, combined oral contraceptives on the incidence of stroke used 7 case control studies from China, the United States, Italy, and the Netherlands.

The forest plot in Figure 3 shows the effect of the use of combined oral contraceptives on the risk of hypertension. Women of childbearing age who used combined oral contraceptives had a risk of developing hypertension 1.44 times compared to not using and the effect was statistically significant (aOR= 1.44; 95% CI= 1.12 to 1.84; p= 0.004). The forest plot in Figure 3 also shows that there is variation in the estimated effect between studies in this meta-analysis ($I^2 = 54\%$). Thus, the calculation of the average effect estimate is carried out using the Random Effect Model (REM) approach.

The funnel plot in Figure 4 shows the distribution of the estimated effects of all the primary studies in this meta-analysis which is mostly to the left of the vertical line. The average of the estimated effects on the right that indicates or indicates slight publication bias. Because the publication bias is in the opposite direction to the diamond in the forest plot, the publication bias tends to underestimate the effect.

The forest plot in Figure 5 shows the effect of the use of combined oral contraceptives on the risk of stroke. Women of childbearing age who used combined oral contraceptives had a risk of stroke 2.08 times compared to not using and the effect was statistically significant (aOR= 2.08; 95% CI= 1.48 to 2.92; p

<0.001). The forest plot in Figure 5 also shows that there is variation in the estimated effect between studies in this meta-analysis ($I^2= 76\%$). Thus, the calculation of the average effect estimate is carried out using the Random Effect Model (REM) approach.

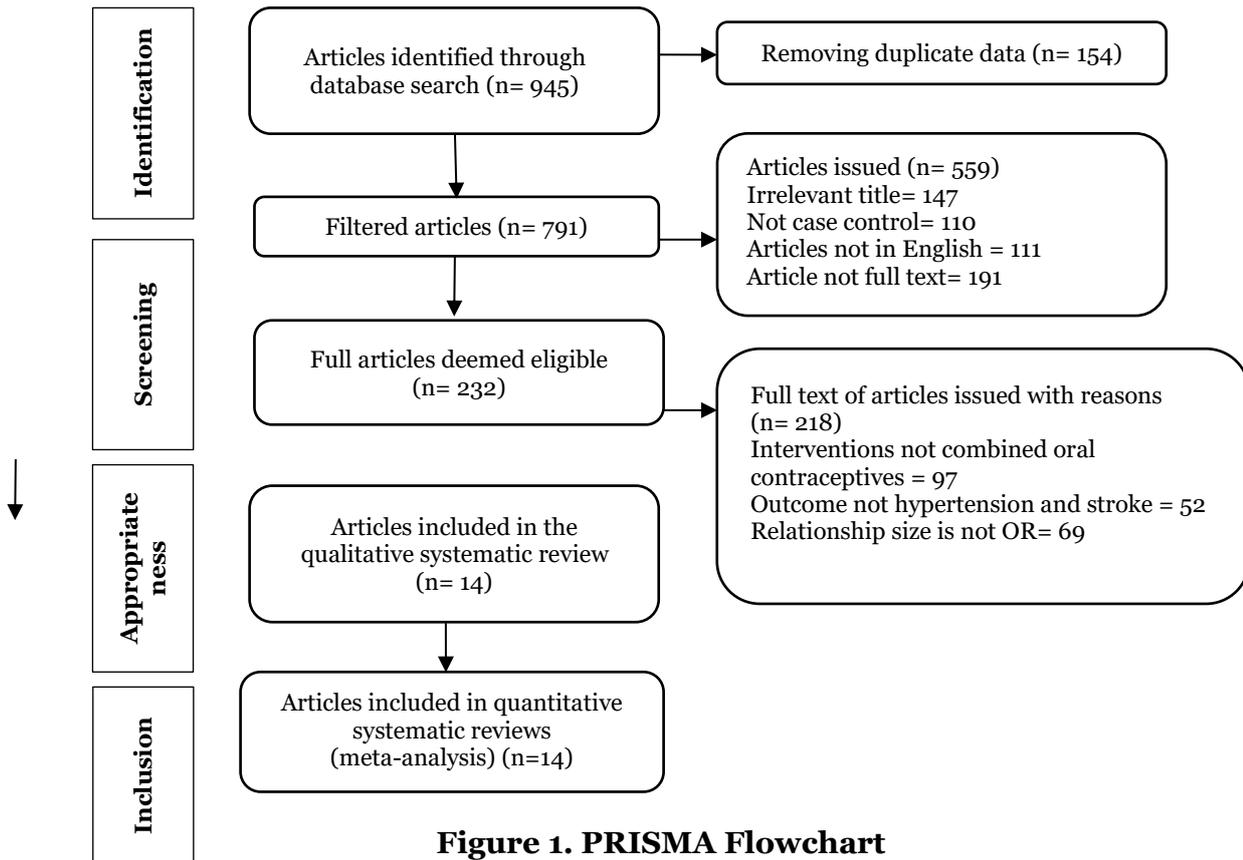


Figure 1. PRISMA Flowchart



Figure 2. Map of Research Locations

1. Research Quality Assessment

a. Assessment of the quality of the case control study the effect of using combined oral contraceptives on the incidence of hypertension

Table 3. Results of the Critical Appraisal Checklist for Case Control Study the Effect of Combination Oral Contraceptive Use on the Incidence of Hypertension

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Wang <i>et al.</i> (2011)	1	1	1	1	1	1	1	1	1	1	1	1	12
Chen <i>et al.</i> (2010)	1	1	1	1	1	1	1	1	1	1	1	1	12
Badlam <i>et al.</i> (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Kilgore <i>et al.</i> (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Xu <i>et al.</i> (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12
Wei <i>et al.</i> (2011)	1	1	1	1	1	1	1	1	1	1	1	1	12
Kahsay <i>et al.</i> (2018)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Yes= 1; No= 0

b. Assessment of the quality of the case control study the effect of using combined oral contraceptives on the incidence of stroke

Table 4. Results of the Critical Appraisal Checklist for Case Control Study the Effect of Combination Oral Contraceptive Use on Stroke Incidence

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Wang <i>et al.</i> (2012)	1	1	1	1	1	1	1	1	1	1	1	1	12
Huang <i>et al.</i> (2014)	1	1	1	1	1	1	1	1	1	1	1	1	12
Xu <i>et al.</i> (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12
Ryan <i>et al.</i> (2014)	1	1	1	1	1	1	1	1	1	1	1	1	12
Pezzini <i>et al.</i> (2007)	1	1	1	1	1	1	1	1	1	1	1	1	12
Urbanus <i>et al.</i> (2009)	1	1	1	1	1	1	1	1	1	1	1	1	12
Siegerink <i>et al.</i> (2012)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Ya= 1; Tidak= 0

1. Effect of Combination Oral Contraceptive Use on Hypertension Incidence

a. Forest Plot

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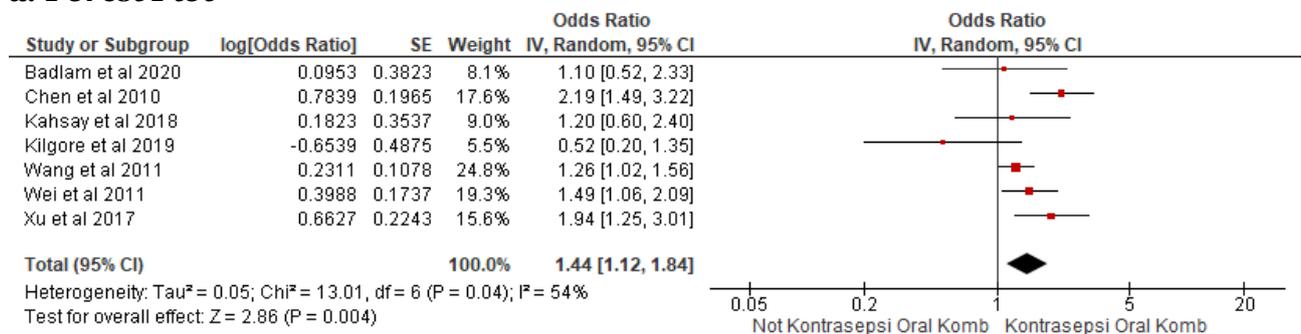


Figure 3. Forest plot of the use of combined oral contraceptives on the incidence of hypertension

2. Summary of Articles

a. Effect of Combination Oral Contraceptive Use on Hypertension Incidence

Table 1. Description of the Primary Study of Hypertension Included in the Meta-Analysis

Author (Year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome	aOR (CI 95%)
Wang et al. (2011)	China	Case Control	1,760	Family planning acceptors <50 years old	Combination oral contraceptives	Not a user of oral contraceptives	Hypertension and obesity	aOR= 1.10 (0.52 to 2.33)
Chen et al. (2010)	China	Case Control	1,242	KB acceptor	Combined oral contraceptives and genetic variants of the beta estrogen receptor	Not a user of oral contraceptives	Hypertension	aOR= 2.19 (1.49 to 3.22)
Badlam et al. (2020)	The USA	Case Control	634	KB acceptor	Combined oral contraceptives and sex hormone exposure	Not a user of oral contraceptives	Hypertension	aOR= 1.20 (0.60 to 2.40)
Kilgore et al. (2019)	The USA	Case Control	149	Family planning acceptors aged 15 to 45 years	Combined oral contraceptives, implants, and non-oral contraceptives	Not a user of oral contraceptives	Hypertension	aOR= 0.52 (0.20 to 1.35)
Xu et al. (2017)	China	Case Control	1,310	KB acceptor	Combined oral contraceptives and the genetic variant ESR2	Not a user of oral contraceptives	Hypertension	aOR= 1.26 (1.02 to 1.56)
Wei et al. (2011)	China	Case Control	1,330	KB acceptor	Combined oral contraceptives and dyslipidemia	Not a user of oral contraceptives	Hypertension	aOR= 1.49 (1.06 to 2.09)
Kahsay et al. (2018)	Ethiopia	Case Control	330	Family planning acceptors aged 18 to 35 years	Combination oral contraceptives	Not a user of oral contraceptives	Hypertension	aOR= 1.94 (1.25 to 3.01)

b. Effect of Combination Oral Contraceptive Use on Stroke Incidence

Table 2. Description of the Primary Stroke Study Included in the Meta-Analysis

Author (Year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome	aOR (CI 95%)
Wang et al. (2012)	China	Case Control	1,282	KB acceptor	Combination oral contraceptives	Not a user of oral contraceptives	stroke	aOR= 1.31 (1.01 to 1.70)
Huang et al. (2014)	China	Case Control	1,372	KB acceptor	Combined oral contraceptives and the pai-1. gene variant	Not a user of oral contraceptives	stroke	aOR= 3.95 (2.29 to 6.81)
Xu et al. (2017)	China	Case Control	1,310	KB acceptor	Combined oral contraceptives and the genetic variant ESR2	Not a user of oral contraceptives	stroke	aOR= 2.00 (1.29 to 3.10)
Ryan et al. (2014)	The USA	Case Control	572	Family planning acceptors aged 15 to 49 years	Combination oral contraceptives	Not a user of oral contraceptives	stroke	aOR= 1.50 (0.60 to 3.75)
Pezzini et al. (2007)	Italy	Case Control	324	KB acceptor	Combination oral contraceptives	Not a user of oral contraceptives	Stroke and thrombophilia	aOR= 2.90 (1.80 to 4.76)
Urbanus et al. (2009)	Netherland	Case Control	803	Family planning acceptors aged 18 to 49 years	Combination oral contraceptives	Not a user of oral contraceptives	Myocardial infarction and stroke	aOR= 4.24 (1.71 to 10.51)
Siegerink et al. (2012)	Netherland	Case Control	813	KB acceptor	Combination oral contraceptives	Not a user of oral contraceptives	Myocardial infarction and stroke	aOR= 1.38 (1.09 to 1.75)

b. Funnel Plot

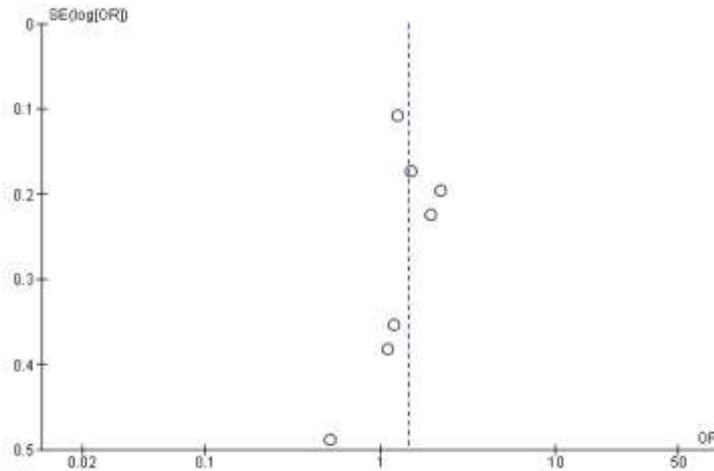


Figure 4. Funnel plot of combination oral contraceptive use on hypertension incidence

2. Effect of Combination Oral Contraceptive Use on Stroke Incidence

a. Forest Plot

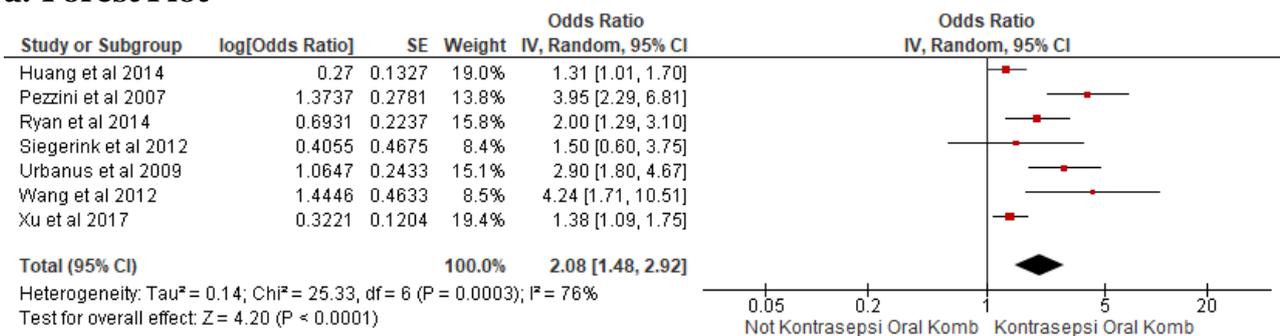


Figure 5. Forest plot of the use of combined oral contraceptives on the incidence of stroke

b. Funnel Plot

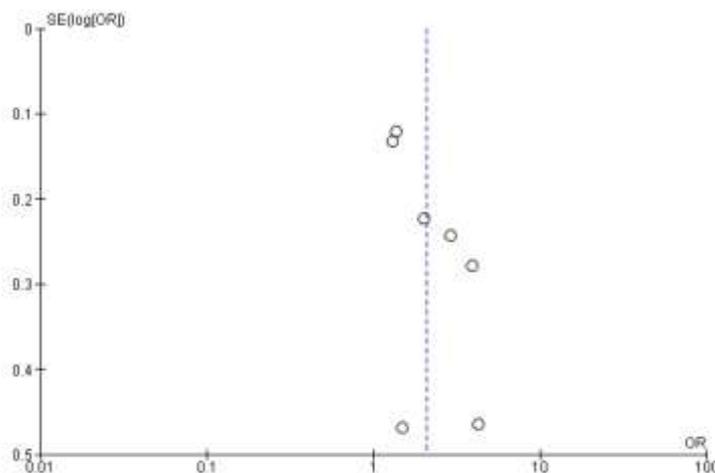


Figure 6. Funnel plot of combination oral contraceptive use on stroke incidence

The funnel plot in Figure 6 shows the distribution of the estimated effects of all the

primary studies in this meta-analysis which lies mostly to the left of the vertical line.

The mean of the effect estimates on the right that indicate or indicate slight publication bias. Because the publication bias is

DISCUSSION

This systematic review and meta-analysis study discusses the effect of the use of combined oral contraceptives on the incidence of hypertension and stroke. The independent variables used in this study were family planning acceptors who used combined oral contraceptives. While the dependent variable used is the incidence of hypertension and stroke.

This study uses the results of the aOR statistic from multivariate analysis, which aims to control for confounding factors. Confounding factors can cause research results to be invalid because confounding factors also affect the relationship or affect the population under study.

Effect of combination oral contraceptive use on hypertension incidence

Based on the analysis of 7 primary studies with case control study designs conducted with a systematic review and meta-analysis showed heterogeneity between studies ($I^2=54\%$) so the analysis used the Random Effect Model (REM). This heterogeneity is based on the asymmetric distribution between the left and right plots in the funnel plot. Publication bias in case control studies due to variation or diversity between populations as seen from the number of different samples shown by the primary study articles is caused by the relatively small number of samples ($n=149$). It also makes the CI range wide. The combination oral contraceptive intervention was able to increase the incidence of hypertension by 1.44 times compared to not using combined oral contraceptives and was statistically significant (aOR= 1.44; 95% CI= 1.12 to 1.84; $p=0.004$).

The results of this study are supported by research conducted by Chen et al. (2010)

in the same direction as the diamond in the forest plot, the publication bias tends to overestimate the true effect.

found that combined oral contraceptive use was considered a risk factor for the development of hypertension especially for women without blood pressure screening. Cumulative duration of combined oral contraceptive use was associated with hypertension risk and the risk increased in the aggregate with prolonged duration of combined oral contraceptive use showing statistically significant results (aOR= 2.19; 95% CI= 1.49 to 3.24; $p=0.001$). Another related study by Wang et al. (2011) stated that the risk of hypertension in Chinese women increased gradually based on the cumulative time duration of combined oral contraceptive use. The use of combined oral contraceptives will increase the risk of hypertension by 1.26 times and statistically significant (aOR= 1.26; 95% CI= 1.02 to 1.56; $p=0.008$). This study is in line with Wei et al. (2011). The aim of this study was to assess the relationship between combined oral contraceptive use and its interaction with the risk of hypertension in Chinese women. The risk of hypertension gradually increases with increasing cumulative time of combined oral contraceptive use in women when compared to non-combined oral contraceptive users. Cumulative time of combined oral contraceptive use 15 years increased the risk of hypertension statistically significant (aOR= 1.49; 95% CI= 1.06 to 2.11; $p<0.001$) combined oral contraceptive use increased the risk of hypertension in Chinese women, currently using oral contraceptives combination in women with hypertension appears to be underappreciated.

Effect of combination oral contraceptive use on stroke incidence

Based on the analysis of 7 primary studies with case-control study designs conducted with a systematic review and meta-analysis

of the effect of the use of combined oral contraceptives on the incidence of stroke, the results from the forest plot showed heterogeneity between studies ($I^2= 76\%$) so that the analysis used Random Effects. Model (REM). The research article showed that the use of combined oral contraceptives had 2.08 times the risk of having a stroke compared to using non-combined oral contraceptives and was statistically significant (aOR= 2.08; 95% CI= 1.48 to 2.92; $p < 0.001$).

The results of this study are supported by research conducted by Wang et al. (2012) showed that current use of combined oral contraceptives was associated with a 4.24-fold increased risk and was statistically significant (aOR= 4.24; 95% CI= 1.71 to 10.49; $p < 0.001$) combined oral contraceptive users who used for more than 15 years were more at risk against strokes. Research from Pezzini et al. (2007) aimed to find out that exposure to the effects of oral contraceptives can increase the risk of ischemic stroke in women. Data were obtained in a single central setting, hospital-based study, designed at the Department of Neurology, University of Brescia, Brescia, Italy, for the associated evaluation of a series of consecutive patients admitted to our department with a first acute ischemic stroke occurring under the age of 45. year. Oral contraceptive use was associated with an approximately nine-fold increased risk of ischemic stroke (aOR= 3.95; 95% CI= 2.29 to 6.78; $p < 0.001$), current use of oral contraceptives resulted in an approximately threefold increased risk of stroke, exposure to oral contraceptives could be significantly increase the incidence of ischemic stroke and prompt consideration of alternative therapeutic or contraceptive approaches. The primary study on combined oral contraceptive use with stroke risk was conducted by Xu et al. (2017) said that combined oral contraceptives can increase the risk of stroke, the results of this study show-

ed the use of combined oral contraceptives against stroke was statistically significant (aOR= 1.38; 95% CI= 1.09 to 1.75; $p= 0.007$).

The limitation of this study is that there is a research bias because it only uses 3 databases, namely Google Scholar, PubMed, and Science Direct, thus ignoring research from other databases. In this study, there is also a language bias because the selected articles are only published in English, thus ignoring articles published in other languages.

AUTHOR CONTRIBUTION

Ulul Azmi Zuhaira is the principal researcher who selects the topic, searches for and collects study data. Eti Poncorini Pamungkasari and Vitri Widyaningsih played a role in analyzing data reviewing study documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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