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REVIEW ARTICLE

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Relationship between Gestational Diabetes Mellitus and Preterm Birth: a Meta-analysis

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Abstract

Background: There were many studies detecting the relationship between Gestational Diabetes Mellitus (GDM) and Preterm Birth (PTB). However, the conclusions were inconsistent. Therefore, to clarify the relationship between GDM and PTB, a meta-analysis was conducted in this study.

Methods: Three computerized literature databases, PubMed, Web of Science and Cochrane Library, were systematically reviewed. The information and data from relevant studies based on incorporation criteria were selected and extracted. The pooled Odds Ratio (OR) with 95% Confidence Interval (CI) was calculated. Subgroup analyses were carried out according to geographical areas and GDM diagnostic criteria.

Results: A total of 10 studies met the inclusion criteria. Pooled results showed that GDM during pregnancy was a risk factor of PTB (OR=1.43, 95% CI 1.30-1.58), which was supported by subgroup analyses as well.

Conclusions: Women with GDM had an increased risk of PTB compared with those who had a normoglycemic pregnancy. Since the potential confounders could not be ruled out completely, further studies are needed to confirm these results.

Keywords: Gestational diabetes mellitus; Preterm birth; Meta-analysis

Abbreviations: GDM: Gestational Diabetes Mellitus; PTB: Preterm Birth; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH: Medical Subject Headings; IADPSG: International Association of the Diabetes and Pregnancy Study Groups; NDDG: National Diabetes Data Group; DPSG: Diabetic Pregnancy Study Group; ICD: International Classification of Diseases; OR: Odds Ratio; CI: Confidence Interval

Introduction

As one of the most common complications during pregnancy, gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy [1]. The incidence of GDM varies with geographic spreading. Approximately 2%-6% pregnancies have GDM in Europe [2], and the number of pregnant women affected by GDM in the United States has reached 9.2 % [3]. Moreover, the incidence of GDM in China is as high as 17.5% [4].

GDM increases the risk of adverse complications for pregnant women and its offspring, such as type 2 diabetes mellitus, shoulder dystocia, macrosomia and so on [5]. In addition, several studies also show that GDM might have a relationship with Preterm Birth (PTB). PTB is defined as the birth of an infant prior to 37 completed weeks of gestation [6]. As is one of the major causes that lead to perinatal morbidity and mortality [7], especially in middle-income and higher-income countries, PTB is accounting for 35% of the 3.1 million deaths worldwide each year [8]. In addition, PTB has lifelong effects on the neurodevelopmental function of surviving infants [9]. Therefore, it is necessary to understand the relationship between GDM and PTB, which may help to reduce the occurrence of PTB at the source.

Recently, several literatures showed that GDM was associated with PTB, but in other published data, it was concluded that there was no clear link between the two [10,11]. A compelling rationale basis based on evidence medicine to prove the relationship between GDM and PTB was scarce. Hence, the objective of this current study was to further confirm the relationship between GDM and PTB by evidence-based medical analysis.

Materials and Methods

Literature searching and screening were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Literature search

An electronic search of PubMed, Web of Science and Cochrane Library from inception to March 30, 2018, was conducted by two investigators independently (Jia Zhou and Mengyao Deng). The Medical Subject Headings (MeSH) and various synonyms were used to search the relevant articles. We used the following search terms: (premature birth) OR (premature labor) OR (preterm birth) OR "Premature Birth" [MeSh]) and (GDM) OR (gestational diabetes) OR (gestational diabetes mellitus, GDM) OR (diabetes in pregnancy) OR (gestational diabetes, GDM) OR ("Diabetes, Gestational" [MeSh]). Additional studies were identified by a manual search of the references of the original studies.

Criteria for inclusion and exclusion

This review followed these inclusion criteria: case-control studies or cohort studies; evaluating the effect of GDM on PTB; focused on humans; published in English language; conducted among pregnant women; reported the relevant information including the number or incidence of cases about PTB with GDM women (case group) and normoglycaemic women (control group). The exclusion criteria were: twin or multiple pregnancies; pregnant women with pre-pregnancy diabetes (type 1 or type 2 diabetes); case reports, systematic reviews and meta-analysis articles, studies only included women with GDM; sample size less than or equal to 10 both in case group and control group.

Study selection

Titles and abstracts were screened to identify the potential eligibility for inclusion. Then the selected articles were further analyzed by a full-text review to assess their eligibility for the final inclusion. The reasons for the final inclusion were reviewed by the second author, and disagreements were resolved by further discussion. The articles retrieved from the literature search were screened to eliminate duplicates.

Data extraction and quality assessment

The characteristics of included studies embodied first author's name, year of publication, country of origin, number of participants, study types, time of the investigation, GDM diagnostic criteria, number of cases with GDM and normal pregnant women. PTB cases in the case group and control group were extracted by two investigators (Wei Li and Jia Zhou). The discrepancies were resolved by discussions with the third author (Mengyao Deng). 9-star Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of the included studies, which involved the assessment of three main domains: participant's selection, comparability, and exposure or outcome [13]. To maximum, a study could be awarded one point for each numbered item within the selection and exposure respectively, and two points for comparability. If the score of the study was up to 6 points or above, the quality of the study would be considered to be good.

Data synthesis and statistical analysis

Heterogeneity between included studies was assessed by the I2 statistics and Q test, and I2>50% or P<0.05 indicated evidence of heterogeneity among studies [14,15]. When substantial heterogeneity was detected, the random-effects model (the DerSimonian-Laird method) was presented for the meta-analysis [16]. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used.

Sensitivity analyses were performed to see the stability of the results, namely, whether any exclusion of the studies could affect the original results. Subgroup analyses were performed to access the impact of geographical areas and GDM diagnostic criteria on pooled results. Begg's funnel plot and Egger's linear regression test were used to assessing possible publication bias. The former was a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision. Formal statistical assessment of funnel plot asymmetry was also incorporated with Egge's regression asymmetry test and Begg's adjusted rank correlation test. Statistical tests were conducted by Review Manager Version 5.0 (Windows, Cochrane Collaboration, Oxford, United Kingdom, 2010) and Stata 12.0 (Stata Corporation, College Station, TX, USA). The P value less than 0.05 was considered as statistically significant.

Results

Literature search

Figure 1 performed the flow of study identification and inclusion process. Electronic literature searching yielded 2673 results. Among them, 321 articles were excluded for animal experiments, and 325 were not published in English. There were 2027 articles identified by reading titles and abstracts. Of which, 33 and 120 articles were excluded for case reports, meta-analysis or systematic review respectively, and 1794 articles were excluded on the bias of clear irrelevant. The remaining 80 full-text articles were selected and scrutinized. We excluded 62 articles, which provided no data or did not detect the association between GDM and PTB. Meanwhile, 2 papers were excluded because of duplicate, and 6 articles did not meet the inclusion criteria of this meta-analysis. Finally, there was a total of 10 eligible studies [10,11,17-24] included in our analysis. In addition, two thresholds were used in Sacks DA' study [17] to distinguish participants groups, so we regarded the two thresholds as two articles with different GDM diagnostic criteria (IADPSG1, IADPSG2). Hence, there were 11 papers included.

Study characteristics and quality assessment

The main characteristics of the included studies were presented in table 1. In total, the 11 eligible papers which were published from 2001 to 2017 included 2618929 participants (99493 GDM participants and 2531522 No-GDM controls). 7 studies were drawn from North American, 2 studies from Asian and 2 studies from Europe respectively. The quality score of 8 studies met 9 scores, and 2 studies met 7 and 8 scores respectively according to the 9-star Newcastle-Ottawa Scale.

Synthesis of results

The homogeneity hypothesis was rejected by Q test ($\chi 2=95.01$, $P<0.001$), and the result showed that there was large heterogeneity among studies (I2=89.0%). Therefore, the random-effect model was applied to calculate the pooled OR and the results showed that GDM during pregnancy was associated with a higher risk of PTB (OR=1.43, 95% CI 1.30-1.58) (Figure 2).

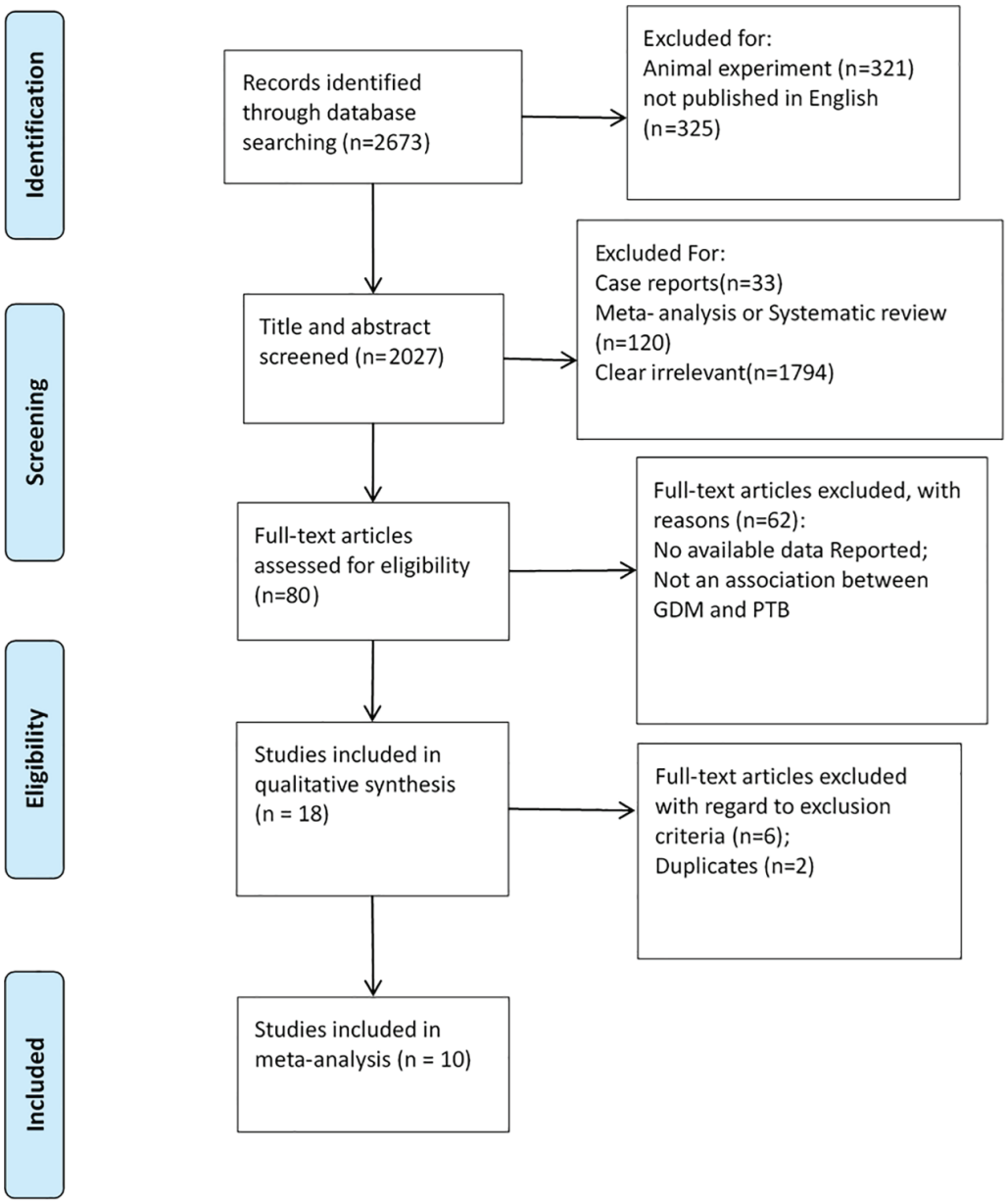

Figure 1: Identification and inclusion process of the studies for the meta-analysis. 10 articles were included in our meta-analysis.

Begg's funnel plot and Egger's linear regression test were performed to assess the publication bias of the literature. The shape of the funnel plot did not reveal any sign of significant asymmetry, and the result of Egger's test also indicated that no evidence of publication bias existed among the studies (P> 0.05). To conduct a sensitivity analysis, we recalculated the combined results by excluding one study per iteration. The results performed that the effect of almost every study included in the pooled estimate was similar in the current meta-analysis.

Subgroup analysis

When stratifying by territory, the included studies were classified as Asian, North American, and European groups. The results indicated that the Asian group (OR=1.45, 95% CI 1.08-1.96), North American group (OR=1.39, 95% CI 1.21-1.59) and European group (OR=1.54, 95% CI 1.16-2.05) all showed an increased risk of PTB with GDM (Figure 3). When stratifying by diagnostic criteria of GDM, these included studies were classified as the NDDG (the National Diabetes Data Group) (fasting, 5.8mmol/l; 1h, 10.6mmol/l; 2h, 9.2mmol/l; 3h, 8.1mmol/l) [25] group, IADPSG1 (fasting, 5.1mmol/l; 1h, 10.0mmol/l; 2h, 8.5mmol/l) [26] group, IADPSG2 (fasting, 5.3mmol/l; 1h, 10.6mmol/l; 2h, 8.9mmol/l) [27] group, and other group (DPSG [28], the Carpenter and Constant Criteria [29]. Similarly, the results indicated that GDM was significantly associated with PTB in the NDDG (OR=1.54, 95% CI 1.29-1.84), IADPSG1 (OR=1.33, 95% CI 1.21-1.46), IADPSG2 (OR=1.60, 95% CI 1.30-1.98) groups (Figure 4).

Discussion and Conclusion

According to the results of our meta-analysis, GDM pregnant

Table 1: Characteristics of the studies that met the inclusion criteria for the meta-analysis.

First author's name	Year of publication	Number of participants	Study types	Country of origin	Survey time	GDM group Preterm	GDM group Total	NO-GDM group Preterm	NO-GDM group Total	GDM diagnostic criteria	Quality assessment (points)
Lai FY, et al. [11].	2016	327198	Case control	Canada (North America)	2005-2011	1435	18137	16917	306576	IADPSG 2	9
Sacks DA, et al. (1) [17].	2015	9835	cohort	Southern California (North America)	2005.10.30-2010.12.30	53	771	491	7943	IADPSG 1	9
Sacks DA, et al. (2) [17].	2015	9835	cohort	Southern California (North America)	2005.10.30-2010.12.30	121	1121	491	7943	IADPSG 2	9
Hirst JE, et al. [18].	2010	2702	cohort	Vietnam (Asian)	2010.12.01-2011.03.31	60	550	141	2152	IADPSG	9
Fadl HE, et al. [19].	2010	1260297	cohort	Sweden (Europe)	1991-2003	905	10525	62489	1249772	DPSG	9
Billionnet C, et al. [20].	2017	796346	cohort	France (Europe)	2012	4591	57383	44475	729105	IADPSG	9
Xiong X, et al. [21].	2001	111419	cohort	Canada (North America)	1991.07.01-1997.12.31	287	2755	8150	108664	Approximate NDDG	9
Feng H, et al. [22].	2017	14741	cohort	China (Asian)	2013.06.20-2013.11.30	184	2927	588	11814	IADPSG	9
Boghossian NS, et al. [23].	2014	62013	cohort	Utah (North America)	2002-2010	156	2275	3005	58478	Unclear	8
Hedderson MM, et al. [24].	2003	46230	cohort	Northern California (North America)	1996.01.01-1998.07.31	102	1523	1541	38515	NDDG	9
Yogev Y, et al. [10].	2007	12086	cohort	San Antonio, Texas (North America)	1995-1999	163	1526	1193	10560	the Carpenter and Coustan Criteria	7

women were with 1.43 times higher risk of PTB than women without GDM. Even considering the potential influence of geographical regions and diagnostic criteria, GDM was still a risk factor of PTB. This meant that GDM controlling might reduce the risk of PTB. Popularizing pregnant women to avoid actively the risk factors that trigger GDM during pregnancy might have a significant contribution to the reduction of neonatal PTB rates.

Different regions had different genetic backgrounds and risk models, so we calculated the subgroup analysis by geographical regions. In addition, the GDM diagnostic criteria might also have an effect on the relationship between GDM and PTB. In Sacks DA's study [17], when GDM was diagnosed by IADPSG2 criteria, there was a significant difference in the incidence of PTB between GDM patients and non-patients, but this relationship was not found in IADPSG1 group. The IADPSG1 criteria are closer to the normal plasma glucose level than IADPSG2 criteria. So the effect of high blood glucose levels on PTB might be affected by specific concentrations. Perhaps, the higher the concentration was, the stronger the association between GDM and PTB was. The dose-response effect between blood glucose levels and PTB risk require further study.

It should be noted that our meta-analysis results indicated a high heterogeneity both in overall impact and subgroup analyses. From the I2 index formula, we could easily find that to some extent, heterogeneity was affected by the degree of freedom. Nevertheless, the Degree of Freedom (DF) was closely related to the size of the sample. The larger the sample size was, the higher heterogeneity was. In these included studies, Lai FY, et al. [11] and Fadl HE, et al. [19] et al. studies were long-term population-based surveys and these studies sample sizes were more than ten thousand. In addition, although the subgroup analyses were conducted, only the diagnostic criteria of GDM and geographical areas were calculated because of the information limitation. The heterogeneity was also affected by many other confounders such as the

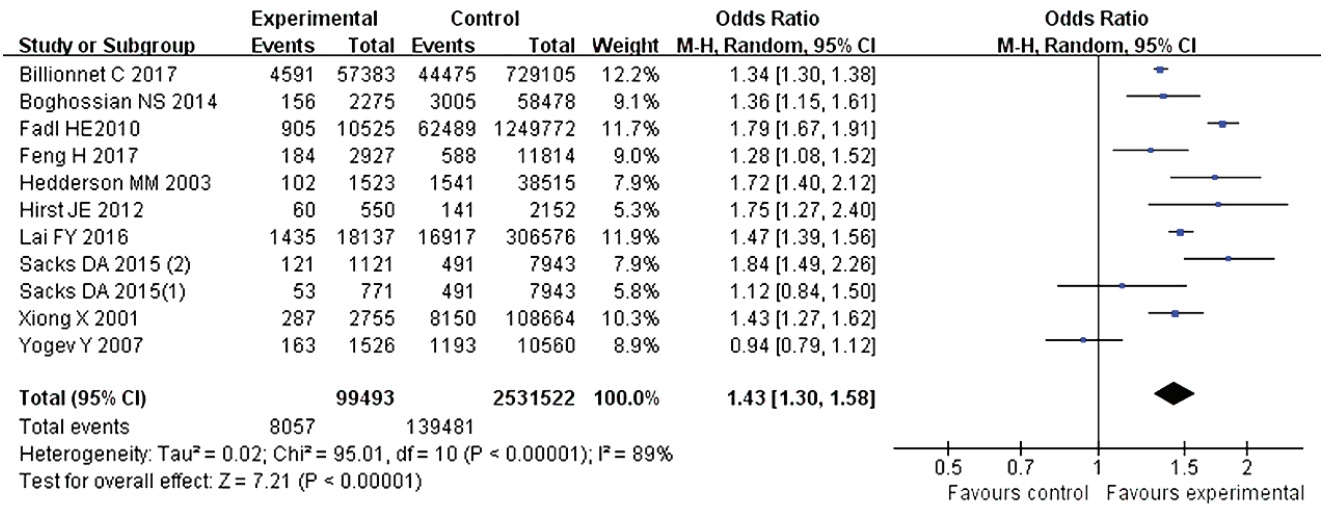

Figure 2: Comparison of PTB cases in pregnant women with GDM and in normal pregnant women.

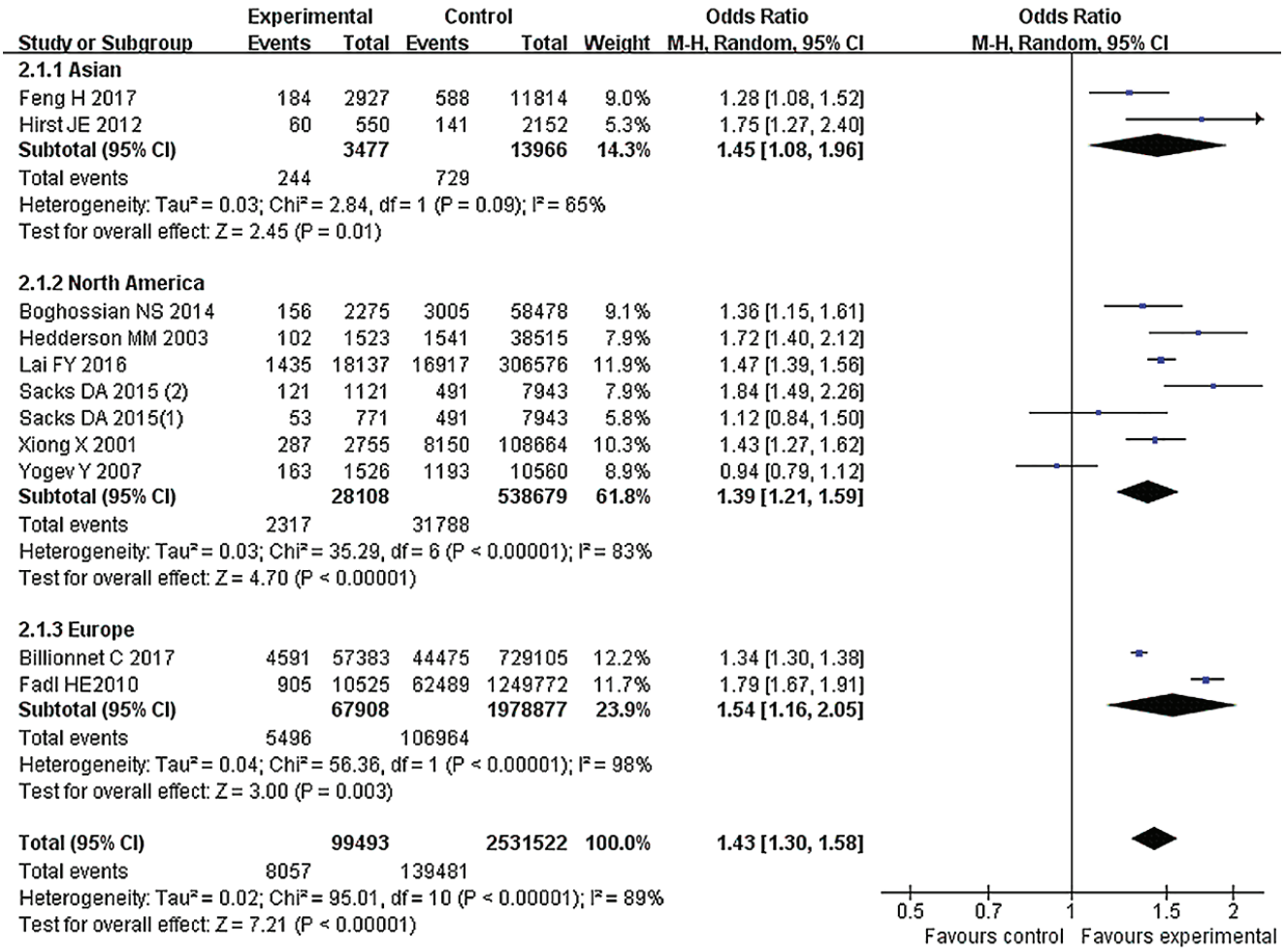

Figure 3: Forest plot of subgroup analyses of relationships between GDM and PTB in different regions. Events, PTB cases; CI, confidence interval; M-H, Mantel-Haenszel.

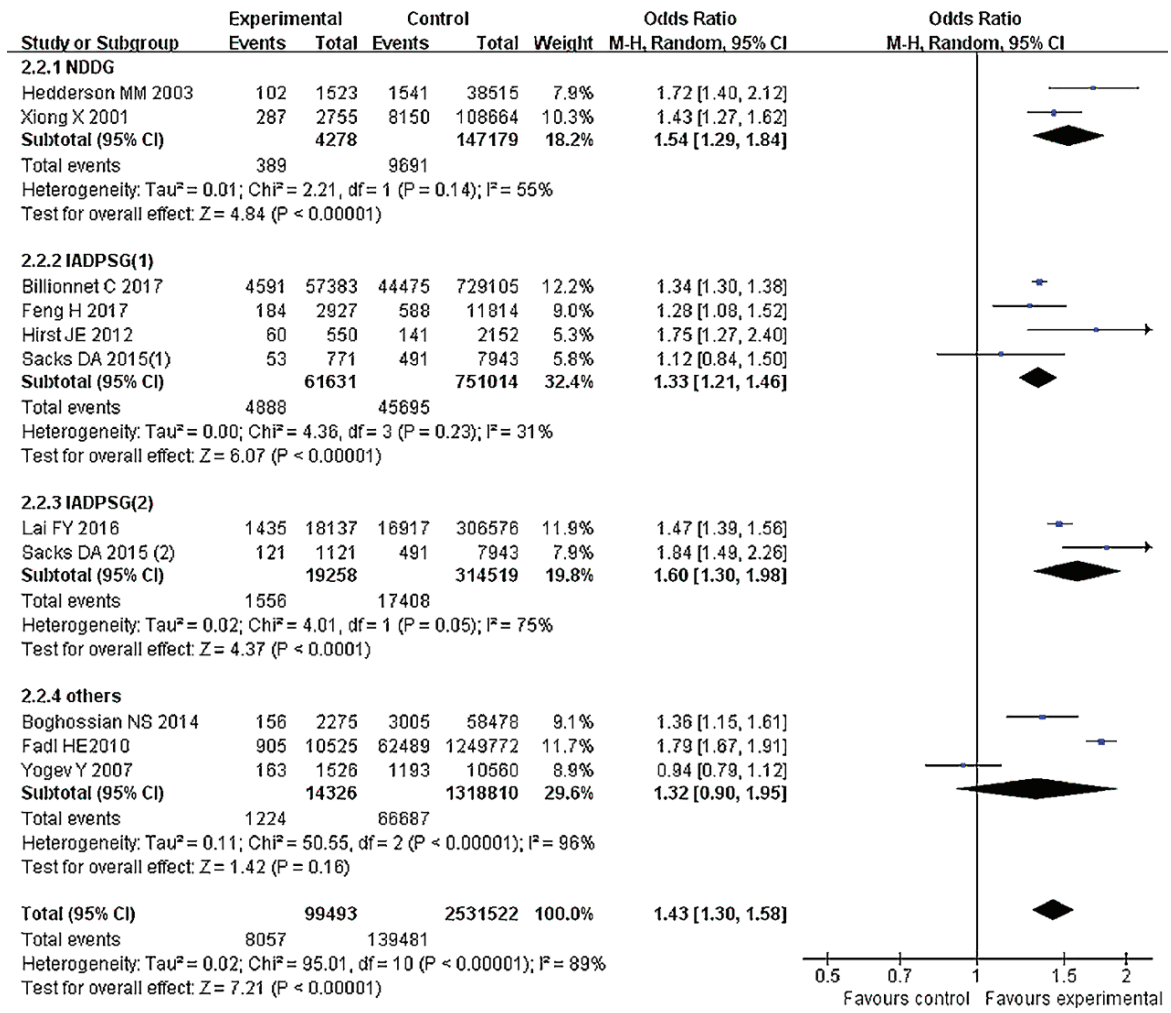

Figure 4: Forest plot of subgroup analyses of relationships between GDM and PTB using different diagnostic criteria. Events, PTB cases; CI, confidence interval; M-H, Mantel-Haenszel.

age of pregnant women [30], raised body-mass index [31], the history of GDM in a previous pregnancy [23], type of PTB, GDM management and so on. However, because of the differences or deficiencies in the research design of each included article, we could not measure all confounders' impact on the relationship between GDM and PTB. Different studies had different PTB definitions and classified methods, which might also have an impact on the results of these analyses. Some of our included studies defined PTB as <37 gestational weeks. Some studies defined it as delivery at gestational age <37 weeks and ≥ 28 weeks. On the other hand, some studies divided PTB into spontaneous, indicated, and elective preterm [32,33]. But it was regretted in certain papers. In addition, GDM management protocols might also affect our research results. Good GDM management would help control the glucose content of plasma; even keep blood glucose at normal levels for a long time, so it would have some influence on the pregnancy out come. For example, the results of Bar-Have I's study [34] showed that blood glucose control in GDM pregnant women would reduce the possibility of PTB.

Although with large sample size and the subgroup analyses by diagnostic criteria for GDM and geographical regions, our results need to be interpreted with caution due to several limitations. Firstly, as mentioned above, we did not identify all sources of heterogeneity and confounders. Secondly, we only considered the impact of GDM, while PTB can be the result of multiple factors, such as maternal hypertension, birth defects and so on. These factors also had an important impact on the overall study outcomes.

In conclusion, the results of our meta-analysis showed that GDM was a risk factor of PTB. On account of the harm of PTB, glycemic control during pregnancy is necessary. However, potential confounders cannot be ruled out completely. Further and in-depth studies are needed to confirm these results.

Declarations

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Availability of data and materials

All data pertaining to this study are included in this published article.

Authors' contributions

W Li: Project development and manuscript reviewing, literature quality assessment, manuscript writing/editing; J Zhou: Literature searching and screening, literature quality assessment, data collection, data analysis, manuscript writing/editing; M Yang: Manuscript reviewing and modification; MY Deng: Literature searching and screening, literature quality assessment, data collection, data analysis, Z Tang: Manuscript reviewing and modification; YGuo: Project development, Idea providing and manuscript reviewing;. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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