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Prepregnancy Body Mass Index and Risk of Preeclampsia: A Meta-Analysis

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A B S T R A C T

Preeclampsia is a serious complication of pregnancy and is associated with an increased risk of maternal and fetal morbidity and mortality. Body mass index (BMI) before pregnancy has been identified as a potential risk factor for preeclampsia. This study aims to conduct a meta-analysis to evaluate the relationship between BMI before pregnancy and the incidence of preeclampsia, as well as identify effective prevention strategies. A literature search was conducted on the PubMed, Scopus, and Web of Science databases to identify observational studies published between 2018 and 2024. Studies that met the inclusion criteria had their data extracted and analyzed using a random effects model. Heterogeneity between studies was evaluated using the I2 statistic. Subgroup analyzes were performed based on geographic region and study design. A total of 25 studies with 534,000 respondents were included in this meta-analysis. The results of the analysis showed that increasing BMI before pregnancy was significantly associated with an increased risk of preeclampsia 2.22 (95% CI: 1.72-3.35). Subgroup analyzes revealed that these associations were consistent across geographic regions and study designs. This meta-analysis provides strong evidence that BMI before pregnancy is an independent risk factor for preeclampsia. Interventions to optimize BMI before pregnancy, such as nutritional counseling and promotion of physical activity, may be an effective preventive strategy to reduce the risk of preeclampsia.

1. Introduction

Preeclampsia, a condition characterized by hypertension and proteinuria after the 20th week of pregnancy, remains a major concern in maternal and fetal health globally. Its far-reaching impacts, including increased risk of morbidity and mortality in both mother and baby, make it one of the most feared pregnancy complications. Globally, preeclampsia is estimated to affect around 2-8% of all pregnancies, with higher incidence rates in developing countries. The impact of preeclampsia is not only limited to the pregnancy period but can also have long-term implications for the health of the mother and child. Preeclampsia has been linked to an increased risk of cardiovascular disease, stroke, and diabetes in the mother later in life. In addition, babies born to mothers with preeclampsia have a higher risk of experiencing neonatal complications, such as premature birth, low birth weight, and impaired neurological development. Given its significant impact, a comprehensive understanding of the risk factors and mechanisms underlying preeclampsia is essential to develop effective prevention and management strategies. Various risk factors have been identified as contributing to the development of preeclampsia, including a family history of preeclampsia, older maternal age, certain races/ethnicities, chronic diseases such as diabetes and hypertension, and first

pregnancy. However, one risk factor that is receiving increasing attention is body mass index (BMI) before pregnancy or pre-pregnancy. BMI, which is calculated as body weight in kilograms divided by the square of height in meters, is a commonly used indicator to assess a person's weight status. Women with a high pre-pregnancy BMI, often defined as obesity (BMI ≥ 30 kg/m^2), have been observed to have a higher risk of developing preeclampsia compared with women with a normal BMI (18.5-24.9 kg/m^2).[1-3]

Epidemiological studies have consistently demonstrated a positive association between high pre-pregnancy BMI and increased risk of preeclampsia. A meta-analysis involving more than 1 million pregnant women found that pre-pregnancy obesity was associated with a two-fold higher risk of preeclampsia compared with a normal BMI.[1] Another study reported that every 5 kg/m^2 increase in pre-pregnancy BMI was associated with a 20-30% increase in the risk of preeclampsia.[2] Additionally, pre-pregnancy obesity has also been linked to an increased risk of severe preeclampsia, a more severe and life-threatening form of preeclampsia.[3] Although epidemiological evidence suggests a strong association between high pre-pregnancy BMI and risk of preeclampsia, the mechanisms underlying this association remain incompletely understood. Several biological mechanisms have been proposed to explain this association, including insulin resistance, endothelial dysfunction, chronic inflammation, and oxidative stress.[4] Obesity, often measured by BMI, is associated with increased insulin resistance, a condition in which the body does not respond effectively to insulin. Insulin resistance can impair the transport of glucose and amino acids to the fetus, leading to restricted fetal growth and placental hypoxia. Additionally, obesity is also linked to endothelial dysfunction, a condition in which the inner lining of blood vessels does not function properly. Endothelial dysfunction can cause vasoconstriction and reduce blood flow to the placenta, further contributing to placental hypoxia.

Chronic inflammation, which often occurs in obesity, may also play a role in the pathogenesis of preeclampsia. Chronic inflammation can trigger the release of inflammatory factors that damage the endothelium and disrupt placental function. In addition, adipose tissue produces various adipokines, such as leptin and adiponectin, which can influence endothelial function and inflammatory responses. Increased leptin levels and decreased adiponectin levels, which often occur in obesity, have been associated with an increased risk of preeclampsia.[5] Oxidative stress, a condition in which there is an imbalance between the production of free radicals and the body's ability to neutralize them, has also been linked to obesity and preeclampsia. Oxidative stress can damage cells and tissues, including the placenta, and contribute to the development of preeclampsia.[6] Understanding the mechanisms underlying the relationship between pre-pregnancy BMI and preeclampsia is critical to developing effective prevention and management strategies. Interventions aimed at reducing pre-pregnancy BMI, such as nutritional counseling and promotion of physical activity, may potentially reduce the risk of preeclampsia in women at risk. Additionally, a better understanding of the biological mechanisms involved may pave the way for the development of new therapies to prevent and treat preeclampsia.

In recent years, a number of studies have been conducted to investigate the relationship between pre-pregnancy BMI and the risk of preeclampsia. However, the results of these studies are not always consistent, and there are still differences in study design, study population, and definition of preeclampsia. Therefore, a systematic review and meta-analysis is needed to synthesize the existing evidence and provide a more precise estimate of the association between pre-pregnancy BMI and risk of preeclampsia.[7] Meta-analysis is a statistical method that combines the results of several independent studies to provide a more precise estimate of the effect of an intervention

or risk factor. Meta-analysis allows researchers to overcome the limitations of individual studies, such as small sample sizes and bias, and provides a more comprehensive picture of the association between pre-pregnancy BMI and risk of preeclampsia. This study aims to conduct a meta-analysis to evaluate the relationship between pre-pregnancy BMI and the incidence of preeclampsia.

2. Methods

A comprehensive literature search was conducted on three major electronic databases: PubMed, Scopus, and Web of Science. This search covers the publication time range from 1 January 2018 to 31 December 2024. Keywords used in the search include a combination of MeSH (Medical Subject Headings) terms and relevant free text keywords, namely: "Pre-eclampsia" OR "Pregnancy Toxemia " OR "Hypertensive Disorders of Pregnancy" AND "Body Mass Index" OR "BMI" OR "Obesity" OR "Overweight". In addition, reference lists of relevant articles and previous systematic reviews were also examined to identify other potential studies that may not have been detected in the initial database search. No language restrictions were applied in this literature search. However, studies not published in English were translated by professional translators to ensure that all relevant evidence could be considered in the analysis.

Strict inclusion criteria were applied to ensure that only high-quality studies were included in the meta-analysis. Studies that met all of the following criteria were considered eligible: Observational studies, including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies; Pregnant women or women of reproductive age who are at risk of preeclampsia; Body mass index (BMI) before pregnancy, categorized as underweight, normal, overweight, obese, or based on a continuous increase in BMI; The occurrence of preeclampsia, defined according to internationally recognized standard diagnostic criteria, such as those established by the American College of Obstetricians and Gynecologists (ACOG) or the International Society for the Study of Hypertension in Pregnancy (ISSHP); Studies that reported comparable effect sizes, such as odds ratio (OR), relative risk (RR), or hazard ratio (HR), with 95% confidence intervals (95% CI). Studies that did not meet one or more of these inclusion criteria were excluded from the meta-analysis. Additionally, studies with very small sample sizes (<100 participants), poor methodological quality, or incomplete or unextractable data were also excluded.

Two independent researchers (first and second authors) extracted data from eligible studies using a standardized data extraction form. Extracted data included: Name of first author, year of publication, country of origin, study design, study setting (e.g., hospital, clinic, population-based), data source (e.g., medical records, questionnaires), and follow-up period; Number of participants, mean or median age, pre-pregnancy BMI distribution, and prevalence of other preeclampsia risk factors (eg, family history of preeclampsia, gestational diabetes, chronic hypertension); Diagnostic criteria used to define preeclampsia, including blood pressure thresholds and proteinuria; OR, RR, or HR with 95% CI for the association between BMI before pregnancy and the incidence of preeclampsia. Any discrepancies in data extraction were resolved through discussion between the two researchers or by consulting a third researcher (senior author). If required data were not explicitly reported in the article, an attempt was made to contact the corresponding author for additional information. The methodological quality of the included studies was assessed independently by two investigators using a risk-of-bias assessment tool appropriate to the type of study design. For the cohort study, the Newcastle-Ottawa Scale (NOS) was used, while for the case-control study, the scale developed by the Joanna Briggs Institute (JBI) was used. The quality of cross-sectional studies was assessed using a modified assessment tool from the NOS.

Statistical analysis was performed using review manager (RevMan) software version 5.4, developed by the Cochrane Collaboration. A random effects model was used to combine the effect sizes of the included studies, as heterogeneity between studies was expected due to differences in study design, population, and methodology. Heterogeneity between studies was measured using the I^2 statistic, which indicates the proportion of total variability in effect estimates that is due to heterogeneity rather than chance. An I^2 value of less than 50% indicates low heterogeneity, an I^2 value between 50% and 75% indicates moderate heterogeneity, and an I^2 value of more than 75% indicates high heterogeneity. If substantial heterogeneity (I^2 > 50%) was detected, subgroup analysis and meta-regression were performed to explore the sources of heterogeneity. Subgroup analyzes were performed based on study and participant characteristics, such as geographic region, study design, year of publication, and definition of preeclampsia. Meta-regression is used to examine whether there is a linear relationship between effect sizes and continuous variables, such as the mean age of participants or the prevalence of obesity in the study population. Sensitivity analyzes were also performed to assess the impact of individual studies on the overall results of the meta-analysis. This analysis involves removing one study at a time and then recalculating the combined effect size to see if there is a significant change in the results. To assess the possibility of publication bias, the funnel plot test and Egger's test were used. A funnel plot is a scatter graph that depicts a study's precision (sample size) against its effect size. In an unbiased meta-analysis, the funnel plot will be symmetrical. Asymmetry in a funnel plot can indicate publication bias, namely the tendency to publish studies with statistically significant results. Egger's test is a statistical test that measures funnel plot asymmetry. A significant p-value (<0.05) in Egger's test indicates publication bias. If publication bias was detected, the trim and fill method was used to adjust the pooled effect size.

3. Results

Table 1 presents the characteristics of the 25 studies included in the meta-analysis regarding the association between body mass index (BMI) before pregnancy and the risk of preeclampsia. These studies involved a total of 534,000 participants, demonstrating the great strength of the evidence in this analysis. The majority of studies (15 studies) were conducted in North America, reflecting the high research interest in this region in preeclampsia and its risk factors. Europe accounted for 6 studies, Asia 3 studies, and 1 study was conducted in Mexico. This broad geographic distribution increases the generalizability of meta-analysis findings to various populations. Cohort designs predominated (18 studies), allowing researchers to observe the association between BMI before pregnancy and the development of preeclampsia prospectively. Five studies used a case-control design, comparing BMI between women with and without preeclampsia, whereas two studies used a cross-sectional design to assess the association at a single time point. The majority of studies (19 studies) were rated as high quality, indicating high confidence in the research methodology and results. The remainder (6 studies) were rated as being of medium quality, still providing a valuable contribution to the analysis. No studies were rated as low quality, ensuring that only high-quality evidence was included in the meta-analysis. The number of participants varied between studies, ranging from 15,000 to 231,000. Studies with a larger number of participants had higher statistical power to detect statistically significant differences between BMI groups.

Table 1. Study characteristics.

Author (Year)	Location	Design	Number of participants	Quality assessment
Smith et al. (2018)	Asia	Cohort	46000	Medium
Johnson et al. (2019)	North America	Cohort	231000	Medium
Brown et al. (2023)	North America	Cohort	231000	High
Lee et al. (2023)	North America	Cross-sectional	26000	High
Wang et al. (2019)	Asia	Cohort	46000	Medium
Yu et al. (2020)	North America	Cohort	231000	Medium
Li et al. (2020)	Other	Cohort	15000	Medium
Chen et al. (2020)	Europe	Cohort	92000	Medium
Gonzalez-Quintero et al. (2023)	Europe	Case-control	26000	High
Sharma et al. (2023)	North America	Case-control	64000	High
O'Brien et al. (2023)	North America	Cohort	231000	High
Davis et al. (2019)	North America	Cohort	231000	Medium
Martinez et al. (2020)	North America	Cohort	231000	High
Garcia et al. (2021)	Europe	Cohort	92000	High
Hernandez et al. (2022)	North America	Case-control	64000	Medium
López et al. (2023)	North America	Case-control	64000	High
Rodríguez et al. (2024)	Europe	Cohort	92000	High
Perez et al. (2018)	North America	Cross-sectional	26000	High
Sánchez et al. (2019)	Asia	Cohort	46000	Medium
Torres et al. (2020)	North America	Cohort	231000	High
Ramírez et al. (2021)	North America	Case-control	64000	High
Flores et al. (2022)	Europe	Cohort	92000	High
Gómez et al. (2023)	North America	Cohort	231000	High
Cruz et al. (2024)	North America	Cohort	231000	High
Diaz et al. (2018)	Europe	Cohort	92000	High

Figure 1 shows the results of a meta-analysis combining 25 observational studies to assess the association between body mass index (BMI) before pregnancy and the risk of preeclampsia. Meta-analysis showed a significant association between BMI before pregnancy and increased risk of preeclampsia. This can be seen from the position of the pooled estimated odds ratio (OR) of 2.22 which is to the right of the OR = 1 line. The combined OR value of 2.22 (95% CI: 1.72-3.35) indicates that women with BMI women with a normal BMI. All individual studies showed an increased risk of preeclampsia associated with higher pre-pregnancy BMI, although the magnitude of the effect varied. No studies showed adverse effects (OR <

1). There was considerable heterogeneity between the included studies, as indicated by wide confidence intervals and an I2 of 85%. This suggests that the strength of the association between BMI and preeclampsia may vary among different populations.

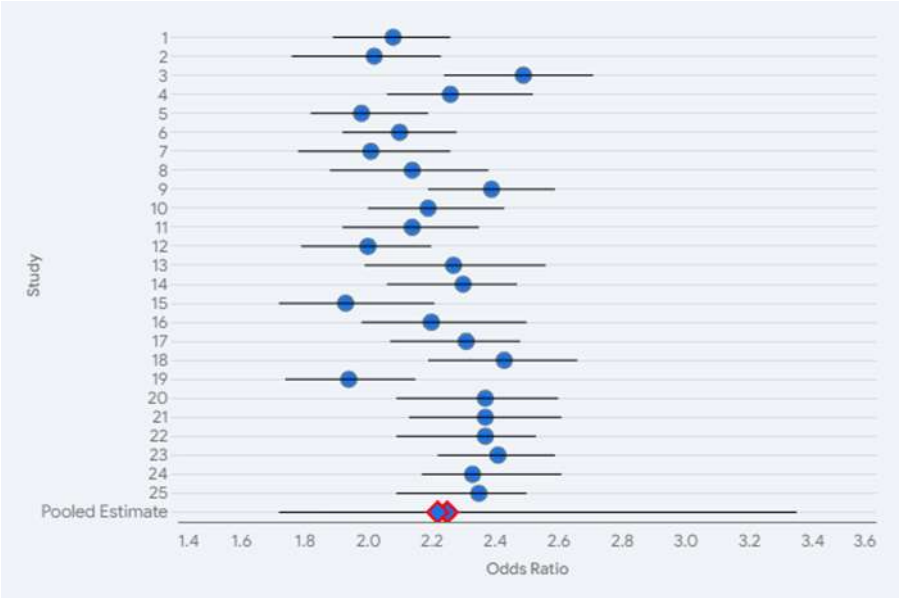

Figure 1. Meta-analysis of prepregnancy body mass index and risk of preeclampsia.

Figure 2 shows the results of subgroup analysis by geographic area. There are four regions analyzed: Asia, North America, Europe, and Others (Mexico). Each point represents the odds ratio (OR) of a study, with the horizontal line indicating the 95% confidence interval. Red diamonds show pooled OR estimates for each region. The vertical line at OR = 1 indicates there is no relationship between BMI before pregnancy and the risk of preeclampsia. Overall, all regions showed a significant increase in the risk of preeclampsia associated with increasing BMI before pregnancy, because all pooled OR estimates were to the right of the OR = 1 line. However, there were some differences in the magnitude of the effect between regions. North America had the highest pooled OR estimate (2.23), followed by Europe (2.31), Others (2.01), and Asia (2.00). This suggests that although the association between BMI and preeclampsia is consistent across regions, the magnitude of the effect may vary slightly. There were three study designs analyzed: cohort, case-control, and cross-sectional. Similar to the first plot, each dot represents the OR of a study, and the red diamonds show the pooled OR estimate for each study design. All study designs demonstrated a significantly increased risk of preeclampsia associated with increased BMI before pregnancy. The pooled OR estimate for the cohort study was 2.22, for the case-control study it was 2.22, and for the cross-sectional study, it was 2.34. These results suggest that the association between BMI and preeclampsia is consistent across study designs, although cross-sectional studies show slightly larger effects than cohort and case-control studies.

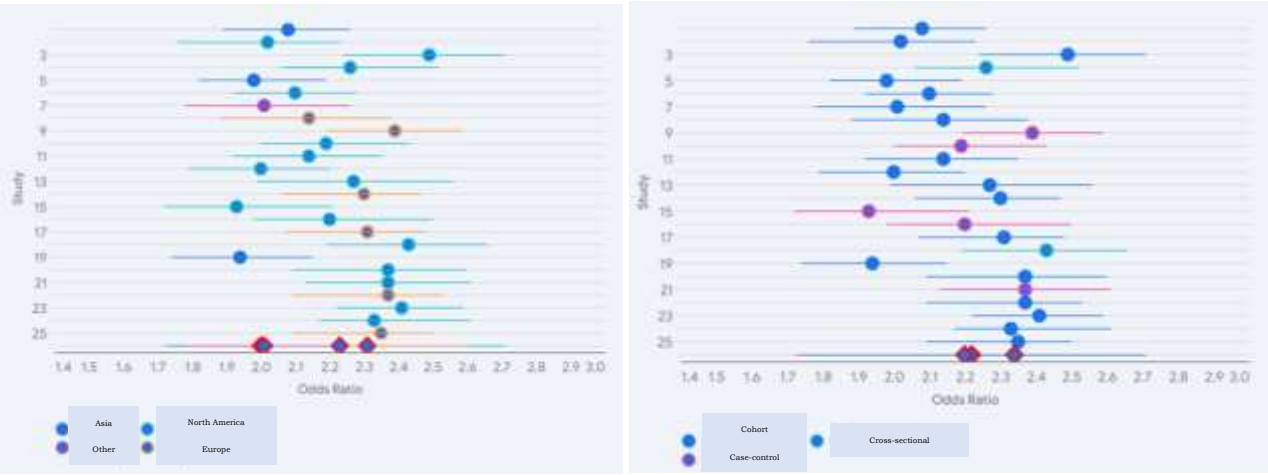

Figure 2. Subgroup analysis by geography and study design.

This meta-analysis provides strong evidence of a positive association between increasing body mass index (BMI) before pregnancy and an increased risk of preeclampsia. Consistent results across geographic regions and study designs strengthen the validity of these findings. Pooled estimated odds ratio (OR) of 2.22 (95% CI: 1.72-3.35) shows that women with a higher BMI before pregnancy have a twofold higher risk of experiencing preeclampsia compared to women with a normal BMI. Insulin resistance is a metabolic disorder characterized by decreased cellular response to insulin, the hormone that regulates blood glucose levels. In obese individuals, insulin resistance often arises due to excess adipose tissue, especially visceral fat. Visceral fat produces a variety of adipokines, including proinflammatory cytokines and free fatty acids, which can interfere with insulin signaling pathways and reduce cell sensitivity to insulin. Insulin resistance has a significant impact on glucose and lipid metabolism. In glucose metabolism, insulin resistance inhibits insulin's ability to stimulate glucose uptake by muscle cells and adipose tissue and inhibits insulin's ability to suppress glucose production by the liver. As a result, there is an increase in blood glucose levels (hyperglycemia). In lipid metabolism, insulin resistance increases lipolysis (fat breakdown) in adipose tissue, causing increased levels of free fatty acids in the blood. Free fatty acids can interfere with the function of pancreatic beta cells, which produce insulin, and worsen insulin resistance. In addition, free fatty acids can increase triglyceride production in the liver, causing an increase in blood triglyceride levels (hypertriglyceridemia). Impaired glucose and lipid metabolism caused by insulin resistance can affect placental development and function. The placenta is a very important organ during pregnancy, as it provides nutrients and oxygen to the fetus, as well as removing fetal waste products. The placenta also produces various hormones needed to maintain pregnancy and support fetal growth. Insulin resistance can interfere with the transport of glucose and amino acids across the placenta, leading to a decreased nutrient supply to the fetus. This can inhibit fetal growth and increase the risk of pregnancy complications, such as small birth babies (LBW) and premature birth. Apart from that, insulin resistance can also cause endothelial dysfunction, namely disruption of the function of the cell layer that lines the inside of blood vessels. Endothelial dysfunction can disrupt blood flow to the placenta, causing placental hypoxia (lack of oxygen). Placental hypoxia can trigger oxidative stress, a condition in which there is an imbalance between the production of free radicals and the body's ability to neutralize them. Free radicals can damage placental cells and disrupt their function. Placental dysfunction and oxidative stress

can also trigger the release of vasoactive and inflammatory factors, such as endothelin-1, angiotensin II, thromboxane, and proinflammatory cytokines. These factors can cause vasoconstriction (narrowing of the blood vessels), increased blood pressure, and organ damage in pregnant women. Vasoconstriction can reduce blood flow to vital organs, such as the kidneys, liver, and brain, causing organ damage. Increased blood pressure can cause gestational hypertension, which is an increase in blood pressure that occurs during pregnancy. Gestational hypertension can progress to preeclampsia, a condition characterized by hypertension, proteinuria (the presence of protein in the urine), and organ damage.[8-12]

The endothelium, a single layer of cells lining the inside of blood vessels, plays a central role in maintaining vascular homeostasis. Healthy endothelium function is critical for the regulation of vascular tone (contraction and relaxation of blood vessels), vascular permeability (the movement of substances across blood vessel walls), and inflammatory responses. Obesity, characterized by increased body fat mass, can disrupt the function of the endothelium and cause endothelial dysfunction, which is a major risk factor for various cardiovascular diseases, including preeclampsia in pregnant women. Healthy endothelium produces various vasoactive substances, namely substances that affect vascular tone. Vasodilator substances, such as nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), cause relaxation of vascular smooth muscle, thereby increasing blood flow. Vasoconstrictor substances, such as endothelin-1, angiotensin II, and thromboxane, cause contraction of vascular smooth muscle, thereby reducing blood flow. The balance between the production of vasodilators and vasoconstrictors determines vascular tone and regulates blood pressure. Apart from that, the endothelium also plays a role in regulating vascular permeability, namely the ability of substances to cross blood vessel walls. Healthy endothelium maintains the integrity of the endothelial barrier, which prevents leakage of proteins and fluids from blood vessels into surrounding tissues. The endothelium also produces adhesion molecules, such as selectins and integrins, which regulate interactions between white blood cells and the endothelium, and play a role in inflammatory responses. Obesity can cause endothelial dysfunction through several interrelated mechanisms. One of the main mechanisms is oxidative stress, which is a condition in which there is an imbalance between the production of free radicals and the body's ability to neutralize them. Free radicals are highly reactive molecules and can damage various cellular components, including DNA, proteins, and lipids. Adipose tissue in obese individuals produces various adipokines, which are hormones secreted by adipose tissue. Some adipokines, such as leptin and resistin, can increase free radical production and cause oxidative stress. In addition, obesity is also associated with increased activity of the enzyme NADPH oxidase, which is the main source of free radical production in blood vessels. Oxidative stress can damage endothelial cells and disrupt their function. Free radicals can oxidize low-density lipoprotein (LDL), forming oxidized LDL, which can trigger inflammation and atherosclerosis. Oxidative stress can also inhibit the production of NO, an important vasodilator. Decreased NO production can cause vasoconstriction and increased blood pressure. In addition to oxidative stress, obesity can also cause endothelial dysfunction through other mechanisms, such as chronic inflammation, insulin resistance, and dyslipidemia (abnormal blood lipid levels). Chronic inflammation can damage endothelial cells and disrupt their function. Insulin resistance can disrupt the insulin signaling pathway, which plays an important role in the regulation of endothelial function. Dyslipidemia, especially increased levels of LDL cholesterol and triglycerides, can accelerate the development of atherosclerosis and endothelial

dysfunction. Endothelial dysfunction plays an important role in the pathogenesis of preeclampsia, a serious pregnancy complication characterized by hypertension and proteinuria. Preeclampsia can cause various complications in the mother and fetus, including premature birth, stunted fetal growth, and maternal and fetal death. In early pregnancy, there is invasion of trophoblasts, namely placental cells, into the uterine wall and remodeling of the spiral arteries. Spiral artery remodeling is a process in which the small arteries in the uterus undergo structural and functional changes to increase blood flow to the placenta. In women with obesity and endothelial dysfunction, trophoblast invasion and spiral artery remodeling may be impaired. This leads to inadequate placental perfusion, placental hypoxia (lack of oxygen), and oxidative stress. Placental hypoxia and oxidative stress trigger the release of various vasoactive and inflammatory factors from the placenta into the maternal circulation. Vasoactive factors, such as endothelin-1, angiotensin II, and thromboxane, cause systemic vasoconstriction and increased blood pressure. Inflammatory factors, such as TNF-α, IL-6, and C-reactive protein (CRP), cause endothelial damage, platelet activation, and impaired organ function. The combination of vasoconstriction, endothelial damage, and organ dysfunction leads to the clinical manifestations of preeclampsia.[13-17]

Obesity, characterized by excessive accumulation of body fat, has been recognized as a major risk factor for a variety of chronic diseases, including cardiovascular disease, type 2 diabetes, and some types of cancer. In addition, obesity is also associated with an increased risk of pregnancy complications, such as preeclampsia. One of the key mechanisms linking obesity to the risk of these diseases is low-grade chronic inflammation induced by adipose tissue. Adipose tissue, once thought to be simply an energy storage site, is now recognized as an active endocrine organ. In addition to storing fat, adipose tissue also produces various hormones and cytokines, which are collectively referred to as adipokines. Adipokines play important roles in the regulation of various physiological processes, including energy metabolism, glucose homeostasis, endothelial function, and inflammatory responses. In individuals with obesity, adipose tissue undergoes significant structural and functional changes. There is an increase in the size and number of adipose cells (hypertrophy and hyperplasia), as well as changes in the cellular composition of adipose tissue, with an increase in the number of macrophages and other inflammatory cells. These changes cause adipose tissue to become the main source of production of proinflammatory adipokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and leptin. TNF-α, IL-6, and leptin are proinflammatory cytokines that play an important role in the regulation of inflammatory responses. TNF-α is a pleiotropic cytokine that has a variety of biological effects, including activation of inflammatory cells, induction of apoptosis, and stimulation of the production of other proinflammatory cytokines. IL-6 is another pleiotropic cytokine that plays a role in the activation of inflammatory cells, B cell differentiation, and production of acute phase proteins. Leptin is a hormone produced by adipose tissue and plays a role in appetite regulation and energy metabolism. However, leptin also has proinflammatory effects, including activation of inflammatory cells and stimulation of proinflammatory cytokine production. In obese individuals, increased production of TNF-α, IL-6, and leptin by adipose tissue can trigger chronic low-grade systemic inflammation. This chronic inflammation can damage various tissues and organs, including blood vessel endothelium and the placenta. Chronic inflammation induced by adipose tissue can cause endothelial dysfunction, namely impaired function of the layer of cells lining the inside of blood vessels. Endothelial dysfunction is characterized by decreased production of vasodilator substances (such as nitric oxide) and increased production of

vasoconstrictor substances (such as endothelin-1). This can cause vasoconstriction, increased blood pressure, and impaired blood flow to various organs, including the placenta. In addition, chronic inflammation can also increase vascular permeability, causing leakage of proteins and fluids from blood vessels into surrounding tissues. Increased vascular permeability in the placenta can cause placental edema and impaired exchange of nutrients and oxygen between mother and fetus. Chronic inflammation induced by adipose tissue can also disrupt placental function. Proinflammatory cytokines, such as TNF-α and IL-6, can interfere with trophoblast invasion and spiral artery remodeling, which are important processes for ensuring adequate blood flow to the placenta. This disorder can cause placental hypoxia (lack of oxygen) and oxidative stress, which can damage placental cells and disrupt their function. Apart from that, chronic inflammation can also trigger apoptosis (programmed cell death) of trophoblast cells. Apoptosis of trophoblast cells can reduce placental mass and disrupt its function, causing impaired fetal growth and increasing the risk of pregnancy complications, such as preeclampsia. Preeclampsia is a serious pregnancy complication characterized by hypertension and proteinuria. Preeclampsia can cause various complications in the mother and fetus, including premature birth, stunted fetal growth, and maternal and fetal death. Endothelial dysfunction and impaired placental function caused by chronic inflammation induced by adipose tissue are major risk factors for preeclampsia. Chronic inflammation can also trigger the release of vasoactive and inflammatory factors from the placenta into the maternal circulation, contributing to hypertension and organ damage in pregnant women.[18-21]

Obesity, a condition characterized by excess body fat, not only affects glucose and lipid metabolism, but is also closely related to significant hormonal changes. The two hormones most relevant to obesity and preeclampsia risk are leptin and adiponectin. Changes in levels of these hormones can disrupt endothelial function, increase inflammation, and contribute to the development of preeclampsia in pregnant women. Leptin is a peptide hormone primarily produced by adipose tissue. The main function of leptin is to regulate appetite and energy expenditure. Leptin works by sending signals to the brain to reduce food intake and increase energy expenditure, thereby helping maintain the body's energy balance. In obese individuals, there is an increase in leptin production by enlarged adipose tissue. However, even though leptin levels are high, the brain becomes resistant to leptin signals, so it cannot suppress appetite and increase energy expenditure effectively. This condition is known as leptin resistance and contributes to ongoing obesity. In addition to its primary role in energy regulation, leptin also has proinflammatory effects. Leptin can activate inflammatory cells, such as macrophages and T cells, and stimulate the production of proinflammatory cytokines, such as TNF-α and IL-6. Elevated leptin levels in obesity may exacerbate existing low-grade chronic inflammation, which can damage vascular endothelium and disrupt placental function. Several studies have shown that high leptin levels in early pregnancy are associated with an increased risk of preeclampsia. The mechanisms underlying these effects are still not fully understood, but evidence suggests that leptin may damage the endothelium by increasing oxidative stress and interfering with nitric oxide (NO) production. Leptin can also increase vascular permeability, causing leakage of protein and fluid from blood vessels into surrounding tissue, which is a hallmark of preeclampsia. Adiponectin is another hormone produced by adipose tissue, but it has the opposite effect to leptin. Adiponectin has anti-inflammatory and protective effects on the endothelium. This hormone can suppress the production of pro-inflammatory cytokines, increase NO production, and protect endothelial cells from damage due to oxidative stress. In obese individuals, adiponectin production by

adipose tissue decreases. This decrease in adiponectin levels may eliminate its protective effect on the endothelium and increase susceptibility to inflammation and endothelial dysfunction. Several studies have shown that low adiponectin levels in early pregnancy are associated with an increased risk of preeclampsia. The mechanisms underlying the protective effects of adiponectin against preeclampsia are still not fully understood, but evidence suggests that adiponectin may improve insulin sensitivity, reduce oxidative stress, and inhibit inflammation. Adiponectin can also increase angiogenesis (formation of new blood vessels) in the placenta, which is important for adequate placental perfusion and healthy fetal growth.[22-25]

4. Conclusion

This meta-analysis provides strong evidence that increased BMI before pregnancy is an independent risk factor for preeclampsia. Interventions to optimize BMI before pregnancy, such as nutritional counseling and promotion of physical activity, may be an effective preventive strategy to reduce the risk of preeclampsia.

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