

## Meta-Analysis The Effect of Maternal Obesity on the Risk of Premature Birth and Neonatal Death

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### ABSTRACT

**Background:** The prevalence of obesity in women of reproductive age worldwide is increasing by an estimated 20-36%. Increased prevalence of obesity also occurs in pregnant women. Obesity increases the risk of poor pregnancy outcome. This study aims to investigate the effect of maternal obesity on preterm birth and neonatal mortality.

**Subjects and Method:** This was a systematic review and meta-analysis. The articles used were obtained from several databases, including: Google Scholar, Science Direct, Springer Link, Proquest, and Scopus published from 2010 to 2021. The population in this study was pregnant women with an intervention in the form of obesity, comparison in the form of normal BMI, and outcome such as premature birth and neonatal death. The keywords used to search for articles were: ("maternal obesity" OR "maternal BMI") AND ("premature birth" OR "preterm birth" OR "preterm delivery" OR "preterm labor") AND ("neonatal mortality" OR "neonatal death") AND "adjusted Odds Ratio", and "maternal obesity" AND ("premature birth" OR "preterm birth" OR "preterm delivery") AND ("neonatal mortality" OR "neonatal death") AND "adjusted Odds Ratio". The article is a full text article with a cross-sectional and cohort study design. Articles were collected using PRISMA flow diagrams and analyzed using the Review Manager 5.3 . application.

**Results:** There were 19 articles reviewed in the study. A meta-analysis of 13 cohort studies showed that obese pregnant women were 1.02 times more likely to have a premature birth when compared to normal BMI pregnant women, but this result was not statistically significant (aOR=1.02; 95% CI=0.93 to 1.13; p=0.630). A meta-analysis of 4 cohort studies showed that maternal obesity increased the risk of neonatal death and was statistically significant (aOR=1.52; 95% CI=1.17 to 1.99; p=0.002). A meta-analysis of 4 cross-sectional studies showed that maternal obesity increased the risk of neonatal death and was statistically significant (aOR=1.44; 95% CI=1.26 to 1.64; p<0.001).

**Conclusion:** Maternal obesity increases the risk of neonatal death which is statistically significant and the risk of preterm birth which is not statistically significant.

**Keywords:** maternal obesity, premature birth, neonatal death.

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### BACKGROUND

Obesity is a growing health problem worldwide. WHO defines obesity as abnormal or

excessive fat accumulation that can interfere with health with a Body Mass Index (BMI) of 30 kg/m<sup>2</sup> or more as obesity in

adults (WHO, 2021). The prevalence of obesity among women of reproductive age is increasing worldwide, with an estimated 20-36% (Ng et al., 2014). As prevalence increases among women of reproductive age group, so does among pregnant women. Recent NCHS data show that 29% of all women who gave birth in 2019 were obese, up 11% compared to 2016 (NCHS, 2021).

In 2016, 39% of adults aged 18 years and over, of whom 40% were women were overweight. Overall, about 13% of the world's adult population, 15% of whom women were obese in 2016 (WHO, 2021). It is estimated that by 2025, more than 21% of women in the world will be obese (Indarti et al., 2021). Pregnant women classified as obese are known to have an increased risk for adverse maternal and fetal/neonatal outcomes (Tenenbaum and Hod, 2013). Maternal obesity has been associated with adverse pregnancy outcomes including preterm birth and neonatal death (Marchi et al., 2015) (Ozodiegwu et al., 2019).

Globally, prematurity is the leading cause of death in children under 5 years of age. Every year, an estimated 15 million babies are born prematurely (before 37 weeks of gestation), and this number continues to increase (WHO, 2018). The number of newborn deaths globally decreased from 5 million in 1990 to 2.4 million in 2019, children face the greatest risk of death in their first 28 days. In 2019, 47% of all under-five deaths occurred in the newborn period with approximately one third dying on the day of birth and nearly three quarters dying within the first week of life (WHO, 2020).

In a cohort study, it was found that in obese women for very preterm delivery with a BMI (25-<30 kg/m<sup>2</sup>) 1.26 times (aOR= 1.26; 95% CI=1.15 to 1.37; p=0.001), women with a BMI (30-<35 kg/m<sup>2</sup>) 1.58 times (aOR= 1.58; 95% CI=1.39 to 1.79; p=0.001),

women with BMI (35-<40 kg/m<sup>2</sup>) 2.01 times (aOR=2.01; 95% CI=1.66 to 2.45; p= 0.001) and women with a BMI (>40 kg/m<sup>2</sup>) 2.99 times (aOR=2.99; 95% CI=2.28 to 3.92; p=0.001) when compared to women with a normal BMI (18.5-25 kg/m<sup>2</sup>) and statistically significant. The risk of spontaneous very premature birth increases with increasing BMI in obese women (BMI > 30 kg/m<sup>2</sup>) (Cnattingius et al., 2013).

In addition, a study conducted in the UK in 2019, found that maternal obesity was associated with a 40% increase in the likelihood of neonatal death. Obese women were more likely to report neonatal death in the first week of life (days 0-1) at 1.39 times the risk (aOR= 1.39; 95% CI= 1.15 to 1.69; p= 0.001) and (days 2-6) at 1.35 times the risk. (aOR= 1.35; 95% CI= 1.02 to 1.79; p= 0.001) and statistically significant (Ozodiegwu et al., 2019).

Maternal obesity increases the risk of early neonatal death and stillbirth. a study points to changes in lipid metabolism as a possible cause. Maternal obesity has been found to be associated with the risk of death in the early neonatal period (Galliano and Bellver, 2013). Several causes of stillbirth or death in the neonatal period, possibly due to conditions such as apnea-hypoxia, fetal growth retardation increasing the risk of fetal loss, and pregnancy-induced hypertension, are all more common in obese women than in normal weight women (Korkmaz et al. ., 2016).

In a cohort study revealed that obese women have a more frequent risk for elective preterm delivery and the rate of spontaneous preterm birth is also higher in obesity. In nulliparous women, the risk for elective preterm delivery increases, but the risk for spontaneous preterm delivery decreases. However, the risk of preterm delivery has been shown to be increased in obese multiparous women (Smith et al.,

2011). Preeclampsia is likely to be a major contributor to the increased risk of elective delivery in nulliparous women. The results of one study revealed that 40% of nulliparous women with morbid obesity who delivered elective preterm had preeclampsia compared to an overall incidence of 2.6%. The results of another cohort study found that the risk of spontaneous preterm delivery is low in obese women when the membranes are intact, but with premature rupture of membranes, the risk of preterm delivery increases, suggesting this condition may be due to obesity-associated metabolic syndrome (Rodie et al., 2004).

## SUBJECTS AND METHOD

### 1. Study Design

This research is a systematic review and meta-analysis using PRISMA flow diagram guidelines. The articles used in this study were obtained from several databases including Google Scholar, Science Direct, Springer Link, Proquest, and Scopus which were published from 2010 to 2021. The keywords used to find these articles were as follows: (“maternal obesity” OR “maternal BMI”) AND (“premature birth” OR “preterm birth” OR “preterm delivery” OR “preterm labor”) AND (“neonatal mortality” OR “neonatal death”) AND “adjusted Odds Ratio”, “maternal obesity ” AND (“premature birth” OR “preterm birth” OR “preterm delivery”) AND (“neonatal mortality” OR “neonatal death” AND “adjusted odds ratio”.

### 2. Inclusion Criteria

The articles included in this study are full text articles with a cross-sectional and cohort study design, in English, and articles mentioning risk factors for preterm birth and neonatal death. The study population was pregnant women and the intervention given was obesity with the outcome being premature birth and neonatal death. The

analysis used is multivariate with adjusted Odds Ratio.

### 3. Exclusion Criteria

The exclusion criteria for this study were primary studies that had meta-analyses and articles published in languages other than English.

### 4. Operational Definition of Variable

The formulation of the research problem here is carried out using PICO. The population in this study were pregnant women with an intervention in the form of obesity and comparison, namely normal BMI. Outcomes are premature birth and neonatal death.

**Maternal obesity** is a mother with a BMI of more than 30 kg/m<sup>2</sup> that is self-reported and objective measurements during pregnancy or before pregnancy.

**Premature birth** is a birth that takes place from 22 weeks to 37 weeks of gestation, either vaginally or by emergency or elective cesarean section.

**Neonatal death** is the death of an infant who was born alive before the 28th day of life ( $\leq 28$  days).

### 5. Study Instruments

Assessment of article quality using the Critical Appraisal Checklist Cohort Study and Critical Appraisal Checklist for Cross-sectional Study (CEBM, 2014).

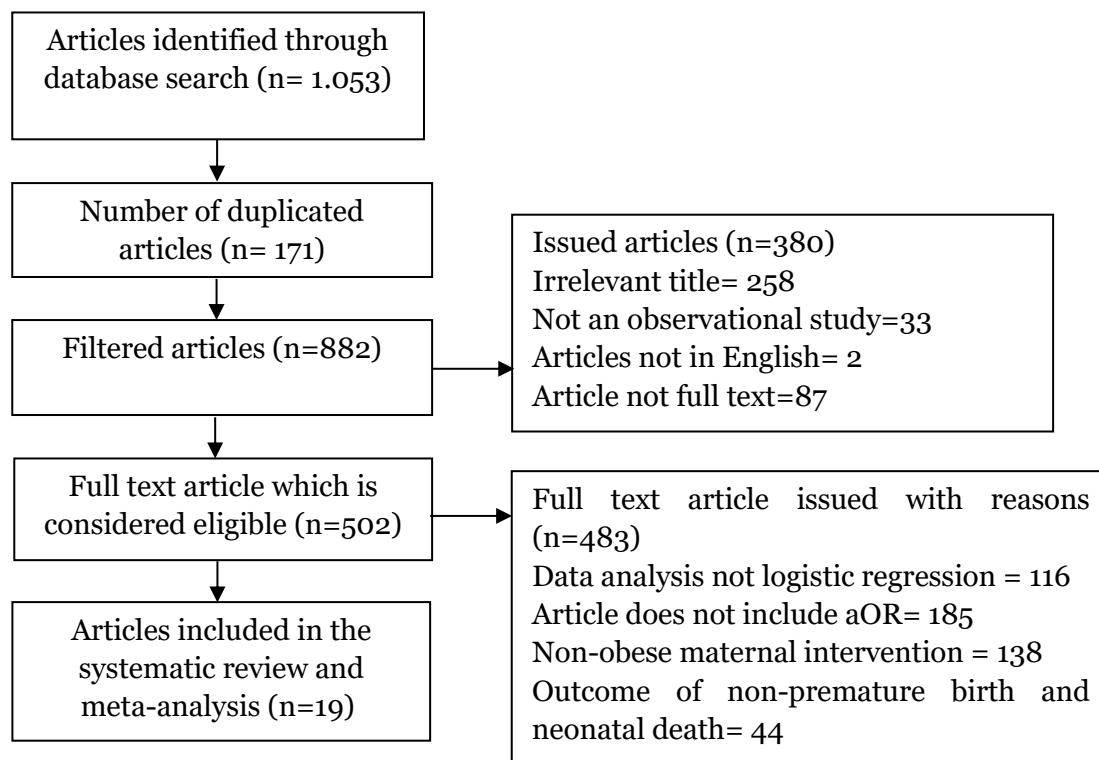
### 6. Data Analysis

Data processing was carried out using Review Manager 5.3 by calculating effect size and heterogeneity to determine the research model that was combined to form the final result of the meta-analysis.

## RESULTS

The article search process is to search through the database with the articles obtained according to Figure 1 in the PRISMA flow diagram. There were 19 articles from 5 continents, namely Asia, Africa, Europe, North America, and Australia which were

declared eligible and included in this meta-analysis.



**Figure 1. PRISMA flow diagram**

**1. The effect of maternal obesity on the risk of preterm birth**

A total of 13 articles were included in the meta-analysis (see Table 1.) based on forest plots (Figure 2), showing that obese pregnant women were 1.02 times more likely to have a premature birth than pregnant women with normal BMI, but not statistically significant (aOR= 1.02; 95% CI= 0.93 to 1.13; p= 0.630). The heterogeneity of the research data showed I<sup>2</sup>= 89%, so that the distribution of the data was declared heterogeneous (random effect model). From the funnel plot (Figure 3), it shows that there is a publication bias which is indicated by the asymmetry of the right and left plots where the distribution of 6 plots is on the left and 8 plots on the right. Figure 3 shows that the publication bias that occurs is an underestimate publication bias. The plot on the left of the graph appears to have a standard

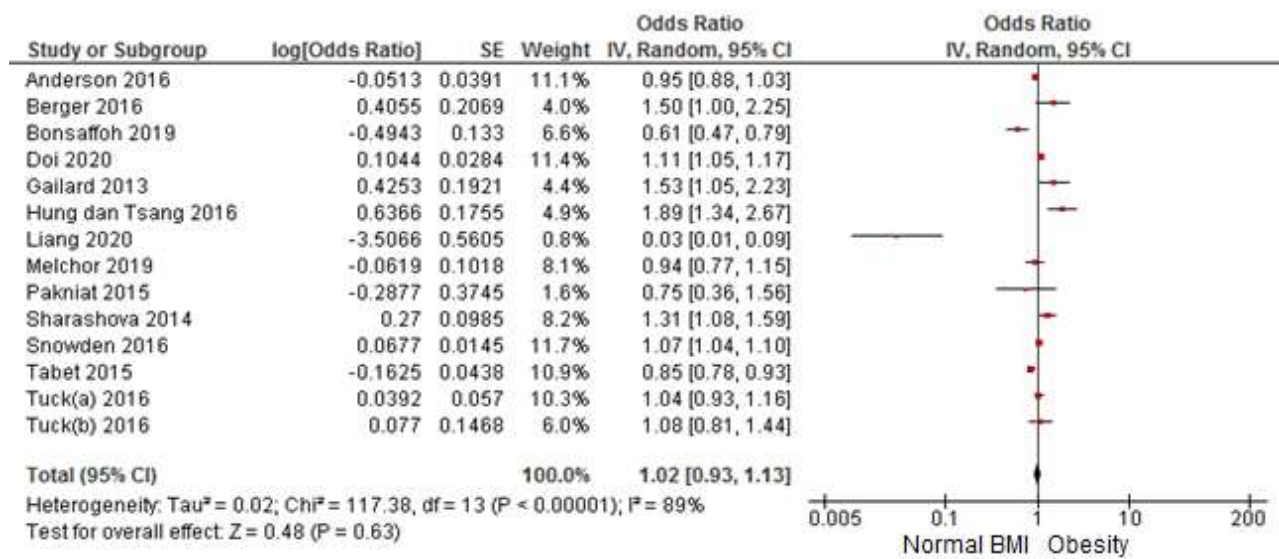
error between 0 and 0.6 and the plot on the right has a standard error between 0 and 0.2.

**2. Effect of maternal obesity on the risk of neonatal death**

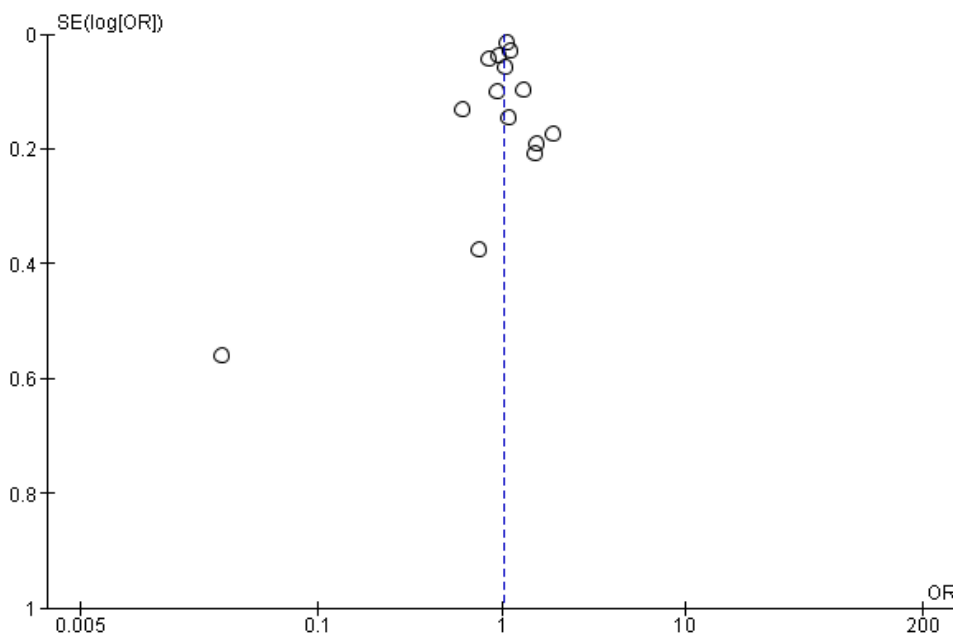
A total of 8 articles included in the meta-analysis (see Table 2.) which can be seen through the forest plot (Figure 4) show that the results of the subgroup analysis in the cohort study showed that obese pregnant women were 1.52 times more likely to experience neonatal death than pregnant women with normal BMI and statistically significant (aOR= 1.52; 95% CI= 1.17 to 1.99; p= 0.002). The heterogeneity of the research data showed I<sup>2</sup>=0%. While the results of the subgroup analysis in a cross-sectional study, pregnant women with obesity had a 1.44 times risk of experiencing neonatal death compared to pregnant women with normal BMI and statistically

significant (aOR= 1.44; 95% CI= 1.26 to 1.64; p<0.001). The heterogeneity of the research data shows I<sup>2</sup>= 0%, so that the distribution of the data is declared homogeneous (fixed effect model). From the funnel plot (Figure 5), it shows that in the cohort study there is a publication bias which is indicated by the asymmetry of the right and left plots where the distribution of 1 plot is on the left and 3 plots are on the right. The

publication bias that occurs in cohort studies is an overestimated publication bias. Meanwhile, the cross-sectional study did not show any publication bias as indicated by the symmetrical right and left plots where 2 plots are on the left and 2 plots are on the right. The plot on the left of the graph appears to have a standard error between 0 and 0.5 and the plot on the right has a standard error between 0 and 1.25 .



**Figure 2. Forest Plot Effect of Maternal Obesity on Risk of Premature Birth**



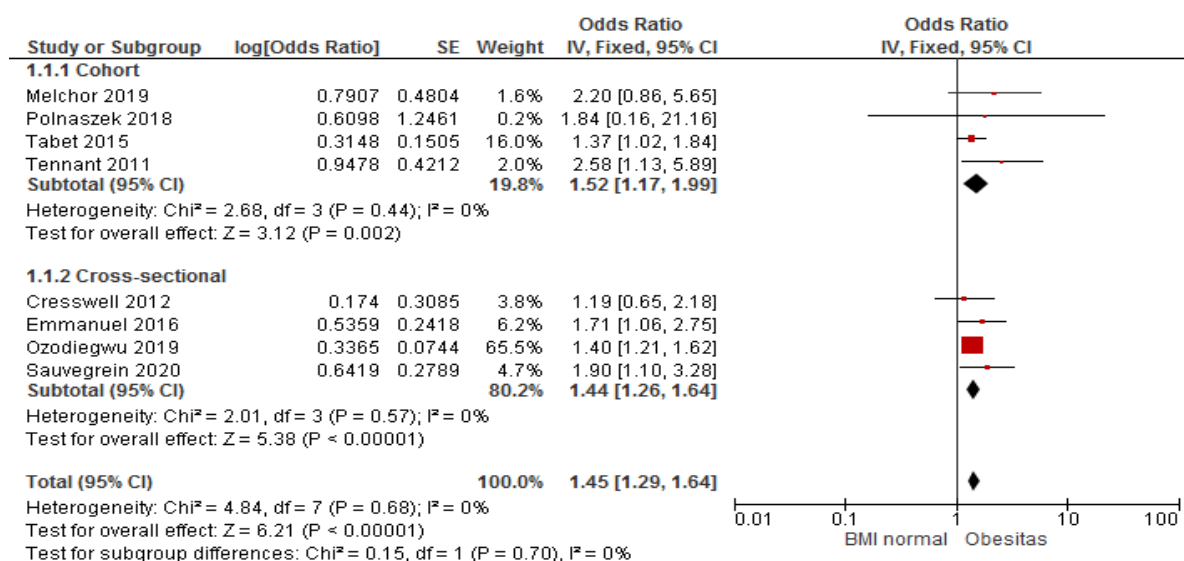
**Figure 3. Funnel Plot Effect of Maternal Obesity on Risk of Premature Birth**

**Table 1. Description of the primary study of preterm birth**

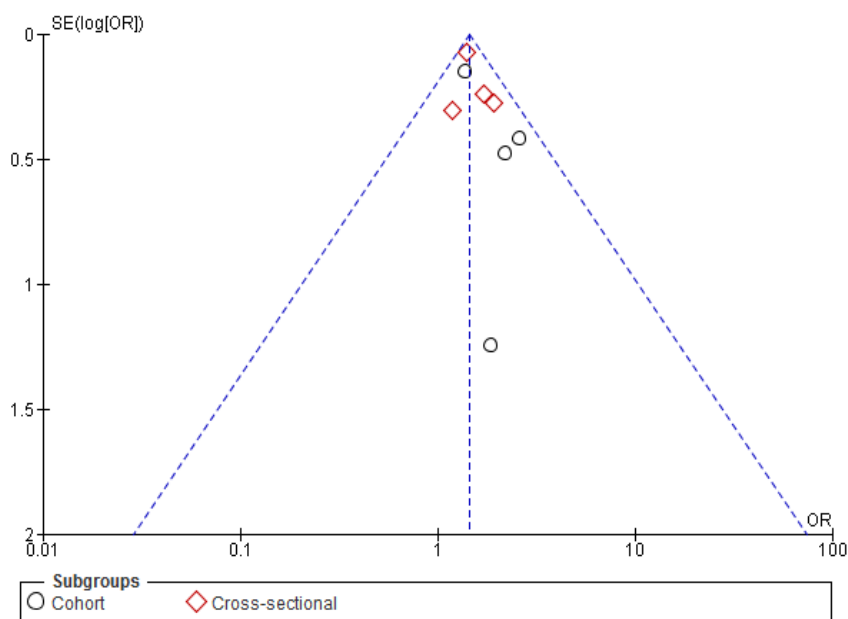
<b>Author (Year)</b>	<b>Country</b>	<b>Study Design</b>	<b>Sample</b>	<b>P Population</b>	<b>I Intervention</b>	<b>C Comparison</b>	<b>O Outcome</b>
Gaillard et al. (2013)	Netherland	Cohort	6,959	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Sharashova et al. (2014)	Rusia	Cohort	29,709	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Pakniat et al. (2015)	Iran	Cohort	1,376	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Hung dan Tsang (2016)	Taiwan	Cohort	12,064	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Snowden et al. (2016)	California	Cohort	385,407	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Tabet et al. (2015)	Missouri	Cohort	121,049	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Tuck et al. (2016a)	Australia	Cohort	18,768	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Tuck et al. (2016b)	South Asia	Cohort	8,342	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Berger et al. (2016)	Palau Republic	Cohort	1,171	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Anderson et al. (2016)	USA	Cohort	5,193,386	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Bonsaffoh et al. (2019)	Ghana	Cohort	7,801	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Melchor et al. (2019)	Spain	Cohort	16,609	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Doi et al. (2020)	Scotland	Cohort	16,609	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth
Liang et al. (2020)	Taiwan	Cohort	2,210	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Premature birth

**Table 2. Description of the primary study of neonatal mortality**

<b>Author (year)</b>	<b>Country</b>	<b>Study Design</b>	<b>Sample</b>	<b>P Population</b>	<b>I Intervention</b>	<b>C Comparison</b>	<b>O Outcome</b>
Tennant <i>et al.</i> (2011)	Northern England	Cohort	29,856	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Tabet <i>et al.</i> (2015)	Missouri	Cohort	121,049	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Polnaszek <i>et al.</i> (2018)	Washington	Cohort	6,458	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Melchor <i>et al.</i> (2019)	Spain	Cohort	16,609	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Cresswell <i>et al.</i> , (2012)	Sub-Saharan Africa	<i>Cross-sectional</i>	81,126	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Emmanuel <i>et al.</i> (2016)	Nigeria	<i>Cross-sectional</i>	30,384	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Ozodiegwu <i>et al.</i> (2019)	Subharan Africa	<i>Cross-sectional</i>	175,860	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death
Sauvegrain <i>et al.</i> (2020)	France	<i>Cross-sectional</i>	647	Pregnant mother	Pre pregnancy, Obese BMI $\geq$ 30 kg/m <sup>2</sup>	BMI normal 20-24.9 kg/m <sup>2</sup>	Neonatal death



**Figure 4. Forest Plot Effect of Maternal Obesity on Neonatal Death Risk**



**Figure 5. Funnel Plot Effect of Maternal Obesity on Neonatal Death Risk**

**DISCUSSION**

This study is a systematic review and meta-analysis that addresses the theme of the effect of maternal obesity on the risk of preterm birth and neonatal death. The independent variable analyzed was maternal obesity. The dependent variables studied were preterm birth and neonatal death. The results of primary studies conducted by systematic reviews and meta-analyses indicate an

epidemiological study design with a larger sample, different demographic characteristics in both developed and developing countries, thus providing the basis for concluding that maternal obesity has a statistical effect on the risk of neonatal death, and had no statistical effect on the risk of preterm birth.

Maternal obesity is one of the main public health problems in the world. This is



a multifactorial disease with many causes, such as a family history of obesity during pregnancy caused by excessive or abnormal fat in the body, which will automatically be passed on to the family (Jeffrey and Eleftheria, 2013), then There are demographic factors which include age, education level, occupation, socioeconomic status according to income, sedentary lifestyle, food security, diet and food consumption such as lack of water consumption, fruits and vegetables, and physical activity (Arredondo et al. , 2019).

In pregnant women with obesity there will be changes in myometrial function which causes a lower frequency and potential for contractions (Kutchi et al., 2020). The myometrium in obese women shows lower connexin43 expression, lower oxytocin receptor function, and higher potassium channel activity. Adipokines, such as leptin, visfatin, and epelin, in higher concentrations in obese women, decrease myometrial contractility, by inhibiting the myometrial RhoA/ROCK pathway. Characteristically higher cholesterol levels in obese women alter the cell membranes of myometrial myocytes, especially caveolae, inhibit oxytocin receptor function, and increase K<sup>+</sup> channel activity. All changes in myometrial cells decrease myometrial contractility (Carvajal and Oporto, 2020).

The results of this study are supported by a cohort study conducted in 2009 in Washington which identified obesity in 1,707 (12%) mothers. In a crude analysis, obese mothers were 20.3% more likely to give birth prematurely when compared to non-obese mothers, but after controlling for complications such as smoking, anemia, hypertension, diabetes and caesarean delivery, it was found that obesity was not associated with prematurity (Aly et al., 2010). In line with this study, in 2019 the results of a Spanish cohort study comparing

normal weight women (n=9,778) with obese women (n=2,207) showed that no association was found with preterm birth (aOR= 0.936). ; 95% CI = 0.77 to 1.13) (Melchor et al., 2019).

In a 2016 meta-analysis in Africa, found that maternal obesity was not independently associated with an increase in preterm labor (Onubi et al., 2016). In addition, this is similar to a study conducted in Portugal in 2020 which showed that obese pregnant women were significantly more likely to undergo caesarean section, gestational diabetes, hypertensive pregnancy disorders and macrosomia infants and no significant differences were found in terms of preterm birth, fetal death. , newborns with low birth weight (Alves et al., 2020).

In contrast to the existing theory, the results of the study on the effect of maternal obesity on the risk of preterm birth were not statistically significant, this was due to the fact that in the search for articles, the researchers found articles with a retrospective cohort design, where the weakness of this design is recall bias which causes memory errors, thus causing underestimation or overestimation of pre-pregnancy and early-pregnancy weight reporting. In addition, due to the retrospective, many significant incomplete data were excluded from the analysis (many missing data) which could affect the results of the study.

Obesity in pregnancy is associated with unfavorable clinical outcomes for both mother and child. It is estimated that 11% of all neonatal deaths can be attributed to the consequences of maternal obesity (Stubert et al., 2018). The risk of neonatal death is lowest in normal weight women (2.2/1000 births) and highest in obese women (3.7/-1000 births) (Nohr et al., 2021). The results of a study conducted in 2020 in 61 low- and middle-income countries showed that compared to normal-weight mothers, the risk of

neonatal death was increased in mothers who were overweight (aOR=1.32; 95% CI= 1.17 to 1.49) and obese (aOR=1.49). 1.50; 95% CI= 1.27 to 1.77 (Wu et al., 2020).

Maternal obesity is associated with an increased risk of neonatal death and overall infant mortality. Among the causes of neonatal death, maternal obesity is associated with death from maternal pregnancy, childbirth, and delivery complications or disorders related to short gestation, unspecified low birth weight, neonatal respiratory conditions, and birth defects (Chen et al., 2009). Results of a cohort study in Denmark showed that compared with normal weight women, the risk of neonatal death increased by 66% with overweight and 78% with obesity. Obese women have a risk for neonatal death due to placental dysfunction with 2.5 times the risk, umbilical cord complications 2.5 times the risk, intrapartum incidence and infection risk 3.5 times increased in obese women (Nohr et al., 2021).

Overweight and obese women who, even without clinical disease, will have an increased inflammatory response, vascular and endothelial dysfunction and altered lipid metabolism, changes similar to those seen in preeclamptic women. Hyperlipidemia can lead to decreased prostacyclin secretion and increased thromboxane production, which can increase the risk of placental thrombosis, decreased placental perfusion, which will result in impaired placental blood flow, resulting in infarction and fetoplacental dysfunction (Korkmaz et al., 2016). One study reported obstetric conditions (29.3%) and placental abnormalities (23.6%) as the most common causes of stillbirth and neonatal death (Bukowski et al., 2011).

In addition, maternal adiposity is associated with an increased risk of macrosomia, which is then associated with an increased risk of neonatal and infant mortality, as well

as death from asphyxia and infection (Ovesen et al., 2011). Prevention of obesity in women of reproductive age is important for their health and for their offspring. To improve preconception health, an integrated approach, including prevention, planning and preparation for pregnancy, is needed, which involves more than the primary health care sector and adopts an ecological approach to risk reduction that addresses personal, social and cultural influences. Interventions to reduce or prevent obesity before conception and during pregnancy can make a substantial contribution to the achievement of global sustainable development goals, in terms of health, well-being, productivity and equity in present and future generations (Hanson et al., 2017).

#### **AUTHORS CONTRIBUTION**

Fitria Wulandari is the main researcher who chooses the topic, searches for and collects research data. Uki Retno Budihastuti and Eti Poncorini Pamungkasari analyze data and review 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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