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Meta-Analysis

Correlations between Obesity, Polycystic Ovary Syndrome, and Sleep Apnea: A Meta-Analysis

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ABSTRACT

Background: Obesity is one of the biggest public health problems in the world. Obesity is associated with various health problems, decreased quality of life and death. Obesity is known to have an impact on women's lives, namely Polycystic Ovary Syndrome (PCOS) which if not treated immediately can cause sleep apnea. This study aims to analyze the relationship between obesity and PCOS and sleep apnea.
Subjects and Method: This research is a systematic review and meta-analysis. Population = women, Intervention = obesity, Comparison = not obese, Outcomes = PCOS and sleep apnea. Article searches through journal databases include: PubMed, Science Direct, Google Scholar, and Springerlink. The keywords used are obesity OR obese AND PCOS OR "Polycystic Ovary Syn- drome" AND "sleep apnea" OR "Poor Sleep" OR "obstructive sleep apnea". Articles were selected with the help of PRISMA flow diagrams. Inclusion criteria include full-text articles with obser- vational studies, multivariate analysis results in the form of aOR values and published from 2012- 2021. Eligible articles were analyzed using the Revman 5.3 application.
Results: Eighteen articles from the United States, Brazil, China, Turkey, Iraq, Pakistan, Sri Lanka, Korea, West Africa, East Africa, Nigeria and the United Kingdom were included in the meta- analysis. A meta-analysis of the results of the case-control study design subgroup (4 articles) and the cross-sectional study (4 articles) showed that obese women had a 1.14-fold increased risk of developing PCOS compared to non-obese women (aOR = 1.14; 95% CI = 1.03 to 1.26; p= 0.010). A meta-analysis of 10 cross-sectional studies showed that obese women increased the risk of developing sleep apnea 4.66 times than non-obese women (aOR = 4.66; 95% CI = 3.23 to 6.71; p = <0.001).
Conclusion: Obesity is a risk factor for PCOS (Polycystic Ovary Syndrome) and sleep apnea in women.

Keywords: obesity, PCOS, sleep apnea, meta-analysis.

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BACKGROUND

Obesity is one of the biggest public health problems in the world. The reason is because of the increase in consumption of fast food, low physical activity, genetic factors, psychological influences, socioeconomic status, age which contribute to changes in energy balance and lead to obesity (Barasi,

2009).

Obesity is associated with various health problems, decreased quality of life and death (Ryan et al., 2014). Obesity is known to have an impact on women's lives, namely Polycystic Ovary Syndrome (PCOS), if not treated immediately it can cause sleep apnea (Ferreira et al., 2010).

The prevalence of PCOS in the world ranges from 5-10% in women of childbearing age, in the Southwestern United States it is around 4% and in India it is around 9.13%. According to the National Institute of Health (NIH), the prevalence of PCOS increased from 6.5% to 6.8% (Sadeeqa et al., 2018). PCOS women in Indonesia in 2000 were found to be 7,419,468 (Muharam et al., 2018).

The exact cause of PCOS is not known, but PCOS has been associated with insulin resistance and obesity (Ndefo et al., 2013). The majority of women with PCOS experience insulin resistance as much as 50% - 90%. Insulin resistance also underlies the association of PCOS with dysmetabolic features (Barber et al., 2019).

In obese patients, insulin resistance and hyperinsulinemia can increase androgen secretion and can also decrease SHBG-binding globulin levels, which can lead to hyperandrogenemia. Resulting in dysfunction of the hypothalamic-pituitary-ovarian axis. This results in an increased LH to FSH ratio and relative FSH insufficiency, allowing follicular development to stall with anovulation and polycystic ovaries. Obesity can increase the release of several growth factors and inflammatory factors, which causes the ovaries to produce more androgens and inhibit the aromatization of androgens to estrogens (Wang et al., 2016).

Based on polysomnography, 66% of women with PCOS and 4% of non-PCOS experienced respiratory tract disorders during sleep (OR= 46.5, 95% CI= 14.6 to 148.4; p= 0.001). After adjustment for BMI and waist circumference (regression analysis), the difference was no longer significant (p= 0.993 and p= 0.931) (Suri et al., 2016). PCOS triggers a decrease in REM sleep in the obese group without PCOS. The cause of decreased REM sleep in PCOS is unknown. The relationship between OSA severity and waist-to-hip ratio and increase in serum testosterone over time contributes to the increased prevalence of OSA with PCOS (Hachul et al., 2019).

Obesity causes several chronic diseases, and 40-90% of obese patients show signs and symptoms of sleep apnea (Kim and Lee, 2017). Sleep apnea occurs significantly in 40% of normal body weight, and 70% in obese sleep apnea patients. A 10% weight gain was associated with a 6-fold increase in the incidence of sleep apnea, and a 10% weight loss was estimated to reduce 26% in the apnea-hypopnea index (Wolk et al., 2003). The prevalence of moderate to severe sleep apnea (AHI > 15) is 3-23%. Obesity is a major factor for sleep apnea. Among overweight women, the prevalence is approximately 5 times higher than that of non-obese (20% vs. 4%) (Antonaglia and Passuti, 2021).

Weight loss in sleep apnea patients causes a significant decrease in apnea frequency. The precise mechanism underlying the effect of obesity on the risk of sleep apnea remains unclear. This may be related to the effects of fat deposition on airway anatomy or changes in upper airway function. Weight loss has been shown to be associated with a reduction in upper airway collapse in sleep apnea (Wolk et al., 2003).

Sleep apnea and obesity affect the occurrence of PCOS, many young people today ignore a healthy lifestyle without thinking about the effects that will arise later in life in reproductive age, one of which is obesity. This study aims to deter-

mine the risk of obesity for polycystic ovary syndrome (PCOS) and sleep apnea.

SUBJECTS AND METHOD

1. Study Design

The study design used in this research is a systematic review and meta-analysis, using PRISMA flow diagram guidelines. Search articles through journal databases including PubMed, Google Scholar, Science Direct, Researchgate and Springerlink. The articles used in this study are articles that have been published from 2012-2021.

The keywords to search for articles were as follows: obesity OR obese AND PCOS OR "Polycystic Ovary Syndrome"AND sleep apnea OR "poor sleep" OR "Obstructive sleep apnea".

2. Inclusion Criteria

In this study, the inclusion criteria werefull-text articles using an observational study design in English, the analysis used was multivariate with adjusted Odds Ratio (aOR), the research subject is a woman, the title is appropriate to mention the relationship of obesity with PCOS and sleep apnea, the outcome is PCOS and sleep apnea.

3. Exclusion Criteria

Exclusion criteria in this study include articles published before 2012, primary study articles with research designs other than observational, articles that use other than English and have been meta-analyzed onthis topic previously.

4. Operational Definition of Variables

In formulating research problems here using PICO. Population is a woman, Intervention is obesity, Comparison is not obesity, Outcomes is the incidence of Polycystic Ovary Syndrome (PCOS) and sleep apnea.

Obesity is an imbalance in the amount of food intake compared to energy expenditure by the body.

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder that affects women of reproductive age.

Sleep apnea is the onset of abnormal episodes of respiratory rate associated with narrowing of the upper airways in the sleep state, which can be in the form of respiretory arrest /apnea or decreased ventilation/ hypoapnea.

5. Instrument

The quality of research articles was assessed using the Critical Appraisal Checklist for cross-sectional Study, Case Control and Cohort published by CEBM University of Oxford 2014 (CEBM, 2014).

6. Data Analysis

Articles were collected using PRISMA Flow diagrams and analyzed using the Review Manager application (RevMan) 5.3 by calculating effect size and heterogeneity to determine the combined research model and form the final result of the meta-analysis.

RESULTS

This study deals with the relationship between obesity and PCOS and sleep apnea. It consists of 18 articles from 4 continents, namely 6 research articles from the Americas, 8 research articles from the Asian continent, 3 research articles from the African continent and 1 research article from the European continent.

The search for articles was carried out using a database based on the PRISMA flow diagram in Figure 1 after the study quality assessment was carried out, there were 18 articles that met the quantitative requirements so that they could be included in a systematic study and meta-analysis. Of the 18 articles, they were divided into 2 categories according to the outcome of the intervention, namely 8 articles for the incidence of PCOS and 10 articles for the incidence of sleep apnea.

Research Quality Assessment

Assessment of the quality of research articles using the Critical Appraisal Checklist for

Case-control Study which can be seen in table 1. The criteria for evaluating articles with case-control and cross-sectional study designs are as follows:

1. Is the study designed to answer the hypotheses associated with obesity as a risk factor for PCOS and sleep apnea?
2. Does the study design clearly explain the causal relationship between exposure and disease?
3. Are population characteristics clearly described?
4. Was the selection of respondents based on clear eligibility criteria?
5. Is the sample representative of the target population (sample size and sampling method)?
6. Is obesity clearly defined?
7. Is a valid measurement of obesity using microtoise and weight scales?
8. Are PCOS and sleep apnea clearly defined?
9. Is the determination of PCOS based on ultrasound diagnostics or from the Rotterdam criteria? As for sleep apnea based on the Berlin questionnaire or the STOP-BANG questionnaire?
10. Are confounding factors in PCOS and sleep apnea clearly defined (age, physical activity, family history of PCOS, family history of snoring, lifestyle)?
11. Is there any control or adjustment for confounding factors?
12. Does the study clearly report the number of respondents?
13. Does the study clearly display the adjusted odds ratio and confident interval in PCOS and sleep apnea?
14. Did the study use multivariate analysis?

After assessing the quality of the study, as many as 18 articles were divided into 2 categories according to the dependent variable included in the meta-analysis quantitative synthesis process using RevMan 5.3.

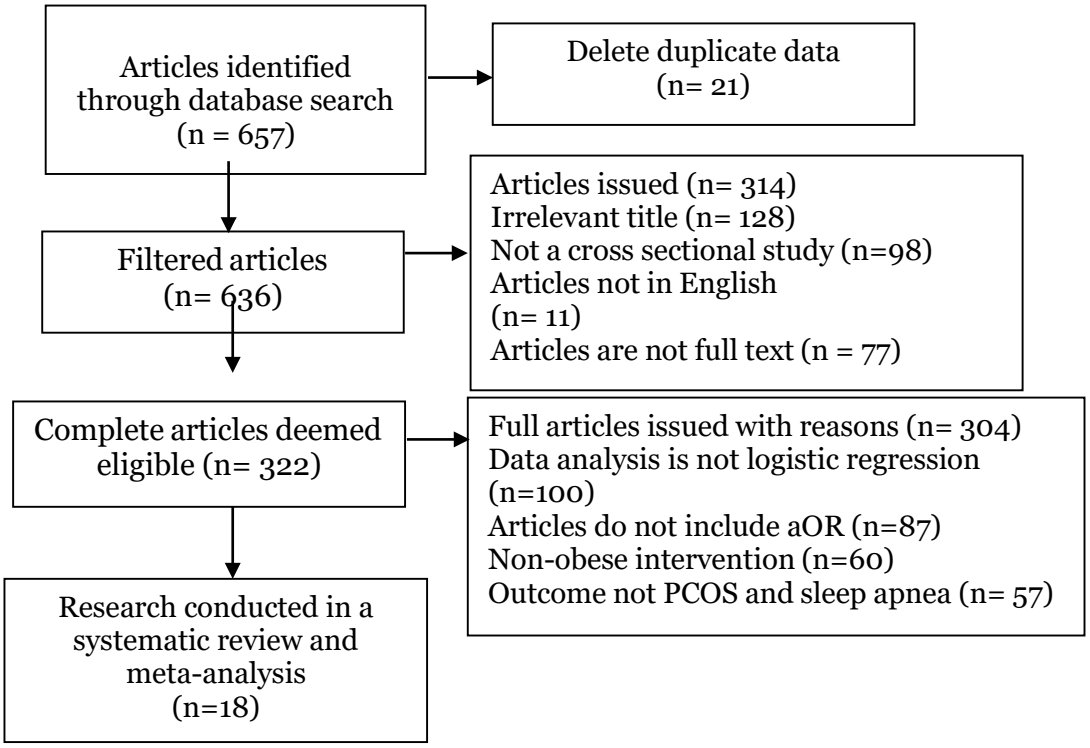

Figure 1. PRISMA flow diagram

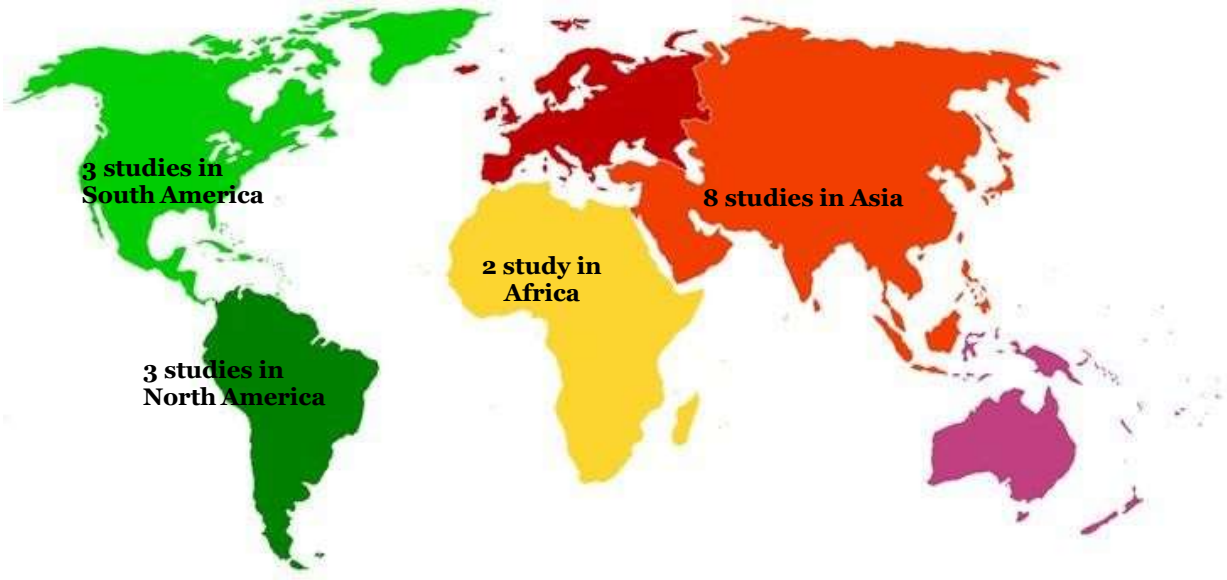

Figure 2. Map of the research area

Table 1. Assessment of research quality in case-control study and cross-sectional study designs

Primary Study	Criteria														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Jamil et al. (2015)	5	5	5	5	5	5	4	5	5	3	5	5	5	5	67
Bedrick et al. (2020)	5	5	5	5	5	4	3	5	5	5	5	5	5	5	67
Branavan et al. (2020)	5	5	5	5	5	5	3	5	5	5	5	5	5	5	68
Lone et al. (2020)	5	5	5	5	5	3	4	5	5	4	5	5	5	5	66
Li et al. (2014)	5	5	5	5	5	5	4	5	5	3	5	5	5	5	67
Esmaeilzadeh et al. (2015)	5	5	5	5	5	5	3	5	3	4	5	5	5	5	65
Usta et al. (2018)	5	5	5	5	5	5	4	5	5	5	5	5	5	5	69
Kogure et al. (2019)	5	5	5	5	5	5	5	5	5	4	5	5	5	5	69
Wall et al. (2012)	5	5	5	5	5	5	4	5	3	5	5	5	5	5	67
Yu et al. (2014)	5	5	5	5	5	4	3	4	3	3	5	5	5	5	62
Tock et al. (2014)	5	5	5	5	5	5	5	5	4	3	5	5	5	5	67
Chen et al. (2014)	5	5	5	5	5	5	5	4	4	5	5	5	5	5	68
Kim dan Lee. (2017)	5	5	5	5	5	5	5	5	5	4	5	5	5	5	69
Barros et al. (2018)	5	5	5	5	5	4	3	4	4	3	5	5	5	5	63
Oyefabi. (2019)	5	5	5	5	5	5	3	5	5	5	5	5	5	5	68
Awopeju et al. (2020)	5	5	5	5	5	5	5	5	4	5	5	5	5	5	69
Pallangyo et al. (2021)	5	5	5	5	5	5	4	4	3	5	5	5	5	5	66
Macewan et al. (2021)	5	5	5	5	5	5	3	4	3	4	5	5	5	5	64

Table 2 Description of the primary studies included in the meta-analysis (Obesity on Polycystic Ovary Syndrome)

Author (Year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Jamil et al. (2015)	Iraq	Case Control	526 (263 Case, 263 control)	Women, age 18-39 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Bedrick et al. (2020)	Amerika	Case Control	101 (51 Case, 50 control)	Women, age 18 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Lone et al. (2020)	Pakistan	Case Control	470 (235 Case, 235 control)	Women, age 25-29 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Branavan et al. (2020)	Sri Lanka	Case Control	165 (55 Case, 110 kontrol)	Women, age 19 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Li et al. (2014)	Cina	Cross- Sectional	833	Women age 20 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Esmaeilzadeh et al. (2015)	Iran	Cross- Sectional	175	Women, age 18 – 38 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Usta et al. (2018)	Turki	Cross- Sectional	124	Women, age 18 – 40 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)
Kogure et al. (2019)	Brasil	Cross- Sectional	94	Women, age 18 – 39 year	Obesity	Non Obesity	Polycystic Ovary Syndrome (PCOS)

Table 3 Description of the primary studies included in the meta-analysis (Obesity on Sleep apnea)

Author (year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Wall et al. (2012)	Inggris	Cross- Sectional	1.073	Women, age 18 - 50 year	Obesity	Non Obesity	Sleep Apnea
Yu et al. (2014)	Cina	Cross-sectional	966	Women, age 30 - 60 year	Obesity	Non Obesity	Sleep Apnea
Tock et al. (2014)	Brasil	Cross-sectional	38	Women, age 16 – 45 year	Obesity	Non Obesity	Sleep Apnea
Chen et al. (2014)	US	Cross-sectional	2.911	Women, age 20 year	Obesity	Non Obesity	Sleep Apnea
Kim dan Lee. (2017)	Korea	Cross-sectional	34	Women, age 36 year	Obesity	Non Obesity	Sleep Apnea
Barros de Carvalho et al. (2018)	Brasil	Cross-sectional	232	Women, age 45 year	Obesity	Non Obesity	Sleep Apnea
Oyefabi (2019)	West Africa	Cross-sectional	694	Women, age 44 year	Obesity	Non Obesity	Sleep Apnea
Awopeju et al. (2020)	Nigeria	Cross-sectional	362	Women, age 44-65 year	Obesity	Non Obesity	Sleep Apnea
Macewan et al. (2021)	US	Cross-sectional	6.331	Women, age 18 year	Obesity	Non Obesity	Sleep Apnea
Pallangyo et al. (2021)	East Africa	Cross- Sectional	1.974	Women, age 18 year	Obesity	Non Obesity	Sleep Apnea

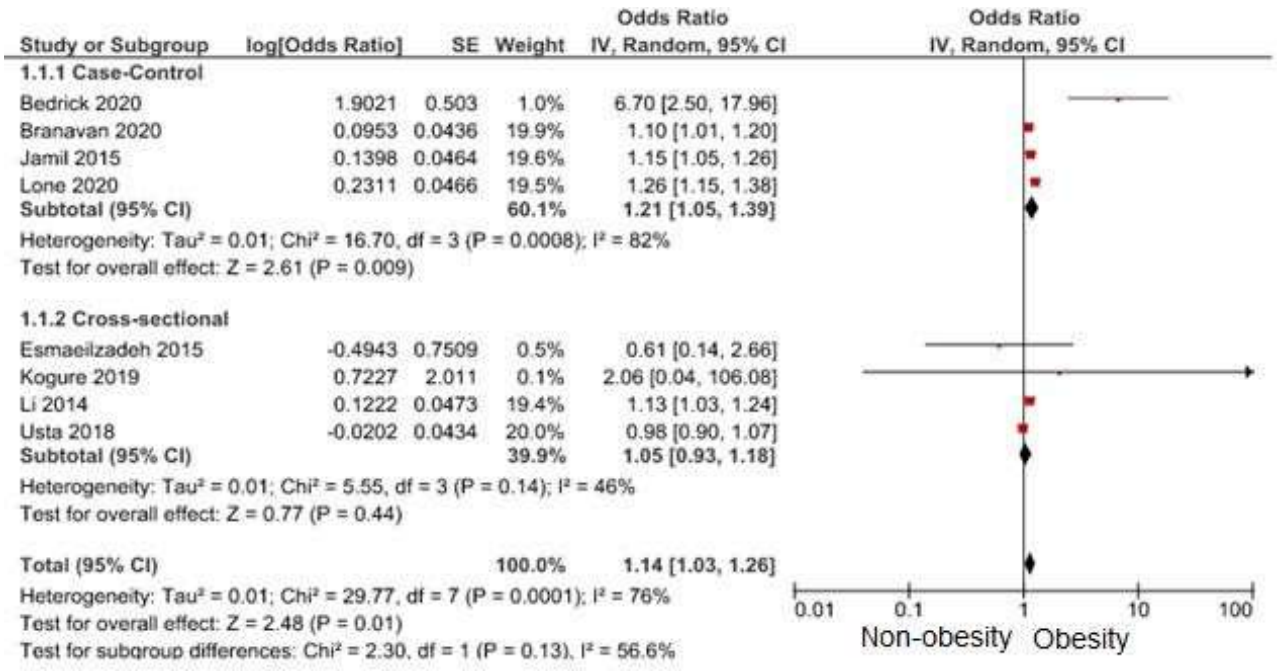

Figure 3. Forest plot of the relationship between obesity and polycystic ovary syndrome (PCOS)

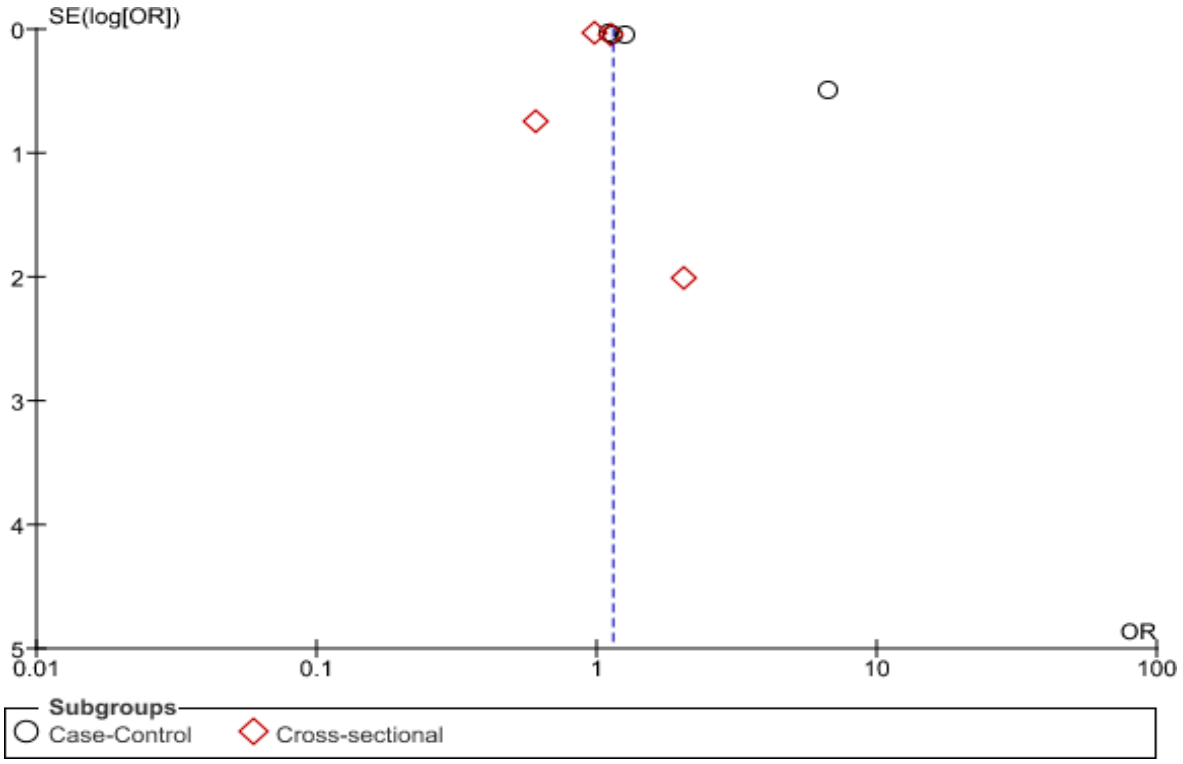

Figure 4. Funnel plot of the relationship between obesity and polycystic ovary syndrome (PCOS)

Relationship between Obesity and Polycystic Ovary Syndrome (PCOS)

1. Forest Plot

Forest plot Figure 3 shows that there is a relationship between obesity and PCOS. Women of childbearing age with obesity had a risk of developing PCOS 1.14 times than those who were not obese, and it was statistically significant (aOR= 1.14; 95% CI= 1.03 to 1.26; p= 0.010). The forest plot meta-analysis also showed a high heterogeneity of effect estimates between primary studies (I^2= 76%). Thus, the calculation of the average estimated effect of obesity on PCOS is carried out using a random effect model approach.

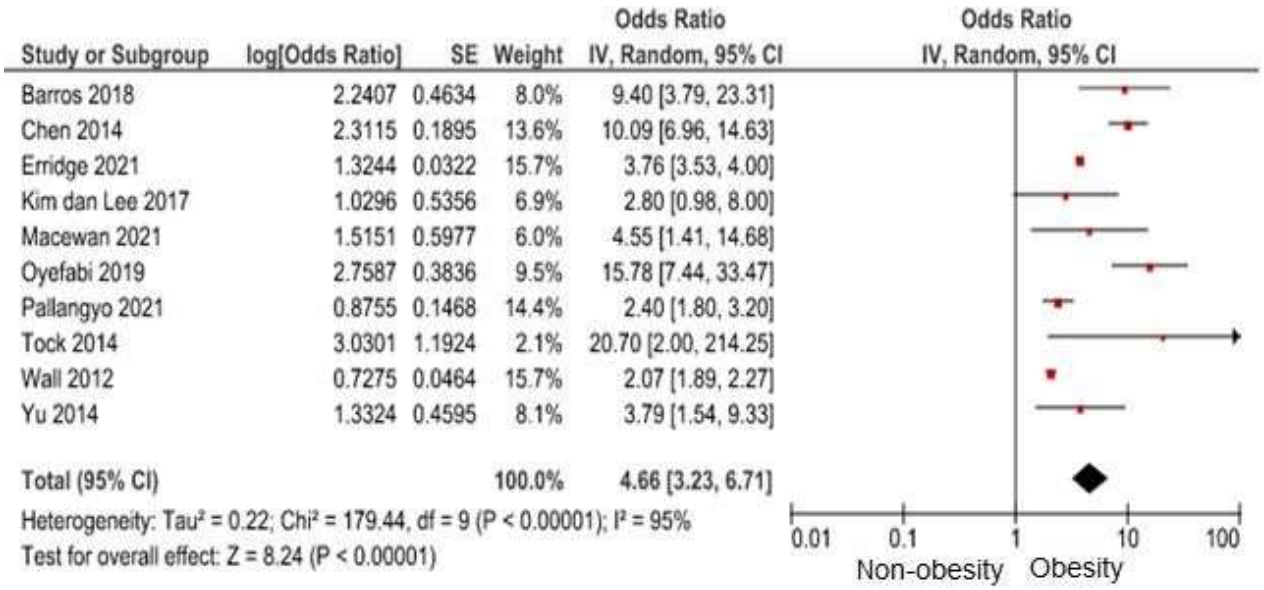

Figure 5. Forest plot of the relationship between obesity and sleep apnea

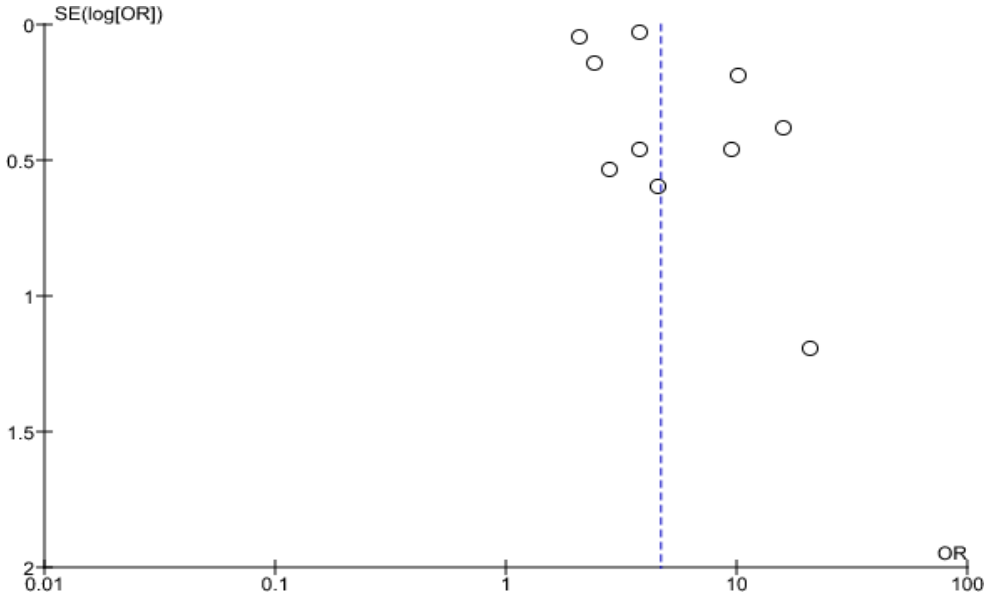

Figure 6. Funnel plot of obesity and sleep apnea

2. Funnel Plot

The funnel plot in Figure 4 shows that there is a tendency for effect estimates to be slightly more on the right of the average effect estimation line than the left. Thus, the funnel plot shows a slight publication

bias, because the distribution of the estimated effects lies to the right in the direction of the diamond in the forest plot of Figure 3, the publication bias tends to overestimate the previous effect.

The relationship between obesity and sleep apnea

1. Forest plot

Forest plot images show that there is a relationship between obesity and sleep apnea. Women of childbearing age with obesity had a risk of developing sleep apnea 4.66 times than those who were not obese, and this association was statistically significant (aOR= 4.66; 95% CI = 3.23 to 6.71). Funel plots in this meta-analysis also demonstrated heterogeneity of effect estimates between primary studies low (I^2= 35%). Thus, the calculation of the average effect estimate is carried out using a fixed effect model approach.

2. Funnel plot

The funnel plot in the figure shows a more or less symmetrical distribution of the estimated effect between studies to the right and left of the estimated vertical line. Thus, the funnel plot does not indicate publication bias.

DISCUSSION

This systematic review and meta-analysis research takes the topic of the relationship between obesity and polycystic ovary syndrome (PCOS) and sleep apnea. The independent variable in this study was obesity and the dependent variables analyzed were polycystic ovary syndrome (PCOS) and sleep apnea. This intervention was designed to determine whether obesity is a risk factor for PCOS (polycystic ovary syndrome) and sleep apnea with a case-control and cross-sectional study design.

This meta-analysis study uses 18 primary study articles identified from around the world from 2012 to 2021. This systematic review and meta-analysis study uses previous primary studies that have controlled for confounding factors which can be seen from the inclusion criteria of previous primary studies. used is the result of multivariate analysis in the form of adjusted odds ratio (aOR).

1. Obesity with Polycystic Ovary Syndrome (PCOS)

There are 8 observational research articles as a source of meta-analysis of obesity as a risk factor for PCOS. The eight articles consisted of 2 study designs, namely 4 case-control articles and 4 cross-sectional articles. The subgroup results show that there is an association between obesity and PCOS. Women of childbearing age with obesityhad a risk of developing PCOS 1.14 times compared to non-obese, and it was statistically significant (aOR= 1.14; 95% CI= 1.03 to 1.26; p= 0.010). In the funnel plot, there is a tendency for the estimated effect to be slightly more on the right side of the average effect estimation line than on the left. Thus, the forest plot shows a slight publication bias because the distribution of effect estimates lies to the right in the direction of the diamond.

The results of this study are in line with Greenwood et al, (2020), that obesity has a risk of developing PCOS by 6.89 times. Women with PCOS who are obese if not treated properly will worsen their metabolic health (aOR= 6.89; 95% CI= 2.70 to 17.62; p <0.010). Obesity can amplify the occurrence of hyperandrogenism in PCOS, which causes an increase in testosterone and a decrease in SHBG. Women with PCOS show high insulin resistance which leads to hyperinsulinemia (Messinis et al., 2015).

Zangeneh et al. (2012), stated that reproductive function in women with PCOS is highly dependent on body weight and metabolic status of 2.98 (aOR = 2.98; 95%

CI= 0.96 to 9,17; p= 0.058). Reproductive function in women with PCOS is associated with an increased risk of infertility and can have a negative effect if pregnancy occurs. The results of the study reported the level of anxiety, depression and aggression in PCOS women with obesity.

This was support by a study of Ding et al, (2019), showing that obesity was a risk factor for PCOS by 0.48 times (aOR= 0.48; 95% CI= 0.34 to 0.69; p <0.001). Obesity can affect reproductive function, especially disrupting neuroendocrine and ovarian function which causes anovulation. PCOS is characterized by phenotypic heterogeneity and various metabolic complications which are important causes of severe stress. In this study, it was also reported that PCOS sufferers suffer from mental health disorders.

Obesity often occurs in women with PCOS, the increase in size in obese women with PCOS also has an impact on one of them, namely an increase in upper airway obstruction. In obese women with PCOS, the incidence of sleep apnea increases from 41 to 58%. Thus, obese women with untreated PCOS can have long-term effects and lead to other health problems (Hachul et al., 2019). In line with this study, Mokhlesi et al, (2012) stated that women with obesity and PCOS can increase the occurrence of sleep apnea by 1.23 times (aOR= 1.23; 95% CI= 1.11 to 1.36; p < 0.001).

The association of sleep apnea prevalence in PCOS women is not only due to an increase in BMI, but is more closely related to the level of visceral adiposity. Visceral fat appears to be more metabolically active and high amounts of visceral fat are at increased risk for sleep apnea. Women with PCOS usually have a high prevalence of visceral adiposity such as from waist to hip. High androgen levels increase the occurrence of central obesity which in turn causes sleep apnea (Tasali et al., 2008).

The things those obese women with PCOS need to do are firstly exercise regularly, with regular exercise can help for weight loss. Weight loss is done to reduce the amount of central fat which aims to reduce insulin resistance and reduce the amount of androgen hormones whose production is associated with obesity conditions. The second is calorie restriction, calculating carbohydrate intake, consuming high protein, eating fruits and vegetables and avoiding calorie-dense snacks (Anisya et al., 2019).

2. Obesity with sleep apnea

The results of the meta-analysis of the relationship between obesity and sleep apnea using 10 primary study articles with a cross-sectional study design showed that obesity was a risk factor for sleep apnea by 4.66 times compared to those who were not significantly obese. This study shows that there is a publication bias which is characterized by the spread of the plots that are not symmetrical to the right and left. Where the right plot is 4, the left plot is 5 and there is 1 that touches the vertical line.

The results of the analysis of 10 articles on obesity can cause sleep apnea, supported by Chen et al. (2014) that obstructive sleep apnea is significantly influenced by being overweight by 24.23 times after adjusting for demographic factors, lifestyle, blood pressure and psychological distress (aOR= 24.23; 95% CI= 15.20 to 38.61). Obesity can increase fat deposits around the upper airway, narrow the upper airway, and reduce muscle activity that causes airway collapse during sleep.

Park et al, (2021) showed that obesity has a risk of sleep apnea by 2,983 times. Sleep apnea significantly occurs in 30% of normal body weight and 70% is experienced by someone who is obese (Wolk et al., 2003).

Weight gain by 10% can increase the risk of sleep apnea 6-fold. Weight gain can

affect the airway during sleep through several mechanisms. The mechanisms are 1) an increase in peripharyngeal fat accumulation that causes upper airway constriction, 2) affecting the nervous compensatory mechanisms to maintain airway potential, 3) respiratory system instability, and 4) a decrease in functional residual capacity due to a resultant decrease in airway caudal traction stability. the top (Punjabi, 2008).

Obesity is one of the most common risk factors for sleep apnea. It is estimated that almost 30% of patients with a BMI 30 kgBW/m^2 and 50% of patients with a BMI 40 kgBW/m^2 suffer from sleep apnea (Plen and Pack, 2010). Accumulation of fat in the area of the tongue that makes the tongue become larger or in the neck area which causes narrowing of the upper airway. This will cause symptoms of snoring during sleep. Snoring is an early symptom due to narrowing of the upper airway during sleep. If there is progressive narrowing of the upper airway in the patient, it will cause sleep apnea (Downey, 2012).

From the results of this study, obesity is a risk factor for PCOS and sleep apnea in women. The limitations of this study are publication bias and search bias.

AUTHORS CONTRIBUTIONS

Saktryana Endang Ragil Jayanti is the main researcher who chooses the topic, conducts a search for data collection in this study. Vitri Widyaningsih and Uki Retno Budihastuti conducted data analysis and reviewed research documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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