Archives of Gynecology and Obstetrics (2019) 300:1491–1506
https://doi.org/10.1007/s00404-019-05376-6

REVIEW

Risk of congenital heart defects in offspring exposed to maternal diabetes mellitus: an updated systematic review and meta-analysis

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Received: 31 March 2019 / Accepted: 25 October 2019 / Published online: 12 November 2019
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Abstract

Purpose A systematic review and meta-analysis was performed to assess the risk of congenital heart defects (CHDs) and its specific phenotypes associated with maternal diabetes mellitus (DM) including pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM).

Methods PubMed, Embase, Medline, Google Scholar, Cochrane Libraries, China National Knowledge Infrastructure, Wanfang Database, Chinese Scientific Journals Fulltext Database and China Biology Medicine disc were searched from the inception dates to 15 December 2018, to identify case–control or cohort studies assessing the association between maternal DM and risk of CHDs. The exposure of interest was maternal DM; the outcomes of interest were CHDs and its specific phenotypes. Either a fixed- or a random-effects model was used to calculate the overall combined risk estimates. Subgroup analyses were performed to explore potential heterogeneity moderators.

Results Total 52 studies, which involved 259,917 patients with CHDs among 16,929,835 participants, were included for analysis. Overall, mothers with DM compared with those without DM had a significantly higher risk of CHDs in offspring [odds ratios (OR) = 2.71, 95% confidence intervals (CI) 2.28–3.23]. When data were restricted to different types of DM, a significantly increased risk of CHDs was observed among mothers with PGDM (OR = 3.18, 95% CI 2.77–3.65) and GDM (OR = 1.98, 95% CI 1.66–2.36). Our study suggested the risk of CHDs was significantly higher among mothers with PGDM than those with GDM. Additionally, this study suggested maternal DM was significantly associated with most phenotypes of CHDs; of these, double outlet of the right ventricle (OR = 10.89; 95% CI 8.77–13.53), atrioventricular septal defect (OR = 5.74; 95% CI 3.20–10.27) and truncus arteriosus (OR = 5.06; 95% CI 2.65–9.65) were identified as the first three of the most common phenotypes of CHDs associated with maternal DM.

Conclusions The maternal DM including PGDM and GDM are significantly associated with risk of CHDs and its most phenotypes. The PGDM seems to be more likely to cause CHDs in offspring than GDM. Further studies are needed to clarify the underlying mechanisms.

Keywords Maternal diabetes mellitus · Congenital heart defects · Pregestational diabetes mellitus · Gestational diabetes mellitus · Phenotypes · Meta-analysis

Introduction

Congenital heart defects (CHDs) are structural problems arising from the abnormal formation of the heart or major blood vessels, considered as the most common types of congenital malformations [1]. With a prevalence of 6–10 per 1000 live births, CHDs affect approximately 1.35 million newborns worldwide each year [2]. In infants and young children, CHDs are the leading proportion of non-infectious morbidity and mortality caused by birth defects [3] and result in 1–1.5% of global mortality among children under 5 years of age [4].

Environmental and genetic factors are generally considered to play an important role in the pathogenesis of CHDs [5–9], but the exact cause remains controversial. Currently, original studies from animal experiments [10, 11]

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and high-quality cohort studies [12–16] generally believe that mothers with diabetes mellitus (DM) compared with non-diabetic increase the risk of CHDs in their offspring. Further studies have shown that although pregestational DM (PGDM) was associated with an increased risk of CHDs, the magnitudes of the association varied between the studies [17–20]. Moreover, it remains unclear enough for the relationships between gestational DM (GDM) and CHDs as well as the precise risks for specific subtypes of CHDs associated with maternal DM.

Although three meta-analyses [21–23] on this topic have been published, they only highlight a limited portion of the associations between maternal DM and CHDs. The latest meta-analysis performed by Hoang et al. [23] showed that maternal DM was associated with CHDs and its some specific phenotypes, but this review only focus on the association between PGDM and a small portion of the CHD phenotypes. According to the previous original studies, the common CHDs could be divided into more than 20 phenotypes [12], which indicated the results of this review were not comprehensive. In addition, when significant heterogeneity was observed, this review did not explore potential heterogeneity moderators. In addition, it only included studies published in English and did not cover Chinese studies. In China, there are many studies to assess the risk of CHDs associated with maternal DM. If these studies from China could be included in the future meta-analysis, it will inevitably increase the statistical power, which will help to find a statistically significant difference for risk of CHDs, especially for specific phenotypes of CHDs.

Given the inconsistency of the original studies and the limitations of the existing meta-analysis, we conducted an up-to-date meta-analysis with the following objectives: (1) to assess the overall risk of CHDs associated with maternal DM (included PGDM and GDM); (2) to assess the risk of specific CHD phenotypes associated with maternal DM; and (3) to identify potential heterogeneity moderators by subgroup and sensitivity analysis.

Materials and methods

Search strategy

We attempted to report this systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [24]. PubMed, Embase, Medline, Google Scholar, Cochrane Libraries, China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journals Fulltext Database (CQVIP) and China Biology Medicine disc (CBMdisc)) were searched from the inception dates to 15 December 2018, to identify case–control or cohort studies that assessed the association between maternal DM and risk of CHDs in offspring. The following search terms were used: (1) congenital heart disease, congenital heart defect, congenital heart malformation, congenital heart anomalies, congenital cardiac disease, congenital cardiac defect, congenital cardiac malformation, congenital cardiac anomalies, congenital cardiovascular disease, cardiovascular malformation, cardiovascular defect, cardiovascular anomalies, birth defect, congenital malformation, congenital anomalies and congenital defect; (2) diabetes mellitus, DM, glycuresis, diabetes, sugar diabetes, pregestational diabetes mellitus, gestational diabetes mellitus, chronic disease, metabolic disease, and maternal disease; and (3) prospective studies, follow-up studies, cohort studies, longitudinal studies, and case–control studies. No restrictions were imposed. An artificial search of the reference lists in the related articles and recent reviews were also conducted as a supplement. The conference abstracts and grey studies were not included. We did not contact the authors of the original studies for additional information.

Exposures and outcomes

The exposure of interest was maternal DM, and it was further divided into PGDM and GDM. The outcome of interest was CHDs that were identified as structural problems arising from malformations in the heart or major blood vessels. Additionally, CHDs were further divided into typical phenotypes according to the World Health Organization International Classification of Disease (ICD-10) as below: heterotaxia; atrioventricular canal defects (AVCD); patent ductus arteriosus (PDA); conotruncal defects [including truncus arteriosus (TA), transposition of great arteries (TGA), tetralogy of Fallot (TOF) and double outlet of the right ventricle (DORV)]; atrioventricular septal defect (AVSD); anomalous pulmonary venous return (APVR); left ventricular outflow tract obstruction (LVOTO) [‘including coarctation of aorta (CoA), valvular aortic stenosis (VAS) and hypoplastic left heart syndrome, (HLHS)]; right ventricular outflow tract obstruction (RVOTO) [including pulmonary valve stenosis (PVS), pulmonary artery stenosis (PAS), Ebstein malformation and tricuspid valve stenosis (TVS)]; septal defects (including ventricular septal defect [VSD], atrial septal defect [ASD], VSD + ASD and valve defects) and single ventricle. Since variations in the definition of exposures and outcomes exist in different countries and cultures, it is extremely difficult to define uniform standards in the present study. Some literatures did not always define exposures and outcomes, and in such cases, we relied on the exposure or outcome terminology in the original articles.

Eligibility criteria

We first performed an initial screening of titles or abstracts. We conducted a second screening based on a full-text review. Studies were eligible if they met the following criteria: (1) studies were published in English or Chinese language; (2) studies were case–control or cohort studies; (3) the exposure of interest was maternal DM; (4) the outcome of interest was CHDs; and (5) odds ratios (ORs) or relative risks (RRs) and their corresponding 95% confidence intervals (CIs) (or data to calculate them) were available. If the same population was studied in more than one study, we included the study with the longest follow-up time or the most information.

Data extraction

Data extraction was performed using a standardized data collection form. We extracted any reported RRs or ORs for risk of CHDs in offspring exposed to maternal DM compared with non-maternal DM. We also extracted the research characteristics of each record. Data were recorded as follows: first author's name; publication time; geographic region; sample source (population vs hospital-based studies); study design (case–control vs cohort studies); the phenotype of maternal DM (including PGDM and GDM); the phenotype of CHDs (including total and specific CHDs); total sample size; number of CHD cases; whether the confounding factors were adjusted (adjusted vs unadjusted); and quality score.

Quality assessment

Two authors (LTC and JBQ) independently conducted the study selection, data extraction, and quality assessment. Any differences were resolved by discussion or a third author to get into consensus. The Newcastle–Ottawa Scale (http://www.ohri.ca/programs/clinicalepidemiology/oxford.asp) was used to assess the quality of included studies. Using the tool, each study is judged on 8 items, categorized into 3 groups: the selection of the study groups; the comparability of the groups; and the ascertainment of outcome of interest for cohort studies. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies can be awarded as many as 9 stars. If a study wins ≥ 7 stars, it will be considered of higher methodologic quality.

Statistical analysis

In the present study, we used OR as a common measure of association between maternal DM and risk of CHDs in offspring. The combined ORs and their corresponding 95% CIs were pooled using either fixed effect models or in the presence of heterogeneity using random effect models. Statistical homogeneity between studies was assessed using the Q statistic and I^2 statistic (significance level at $P < 0.10$).

Subgroup analysis was performed based on whether the confounding factors were adjusted, geographic region, sample source, and study design, to identify potential heterogeneity moderators. In addition, sensitivity analyses were conducted to explore possible interpretations of heterogeneity and to examine the influence of various exclusion criteria on overall risk estimates. We also investigated the influence of a single study on the overall risk estimate by omitting 1 study in each turn. Potential publication bias was assessed using funnel plots and Begg's rank correlation test (significance level at $P < 0.10$). Subgroup analysis, sensitivity analysis and assessment of publication bias were considered only for the association between maternal DM and total CHDs due to the limited studies.

Sensitivity analysis and Begg's rank correlation test were performed using Stata version 12.0 (StataCorp LP, College Station, TX). Other analyses were performed using Review Manager version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration). Statistical tests were declared significant for a two-sided P value not exceeding 0.05, except where otherwise specified.

Results

Search results

We totally searched 3871 potentially eligible studies from English and Chinese databases. Of these, 3585 studies due to duplicates, reviews, letters, or unrelated to our analysis were excluded after the first screening on titles and/or abstracts. After a full-text review of 286 studies, 52 studies [12–20, 23, 25–66] including 36 case–control and 16 cohort studies met the inclusion criteria (Fig. 1). The main reasons for not including the studies were: (1) the outcome of interest was not CHDs ($n = 89$); (2) the exposure of interest was not maternal DM ($n = 107$); (3) lack of appropriate control groups ($n = 26$); and (4) data could not be extracted or calculated ($n = 12$).

Study characteristics

The characteristics of included studies, which involved 259,917 CHDs patients among 16,929,835 participants, and were published between 1975 and 2018, were summarized in Table 1. These studies came from four continents: 22 (42.3%) in North America, 18 (34.6%) in Asia, 11 (21.1%) in Europe, and only 1 (2.0%) in Oceania. Among the CHD patients, 78.0%, 17.9%, 3.1% and 1.0% of patients were distributed in North America, Europe, Asia, and Oceania, respectively. Among the total participants, 63.7%, 24.9%,

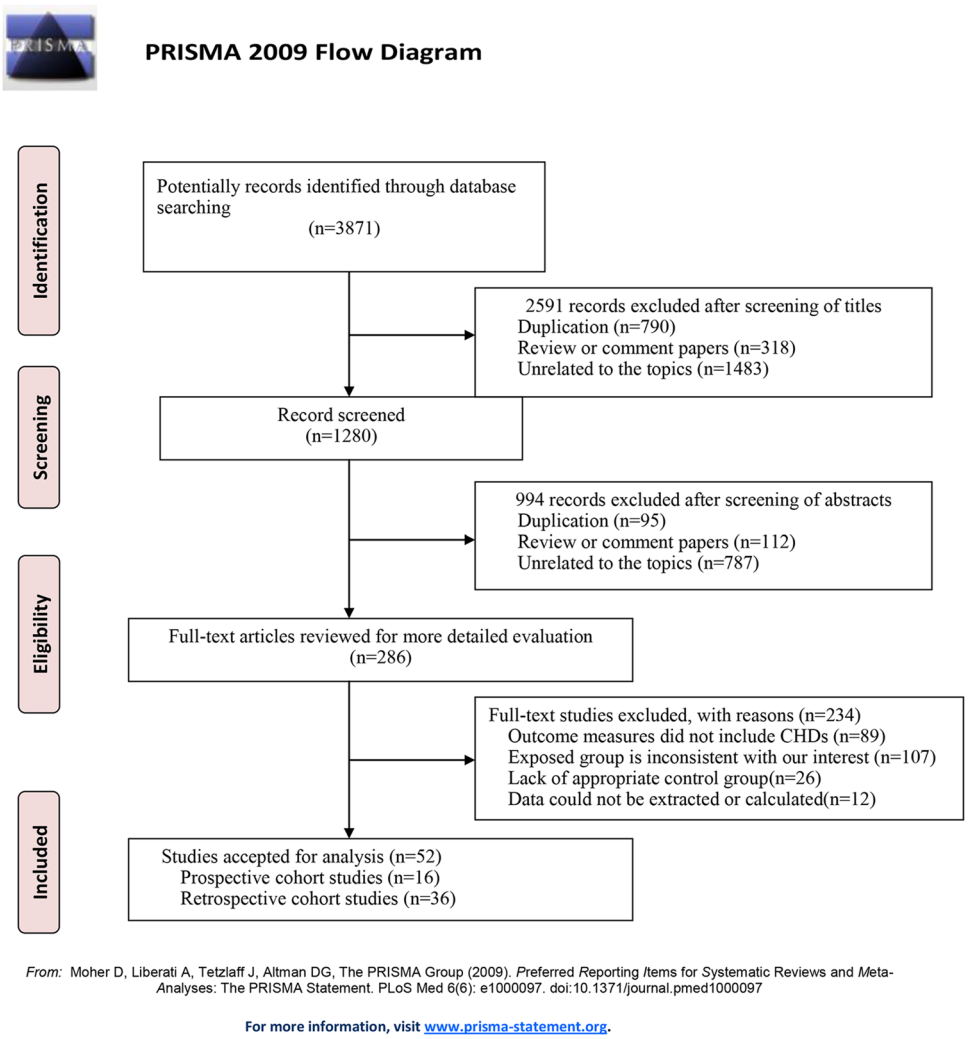

Fig. 1 PRISMA statement flow diagram

9.7% and 1.7% of them were distributed in North America, Europe, Asia, and Oceania, respectively.

The sample source varied across studies, with more than half (65.4%) based on population. Forty-six (88.5%) studies were considered of higher methodological quality, achieving a quality score of ≥ 7 out of 9; these 46 studies contributed 99.98% of the participants. Twenty-seven studies (51.9%) did not adjust any factors when estimating the effect of maternal DM on CHDs in offspring, whereas other studies adjusted for a wide range of potential confounders for poor outcomes.

Maternal DM and risk of CHDs

Overall, mothers who had DM compared with those without DM experienced a significantly increased risk of CHDs in offspring (OR = 2.71, 95% CI 2.28–3.23; $P < 0.00001$) (Fig. 2). However, substantial heterogeneity was observed across studies ($I^2 = 98.0\%$; $P < 0.00001$).

When maternal DM was further divided into PGDM and GDM, we found that both mothers with PGDM (OR = 3.18, 95% CI 2.77–3.65; $P < 0.00001$) (Fig. 3) and mothers with GDM (OR = 1.98, 95% CI 1.66–2.36; $P < 0.00001$) (Fig. 4) had a significantly higher risk of CHDs in offspring. Of note, the risk of PGDM on CHDs was significantly higher than GDM. Yet, there was substantial heterogeneity across studies ($I^2 = 79\%$ and $P < 0.00001$ for PGDM; $I^2 = 90\%$ and $P < 0.00001$ for GDM).

Maternal DM and risk of specific subtypes of CHDs

Overall, maternal DM was significantly associated with the risk of most subtypes of CHDs such as heterotaxia, AVCD, PDA, conotruncal defects, TA, TGA, TOF, DORV, AVSD, APVR, LVOTO, CoA, VAS, HLHS, RVOTO, PAS, TVS, Septal defects, VSD, ASD, VSD + ASD, valve defects and single ventricle (Fig. 5). Of these, DORV (OR = 10.89; 95% CI 8.77–13.53), AVSD (OR = 5.74; 95% CI 3.20–10.27), TA (OR = 5.06; 95% CI 2.65–9.65), heterotaxia (OR = 4.29; 95%

Table 1 Characteristics of 52 included studies

First author/publication year	Country	Sample source[a]	Study design	Diabetes type	CHD phenotypes	Participants	CHD numbers	Adjusted/unadjusted	NOS[b]
Chung CS/1975 [25]	America	Population	Prospective cohort	PGDM	CHD	47,975	NA	Unadjusted	7
Mccarter RJ/1987 [26]	America	Population	Prospective cohort	PGDM	CHD	1226	22	Unadjusted	7
Adams MM/1989 [27]	America	Population	Case–control	PGDM	Conotruncal defects	1383	83	Unadjusted	6
Ferencz C/1990 [28]	America	Population	Case–control	PGDM/GDM, PGDM, GDM,	CHD, Heterotaxia, TA, TGA, TOF, DORV, CoA, VAS, HLHS, PAS, PVS, Ebstein malformation, VSD, ASD	5060	2.259	Unadjusted	8
Becerra JE/1990 [29]	America	Population	Case–control	PGDM/GDM, GDM	CHD	NA	NA	Adjusted	7
Erickson/1991 [30]	America	Population	Case–control	PGDM	CHD, Conotruncal defects, PDA, TA, TGA, TOF, CoA, PAS, VSD, ASD, Valve defects	4021	1.041	Adjusted	7
Pradat P/1992 [31]	Sweden	Population	Case–control	PGDM	CHD, VSD + ASD, TA	3972	1.324	Adjusted	8
Martínez-Frías ML/1994 [32]	Spain	Hospital	Case–control	PGDM	CHD	18,759	76	Unadjusted	7
Khoury MJ/1994 [33]	America	Population	Case–control	PGDM	CHD	3931	32	Unadjusted	7
Janssen PA/1996 [34]	America	Population	Case–control	PGDM, GDM	CHD	10,445	1.511	Adjusted	7
Moore LL/2000 [17]	America	Hospital	Prospective cohort	PGDM, GDM	CHD	22,951	60	Adjusted	8
Loffredo CA/2001 [35]	America	Hospital	Case–control	PGDM	CHD, TGA, AVSD, LVOTO, RVOTO, VSD, ASD	4818	1.250	Unadjusted	7
Sheffield JS/2002 [20]	America	Hospital	Prospective cohort	PGDM, GDM	CHD	142,919	211	Unadjusted	7
Wren C/2003 [36]	UK	Population	Prospective cohort	PGDM	CHD	192,618	609	Unadjusted	7
Yauck JS/2004 [37]	America	Hospital	Case–control	PGDM	CHD	4025	245	Adjusted	7
Martinez-Frias ML/2005 [38]	Spanish	Hospital	Case–control	GDM	CHD	6743	813	Unadjusted	7
Nielsen GL/2005 [39]	America	Population	Case–control	PGDM	CHD	42,630	4.479	Adjusted	7
Sharpe PB/2005 [13]	Australia	Population	Prospective cohort	PGDM, GDM	CHD, TGA	283,206	2.441	Adjusted	8
Kuehl KS/2006 [40]	America	Population	Nested case–control	PGDM/GDM[c]	HLHS	1963	77	Adjusted	8
Ning XF/2008 [41]	China	Hospital	Case–control	PGDM	CHD	600	200	Adjusted	7
Wu JH/2008 [42]	China	Population	Nested case–control	GDM	CHD	180	45	Unadjusted	6

Table 1 (continued)

First author/publication year	Country	Sample source[a]	Study design	Diabetes type	CHD phenotypes	Participants	CHD numbers	Adjusted/unadjusted	NOS[b]
Correa A/2008 [19]	America	Population	Case–control	PGDM, GDM	CHD, Heterotaxia, TGA, TOF, APVR, LVOTO, CoA, VAS, HLHS, RVOTO, PVS, VSD, ASD, VSD + ASD	8208	3.519	Adjusted	8
Yang XY/2009 [43]	China	Hospital	Case–control	PGDM	CHD	600	200	Adjusted	7
Peticca P/2009 [18]	Canada	Population	Retrospective multi-cohort	PGDM, GDM	CHD	51,461	262	Unadjusted	7
Guo GL/2010 [44]	China	Hospital	Case–control	PGDM/GDM[c]	CHD	367	165	Unadjusted	7
Eidem I/2010 [14]	Norway	Population	Prospective cohort	PGDM	CHD, PDA, VSD	350,961	3.330	Unadjusted	7
Alverson CJ/2011 [45]	America	Population	Case–control	GDM	CHD	5960	2.525	Unadjusted	7
Chen LL/2012 [46]	China	Hospital	Case–control	GDM	CHD	630	315	Adjusted	6
Agopian AJ/2012 [47]	America	Population	Case–control	PGDM, GDM	AVCD	3,675,838	551	Unadjusted	7
Bell R/2012 [48]	UK	Population	Retrospective cohort	PGDM	CHD, AVCD, TGA, TOF, AVSD, APVR, CoA, HLHS, PVS, VSD, ASD, Single ventricle	401,149	2.963	Unadjusted	8
Wu P/2013 [49]	China	Hospital	Case–control	GDM	CHD	326	163	Unadjusted	6
Zhang XJ/2013 [50]	China	Hospital	Case–control	GDM	CHD	609	203	Adjusted	7
Madsen NL/2013 [51]	America	Population	Case–control	GDM	CHD	151,733	11.263	Unadjusted	7
Liu SL/2013 [15]	Canada	Population	Cohort	PGDM	CHD, Heterotaxia, Conotruncal defects, AVSD, LVOTO, RVOTO, VSD, ASD	2,278,838	23.200	Adjusted	8
Csáky-Szunyogh M/2014 [52]	Hungary	Population	Case–control	PGDM, GDM	LVOTO, CoA, VAS, HLHS	771	302	Adjusted	7
Guo M/2014 [53]	China	Hospital	Case–control	PGDM/GDM[c]	CHD	278	139	Adjusted	7
Vereczkey A/2014 [54]	Hungary	Population	Case–control	PGDM	CHD, AVCD, Conotruncal defects, PDA, TGA, LVOTO, CoA, VAS, HLHS, RVOTO, PAS, PVS, TVS, VSD, ASD, Single ventricle	41,713	3.562	Unadjusted	8
Brite J/2014 [55]	America	Population	Cohort	GDM	CHD	121,815	1.388	Unadjusted	7
Vinceti M/2014 [56]	Italy	Population	Cohort	PGDM	CHD, TGA, TOF, VSD, ASD	12,917	79	Adjusted	7
Guo YZ/2016 [57]	China	Hospital	Case–control	PGDM/GDM[c]	CHD	684	228	Adjusted	7

Table 1 (continued)

First author/publication year	Country	Sample source[a]	Study design	Diabetes type	CHD phenotypes	Participants	CHD numbers	Adjusted/unadjusted	NOS[b]
Li J/2016 [58]	China	Hospital	Case–control	PGDM/GDM, GDM	CHD	560	260	Adjusted	7
Yan JB/2016 [59]	China	Hospital	Case–control	GDM	CHD	200	50	Unadjusted	6
Øyen N/2016 [12]	Denmark	Population	Cohort	PGDM, GDM	CHD, Heterotaxia, Conotruncal defects, TA, TGA, TOF, DORV, AVSD, APVR, LVOTO, CoA, VAS, RVOTO, PVS, Septal defects, VSD, ASD, VSD + ASD, Valve defects	2,025,727	16.325	Adjusted	8
Ou YQ/2016 [60]	China	Population	Case–control	GDM	CHD, TOF, PAS, VSD, ASD	7890	3856	Adjusted	7
Tain YL/2016 [16]	China	Population	Cohort	PGDM/GDM, GDM	CHD	1,603,794	1665	Unadjusted	7
Zhang H/2017 [61]	China	Population	Cohort	GDM	CHD	16,000	155	Unadjusted	7
Chen J/2017 [62]	China	Population	Case–control	PGDM/GDM[c]	CHD	500	250	Adjusted	7
Li Y/2017 [63]	China	Hospital	Case–control	GDM	CHD	150	50	Unadjusted	6
Hoang TT/2017 [23]	America	Population	Case–control	PGDM/GDM[c]	CHD, AVCD, TA, TOF, APVR, LVOTO, COA, VAS, HLHS, RVOTO, VPS, Ebstein malformation, TVS, VSD, ASD, Single ventricle	4,207,896	148,869	Adjusted	8
Akbariasbagh P/2017 [64]	Iran	Hospital	Case–control	PGDM/GDM[c]	CHD	70	21	Unadjusted	7
Arjmandnia M/2018 [65]	Iran	Hospital	Case–control	PGDM/GDM[c]	CHD	442	39	Unadjusted	7
Ludvigsson JF/2018 [66]	Sweden	Population	Cohort	PGDM	CHD	1,162,323	17,242	Adjusted	8

CHD congenital heart defects, *PGDM* pregestational diabetes mellitus, *GDM* gestational diabetes mellitus, *TA* truncus arteriosus, *TGA* transposition of great arteries, *TOF* tetralogy of Fallot, *DORV* double outlet of the right ventricle, *CoA* coarctation of aorta, *VAS* valvular aortic stenosis, *HLHS* hypoplastic left heart syndrome, *PAS* pulmonary artery stenosis, *PVS* pulmonary valve stenosis, *VSD* ventricular septal defect, *ASD* atrial septal defect, *PDA* patent ductus arteriosus, *AVSD* atrioventricular septal defect, *LVOTO* left ventricular outflow tract obstruction, *RVOTO* right ventricular outflow tract obstruction, *APVR* anomalous pulmonary venous return, *AVCD* atrioventricular canal defects, *TVS* tricuspid valve stenosis, *NA* not available

[a]Population versus hospital-based sample

[b]Each study was assigned a score out of 9; higher quality studies with scores ≥ 7, low quality with scores < 7

[c]These papers did not provide the data for relationships in CHDs with PGDM and GDM separately

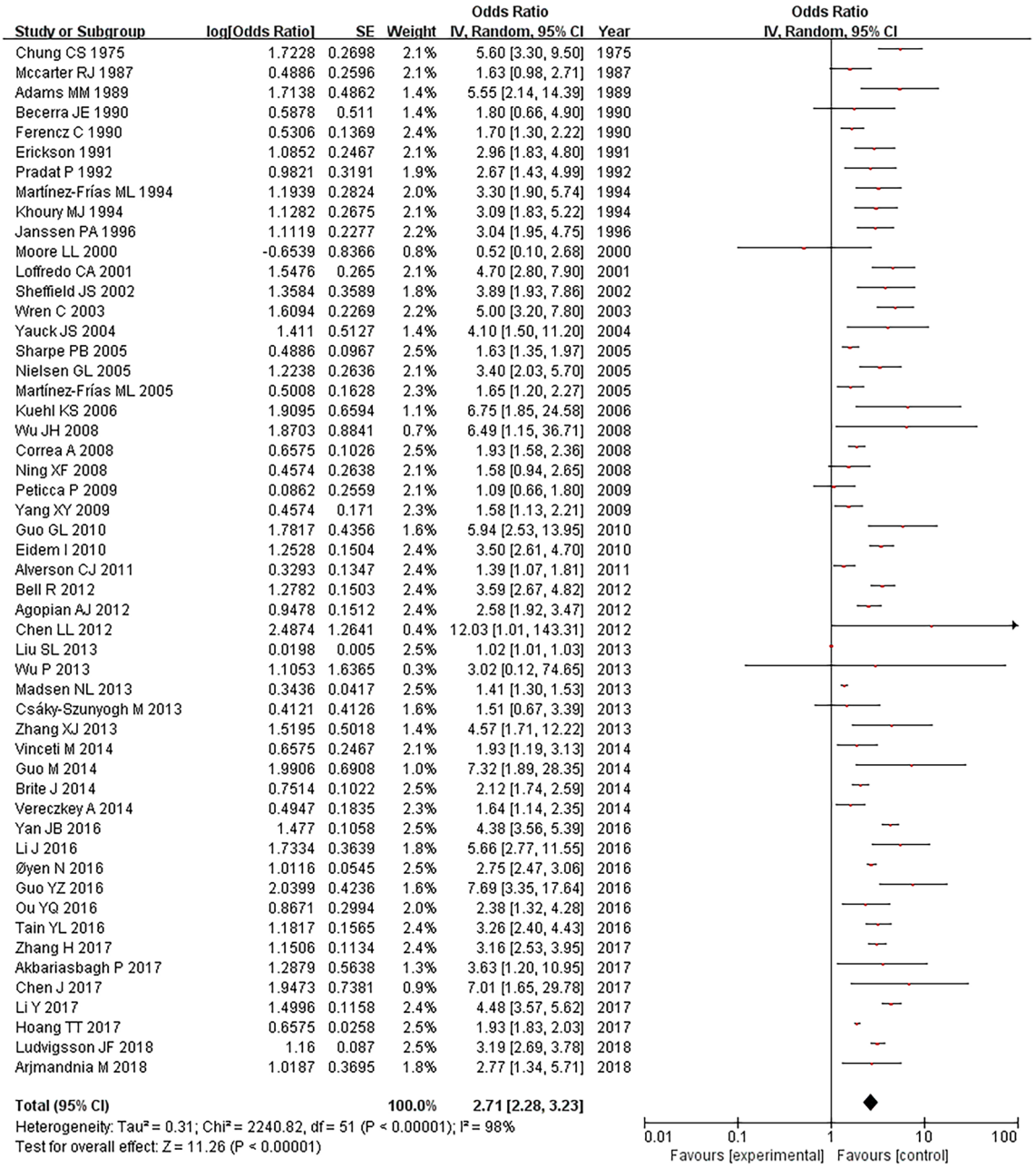

Fig. 2 Forest plot for maternal DM and risk of CHDs

CI 2.09–8.78), and PDA (OR = 4.22; 95% CI 2.79–6.40) were identified as the first five of the most common subtypes of CHDs associated with maternal DM.

Positive associations were also observed between PGDM and risk of most subtypes of CHDs including heterotaxia, AVCD, PDA, conotruncal defects, TA, TGA, TOF, DORV, AVSD, APVR, LVOTO, CoA, VAS, HLHS, RVOTO, PAS, Ebstein malformation, TVS, septal defects, VSD, ASD, VSD + ASD, valve defects, and single ventricle (Fig. 6). Of these, DORV (OR = 11.51; 95% CI 9.24–14.32), TA (OR = 7.81; 95% CI 3.50–17.43), heterotaxia (OR = 7.80; 95% CI 5.64–10.78), TVS (OR = 7.61; 95% CI 4.19–13.84), Ebstein malformation (OR = 6.28; 95% CI 1.06–37.21), and AVCD (OR = 6.12; 95% CI 4.05–9.26) were identified as the first six of the most common subtypes of CHDs associated with PGDM.

Similarly, mothers with GDM were at a higher risk for some subtypes of CHDs in their offspring such as AVCD, TA, TOF, LVOTO, CoA, VAS, RVOTO, PAS, TVS, septal defects, VSD, ASD, VSD + ASD, and valve defects (Fig. 7). Of these, TA (OR = 2.38; 95% CI 1.07–5.26), CoA (OR = 2.08; 95% CI 1.70–2.54) and PAS (OR = 1.89; 95%

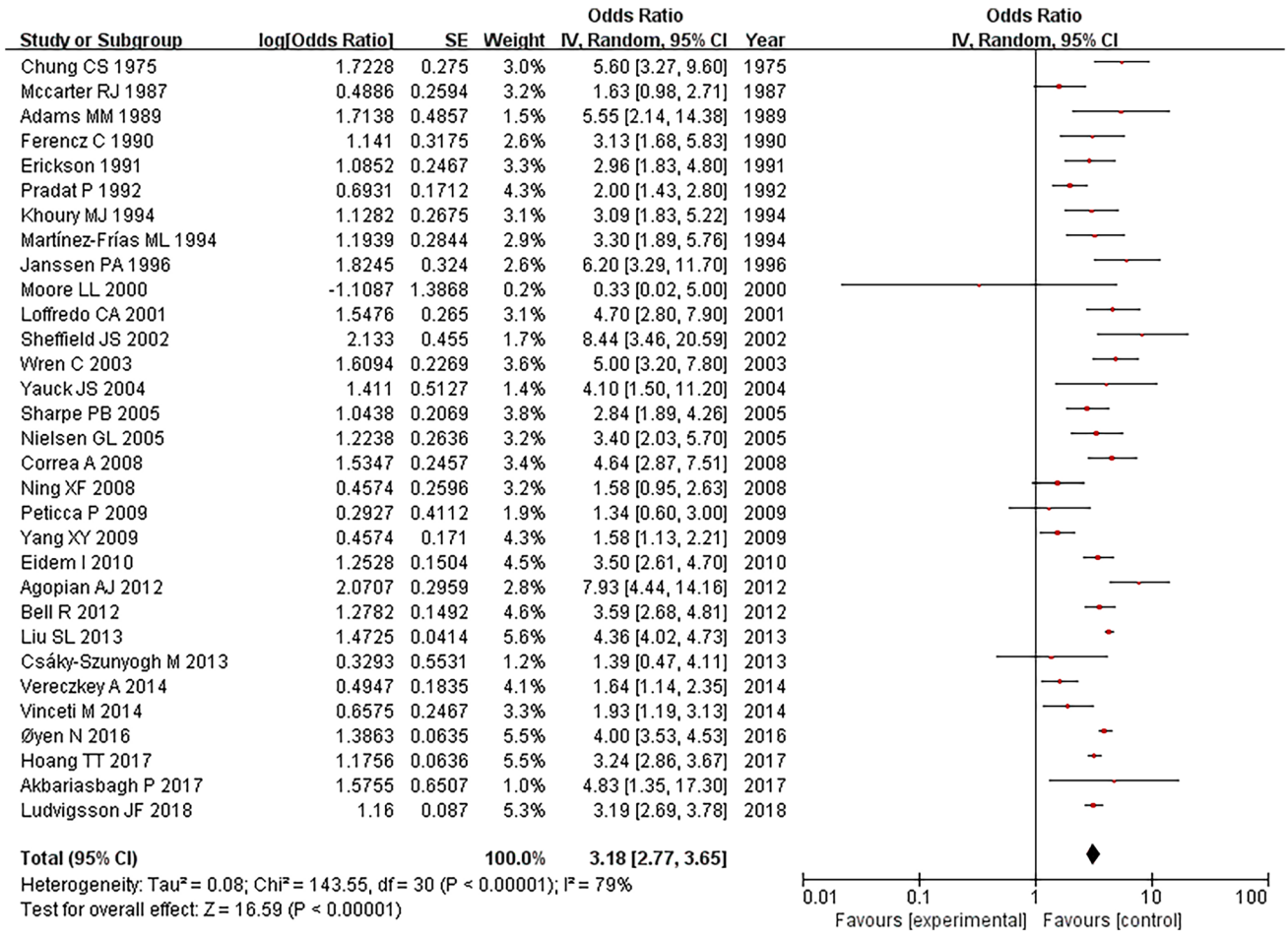

Fig. 3 Forest plot for PGDM and risk of CHDs

CI 1.17–3.05) were identified as the first three of the most common subtypes of CHDs associated with GDM.

Subgroup analyses

Subgroup analyses were conducted to identify potential heterogeneity moderators for the association between maternal DM and the risk of CHDs, and the results are summarized in Table 2. After subgroup analyses, geographic region (test for subgroup differences [TSD]: $I^2 = 89.6\%$) and sample source (TSD: $I^2 = 69.9\%$) were identified as the first two of the most relevant heterogeneity moderators for the association between maternal DM and CHDs. These differences for the risk of CHDs associated with maternal DM were statistically significant among geographic regions ($\chi^2 = 28.74$, $P < 0.00001$).

For the association between PGDM and CHDs, geographic region (TSD: $I^2 = 79.9\%$), whether the confounding factors were adjusted (TSD: $I^2 = 31.2\%$) were identified as the first two of the most relevant heterogeneity moderators. There were statistically significant differences for the risk of CHDs associated with PGDM between different geographic regions ($\chi^2 = 14.95$, $P < 0.00001$).

For the association between GDM and CHDs, geographic region (TSD: $I^2 = 96.6\%$), sample source (TSD: $I^2 = 90.8\%$), and whether the confounding factors were adjusted (TSD: $I^2 = 81.2\%$) were identified as the first three of the most relevant heterogeneity moderators. These differences for risk of CHDs associated with GDM were statistically significant across geographic regions ($\chi^2 = 87.90$, $P < 0.00001$), sample sources ($\chi^2 = 10.83$, $P = 0.001$), and whether the confounding factors were adjusted ($\chi^2 = 5.32$, $P = 0.02$).

Heterogeneity, sensitivity analyses and publication bias

Sensitivity analyses were conducted to explore possible interpretations of heterogeneity in the relationships between maternal DM and risks of CHDs in offspring and to examine the influence of various exclusion criteria on overall risk assessment. Substantial heterogeneity was observed in pooled estimates of confounding factors, geographic

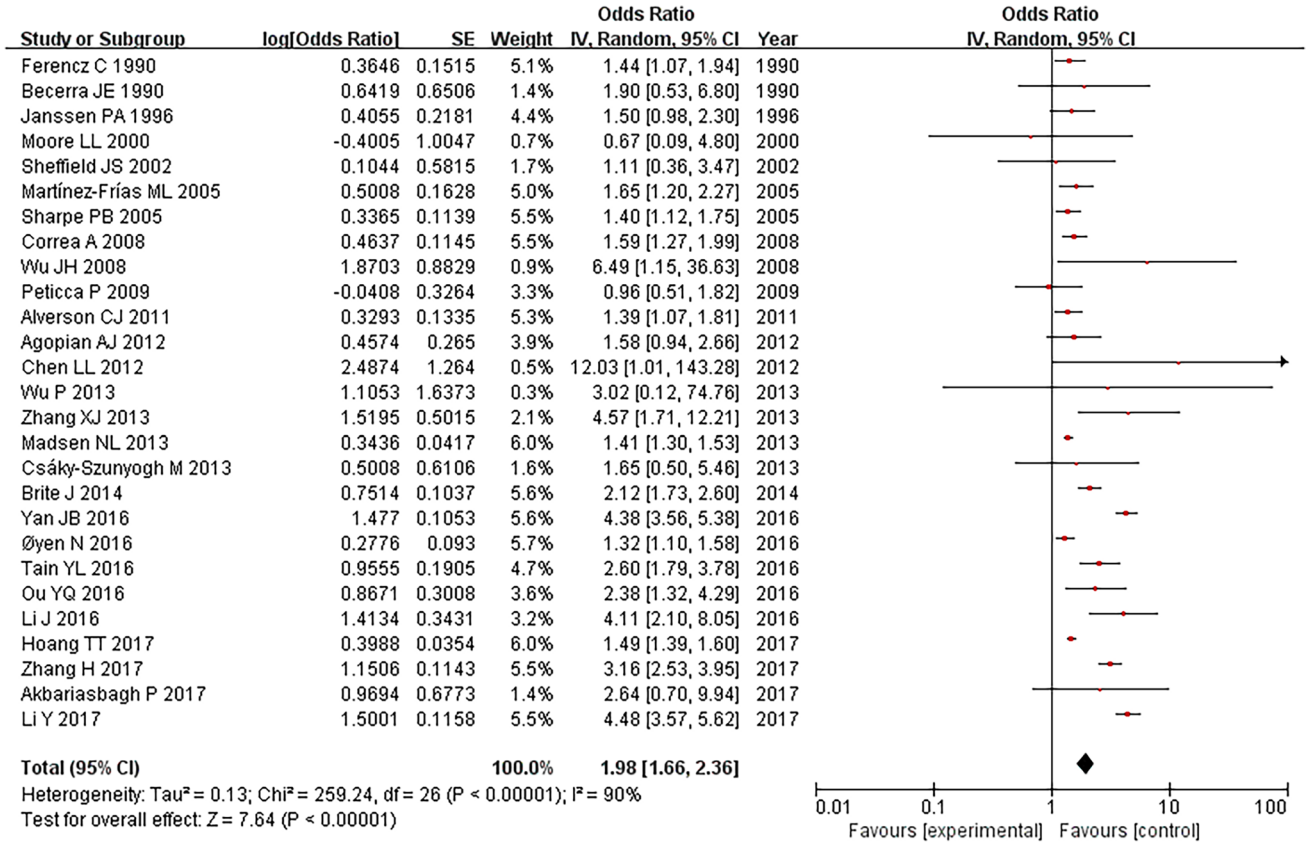

Fig. 4 Forest plot for GDM and risk of CHDs

region, sample sources and study design for the associations between maternal DM and risk of total CHDs (I^2 range from 68 to 98%; $P < 0.00001$) (Table 2). Furthermore, exclusion of any single study did not materially change the overall risk estimates, which proved that the results were reliable. The funnel plot did not show any substantial asymmetry. Besides, Begg's rank correlation test also indicated little evidence of publication bias ($P = 0.103$ for maternal DM, 0.792 for PGDM, and 0.152 for GDM).

Discussion

To the best of our knowledge, this review is the most comprehensively updated meta-analysis that quantifies the risks of CHDs and the phenotype of more than 20 specific CHDs in maternal DM patients. We evaluated the risk of CHDs and its phenotypes associated with maternal DM using data from 52 case–control and cohort studies, which met eligibility criteria and involved 259,917 CHDs patients in a total of 16,929,835 participants, with sufficient statistical power. In this study, the sample sizes were more than 2000 among 62% of the studies; more than three-quarters (88.5%) of the studies were considered to have higher methodological quality, which contributed 99.98% of the participants. Potential heterogeneity moderators could be identified by subgroup and sensitivity analysis.

Previous studies, such as the large-sample size cohort studies from developed countries, indicated that maternal DM was associated with CHDs in offspring [12–16]. However, the magnitude of the associations varied (ranging from 0.52 to 12.03) across studies, and there was insufficient evidence for the CHD phenotypes. This review and meta-analysis brought about three major findings. First, we found that all types of DM including any DM, PGDM and GDM were significantly associated with risk of CHDs in offspring. Second, all types of DM were almost significantly associated with most phenotypes of CHDs. Third, there were geographic differences for risk of CHDs associated with maternal DM.

It was worth noting that the risk of CHDs in offspring seems to be significantly higher among mothers with PGDM (OR = 3.18) than those with GDM (OR = 1.98). A common view was that the mechanisms of maternal DM on CHDs in offspring were quite different between PGDM and GDM women. It was well known that the critical stage of fetal heart development was 3–7 weeks of gestation [67]. Pre-pregnancy diabetic may lead to hyperglycemia conditions in

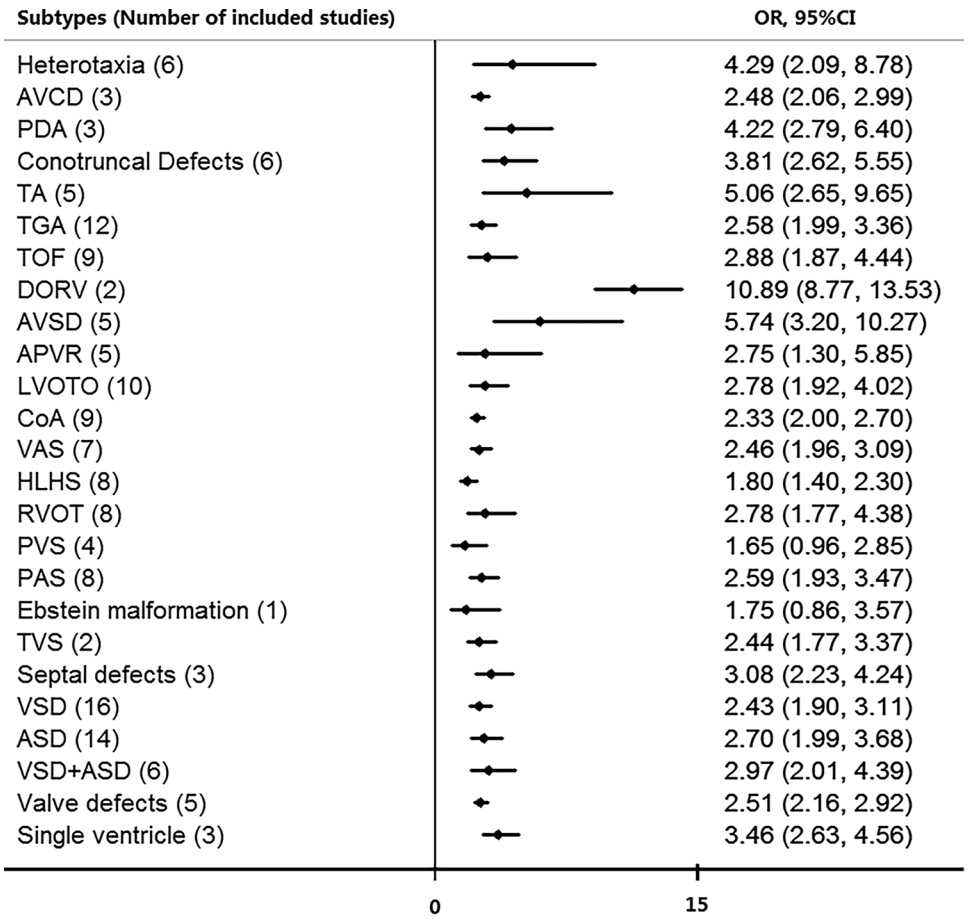

Fig. 5 Maternal DM and risk of specific subtypes of CHDs

the uterine environment at this stage, which may change the key molecular pathways during cardiac development, resulting in abnormal embryonic heart development [8, 23]. However, GDM is usually diagnosed between 24 and 28 weeks of gestation, which has missed the critical stage of embryonic heart development [68]. Therefore, there was a possibility that women with PGDM were at a higher risk of developing CHDs in offspring than those with GDM.

Compared with previous studies on this topic, we comprehensively evaluated the association between different types of diabetes and various subtypes of congenital heart malformations. Findings from the present study suggested that maternal DM, especially for PGDM, were significantly associated with most of phenotypes of CHDs. The number of specific CHD phenotypes with statistically significant differences was more found among women with PGDM than women with GDM. Typically, TA (OR = 7.81), AVCD (OR = 6.12) and TOF (OR = 4.25) were identified as the top three of the most common phenotypes of CHDs associated with PGDM, which was consistent with the results of the meta-analysis performed by Hoang et al. [23] (OR = 14.49 for TA, 5.78 for AVCD, and 4.14 for TOF). Of note, our study indicated that there was a strong association between PGDM and outflow tract defects. The formation and remodeling of the mature outflow tract (OFT) was established by cardiac neural crest cell (CNCC) [69]. An animal study from Morgan [70] found that CNCC migrated more in diabetic mouse embryos compared with non-diabetic mice, which may bring about an increase of cell apoptosis and outflow tract defects.

Subgroup analysis was used to explore heterogeneity sources of included studies. Our subgroup analysis indicated that geographic region was the most relevant heterogeneity source. However, the results of all subgroup analyses did not substantially change our conclusions. Previous studies [2] have shown that there were significant regional differences in the birth prevalence of CHDs, the highest reported in Asia (9.3 per 1000 live births), and the prevalence reported in Europe and North America are moderate (8.2 and 6.9 per 1000 live births, respectively). The differences might be due to differences in the healthcare system, socio-economic, ethnic and environmental. In particular, most of the included studies from Asia were based primarily on retrospective case–control studies, which may be biased by the quality and intensity of the evidence due to recall bias and selection bias. In addition, our meta-analysis only included one study from Oceania, and did not provide sufficient statistical power to develop accurate effect estimates in this area. Therefore,

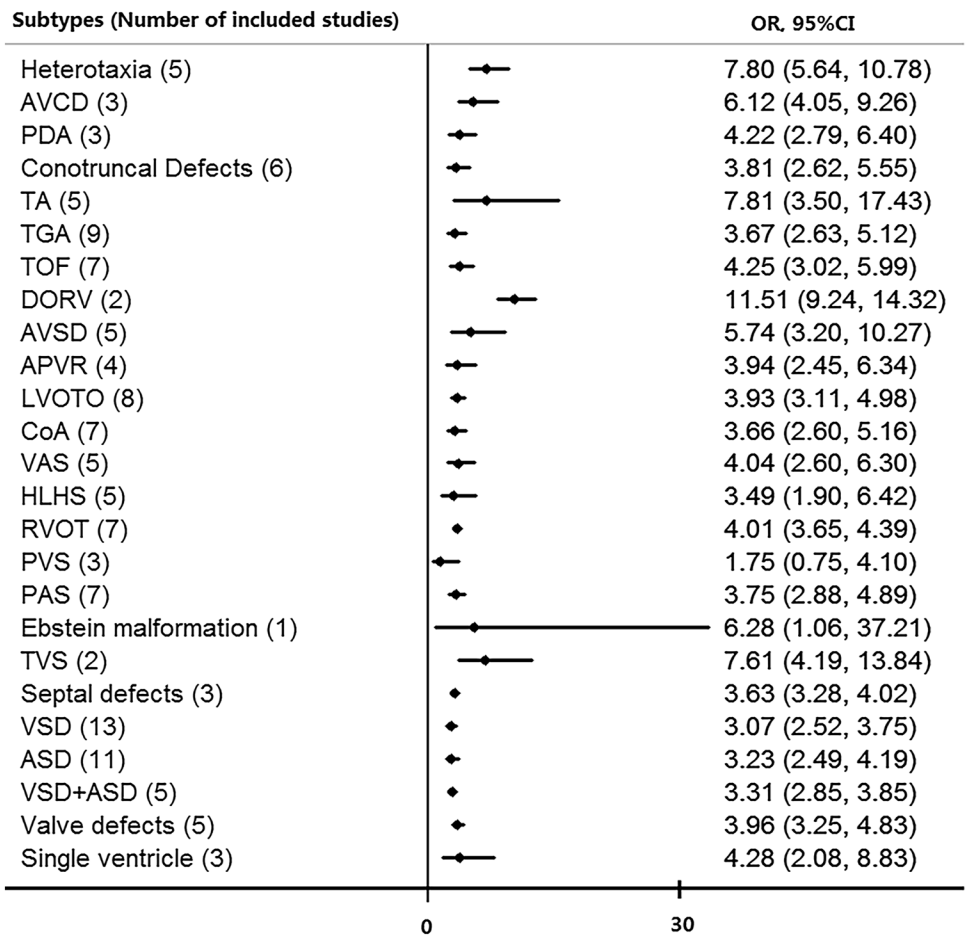

Fig. 6 PGDM and risk of specific subtypes of CHDs

more large sample, prospective cohort studies should be carried out to obtain higher quality results.

This study still had some limitations. First of all, due to language restrictions, we could only search English and Chinese databases. As a result, other studies published in other foreign languages were accidentally eliminated. Additionally, the included studies in the present review, mainly from North America, Asia, and Europe, did not represent the entire world. Therefore, additional research in other populations is warranted to generalize the findings. Second, CHDs were classified as more than 20 typical phenotypes, but not all included studies fully analyzed the associations with maternal DM types and typical CHD phenotypes. Therefore, some specific CHD phenotypes only relied on few total studies, which indicated that more studies should be included in future reviews, to provide further support for our results, especially for specific phenotypes. Third, residual confounding is of concern. Uncontrolled or unmeasured risk factors potentially produce biases. In the present review, 27 studies (51.9%) did not control any factors when estimating the effect of maternal DM on CHDs, whereas other studies adjusted and/or matched for a wide range of potential confounders for poor outcomes. Although restricting analysis to studies that have controlled confounding factors did not materially alter the combined risk estimate, we still cannot rule out the possibility that residual confounding could affect the results, because these factors that have been controlled do not explain all of the risk of CHDs. Fourth, in the present study, because variations in the definition of exposures and outcomes exist in different countries and cultures, it is extremely difficult to define uniform standards. Additionally, some literatures did not always define exposures and outcomes, and in such cases, we have to rely on the exposure or outcome terminology in the original articles. In fact, this problem mentioned above could not be solved at present, which may lead to false classification bias. Fifth, although we assessed the influence of different types of DM on CHDs, it is difficult for us to estimate the effect of type 1 diabetes and type 2 diabetes because most included study did not state the type of PGDM. Last but not least, there was substantial heterogeneity among studies for association between maternal DM and risk of CHDs. However, we can detect the major source of heterogeneity by the subgroup analysis and the sensitivity analysis. The sensitivity analysis that omitted one study at a time and calculated the combined OR for the remaining studies yielded similar results. After subgroup

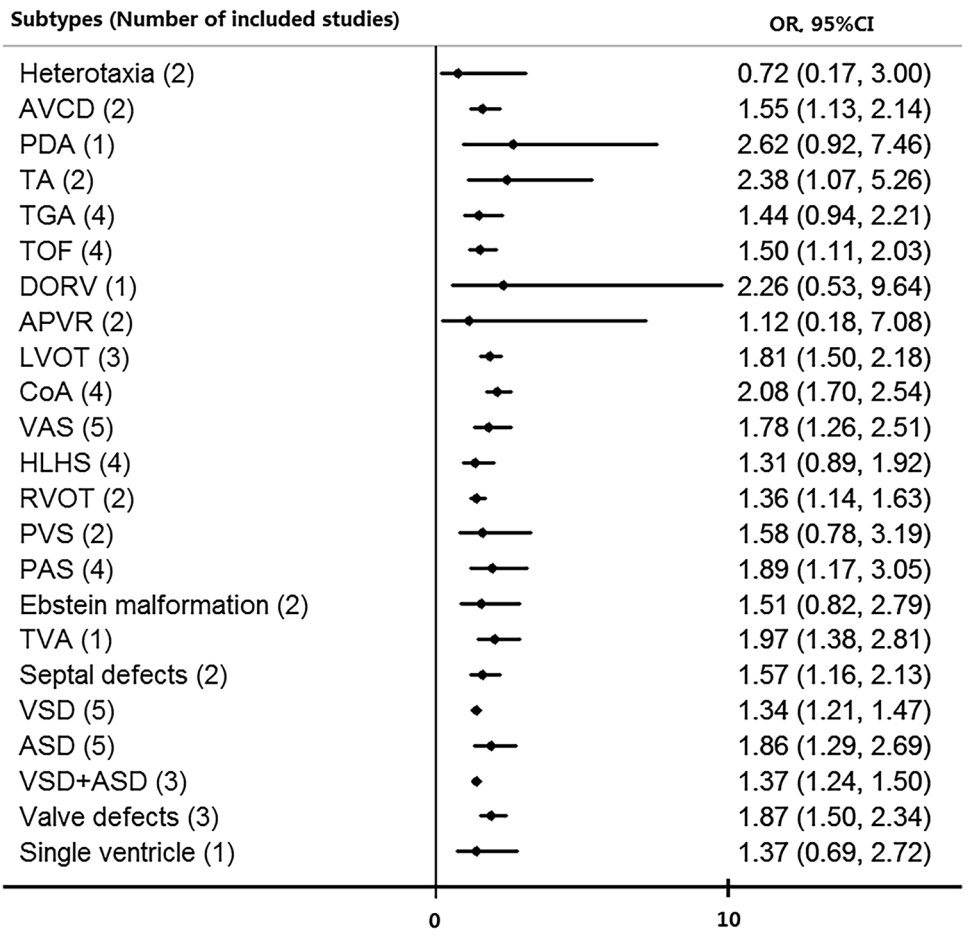

Fig. 7 GDM and risk of specific subtypes of CHDs

analysis, the heterogeneity was obviously decreased. However, our estimates have to be viewed with caution because of evidence of heterogeneity. Again, potential publication bias could influence the findings, but little evidence of publication bias was found.

Conclusion

In summary, the present study, which includes a large proportion of participants, with sufficient statistical power, aims at assessing the risk of CHDs and its specific phenotypes associated with maternal DM including PGDM and GDM. Although the role of potential bias and evidence of heterogeneity should be carefully evaluated, our meta-analysis indicates that the maternal DM including PGDM and GDM are significantly associated with risk of CHDs and its most phenotypes. Additionally, the PGDM seems to be more likely to cause CHDs in offspring than GDM. However, it remains unknown why maternal DM can increase the risk of CHDs in offspring. Further studies are needed to clarify the underlying mechanisms.

Table 2 Subgroup analysis for maternal DM and risk of total CHDs

Subgroup variables	Total diabetes mellitus ($n=52$) 2.69 (2.25–3.20) $\chi^2=2075.08$, $P<0.00001$; $I^2=98\%$	Pregestational diabetes mellitus ($n=31$) 3.17 (2.74–3.67) $\chi^2=140.81$, $P<0.00001$; $I^2=80\%$	Gestational diabetes mellitus ($n=27$) 1.97 (1.65–2.36) $\chi^2=259.26$, $P<0.00001$; $I^2=90\%$
Whether the effects were adjusted	TSD: $\chi^2=0.39$, $P=0.53$; $I^2=0\%$	TSD: $\chi^2=1.45$, $P=0.23$; $I^2=31.2\%$	TSD: $\chi^2=5.32$, $P=0.02$; $I^2=81.2\%$
Adjusted	2.55 (1.99–3.27) ($n=25$) $\chi^2=1293.33$, $P<0.00001$; $I^2=98\%$	2.95 (2.48–3.51) ($n=16$) $\chi^2=91.48$, $P<0.00001$; $I^2=84\%$	1.50 (1.35–1.67) ($n=11$) $\chi^2=13.31$, $P=0.21$; $I^2=25\%$
Unadjusted	2.83 (2.28–3.51) ($n=27$) $\chi^2=310.05$, $P<0.00001$; $I^2=92\%$	3.57 (2.76–4.61) ($n=15$) $\chi^2=50.49$, $P<0.00001$; $I^2=72\%$	2.18 (1.64–2.92) ($n=16$) $\chi^2=215.65$, $P<0.00001$; $I^2=93\%$
Study design	TSD: $\chi^2=0.24$, $P=0.62$; $I^2=0\%$	TSD: $\chi^2=0.55$, $P=0.46$; $I^2=0\%$	TSD: $\chi^2=0.99$, $P=0.32$; $I^2=0\%$
Case–control studies	2.70 (2.31–3.16) ($n=36$) $\chi^2=267.46$, $P<0.00001$; $I^2=87\%$	3.08 (2.48–3.82) ($n=18$) $\chi^2=64.56$, $P<0.00001$; $I^2=74\%$	2.12 (1.69–2.65) ($n=19$) $\chi^2=204.19$, $P<0.00001$; $I^2=91\%$
Cohort studies	2.45 (1.70–3.52) ($n=16$) $\chi^2=961.01$, $P<0.00001$; $I^2=98\%$	3.41 (2.89–4.03) ($n=13$) $\chi^2=50.95$, $P<0.00001$; $I^2=76\%$	1.74 (1.27–2.38) ($n=8$) $\chi^2=52.23$, $P<0.00001$; $I^2=87\%$
Continents	TSD: $\chi^2=28.74$, $P<0.00001$; $I^2=89.6\%$	TSD: $\chi^2=14.95$, $P<0.00001$; $I^2=79.9\%$	TSD: $\chi^2=87.90$, $P<0.00001$; $I^2=96.6\%$
North America	2.27 (1.83–2.81) ($n=22$) $\chi^2=963.98$, $P<0.00001$; $I^2=98\%$	3.81 (3.17–4.57) ($n=17$) $\chi^2=53.41$, $P<0.00001$; $I^2=70\%$	1.52 (1.39–1.65) ($n=12$) $\chi^2=16.75$, $P=0.12$; $I^2=34\%$
Asia	3.52 (2.81–4.43) ($n=18$) $\chi^2=53.21$, $P<0.00001$; $I^2=68\%$	1.72 (1.19–2.50) ($n=3$) $\chi^2=2.82$, $P=0.24$; $I^2=29\%$	3.67 (3.07–4.38) ($n=10$) $\chi^2=14.25$, $P=0.11$; $I^2=37\%$
Europe	2.70 (2.25–3.24) ($n=11$) $\chi^2=37.75$, $P<0.0001$; $I^2=74\%$	2.92 (2.36–3.61) ($n=10$) $\chi^2=43.24$, $P<0.00001$; $I^2=79\%$	1.41 (1.21–1.64) ($n=4$) $\chi^2=2.37$, $P=0.50$; $I^2=0\%$
Oceania	1.63 (1.35–1.97) ($n=1$) not applicable	2.84 (1.89–4.26) ($n=1$) not applicable	1.40 (1.12–1.75) ($n=1$) not applicable
Sample source	TSD: $\chi^2=3.32$, $P=0.07$; $I^2=69.9\%$	TSD: $\chi^2=0.95$, $P=0.33$; $I^2=0\%$	TSD: $\chi^2=10.83$, $P=0.001$; $I^2=90.8\%$
Population-based studies	2.46 (2.03–2.98) ($n=34$) $\chi^2=1758.13$, $P<0.00001$; $I^2=98\%$	3.33 (2.90–3.81) ($n=24$) $\chi^2=104.53$, $P<0.00001$; $I^2=78\%$	1.66 (1.47–1.89) ($n=18$) $\chi^2=73.74$, $P<0.00001$; $I^2=77\%$
Hospital-based studies	3.43 (2.54–4.64) ($n=17$) $\chi^2=76.14$, $P<0.00001$; $I^2=79\%$	2.61 (1.63–4.17) ($n=7$) $\chi^2=20.31$, $P=0.002$; $I^2=70\%$	3.33 (2.25–4.94) ($n=9$) $\chi^2=34.22$, $P<0.0001$; $I^2=77\%$

TSD Test for subgroup differences

Acknowledgements The authors would like to thank the editors and reviewers for their suggestions.

Author contribution LTC: literature searching, data collection and manuscript writing. TBY: manuscript writing. LZC: manuscript revision. LSW: data management. TTW: data analysis. LJZ: data collection. ZWY: data interpretation. SMZ: literature searching. LL: data collection. ZZ: data analysis. JBQ: conception, design and revise the manuscript.

Funding This work was supported by the Project Funded by Natural Science Foundation of Hunan Province [Grant numbers 2018JJ2551], National Natural Science Foundation Program of China [Grant numbers 81803313], Hunan Provincial Key Research and Development Program [Grant numbers 2018SK2063; 2018SK2062], and New Teachers' Scientific Research Driven Foundation of Central South University [Grant numbers 502045001].

Compliance with ethical standards

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

Ethical approval Not applicable.

Informed consent Not applicable.

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