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Association between pregnancy-associated diabetes and macrosomia: A Systematic Review and Meta-analysis

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Abstract

Background: Diabetes mellitus (DM) is a major challenge for public health worldwide. Pre-existing diabetes and gestational diabetes (GDM) are linked to poor outcomes in pregnancy, perinatal and maternal. Research indicates that GDM has become significantly more prevalent in several countries, increasing by over 30%. Glycemic control in women during pregnancy plays a major role in the health status of the mother and fetus. Macrosomia is one of the most critical adverse outcomes of DM, which results in negative consequences for the health of infants. This systematic review and meta-analysis study aimed to investigate the association between pregnancy diabetes and macrosomia in infants.

Methods: A comprehensive systematic search was conducted in electronic databases, from inception up to August 2024 to obtain related studies. Two independent researchers evaluated the studies based on the objectives of the study. The pooled effect size was computed using pooled odds risks (ORs) with 95% confidence intervals (CIs). Additionally, we conducted publication bias assessments, sensitivity analyses, and subgroup analyses. The statistical analysis incorporated twelve studies. Quality assessment of included studies was conducted using the Newcastle-Ottawa Scale (NOS).

Results: Statistical analysis in the present study on the pregnant diabetic mother and infants with macrosomia demonstrated a direct significant association between DM and macrosomia (OR: 2.94, 95% CI: 2.06-4.20, P <0.0001) and (OR: 8.17, 95% CI: 4.85-13.75, P<0.0001), respectively. Sub-group analysis revealed subjects with pre-gestational diabetes against GDM, had a greater risk of delivering an infant with macrosomia.

Conclusion: The results revealed a significant association between all three types of GDM. All three types of diabetes can lead to macrosomia, but pre-gestational diabetes has a more significant positive relationship with macrosomia. However, improving lifestyle can be considered as key strategy against macrosomia and associated diabetic complications.

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Highlights

What is current knowledge?

Pre-existing diabetes (Type 1 or type 2), as well as gestational diabetes (GDM), are linked to poor pregnancy outcomes, poor perinatal outcomes, and poor maternal outcomes.

What is new here?

There is a significant association between all three types of diabetes mellitus-gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM)-and macrosomia.

Introduction

Diabetes mellitus (DM) is a prevalent endocrine disease recognized by hyperglycemia which is associated with insulin resistance, insufficient insulin secretion, or their combination (1). This endocrine disorder is classified into three major forms: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (2). The incidence and prevalence of diabetes mellitus (DM) are increasing across the world, and it has become a global challenge (3). Evidence shows various risk factors for this disease, including genetics, environment, loss of the initial phase of insulin release, a sedentary lifestyle, lack of exercise, smoking, alcohol consumption, dyslipidemia, reduced β-cell sensitivity, hyperinsulinemia, and increased glucagon activity (4-11).

The pregnancy period is a crucial time in a woman's life that can significantly impact the health of infants. Many healthcare workers believe infant health requires providing a healthy environment for mothers during pregnancy. DM poses significant risks to both mothers and infants, including fetal and infant loss, various congenital abnormalities, malfunctions, premature birth, and macrosomia (Birth weight greater than 4000 gr or weight for gestational age larger than 90th percentile). Macrosomia is a significant risk to infants since it is associated with emergency cesarean section (CS), postpartum hemorrhage (PPH), obstetric sphincter injury (OASIS), shoulder dystocia, obstetric brachial plexus injury (OBPI), and birth fractures (12). The development of obesity, diabetes, and metabolic syndrome in childhood is influenced by genetic predisposition; however, gestational diabetes mellitus (GDM) also imposes an additional environmental risk factor during pregnancy (13).

Over 10% of pregnancies in the US are complicated by fetal macrosomia, which can lead to various complications and a decreased quality of life (13). Several factors can contribute to macrosomia, including maternal age, overweight and obesity, male fetal sex, weight gain during pregnancy, high parity, and, most importantly, diabetes mellitus (14). Fetal macrosomia is among the most common abnormalities associated with DM, especially GDM. There is evidence that the prevalence of macrosomia in mothers with and without diabetes is %88.9 and %3.9, respectively (15). DM increases glucose and insulin levels in the mother's blood, which can cross the placenta and enter the fetus's bloodstream. Excess glucose in the baby's body is stored as fat tissue, which results in macrosomia (12). According to several studies, the glycated hemoglobin (HbA1c) levels at approximately 24 to 28 weeks may predict the development of fetal macrosomia or a large-for-gestational-age (LGA) baby in women with GDM, which could be helpful in better prevention of fetal macrosomia and LGA (16).

Although previous studies have demonstrated the association between DM and macrosomia (17-19), several studies could not reveal a significant association. For example, one study did not report any significant difference between DM and healthy mothers in regards to delivering macrosomia infants (20). On the contrary, another study indicated that obesity and gestational weight gain were risk factors for macrosomia (20).

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Due to the inconsistencies in the literature, the present systematic review and meta-analysis aimed to investigate the association between DM and macrosomia.

Methods

The present study was based on the guidelines for the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (21). Moreover, it adhered to the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions (21).

2.1. Search strategy

The author performed a comprehensive and systematic search in electronic databases to find relevant studies. Systematic search was carried out in Scopus (http://www.scopus.com), PubMed (http://www.pubmed.com), and ISI Web of Science (http://www.webofscience.com). Furthermore, a hand search was conducted on Google Scholar (https://scholar.google.com) from its inception up to August 2024. The purpose of the search was to determine the association between diabetes mellitus and macrosomia, and the search strategy used a combination of the following keywords: diabetes, diabetes mellitus, type 2 diabetes mellitus, type 1 diabetes mellitus, T2DM, T1DM, gestational, gestational diabetes, pregnancy-induced diabetes, GDM, fetal macrosomia, and macrosomia. The title, abstract, and full text of all studies were assessed for eligibility by two independent reviewers, and a third reviewer addressed any disagreements between the first two reviewers.

2.2. Inclusion and exclusion criteria

Original studies were included in the meta-analysis according to the following criteria: case-control and cohort studies that reported the association between maternal diabetes (GDM, T2DM, and T1DM) and delivering an infant with macrosomia, reported their findings in English as odds ratios (OR), risk ratios, relative risk (RRs), or hazard ratios (HRs) with corresponding 95% confidence intervals (CI). Exclusion criteria in this meta-analysis were in vivo and in vitro studies, randomized clinical trials, abstracts and patents, and studies without the required data. All relevant data, including the first authors' names, publication year, country, design, type of diabetes, total subjects, the number of cases, OR, RR, and (95% CI) and adjusted (Confounding) variables, was extracted using a standard form. Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS), which has a score ranging from 0 to 9 (22). Scores lower than 4 were considered low quality, scores between 4 and 6 were moderate, and scores higher than 6 were high quality.

2.3. Statistical analysis

In the present study, statistical analysis was performed using STATA version 14.0. A random-effects model was used to assess pooled effect size, and the I2 statistic was considered a heterogeneity index in the association between diabetes and macrosomia. In this regard, the range of lower than %50 is acceptable, and analysis that shows a higher value needs adjusting. Subgroup analysis based on the probable confounder variables was conducted to minimize heterogeneity. The sensitivity analysis was also performed using metaninf command to assess whether the pooled effect-size estimate was affected by single studies. Publication bias was evaluated using Egger's and Begg's regression asymmetry test. Also, a funnel plot was conducted to assess publication bias visually. Subgroup analysis was aimed at identifying the origins of heterogeneity. All tests were considered statistically significant if the p-value was less than 0.05.

Results

3.1. Selection study

The selection process of the study is presented in Figure 1. At first, 7682 studies were identified via systematic search in electronic databases. After removing duplicate studies (N = 1229), the titles and abstracts of 6460 articles were screened. Following that, 6,434 records were excluded due to review articles (N = 328), animal studies (N = 1,537), and unrelated studies (N = 4,568). Seven and eight studies were eliminated due to unreported data and unrelated outcomes, respectively. Finally, 12 studies were included in the quality and quantity analysis.

3.2. Study characteristics

Characteristics of the included studies are demonstrated in Table 1. All included studies had case-control designs. Seven studies were carried out on the pregnant women (17,19,23-27), and five were performed on the macrosomia babies (28-32). The number of case/control participants in the studies conducted on pregnant women was 1779/2086. In the studies conducted on infants, 452 were macrosomia infants, 1,884 were non-macrosomia infants, and they were classified as case and control groups, respectively. The quality assessment of the included studies is demonstrated in Table 2. Based on the NOS tool, the quality of four studies was moderate (19,23,26,31), and eight studies had high quality (17,24,25,27-30,32).

3.3. Association between DM and macrosomia based on the mothers with DM

Figure 2 demonstrates the association between DM and the risk of macrosomia based on the diabetic status of participants. The risk of macrosomia was significantly elevated by DM (OR: 2.94, 95% CI: 2.06-4.20, P < 0.0001), based on the pooled effect size derived from included studies; however, there was a high degree of heterogeneity among studies (I2: %84.6). No evidence of publication bias was found in the statistical study. (Begg's P: 0.076 and Egger's P = 0.063). In addition, sensitivity analysis revealed that the omission of each study did not have any significance on the pooled effect size.

3.4. Association between macrosomia and DM based on the macrosomia in infants

The relationship between DM and the risk of macrosomia based on infants with macrosomia is shown in Figure 3. The pooled effect size indicates that the risk of having a mother with diabetes in children weighing more than 4000 grams was higher than in children weighing less than 4000 grams (OR: 8.17, 95%CI: 4.85-13.75, P: <0.0001). Moreover, there was no heterogeneity among the included studies (I2: %0, P: 0.989). Furthermore, statistical analysis did not show any publication bias between the included studies (Begg's P = 0.624 and Egger's P = 0.112), and sensitivity analysis indicated that pooled effect size did not influence the elimination of each study.

3.5. Subgroup analysis

The findings of subgroup analysis based on the type of participants (GDM vs other types of DM) are presented in Table 3. It was revealed, as demonstrated in Figure 4, that both situations, including GDM (OR: 1.87, 95%CI: 1.20, 2.90) and other types of DM (OR: 6.92, 95%CI: 3.78, 12.67)) increased the risk of macrosomia. However, both mentioned conditions increased the risk of macrosomia, and participants who suffered from different types of DM had a greater risk of delivering an infant with macrosomia (OR: 6.92 VS. OR: 1.87).

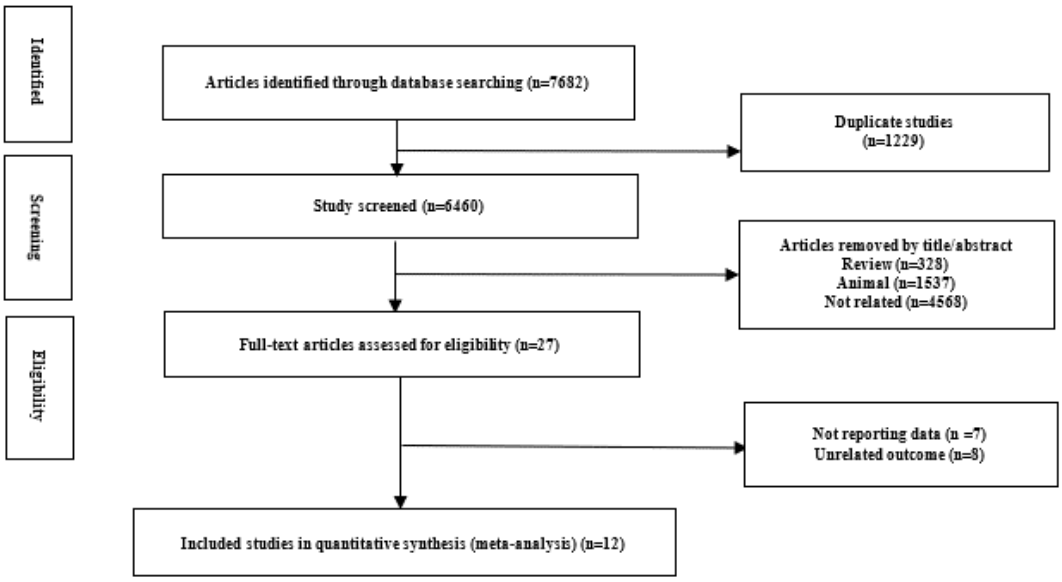

Figure 1. Flow chart of included studies

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Table 1. Characteristic of included studies in meta-analysis

Studies	Year	Country	Type of study	Type of participant (Case/Control)	Number (Case/Control)	Age		Maternal BMI (Case/control)	Variables adjusted for odds ratio
						Case	Control		
Wang et al.	2021	China	Case-control	GDM resistance /non-DM	121/204	31 (28.0, 34.75)*	31 (28.0, 34.0)*	25.22 ± 2.82/ 22.99 ±3.23$	Pre-BMI groups, GDM subtypes, gestational weight-gain groups, maternal age, diet, and exercise during pregnancy
Wang et al.	2021	China	Case-control	GDM dysfunction /non-DM	87/204	32 (29.0, 35.0) *	31 (28.0, 34.0)*	21.30 ±3.01 / 22.99 ±3.23$	Pre-BMI groups, GDM subtypes, gestational weight-gain groups, maternal age, diet, and exercise during pregnancy
Wang et al.	2021	China	Case-control	GDM mix/non-DM	66/204	30 (29.0, 34.75) *	31 (28.0, 34.0)*	21.39±2.16 / 22.99 ±3.23$	Pre-BMI groups, GDM subtypes, gestational weight-gain groups, maternal age, diet, and exercise during pregnancy
Capobianco et al.	2020	Italy	Case-control	GDM/non-DM	183/207	NP	NP	25.5 (22.6–30.1) / 22.0 (19.8–24.0) *	NP
Capobianco et al.	2020	Italy	Case-control	T1DM/non-DM	17/207	NP	NP	25.7 (21.2–30.1) / 22.0 (19.8–24.0) *	NP
Capobianco et al.	2020	Italy	Case-control	T2DM/non-DM	7/207	NP	NP	25.7 (21.2–30.1) / 22.0 (19.8–24.0) *	NP
Du et al.	2020	China	Case-control	Macrosomia/non-macrosomia	95/1454	31.46±3.65$	30.91±3.64$	NP	Not adjusted
Bawah et al.	2019	Ghana	Case-control	GDM/non-GDM	80/120	NP	NP	NP	NP
Timur et al.	2018	Turkey	Case-control	DM/non-DM	607/586	32.3 ± 5.7$	26.6 ± 5.6$	27.7 ± 5.0 / 23.3 ± 3.8$	NP
Agudelo-Espitia et al.	2018	Colombia	Case-control	Macrosomia/non-macrosomia	61/61	15-45#	15-45#	NP	Yes/NP
Said et al.	2016	Tanzania	Case-control	Macrosomia/non-macrosomia	103/ 103	29.99 ± 5.61$	28.45 ± 5.97$	NP	Not adjusted
Akindele et al.,	2015	Nigeria	Case-control	Macrosomia/non-macrosomia	120/120	NP	NP	NP	Yes/NP
Cruz MD MS et al.	2015	Cuba	Case-control	GDM with macrosomia/ GDM without macrosomia	118/118	30.58 ± 5.83$	27.57 ± 7.96$	27.43±4.41/ 26.26 ± 5.11$	Not adjusted
Mamta et al.	2012	India	Case-control	GDM/non-GDM	286/292	26.63 ± 4.547$	26.43 ± 4.412$	NP	Not adjusted
Saleh et al.	2009	Saudi Arabia	Case-control	DM/non-DM	207/559	33.6±5.8$	30.5±6.2$	NP	Not adjusted
Clausen et al.	2005	Norway	Nested case-control	Macrosomia/non-macrosomia	73/ 146	31.0 ± 4.2$	31.0 ± 4.8$	24.8 ± 4.3 / 22.9±3.7$	Age, parity, smoking, weight gain, placental weight, gestational diabetes, first trimester BMI.

$ data was reported as mean ± SD
* data was reported as median (25th,75th)
# data was reported as range
GDM: Gestational Diabetes Mellitus, DM: Diabetes Mellitus, NP: Not-reported

Table 2. Quality assessment of the included studies

Case-control studies	Case definition	Selection of cases	Selection of controls	Definition of controls	Control for the most critical factor 1	Control for any additional factor 2	Ascertainment of exposure	The same method of ascertainment for cases and controls	Non-response rate	Total scores
Wang, 2021	1	1	1	1	1	1	0	1	1	8
Capobianco, 2020	1	1	1	1	1	1	0	1	1	8
Du, 2020	1	1	1	1	1	1	0	1	0	7
Bawah, 2019	1	1	1	1	0	0	0	1	0	6
Timur, 2018	1	1	1	1	1	1	0	1	1	8
Agudelo-Espitia, 2018	1	1	1	1	0	0	0	1	0	5
Said, 2016	1	1	1	1	1	1	0	1	0	7
Akindele, 2015	1	1	1	1	1	1	0	1	1	8
Cruz MD MS, 2015	1	1	1	1	1	0	0	1	0	6
Mamta, 2012	1	1	1	1	0	0	0	1	0	5
Saleh, 2009	1	1	1	1	1	1	0	1	1	8
Clausen, 2005	1	1	1	1	1	1	0	1	0	7

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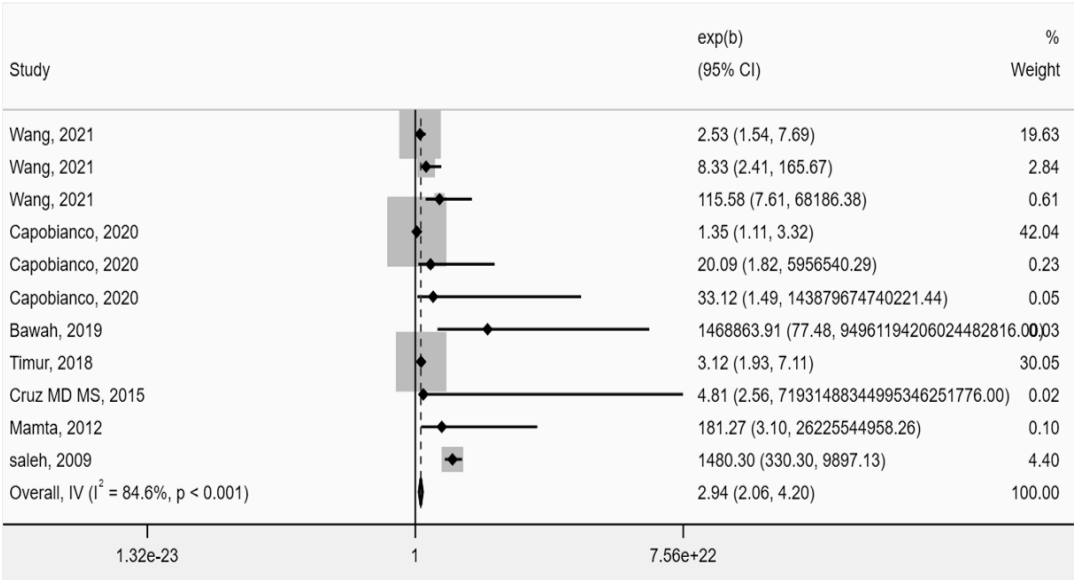

Figure 2. Association between DM and macrosomia based on the DM subjects

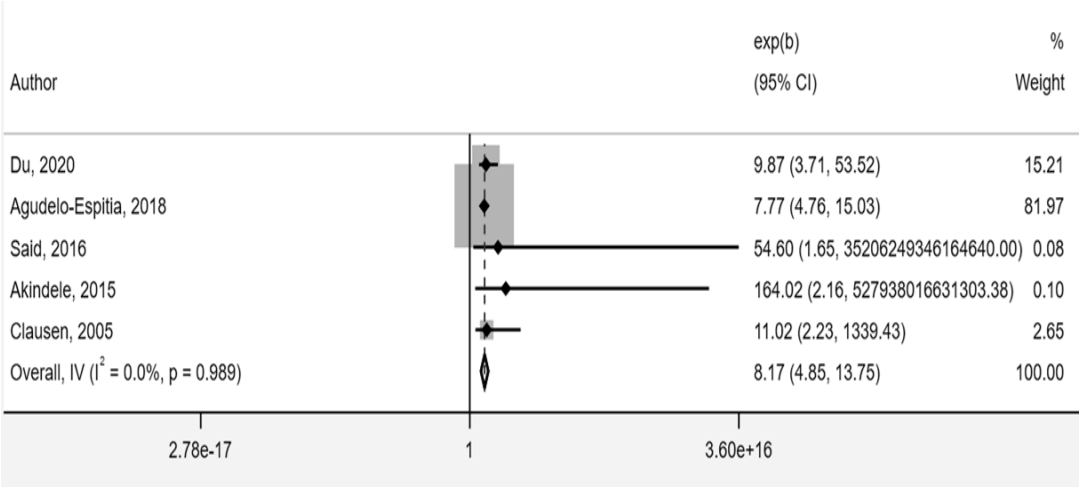

Figure 3. Association between macrosomia and DM based on the infants with macrosomia

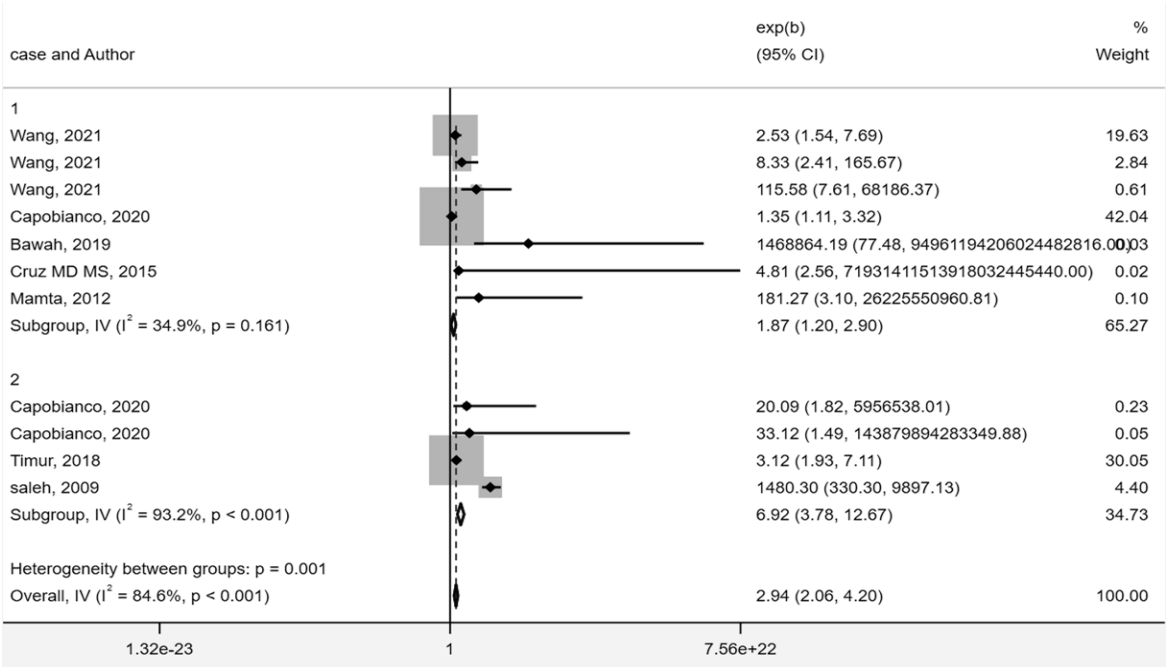

Figure 4. Subgroup analysis based on type of case (1= GDM, 2=others)

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Table 3. Association between GDM and risk of macrosomia

Participants	No.	ES (95%CI)	P-value	I^2	P-heterogeneity
Diabetic mother					
Total	11	2.94 (2.06, 4.20)	< 0.0001	% 84.6	< 0.0001
GDM	7	1.87 (1.20, 2.90)	0.006	% 34.9	0.161
Others	4	6.92 (3.78, 12.67)	< 0.0001	% 93.2	< 0.0001
Macrosomia infant					
Total	5	8.17 (4.85, 13.75)	< 0.0001	0	0.989

Discussion

According to the findings of the current systematic review and meta-analysis, there is a significant and direct relationship between diabetes mellitus (DM) and the risk of macrosomia. In addition, sub-group analysis revealed that infants of women with gestational diabetes mellitus (GDM), in comparison with other conditions associated with DM, had a lower risk of macrosomia. A comprehensive search was carried out to obtain eligible studies based on the Newcastle-Ottawa Scale (NOS) tool; most included studies were of high quality.

DM has alarmingly increased in developed countries over the past 40 years, along with an increase in the prevalence of macrosomia (33-36). Based on previous studies, women with DM are at more risk for delivering an infant with macrosomia (37-39). Physical activity and diet are critical factors in preventing macrosomia and other adverse effects of diabetes management. A clinical trial revealed that regular exercise reduced the risk of macrosomia by %58 (40). In addition, a clinical trial by Asemi et al. showed that a dietary strategy against hypertension (DASH) for four weeks reduced the risk of macrosomia (41). In addition, A systematic review and meta-analysis of ten primary studies demonstrated that the treatment of mothers with gestational diabetes mellitus (GDM), whether through diet or medication, significantly reduced the risk of macrosomia. (42). The results of the current study were consistent with those of the mentioned study (43). It should be noted that this meta-analysis was conducted on all types of DM, not only GDM. In subgroup analysis, it was demonstrated that mothers with pre-gestational diabetes, in comparison with GDM, had a greater risk of delivering an infant with macrosomia. This was approved by another study in New York (44), but another longitudinal study revealed contradicting results (45). This can be attributed to the varying criteria used to define macrosomia. The available data regarding the correlation between DM and macrosomia is compiled in the current review and meta-analysis. However, in different studies, other risk factors are reported for GDM, such as genetic and environmental factors, maternal obesity, excessive weight gains during pregnancy, pre-gestational high body mass index (BMI), DM, gestational age at delivery, hypertension, and smoking; they are also considered major independent risk factors for macrosomia (46). A previous study has demonstrated that obesity during pregnancy is another warning sign for macrosomia in babies, and it has been reported that obesity before pregnancy in mothers might be a risk factor for macrosomia through increasing insulin resistance, which raises fetal glucose and insulin levels and increases hepatic glucose production (47). Most of the included studies reported their results after adjusting for confounding variables. DM results in a high concentration of serum glucose in pregnant mothers, which increases the transportation of glucose from the placenta and provides a high quantity of glucose and other nutrients for the fetus, thereby increasing the risk of macrosomia. Several studies have reported various factors involved in the growth of a fetus, including environmental factors, genetics, the health condition of the mother and placenta, and, top of all, the amount of available energy substrate for the fetus. Hyperglycemia in mothers leads to hyperglycemia and hyperinsulinemia in the fetus, which leads to hyperplasia and hypertrophy of the Langerhans' islets and finally stimulates the growth of the fetus. High blood glucose levels in the fetus increase lipogenesis and excessive fetus growth (48). Also, the insulin of the fetus does not pass the placenta. At the same time, a large amount of the mother's glucose reaches the fetus and is metabolized, stimulating lipogenesis and excessive fetus growth (49). Previous studies indicated that infants with macrosomia from diabetic mothers have a greater concentration of insulin in their umbilical veins than infants without macrosomia, and insulin plays a significant role in tissue growth (50). Furthermore, previous studies indicated that insulin growth factor-1 (IGF-1) was correlated with the fetus's growth, and this hormone's level was higher in the hypertrophic fetuses compared to eutrophic- or hypotrophic fetuses (51). Based on the findings of the present meta-analysis, pre-gestational diabetes is a more significant risk factor than GDM, given that nearly 90% of DM is related to T2DM and over-weight or obesity is one of the well-known characteristics of this type of diabetes (52,53). In addition, maternal obesity is an independent risk factor for macrosomia (53). Thus, the results of the current meta-analysis indicate a strong association between pre-gestational diabetes and the delivery of infants with macrosomia, likely due to a higher prevalence of type 2 diabetes mellitus (T2DM).

The current systematic review and meta-analysis has many strengths. The first is a comprehensive, systematic search to obtain all related studies. The second strength is that the studies were conducted in different countries, resulting in a comprehensive conclusion. Third, a thorough statistical analysis, such as sensitivity analysis, subgroup analysis, and publication bias, was performed. However, the current systematic review and meta-analysis faced several shortcomings. First, there was a significant variation among the listed studies. Although researchers tried to address heterogeneity by subgroup analysis, it wasn't carried out based on all demographic characteristics because the studies did not report them. Second, none of the included studies received all scores of the NOS tool, although most had a high quality. Third, some of the included studies did not report the adjusted variables for the regression model. Fourth, there may have been variations in the diagnostic criteria for diabetes mellitus (DM) across the studies included.

Conclusion

The findings of this systematic review and meta-analysis demonstrate a significant association between all three types of diabetes mellitus-gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM)-and macrosomia. All three types of diabetes can lead to macrosomia; however, pre-gestational diabetes shows a stronger and more significant relationship with macrosomia. Changes in lifestyle, such as increased physical activity, calorie-restricted diets, and weight loss through glycemic management techniques, are the primary defenses against macrosomia and associated diabetic complications.

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Ethical statement

This article is based on the author's PhD thesis (Salah Faaez Abdulnabi) and has been ethically approved by Golestan University of Medical Sciences in Gorgan, Iran (IR.GOUMS.REC.1403.006).

Conflicts of interest

The authors affirm no conflict of interest in publishing this article.

Author contributions

SFA, AJ, and ON designed the experiments and prepared the manuscript. SGH-GH and AF analyzed the data. SAA and MM helped in revising the manuscript. All authors approved the final manuscript.

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