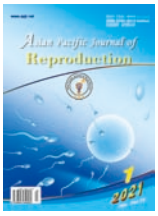

Meta-Analysis

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Association between pre-pregnancy body mass index and gestational weight gain and the risk of preeclampsia: A systematic review and meta-analysis

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ABSTRACT

Objective: To analyze the relationship between body mass index (BMI) before pregnancy and gestational weight gain throughout pregnancy with the incidence of preeclampsia.

Methods: This was a systematic review-meta analysis of literature collected from three e-databases: Scopus, PubMed, and Science Direct. Quality assessment was measured with the Effective Public Health Practice Project methods. Meta-analysis was done by calculating the fixed and random-effects of odds ratio (*OR*) for each BMI category and gestational weight gain as compared with the incidence of preeclampsia.

Results: Overweight was associated with a significantly increased risk of preeclampsia (*OR*=2.152, 95% *CI* 1.363-3.400; *P*=0.001). Obesity was also associated with a noticeably increased risk of preeclampsia (*OR*=2.856, 95% *CI* 1.755-4.649; *P*<0.001). Meanwhile, underweight was associated with a significantly reduced risk of preeclampsia (*OR*=0.639, 95% *CI* 0.500-0.817; *P*<0.001) when compared with normal BMI. Pregnant women who gained weight below the standard throughout pregnancy was a protective factor from preeclampsia (*OR*=0.813, 95% *CI* 0.610-1.083; *P*=0.157) whereas pregnant women who gained weight above the standard had almost doubled risk of preeclampsia (*OR*=1.850, 95% *CI* 1.377-2.485; *P*<0.001).

Conclusions: The result of this study affirms the role of overweight-obesity pre-pregnancy, and gestational weight gain above the standard during pregnancy as significant risk factors for developing preeclampsia.

KEYWORDS: Body mass index; Gestational weight gain; Preeclampsia; Risk factors

1. Introduction

Maternal mortality rate is an important indicator to determine the degree of public health in a country. One of the biggest factors causing maternal mortality is preeclampsia. Worldwide, the incidence of preeclampsia ranges between 2% and 10% of pregnancies. World Health Organization estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live birth) than in developed countries (0.4%)[1]. It is estimated that in developing countries, preeclampsia accounts for 15% of maternal deaths every year[2]

The cause of preeclampsia is uncertain, but recent evidence suggests that excessive gestational weight gain and elevated prepregnancy body mass index (BMI) may be the important factors[3]. Underlying mechanisms for a potential causal association between weight gain and preeclampsia could be that excessive gestational weight gain may increase oxidative stress, and thereby stimulate or aggravate a systemic inflammatory response which could accelerate damage to vascular endothelial cells leading to preeclampsia[4]. Magnus *et al* argue that reverse causation must be considered as an explanation of the association between gestational weight gain and preeclampsia because edemas will also cause increased weight gain[5]. The findings of Hillesund *et al* by including body composition measurements in the models supported this view[6].

Many studies have shown a variety of results about this topic, but to get a clearer understanding of the relationship between BMI pre-pregnancy and gestational weight gain throughout pregnancy with the incidence of preeclampsia, a meta-analysis is needed. This study aims to provide summary results of previous studies about this topic.

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2. Materials and methods

The standard criteria for prepregnancy BMI and gestational weight gain (GWG) that used in this study were based on the Institute of Medicine guideline 2009, as attached in the following Table 1 [7].

2.1. Search strategy

We searched Scopus, PubMed, and Science Direct databases to identify relevant studies. We used the following search terms: ("Gestational Weight Gain" OR GWG) AND ("Body Mass Index" OR BMI) AND (preeclampsia OR pre-eclampsia). Because this systematic review only re-identified pooled data from primer studies, ethics approval was unnecessary for this study.

2.2. Inclusion and exclusion criteria

The inclusion criteria of this study were: (1) research published in the last 5 years (2015-2020); (2) literature in English; (3) full-text accessible literature; (4) open access and (5) single pregnancy, while the exclusion criteria were: (1) sources from non-primary studies such as case report, review article, conference result, or book chapters (2) multiple pregnancies; (3) study with certain interventions; (4) different study with the same sample.

2.3. Quality assessment and data extraction

We measured the quality of the study by using a quality assessment tool for quantitative studies from Effective Public Health Practice Project[8]. There were 6 components assessed in this assessment tool such as selection bias, study design, confounders, blinding, data collection method, withdrawals, and dropouts. Each component was graded with 3 ratings (1=strong, 2=moderate, 3=weak). After evaluating each component, it could be concluded that the global rating for the paper was strong if there was no weak rating, moderate if there was one weak rating, and weak if there were two or more weak ratings. For each study, we extracted the following information: author, title, setting, method of studies, year of publication, year of research, participants, anthropometric measurement, inclusion & exclusion criteria, dependent & independent variable, and results.

2.4. Statistical analysis

Individual studies odds ratio (*OR*) and 95% confidence interval (*CI*) were calculated based on the event numbers extracted from each study before data pooling. The heterogeneity among the studies was quantified and tested by using the I^2 statistic, which represented the percentage of total variation across studies due to heterogeneity rather than chance. The assumption of homogeneity was considered if I^2 values 50% or less, whereas if I^2 values >50% indicate that the studies were heterogeneous. Statistical analysis was performed by using the Comprehensive Meta-Analysis software. This analysis was carried out by using 2 methods, the fixed-effect model for homogeneous articles and the random-effect model for heterogeneous articles. Then, the results of this statistical analysis were presented in the forest plots. Each forest plot displayed *OR*, *CI*, *Z* value, and *P*-value data from each article. The summaries *OR* and *CI* from the analysis result carried out according to the model (fixed/random effect model) were also displayed to describe the overall treatment effect.

3. Results

3.1. Selection of studies

We identified 666 articles from our initial electronic database search. Of these articles, 620 were excluded based on the incompatibility of the abstract and title with the study topic. The full texts of the remaining 46 articles were assessed for eligibility. Among 46 articles, 36 articles were excluded: Eleven articles were excluded because there was a duplication in each database, seven were review articles, five articles did not investigate the relationship between BMI-gestational weight gain and preeclampsia, six articles did not present clear results about BMI-gestational weight gain and preeclampsia, two articles were studies in the multiple pregnancies, four articles were interventional studies, and one article reported the same populations. Finally, ten articles met our inclusion criteria and were included in the meta-analysis (Figure 1).

Table 1. The standard criteria for prepregnancy body mass index and gestational weight gain [7].

Prepregnancy body mass index	Total weight gain		Rates of weight gain in the 2nd and 3rd trimester	
	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (<18.5 kg/m^2)	12.5-18.0	28.0-40.0	0.51 (0.44-0.58)	1.0 (1.0-1.3)
Normal weight [(18.5-24.9) kg/m^2]	11.5-16.0	25.0-35.0	0.42 (0.35-0.50)	1.0 (0.8-1.0)
Overweight [(25.0-29.9) kg/m^2]	7.0-11.5	15.0-25.0	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (⩾30.0 kg/m^2)	5.0-9.0	11.0-20.0	0.22 (0.17-0.27)	0.5 (0.4-0.6)

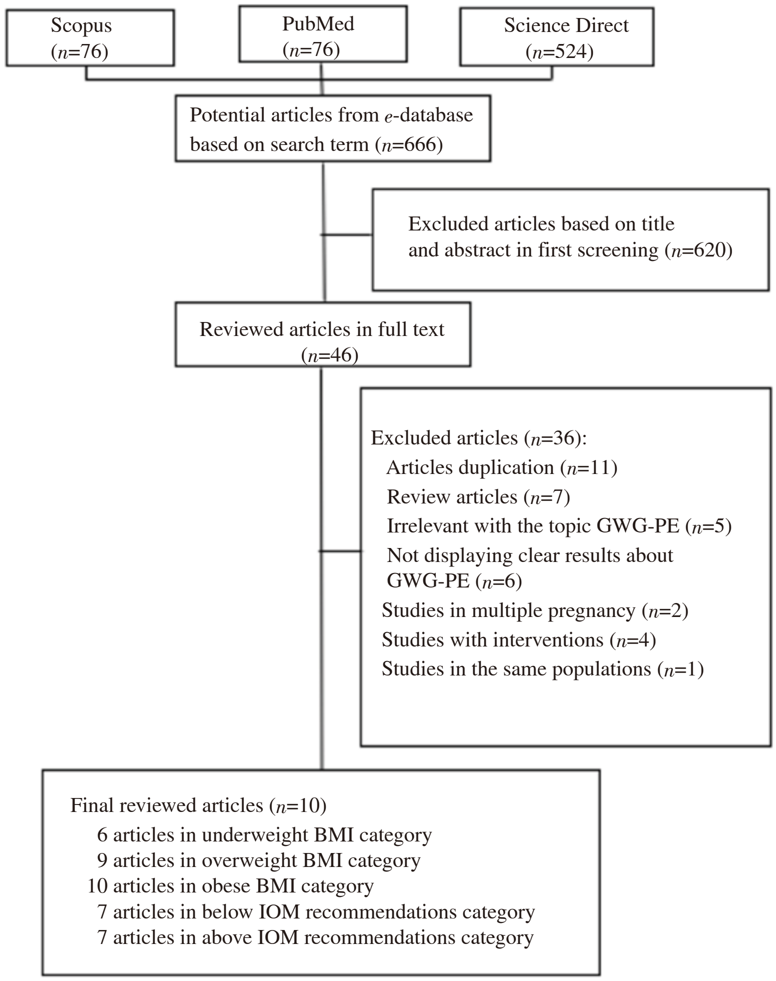


Figure 1. Flowchart of the article selection process. GWG-PE: gestational weight gain-preeclampsia; BMI: body mass index; IOM: the Institute of Medicine.

3.2. Characteristics of studies included

The authors, methodology, participants, research periods, and outcomes were identified and summarized in Table 2. The 10 studies consisted of a total of 2 849 436 participants. Four articles were retrospective cohort study[9–12], three were prospective cohort study[3,13,14], one was a case-cohort study[15], one was a retrospective hospital-based study[16] and one was electronic medical record cross-stratified data analysis[17]. From 10 articles that were reviewed, four were studied in Asia[9,10,13,14], three were studied in America[3,15,17], two were studied in Europe[12,16], and one was studied in Africa country[10]. All studies were included in the quality assessment with Effective Public Health Practice Project tools. Seven studies were categorized as a strong rating and three studies were moderate rating.

3.3. Meta analysis outcomes

We analyzed the risk of developing preeclampsia based on the category of BMI pre-pregnancy and the gestational weight gain during pregnancy. Six studies showed that the underweight category decreased the risk of preeclampsia (*OR*=0.639; 95% *CI* 0.500-0.817; $P<0.001$). In this category, we used the fixed-effect model because the I^2 value indicated homogeneity (I^2=28.737). Nine studies with the overweight category and ten studies with the obese category of BMI were eligible for the meta-analysis, showed significant heterogeneity (I^2=96.006 for overweight and I^2=97.705 for obese), and random-effect models were employed for the meta-analysis. Women who were overweight and obese before pregnancy had a greater risk of developing preeclampsia when compared to those who had a normal BMI (*OR*=2.152; 95% *CI* 1.363-3.400; $P<0.0001$ for overweight, and *OR*=2.856, 95% *CI* 1.755-4.649; $P<0.001$ for obese).

We analyzed the effects of inadequate and excessive gestational weight gain as compared with the Institute of Medicine recommendation and measured the risk of developing preeclampsia. Seven studies showed results in both categories. The results of the meta-analysis showed that gestational weight gain below the Institute of Medicine recommendations was not associated with the risk of preeclampsia (P=0.157). Gestational weight gain above the Institute of Medicine recommendations had a significant correlation ($P<0.001$) and a greater risk of developing preeclampsia (*OR*=1.850 95% *CI* 0.377-2.485).

Table 2. Summary of the studies.

Number	Author	Title	Setting	Research method	Time of research	Participant	Result
1	Bravadharini, 2017	Gestational weight gain and pregnancy outcomes in relation to body mass index in Asian Indian women	Chennai, South India	Retrospective cohort study	January 2011-January 2014	2 728 participants	Obese women who gained more weight during pregnancy were at high risk of preterm labor (*OR*: 2.1, 95% *CI*: 1.1–3.8; *P*=0.01), cesarean section (*OR*: 1.9, 95% *CI*: 1.4–2.5; *P*<0.001), and preeclampsia (*OR*: 2.8, 95% *CI*: 1.1–7.2, *P*=0.03).
2	Bodnar, 2018	Early-pregnancy weight gain and the risk of preeclampsia: A case-cohort study	Pittsburgh Pennsylvania	Case-cohort study	1998-2011	6 314 participants (1 197 preeclampsia cases)	For normal weight women, there was a steady increase in preeclampsia risk with increasing early gestational weight gain z-score. Weight loss at 16-19 weeks was associated with a reduced risk of preeclampsia.
3	Chen, 2020	Maternal prepregnancy body mass index, gestational weight gain, and risk of adverse perinatal outcomes in Taiwan: A population-based birth cohort study	Taiwan	Cohort study	January 1, 2005-December 31, 2005	19 052 participants	Women with excessive gestational weight gain had a greater risk of gestational hypertension, preeclampsia, caesarean delivery, and macrosomia.
4	Fouelifack, 2015	Associations of body mass index and gestational weight gain with term pregnancy outcomes in urban Cameroon: A retrospective cohort study in a tertiary hospital	Cameroon	Retrospective cohort study	January 2, 2014-April 30, 2014	462 participants	Gestational weight gain above the Institute of Medicine recommendation was significantly associated with poor maternal outcome (*aOR*:1.7, 95% *CI* 1.1-2.8)
5	Hung, 2016	Pregestational body mass index, gestational weight gain, and risks for adverse pregnancy outcomes among Taiwanese women: A retrospective cohort study	Taipei, Taiwan	Retrospective cohort study	January 1, 2009-December 31, 2015	12 064 participants (cohort 1) & 10 973 participants (cohort 2)	Gestational weight gain above the recommendation were with higher risk of preeclampsia (*aOR* 3.65, 95% *CI* 2.18-6.10), primary cesarean delivery (*aOR* 1.35, 95% *CI* 1.16-1.56), cephalopelvic disproportion (*aOR*1.88, 95%*CI* 1.30-2.71), large-for-gestational-age (*aOR* 1.80, 95% *CI* 1.51-2.15), and macrosomia (*aOR* 2.16, 95% *CI* 1.53-3.06).
6	Hutcheon, 2018	Pregnancy weight gain before diagnosis and risk of pre-eclampsia: A population-based cohort study in nulliparous women.	Stockholm-Gotland (Swedia)	Cohort study	2008-2013	62 705 participants (2 770 preeclampsia case)	Odds of preeclampsia increased by approximately 60% with every 1 z-score increase in pregnancy weight gain among normal weight and overweight women, and by 20% among obese women.
7	Shao, 2017	Pre-pregnancy BMI, gestational weight gain and risk of preeclampsia: A birth cohort study in Lanzhou, China	Lanzhou, China	Cohort study	2010-2012	9 863 participants	Women with excessive gestational weight gain had an increased risk of preeclampsia (*OR*=2.28; 95% *CI*: 1.70-3.05) compared to women with adequate gestational weight gain. Overweight/ obese women with excessive gestational weight gain had the highest risk of developing preeclampsia compared to normal weight women with no excessive weight gain (*OR*=3.78; 95% *CI*: 2.65-5.41).
8	Simko, 2019	Maternal body mass index and gestational weight gain and their association with pregnancy complications and perinatal conditions	Bratislava, Slovakia	Retrospective hospital-based study	2013-2015	7 122 participants	Gestational weight gain above the Institute of Medicine recommendations was associated with a higher risk of pregnancy terminated by C-section (*AOR*=1.2; 95% *CI* 1.0-1.3), gestational hypertension (*AOR*=1.7; 95% *CI* 1.0-2.7), and macrosomia (*AOR*=1.7; 95% *CI* 1.3-2.1).
9	Taber, 2016	Gestational weight gain, body mass index, and risk of hypertensive disorders of pregnancy in a predominantly Puerto Rican population	Caribbean islands	Prospective cohort study	2006-2011	1 293 participants	As compared to women who gained within the Institute of Medicine gestational weight gain guidelines (22.8%), those who gained above guidelines (52.5%) had an *OR* 3.82 for hypertension disorders (95% *CI* 1.46-10.00; *P*=0.003) and *OR* 2.94 for preeclampsia (95% *CI* 1.00-8.71, *P*=0.03) after adjusting for important risk factors.
10	Thompson, 2019	An evaluation of whether a gestational weight gain of 5 to 9 kg for obese women optimizes maternal and neonatal health risks	USA	Eelectronic medical record-crossstratified data analysis	2014-2016	2 716 860 participants (pregnant women with obese)	Obese women gaining less than 5 kg during pregnancy had reduced maternal risk for gestational hypertension, eclampsia, induction of labor, and C-section.

Study name	Odds ratio	Lower limit	Upper limit	*Z*–value	*P*-value
	Statistics for each study				
Chen, 2020	0.370	0.179	0.765	-2.682	0.007
Fouelifack, 2015	0.500	0.200	1.250	-1.483	0.138
Hung, 2016	0.440	0.241	0.803	-2.673	0.008
Shao, 2017	0.760	0.542	1.065	-1.595	0.111
Simko, 2019	1.100	0.513	2.359	0.245	0.807
Taber, 2016	0.440	0.058	3.317	-0.797	0.426
	0.639	0.500	0.817	-3.572	0.000

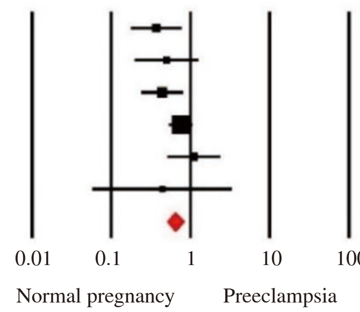


Figure 2. Forest plot analysis of the underweight body mass index category and the risk of preeclampsia. *CI*: Conftdential interval.

Study name	Odds ratio	Lower limit	Upper limit	*Z*–value	*P*-value
	Statistics for each study				
Bravadharini, 2017	2.800	0.326	24.032	0.939	0.348
Bodnar, 2018	4.700	4.095	5.394	22.026	0.000
Chen, 2020	1.870	1.076	3.249	2.221	0.026
Fouelifack, 2015	0.800	0.500	1.280	-0.931	0.352
Hung, 2016	3.740	2.752	5.083	8.425	0.000
Hutcheon, 2018	1.590	1.451	1.742	9.970	0.000
Shao, 2017	1.810	1.370	2.391	4.179	0.000
Simko, 2019	3.400	1.913	6.042	4.172	0.000
Taber, 2016	1.430	0.632	3.238	0.858	0.391
	2.152	1.363	3.400	3.286	0.001

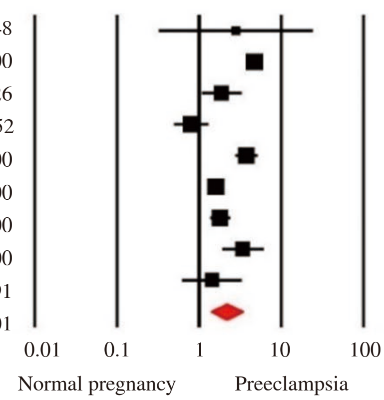


Figure 3. Forest plot analysis of the overweight body mass index category and the risk of preeclampsia.

Study name	Odds ratio	Lower limit	Upper limit	*Z*–value	*P*-value
	Statistics for each study				
Bravadharini, 2017	2.800	1.094	7.164	2.148	0.032
Bodnar, 2018	5.900	5.100	6.825	23.875	0.000
Chen, 2020	5.010	2.529	9.925	4.620	0.000
Fouelifack, 2015	0.700	0.400	1.225	-1.249	0.212
Hung, 2016	7.850	5.133	12.006	9.505	0.000
Hutcheon, 2018	1.190	1.062	1.333	3.005	0.003
Shao, 2017	1.810	1.370	2.391	4.179	0.000
Simko, 2019	13.200	7.722	22.564	9.432	0.000
Taber, 2016	1.270	0.540	2.988	0.547	0.584
Thompson, 2019	2.100	1.900	2.321	14.530	0.000
	2.856	1.755	4.649	4.223	0.000

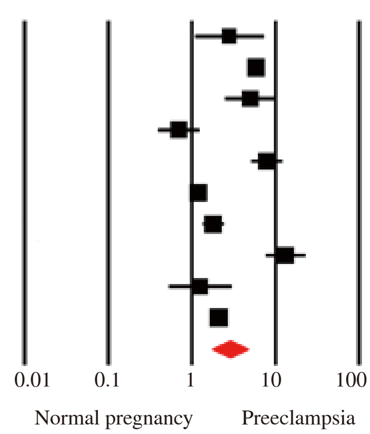
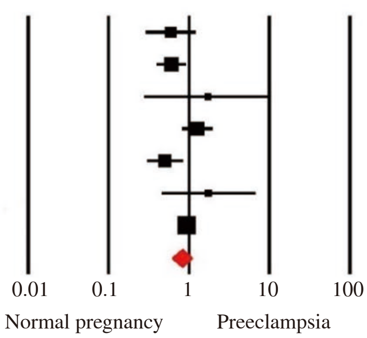


Figure 4. Forest plot analysis of the obese body mass index category and the risk of preeclampsia.

A

Study name	Odds ratio	Lower limit	Upper limit	*Z*–value	*P*-value
Chen, 2020	0.590	0.292	1.190	-1.474	0.141
Fouelifack, 2015	0.600	0.400	0.900	-2.469	0.014
Hung, 2016	1.720	0.281	10.523	0.587	0.557
Shao, 2017	1.270	0.821	1.963	1.075	0.282
Simko, 2019	0.500	0.300	0.833	-2.660	0.008
Taber, 2016	1.750	0.461	6.644	0.822	0.411
Thompson, 2019	0.930	0.831	1.041	-1.261	0.207
	0.813	0.610	1.083	-1.414	0.157

Statistics for each study



B

Study name	Odds ratio	Lower limit	Upper limit	*Z*–value	*P*-value
Chen, 2020	3.170	2.039	4.928	5.125	0.000
Fouelifack, 2015	1.700	1.100	2.627	2.389	0.017
Hung, 2016	4.580	0.617	33.986	1.488	0.137
Shao, 2017	2.280	1.702	3.054	5.527	0.000
Simko, 2019	0.900	0.600	1.350	-0.509	0.611
Taber, 2016	2.920	0.990	8.616	1.941	0.052
Thompson, 2019	1.590	1.460	1.732	10.656	0.000
	1.850	1.377	2.485	4.088	0.000

Statistics for each study

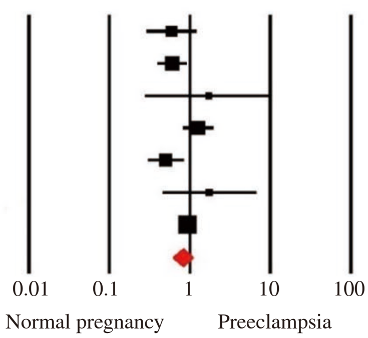


Figure 5. Forest plot analysis of gestational weight gain below the Institute of Medicine (IOM) recommendations (A), above the IOM recommendations (B) and the risk of preeclampsia.

4. Discussion

4.1. Relationship between pre–pregnancy BMI and the risk of preeclampsia

The results of the meta-analysis showed that there is a relationship between pre-pregnancy BMI and the risk of preeclampsia. Six studies report the incidence of preeclampsia in the underweight category. Five studies showed a lower risk of preeclampsia in underweight pregnant women when compared with a normal BMI pre-pregnancy[3,10,11,13,14] whereas one study from Simko *et al*[15] showed insignificant result (*OR*=1,100; 95% *CI* 0.513-2.359; *P*=0.807). The final results of the meta-analysis in this study indicated that pre-pregnancy underweight is a protective factor against the incidence of preeclampsia. Thus, pre-pregnancy underweight reduces the risk of developing preeclampsia but remains at risk of other maternal and perinatal complications.

Studies conducted by Pusparini *et al* showed that vitamin A deficiency (serum retinol <20 μg/dL) of the second trimester and BMI<18.5 kg/m^2 at early pregnancy, are risk factors for the linear growth of newborns (*OR*=11.12 and 8.84). This implies that normal nutritional status at early pregnancy is important in preventing stunting among newborn infants[18].

The results of this study are in line with Andriani *et al*, who found no differences in the proportion of underweight in preeclampsia and non-preeclampsia pregnant women. Pregnant women with underweight have a higher risk of developing preeclampsia if there are other comorbidities such as severe anemia or micronutrient deficiency. These conditions can cause preeclampsia through the mechanism of endothelial dysfunction triggered by oxidative stress reactions[19].

In the overweight category, 8 of 9 studies showed a higher risk of developing preeclampsia when compared to normal pre-pregnancy BMI. Even according to the study of Bodnar *et al*, mothers with

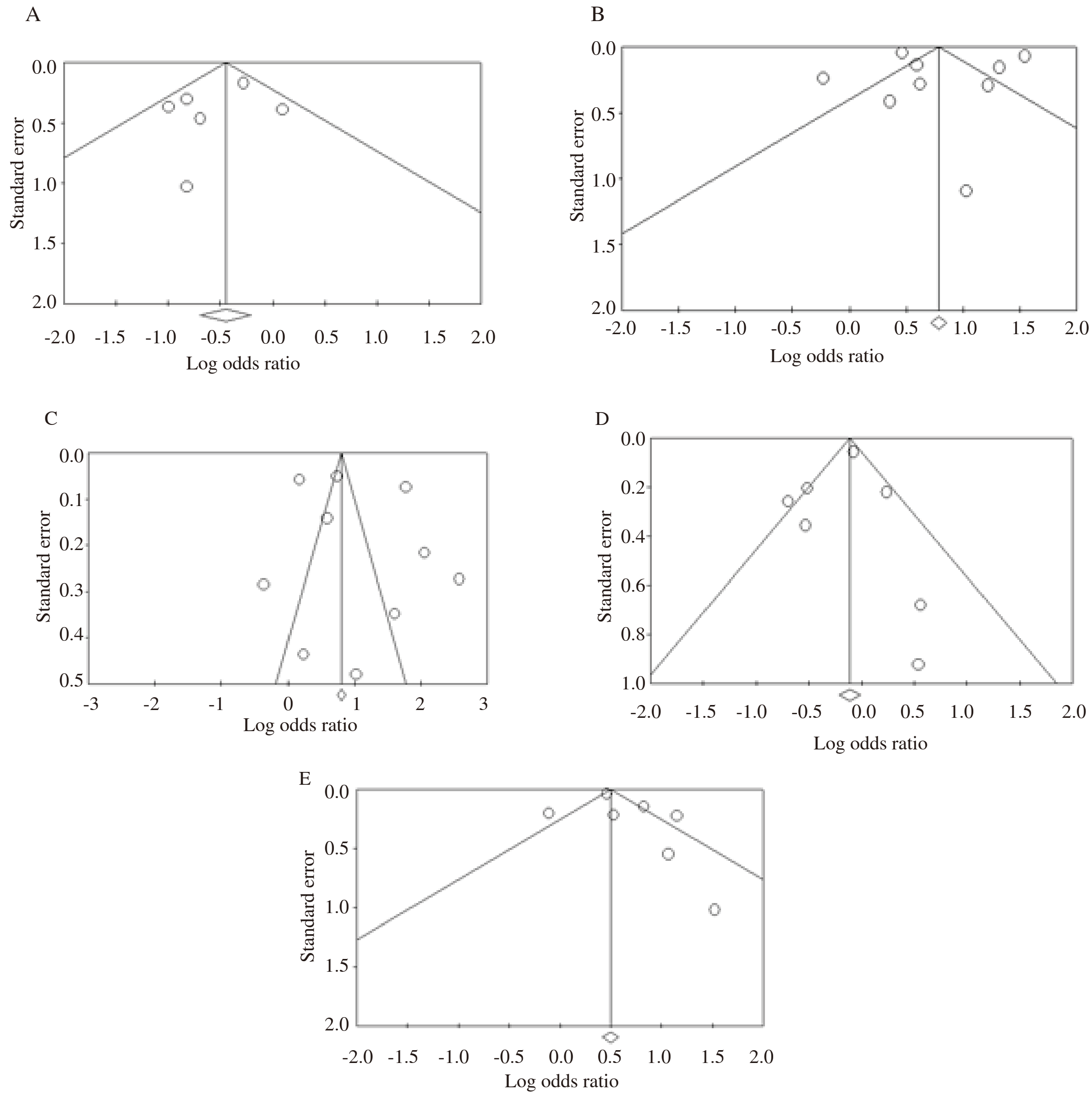


Figure 6. Funnel plot analysis of underweight body mass index category (A), overweight body mass index category (B), obese body mass index category (C), gestational weight gain below the IOM recommendations (D), and gestational weight gain above the IOM recommendations (E) and the risk of preeclampsia.

pre-pregnancy overweight have a risk of up to 4 times greater as compared with the mothers who have a normal BMI (*OR*=4.7, 95% *CI* 4.095-5.394). From the 10 studies examined in the obese category, the odds ratio varies ranging from *OR*=1.27 to the highest with *OR*=13.2[16].

There are differences in the way of determining pre-pregnancy BMI in this systematic review, namely by participant's self-reported and direct measurement by health workers. However, according to research conducted by Shin (2014) pre-pregnancy BMI determination in self-reported is almost in accordance with direct measurement by health workers[20]. In other studies it was reported that the general correlation coefficient between the two methods was 0.99, indicating that both methods have the same accuracy[21].

The results of this meta-analysis are in accordance with several previous studies. Although many studies have suggested that the relationship between pre-pregnancy BMI and the incidence of preeclampsia is likely obscured by the presence of comorbidities such as chronic hypertension, diabetes mellitus, and other elements of the metabolic syndrome which are a risk factor of preeclampsia. In a previous study by He *et al*, the results were unchanged even though the comorbidities factors were excluded. Thus, a high BMI may be an independent predictor of preeclampsia, as it is the risk for other adverse maternal outcomes[22].

Important features of systemic inflammation in preeclampsia are the predominance of Th1-type immunity and the absence of Th2 tendencies. T cells can be classified as Th1 cells, which synthesize pro-inflammatory cytokines such as interleukin (IL)-2, IL-12, interferon- and tumor necrosis factor-α (TNF-α), and induce cellular immunity, or Th2 cells, which synthesize IL-4, IL-5, IL-6 and IL-10, and induce antibody production[23]. In pre-eclamptic patients, the decidual lymphocytes and peripheral blood mononuclear cells are generally primed to synthesize high levels of Th1. Besides, circulating levels of pro-inflammatory cytokines such as IL-6, TNF-α, chemokines IL-8, interferon-γ-inducible protein 10, and monocyte chemoattractant protein-1 are also elevated in preeclampsia[24].

In people with obesity, not only the amount of fat, but the distribution of fat is also very important. Central obesity as a marker of visceral obesity has a higher risk of preeclampsia as compared with peripheral obesity. Visceral fat produces more *C*-reactive protein and inflammatory cytokines, resulting in more oxidative stress. Diet is also mentioned as one of the causes of increased oxidative stress. Antioxidant levels in people with obesity are relatively low which is likely due to the low consumption of foods that contain antioxidants and high consumption of carbohydrates and fats. This dietary pattern is more often found in obese people and women who will then develop preeclampsia[25].

Although the pathophysiology of preeclampsia remains unclear, placental ischemia/hypoxia is widely regarded as a key factor. Placental hypoxia is a condition that occurs due to abnormal spiral artery remodeling during preeclampsia. This appears to be the leading cause of placental insufficiency. Placental hypoxia is shown to upregulate the expression of sFlt-1 protein in trophoblast culture from the first trimester placentas[26]. The poorly perfused and hypoxic placenta is thought to synthesize and release elevated amounts of factors, such as sFlt-1 and sEng. Elevation in these factors is proposed to result in endothelial dysfunction, by decreasing bioavailable nitric oxide, and increasing reactive oxygen species and endothelin-1, which in turn results in altered renal function, increased total peripheral resistance, and ultimately, hypertension[27].

Another factor that supports the mechanism of obesity as a risk factor for preeclampsia is inflammation. Adipose tissue, especially in obese individuals, produces several inflammatory mediators/cytokines that change the endothelial function[25]. *C*-reactive protein is higher in obese individuals and predicts both worse cardiovascular outcomes and cardiovascular morbidity[28]. *C*-reactive protein is also elevated in early pregnancy in women who later develop preeclampsia. TNF-α is higher in obesity and may contribute to insulin resistance in obesity. TNF-α is also elevated in preeclampsia, possibly from adipose tissue as placental mRNA is not increased[29]. IL-6 is higher with obesity and is also in preeclampsia[30]. The IL-6 produced in adipose tissue accounts for 30% of circulating IL-6. IL-6 is associated with later-life cardiovascular disease and with an increased risk of insulin resistance[31]. It is a major stimulator of acute-phase reactants with consequent effects on vessel wall function and blood clotting, and it has been proposed as a major mediator of inflammation-induced vascular damage[32]. Further evidence of increased inflammation in preeclampsia is demonstrated through increased uncontrolled complement system activity as compared with normal pregnancy. The activity of the complement system strengthens inflammatory cells and produces proteolytic fragments that increase phagocytosis by neutrophils and monocytes[23]. There is no doubt that angiogenic imbalance and systemic inflammation increase in preeclampsia. Based on a study from Ramma and Ahmed, pregnant women who have risk factors of chronic inflammation, such as obesity, pre-pregnancy hypertension diabetes mellitus, and dyslipidemia, are more likely to develop preeclampsia[23]. A previous qualitative study by Haby *et al*, found that midwife-led lifestyle interventions with small changes in lifestyle such as: not skipping breakfast, avoiding midnight meals, and planning a diet, can influence the reduction of excessive gestational weight gain in obese women[33].

4.2. Relationship between gestational weight gain and the risk of preeclampsia

From the meta-analysis, it was found that there was a relationship between pregnant women who gained weight above the gestational weight gain recommendations from the Institute of Medicine with the risk of preeclampsia, while the meta-analysis of gestational weight gain under the Institute of Medicine recommendations showed no significant difference (P=0.157).

High pregnancy weight gain before the diagnosis is an important risk factor for preeclampsia in nulliparous women, particularly in leaner women. A previous study found that the association between pregnancy weight gain and preeclampsia was more pronounced in preeclampsia developing later in gestation supports the hypothesis that early preterm and term onset preeclampsia may have different pathogenic pathways[12].

Based on epidemiological studies reported in the Institute of Medicine pregnancy weight guidelines, gestational weight gain generally shows the inverse relationship with the pre-pregnancy BMI. According to the study of Chu *et al* (2009) in the Institute of Medicine pregnancy weight guidelines, conducted by using Pregnancy Risk Assessment Monitoring System data from 2004-2005 to find out the number of gestational weight gain among 52 988 women in the US with BMI categories underweight, normal weight, overweight and obese giving birth to a single fetus, indicated that the overall gestational weight gain decreases with an increase in BMI. When stratified with BMI, it was found that women with obesity gained less weight gain as compared with women who were overweight or normal weight. In the multivariable regression model, pre-pregnancy obesity is the strongest predictor of low gestational weight gain, followed by high parity, African American or Hispanic race, and high maternal age during pregnancy[7]. Although pre-

pregnant BMI can predict gestational weight gain, there are also metabolic changes in pregnancy such as basal metabolic rate, total energy expenditure, and hormonal changes that are independent of BMI, which can affect gestational weight gain[7].

In the GWG category more than IOM's recommendation, there is a spectrum risk varies widely from as low as *OR*=0.90 [95% *CI* 0.600-1.350; *P*=0.611] up to the highest risk with *OR*=4.58 [95% *CI* 0.617-33.986; *P*=0.137]. From the results of the meta-analysis, it can be concluded that pregnant women who experience weight gain above the Institute of Medicine recommendations have almost a 2-fold risk of developing preeclampsia. Excessive gestational weight gain is closely related to increased risk of maternal and perinatal complications, including hypertensive disorder in pregnancy[34]. In obese pregnant women in all obesity categories, weight gain of less than 5 kg during pregnancy has a significant effect on reducing the risk of hypertensive disorder in pregnancy, including both preeclampsia and eclampsia. Vice versa, weight gain of more than 9 kg during pregnancy in obese mothers, increases the risk of hypertensive disorder in pregnancy[17].

The causes of excessive weight gain are often multifactorial and complex. Pregnant women with low incomes have a high risk of excessive weight gain, this is related to lack of access to healthy food, unbalanced composition of diet (tend to have a lot of carbohydrate and sugar, but low protein intake), less physical activity, and/or lack of awareness and literacy about healthy food choices[35]. Psychosocial factors such as stress, depression, and lack of social support are also associated with excessive weight gain in pregnancy[36].

Weight gain in pregnancy is normal, but gaining more or less than the standard recommendation can lead to maternal-fetal and neonatal complications. The National Health and Medical Research Council recommends that all pregnant women be weighed each time they do antenatal care because the data shows that 50% of pregnant women have excessive weight gain during pregnancy. This data indicates the need for health worker's role in conducting preventive measures so that complications such as preeclampsia can be reduced[37].

Healthcare providers who focus on preventive domains such as midwives and public health experts must provide quality communication, information, and education to encourage healthy lifestyles for pregnant women to be able to have good planning and preparation for pregnancy in optimal conditions and can control their weight gain during pregnancy according to the standard recommendation.

In conclusion, the result of this study affirms the role of overweight-obesity pre-pregnancy, and gestational weight gain above the standard during pregnancy as significant risk factors for developing preeclampsia. Additional studies are needed to confirm that this result is causal or reflects a common cause.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Authors' contributions

Renata Alya Ulhaq and Muhammad llham Aldika Akbar conceived and designed the study. Renata Alya Ulhaq performed the analyses. Renata Alya Ulhaq, Wahyul Anis, Widati Fatmaningrum, and Muhammad llham Aldika Akbar prepared and approved the manuscript.

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