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ORIGINAL ARTICLE

Maternal diabetes and risk of childhood malignancies in the offspring: a systematic review and meta-analysis of observational studies

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Abstract

Aims Diabetes mellitus (DM) is widely recognized as a risk factor for diverse cancers in adults. However, the association between maternal diabetes and risk of childhood cancer in the offspring has so far not been well studied. We thus conducted a meta-analysis to evaluate the role of maternal diabetes on the risk of childhood cancer.

Methods We performed a comprehensive literature search to identify eligible studies published up to June 20, 2020, including the PubMed, Web of science and Embase databases. Summary odds ratios (OR) and 95% confidence intervals (CI) were computed using a random-effects model ($I^2 \geq 25\%$) or a fixed-effect model ($I^2 < 25\%$).

Results Totally, sixteen case–control and six cohort studies on the risk of childhood cancer associated with maternal diabetes were included. Overall, children of diabetic women had a significantly increased risk in childhood malignancy (OR, 1.30; 95% CI, 1.10–1.53). Notably, a significantly elevated risk of childhood cancer in the offspring was found for women with pre-existing diabetes (OR, 1.41; 95% CI, 1.17–1.70), but not for women with gestational diabetes mellitus (GDM) (OR, 1.10; 95% CI, 0.94–1.28). For site-specific cancers, maternal diabetes was associated with a higher risk of leukemia in offspring (OR, 1.30; 95% CI, 1.15–1.48), especially for acute lymphoblastic leukemia (OR, 1.44; 95% CI, 1.27–1.64). However, no significant associations were observed between maternal diabetes and the risk of lymphomas and retinoblastoma.

Conclusions Our meta-analysis indicates that maternal diabetes is associated with an increased risk of childhood cancer in the offspring, particularly for acute lymphoblastic leukemia. Future study should investigate the underlying biological mechanisms behind the association.

Keywords Maternal diabetes · Gestational diabetes mellitus · Childhood cancers · Childhood leukemia

Introduction

Cancer is the leading cause of death among children worldwide, and the recorded incidence is still on the rise [1, 2]. Approximately 416,500 new childhood cancer cases were diagnosed in 2017, which resulted in 11.5 million disability-adjusted life-years (DALYs) globally [3]. Moreover, childhood cancer is substantially underdiagnosed due to the limited data for low-income and middle-income countries [4]. The cause of childhood cancer is not well understood, and known risk factors only include some congenital genetic syndromes, prenatal and perinatal factors. However, only 5–10% of childhood cancers are suspected to be attributable to inherited syndromes [5]. Therefore, it is necessary to evaluate the effect of prenatal and perinatal factors on the development of childhood malignancy.

Diabetes during pregnancy conferred an elevated risk of adverse pregnancy outcomes, including caesarean section

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and fetal macrosomia [6]. Besides, children born to women with gestational diabetes mellitus (GDM) are at greater risk of obesity, type 2 diabetes and cardiovascular disease [7–9]. Additionally, epidemiological studies have extensively established the relationship between diabetes and cancer incidence in adults [10–13]. Thereby, there is an urgent need to assess whether maternal diabetes increases the incidence of childhood cancers in the offspring.

Several studies have assessed the risk of development of childhood malignancy in the children of diabetic mothers, but the results were not consistent. Therefore, a detailed meta-analysis of observational studies was performed to determine the association of childhood cancer with maternal diabetes.

Methods

Search strategy and study selection

We performed a comprehensive literature search, including the PubMed, Embase and Web of science databases from their inception to June 30, 2020, to identify studies that investigated the association between maternal diabetes and risk of childhood cancer in the offspring. The literature search strategy included the following key terms (Supplementary Table 1): "maternal diabetes", "gestational diabetes mellitus", "pre-gestational diabetes", "pre-pregnancy diabetes", "pre-existing diabetes" (PDM), "childhood cancer", "childhood malignancies", "pediatric neoplasms" and "pediatric cancers". Besides, we manually searched for references cited in the original study and the review.

Eligible studies should meet the following inclusive criteria: (1) studies were cohort or case–control studies; (2) the exposure of interest was maternal diabetes including PDM and GDM, and the outcome of interest was the diagnosis of childhood malignancy in the offspring; (3) the sample size with maternal diabetes was available; (4) reported the effect estimates (ESs) (odds ratio (OR), relative risk (RR), standard incidence ratio (SIR), or hazard ratio (HR)) and their corresponding 95% confidence intervals (CIs) or gave sufficient data to compute them.

Data extraction and quality assessment

The following data were extracted independently from the included literature by two reviewers: first author, year of publication, country, study type (cohort or case–control study), study period, type of maternal diabetes (diabetes (any), PDM and GDM), type of childhood cancer, number of cases with maternal diabetes, number of cancer cases, and ascertainment of maternal diabetes and cancer, adjusted ESs and corresponding 95% CIs, as well as confounders for adjustment.

Newcastle–Ottawa Scale (NOS) guidelines include 3 quality parameters: four items for selection, two items for comparability and three items for outcomes, to assess the quality of studies included in our meta-analysis [14]. Studies scoring 7–10 were identified as high-quality, those with scores of 3–6 were considered moderate quality, and the others were of low quality.

Statistical analysis

The summary ORs and corresponding 95% CIs were calculated to examine the effect of maternal diabetes on the incidence of childhood cancer in the offspring. Since the risk of childhood cancer in the general population was very low, all ESs were interpreted as OR for simplicity. A fixed-effect model was used for outcomes with low heterogeneity ($I^2 < 25\%$) among included studies; otherwise, a random-effect model was used ($I^2 > 25\%$). Cochran Q and I^2 statistics were used to evaluate statistical heterogeneity between the included studies. I^2 values of $< 25\%$, 25–75% and $> 75\%$ were defined as low, medium and high heterogeneity, respectively [15]. To investigate the sources of heterogeneity, we conducted subgroup analyses and meta-regression analyses according to maternal diabetes types (diabetes (any), PDM and GDM), study design (cohort and case–control studies), study location (Europe and other regions), number of cancer cases (≥ 3000 and < 3000), cancer diagnosis (medical records and cancer registry) and whether adjusted for birth weight and birth order (Yes and No). Sensitivity analyses were performed to evaluate the robustness of the results of our meta-analysis. Funnel plots were used to assess publication bias. Furthermore, Egger's linear regression tests and Begg's adjusted rank correlation test were conducted and a P value of < 0.05 indicated potential publication bias [16, 17]. All statistical analyses were performed using Stata, version 14.0 (Stata Corp, College Station, Texas).

Results

Study selection

Figure 1 displayed a flow diagram of the identification process of the eligible studies. A total of 527 citations were originally retrieved by searching PubMed, Embase and Web of Science, whereas four studies were manually identified by reviewing the reference list of the relevant literature. After removing duplicate articles, 477 citations reminded. Then, 432 articles were excluded after screening the titles and abstracts. Finally, we carefully reviewed the full text of

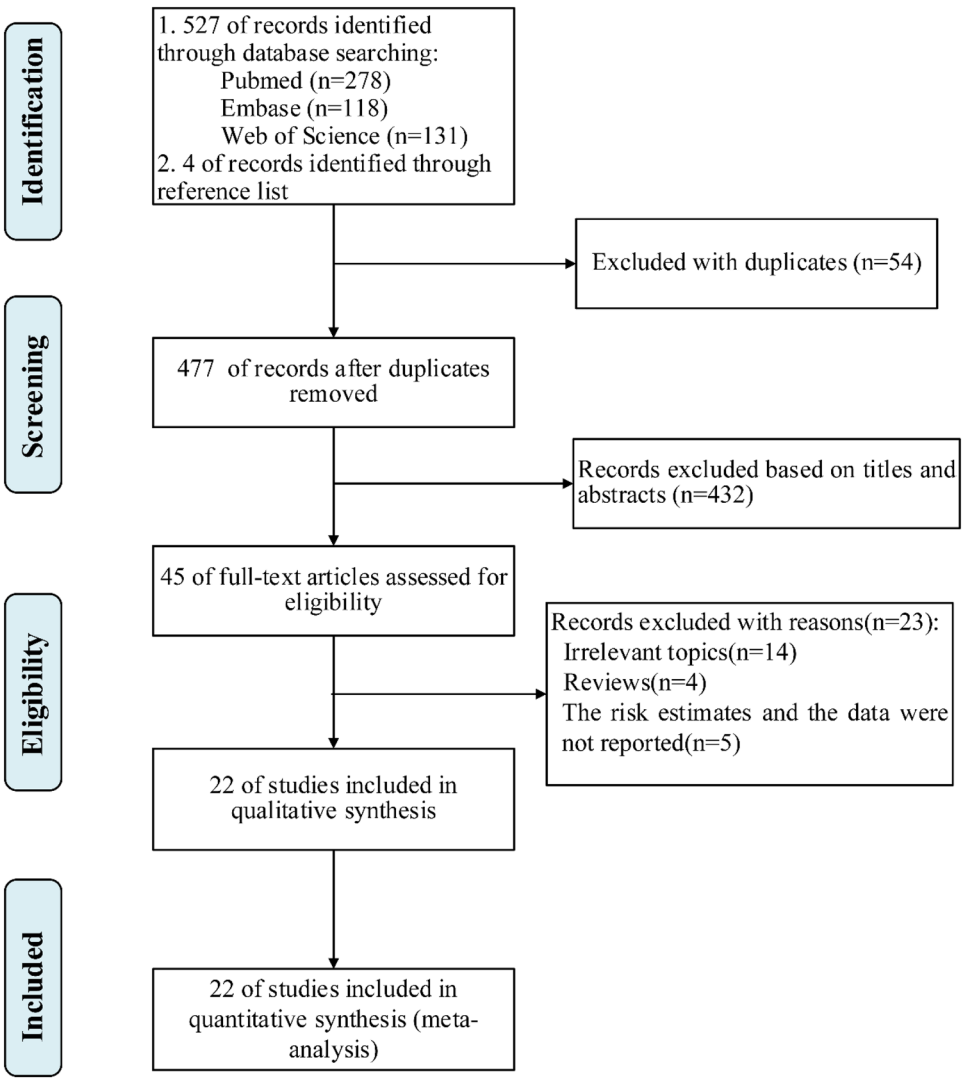

Fig. 1 PRISMA flow diagram for identification of relevant articles for the meta-analysis

the remaining 45 articles, 22 of which were enrolled in our meta-analysis [18–39].

Study characteristics

The baseline characteristics of the eligible studies were shown in Table 1. Of the 22 articles included in our meta-analysis, 16 were case–control studies [18, 19, 21–27, 29–33, 37, 39] including a total of 23,015 cancer cases and 3,974,960 controls, and the remaining six were cohort studies [20, 28, 34–36, 38], with sample sizes ranging from 8839 to 1,226,515. Most included studies ($n=15$) focused on a single cancer site [18, 19, 21, 23–27, 29, 30, 32, 33, 35–37], and seven studies assessed the overall childhood cancer risk in offspring [20, 22, 28, 31, 34, 38, 39]. Three studies reported risk estimates for multiple types of cancer [31, 34, 39]. As for the exposure of interest, ten studies gave data on maternal diabetes and did not specify diabetes type [18, 19, 21–23, 27, 30, 32–34], while 11 reported the risk estimates for GDM women [20, 24–26, 28, 29, 31, 35, 37–39]. These studies were conducted in the following countries: the USA ($n=6$), Sweden ($n=5$), Greece ($n=2$), Denmark ($n=2$), Canada ($n=2$), Italy ($n=1$), Finland ($n=1$), Israel ($n=1$), Norway ($n=1$) and Switzerland ($n=1$).

The majority of studies ($n=17$) identified maternal diabetes according to the medical birth registries or medical records [18, 20, 22–28, 30–32, 34–36, 38, 39]. However, five studies were based on self-report methods (questionnaire or telephone interview) [19, 21, 29, 33, 37]. All the included studies ascertained cancers based on cancer registries or medical records. Twenty studies reported risk estimates calculated using multivariate statistical models to adjust for significant confounders [18–31, 33–36, 38, 39], while two studies [32, 37] only provided data that can be used to calculate ORs. Fourteen studies [19, 20, 22–24, 28, 30, 31, 33–36, 38, 39] were adjusted for maternal age, five [18, 22, 23, 28, 34] were adjusted for birth weight, six [19, 28, 30, 34, 35, 39] were adjusted for birth order, and four [19, 20,

Table 1 Main characteristics of the included studies included in the meta-analyses

First author, year, country	Study type	Study period	Type of maternal diabetes	Type of cancer	No. of sample (cases/controls)	No. of maternal diabetes	Ascertainment of maternal diabetes	Ascertainment of cancer	OR (95%CI)	Adjustment variables
Cnattingiu et al. 1995, Sweden [18]	Case–control	1973–1989	Diabetes (any)	Childhood LL	613/3,065	5/12	The Medical Birth Register	National Cancer Register	2.1 (0.7–6.0)	Postpartum asphyxia, supplementary oxygen and birth weight
Petridoul et al. 1997, Greece [19]	Case–control	1993–1994	Diabetes (any)	Childhood leukemia (89% ALL)	153/180	3/2	Self-report (an interviewer-administered questionnaire)	A nationwide network of childhood hematologists / oncologists	2.99 (0.30–29.56)	Maternal age at birth, maternal education, birth order, maternal smoking, alcohol consumption, coffee drinking, environmental variables, biomedical variables (Birthweight, anemia during pregnancy, etc.)
Aberg et al. 2001, Sweden [20]	Cohort	1987–1997	PDM, GDM	All types	GDM: 8684 PDM: 3874 Controls: 1,213,957	GDM: 20 PDM: 20 Controls: 6,264	Swedish Medical Birth Registry, hospital data	Hospital Discharge Registry; National Board of Health, Stockholm	GDM: 0.91(0.58–1.43) PDM: 1.64(1.06–2.54)	Year of birth, maternal age, parity and smoking in early pregnancy
Hamrick et al. 2001, USA and Canada [21]	Case–control	1992–1994	Diabetes (any)	Neuroblastoma	504/504	28/24	Self-report (telephone interview)	Children's Cancer Group; the Pediatric Oncology Group	1.1 (0.6, 2.1)	The child's gender, mother's race and education, and household income in the birth year

Table 1 (continued)

First author, year, country	Study type	Study period	Type of maternal diabetes	Type of cancer	No. of sample (cases/controls)	No. of maternal diabetes	Ascertainment of maternal diabetes	Ascertainment of cancer	OR (95%CI)	Adjustment variables
Westbom et al. 2002, Sweden [22]	Case–control	1987–1997	Diabetes (any)	All types	4,380	10	The Medical Birth Registry	The Cancer Registry	2.25 (1.22–4.15)	Year of birth, maternal age, parity, multiple birth, and 500 g birth weight class
Podvin et al. 2006, USA [24]	Case–control	1981–2003	PDM, GDM	Leukemia	595/5,950	GDM: 2/9 PDM: 13/77	Birth certificate records	Washington State Cancer Registry	GDM: 2.3 (0.5–11.0) PDM: 1.4 (0.8–2.7)	Maternal age
McLaughlin et al. 2006, USA [23]	Case–control	1985–2001	Diabetes (any)	ALL, AML	ALL:916 AML:154 Controls: 9,686	ALL:25 AML:1 Controls: 164	The birth certificates	New York State Cancer Registry	ALL:1.44 (0.91–2.18) AML:0.26 (0.02–1.18)	Birth year, gender, race and ethnicity, maternal age, gestational age and birth weight
Chow et al. 2007, USA [25]	Case–control	1980–2004	Diabetes (any), GDM	Neuroblastoma	240/2,400	All types: 12/72 GDM: 12/67	Washington State birth certificate records	Cancer Surveillance System; the Washington State Cancer Registry	Diabetes (any): 1.71(0.91–3.22) GDM:1.84(0.98–3.47)	Birth year
Milne et al. 2007, Australia [26]	Case–control	1980–2004	GDM	ALL, AML	ALL:243 AML:36 Controls: 576,314	ALL:3 AML:1 Controls: 9,587	Western Australian Birth Defects Registry	Cancer registrations	ALL:1.03(0.33–3.22) AML:2.15(0.29–15.72)	No
Wu et al. 2012, Denmark [28]	Cohort	1977–2008	T1DM, T2DM, GDM	All types	1,781,576	T1DM:3 T2DM:19 GDM:8	Danish National Diabetes Register	Danish National Hospital Register	Diabetes (any): 1.3 (1.0–1.7) T1DM: 1.2 (0.4–3.9) T2DM: 1.9 (1.2–3.0) GDM: 0.7 (0.3–1.3)	Maternal age, parity (1, 2, and 3+), sex, maternal education, maternal marital status, calendar year, birth weight, and square of the birth weight

Table 1 (continued)

First author, year, country	Study type	Study period	Type of maternal diabetes	Type of cancer	No. of sample (cases/controls)	No. of maternal diabetes	Ascertainment of maternal diabetes	Ascertainment of cancer	OR (95%CI)	Adjustment variables
Heck et al. 2012, USA [27]	Case–control	1988–2007	Chronic diabetes	Retinoblastoma	609/209,051	10/3,755	California birth certificates record	California Cancer Registry records	0.86 (0.46, 1.62)	Year of birth, father's age, urban or rural county of residence, mother's race and birthplace
Heck et al., 2015, USA and Canada [29]	Case–control	2006–2011	Diabetes (any), GDM	Retinoblastoma	280/146	6/22	Self-report (telephone interview)	Children's Oncology Group	All types: Unilateral cases: 2.2(0.8, 6.6) Bilateral cases: 1.9 (0.6, 6.6) GDM: Unilateral cases: 1.9 (0.6. 5.7) Bilateral cases: 1.9 (0.6, 6.6)	Child age at interview, mother's race/ethnicity, mother's educational attainment, household income, mother's age at birth, and maternal smoking in the month before or during pregnancy
Petridou et al. 2015, Sweden [30]	Case–control	1973–2007	Diabetes (any)	NHL, HL	NHL:515/3,443,621 HL:169/3,443,967	NHL: 4/14,969 HL:1/14,972	Standardized antenatal record	Swedish Cancer Register	NHL: 1.79(0.67–4.79) HL: 1.45(0.20–10.4)	Sex, maternal education and age, birth order, and gestational age

Table 1 (continued)

First author, year, country	Study type	Study period	Type of maternal diabetes	Type of cancer	No. of sample (cases/controls)	No. of maternal diabetes	Ascertainment of maternal diabetes	Ascertainment of cancer	OR (95%CI)	Adjustment variables
Contreras et al. 2016, USA [31]	Case–control	1988–2013	PDM, GDM	All types	11,149/270,147	PDM: 4,289/292 GDM: 1,667/68	California birth records	California Cancer Registry	PDM:ALL:1.37(1.11,1.69) Brain tumors: 0.54(0.24,1.20) Neuroblastoma:0.85(0.53,1.35) Retinoblastoma:0.93(0.51,1.69) GDM: ALL: 1.26(0.77,2.05) Brain tumors: 1.25(0.51,3.07) Neuroblastoma:1.31(0.73,2.34) Retinoblastoma:1.34(0.63,2.88)	Year of birth, maternal/paternal race/ethnicity, maternal age
Triebwasser et al. 2016, USA [32]	Case–control	1978–2009	Diabetes (any)	HL	1,216/4,485	9/40	California statewide birth records	California Cancer Registry	0.83(0.40–1.71)	No
Vienneau et al. 2016, Denmark, Sweden, Norway and Switzerland [33]	Case–control	2004–2008	Diabetes (any)	Brain tumors:	352/646	6/14	Self-report (an interviewer-administered questionnaire)	Medical records	0.76 (0.29–2.02)	Sex, age-group and geographical region, maternal age and parental education
Deleskog et al. 2017, Sweden [34]	Cohort	1973–2015	Diabetes (any)	All types	8,839	61,212	Swedish Medical Birth Register; Swedish hospital inpatient register	National Cancer Register	All types:1.06(0.89, 1.26) brain tumor:0.56(0.35, 0.91) Leukemia:1.47(1.13, 1.92) ALL: 1.64(1.23, 2.18) Lymphoma:1.45(0.90, 2.36)	Sex, decade of birth, maternal age, highest attained parental education level, birth order, birth weight by gestational age, gestational age, child's diabetes status and child birth defects

Table 1 (continued)

First author, year, country	Study type	Study period	Type of maternal diabetes	Type of cancer	No. of sample (cases/controls)	No. of maternal diabetes	Ascertainment of maternal diabetes	Ascertainment of cancer	OR (95%CI)	Adjustment variables
Søegaard et al. 2018, Denmark [35]	Cohort	1996–2015	PDM, GDM	ALL	1,187,482	PDM: 5409 GDM: 24,306	Danish National Patient Register (NPR)	Nordic Society of Pediatric Hematology and Oncology leukemia database	PDM:2.90(1.30–6.51) GDM:1.75(1.02–2.98)	Maternal age at delivery (linearly), ethnicity (Danish or other), birth order (1, 2, or ≥ 3), maternal smoking (yes or no) and birth cohort (5-year intervals)
Borsari et al. 2019, Italy [36]	Cohort	1998–2010	PDM	ALL	1,321/240,637	1,321	Hospital discharge (HD) records	National Childhood Cancer Register	2.6 (0.6–10.5)	Maternal demographic characteristics (age, maternal ethnicity)
Georgakis et al. 2019, Greece [37]	Case–control	2010–2016	GDM	Brain tumors	203/406	11/26	Self-report (questionnaire)	National Registry for Childhood Hematological Malignancies and Solid Tumors	0.84(0.41–1.73)	No
Seppälä et al. 2019, Finland [39]	Case–control	1996–2014	PDM, GDM	All types	2,037/10,185	241/940	The Care Register for Health Care	The Finland Cancer Registry	PDM: All types: 1.11(0.73–1.69) ALL:2.10(1.05–4.21) Leukemia:1.56(0.80–3.04) GDM: All types: 1.31(1.11–1.54) ALL:1.10(0.78–1.55) Leukemia:1.26(0.94–1.70) Lymphoma:1.59(0.81–3.12) Other types:1.35(1.04–1.77)	Maternal age, parity, smoking status

Table 1 (continued)

First author, year, country	Study type	Study period	Type of maternal diabetes	Type of cancer	No. of sample (cases/controls)	No. of maternal diabetes	Ascertainment of maternal diabetes	Ascertainment of cancer	OR (95%CI)	Adjustment variables
Kessous et al. 2019, Israel [38]	Cohort	1991–2014	GDM	All types	10,294/226,599	10,294	The perinatal database	Medical records	1.03 (0.58–1.82)	Maternal age, gestational age at delivery and hypertensive disorders

GDM Gestational diabetes mellitus, *PDM* preexisting diabetes mellitus, *OR* odds ratio. *CI* confidence interval, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *AML* acute myeloid leukemia, *LL* lymphoblastic leukemia, *ALL* acute lymphoblastic leukemia

29, 39] were adjusted for maternal smoking status. As shown in Supplementary Table 2, seventeen studies [19, 21, 22, 33, 37] were considered as high quality, and the other 17 were of moderate quality [18, 20, 23–32, 34–36, 38, 39] according to the Newcastle–Ottawa quality tool.

Maternal diabetes and childhood cancer risk

Seven studies [20, 22, 28, 31, 34, 38, 39] explored the childhood cancer risk associated with maternal diabetes when all cancer subtypes were combined, with a total of 7,545,946 participants and 34,351 cases with childhood cancer. The ascertainment of exposure and outcome was based on birth registries, cancer registry and medical records. Three studies [22, 28, 39] reported a significant positive association, two [34, 38] found a positive, though non-significant association. The other two studies [20, 31] reported the ORs for GDM and PDM, respectively. Interestingly, they both reported that PDM conferred elevated risk of cancer, but GDM did not. As shown in Fig. 2, the summary RR was 1.30 (95% CI, 1.10–1.53; $P=0.002$), with substantial heterogeneity in the included studies ($P<0.001$; $I^2=73.3\%$). Egger's and Begg's tests suggested no evidence of publication bias (P value for Egger: 0.525; P value for Begg: 0.917).

Subgroup analyses were conducted to explore the sources of the high heterogeneity in the included studies (Table 2). First, we investigated the impact of diabetes types on the estimates of relative risk. We found a significantly positive association between maternal PDM and childhood cancer risk (The pooled OR, 1.41; 95% CI, 1.17–1.70; $P<0.001$; $I^2=50.8\%$). However, this positive association was not significant in women with GDM (The summary OR, 1.10; 95% CI, 0.94–1.28; $P=0.223$; $I^2=33.2\%$). The summary OR was 1.26 (95% CI, 1.05–1.51; $P=0.013$; $I^2=56.8\%$) when all diabetes subtypes were combined. Univariate meta-regression analysis showed that maternal diabetes type was one of the important sources of variability between studies (Adj $R^2=18.91\%$). In addition, although some variations were discovered in the subgroup analyses of study type, study location, number of cancer cases and adjustment for birth weight and birth order, all the pooled ORs were still greater than 1.

Childhood leukemia

Of six studies [18, 19, 31, 34, 39] reported childhood leukemia risk, two [31, 34] documented a significant positive association, while the other four studies [18, 19, 24, 39] found a positive, but non-significant association. As shown in Fig. 3a, the summary OR revealed that children of diabetic mothers have a higher risk of childhood leukemia compared to the offspring of the non-diabetic mothers (The summary OR, 1.30; 95% CI, 1.15–1.48;

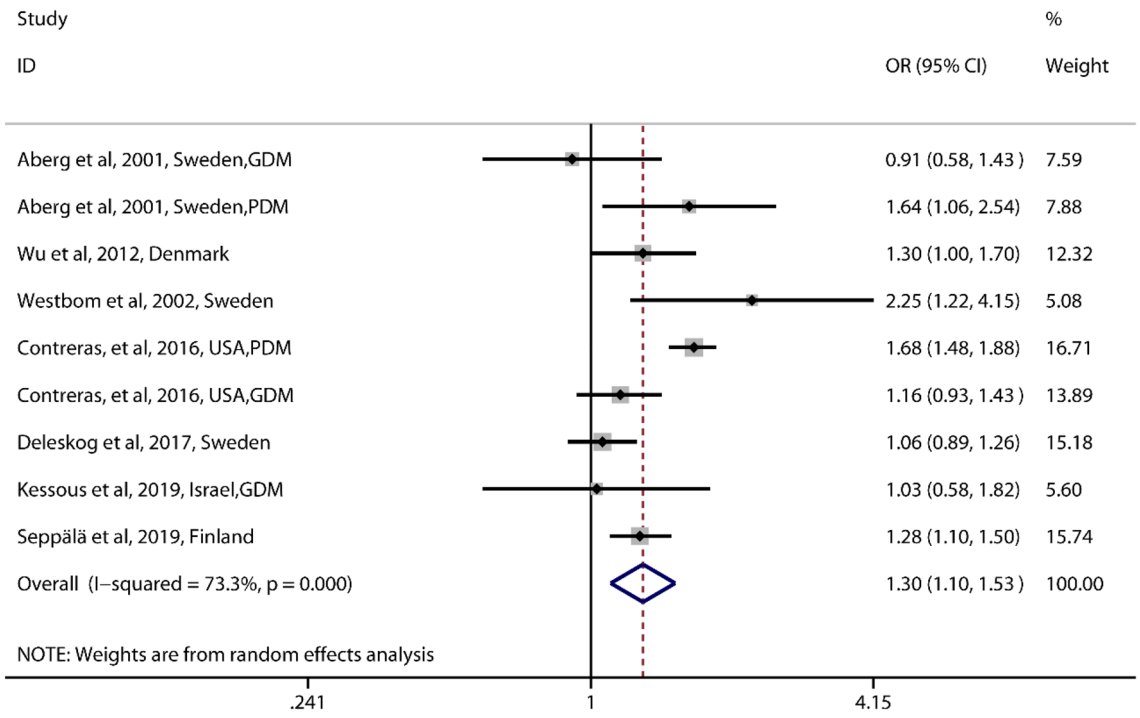

Fig. 2 Pooled effect of maternal diabetes on the risk of childhood cancers in the offspring. Data are presented as OR for each study (boxes), 95% CIs (horizontal lines) and summary as RR with 95% CI (diamond). OR odds ratio, CI confidence interval, GDM gestational diabetes mellitus, PDM preexisting diabetes mellitus

Table 2 Subgroup analysis for the association of maternal diabetes and childhood malignancy

	Number of References	Summary OR (95%CI)	Test(s) of heterogeneity			$P_{RR=1}$	$P_{Meta\text{-}regression}$
			Q	P	I^2 (%)		
Total	7	1.30 (1.08–1.56)	29.83	< 0.001	76.5	0.005	
Maternal diabetes types							
Diabetes (any)	4	1.26 (1.05–1.51)	6.94	0.074	56.8	0.013	0.266
PDM	5	1.41 (1.17–1.70)	12.2	0.058	50.8	< 0.001	0.049
GDM	6	1.10 (0.94–1.28)	7.49	0.187	33.2	0.223	Reference
Study design							
Case–control	3	1.44 (1.15–1.80)	14.36	0.002	79.1	0.001	0.202
Cohort	4	1.16 (0.98–1.37)	5.35	0.253	25.3	0.087	
Study location							
Europe	5	1.25 (1.06–1.48)	10.32	0.067	51.6	0.008	0.701
Other region	2	1.33 (0.97–1.84)	10.53	0.005	81.0	0.081	
Number of cancer cases							
≥ 3000	4	1.27 (1.03–1.58)	25.79	< 0.001	80.6	0.027	0.750
< 3000	3	1.37 (0.98–1.91)	3.76	0.153	46.8	0.065	
Cancer diagnosis							
Medical records	3	1.24 (1.03–1.50)	3.91	0.272	23.2	0.026	0.605
Cancer Registry	4	1.35 (1.09–1.67)	25.09	0	84.1	< 0.001	
Adjustment for birth weight and birth order							
Yes	3	1.30 (0.96–1.77)	6.23	0.044	67.9	0.092	0.930
No	4	1.31 (1.08–1.59)	18.06	0.003	72.3	0.007	

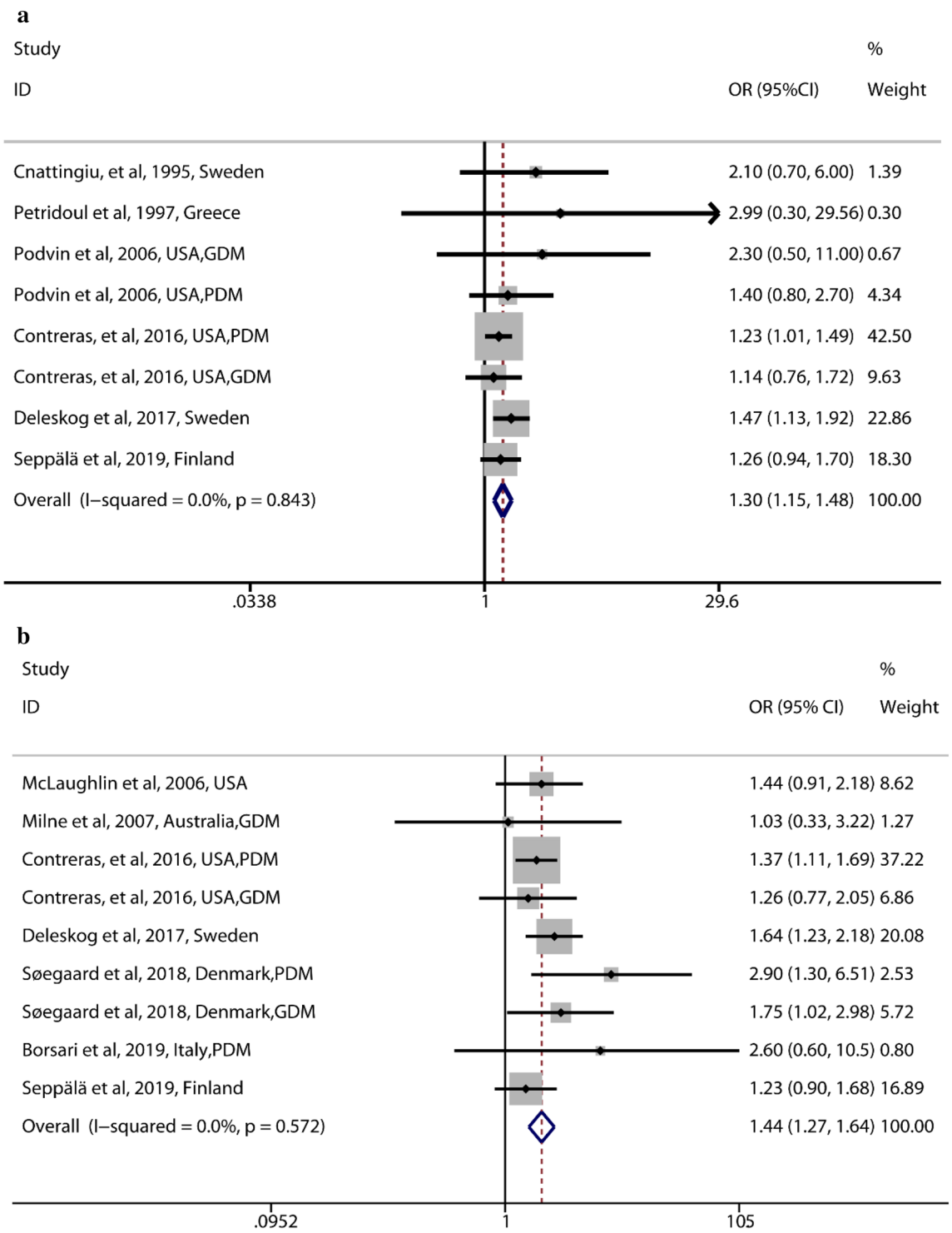

Fig. 3 Pooled effect of maternal diabetes on the risk of childhood leukemia (**a**) and ALL (**b**) risk in the offspring. ALL acute lymphoblastic leukemia

$P < 0.001$; $I^2 = 0.0\%$). The funnel plot could not rule out potential publication bias (Fig. 4). However, Egger's tests ($P = 0.072$) and Begg's tests ($P = 0.386$) showed no evidence of publication bias.

Of seven studies [23, 26, 31, 34–36, 39] reported childhood acute lymphoblastic leukemia (ALL) risk, three [31, 34, 35] reported a significant positive association, and three studies [23, 26, 39] found a positive but non-significant

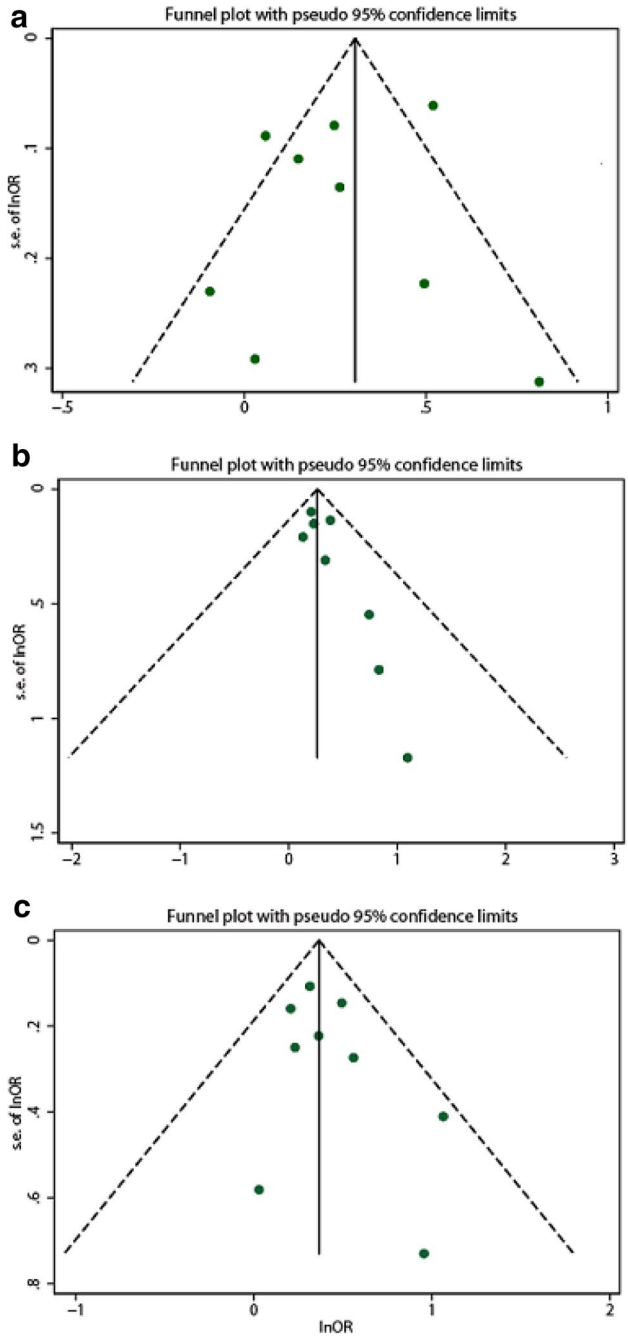

Fig. 4 Funnel plots of studies exploring the association between maternal diabetes and the risk of childhood cancer (**a**), leukemia (**b**) and ALL (**c**) in the offspring. ALL acute lymphoblastic leukemia

association. A study documented that the increased incidence of childhood ALL in the offspring was linked to maternal PDM, but not GDM. The summary OR was 1.44 (95% CI, 1.27–1.64; $P < 0.001$; $I^2 = 0.0\%$), indicating that maternal diabetes was correlated with a significantly increased risk of ALL in the offspring (Fig. 3b). What's more, both PDM (The summary OR, 1.69; 95% CI, 1.31–2.17; $P < 0.001$; $I^2 = 27.0\%$) and GDM (the summary OR, 1.32; 95% CI, 1.06–1.63; $P = 0.013$; $I^2 = 0.0\%$) were linked to a statistically significant increased risk of childhood ALL in the offspring. The results of sensitivity analysis were presented in Supplementary Table 3, indicating a robust association. There was no evidence of publication bias (P value for Egger's test: 0.285; P value for Bgge's test: 0.348) (Fig. 4c).

Other types of cancer

We also explored the risk of other common cancers in children of diabetic mothers. Three case–control studies explored the risk of neuroblastoma associated with maternal diabetes and did not report significant associations (Supplementary Fig. 3). However, the summary OR for women with GDM was 1.53 (95% CI, 1.00–2.35; $P = 0.051$) with no evidence of heterogeneity ($P = 0.439$; $I^2 = 0.0\%$). As to the brain cancers, 2 ORs were synthesized for maternal diabetes (any types) and yielded a summary OR of 0.59 (95% CI, 0.39–0.91), suggesting an inverse association (Supplementary Fig. 2). However, this inverse association was not evident in women diagnosed with PDM (OR, 0.69; 95% CI, 0.37–1.29) and GDM (OR, 0.73; 95% CI, 0.37–1.46). In addition, we found that maternal diabetes was not associated with the risk of lymphomas (OR, 1.29; 95% CI, 0.94–1.78) (Supplementary Fig. 1) and retinoblastoma (OR, 1.32; 95% CI, 0.71–2.47) (Supplementary Fig. 4) in the offspring. Funnel plots showed no evidence of publication bias (Supplementary Fig. 5). In addition, the risk estimates for some other cancer types that explored in insufficient studies are presented in Table 3.

Discussion

The aim of this study was to determine whether maternal diabetes increases the risk of childhood cancer in the offspring. Based on the 18 observational studies, we found that children of mothers with PDM had a higher risk of developing childhood cancer compared to the offspring of the non-diabetic mothers. Surprisingly, the increased risk of childhood cancer was not significant in children born to GDM women, although the pooled OR was greater than 1. For site-specific cancer, both PDM and GDM conferred an elevated risk of leukemia in the offspring, especially for ALL. However, maternal diabetes was not associated with an increased risk of lymphoma and retinoblastoma in offspring.

We found that maternal diabetes was correlated with a 30% increased risk of childhood cancer in the offspring when all cancer subtypes were combined. Intriguingly, in the subgroup analyses of maternal diabetes type, the results suggested that mothers with PDM but not GDM conferred

Table 3 Cancer risk associated with maternal diabetes for cancer types with limited numbers of studies

Cancer	Maternal diabetes types	Reference	OR (95% CI)
AML	Diabetes (any), GDM	McLaughlin et al. 2006 [23]; Milne et al. 2007 [26]	0.76 (0.10–5.99)
NHL	Diabetes (any)	Petridou et al. 2015 [24]	1.79 (0.67–4.79)
HL	Diabetes (any)	Petridou et al. 2015 [24]; Triebwasser et al. 2016 [32]	0.89 (0.45–0.75)
Astrocytomas	PDM, GDM	Contreras et al. 2016 [31]	0.91 (0.50–1.64)
Germ cell tumors	PDM	Contreras et al. 2016 [31]	0.97 (0.46–2.06)
Hepatoblastoma	PDM, GDM	Contreras et al. 2016 [31]	1.32 (0.74–2.36)
Rhabdomyosarcoma	PDM	Contreras et al. 2016 [31]	0.66 (0.27–1.60)
Wilms' tumor	PDM, GDM	Contreras et al. 2016 [31]	1.40 (0.98–2.00)

an elevated incidence childhood cancer in the offspring. This difference may be attributed to the fact that, in patients with GDM, the intrauterine environment of hyperglycemia only occurs in the later stages of pregnancy, whereas in patients with PDM, it is already present early in pregnancy. Thus, GDM showed a weaker effect on the development of childhood cancer in the offspring. Besides, metformin use in pregnancy is increasing worldwide, which may reduce the risk of pediatric cancer in the offspring to some extent. A case–control study conducted by Seppälä et al. has assessed the role of diabetes medication and found a possible risk-reducing impact on the risk of childhood cancer [39]. Furthermore, among the different hypoglycemic drugs, metformin has the most significant effect. Additionally, the summary RR for cohort studies was not statistically significant. However, the result might be due to the insufficient power. There were only three cohort studies with 173 cases of childhood malignancy on the association between maternal diabetes and childhood cancer in the offspring, which may reduce their statistical power.

Our study also reported that children born to women diagnosed with diabetes had a 29% increased risk of childhood leukemia and a 45% increased risk of ALL as compared with children born to non-diabetic mothers. Leukemia is the most common pediatric cancer worldwide, accounting for about 30% of all cases [1, 40], and ALL represents up to 80% of all pediatric leukemia [41]. Although approximately 90% are ultimately cured of their disease in many developed countries [42], ALL remains a significant cause of childhood morbidity and mortality. The positive association between birth weight and the risk for childhood leukemia, especially for ALL, has been declared in multiple epidemiological studies [43–45]. Besides, numerous studies have supported a link of high birth weight with maternal diabetes. Birth weight may thus mediate the association between maternal diabetes and childhood ALL in the offspring. Additionally, hyperglycemia and hyperinsulinism may also play an influential role in the development of childhood leukemia. First, maternal hyperglycemia could increase fetal growth, affect some epigenetic modifications in the offspring [46, 47], which may play an important role in offspring's development of ALL. Second, hyperinsulinism could strongly activate the insulin receptor (IR) signaling pathways and increase the production of insulin-like growth factor (IGF)-1, which may cause proliferation of progenitor or preleukemic cells and lead to childhood leukemia [48, 49].

We also reported that women with GDM conferred an elevated risk of neuroblastoma in the offspring. Of note, only two studies on the association between GDM and the risk of neuroblastoma in the offspring were included. The inverse association between maternal diabetes and brain cancers has the same limitations. Therefore, due to the limited data, these findings need further studies to identify. In addition, our study failed to find any significant associations between maternal diabetes and the risk of lymphomas, retinoblastoma in the offspring. However, considering that the pooled OR for lymphoma was significantly greater than 1, further studies of the association between childhood lymphoma and maternal diabetes appear to be warranted. Retinoblastoma is related to the loss or mutation of both alleles of the RB1 tumor suppressor gene [50] and may be unaffected by diabetes.

Our study has two major strengths. First, this is the first meta-analysis to assess the association between maternal diabetes and the risk of childhood cancer in the offspring. Second, we distinguished between PDM and GDM and explored their effects on the risk of childhood malignancy in offspring separately. However, several limitations in our study should be recognized. First, the included studies have different adjusted models, and some did not take into account potential confounders such as hypertensive disorders, birth weight, other related environmental exposures and lifestyle factors associated with childhood cancer. There is an obvious need to study the role of these confounding factors. Second, whether the use of diabetes medication modifies the association between maternal diabetes and childhood cancer risk in the offspring is not clear and need more research to identify. Third, several studies included a limited number of

childhood cancer cases born to women with diabetes, thus may reduce the precision of risk estimates. Fourth, most of the included studies were case–control studies, so recall bias was unavoidable. Finally, for certain types of childhood cancer, there were limited data on their risk associated with maternal diabetes.

Conclusion

Our meta-analysis provides evidence that maternal diabetes is associated with an increased risk of childhood cancer in offspring, particularly for ALL. Future studies should explore the role of potential confounders in the association between maternal diabetes and childhood cancer risk in the offspring, such as hypertensive disorders, diabetes medication, birth weight, other related environmental exposures and lifestyle factors.

Author contributions All authors contributed to the study conception and design. PY conceived of the idea and designed the study. PY, YW and XY collected the data, analyzed the data and wrote the manuscript. YL and ZJZ participated in the critical revision of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

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

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