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Maternal infection during pregnancy and type 1 diabetes mellitus in offspring: a systematic review and meta-analysis

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Abstract

Previous studies have demonstrated that type 1 diabetes mellitus (T1DM) could be triggered by an early childhood infection. Whether maternal infection during pregnancy is associated with T1DM in offspring is unknown. Therefore, we aimed to study the association using a systematic review and meta-analysis. Eighteen studies including 4304 cases and 25 846 participants were enrolled in this meta-analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were synthesised using random-effects models. Subgroup analyses and sensitivity analyses were conducted to assess the robustness of associations. Overall, the pooled analysis yielded a statistically significant association between maternal infection during pregnancy and childhood T1DM (OR 1.31, 95% CI 1.07–1.62). Furthermore, six studies that tested maternal enterovirus infection showed a pooled OR of 1.54 (95% CI 1.05–2.27). Heterogeneity from different studies was evident ($I^2 = 70.1\%$, $P < 0.001$) and was mainly attributable to the different study designs, ascertaining methods and sample size among different studies. This study provides evidence for an association between maternal infection during pregnancy and childhood T1DM.

Introduction

Type 1 diabetes mellitus (T1DM) is caused by damage to beta cells in the pancreatic islets and often develops from a preclinical phase of islet autoimmunity [1]. T1DM represents the primary form of diabetes in children <10-years-old. It can cause serious short-term consequences, such as hypoglycaemia and diabetic ketoacidosis, as well as a series of macrovascular or microvascular complications in later life [2]. It is estimated that 10-year-old children with diabetes would lose approximately 19 life-years compared with non-diabetic children [3]. The aetiology of T1DM is considered to be a combination interplay of genetic and environmental factors. The incidence of T1DM has been increasing at the rate of 2–5% a year worldwide, especially in children <5-years-old and genetic factors alone could not account for this proportion [2]. Therefore, environmental factors initiating this process should be explored for early intervention. Several studies have reported that the process of T1DM may originate from intrauterine factors such as maternal infection. Antibodies produced after infection could be transmitted to newborns through the placenta [4, 5]. On the other hand, the fetal immune system could also drive the T cells to respond to infection. Pathogen-specific T cells can be found in cord blood samples from children whose mothers had infections during pregnancy [6]. Studies on whether maternal infection could trigger the initial destruction to fetal beta cells have recently increased. However, the findings of these studies are not consistent. Therefore, we conducted a systematic review and meta-analysis to investigate the association between maternal infection during pregnancy and the risk of childhood T1DM.

Methods

This study is reported following the *Meta*-analysis of Observational Studies in Epidemiology (*MOOSE*) guidelines and was registered at the International Prospective Register of Systematic Reviews (number CRD42018091459).

Literature search

The systematic search was conducted using PubMed, Embase, the Cochrane Library and Web of Science. In each database, the studies were limited to those published before June 2018. The search strategy had no restrictions on language. The following medical subject heading terms

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and free-text terms were used to search for articles: 'gestational', 'mother', 'pregnancy', 'prenatal', 'maternal' and 'child', or 'offspring'; and 'infection', 'risk factors' and 'Diabetes Mellitus, Type 1', 'Insulin-Dependent Diabetes Mellitus', 'type 1 diabetes mellitus', 'islet autoimmunity', or 'Autoimmune Diabetes'. In addition, eligible studies were added by searching reference lists in the included articles.

Study selection

Study selection was independently conducted by two reviewers (YY and YT). Disagreements were settled by discussions with another author (TZ). Irrelevant studies were excluded after screening titles and abstracts. Furthermore, an additional screening was conducted by reviewing the full texts. Inclusion criteria were: (1) cohort or case-control studies; (2) studies evaluating the association between childhood T1DM and maternal gestational infection; and (3) studies in which odds ratios (ORs), risk ratios, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) (or the total number of participants and number of cases) were reported. Exclusion criteria included studies that were reviews, case reports, animal studies, abstracts and letters. Many studies were conducted in the same centers. When two or more studies appeared to have overlapping data, only the data with the larger sample size or those recently published were included.

Data extraction

For included studies, data extraction was independently carried out by two reviewers (YY and YT). Information about the first author, publication years, study design, source of participants, number of patients, ways to define the exposure and source of information, risk estimates with associated 95% CIs were collected. Disagreements were settled by discussions with another author (TZ).

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included studies according to the recommendation from Cochrane collaboration [7]. NOS contains eight items with a maximum score of 9. The quality of studies was divided into three categories: low quality with a 0–3 score, moderate quality with 4–6 score and high quality with a 7–9 score. Quality assessment was independently conducted by two reviewers (YY and YT) Disagreements were settled through discussions with the third reviewer (TZ).

Statistical analysis

ORs were used to determine the association between maternal gestational infection and the risk of T1DM in the offspring among studies. HRs were considered as relative risks (RRs); RRs were transformed into ORs based on the formula $RR = OR/[(1-P_0) + (P_0 \times OR)]$, where P_0 represents the incidence of T1DM in the group with mothers without infections during pregnancy. Heterogeneity was explored using the I^2 statistic and Q statistic among studies. Statistical significance of the meta-analysis was set at $P < 0.05$. Because there is significant heterogeneity, we only presented the results from a random-effects model. Subgroup analyses were performed based on study design, study quality, pathogens, methods of determining maternal infection (serological tests or mothers' recall or medical records) and stage of T1DM (islet autoimmunity or developed T1DM). Furthermore, a sensitivity analysis was used to assess the robustness of the associations. A funnel plot, as well as Begg's and Egger's tests, were performed to test for publication bias. All analyses were conducted using Stata version 12.0 (StataCorp, College Station, TX).

Results

Results of literature search

Overall, 594 publications were identified. After 72 duplicates were removed, 522 articles were screened and the full texts of 71 articles were reviewed. Two case reports were excluded [8, 9]. one letter and two abstracts were excluded according to our exclusion criteria [10–12]. One study that tested islet autoantibodies in cord blood was excluded because the islet autoantibodies came from their mother [13]. Six studies were excluded because their participants were overlapped and had a small sample size [14–19] compared with the four studies [20–23]. Finally, 18 studies were included in our study [20–37] (Fig. 1).

Study characteristics

Ten case-control studies [20, 21, 23, 24, 28–31, 34, 36], seven nest case-control studies [22, 25, 26, 32, 33, 35, 37] and one cohort [27] study were identified in this meta-analysis, comprising a total of 4304 cases and 25 846 participants. Six studies [25, 27, 32, 33, 35, 37] examined islet autoimmunity as the outcome, while another 12 studies [20–24, 25, 28–31, 34, 36] examined type 1 diabetes. Nine studies confirmed maternal infection based on mothers' recall through questionnaires or interviews regarding gestational infection at any stage [20, 24, 27–29, 34–37]. Three studies carefully assessed medical records to investigate whether the mothers had any infectious diseases during pregnancy [26, 30, 31]. Additional six studies ascertained maternal infection using serological tests to detect viral IgM, IgG, antibodies, or viral RNA at the end of the first trimester or/and at delivery [21–23, 25, 32, 33]; all these six studies tested for enterovirus or subtypes of enterovirus. Study characteristics are presented in Table 1. NOS demonstrated that the overall methodological quality was good with scores ranging from 6 to 8 in all studies (Supplementary Table S1).

Maternal infection and the risk of T1DM in the exposed offspring

Maternal infection during pregnancy increased the risk of childhood T1DM with a pooled adjusted OR of 1.32 (95% CI 1.08–1.62) from all 18 studies, indicating a statistically significant positive association. Statistically significant heterogeneity was observed between the included studies ($I^2 = 70.1\%$; $P < 0.001$) (Fig. 2).

Subgroup and sensibility analysis

Subgroup analyses by study design, islet autoimmunity or T1DM, methods to confirm gestational infection, pathogens and study quality are presented in Table 2. Subgroup analysis stratified by study design demonstrated that the association was only

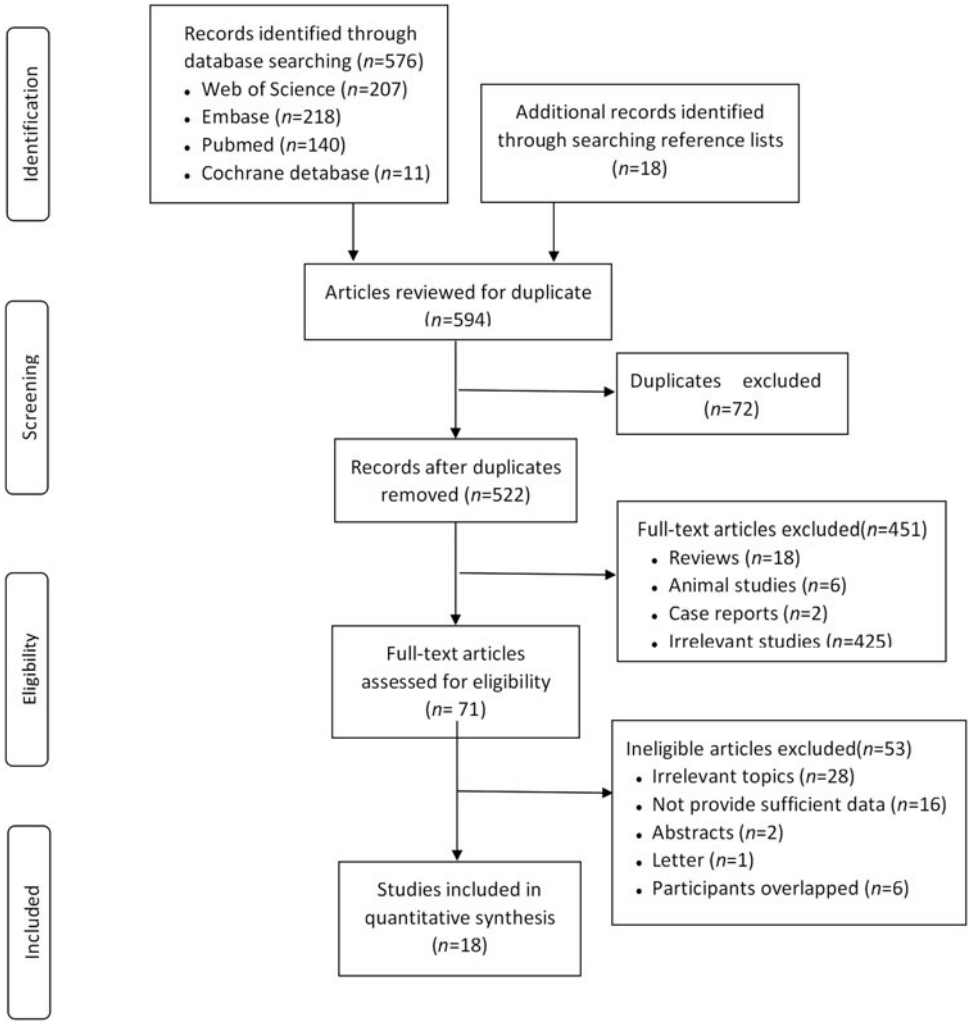

Fig. 1. Flow diagram of the study selection process.

significant in the case-control studies with a pooled OR of 1.74 (95% CI 1.28–2.35). The association was not significant among nest case-control studies and in the cohort study (Supplementary Fig. S1). We completed subgroup analysis according to the different outcomes for islet autoimmunity or T1DM. Twelve studies measured T1DM as the outcome demonstrated by a pooled OR of 1.64 (95% CI 1.26–2.13). For six other studies that estimated islet autoimmunity as the outcome, the pooled OR was 0.92 (95% CI 0.71–1.20), indicating that the association between maternal gestational infection and islet autoimmunity in the offspring was not significant (Supplementary Fig. S2). The subgroups in which maternal infection was detected by mothers' recall or serological tests demonstrated a pooled OR of 1.36 (95% CI 1.01–1.82) and 1.54 (95% CI 1.05–2.27), respectively. However, in studies that examined the mothers' medical records, the association was not significant, with a pooled OR of 1.04 (95% CI 0.82–1.32) (Supplementary Fig. S3). Notably, there were six studies that tested the IgG, IgM and viral RNA of enterovirus or subtypes of enterovirus in cord blood or mothers' serum samples, yielding a pooled OR of 1.54 (95% CI 1.05–2.27) with no significant heterogeneity ($I^2 = 35.4\%$; $P = 0.171$) (Supplementary Fig. S4). Furthermore, we conducted a subgroup analysis based on study quality. It demonstrated that the pooled OR of studies with a NOS score of <7 is 1.34 (95% CI 0.98–1.82), While for the studies with scores of ⩾7, the pooled OR among studies was 1.37 (95% CI 1.01–1.86) (Supplementary Fig. S5).

Sensitivity analyses show that no single study affected the overall result after individually removing each study (Supplementary Table S2). In addition, we performed a sensitivity analysis based on the study size: four studies had participants >2000, with two studies conducted in a multicenter setting, yielding a pooled OR of 1.04 (95% CI 0.94–1.15) with no significant heterogeneity ($I^2 = 0\%$; $P = 0.51$). The combined OR among studies with <2000 participants was 1.55 (95% CI 1.14–2.10), with significant heterogeneity ($I^2 = 69\%$; $P < 0.0001$) (Supplementary Fig. S6). In addition, we removed three small studies with cases <50 and the overall result did not substantially change.

Several studies reported that specific HLA genotypes could affect the risk of T1DM and the incidence of infection in children [32]. For example, newborn infants bearing the HLA-DR-DQB1 genotype are prone to develop T1DM and have more enterovirus infections than children without this genotype [32]. Previous findings demonstrated an association of HLA-DR3 with increased beta cell responses to enterovirus [25]. Thus, we estimated the pooled OR of the five studies that matched for HLA-DR

Table 1. Characteristics of studies investigating maternal infection during pregnancy and childhood T1DM or islet autoimmunity

Study	Country	Study types	Cases/ Total	Age	Source of participants		Methods to confirm infection	Pathogens	Odds ratio (95% CI)
					cases	Controls(matching criteria)			
Awadalla [24]	Egypt	Case-control	204/ 480	6–16	Children with T1DM from Assuit Health Insurance Hospital	Children without T1DM from the same hospital (age and sex)	Mothers' recall	Unknown	2.89 (1.02–10.76)
Blom [20]	Sweden	Case-control	239/ 767	0–14	Children with T1DM from Swedish population register (1985–1986)	Children without T1DM from the Swedish population register (age, sex and county)	Mothers' recall	Unknown	1.11 (0.76–1.61)
Dahlquist [21]	Sweden	Case-control	57/260	0–15	Children with T1DM born at Malmo University Hospital (born from 1969 to 1972)	Children without T1DM born at the same hospital (time of birth)	Serological tests (sample was taken from mother at delivery)	Enterovirus	3.19 (1.39–7.3)
Füchtenbusch [25]	Germany	Nest case-control	16/126	0–9	Islet antibodies positive children of parents diabetes from German BABYDIAB study (1989–2000)	Children from the same cohort negative for antibodies (HLA-DR, place, date of birth)	Serological tests (sample taken from mother at delivery)	Enterovirus	0.55 (0.17–1.75)
Lee [26]	China Taiwan	Nest case-control	259/ 2835	0–8	Children with T1DM provided by NHIRD (born from 2000 to 2005)	Children without T1DM in the same cohort (age, sex, index date and beneficiary)	Medical records	Unknown	1.15 (0.24–5.51)
Lynch [27]	Six centers in the USA and Europe	Cohort	417/ 7058	0–6	Mother of children with HLA-DR-DQ genotypes have an infection from TEDDY study	Mother of children with HLA-DR-DQ genotype without infection from the same study	Mothers' recall	Unknown	0.92 (0.76–1.11)
Majeed [28]	Iraq	Case-control	96/395	0–17	Children with T1DM at 3 main Basrah hospitals from 2006 to 2007	Children without T1DM at the same hospital (age)	Mothers' recall	Unknown	2.67 (1.27–5.59)
Marshall [29]	UK	Case-control	196/ 577	0–16	Children with T1DM registered at pediatric diabetic clinics in Morecambe Bay and East Lancashire in October 1998	Children without T1DM selected from a register of all local children (age, time of birth)	Mothers' recall	Unknown	2.45 (1.01–5.95)
McKinney [30]	UK	Case-control	196/ 521	0–15	Children with T1DM from Yorkshire Childhood Diabetes Register (1993 and 1994)	Children without T1DM from The Family Health Service Authority (age and sex)	Medical records	Unknown	1.06 (0.64–1.74)
Patterson [31]	Seven centres in Europe	Case-control	900/ 3203	0–15	Children with T1DM from population-based register	Children with T1DM from the same register (age)	Medical records	Unknown	1.03 (0.78–1.37)
Sadeharju [32]	Finland	Nest case-control	19/103	0–2	Autoantibody-positive children from TRIGR study born between 1995 and 1997	Children from same cohort negative for autoantibodies (time of birth, sex and HLA DQB1 genotype)	Serological tests (sample was taken from mother at the end of the first trimester and delivery)	Enterovirus	2.3 (0.79–6.73)
Salminen [33]	Finland	Nest case-control	41/237	0–5	Autoantibody positive children from DIPP study	Children from the same cohort negative for autoantibody (time of	Serological tests (sample was taken from mother at the end of the first	Enterovirus	0.99 (0.28–2.56)

					birth, sex and HLA DQB1 genotype)	trimester and at delivery from cord blood)		
Šipetić [34]	Serbia and Montenegro	Case-control	105/315	0–16	Children with T1DM diagnosed in hospitals in Belgrade from 1994 to 1997	Outpatient children treated for skin diseases in the same hospital (age, sex, place of residence)	Mothers' recall	Unknown	11.5 (3.25–40.71)
Stene [35]	USA	Nest case-control	818/1237	0–10	Autoantibody-positive children born at St. Joseph's Hospital in Denver 1994–2003	Children from the same cohort negative for autoantibody	Mothers' recall	Unknown	0.48 (0.27–0.83)
Visalli [36]	Italy	Case-control	150/900	6–18	Children with T1DM from population-based T1DM register (born between 1977 and 1989)	Children without T1DM chosen from school (time of birth and region)	Mothers' recall	Unknown	1.6 (1.32–2.2)
Viskari [22]	Finland	Nest case-control	680/1360	0–7	Children without T1DM from Finnish national diabetes register (manifested with diabetes from 1983 to 1995)	Children without T1DM from Central Population Registry (age, sex and area)	Serological tests (sample was taken from mother at the end of the first trimester)	Enterovirus	1.33 (0.85–2.08)
Viskari [23]	Finland	Case-control	171/487	0–11	Children without T1DM from DIPP study (born between 1994 and 2004)	Children without T1DM From the same Study (date, place, sex and HLA-DQ genotype)	Serological tests (sample was taken from mother at the end of the first trimester and at delivery from cord blood)	Enterovirus	1.74 (1.03–2.94)
Wahlberg [37]	Sweden	Nest case-control	240/4985	0–1	Autoantibody-positive children from ABIS (born between 1997 and 1999)	Children from the same cohort negative for autoantibody	Mothers' recall	Unknown	1.1 (1–1.3)

genotypes in cases and controls demonstrates a pooled OR of 1.16 (95% CI 0.76–1.77) (Supplementary Fig. S7). In addition, eight studies that investigated children with islet autoimmunity or T1DM under the age of 10 demonstrated a combined OR of 1.01(95% CI 0.79–1.29) (Supplementary Fig. S8).

Publication bias

The funnel plot indicated no significant asymmetry among studies (Fig. 3), in accordance with the results of the Begg's test and Egger's test (all $P > 0.05$), which revealed no evidence of publication bias.

Discussion

Eighteen studies were included in this meta-analysis, comprising 4304 cases and 25 846 participants. Most of the studies were conducted in Finland and Sweden, where T1DM incidence is high. The results demonstrated that maternal gestational infection is associated with 32% increased odds of T1DM or islet autoimmunity in the offspring in the pooled estimate, with significant heterogeneity across studies.

Subgroup analysis was conducted according to study design and no significant association was found in the cohort study and among the seven nest case-control studies. Subgroup analysis performed according to the different methods of determining maternal infection demonstrated a non-significant association among the studies using medical records and low pooled OR depending on mothers' recall, which may account for selection or recall bias in those studies.

We analysed studies that matched for HLA-DR genotypes, resulting in a pooled OR of 1.16 (95% CI 0.76–1.77). Some studies reported that while gestational infection together with HLA-DR genotypes did not influence the overall incidence of beta-cell autoantibodies, they may delay the appearance of these autoantibodies [27, 38]. Thus, for infants with HLA-DR genotypes combined with maternal infection, the onset of T1DM may occur after several years. All five studies that matched for HLA-DR genotypes investigated children <10-years-old or a short follow-up time. Therefore, the islet autoantibodies may not yet have appeared at the end of the studies, which may have resulted in the low OR and non-significant association between maternal infection and childhood T1DM among these five studies.

Our results demonstrate that the pooled OR of the studies in children <10-years-old was 0.98 (95% CI 0.79–1.23). It is suggested that patients often undergo a long prodromal stage before clinical onset of T1DM [2, 39]. Recent studies have indicated that only approximately 60% patients with T1DM are younger than 10-years-old [2]. Thus, studies that investigated the incidence of T1DM in children <10-years-old yielded an insignificant effect. The subgroup analysis conducted according to different sample sizes yielded a summary OR of 1.04 (95% CI 0.94–1.15) in the studies with >2000 participants. The obtained non-significant association may also be a result of the younger age of participants, considering that three of the four studies included children <10-years-old. In this study, we conducted subgroup analysis according to different outcomes (T1DM or islet autoimmunity). We observed that the association was only significant in the group with T1DM but not islet autoimmunity. In the six studies that investigated the incidence of islet autoimmunity in the offspring, four matched for HLA genotypes and all studies had a short follow-up time, this may have caused missed diagnosis in

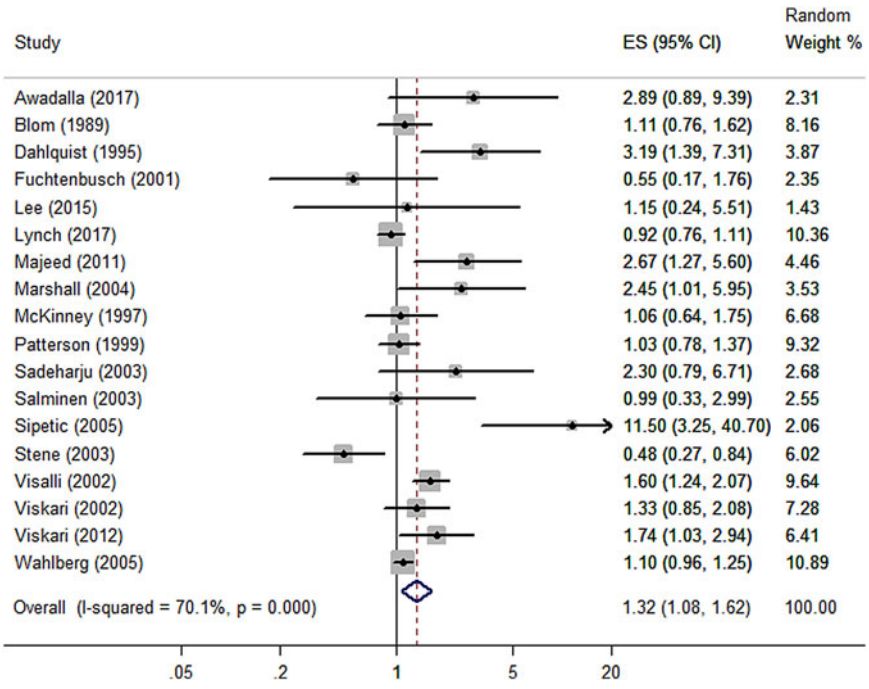

Fig. 2. Forest plot of odds ratios for the association between maternal infection during pregnancy and T1DM or islet autoimmunity in the offspring. Weights are from the random-effects analysis. ES, effect size.

Table 2. Pooled OR and heterogeneity in subgroups and sensibility analysis

Variables	No of studies	OR (95% CI)	Weight (%)	I^2%	*P* for Heterogeneity
Study design					
Case control	10	1.74 (1.28–2.35)	56.4	69.2	0.001
Nest case control	7	0.99 (0.71–1.39)	33.2	50.5	0.059
Cohort	1	0.92 (0.76–1.11)	10.4	–	–
Methods to confirm infection					
Serological tests	6	1.54 (1.05–2.27)	25.1	35.4	0.17
Mothers' recall	9	1.36 (1.01–1.82)	57.4	81.9	<0.001
Medical records	3	1.04 (0.82–1.32)	17.4	0	0.99
Outcomes					
T1DM	6	1.64 (1.26–2.13)	65.1	62.5	0.002
Islet autoimmunity	12	0.92 (0.71–1.20)	34.9	60.4	0.027
Pathogens					
Enterovirus	6	1.54 (1.05–2.27)	25.1	35.4	0.17
Unknown	12	1.25 (1.0–1.58)	74.9	75.4	<0.001
Study quality					
High	6	1.37 (1.01–1.86)	44.83	74.1	0.002
Moderate	12	1.48 (0.98–1.82)	55.17	70.3	<0.001
Sample size					
>2000	14	1.04 (0.94–1,15)	32	0	0.5
<2000	4	1.55 (1.14–2.10)	68	69.3	<0.001

some patients in whom the onset of T1DM started later and resulted in a low effect size.

It is noteworthy that studies that tested the enterovirus or subtypes of enterovirus infection in pregnancy yielded a pooled OR of 1.54 (95% CI 1.05–2.27), indicating that maternal enterovirus infection during pregnancy results in 54% increased risk of T1DM in the offspring. Evidence has demonstrated that some pathogens can cause cross-reactive immune responses against islet beta cells and thus generate beta-cell autoantibodies [7, 40]. Therefore, the possibility that maternal enterovirus

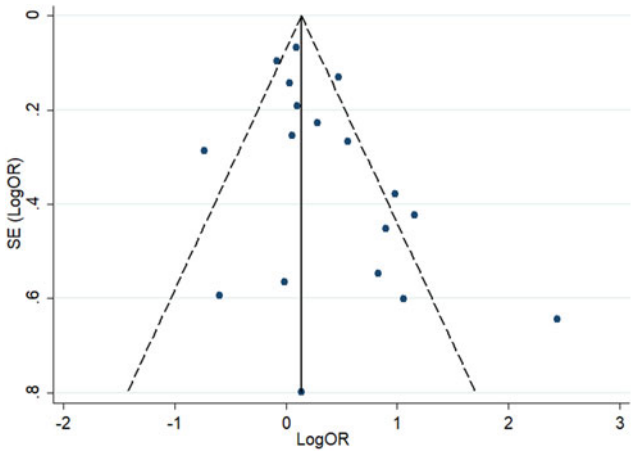

Fig. 3. Funnel plot of the association between maternal infection and T1DM or islet autoimmunity in the offspring.

infection could cause childhood T1DM should be considered. If necessary, specific vaccines should be used to prevent such infections, to reduce the incidence of T1DM in the offspring [41].

However, the question of whether the association between maternal infection and the incidence of T1DM in the offspring is sex-dependent remains [23, 35]. But the pooled OR of studies investigating the association between different sexes could not be performed because only one study reported a negative association among girls but not boys [35].

Our study has several merits. To reduce potential bias, we prepared pre-defined inclusion criteria, searching eligible studies from several approaches without geographical and linguistic restrictions and the process was conducted by two reviewers. The random-effects models were used to provide more conservative effect estimates. In addition, this analysis includes 25 846 participants and all included studies were of moderate to high quality, which provides high reliability for our findings. However, our study has several limitations that should be considered. First, our study demonstrated significant heterogeneity. After performing subgroup analyses and sensitivity analyses, heterogeneity still existed among the studies (Table 2). We noted that three factors that may explain the presence of heterogeneity: (i) different study designs (case-control, nest case-control and cohort); (ii) different methods of determining maternal infection during pregnancy (serological tests, extracted from medical records or mothers' recall); (iii) the greatly varied sample size among different studies. Second, some studies performed serological tests to determine maternal infection using samples taken only at the end of the first trimester [22] or at delivery [21, 25], instead of selecting multiple sampling points, which may result in missed diagnoses. Third, studies using the method of medical records or mothers' recall were prone to selection or recall bias. Moreover, some other confounders such as birth weight, birth order and caesarean section may modify the risk of T1DM [20, 36], but it is impossible to control all of these potential confounders.

In conclusion, this meta-analysis demonstrated an association between maternal gestational infection and the risk of childhood T1DM. We recommend further studies investigating how T1DM risk varies by different pathogens and by different HLA genotypes. More studies with a longer follow-up time are needed to determine the interactions between environmental and genetic factors with the development of diabetes, to provide a guideline for preventing the development of T1DM and curb expenses related to health care.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268818002455.

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Conflict of interest. None.

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