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SYSTEMATIC REVIEWS/META-ANALYSIS

Association between Maternal Birth Weight and Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstracts

Background and Aims Gestational diabetes mellitus is one of the most important issue related to health status of mothers and their children throughout life. This meta-analysis has been conducted to assess relationship between maternal birth weight and gestational diabetes.

Methods and Results This article is written using PRISMA guideline for systematic review and meta-analysis. We searched epidemiological studies without a time limit from following databases - Scopus, PubMed, Science Direct, Embase, Web of Science, CINAHL, Cochrane, EBSCO, and Google Scholar search engine using MESH keywords. Heterogeneity was determined using the Cochran Q test and I^2 index. Data were analyzed using comprehensive meta-analysis, version 2. The significance level of the tests was considered as $P < 0.05$.

Results The result of combining ten studies with a sample size of 228,409 cases using a fixed-effect model showed that low maternal birth weight increased the risk of gestational diabetes mellitus (1.71 [95% CI 1.43–2.06, $P < 0.001$]). In addition, the result of combining nine studies with a sample size of 227,805 cases using a random-effects model showed that macrosomia did not increase the risk of gestational diabetes mellitus, and there was no significant relationship between them (1.04 [95% CI 0.79–1.38; p value: 0.730]).

Conclusion The results of this systematic review and meta-analysis showed that low maternal birth weight could be a risk factor for gestational diabetes in adulthood.

Keywords Gestational diabetes · Maternal birth weight · Systematic review · Meta-analysis

Introduction

Appropriate weight for full-term infants is 2.3 to 4.3 kg, but the acceptable range of birth weight is between 2.5 and 4 kg. Therefore, birth weight is the most important factor in determining infant health and growth [1, 2]. Low-birth-weight (LBW) infants are two to three times more likely to suffer from neurological, ophthalmic, hearing complications and mental retardation than normal infants [3, 4]. Animal and epidemiological studies have shown that both LBW and macrosomia are associated with the development of diabetes in adulthood [1, 5–8]. Many studies have investigated the abnormal effects of LBW and maternal macrosomia at birth, some of which were related to gestational diabetes [12–18]. Gestational diabetes mellitus is a state of glucose intolerance and, despite its incompatibility with the body, appears in pregnant women with no history of diabetes. The disease

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usually occurs between 24 and 28 weeks of pregnancy at the same time when placental lactogen is secreted by the placenta, which reduces insulin sensitivity in the mother. The prevalence is 3 to 6% of all pregnancies, 4% on an average. Gestational diabetes can cause serious problems for the mother and fetus, such as weight gain at birth, stillbirth in the last 4 weeks, preterm labor and neonatal respiratory distress syndrome, low blood sugar at birth, and possibility of seizures [9, 10]. Meta-analysis is the combination of data and results from a systematic review using statistical methods. After a systematic review, which is the prerequisite for meta-analysis, and based on the results, we obtain a single estimate for solving the problem or answering the question. One of the important goals of meta-analysis is to find out the inconsistencies of the results and their causes [12, 13, 24]. This study aimed to investigate the possible relationship between maternal birth weight and gestational diabetes.

Methods

Study Protocol

This review article is written using PRISMA Guideline for systematic review and meta-analysis studies [21]. The stages of the study include search strategy, selection of studies, qualitative assessment of studies, and data extraction. All procedures were performed independently by two researchers. The third researcher examined the agreement between the results, and in cases of disagreement, resolved the disagreement.

Search Strategy

We searched for epidemiological studies published till December 23, 2020, in English databases including Scopus, PubMed, Science Direct, Embase, Web of Science, CINAHL, Cochrane, EBSCO, and Google Scholar search engine using MeSH Keywords "pregnancy diabetes" and "low birth weight." Combined searches were performed using the AND and OR functions. An example search in PubMed is given in the following:

1. Exp *birth weight*
2. Exp *low birth weight*
3. Exp *macrosomia birth weight*
4. Exp maternal
5. Exp ***gestational Diabetes Mellitus***
6. Exp pregnancy diabetes.

Study Selection

We screened the studies by reviewing the title and abstract by two reviewers (SHR and MSH). Duplicate studies were eliminated manually or using Endnotes, version 5. We reviewed the full text of articles to evaluate the inclusion and exclusion criteria and did the final selection of articles after quality assessment.

Inclusion and Exclusion Criteria

The studies which qualified for inclusion were epidemiological studies published in English language that examined the association between gestational diabetes and maternal birth weight. Exclusion criteria were: (1) lack of relationship between gestational diabetes mellitus as an outcome and maternal weight loss as maternal exposure; (2) samples other than gestational diabetes mellitus; (3) letters to the editors without original data, review articles, and case reports, and (4) duplicate studies.

Qualitative Assessment

Two independent reviewers (SHR and MSH) included qualified articles in a checklist for qualitative assessment. The Newcastle–Ottawa Scale (NOS) was used for evaluating the quality of nonrandomized studies in the meta-analysis [18]. Based on the scores from the checklist, studies were divided into three categories: low quality (below 6 points), medium quality (between 6 and 8 points), and high quality (between 9 and 10 points).

Data Extraction

Data were independently extracted by two researchers (SHR and MSH), which included the first author's name, year of study, study location, type of study, country, continent, sample size (total, case and control), study outcomes (including LBW and macrosomia), odds ratio or relative risk, and *P* value.

Definitions

Newborns weighing less than 2500 g are known as low birth weight regardless of gestational age [20]. Newborns born weighing more than 4000 g at birth, regardless of gestational age, are known as macrosomia (high birth weight) [20]. Gestational diabetes mellitus is a state of glucose intolerance and, despite its incompatibility with the body, appears in pregnant women with no history of

diabetes. The disease usually occurs between weeks 24 and 28 of pregnancy at the same time when placental lactogen is secreted by the placenta, which reduces insulin sensitivity in the mother [9–11]. In the primary studies used in this meta-analysis, the diagnostic criteria were based on the World Health Organization, the American Diabetes Association, and the International Classification of Disease (ICD-9) [17, 22, 23].

Statistical Analysis

Data were entered into Excel 2016 and then transferred to comprehensive meta-analysis, version 2, for meta-analysis, and the results of the studies were analyzed using this software. Heterogeneity was determined using the Cochran Q test and the I^2 index. There are three classifications in this area (below 25% is considered low heterogeneity, 25–75% is medium heterogeneity, and over 75% is high heterogeneity). The random-effects model was used in medium and high heterogeneity cases, while the fixed-effects model was used in cases of low heterogeneity.

In this study, a fixed-effects model was used to determine the relationship between gestational diabetes and maternal birth weight because of low heterogeneity. A random-effects model was used to determine the relationship between gestational diabetes and maternal weight gain. Sensitivity analysis was also performed. The level of significance was considered 0.05.

Influence Analysis

The robustness of the pooled estimate was evaluated by influence analysis (fixed- and random-effects model). Each study estimate was individually omitted from the dataset, and in each case, recalculation was done for a pooled estimate of the remaining studies. Finally, the OR (odds ratio) and 95% confidence interval were calculated for each study.

Publication Bias and Statistical Software

Publication bias was assessed by inspecting the funnel plot, and formal testing for funnel plot asymmetry was done using Begg's test and Egger's test.

Results

Search Results and Characteristics of Studies

In this meta-analysis, 520 articles were identified based on primary search, and 248 duplicate articles were removed. After reviewing the abstracts, 210 articles were removed

Table 1 Summary of the included studies

First author, publication years (reference)	Type of study/type of time	Country/continent	Years of follow	Sample size	RR (95% CI) for low birth weight (< 2500 gr)	RR (95%CI) for microsomal (> 4000 gr)
Ogonowsk, 2014 [12]	Cohort retrospective	Poland/Europe	2000–2007	1588	1.59 (95% CI 1.03–2.46)	0.92 (95% CI 0.59–1.42)
Seghieri, 2002 [13]	Cohort retrospective	Italy/Europe	–	604	1.89 (95% CI 1.09–3.28)	–
Zhu, 2017 [14]	Cohort retrospective	Beijing/Asia	2013	15,194	0.65 (95% CI 0.30–1.43)	0.331 (95% CI 0.16–0.333)
Innes, 2002 [15]	Case–control/retrospective	New York/USA	2000–2010	23,395	2.16 (95% CI 1.04–4.50)	1.53 (95% CI 1.03–2.27)
Savona, 2003 [16]	Cohort/prospective	Malta/Europe	1996–2001	7075	1.40 (95% CI 0.79–2.49)	0.93 (95% CI 0.56–1.52)*
Williams, 1999 [17]	Cohort retrospective	Washington/USA	1987–1995	21,528	2.05 (95% CI 1.35–3.15)	0.90 (95% CI 0.70–1.30)
Williams, 1999 [17]	Cohort retrospective	Washington/USA	1987–1995	6359	1.75 (95% CI; 0.85–3.45)	2.20 (95% CI 1.10–4.60)
Williams, 1999 [17]	Cohort retrospective	Washington/USA	1987–1995	7456	2.15 (95% CI 0.95–4.90)	0.90 (95% CI 0.50–1.60)
Williams, 1999 [17]	Cohort retrospective	Washington/USA	1987–1995	6496	2.10 (95% CI 0.95–4.50)	1.10 (95% CI 0.60–2)
Egeland, 2000 [18]	Cohort retrospective	Norway/Europe	1988–1998	138,714	1.80 (95% CI 1.10–3)	1.50 (95% CI 0.80–2.90)

*It was calculated based on the number of exposures and the total number in both groups

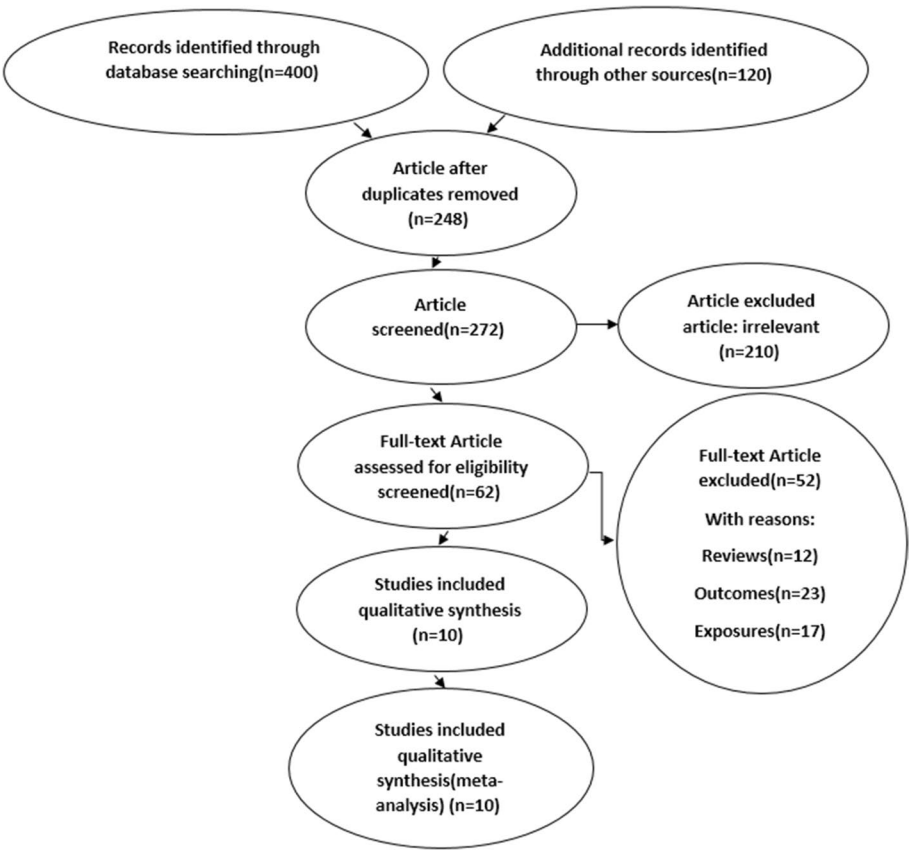

Fig. 1 Flowchart of study selection

for being irrelevant. After thoroughly reviewing the remaining 62 articles were evaluated for their quality, ten articles entered the meta-analysis process (Table 1 and Fig. 1).

Relationship Between Gestational Diabetes, Maternal LBW and Macrosomia

The results of combining ten studies with a sample size of 228409 using a fixed-effects model showed that maternal LBW increased the risk of gestational diabetes mellitus (1.71 [95% CI 1.43–2.06, $P < 0.001$]) (Fig. 2A).

In addition, the results of combining nine studies with a sample size of 227,805 using a random-effects model showed that maternal macrosomia did not increase the risk of gestational diabetes mellitus, and there was no significant relationship between them (1.04 [95% CI 0.79–1.38; p value: 0.730]) (Fig. 2B).

Subgroup Analysis of the Relationship between Gestational Diabetes and Maternal Birth Weight:

Based on Type of Study

In eight cohort studies and one case–control study, RR and 95% CI of the correlation between gestational diabetes and maternal macrosomia were 0.98 (95% CI 0.74–1.32; $p = 0.94$) and 1.53 (95% CI 1.03–2.27; $p = 0.35$), respectively, and no significant difference was observed ($p = 0.080$).

Based on Year of Publication

There were four, three, and two studies of the years < 2000, 2000–2010, and > 2010, with RR and 95% CI 1.13 (95% CI 0.82–1.55), 1.29 (95% CI 0.93–1.78), and 0.57 (95% CI 0.21–1.56), respectively, and no significant difference was observed ($p = 0.308$).

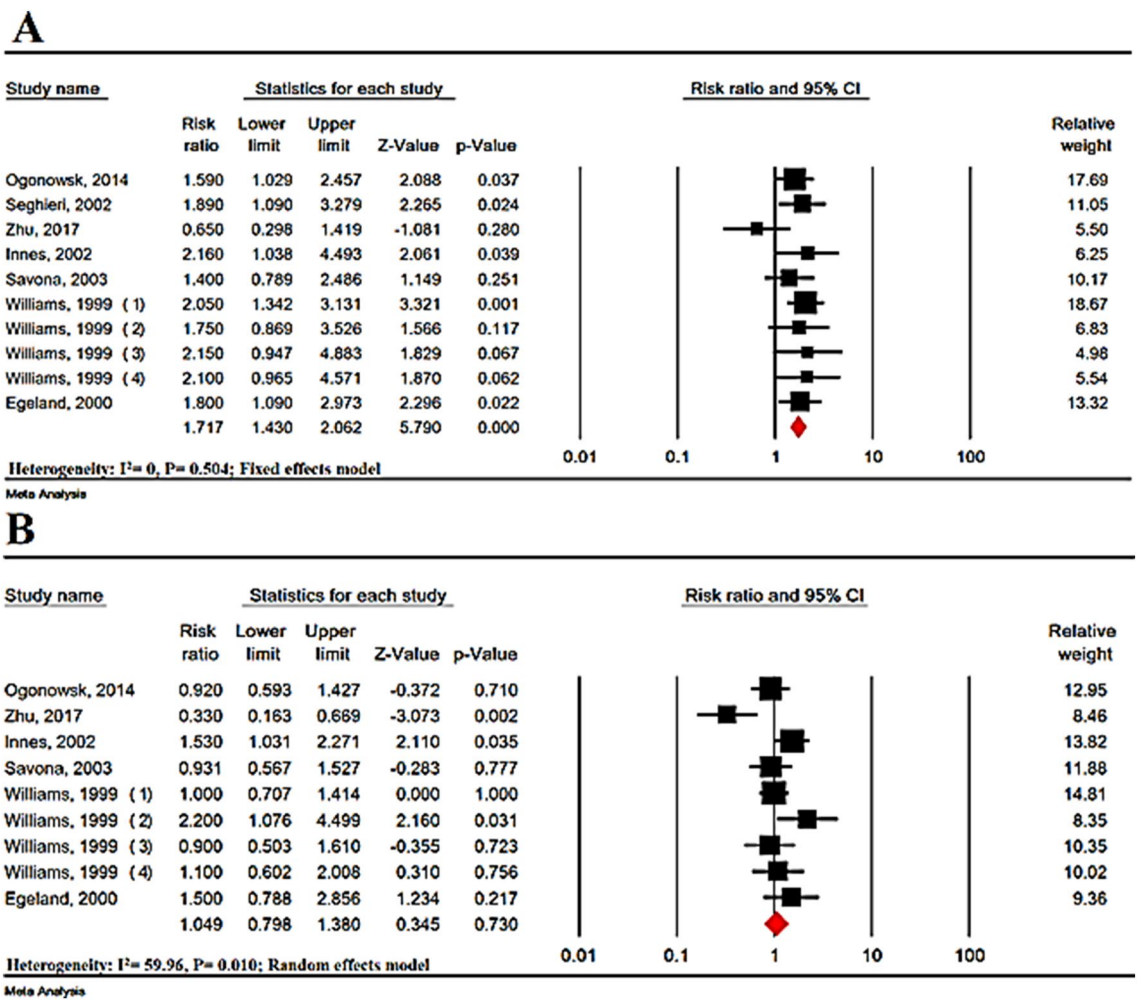

Fig. 2 Relationship between gestational diabetes, maternal LBW and macrosomia

Based on Continent

There were five, five, and one study respectively from continents of USA, Europe, and Asia with RR and 95% CI of 1.22 (95% CI 0.92–1.61), 1.02 (95% CI 0.76–1.36) and 0.33 (95% CI 0.16–0.67) respectively, a significant difference was observed ($p=0.004$).

Based on Quality

There were three and six studies of high quality, and six medium-quality studies with RR and 95% CI were 0.81 (95% CI 0.38–1.73) and 1.11 (95% CI 0.88–1.40), respectively, and no significant difference was observed ($p=0.308$).

Publication Bias

Egger's test is more capable of detecting publication bias. *P* values for Begg's and Egger's tests for "association between gestational diabetes and maternal LBW" were $p=0.928$ and $p=0.578$, respectively, indicating that publication bias does not affect the results (Fig. 3A). *P* values for Begg's and Egger's tests for "association between gestational diabetes and maternal macrosomia" were $p=0.928$ and $p=0.578$, respectively, indicating that the publication bias did not affect the results (Fig. 3B).

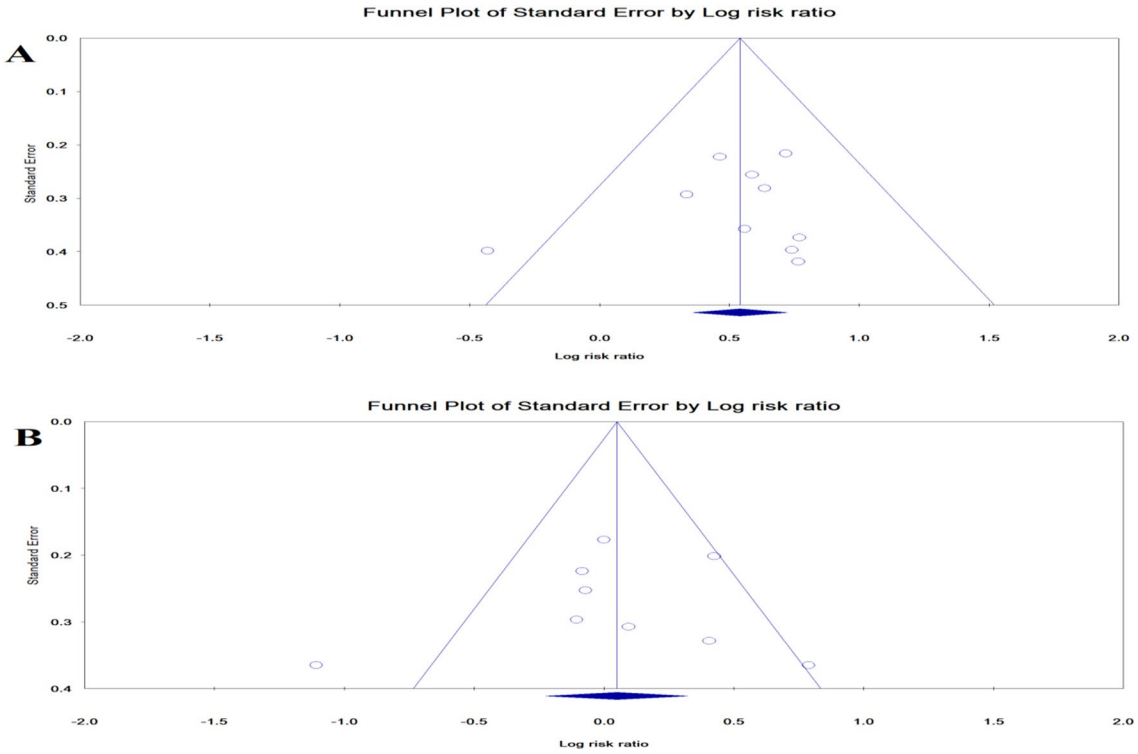

Fig. 3 Funnel chart for detecting the publication bias for the association between gestational diabetes mellitus, maternal LBW and maternal macrosomia

Sensitivity Analysis

Sensitivity analysis shows whether omitting a study can change the result. According to Fig. 4A and B, the present study showed that omitting a study at a time did not affect the result of the association between gestational diabetes, "maternal LBW" and "maternal macrosomia" (Fig. 4).

Discussion

The present study is systematic review and meta-analysis about the relationship between gestational diabetes mellitus (GDM) and maternal birth weight. Several studies have shown no association between gestational diabetes mellitus and macrosomia [12, 14, 16–18]. However, some studies have reported a significant association [15, 17]. In addition, some studies have not found a significant relationship between gestational diabetes mellitus and LBW [14, 16, 17], but in some studies, this relationship has been significant so that low maternal birth weight can increase the risk of diabetes at gestational age [12, 13, 15, 17, 18]. Therefore, the present analysis showed that maternal LBW increases the risk of gestational diabetes.

This shows a U-shaped pattern of overall risk. These discrepancies might be explained, at least partially, by the different ethnicities of the studied populations. For example, in a population-based study, Williams et al. [17] found a U-shaped relationship only among African–American women; this relationship was inversely linear among Native American and Hispanic women. A similar U-shaped relationship was also found among Pima Indian women [23, 24]. However, a high incidence of gestational diabetes mellitus among women with high birth weights seems to reflect the overall high genetic predisposition in this ethnic group to develop early insulin resistance.

Low birth weight is a term used to describe newborns' weighing less than 2500 g. A typical baby usually weighs about 8 pounds (3500 g). A low-birth-weight baby may be healthy, even if he or she is small. But a low-birth-weight baby can also have many serious health problems, so birth weight is considered to be the most important factor in newborns' health [19]. It is a vital determinant of one's health throughout life, as studies have shown that birth weight may strongly influence metabolic status in adulthood [12].

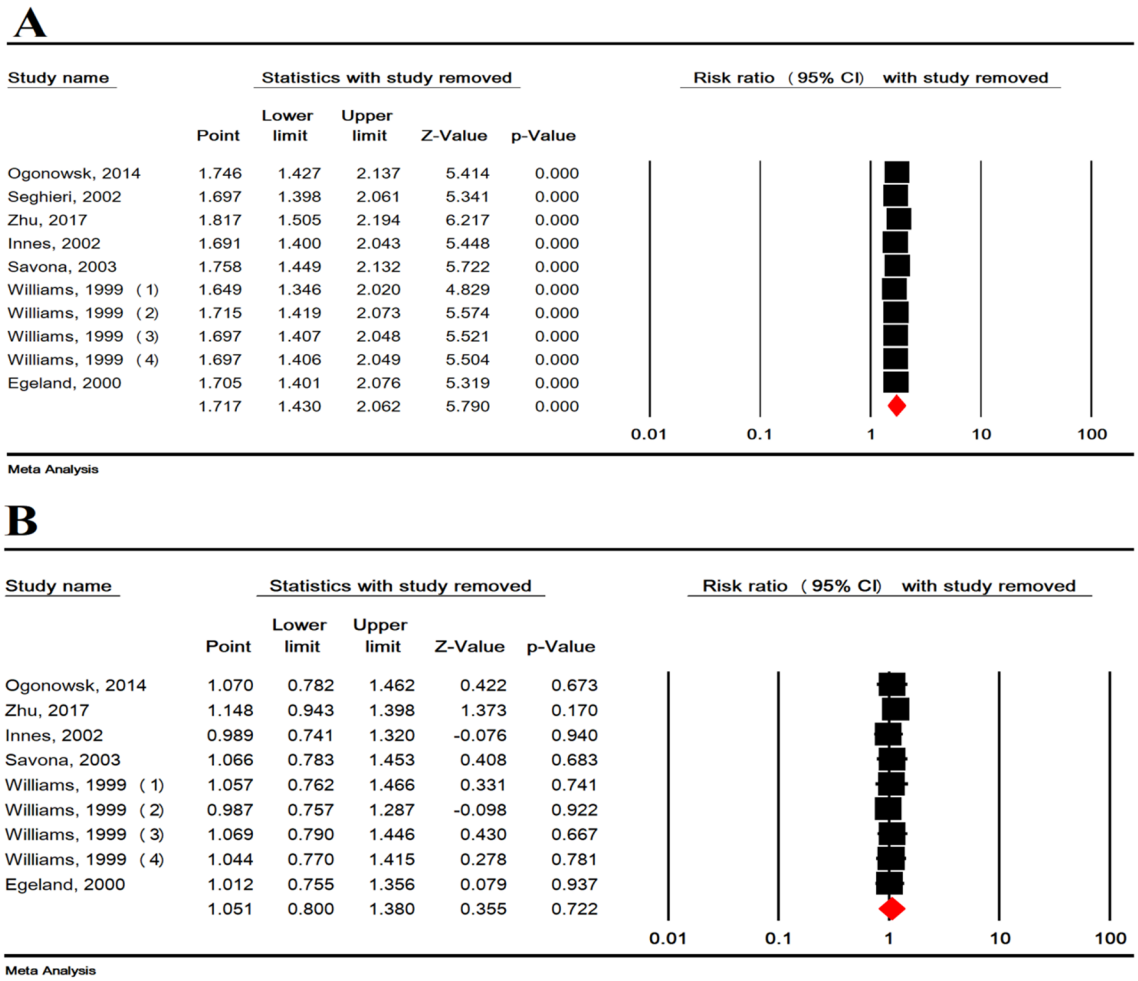

Fig. 4 Sensitivity analysis of the association between gestational diabetes, "maternal LBW" and "maternal macrosomia"

However, the exact mechanism by which birth weight affects the risk of diabetes is still unclear. Increasing evidence links birth weight to possible epigenetic changes associated with chromatin remodeling and gene expression that underlie the developmental programming of metabolic disturbances [25]. Other theories support the role of genetic factors, which may determine both low birth weight and defective insulin secretion [26].

The *P* value of publication bias for studies was higher than 0.05 based on Egger's and Begg's tests, indicating that publication bias did not affect the results of the studies. It is assumed that the observed differences are due to differences in sampling and measurement of parameters in different communities.

The type of cohort studies have been retrospective and the data already existed and has not been recalled in this study. All studies had a similar method and definition for exposure (low birth weight [LBW] is defined as birth weight less than 2500 g, and macrosomia is defined as birth weight more than 4000 g), and they had a similar outcome of gestational diabetes; this quality of the primary studies was the main strength of this meta-analysis.

Study Limitations

1. The inability of national and international databases to perform combined search using the keywords; this means that the database is not familiar with the composition of these keywords.

2. Some studies were omitted due to low quality, such as medical dissertations that did not have a clear method and correct sampling.
3. Exclusion of some studies due to lack of uniform reporting of articles and publication bias.
4. Exclusion of some studies because of inadequate information.
5. Exclusion of studies that did not have a specific outcome.
6. Exclusion of studies in which the definition of outcomes and exposures was unclear.

Conclusions

The results of the present study, which were the general result of a variety of studies on the relationship between birth weight and gestational diabetes mellitus, showed that maternal LBW almost doubled the risk of gestational diabetes mellitus. However, in a group of mothers with macrosomia at birth, the association with gestational diabetes mellitus was not significant.

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Authors' Contributions All the authors contributed to conceptualization, study design, and data analysis. Screening was completed by SHR, MP and MSH. SHR and MR supervised the screening process. Data extraction was carried out by MSH and SHR. Data analysis was performed by MR and SHR. SHR wrote the first draft of the manuscript. The manuscript was read and approved by all the authors.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by IUMS.

Human and animal rights statement Research involving human participants and/or animals not applicable.

Informed consent Data was analyzed from published articles.

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