

## Meta-Analysis the Effect of Hormonal Contraception on the Weight Gain and Hypertension in Women of Reproductive Age

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### ABSTRACT

**Background:** Hormonal contraception is a contraceptive method that can prevent pregnancy because it contains estrogen and progesterone. The use of hormonal contraception for a long time can cause side effects including increased body weight, cholesterol deposits, and hypertension. The purpose of this study was to examine, analyze, and estimate the magnitude of the effect of the use of hormonal contraception on the incidence of weight gain and hypertension in women of childbearing age based on the results of previous similar studies.

**Subjects and Method:** This study is a systematic review and meta-analysis using PRISMA flowchart diagrams. The process of searching for articles was carried out between 2004-2021 using 3 databases, including Google Scholar, PubMed, and Science Direct. The keywords used in the database search are "Hormonal Contraception" AND "DPMA injection" AND "Weight Gain" AND "Hypertension". Inclusion criteria for full text articles used the observational Randomized Controlled Trial method, the articles used English, and reported the Mean and SD in multivariate analysis. Articles that met the requirements were analyzed using the RevMan 5.3 application.

**Results:** A total of 14 articles with a Randomized Controlled Trial study design originating from Thailand, Indonesia, Pakistan, America, California, Africa, Ethiopia, and Kenya were meta-analyzed in this study. Meta-analysis of 7 articles showed that hormonal contraception had an effect on weight gain in women of childbearing age by 0.03 units but not statistically significant (SMD= 0.03; 95% CI= 0.07 to 0.14; p= 0.530). Meanwhile, 7 articles showed that hormonal contraception increased the incidence of hypertension in women of childbearing age by 0.10 units, but it was not statistically significant (SMD= 0.10; 95% CI= 0.17 to 1.37; p= 0.460).

**Conclusion:** Hormonal contraception increases body weight and hypertension in women of childbearing age.

**Keywords:** hormonal contraception, weight gain, hypertension, meta-analysis.

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### BACKGROUND

Hypertension is one of the most common public health problems throughout the world, including Indonesia. There are risk

factors that cannot be changed, namely age, sex and genetics, while risk factors that can be changed include obesity/ overweight, psychosocial and stress, smoking, lack of

exercise, excessive alcohol consumption, hyperlipidemia/ hypercholesterolemia, while secondary causes include kidney disease, endocrine disorders and use of drugs such as contraception (Martuti, 2009).

The use of hormonal contraception for a long time can cause side effects including increased body weight, cholesterol deposits, and hypertension. The hormones estrogen and progesterone which can affect the increase in blood pressure. This is due to cardiac hypertrophy and an increase in the response to pressor angiotensin II by involving the Renin Angiotensin System pathway. Apart from that, it also contains ethinyles-tradiol which is a cause of hypertension, while Gestagen has minimal effect on blood pressure. Ethinylestradiol can increase angiotensinogen 3-5 times (Baziad, 2008).

Weight gain occurs more in association with the use of hormonal injections than oral ones. As a result of the response of contraceptives there is a reduction in water retention in the body resulting in obesity. One of the side effects of the hormone progesterone can stimulate the appetite control center called the hypothalamus which will increase appetite and facilitate the conversion of carbohydrates into fat, resulting in accumulation of fat which causes weight gain. Meanwhile, estrogen also affects lipid metabolism which leads to an increase in body fat reserves, especially in the abdominal area, resulting in weight gain (Rufaridah et al., 2017). In addition, the estrogen component can also cause fluid retention resulting in weight gain (Hariadini et al., 2017). Weight gain in this 3-month injectable birth control is an average of 1-5 kg in the first year. Meanwhile, the average weight gain in 1-month injectable birth control is 2-3 kg in the first year of use (Rufaridah et al., 2017).

Based on this background, more comprehensive research is needed from various primary studies on the effect of hormonal

contraception on weight gain and hypertension in women of childbearing age. The data obtained will be analyzed using a systematic review and meta-analysis in an effort to obtain comprehensive results by synthesizing the results of primary studies involving hormonal contraception, weight gain and hypertension. The purpose of this study was to examine, analyze, and estimate the magnitude of the effect of the use of hormonal contraception on the incidence of weight gain and hypertension in women of childbearing age based on the results of previous similar studies.

## SUBJECTS AND METHOD

### 1. Study Design

This research was conducted using systematic reviews and meta-analyses between 2004 and 2021. Article searches used databases, including Google Scholar, Pubmed, and Science Direct. The keywords used in searching the database are "Hormonal Contraception" AND "DPMA injection" AND "Weight Gain" AND "Hypertension".

### 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 PubMed, Scopus, Science Direct, and Google Scholar.
- 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.

### 3. Inclusion Criteria

The inclusion criteria used in this study were full-text articles using a Randomized

Controlled Trial design. The analysis used multivariate with Randomized Controlled Trial.

#### 4. Exclusion Criteria

The exclusion criteria in this study were articles published before 2004, articles that did not use English, and previous studies using meta-analysis

#### 5. Operational Definition of Variables

The articles included in this study were adjusted according to the PICO. The article search was carried out by considering the eligibility criteria using the PICO model as follows: Population= Women of Reproductive Age, Intervention= Using Hormonal Contraception, Comparison= Not using hormonal contraception, Outcome= Weight gain and hypertension.

**Hormonal contraceptives** were contraceptives that are being used by women, containing the hormones estrogen and progesterone to prevent pregnancy.

**Weight gain** was a condition in which all tissues gain weight, including bones, muscles, fat and body fluids due to the use of hormonal contraception.

**Hypertension** was a condition where the systolic blood pressure increases  $\geq 140$  mmHg and diastolic  $\geq 90$  mmHg.

#### 6. Instrument

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

1. Does this objective clearly address the research focus/problem?
2. Is the case control research method suitable for answering research questions?
3. Are the cases representative of the designated population?
4. Are the controls selected 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 effect size of the exposure assessed?
10. Are confidence intervals 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?

#### 7. Data Analysis

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

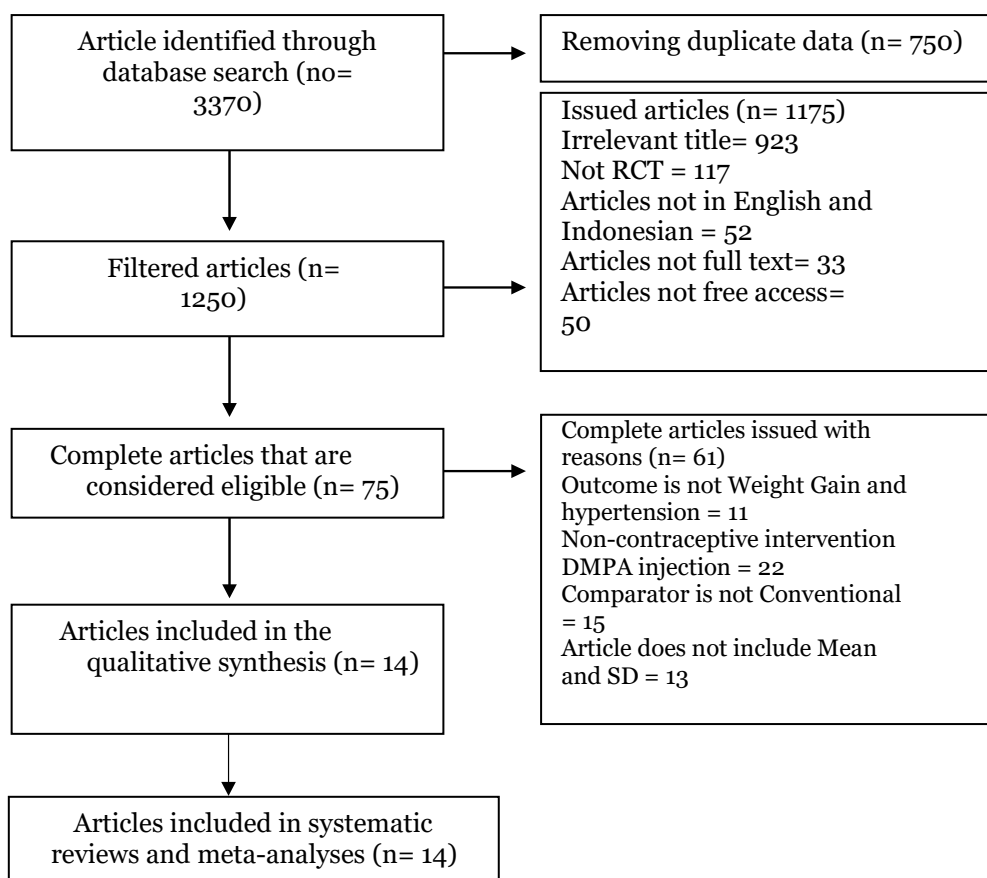
## RESULTS

The article review process using a database based on the PRISMA flowchart diagram can be seen in Figure 1. The total number of articles obtained was 14 articles spread across 4 continents, namely Asia, Africa and America. 7 articles in Asia 4 articles, in Africa 5 articles in America 5 articles, can be seen in Figure 2.

The total number of primary studies included in this meta-analysis synthesis amounted to 14 articles originating from Thailand, Indonesia, Pakistan, America, California, Africa, Ethiopia, and Kenya. Primary research on the effect of hormonal contraception on weight gain in women of childbearing age used 7 randomized control trials from Thailand, Indonesia, Africa and America). Meanwhile, the effect of hormonal contraception on hypertension in wo-

men of childbearing age used 7 randomized control trials from Pakistan, Kenya, Africa,

Thailand, Ethiopia and California.



**Figure 1. PRISMA diagram the effect of hormonal contraception on the weight gain and hypertension in women of reproductive age**



**Figure 2. Research Area the effect of hormonal contraception on the weight gain and hypertension in women of reproductive age**

**1. Summary of Articles**

**a. The Effect of Hormonal Contraception on Weight Gain in Women of Reproductive Age**

**Table 1. Primary Study Descriptions of Weight Gain Included in the Meta-Analysis**

Author (Year)	Country	Study Design	Sample		Population	Intervention	Comparison	Outcome	Mean		SD	
			DMPA	Non DPMA					DMPA	Non DMPA	DMPA	Non DMPA
Jirakittidul et al. (2019)	Thailand	RCT	231	203	Women aged 19-35 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Weight gain	52.19	52.10	9.46	9.47
Ardiani et al. (2020)	Indonesia	RCT	55	55	Women aged 20-35 years	Contraceptive injection 3 months	Not using 3 months contraception	Weight gain	60.4	57.4	9.17	8.96
Beksinska et al. (2010)	Africa	RCT	72	59	Women aged 17-25 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Weight gain	59.4	58.9	11.9	10.9
Berenson and Rahman (2009)	The USA	RCT	58	51	Women aged 20-25 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Weight gain	71.8	73.2	19.2	18.6
Bonny et al. (2006)	The USA	RCT	115	160	Women aged 15-25 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Weight gain	62.05	60.74	1.26	1.04
Clark et al. (2005)	The USA	RCT	178	145	Female, aged 18-35 years	DMPA injectable contraceptives	Not a DMPA Contraceptive user	Weight gain	69.4	67.9	16.9	14.9
Bonny et al. (2004)	The USA	RCT	26	15	Female, aged 18-25 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Weight gain	60.2	59.9	10.9	10.4

**b. The Effect of Hormonal Contraception on Hypertension in Women of Reproductive Age****Table 2. Description of the Primary Hypertension Studies Included in the Meta-Analysis**

Author (Year)	Country	Study Design	Total sample		Population	Intervention	Comparison	Outcome	Mean		SD	
			DMPA	Non DPMA					DMPA	Non DMPA	DMPA	Non DMPA
Haroon and Naveed (2014)	Pakistan	RCT	30	30	women of childbearing age group (14-49 years)	Contraceptive injection 3 months	Not a 3-month injection contraceptive user	Hypertension	118.33	112.0	9.85	1.36
Wanyoike Gichuhi et al. (2014)	Kenya	RCT	50	50	Women aged 20-35 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Hypertension	112.52	115.27	3.21	8.96
Aasare et al. (2014)	Africa	RCT	71	21	Women aged 17-25 years	DMPA injectable contraceptives	Not a DMPA injection con- traception user	Hypertension	117.75	113.04	15.88	1.89
Murayam a et al (2003)	Thailand	RCT	17	8	Women aged 20-29 years	Contraceptive injection 3 months	Not a 3-month injection contraceptive user	Hypertension	113.4	109,8	13.1	7.6
Shiferaw et al (2021)	Ethiopia	RCT	45	50	Women aged 20-25 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Hypertension	113.3	113.9	6.1	5.5
Zerihun et al., (2019)	Ethiopia	RCT	50	50	Female, aged 18-35 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Hypertension	83.22	82,91	8.68	6.98
Xiang et al., (2007)	Californian	RCT	94	448	Female, aged 20-35 years	DMPA injectable contraceptives	Not a DMPA injection contraception user	Hypertension	114	114	13	13

**Research Quality Assessment**

**a. Quality assessment Randomized Control Trial study of the effect of hormonal contraception on weight gain in women of childbearing age**

**Table 3. Results of Critical Appraisal Checklist for Randomized Control Trial Study Effect of Hormonal Contraception on Weight Gain in Women of Reproductive Age**

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Jirakittidul et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Ardiani et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Beksinsk et al. (2010)	1	1	1	1	1	0	1	1	1	1	1	1	11
Berenson et al. (2009)	1	1	1	1	1	1	1	1	1	1	0	1	11
Bonny et al. (2006)	1	1	1	1	1	1	1	1	1	1	0	1	11
Clark et al. (2005)	1	1	1	1	1	1	1	1	1	1	1	1	12
Bonny et al. (2004)	1	1	1	1	1	1	1	1	1	1	0	1	11

Note: Yes= 1; No= 0

**b. Quality assessment Randomized Control Trial study of Hormonal Effects on Hypertension in Women of Reproductive Age**

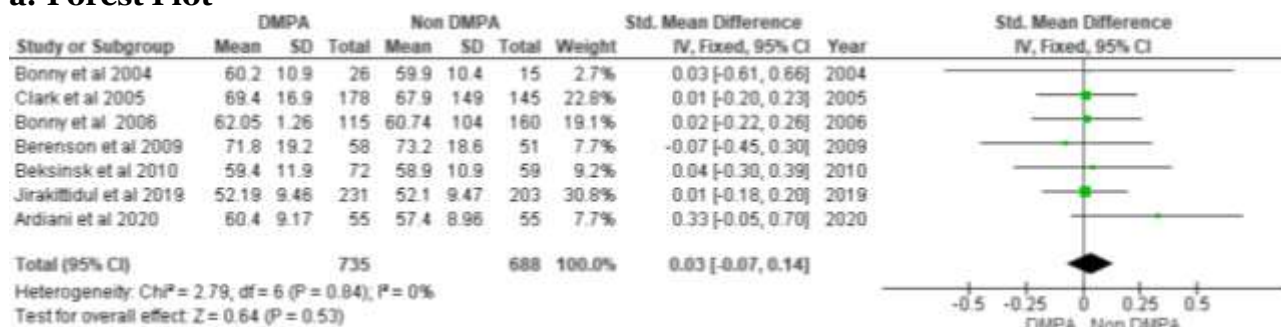
**Table 4. Results of Critical Appraisal Checklist for Randomized Control Trial Study Effect of Hormones on Hypertension in Women of Reproductive Age**

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Haroon (2014)	1	1	1	1	1	1	1	1	1	1	1	1	12
Gichuchi (2014)	1	1	1	1	1	1	1	1	1	0	1	1	11
Asare et al. (2014)	1	1	1	1	1	1	1	1	1	1	0	1	11
Murayama et al. (2003)	1	1	1	1	1	1	1	1	1	1	1	1	12
Shiferaw et al (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Zerihun et al. (2012)	1	1	1	1	1	1	1	1	1	1	1	1	12
Xiang et al (2007)	1	1	1	1	1	1	1	0	1	1	1	1	11

Note: Yes= 1; No= 0

**1. The Effect of Hormonal Contraception on Weight Gain in Women of Reproductive Age**

**a. Forest Plot**



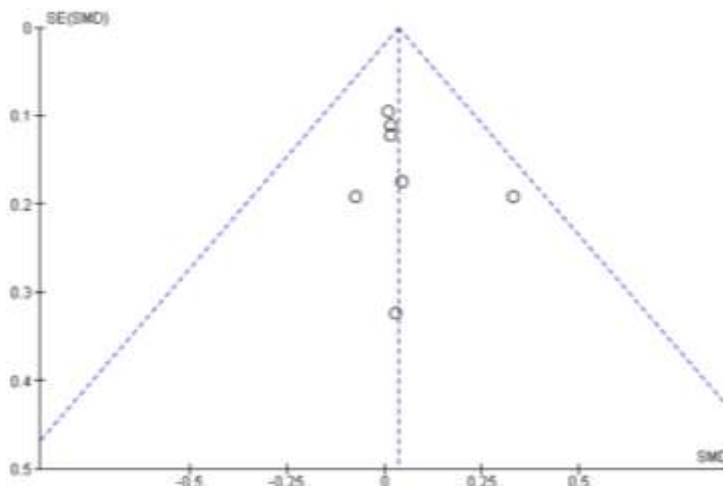
**Figure 3. Forest Plot Effect of Hormonal Contraception on Weight Gain in Women of Reproductive Age**

The forest plot in Figure 3 shows that DMPA Hormonal Contraceptives increased

the weight of women of childbearing age by 0.03 units but not statistically significant (SMD =0.03; 95% CI= 0.07 to 0.14; p=

0.530). Intervention of DMPA hormonal contraception was able to increase body weight by 0.03 times compared to not using DMPA hormonal contraception. The forest plot in Figure 3 also shows that there are

**b. Funnel Plot**

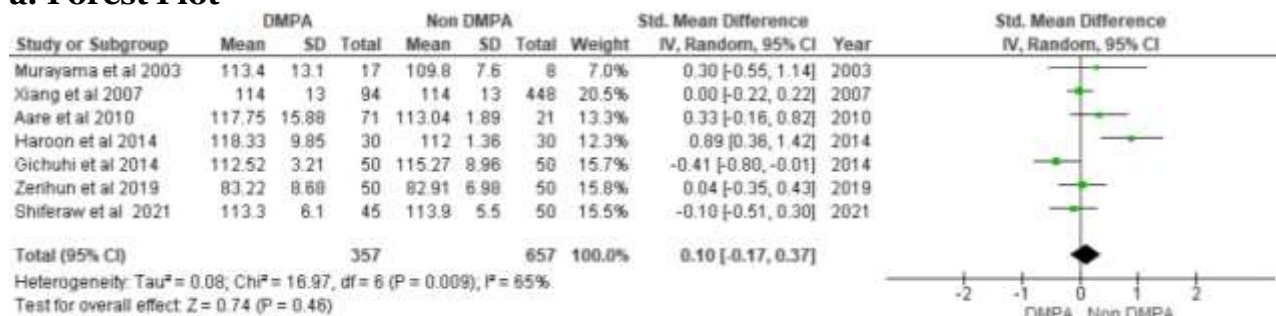


**Figure 4. Funnel plot of the effect of hormonal contraception on weight gain in women of childbearing age**

The funnel plot in figure 4 shows the distribution of effect estimates of all primary studies in this meta-analysis which are mostly located to the left of the vertical line. Mean effect estimates on the right show or

**2. The effect of hormonal contraception on hypertension in women of reproductive age**

**a. Forest Plot**



**Figure 5. Forest Plot Effect of Hormonal Contraception on Hypertension in Women of Reproductive Age**

The forest plot in Figure 5 shows that DMPA Hormonal Contraceptives increased the incidence of hypertension in women of childbearing age by 0.10 units, but not statistically significant (SMD= 0.10; 95% CI=

variations in effect estimates between studies in this meta-analysis (I<sup>2</sup>= 0%). Thus the calculation of the average effect estimate is carried out using Fixed Effect Model.

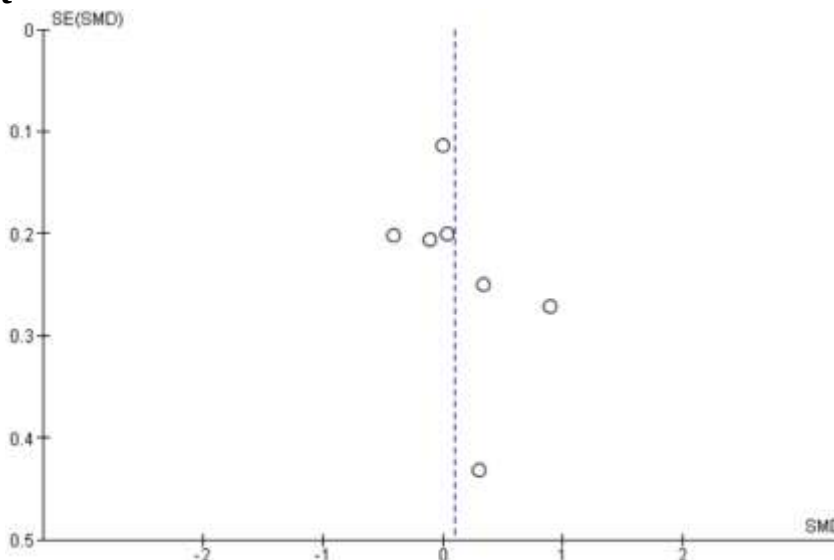
indicate slight publication bias. Because the publication bias is in the opposite direction to the location of the diamonds in the forest plot, the publication bias tends to underestimate the true effect.

0.17 to 1.37; p= 0.460). Intervention of DMPA hormonal contraception was able to increase body weight by 0.10 times compared to not using DMPA hormonal contraception. The forest plot in Figure 5 also



shows that there is variation in effect estimates between studies in this meta-analysis ( $I^2 = 65\%$ ). Thus, the calculation of the

#### b. Funnel Plot



**Figure 6. The funnel plot of the effect of hormonal contraception on hypertension in women of reproductive age**

The funnel plot in figure 6 shows the distribution of effect estimates of all primary studies in this meta-analysis which are mostly located to the left of the vertical line. Mean effect estimates on the right show or indicate slight publication bias. Because the publication bias is in the direction of the location of the diamonds in the forest plot, the publication bias tends to overestimate the actual effect.

### DISCUSSION

This systematic review and meta-analysis study discusses the effect of hormonal contraception on weight gain and hypertension in women of childbearing age. The independent variable used in this study was women of childbearing age using hormonal contraception. While the dependent variable used is weight gain and hypertension.

This study uses the results of multivariate analysis, which aims to control for confounding factors. Confounding factors can cause research results to be invalid be-

cause confounding factors also affect relationships or affect the population studied. average effect estimate is carried out using the Random Effect Model (REM) approach.

cause confounding factors also affect relationships or affect the population studied.

#### Effect of Using Combined Oral Contraception on Hypertension

Based on the analysis of 7 primary studies with a randomized control trial study design conducted with a systematic review and meta-analysis showed heterogeneity between studies ( $I^2 = 0\%$ ;  $p \geq 0.84$ ) so that the analysis used the Fixed Effect Model (FEM). This heterogeneity is based on the asymmetrical distribution between the left and right plots in the funnel plot. Publication bias in randomized control trials is due to variation or diversity between populations as seen from the different number of samples indicated by the primary study articles. It also makes the CI range wide. Intervention of DMPA hormonal contraception was able to increase body weight by 0.03 times compared to not using DMPA hormonal contraception (SMD= 0.03; 95% CI= 0.07 to 0.14;  $p < 0.53$ ).

There are 5 primary research articles

that show significant value in the study of the effect of oral contraception on weight gain in women of childbearing age which is marked as not touching the horizontal line of each study with a vertical line in the forest plot including Bonny et al (2004), Bonny et al (2006), Bereson et al (2009), Besinsk et al (2010), Ardian et al (2020). This significance value was influenced by several factors in the 7 articles. The number of samples between the control group and the intervention group was the same so that the number of proportions for both was balanced.

#### **Effect of Using Combined Oral Contraception on Stroke Incidence**

Based on the analysis of 7 primary studies with a randomized control trial study design conducted with a systematic review and meta-analysis of the effect of hormonal contraception on hypertension in women of reproductive age, the results obtained from the forest plot showed heterogeneity between studies ( $I^2= 65\%$ ;  $p < 0.009$ ) so that the analysis uses the Random Effect Model (REM). Intervention of DMPA hormonal contraception was able to increase body weight by 0.10 times compared to not using DMPA hormonal contraception (SMD= 0.10; 95% CI= 0.17 to 1.37;  $p= 0.460$ ).

There are 5 primary research articles that show significant value in the study of the effect of oral contraception on weight gain in women of childbearing age which is marked as not touching the horizontal line of each study with a vertical line on the forest plot including Haroon et al. (2014), Gichuhi et al. (2014), Asare et al. (2010), Murayama et al. (2003), Shiferaw et al. (2021), and Zerihun et al. (2019). This significance value was influenced by several factors in the 7 articles. The number of samples between the control group and the intervention group was the same so that the number of proportions for both was

balanced.

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 only the selected articles are published in English, thus ignoring articles published in other languages.

#### **AUTHOR CONTRIBUTION**

Zonna Aditiya Kusumaningtiyas is the main researcher who selects topics, searches for and collects study data. Didik Tamtomo and Bhisma Murti played a role in analyzing the data by 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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