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Original Article

Prepregnancy body mass index and the risk of preeclampsia: a meta-analysis of cohort studies

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Abstract: Background: Prepregnancy maternal obesity is an important risk factor for the development of preeclampsia. However, the reports on the incidence of preeclampsia in women with low body mass index (BMI) are controversial. Methods: We searched PubMed up to April 2014 and identified 35 cohort studies reporting an odds ratio (OR) as a common measure for the association between prepregnancy BMI and the risk of preeclampsia. We used a random-effects model to calculate the combined risk estimates due to heterogeneity and also evaluated a potential curve linear association using restricted cubic splines (RCS). Sensitivity meta-regression and subgroup analyses were conducted to explore the possible explanation for heterogeneity. Results: Women with a low BMI compared to those within normal range had 28% lower risk of developing preeclampsia (pooled OR = 0.72, 95% CI 0.66-0.78, $p < 0.001$). The pooled OR for overweight and obese women were 1.64 (95% CI 1.54-1.76) and 2.86 (95% CI 2.56-3.19), respectively. Specifically, one unit increase in prepregnancy BMI yields a 0.432% (95% CI 0.224-0.640) increase in the prevalence of preeclampsia by restricted cubic spline function. Maternal age, parity, multi-fetal pregnancy, sample size and the source of BMI were not significantly associated with risk estimates on meta-regression and subgroup analyses. Sensitivity analysis revealed that the pooled ORs are stable. Conclusion: Our finding suggested that low prepregnancy maternal BMI was associated with decreased risk of preeclampsia, whereas overweight and obese women had increased risk to the development of preeclampsia.

Keywords: Body mass index, preeclampsia, obesity, prepregnancy, meta-analysis

Introduction

Preeclampsia, diagnosed by newly onset hypertension and proteinuria after 20 weeks of gestation, can develop into to eclampsia with life threatening complications if left untreated and is a major contributor to maternal and neonatal morbidity and mortality worldwide. Preeclampsia not only causes a multisystem disorder to both mother and fetus [1, 2], it also predisposes them both to future cardiovascular disease and other disorders [3-5].

Preeclampsia can go unnoticed in the early stages due to long preclinical phase before signs and symptoms becoming apparent in the second half of pregnancy. Despite extensive investigation, preventive or therapeutic intervention for preeclampsia is hampered due to the fact that the etiology still remains largely unknown [6] and the etiological prevention is hard to reach. Therefore, identifying the factors that determine the risk of preeclampsia is of critical important for effective monitoring before and during pregnancy, which could be an effective way to prevent such disease. Risk factors of preeclampsia in previous pregnancy, including extreme maternal age, nulliparity, multi-fetal gestation, pre-existing maternal diseases, and high body mass index (BMI) have been recognized in preeclampsia by numerous studies [7-9]. Although an increased risk for preeclampsia in women with higher BMI compared with those in the normal range was iden-

tified, this increased risk varies widely across publications. Moreover, limited data available on the impact of prepregnancy maternal underweight in preeclampsia development and the association remains less clear. One previous systematic review [10] pointed out that the prevalence of obesity may increase the risk of preeclampsia and the risk of preeclampsia typically doubled for each 5 to 7 kg/m^2 increase in BMI. However, the evidence from this article was limited because only 13 studies were available at that time and the prepregnancy BMI category was limited to overweight and non-overweight categories, which might have lost some valuable information. The recent meta-analysis paper [11] did quantify the impact of all prepregnancy BMI categories on the risk of developing preeclampsia. Nevertheless, this study calculated the pooled RR based on reported relative risks (RR), hazard ratios (HR) or odds ratio (OR) rather than one measure. Although there is a conceptual relationship among these three measures, they are still different enough that the author should probably report separate pooled estimates for the studies using different measures. Since the condition and formulas used of these indicators are different, the direct combination of these measures can pose a potential for poor estimation of risk. Moreover, two [12, 13] out of 29 included articles have the exact same population for pooled RR calculation, which may amplify the effect of one single population and lower heterogeneity. Unfortunately, the authors did not provide any information to explain how they combined different measures for a single RR estimation and how they calculated pooled RR with the same population and all of these could make the interpretation of the results difficult.

Herein, to avoid the limitation of previous systematic reviews, and to provide more precise data and stronger evidence for the relationship between preeclampsia, we conducted a meta-analysis to quantify the change in the risk of preeclampsia according to prepregnancy BMI category.

Methods

Literature search strategy

This systematic review was reported in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [14]. The online database of PubMed was searched up to April 2014 to identify studies reporting an association between prepregnancy BMI and preeclampsia. The following search terms were used: 1) body mass index or Quetelet Index or BMI or body size or body weight or body mass or body weight changes or obesity or overweight or adiposity or over nutrition or morbid obesity, 2) preeclampsia or eclampsia or eclamptic convulsion or eclampsia seizure. These two search themes were combined using an "and". No restrictions on language, geographical location, or study design were applied in this searching process. Reference lists of the retrieved articles were also reviewed for additional studies and no non-English peer reviewed publications were translated. Authors were contacted for necessary information.

Study inclusion and exclusion criteria

Cohort studies including prospective and retrospective cohort, were considered for inclusion in this systematic review and meta-analysis if they met the following criteria: (a) original, empirical research published in a peer-reviewed journal, (b) preeclampsia as an outcome variable or to define cases, and (c) BMI (either self-reported or measured) of prepregnancy or before 20 weeks gestation as an exposure variable or one of the risk factors. When multiple publications were available from a single population, the paper that provided a larger sample size or better study design was chosen in order to maximize information. BMI was accepted as the only measurement of obesity as exposure, and BMI categories defined by the author in each article was applied directly in this systematic review since exact cut-offs for these categories varied slightly and there was not consensus on this through all included countries. Any criterion used to diagnose preeclampsia was accepted.

Studies were excluded using the following criteria: (a) no definition of BMI categories, (b) no normal weight information, and (c) no odds ratio (OR) and confidence interval (CI) or insufficient data available for recalculation.

Study selection and data extraction

Studies were assessed in three levels: title, abstract and full paper screening and then

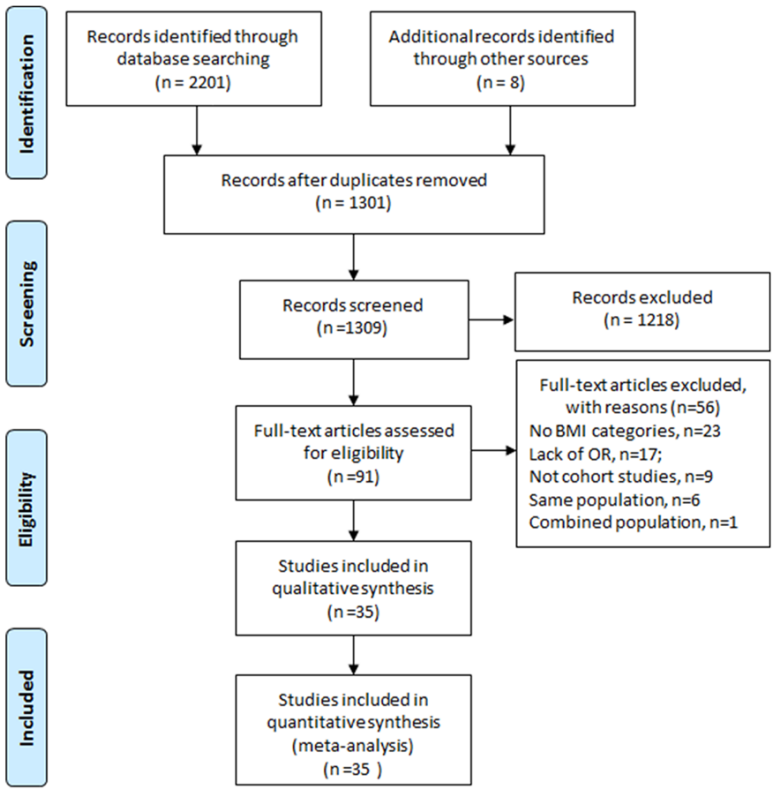

Figure 1. Flow chart of study selection.

were extracted independently by two researchers (ZW and YT) and the following information was collected: (a) general characteristics of study, including study design, geographical location of study, sample size; (b) BMI assessment and categorization, (c) odds ratio (OR) and data to calculate unadjusted estimates of odds ratio with the confidence interval (CI), if available, (d) factors controlled by study design or confounders adjusted for odds ratio. Disagreements at any stages between the two researchers were resolved by consensus or with other reviewers if agreement could not be reached.

Quality assessment

The quality of each included study was evaluated using the Newcastle-Ottawa Scale [15] by two reviewers (XH and YT) independently. The quality score was calculated based on 3 major components of cohort studies: quality of selection (0-4 stars), comparability (0-2 stars), exposure and outcome of study participants (0-3 stars). A higher score represents better methodological quality. According to the star achieved (maximum of 9), studies were classified as high (> 7), medium (6-7) or low quality (< 6).

Statistical analysis

Odds ratio (OR), either adjusted or unadjusted, was used as a common measure for the association between BMI and the risk of preeclampsia in our review. Normal weight BMI was set as reference group. The unadjusted OR with 95% CI for preeclampsia was recalculated if not presented in the papers. The combined OR for each BMI category, namely underweight, overweight and obese, was calculated and obese OR values were pooled if the primary articles provided more than one category of obese.

The method described by Loic Desquilbet [16] was used to calculated the trend from correlated estimates for risk of preeclampsia across categories of BMI. Due to distinct cut-off point for categories in different articles, the mean BMI in each category was used as the corresponding dose. For the open-ended upper and lower categories, the midpoint of the category was set at 1.2 times the lower or higher boundary.

We evaluated a potential curve linear association between BMI and prevalence of preeclampsia using restricted cubic splines (RCS) with 3, 4 and 5 knots at different percentiles of distribution. A *p*-value for curve linearity or non linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

The heterogeneity across studies was estimated by the Q test and quantified by the I^2 statistic [17]. I^2 values of 25%, 50% and 75% were considered low, moderate and high heterogeneity, respectively. We used a random-effects model to calculate the combined risk estimates when heterogeneity was significant; otherwise, a fixed-effects model was applied.

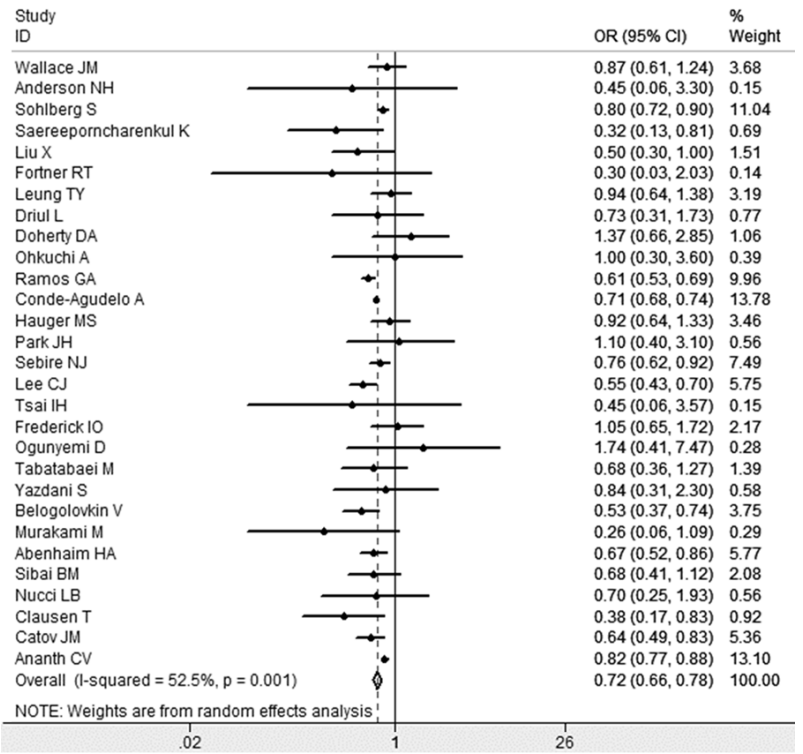

Figure 2. Forest plot for meta-analysis of the association between prepragnancy underweight BMI category and risk of preeclampsia with random effects model.

Sensitivity analysis was conducted to estimate the variation of the combined OR of different inclusion/exclusion criteria on the overall risk estimate, and also to explore possible explanations for heterogeneity due to inconsistent confounding factors across studies including maternal age, parity, multi-fetal pregnancy and pre-exist chronic diseases. Subgroup analysis was also performed based on region, source of BMI and study design for potential sources of heterogeneity.

Publication bias was assessed by funnel plots and the Begg rank correlation test. Egger linear regression test were also performed to quantify the potential publication bias.

Dose response association by RCS function was conducted in SAS9.2. All other analyses were performed in STATA version 12.0 (Stata Corp LP, College Station, Texas). A p value < 0.05 was considered statistically significant, except where otherwise specified.

Result

Literature search

A total of 1309 citations from the PubMed and reference lists were identified, and 1218 were excluded due to review, commentary, letter articles or not relevant to our topic based on abstracts screening. 49 out of 81 remaining studies were further excluded after full-text evaluation due to lacking of BMI category (23 articles) or ORs (17 articles), or not cohort studies (9 articles). 7 studies used the same population and only one with more population and better study design was included. Additionally, two articles [18, 19] were considered as one study because they were performed by the same author using the same population to explain the risk of preeclampsia in different BMI categories. Finally, 35 cohort studies [13, 18-52] (36 articles, 11 prospective and 25 retrospective, Table S1) were included in our meta-analysis. A flow chart showing the study selection was presented in **Figure 1**.

Study characteristics and quality assessment

The included studies were published between 1998 and 2012. Studies were performed in 5 regions: 11 in Asia, 10 in North America, 8 in Europe, 3 in Australia/Oceania and 3 in South America. The study period ranged from half a year to 30 years. A total of 2 079 586 pregnant women were included with the sample sizes of studies ranging from 582 to 878 680, of which 4.47% developed into preeclampsia. The BMI categories varied across studies, with most commonly used standard World Health Organization (WHO) criteria (underweight: < 18.5, normal: 18.5-24.9, overweight: ≥ 25, obesity: ≥ 30) [53]. 24 studies reported OR of underweight and overweight, and 23 studies reported OR of obese categories.

Among the varied confounding factors, 14 studies adjusted for maternal age, 17 for parity, and 25 adjusted for multi-fetal pregnancy. Moreover, 15 studies excluded participants with pre-existing diabetes, and 16 excluded chronic hypertension patients.

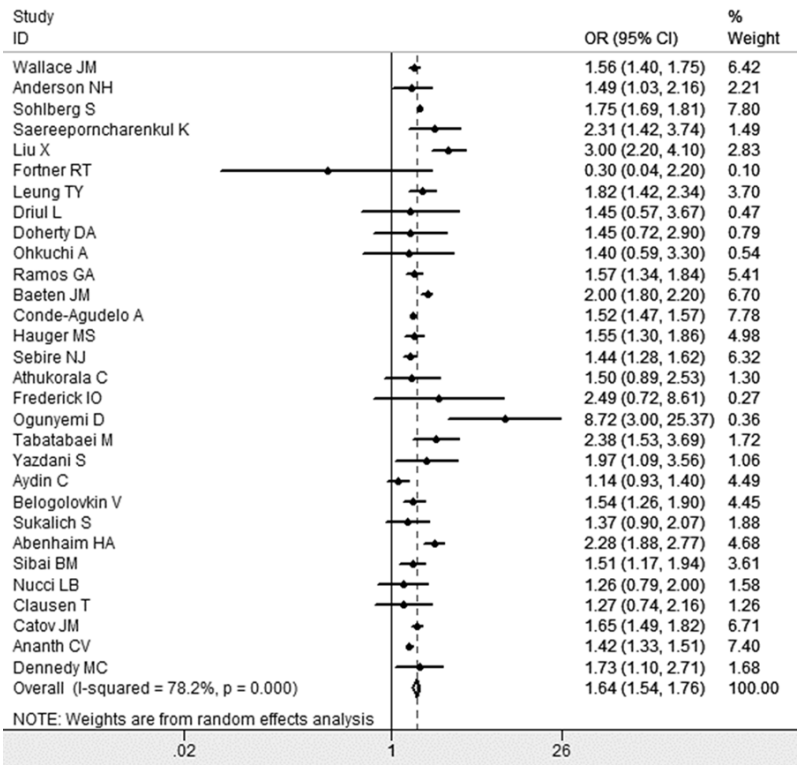

Figure 3. Forest plot for meta-analysis of the association between prepragnancy overweight BMI category and risk of preeclampsia with random effects model.

Quality assessments indicated that 16 studies were high quality, 17 were medium, and only 2 studies were low quality (Table S2).

Prepregnancy BMI and risk of preeclampsia

Underweight risk: The combined OR of underweight women for preeclampsia was 0.72 (95% CI: 0.66-0.78) compared with normal BMI group (**Figure 2**). Of the 29 studies which reported data for underweight category (Table S1), only 12 showed that underweight was a protective factor for preeclampsia and the rest were uncertain. The ORs for the association varied from 0.26 to 1.74 across studies. We observed moderate heterogeneity across studies (I^2 = 52.5%).

Overweight and obese risk: Out of 35 included studies, there is 29 and 28 studies present data for preeclampsia risk in overweight and obesity, respectively (Table S1). Compared to the women with normal BMI, the pooled OR for the overweight and obese women was 1.64 (95% CI: 1.54-1.76, I^2 = 78.2%, **Figure 3**) and 2.86 (95% CI: 2.56-3.19, I^2 = 91.5%), respectively (**Figure 4**).

Dose-response analysis

The restricted cubic spline (RCS) model that included all studies on prepregnancy BMI indicated a linear relation between risk of preeclampsia and prepregnancy BMI (p for Overall association < 0.0001; p for Nonlinear association > 0.05, **Figure 5A**). The linear association was stable after controlling for co-variables or stratifying by study design (data no shown).

Furthermore, we performed the dose-response analysis based on 107 BMI categories from the 28 studies (8 prospective cohorts and 20 retrospective cohorts) that provided raw data for prevalence of preeclampsia, and found a curve linear association between BMI and risk of preeclampsia (p < 0.0001 for overall association and p > 0.05 for non linearity) using 3 knots RCS function (smallest AIC value). The combined prevalence of preeclampsia for an increment of one unit of BMI was 0.432% (95% CI: 0.224-0.640) (**Figure 5B**).

Sensitivity analysis

Sensitivity and subgroup analyses were performed to explore the potential sources of heterogeneity and results were summarized in **Table 1**. First, we omitted one study at a time to evaluate whether any single study could materially alter the overall combined OR. The results showed that the combined OR are stable (underweight: range from 0.70 [95% CI 0.65-0.76] to 0.73 [95% CI 0.67-0.79], overweight: range from 1.62 [95% CI 1.52-1.73] to 1.67 [95% CI 1.57-1.78], obesity: range from 2.77 [95% CI 2.48-3.10] to 2.94 [95% CI 2.63-3.30]).

Analyses were also performed by changing the inclusion/exclusion criteria. Analyses of 14 studies that adjusted for maternal age only did not change the overall OR. Similar results were

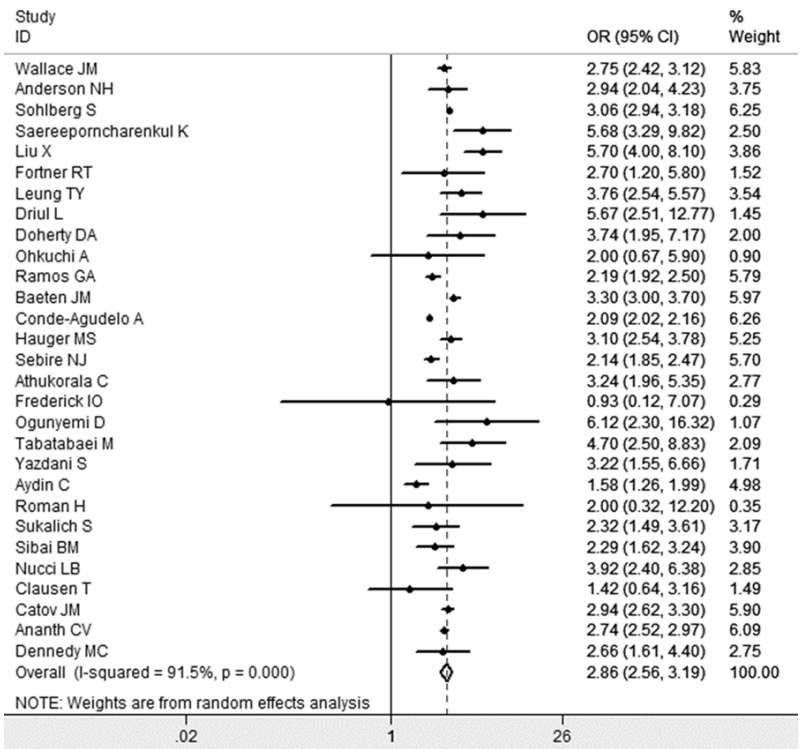

Figure 4. Forest plot for meta-analysis of the association between prepragnancy obese BMI category and risk of preeclampsia with random effects model.

also observed in 17 studies adjusted for parity and 25 studies controlling for multi-fetal pregnancy. When 15 studies that excluded patients with pre-exist diabetes or 16 studies with pre-existing hypertension participants were excluded, the OR for preeclampsia also changed slightly (**Table 1**).

Subgroup analysis

We also conducted subgroup analysis based on study design, study region and the source of BMI (**Table 1**). The evidence of heterogeneity disappeared in prospective cohorts but still remained significantly higher in retrospective ones. Neither study region nor source of BMI could explain the heterogeneity. Meta-regression analyses according to study period, quality of studies and sample size did not find the source of heterogeneity (data not shown), either.

Publication bias

We did not identify substantial asymmetry by visual inspection of the funnel plot. Also no evidence of publication bias (underweight: p = 0.582, overweight: p = 0.716, obesity: p = 0.199) was observed via Begg rank (Figure S1) and confirmed by Egger linear regression (Figure S2).

Discussion

Main findings

Our meta-analysis provides strong evidence that maternal prepregnancy BMI is significantly and independently associated with the risk of developing preeclampsia during pregnancy. Women with prepregnancy underweight had lower risk of preeclampsia, while overweight and obese women had a substantially increased risk of preeclampsia when compared with normal BMI women.

Despite the worldwide obesity epidemic, at the other end of the BMI spectrum, prepregnancy underweight is also common in both developed and developing countries. For instance, a public health survey in Scania, a third largest city in Sweden, reported [54] a 17.5% of young women aged 18-34 years had a BMI below 20.0 kg/m^2, 13.3% of women in Chile [55] had a BMI < 21 kg/m^2, and 9.0% of women in China are underweight at the first antenatal visit according to the WHO criteria [53]. Currently, the data are limited and controversial on the effect of maternal underweight in preeclampsia. Previous studies suggested that underweight may be protective factor against this disorder [13, 36, 43, 49], others did not find a significant decrease [46-48, 50]. Although our meta-analysis suggest that underweight women had lower risk of preeclampsia, women with lower BMI were also observed to have a higher incidence of preterm birth (PTB) and low birth weight (LBW). LBW is the leading cause of infant morbidity and mortality, also a potential risk for subsequent development of various complications in adulthood [4]. Therefore, our findings should be put in perspective when applied in clinic management. In addition to gestational age and environmental influence, genetic factor also plays an important role in

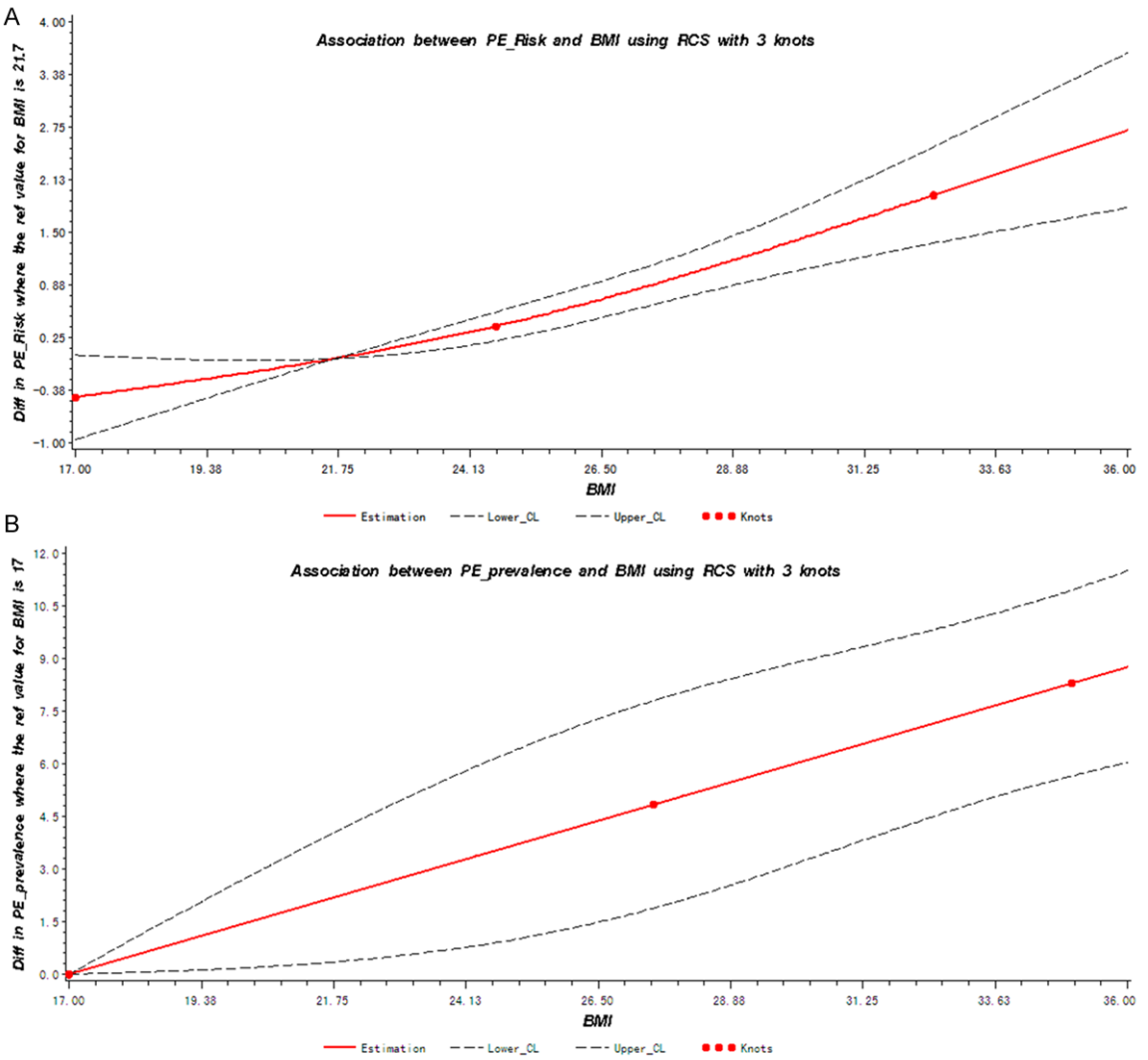

Figure 5. Dose-response association between prepregnancy BMI and preeclampsia. A: A linear dose-response relation between OR from all included studies and prepregnancy BMI, Y-axis represents the difference of risk preeclampsia compared to reference group of BMI 21.7, dash lines are 95% percent confidence intervals. Knots are represented by red dots and 3 knots located at the 10th, 50th, 90th percentiles; B: Dose-response association between preprgnancy BMI and the prevalence of preeclampsia with 3 knots located at the 10th, 50th, 90th percentiles. Y-axis represents the difference of prevalence compared to the reference group of prepregnancy BMI 17. Dash lines are 95% percent confidence intervals.

fetal growth. Fetal size is significantly influenced by maternal size [56]. Ponderal index (PI = weight x 100/length, g/cm^3), which takes both fetus length and weight into account, could be more accurate to distinguish "growth restricted" LBW infants from normal constitutively small [57].

On the other hand, lack of nutrients such as iron deficiency, not underweight itself, might underlie the association between maternal underweight and LBW. A recent meta-analysis revealed a significantly higher risk of LBW and PTW with anemia in the first or second trimester, and daily prenatal use of iron substantially improved birth weight in a linear dose response fashion [58]. Moreover, lower social-economic status, imbalance diet, smoking, and medical conditions, may act as confounding factors rather than underweight itself, predispose underweight women to preterm delivery and LBW. Unfortunately, in our systematic review, no specific information on social class was available except one study with relative small

Table 1. Stratified analyses for risk of preeclampsia and prepregnancy BMI

Control variable of sensitivity analysis		Underweight OR (95% CI)	I-squared (%)	*P* value	Overweight OR (95% CI)	I-squared (%)	*P* value	Re-Obese 1 OR (95% CI)	I-squared (%)	*P* value
Age (n = 14)		0.74 (0.61-0.89)	40.7	0.086	1.79 (1.51-2.08)	77.3	0.000	2.99 (2.41-3.72)	77.6	0.000
Parity (n = 17)		0.75 (0.69-0.81)	28.1	0.162	1.75 (1.60-1.92)	71.1	0.000	3.04 (2.73-3.38)	69.0	0.000
Singleton (n = 25)		0.75 (0.68-0.83)	42.3	0.024	1.63 (1.50-1.77)	77.5	0.000	2.83 (2.57-3.12)	79.4	0.000
Diabetes (n = 15)		0.71 (0.63-0.80)	16.4	0.283	1.71 (1.47-2.00)	79.4	0.000	2.87 (2.28-3.61)	84.9	0.000
Hypertension (n = 16)		0.75 (0.69-0.81)	22.6	0.215	1.68 (1.51-1.86)	76.2	0.000	2.93 (2.56-3.36)	82.5	0.000
Subgroup analyses										
Study Region	North America (n = 10)	0.70 (0.58-0.85)	73.10	0.000	1.71 (1.45-2.03)	84.9	0.000	2.66 (2.25-3.14)	75.2	0.000
	South America (n = 3)	0.71 (0.68-0.74)	0	0.370	1.52 (1.47-1.57)	0	0.715	2.79 (1.94-4.02)	90.4	0.000
	Australia/Oceania (n = 3)				1.49 (1.12-1.96)	0	0.997	3.15 (2.41-4.12)	0	0.810
	Europe (n = 8)	0.77 (0.71-0.84)	18.8	0.291	1.61 (1.49-1.74)	57.5	0.028	2.72 (2.38-3.11)	76.0	0.000
	Asia (n = 11)	0.63 (0.53-0.75)	21.4	0.247	1.93 (1.40-2.66)	81.2	0.000	3.51 (2.11-5.83)	88.3	0.000
Study Design	Prospective (n = 11)	0.80 (0.76-0.85)	44.0	0.065	1.49 (1.42-1.56)	8.8	0.361	2.81 (2.65-2.99)	0.7	0.432
	Retrospective (n = 24)	0.71 (0.65-0.77)	39.6	0.039	1.73 (1.58-1.88)	83.2	0.000	2.94 (2.54-3.41)	94.1	0.000
Source of BMI	measured (n = 10)	0.74 (0.60-0.90)	36.2	0.129	1.73 (1.43-2.09)	64.6	0.006	3.33 (2.61-4.25)	72.1	0.001
	self-reported (n = 16)	0.72 (0.69-0.75)	28.0	0.170	1.77 (1.61-1.95)	82.6	0.000	3.01 (2.52-3.60)	94.9	0.000

n: number of included studies.

sample size in Korea [44]. Out of 29 studied with underweight category, only 7 have taken smoking as a confounding factor. Furthermore, none of the studies distinguished the underweight women by their health status. LBW in many studies did not adjust for gestational age or stratify by term and preterm delivery. Therefore, the included original studies can not determine if LBW infants who were born to underweight women were appropriately grown or growth restricted.

Although the OR varied across included studies, overweight or obesity is a definite risk for preeclampsia in our meta-analysis. Obesity has a strong link with insulin resistance, and also is a risk factor for type II diabetes. Previous studies showed that preeclampsia and raised BMI occur both in glucose tolerant mothers and women with diabetes [59, 60]. Moreover, tight glucose control in women with gestational diabetes mellitus (GDM) reduces the risk of preeclampsia [61, 62]. However, the precise mechanism directly linking diabetes or insulin resistance with preeclampsia is still unknown. Our sensitivity analysis restricted to studies controlled for patients with diabetes revealed slightly changed in combined OR. Therefore, whether diabetes does play a crucial role in the association between maternal BMI and the development of preeclampsia needs further investigations.

Strengths and limitations

The major strength of our study is that all the included studies used a cohort design, which minimized the possibility of selection bias. Another strong point is that a single measure of obesity (BMI) was used as a defined exposure for identifying risk of preeclampsia. Instead of using the mixture of multiple obesity measurement such as waist hip rate or skinfold measurement, single measure better standardized the variation among studies. In addition, BMI is virtually free of cost, non-invasive, and ubiquitously available. Self-reported prepregnancy BMI is a reliable indicator of obesity and has been validated in previous publications [63]. Third, the diversity of included studies, which were conducted in Asia, North America, Europe, Australia/Oceania and South America, represents most of the global regions. Finally, our meta-analysis is based on 4 BMI categories, making it possible to examine a dose-response relationship between prepregnancy BMI and the development of preeclampsia.

One potential limitation is the substantial heterogeneity. Although restricting analysis by changing the inclusion/exclusion criteria was able to detect the possible source of heterogeneity, we still cannot eliminate the possibility of residual confounding on the results. Moreover, we used both the adjusted and unadjusted ORs as the indicator to estimate the risk, uncontrolled or unmeasured risk factors including smoking, social-economic status, gestational weight gain may also produce bias. However, the crude odds ratio didn't change significantly after adjusting for possible confounders (e.g. age, parity, history of hypertension and smoking) [38]. Also, maternal smoking may also be associated with pregnancy complications such as preterm delivery and intrauterine growth restriction, but Sebire NJ found that when including smoking as an additional confounding factor in the logistic regression model, the increased prevalence of low birth weight reported in women with low BMI is truly due to factors directly related to BMI rather than other known confounders [19].

A second limitation is that the included studies used different categorizations of BMI and different criteria for preeclampsia diagnosis. This lack of consensus in exposure and outcome of the participants posed a potential bias. In addition, although little evidence of publication bias was observed, the statistical power for the obese category test was limited due to a single database being used and all the included studies were limited to English.

Interpretation

Based on our findings, a dose-response relationship between maternal BMI and the risk of developing preeclampsia is established. Meads et al proposed 27 tests to predict which gravida were likely to develop preeclampsia [64], and found a BMI of 34 kg/m^2 or higher was one of three that reached specificities above 90%. Furthermore, among the major risk factors for developing preeclampsia, maternal BMI is the one which is possibly modifiable. A meta-analysis of 44 RCTs showed that weight management, especially dietary interventions during pregnancy resulted in a significant reduction in the risk of preeclampsia [65]. Hence, over-

weight or obese women who plan to get pregnant should be counseled about their risk from being obese and encouraged to reduce their body weight via dietary planning and physical activity.

The significant role of maternal prepregnancy underweight in reducing the risk of developing preeclampsia had raised concerns regarding the fetal birth weight. Despite widely disputed in the literature, fetal growth is more likely determined by maternal adequate energy intake and weight gain during gestation rather than prepregnancy underweight. The evidence is that the unfavorable effect of maternal low prepregnancy BMI on fetal growth is compensated by optimal maternal gestational weight gain [66-68]. It should be noted that one study revealed that optimal gestational weight gain significantly reduce, but cannot abolish the unfavorable association of maternal underweight and fetal growth [69]. Although more population studies in fetal growth and development influenced by maternal underweight are required to clarify the contributions of potential confounding factors, women with low pregestational BMI should achieve gestational weight gain of 12.5-18 kg based on the institute of medicine (IOM) recommendations to reduce adverse effect [69].

Conclusions

Our findings revealed that prepregnancy underweight may be a protective factor of preeclampsia, while overweight and obesity increased the risk of developing preeclampsia compared with normal BMI women. Prepregnancy and pregnancy periods provide a unique window of opportunity for health promotion, and targeting weight management among women in fertile age is of the most importance for clinical practice and population health.

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Disclosure of conflict of interest

None.

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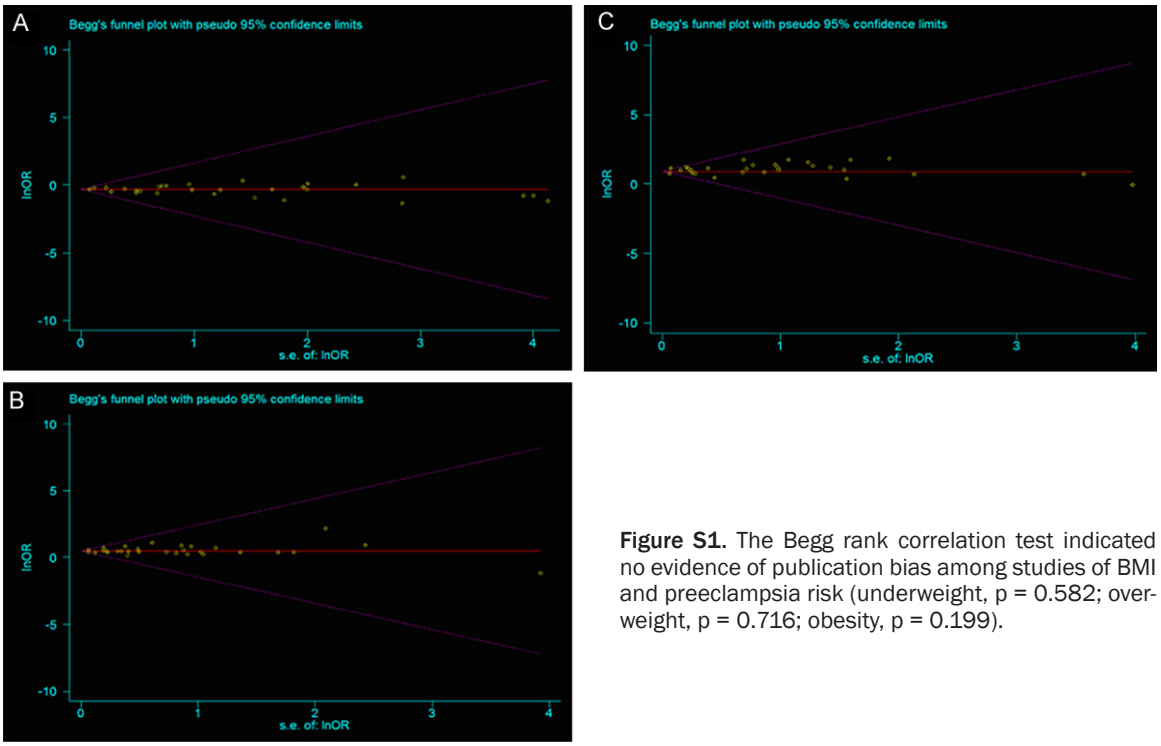

Figure S1. The Begg rank correlation test indicated no evidence of publication bias among studies of BMI and preeclampsia risk (underweight, p = 0.582; overweight, p = 0.716; obesity, p = 0.199).

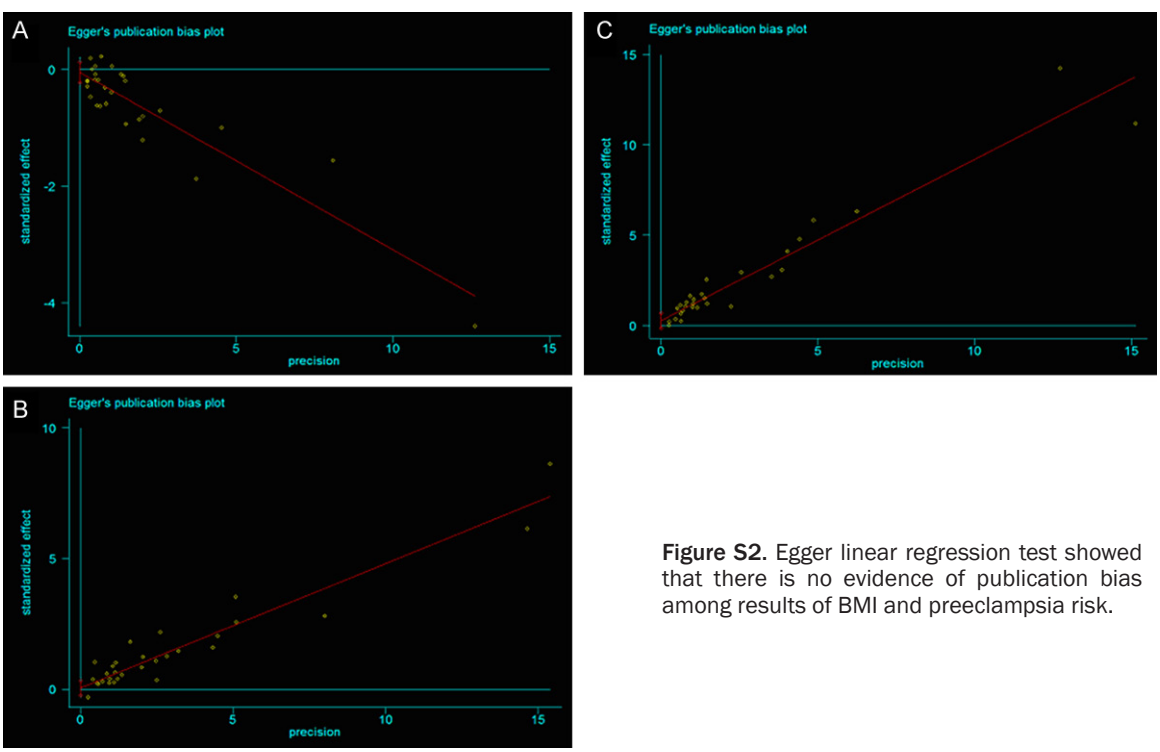

Figure S2. Egger linear regression test showed that there is no evidence of publication bias among results of BMI and preeclampsia risk.

Table S1. Characteristics of included studies for the association between prepregnancy BMI and risk of preeclampsia

Citation	Study Design	Study Location	Study period	Sample size	Preeclampsia prevalence	Study Quality	Source of BMI	Factors adjusted in multivariate analysis	Factors controlled for study design	BMI categories				
										Under-weight	Normal weight	Over-weight	Obese	
Sibai BM (1997) [17]	Prospective	America	1992-1996	4310	7.56%	7	NI			< 19.8	19.8-26	26-35	≥35.0	
Ogunyemi D (1998) [18]	Retrospective	America	1990-1995	582	7.90%	5	self-reported			< 19.8	19.8-26	26.1-29	>29	
Conde-Agudelo A (2000) [19]	Retrospective	Latin America and the Caribbean	1985-1997	878680	5.13%	8	self-reported		≥ 20 W of gestation or at least 500 g birth weight	< 19.8	19.8-26.0	26.1-29.0	>29.0	
Lee CJ (2000) [20]	Retrospective	Taiwan	1990.7-1998.12	27629	1.23%	8	NI		Excluded women with chronic hypertension and fetal malformations.	< 19.8	19.8-24.2			
Sebire NJ (2001) [21, 22]	Retrospective	UK	1989-1997	287213	0.82%	8	NI	Maternal age, Ethnic group, Parity, history of hypertension, gestational diabetes, pre-existing diabetes, smoking	Singleton		20-24.9	25.0-29.9	≥ 30.0	
Nucci LB (2001) [23]	Prospective	Brazil	1991-1995	5314	NI	6	measured			< 18.5	18.5-24.9	25-29.9	≥30.0	
Baeten JM (2001) [24]	Retrospective	America	1992-1996	96384	6.76%	7	self-reported	Maternal age, smoking, education, marital status, trimester prenatal care began, payer of prenatal care, and gestational weight	Nulliparous; Singleton; Excluded women with hypertensive or diabetic conditions	< 20.0	20.0-24.9	25.0-29.9	≥ 30.0	
Murakami M (2005) [25]	Retrospective	Japan	2001-2001	583	NI	8	measured	Maternal age, Parity, smoking, gestational weight gain, gestational weeks		< 18.5	18.5-25			
Ramos GA (2005) [26]	Retrospective	America	1981-2001	22658	8.33%	8	NI		Singleton, Excluded multiple gestations and fetal anomalies.	< 19.8	19.8-26	26.1-29	>29.0	
Frederick IO (2006) [27]	Prospective	America	1996.12-2002.9	1644	4.32%	7	self-reported		Maternal Age above 18; ≥ 28 W of gestation; Excluded abortion, pre-gestational diabetes, chronic or essential hypertension	< 19.8	19.8-26	26.1-29	>29.0	
Ohkuchi A (2006) [28]	Retrospective	Japan	1996.1-1999.12	1518	2.50%	6	measured	Blood pressure level in second trimester	Singleton, ≥ 22 W of gestation	< 18.5	18.5-24.9	25.0-29.9	≥ 30.0	
Sukalich S (2006) [29]	Retrospective	America	1998-2003	4822	2.90%	7	self-reported		Maternal age > 19; ≥ 23 W of gestation		18.5-24.9	25-29.9	30-34.9	≥35

Clausen T (2006) [30]	Prospective	Norway	1995-1997	3523	2.64%	8	measured		Excluded women with type 1 diabetes, abortion, multiple pregnancies	≤ 20	20-25	25.1-30	> 30.0
Doherty DA (2006) [31]	Retrospective	Australia	NI	2827	NI	8	self-reported	Maternal age and Parity	Singleton	< 18.5	18.5-24.9	25.0-29.9	≥ 30.0
Abenhaim HA (2007) [32]	Retrospective	Canada	1987.4-1997.3	17392	NI	6	self-reported	Maternal age, Parity, smoking and diabetes		< 20	20-24.9	25-29.9	
Roman H (2007) [33]	Retrospective	France	2001.1-2005.6	4162	2.14%	4	self-reported	In utero fetal death	Singleton; ≥ 22 W of gestation; control group was age and parity-matched		18.5-25		> 30.0
Belogolovkin V (2007) [34]	Prospective	America	1999-2002	29268	NI	8	NI	Maternal age, Race, Parity, ART; gestational diabetes, pre-gestational diabetes, cocaine use and smoking		< 19.8	19.8-26	26.1-29	
Catov JM (2007) [35]	Prospective	Denmark	1997-2003	42066	5.85%	7	self-reported		Singleton; Primiparous; < 20 W of gestation; Excluded women with chronic hypertension or renal disease	< 18.5	18.5-24.9	25-29.9	> 30.0
Driul L (2008) [36]	Retrospective	Italy	2006.1-2006.8	916	4.91%	7	NI		Singleton; Excluded women with chronic hypertension, history of preterm < 37 W, history of neonatal death, diabetes and gestational diabetes	< 18.5	18.5-24.9	25.0-29.9	≥ 30.0
Hauger MS (2008) [37]	Prospective	Argentina	2003-2006	62346	2.02%	7	measured	Maternal age, Parity, history of hypertension and smoking	≥ 22 W of gestation or birth weight higher than 500 grams; Excluded fetuses with congenital malformation and multiplets	< 18.5	18.5-24.9	25.0-29.9	≥ 30.0
Leung TY (2008) [38]	Retrospective	China	1995-2005	29303	1.37%	8	self-reported		Singleton; ≤ 24 W of gestation.	< 18.5	18.5-24.9	25.0-29.9	≥ 30.0
Fortner RT (2009) [39]	Prospective	America	2000-2004	1024	2.93%	7	self-reported	Maternal age and Parity	Excluded women with multiple gestation, preexisting diabetes, hypertension, heart disease, chronic renal disease or glucose tolerance; 16 ≤ women age ≤ 40	< 19.8	19.9-26.0	26.1-29.0	> 29.0

Aydin C (2010) [40]	Retrospective	Turkey	2000.1-2005.12	9112	6.29%	6	NI		Singleton, Excluded women with systemic diseases (type 1 diabetes mellitus, chronic hypertension, renal insufficiency, etc).		20-25	25-30	> 30.0	
Athukorala C (2010) [41]	Retrospective	Australia	2001.12-2005.1	1661	5.54%	8	self-reported		Nulliparous; Singleton, Women with normotensive at the first measurement		18.5-24.9	25.0-29.9	≥ 30	
Liu X (2011) [42]	Retrospective	China	2007-2009	5047	4.74%	6	measured	Maternal age, education, and gestational weight gain	Singleton; Nulliparous; Excluded women with the history of hypertension and diabetes.	< 18.5	18.5-23.9	24.0-27.9	≥ 28.0	
Park JH (2011) [43]	Retrospective	Korea	2005-2007	1697	2.53%	8	measured	Maternal age, Parity, Gestational age, Weight gain, Occupation and Education; Husband's education, economic status.	Singleton, Excluded women with history of hypertension or diabetes, fetus with a known congenital anomaly, stillbirth, and previous cesarean section	< 18.5	18.5-22.9			
Saereeporncharenkul K (2011) [44]	Retrospective	Thailand	2009.1-2009.12	3715	2.83%	7	measured			< 18.5	18.5-24.9	25.0-29.9	≥ 30.0	
Tabatabaei M (2011) [45]	Retrospective	Iran	2007.1-2010.1	5172	5.61%	6	self-reported	Gestational diabetes	Excluded women with multiple gestation, with history of hypertension, diabetes, heart disease, hepatitis, chronic renal disease, or other systemic disease; pregnancy terminated for fetal malformations	< 19.8	19.8-26	26.1-29	> 29	
Ananth CV (2011) [13]	Prospective	America	1959-1965	43519	20.18%	8	NI		Singleton, ≥ 20 W of gestation; Excluded women with placenta previa.	< 19.8	19.8-24.9	25.0-29.9	30.0-34.9	≥ 35.0
Tsai IH (2012) [46]	Retrospective	Taiwan	2007.4-2007.6	726	NI	7	self-reported		Excluded stillbirth and multiple pregnancies.	< 18.5	18.5-24.0			
Yazdani S (2012) [47]	Retrospective	Iran	2008-2009	1000	6.90%	7	NI		Primiparous; Singleton, ≥ 38 W of gestation	≤ 19.9	20-24.9	25-29.9	30-34.9	> 35
Sohlberg S (2012) [48]	Retrospective	Sweden	1992-2006	421842	4.78%	8	self-reported		Primiparous; Singleton; ≥ 22 W of gestation; Excluded women with gestational hypertension	< 18.5	18.5-24.9	25.0-29.9	30.0-34.9	≥ 35.0

Wallace JM (2012) [49]	Retrospective	UK	1976-2007	55105	3.12%	8	measured		Singleton; ≥ 24 W of gestation; Excluded women with the lowest 0.5% of placental weight	< 18.5	18.5-24.9	25.0-29.9	30.0-34.9	≥ 35.0
Dennedy MC (2012) [50]	Prospective	Ireland	2006-2009	3656	NI	8	measured	Maternal age, parity, smoking, and ethnicity	Singleton; Euthyroid women with normal glucose tolerance		18.5-25	25-29.9	> 30	
Anderson NH (2012) [51]	Prospective	New Zealand, Australia	2004.11-2008.10	3170	5.62%	8	self-reported		Nulliparous; Singleton; Excluded high risk women with chronic hypertension, diabetes, gynecological history or received interventions	ethnicity-specific				

NI: no information; W: week;

Table S2. Quality assessment of included studies

First Author (year of publication) (reference)	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor	Control for additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Score
Sibai BM (1997) [17]	a	a	d	b	a	b	a	a	a	7
Ogunyemi D (1998) [18]	c	a	c	b	a		b	a	a	
Conde-Agudelo A (2000) [19, 23]	a	a	a	b	a	b	a	a	a	8
Lee CJ (2000) [20]	b	a	a	b	a	b	b	a	a	8
Sebire NJ (2001) [21, 22]	a	a	a	b	a	b	b	a	a	8
Nucci LB (2001) [23]	a	a	a	b	a		a	a	a	6
Baeten JM (2001) [24]	a	a	c	b	a	b	b	a	a	7
Murakami M (2005) [25]	b	a	a	b	a	b	b	a	a	8
Ramos GA (2005) [26]	b	a	a	b	a	b	a	a	a	8
Frederick IO (2006) [27]	b	a	c	b	a	b	b	a	a	7
Ohkuchi A (2006) [28]	b	a	d	b	a		b	a	a	6
Sukalich S (2006) [29]	a	a	c	b	a	b	b	a	a	7
Clausen T (2006) [30]	a	a	a	b	a	b	b	a	b	8
Doherty DA (2006) [31]	b	a	a	b	a	b	b	a	a	8
Abenhaim HA (2007) [32]	b	a	c	b	a	b	d	a	a	6

Roman H (2007) [33]	c	b	c	b	a	b	a	a	d	4
Belogolovkin V (2007) [34]	a	a	a	b	a	b	b	a	a	8
Catoy JM (2007) [35]	a	a	c	b	a	b	a	a	a	7
Driul L (2008) [36]	b	a	a	b	a	b	d	a	a	7
Hauger MS (2008) [37]	a	a	c	b	a	b	b	a	a	7
Leung TY (2008) [38]	a	a	a	b	a	b	b	a	a	8
Fortner RT (2009) [39]	a	a	c	b	a	b	b	a	a	7
Aydin C (2010) [40]	b	a	a	b	a		d	a	a	6
Athukorala C (2010) [41]	b	a	a	b	a	b	b	a	a	8
Liu X (2011) [42]	b	a	d	b	a	b	d	a	a	6
Park JH (2011) [43]	b	a	a	b	a	b	b	a	a	8
Saereeporncharenkul K (2011) [44]	b	a	a	b	a		b	a	a	7
Tabatabaei M (2011) [45]	a	a	c	b	a	b	c	a	a	6
Ananth CV (2011) [13]	a	a	a	b	a	b	a	a	a	8
Tsai IH (2012) [46]	b	a	c	b	a	b	a	a	a	7
Yazdani S (2012) [47]	b	a	a	b	a	b	d	a	a	7
Sohlberg S (2012) [48]	b	a	a	b	a	b	b	a	a	8
Wallace JM (2012) [49]	a	a	a	b	a	b	a	a	a	8
Dennedy MC (2012) [24, 50]	a	a	a	b	a	b	a	a	a	8
Anderson NH (2012) [51]	a	a	a	b	a	b	b	a	b	8