Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

META-ANALYSIS

Zhang et al: Maternal smoking and childhood T1D risk

Maternal smoking during pregnancy and risk of childhood-onset type 1 diabetes in offspring: A systematic review and meta-analysis

Shu Zhang[1], Lishi Zhao[2], Jiao Li[1*]

[1]Department of Endocrinology, Chongqing Youyoubaobei Women and Children's Hospital, Chongqing, China;

[2]Department of Pediatrics, Chongqing Youyoubaobei Women and Children's Hospital, Chongqing, China.

*Correspondence to Jiao Li: jiaoli_yybb@hotmail.com.

DOI: https://doi.org/10.17305/bb.2025.13063

ABSTRACT

Childhood-onset type 1 diabetes (T1D) is a chronic autoimmune disease characterized by a steadily increasing global incidence and significant public health implications. The relationship between maternal smoking during pregnancy and T1D risk remains uncertain. To clarify this association, we conducted a meta-analysis of prospective cohort studies to enhance methodological reliability. We systematically searched PubMed, Embase, and Web of Science from their inception to May 2025 for prospective cohort studies examining the link between maternal smoking during pregnancy and the incidence of T1D in offspring. Risk ratios (RRs) and 95% confidence intervals (CIs) were pooled using a random-effects model, accounting for heterogeneity. Twelve prospective cohort datasets from ten studies, encompassing over 5.9 million children, were included. Maternal smoking during pregnancy was significantly associated with a reduced risk of childhood-onset T1D (RR: 0.74, 95% CI: 0.72–0.76, $p < 0.001$), with no evidence of statistical heterogeneity ($I^2 = 0\%$, $p = 0.48$). This association remained robust across sensitivity analyses that excluded one dataset at a time. Subgroup analyses demonstrated consistent results across various categories, including cohort size, prevalence of maternal smoking, method of T1D diagnosis, and adjustments for maternal age, diabetes, and delivery mode. Notably, the inverse association was significantly weaker in studies that did not adjust for maternal diabetes (RR: 0.79 vs. 0.72, p for subgroup difference = 0.01). We found no substantial evidence of publication bias (Egger's test, $p = 0.55$). In conclusion, this meta-analysis identified an inverse association between maternal smoking during pregnancy and the incidence of childhood-onset T1D. However, this finding should be interpreted cautiously, as residual confounding cannot be ruled out, and maternal smoking is associated with numerous serious adverse health consequences.

Keywords: Type 1 diabetes, children, smoking, pregnancy, risk factor.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the destruction of pancreatic β-cells, leading to lifelong insulin dependence (1, 2). The global incidence of childhood-onset T1D has been steadily increasing, especially in developed countries, posing a significant public health challenge due to its substantial burden on patients, families, and healthcare systems (3). Children with T1D are at risk of acute metabolic complications, long-term microvascular and macrovascular sequelae, and psychosocial stress, emphasizing the need for early prevention strategies (4-6). While genetic susceptibility is a key determinant, growing evidence suggests that environmental exposures in early life also play a crucial role in T1D development (7). Established maternal and perinatal risk factors include advanced maternal age, maternal diabetes, and cesarean delivery, yet they explain only a portion of the disease variability (8-10).

Maternal smoking during pregnancy remains a prevalent exposure, with estimates ranging from 9% to over 50% in some populations (11). Smoking during gestation is known to influence fetal growth and development (12), and has been implicated in a wide array of adverse offspring outcomes, including low birth weight (13), respiratory illness (14), and neurodevelopmental disorders (15). Maternal smoking during pregnancy may influence the risk of childhood-onset T1D through several potential mechanisms. Nicotine and other components of tobacco smoke have immunomodulatory properties, which could alter fetal immune system development and susceptibility to autoimmune disease (11, 16, 17). These biological considerations, together with inconsistent epidemiological findings (18), highlight the need for systematic evaluation of this association. A prior meta-analysis suggested an inverse association between maternal smoking during pregnancy and offspring T1D risk, but this finding was based primarily on retrospective studies and was subject to considerable heterogeneity, raising concerns about the validity of the conclusion (18). Given the accumulation of large, population-based prospective cohort studies in recent years (19-23), a re-evaluation using methodologically robust data is warranted. Accordingly, the present study aimed to comprehensively assess the association between maternal smoking during pregnancy and the incidence of childhood-onset T1D in offspring by synthesizing evidence from prospective cohort studies only. By limiting inclusion to studies with prospective exposure assessment and longitudinal

outcome follow-up, we sought to minimize bias and provide more reliable evidence to inform public health understanding and future research on prenatal risk factors for T1D.

MATERIALS AND METHODS

The study was conducted in accordance with the PRISMA 2020 guidelines (24, 25) and the Cochrane Handbook (26) for Systematic Reviews of Interventions, ensuring methodological rigor in study selection, data extraction, statistical analysis, and result interpretation. The protocol was prospectively registered on PROSPERO with the registration ID CRD420251116685.

Literature search

A comprehensive literature search was performed in PubMed, Embase, and Web of Science, utilizing a broad set of search terms that integrated the following keywords and concepts: (1) "pregnant" OR "pregnancy" OR "prenatal" OR "pre-natal"; (2) "smoking" OR "smoke" OR "cigarette" OR "cigarettes" OR "nicotine" OR "tobacco"; (3) "diabetes" OR "diabetic" OR "type 1 diabetes" OR "T1D" OR "T1DM"; and (4) "child" OR "children" OR "adolescent" OR "adolescents" OR "pediatric" OR "paediatric" OR "offspring" OR "childhood" OR "adolescence". The search was limited to human studies and included only full-text articles published in English in peer-reviewed journals. To ensure completeness, we also manually screened the reference lists of relevant original and review articles for additional eligible studies. The search covered all publications from database inception up to May 25, 2025.

Study eligible criteria

We applied the PICOS framework to define the inclusion criteria:

Population (P): Children (aged 0 to 18 years) born to mothers with documented smoking status during pregnancy.

Intervention/Exposure (I): Maternal smoking during pregnancy (any trimester), as assessed by self-report, medical records, or biomarker validation.

Comparator (C): Children born to non-smoking mothers during pregnancy.

Outcome (O): Incidence of childhood-onset T1D, diagnosed by clinical or registry-based criteria.

Study design (S): Prospective cohort studies with follow-up from birth to ascertain incident T1D in offspring, published as full-length articles in peer-reviewed journals.

Studies were excluded if they were reviews, editorials, meta-analyses, retrospective cohort or retrospective case-control studies, cross-sectional studies, studies reporting maternal smoking outside of pregnancy or passive smoking, or including adult-onset T1D in offspring. In cases of overlapping populations, only the study with the largest sample size was retained for inclusion in the meta-analysis.

Study quality evaluation

Two reviewers independently conducted the literature search, screened studies, assessed methodological quality, and extracted data. Any discrepancies were resolved through consultation with the corresponding author. The quality of included studies was evaluated using the Newcastle–Ottawa Scale (NOS) (27), which examines study selection, control of confounding variables, and outcome assessment. The NOS assigns scores ranging from 1 to 9, with a score of 8 or above indicating high methodological quality.

Data collection

The data collected for the meta-analysis included study details (author, year, and study country), participants characteristics (source of the cohort, number of children in each study, and sex distribution), exposure details (methods for evaluating maternal smoking during pregnancy, number of children born to mothers who smoked during the index pregnancy), age of children (range and mean) for the diagnosis of T1D, methods for the diagnosis of T1D, number of children who developed T1D, and covariates adjusted for in the regression models.

Statistical analysis

We used risk ratios (RRs) and 95% confidence intervals (CIs) to assess the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. RRs and their standard errors were either directly extracted or derived from reported 95% confidence intervals or p-values, followed by logarithmic transformation to stabilize variance and achieve a normal distribution (26). If multiple RRs were reported from different models, we used the one with the most complete adjustment. Heterogeneity was assessed using the Cochrane Q test and the I^2 statistic (28), with a p-value < 0.10 indicating significant heterogeneity and I^2 values of < 25%,

25–75%, and > 75% indicating low, moderate, and high heterogeneity, respectively. A random-effects model was applied to synthesize the data, allowing for variability across studies (26). We used a random-effects model for all meta-analyses to account for potential clinical heterogeneity across studies (e.g., differences in populations, exposure definitions, and study periods), even when statistical heterogeneity was minimal ($\tau^2 = 0$, $I^2 = 0\%$). To assess the stability of the results, sensitivity analyses were conducted by sequentially excluding each study. In addition, subgroup analyses were performed to evaluate the predefined study characteristics on the results of the meta-analysis, which included sample size, prevalence of maternal smoking during pregnancy in each study, method for the diagnosis of T1D (clinical diagnosis vs. database codes), incidence of T1D in children of each study, and whether the potential confounding factors, such as maternal age, maternal diabetes, and delivery types were adjusted. For continuous study-level variables, subgroup analyses were stratified at the median to provide balanced comparisons in the absence of universally accepted clinical cut-offs. Publication bias was evaluated through funnel plot visualization and assessed for asymmetry using Egger's regression test (29). All analyses were performed using RevMan (Version 5.3; Cochrane Collaboration, Oxford, UK) and Stata (Version 17.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study inclusion

The study selection process is shown in **Figure 1**. We first identified 3,896 records from the three databases. Following the removal of 1,042 duplicate records, 2,854 articles underwent title and abstract screening. Of these, 2,824 were excluded for not aligning with the objectives of the meta-analysis. The remaining 30 full-text articles were assessed independently by two reviewers, resulting in the exclusion of 20 studies for specific reasons detailed in **Figure 1**. At last, 10 studies were included in the subsequent analysis (19-23, 30-34).

Summary of study characteristics

Overall, ten prospective cohort studies were included in the meta-analysis (19-23, 30-34). Notably, the study by Magnus 2018 (19) reported three independent cohorts, which were separately included in the meta-analysis: the Norwegian Mother and Child Cohort Study (MoBa), the Danish National Birth Cohort (DNBC), and the

Norwegian Registry Birth Cohort (NRBC), making 12 datasets available. The characteristics of the 12 prospective cohort datasets included in this meta-analysis are summarized in **Table 1**. These studies were conducted in the United States, Australia, Sweden, Norway, Denmark, and Finland, and were published between 2013 and 2023. All studies adopted a prospective design, enrolling large, population-based or high-risk birth cohorts to examine the association between maternal smoking during pregnancy and childhood-onset T1D. The sample sizes varied widely, ranging from 726 to 3,170,386 children. Maternal smoking during pregnancy was primarily assessed via self-report at various time points, including the first prenatal visit, gestational weeks 12 to 18, or via postnatal questionnaires; one study also used cord blood cotinine for partial validation (19). The diagnosis of T1D was based on clinical criteria (19, 30, 31, 34) or national diabetes or patient registries using International Classification of Diseases (ICD) codes (19-23, 32, 33). All studies reported the incidence of childhood-onset T1D, with age at diagnosis before 18 years. The number of children with T1D ranged from 25 to 18,745 per study. In the study by Metsälä et al. (2020) (21), all 6,862 T1D cases and a 10% random reference cohort of 127,216 non-cases were analyzed, yielding 134,078 children in total. The relatively high proportion of cases (5.1%) arises from this case–cohort sampling scheme rather than the underlying population incidence. All studies adjusted for key confounding variables, typically including child's age and sex, maternal age, socioeconomic status, parity, delivery mode, and family history of diabetes, to a varying extent. The prevalence of mothers who smoked during the index pregnancy varied from 9.2% to 56.6%, and the incidence of T1D of children in each study ranged from 0.13% to 5.12%. Study quality was evaluated using the NOS (**Table 2**), with total scores ranging from 8 to 9, indicating consistently high methodological quality across all studies. Five datasets received the maximum score of 9 (19, 30, 31, 34), reflecting excellent cohort representativeness, exposure and outcome ascertainment, and adequate follow-up. The remaining seven datasets scored 8 (19-23, 32, 33), primarily due to that the diagnosis was rely on ICD codes rather than clinical evaluation. Nevertheless, the overall robustness of exposure definition, longitudinal outcome assessment, and adjustment for major confounders enhance the validity of the synthesized findings in this meta-analysis.

Association between maternal smoking in pregnancy and childhood-onset T1D

Pooled results from a random-effects model including the 12 prospective cohort datasets showed that overall, maternal smoking during pregnancy was associated with a significantly reduced incidence of childhood-onset T1D in offspring (RR: 0.74, 95% CI: 0.72–0.76, $p < 0.001$; **Figure 2A**) with no significant heterogeneity (p for the Cochrane Q test = 0.48; $I^2 = 0\%$). Sensitivity analyses were performed by removing one dataset at a time, and the results remained stable (RR: 0.72–0.76, $p < 0.05$ for all comparisons; **Table 3**). Further subgroup analyses indicated that the association was consistent in studies with included children < or ≥ 150,000 (RR: 0.72 vs. 0.75; p for subgroup difference = 0.36; **Figure 2B**), in studies with the prevalence of maternal smoking in pregnancy < or ≥ 20% (RR: 0.73 vs. 0.78; p for subgroup difference = 0.13; **Figure 3A**), in studies with T1D diagnosed by clinical evaluation or ICD codes (RR: 0.71 vs. 0.74; p for subgroup difference = 0.68; **Figure 3B**), and between studies with the incidence of T1D in offspring < or ≥ 0.5% (RR: 0.74 vs. 0.74; p for subgroup difference = 0.92; **Figure 4A**). In addition, the subgroup results were all significant for studies with and without the adjustment of maternal age (RR: 0.75 vs. 0.72; p for subgroup difference = 0.15; **Figure 4B**), maternal diabetes (RR: 0.72 vs. 0.79; p for subgroup difference = 0.01; **Figure 5A**), and delivery type of the children (RR: 0.76 vs. 0.72; p for subgroup difference = 0.07; **Figure 5B**).

Publication bias

Funnel plots assessing the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring are presented in **Figure 6**. The visual symmetry of the plots indicates a low likelihood of publication bias. In addition, Egger's test also did not detect a strong evidence of publication bias ($p = 0.55$).

DISCUSSION

This meta-analysis of twelve prospective cohort datasets provides updated and robust evidence on the relationship between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. By including over 5.9 million children from well-characterized cohorts across multiple countries, the findings indicate a consistent inverse association between maternal smoking during pregnancy and the subsequent development of T1D in children. Notably, the lack of heterogeneity across studies and

the stability of results in sensitivity analyses strengthen the reliability of this observed association.

Several potential biological mechanisms may explain how maternal smoking during pregnancy could influence the risk of T1D in offspring. Nicotine, a key component of cigarette smoke, readily crosses the placenta and may modulate fetal immune development by altering cytokine expression and immune tolerance, potentially dampening autoimmune responses later in life (35, 36). Additionally, prenatal exposure to smoking has been associated with increased levels of regulatory T cells and reduced pro-inflammatory responses in the offspring, which may protect against the development of autoimmune diseases such as T1D (37, 38). Epigenetic modifications, including DNA methylation changes induced by tobacco exposure, may also play a role in reprogramming immune pathways and pancreatic β-cell development, although the precise mechanisms remain to be fully elucidated (16, 39).

The subgroup analyses provide important insights into the robustness and potential modifiers of the observed association. The inverse relationship persisted across studies regardless of sample size, prevalence of maternal smoking, and methods used for T1D diagnosis, suggesting that these factors do not materially affect the findings. Interestingly, the association appeared weaker in studies that did not adjust for maternal diabetes, highlighting the importance of adequately controlling for confounding maternal metabolic factors. Similarly, adjustment for maternal age and delivery mode did not substantially alter the results, suggesting that these variables may not be major confounders in this context. These findings support the consistency of the inverse association across various study settings and populations.

The strengths of this meta-analysis are several. First, it is the most comprehensive and up-to-date synthesis of prospective cohort studies addressing this research question, improving upon earlier meta-analyses that included retrospective designs and mixed-age outcomes. By restricting inclusion to prospective studies with prenatal exposure assessment and longitudinal follow-up, the risk of recall bias, selection bias, and reverse causality is minimized (40). Second, all included studies employed multivariable regression models, adjusting for a wide range of relevant confounders such as child's age and sex, maternal age, diabetes status, socioeconomic factors, parity, and delivery mode, thereby enhancing the validity of the findings. Third, the consistently high quality of the included studies, as assessed by the NOS, adds to the credibility of the results. Lastly, the large cumulative sample size ensures sufficient

power to detect associations and allows for informative subgroup and sensitivity analyses.

Nevertheless, certain limitations should be considered when interpreting the findings. Although all studies adjusted for multiple confounders, the possibility of residual confounding from unmeasured or imprecisely measured factors cannot be excluded. For example, maternal lifestyle behaviors, genetic predisposition, or exposure to other environmental factors could influence both smoking behavior and T1D risk in offspring (41, 42). Moreover, the exposure to maternal smoking was primarily assessed through self-report, which may be subject to misclassification bias; however, this bias is likely to be non-differential and would tend to attenuate the observed associations. Only one study incorporated biomarker validation using cord blood cotinine (19), underscoring the need for future studies with more objective exposure measures. Additionally, while the studies uniformly focused on childhood-onset T1D, variation in diagnostic criteria or registry accuracy may still exist, although subgroup analysis by diagnostic method did not reveal significant heterogeneity. A further limitation is that most included studies did not provide information on smoking intensity (e.g., cigarettes per day) or trimester-specific exposure, which precluded a dose–response meta-analysis. Future research with more detailed exposure data is warranted to clarify potential dose–response relationships. Moreover, although the contour-enhanced funnel plot did not suggest substantial publication bias, the small number of available datasets limits the reliability of such assessments. Hence, the possibility of publication bias cannot be ruled out and the results should be interpreted with caution. Finally, the observational nature of the included studies precludes any inference of causality, and the counterintuitive direction of association warrants cautious interpretation.

From a clinical and public health perspective, these findings do not imply that maternal smoking should be encouraged during pregnancy. The well-established adverse effects of prenatal tobacco exposure on fetal growth, neurodevelopment, and respiratory health outweigh any potential protective association with T1D. Rather, the results may point to underlying biological pathways activated by tobacco exposure that could inspire mechanistic studies into immune modulation and β-cell preservation. Understanding these pathways may eventually inform preventive or therapeutic strategies that mimic the immunoregulatory effects without the harmful consequences of smoking. In this context, the inverse association observed may serve as a starting

point for future research, rather than a clinical recommendation. Future studies are warranted to explore the biological plausibility and mechanistic basis of this association. Prospective cohorts with biomarker-confirmed exposure data and detailed immune phenotyping of offspring would be particularly valuable. Investigations into gene–environment interactions, including maternal and fetal genotypes related to immune regulation, xenobiotic metabolism, and nicotine sensitivity, may help clarify whether specific subpopulations are more susceptible to the protective or harmful effects of prenatal smoking exposure (43). Moreover, exploring whether timing, dose, or cessation of maternal smoking differentially influences T1D risk may refine our understanding of critical windows of susceptibility. It is also important to examine whether similar associations exist for other autoimmune conditions, such as multiple sclerosis (44), which may share pathophysiological pathways with T1D. Finally, residual confounding remains a major limitation of our findings. Socioeconomic, behavioral, or familial factors may plausibly explain the observed association, and cannot be fully accounted for in conventional cohort analyses. Future research should incorporate negative-control exposures (such as paternal smoking) and within-family or sibling-comparison designs to better separate causal effects from unmeasured confounding.

Although our meta-analysis consistently indicated a modest inverse association between maternal smoking during pregnancy and risk of type 1 diabetes in offspring, this finding should be interpreted with caution. The observed “protective” effect is counter-intuitive given the well-established adverse consequences of tobacco exposure on maternal and child health. Importantly, statistical homogeneity across studies does not eliminate the presence of clinical heterogeneity, including differences in exposure assessment, adjustment for confounders, follow-up periods, and population characteristics. Moreover, residual confounding by socioeconomic status, parental health behaviors, or unmeasured genetic–environmental interactions cannot be excluded. Case–control and sibling-comparison designs, although methodologically different from prospective cohorts, have sometimes reported attenuated or null associations, underscoring the importance of study design in shaping observed results. Taken together, our findings add to the existing body of evidence but do not imply a causal protective effect of maternal smoking. Instead, they highlight the need for further high-quality studies with careful control for familial, behavioral, and socioeconomic factors to clarify whether the observed

association reflects a true biological mechanism, residual confounding, or methodological artifact.

CONCLUSION

In conclusion, this meta-analysis of prospective cohort studies found an observed inverse association between maternal smoking during pregnancy and the incidence of childhood-onset T1D in offspring. While the association was consistent across subgroups and robust in sensitivity analyses, the counterintuitive direction of effect and the inherent limitations of observational research indicate that these results should be interpreted with caution. Residual confounding by socioeconomic, behavioral, or genetic factors may plausibly account for the observed association. Therefore, the findings should not be taken as evidence of a causal protective effect. Instead, they highlight the complexity of prenatal influences on immune-mediated diseases and the need for future studies using robust causal-inference methods to disentangle biological mechanisms from confounding. Importantly, these results do not alter the clear imperative to discourage maternal smoking during pregnancy due to its well-established adverse health consequences.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Data availability: All data generated or analyzed during this study are included in this published article.

Submitted: August 1, 2025

Accepted: September 20, 2025

Published online: November 10, 2025

REFERENCES

1. Roy S, Pokharel P, Piganelli JD. Decoding the immune dance: Unraveling the interplay between beta cells and type 1 diabetes. Mol Metab. 2024;88:101998.
2. Quattrin T, Mastrandrea LD, Walker LSK. Type 1 diabetes. Lancet. 2023;401(10394):2149-62.
3. Ogrotis I, Koufakis T, Kotsa K. Changes in the Global Epidemiology of Type 1 Diabetes in an Evolving Landscape of Environmental Factors: Causes, Challenges, and Opportunities. Medicina (Kaunas). 2023;59(4).
4. Monaghan M, Helgeson V, Wiebe D. Type 1 diabetes in young adulthood. Curr Diabetes Rev. 2015;11(4):239-50.
5. Bjornstad P, Donaghue KC, Maahs DM. Macrovascular disease and risk factors in youth with type 1 diabetes: time to be more attentive to treatment? Lancet Diabetes Endocrinol. 2018;6(10):809-20.
6. White NH. Long-term outcomes in youths with diabetes mellitus. Pediatr Clin North Am. 2015;62(4):889-909.
7. Mittal R, Camick N, Lemos JRN, Hirani K. Gene-environment interaction in the pathophysiology of type 1 diabetes. Front Endocrinol (Lausanne). 2024;15:1335435.
8. Tanoey J, Gulati A, Patterson C, Becher H. Risk of type 1 diabetes in the offspring born through elective or non-elective caesarean section in comparison to vaginal delivery: a meta-analysis of observational studies. Curr Diab Rep. 2019;19(11):124.
9. Pirkola J, Vääräsmäki M, Leinonen E, Bloigu A, Veijola R, Tossavainen P, et al. Maternal type 1 and gestational diabetes: postnatal differences in insulin secretion in offspring at preschool age. Pediatr Diabetes. 2008;9(6):583-9.
10. Elfving M, Svensson J, Oikarinen S, Jonsson B, Olofsson P, Sundkvist G, et al. Maternal enterovirus infection during pregnancy as a risk factor in offspring diagnosed with type 1 diabetes between 15 and 30 years of age. Exp Diabetes Res. 2008;2008:271958.
11. Nakamura A, François O, Lepeule J. Epigenetic alterations of maternal tobacco smoking during pregnancy: a narrative review. Int J Environ Res Public Health. 2021;18(10).

12. Abraham M, Alramadhan S, Iniguez C, Duijts L, Jaddoe VW, Den Dekker HT, et al. A systematic review of maternal smoking during pregnancy and fetal measurements with meta-analysis. PLoS One. 2017;12(2):e0170946.
13. Di HK, Gan Y, Lu K, Wang C, Zhu Y, Meng X, et al. Maternal smoking status during pregnancy and low birth weight in offspring: systematic review and meta-analysis of 55 cohort studies published from 1986 to 2020. World J Pediatr. 2022;18(3):176-85.
14. Vanker A, Gie RP, Zar HJ. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. Expert Rev Respir Med. 2017;11(8):661-73.
15. Han VX, Patel S, Jones HF, Nielsen TC, Mohammad SS, Hofer MJ, et al. Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: a systematic review. Transl Psychiatry. 2021;11(1):71.
16. Barchetta I, Arvastsson J, Sarmiento L, Cilio CM. Epigenetic changes induced by maternal factors during fetal life: implication for type 1 diabetes. Genes. 2021;12(6):887.
17. Zakarya R, Adcock I, Oliver BG. Epigenetic impacts of maternal tobacco and e-vapour exposure on the offspring lung. Clin Epigenetics. 2019;11(1):32.
18. Hidayat K, Zou SY, Shi BM. The influence of maternal body mass index, maternal diabetes mellitus, and maternal smoking during pregnancy on the risk of childhood-onset type 1 diabetes mellitus in the offspring: Systematic review and meta-analysis of observational studies. Obes Rev. 2019;20(8):1106-20.
19. Magnus MC, Tapia G, Olsen SF, Granstrom C, Marild K, Ueland PM, et al. Parental smoking and risk of childhood-onset type 1 diabetes. Epidemiology. 2018;29(6):848-56.
20. Begum M, Pilkington RM, Chittleborough CR, Lynch JW, Penno M, Smithers LG. Effect of maternal smoking during pregnancy on childhood type 1 diabetes: a whole-of-population study. Diabetologia. 2020;63(6):1162-73.
21. Metsala J, Hakola L, Lundqvist A, Virta LJ, Gissler M, Virtanen SM. Perinatal factors and the risk of type 1 diabetes in childhood and adolescence-A register-based case-cohort study in Finland, years 1987 to 2009. Pediatr Diabetes. 2020;21(4):586-96.

22. Raisanen L, Viljakainen H, Sarkkola C, Kolho KL. Perinatal risk factors for pediatric onset type 1 diabetes, autoimmune thyroiditis, juvenile idiopathic arthritis, and inflammatory bowel diseases. Eur J Pediatr. 2021;180(7):2115-23.
23. Wei Y, Edstorp J, Feychting M, Andersson T, Carlsson S. Prenatal and adult exposure to smoking and incidence of type 1 diabetes in children and adults-a nationwide cohort study with a family-based design. Lancet Reg Health Eur. 2023;36:100775.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
25. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
26. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. The Cochrane Collaboration. 2021;www.training.cochrane.org/handbook.
27. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2010;http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
30. Frederiksen B, Kroehl M, Lamb MM, Seifert J, Barriga K, Eisenbarth GS, et al. Infant exposures and development of type 1 diabetes mellitus: The Diabetes Autoimmunity Study in the Young (DAISY). JAMA Pediatr. 2013;167(9):808-15.
31. Haynes A, Cooper MN, Bower C, Jones TW, Davis EA. Maternal smoking during pregnancy and the risk of childhood type 1 diabetes in Western Australia. Diabetologia. 2014;57(3):469-72.
32. Adlercreutz EH, Wingren CJ, Vincente RP, Merlo J, Agardh D. Perinatal risk factors increase the risk of being affected by both type 1 diabetes and coeliac disease. Acta Paediatr. 2015;104(2):178-84.

33. Hussen HI, Persson M, Moradi T. Maternal overweight and obesity are associated with increased risk of type 1 diabetes in offspring of parents without diabetes regardless of ethnicity. Diabetologia. 2015;58(7):1464-73.
34. Lund-Blix NA, Stene LC, Rasmussen T, Torjesen PA, Andersen LF, Ronningen KS. Infant feeding in relation to islet autoimmunity and type 1 diabetes in genetically susceptible children: the MIDIA Study. Diabetes Care. 2015;38(2):257-63.
35. Suter MA, Aagaard KM. The impact of tobacco chemicals and nicotine on placental development. Prenat Diagn. 2020;40(9):1193-200.
36. Zhang W, Lin H, Zou M, Yuan Q, Huang Z, Pan X, et al. Nicotine in Inflammatory Diseases: Anti-Inflammatory and Pro-Inflammatory Effects. Front Immunol. 2022;Volume 13 - 2022.
37. Janbazacyabar H, van Daal M, Leusink-Muis T, van Ark I, Garssen J, Folkerts G, et al. The effects of maternal smoking on pregnancy and offspring: possible role for EGF? Front Cell Dev Biol. 2021;9:680902.
38. Zhao WH, Wen X, Qu W, Liu HX, Yan HY, Hou LF, et al. Attenuated Tregs increase susceptibility to type 1 diabetes in prenatal nicotine exposed female offspring mice. Toxicol Lett. 2019;315:39-46.
39. Vanderlinden LA, Wong E, Johnson RK, Carry P, Dong F, Kechris K, et al. DNA methylation smoking scores and risk of islet autoimmunity and type 1 diabetes. Diabetes Care. 2025:dc250330.
40. Hammerton G, Munafò MR. Causal inference with observational data: the need for triangulation of evidence. Psychol Med. 2021;51(4):563-78.
41. Romero Villela PN, Kelly KM, Balbona JV, Ehringer MA, Keller MC. Maternal smoking during pregnancy interacts with genetic factors to increase risk for low birth weight but not harmful offspring smoking behaviors in europeans. Nicotine Tob Res. 2024.
42. Ye Z, Li J, Gu P, Zhang Y, Xie Y, Yang S, et al. Early-life tobacco smoke exposure, genetic susceptibility and the risk of type 2 diabetes in adulthood: A large prospective cohort study. Sci Total Environ. 2023;893:164698.
43. Kobayashi S, Sata F, Kishi R. Gene-environment interactions related to maternal exposure to environmental and lifestyle-related chemicals during pregnancy and the resulting adverse fetal growth: a review. Environ Health Prev Med. 2022;27:24.

44. Badihian N, Riahi R, Goli P, Badihian S, Poursafa P, Kelishadi R. Prenatal and perinatal factors associated with developing multiple sclerosis later in life: A systematic review and meta-analysis. Autoimmun Rev. 2021;20(6):102823.

TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included prospective studies

Study	Country	Cohort source	No. of children included	Male (%)	Methods for validation of MSDP	No. of children born to MSDP	Age at T1D diagnosis (years)	Methods for the diagnosis of T1D	No. of children with T1D	Variables adjusted or controlled	Prevalence of MSDP (%)	Incidence of T1D in offspring (%)
Frederiksen 2013	USA	Prospective birth cohort of children at increased genetic risk for T1D	1835	48.7	Maternal self-report during pregnancy	183	< 18 (mean: 5.9)	Physician-diagnosed T1D based on symptoms (polyuria/polydipsia) + random glucose ≥ 200 mg/dL or OGTT (fasting ≥ 126 mg/dL	53	Age, sex, HLA genotype, first-degree relative with T1D, maternal education, and delivery type	10.0	2.89

								or 2h ≥ 200 mg/dL).				
Haynes 2014	Australia	Population-based birth cohort to mother without diabetes in West Australia	226233	NR	Maternal self-report during pregnancy	40876	< 15 (mean: NR)	Physician-diagnosed based on clinical, biochemical, and autoantibody criteria	287	Age, sex, maternal socioeconomic status, birthweight, gestational age, maternal age, birth order, and year of birth	18.1	0.13
Adlercreutz 2015	Sweden	Population-based birth cohort (singlet	768395	51.4	Maternal self-report at first antenatal visit	176044	< 14 (median: 4.7)	Hospital registry (ICD codes)	4518	Age, sex, maternal age, small for gestational age,	22.9	0.59

		on births)								delivery mode, preterm birth, season of birth, maternal birth country, congenital malformations, socioeconomic factors		
Lund-Blix 2015	Norway	Prospective birth cohort of children at	726	50.6	Maternal smoking during pregnancy reported via	116	< 12 (mean: 7.7)	National Childhood Diabetes Registry clinical diagnosis)	25	Age, sex, first-degree relative with T1D, vitamin D supplementation,	16.0	3.44

		increased genetic risk for T1D			questionnaire at child's age 3 months.					maternal education, and delivery type		
Hussen 2015	Sweden	Population-based birth cohort (Migration and Health Cohort)	1176155	NR	Maternal self-report at first antenatal visit	136719	< 18 (mean: 7.8)	National Patient Register (ICD codes)	5771	Age, sex, birth cohort, maternal diabetes, paternal diabetes, maternal BMI, maternal age, gestational age, parental education, mode of	11.6	0.49

										delivery		
Magnus 2018 MoBa	Norway	Prospective pregnancy cohort (1999–2008)	98287	51	Maternal self-reported at gestational week 18; cord blood cotinine measured in a subset (n=630)	26098	< 15 (median : 7.1)	National Childhood Diabetes Registry clinical diagnosis)	349	Age, sex, maternal age, parity, education, prepregnancy BMI, diabetes; HLA genotype in subset	26.6	0.36
Magnus 2018 DNBC	Denmark	Prospective pregnancy cohort (1996–	86785	51	Maternal self-reported at gestational week 12	26262	< 17 (median : 10.1)	National Childhood Diabetes Registry clinical diagnosis)	340	Age, sex, maternal age, parity, education, prepregnancy BMI, diabetes	30.3	0.39

		2002)										
Magnus 2018 NRBC	Norway	National registry linkage	434627	NR	Maternal self-reported at delivery	245999	< 11 (mean: 4.7)	Patient registry (ICD codes)	692	Age, sex, maternal age, parity, education, insulin-treated diabetes	56.6	0.16
Begum 2020	Australia	Population-based birth cohort in South Australia	286058	NR	Maternal self-reported at first antenatal visit (<20 weeks) and second half of pregnancy (≥20 weeks)	62216	< 15 (mean: NR)	Patient registry (ICD codes)	557	Age, sex, maternal birth region, ethnicity, remoteness, socioeconomic status, hospital category, parity, and pre-	21.7	0.19

										pregnancy hypertension/diabetes		
Metsala 2020	Finland	Population-based birth cohort	134078	51.3	Maternal self-reported during first trimester	20378	< 16 (mean: 7.1)	Patient registry (ICD codes)	6862	Age, sex, maternal age, diabetes, asthma; birth decade, gestational age, birth weight/length, mode of delivery, parity, and socioeconomic factors	15.2	5.12
Raisanen 2021	Finland	Nation wide register	11407	52.2	Maternal self-reported	1048	< 17 (mean: 8.6)	Patient registry (ICD	102	Age, sex, maternal age,	9.2	0.89

		-based cohort study			during first trimester			codes)		employment, parity; gestational age, birthweight, delivery method, postnatal antibiotics		
Wei 2023	Sweden	Nationwide Swedish registers	3170386	NR	Maternal self-reported smoking status at first prenatal visit (8–12 weeks of pregnancy).	NR	< 18 (mean: NR)	Patient registry (ICD codes)	18745	Age, sex, calendar year, family history of diabetes, maternal BMI, and parental education	NR	0.59

The study by Magnus 2018 reported three cohorts, which were independently included in the meta-analysis: the Norwegian Mother and Child Cohort Study (MoBa), the Danish National Birth Cohort (DNBC), and the Norwegian Registry Birth Cohort (NRBC). Numbers for Metsälä et al. (2020) reflect the case–cohort design of the Finnish registry study, in which all 6,862 children with type 1 diabetes were included alongside a 10% random sample of 127,216 children without T1D. The resulting proportion of cases should not be interpreted as population incidence, but rather as a feature of the study design. Abbreviations: MSDP: Maternal smoking during pregnancy; T1D: Type 1 diabetes; OGTT: Oral glucose tolerance test; ICD: International Classification of Diseases; NR: Not reported.

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Frederiksen 2013	1	1	1	1	1	1	1	1	1	9
Haynes 2014	1	1	1	1	1	1	1	1	1	9
Adlercreutz 2015	1	1	1	1	1	1	0	1	1	8
Lund-Blix 2015	1	1	1	1	1	1	1	1	1	9
Hussen 2015	1	1	1	1	1	1	0	1	1	8
Magnus 2018 MoBa	1	1	1	1	1	1	1	1	1	9
Magnus	1	1	1	1	1	1	1	1	1	9

2018 DNBC										
Magnus 2018 NRBC	1	1	1	1	1	1	0	1	1	8
Begum 2020	1	1	1	1	1	1	0	1	1	8
Metsala 2020	1	1	1	1	1	1	0	1	1	8
Raisanen 2021	1	1	1	1	1	1	0	1	1	8
Wei 2023	1	1	1	1	1	1	0	1	1	8

The study by Magnus 2018 reported three cohorts, which were independently included in the meta-analysis: the Norwegian Mother and Child Cohort Study (MoBa), the Danish National Birth Cohort (DNBC), and the Norwegian Registry Birth Cohort (NRBC).

Table 3. Sensitivity analysis by excluding one dataset at a time

Dataset excluded	RR (95% CI)	I^2	*p* for Cochrane Q test	*p* for effect
Frederiksen 2013	0.74 [0.72, 0.76]	0%	0.48	< 0.001
Haynes 2014	0.74 [0.72, 0.76]	5%	0.40	< 0.001
Adlercreutz 2015	0.72 [0.70, 0.75]	0%	0.93	< 0.001
Lund-Blix 2015	0.74 [0.72, 0.76]	5%	0.39	< 0.001
Hussen 2015	0.74 [0.71, 0.76]	5%	0.39	< 0.001
Magnus 2018 MoBa	0.74 [0.72, 0.76]	3%	0.41	< 0.001
Magnus 2018 DNBC	0.74 [0.72, 0.76]	0%	0.44	< 0.001
Magnus 2018 NRBC	0.74 [0.72, 0.76]	0%	0.44	< 0.001
Begum 2020	0.74 [0.71, 0.76]	0%	0.51	< 0.001
Metsala 2020	0.74 [0.72, 0.76]	1%	0.43	< 0.001
Raisanen 2021	0.74 [0.72, 0.76]	3%	0.41	< 0.001
Wei 2023	0.76 [0.73, 0.79]	0%	0.648	< 0.001

The study by Magnus 2018 reported three cohorts, which were independently included in the meta-analysis: the Norwegian Mother and Child Cohort Study (MoBa), the Danish National Birth Cohort (DNBC), and the Norwegian Registry Birth Cohort (NRBC). Abbreviations: RR: Risk ratio; CI: Confidence interval.

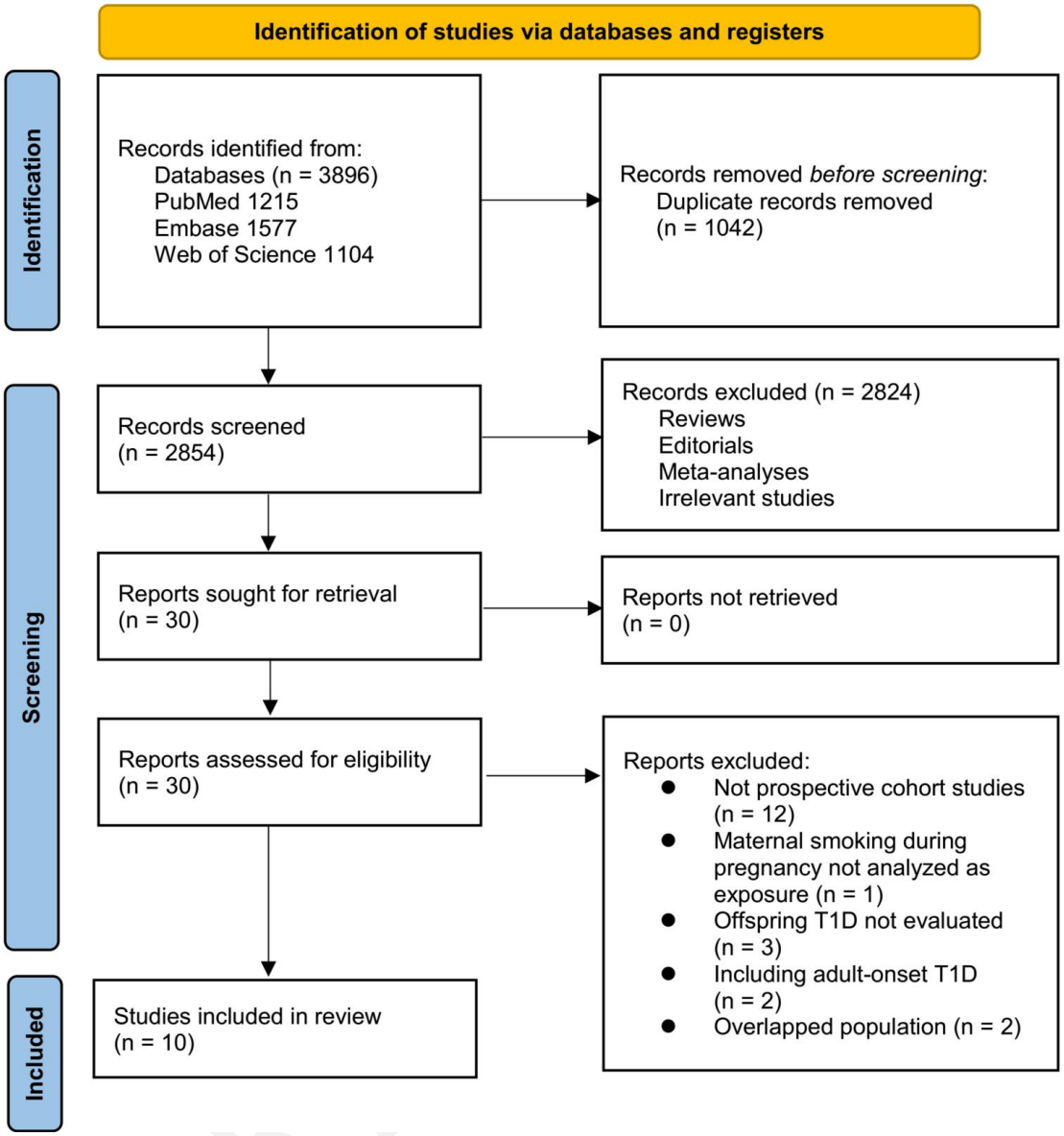

Figure 1. Flowchart of database search and study inclusion

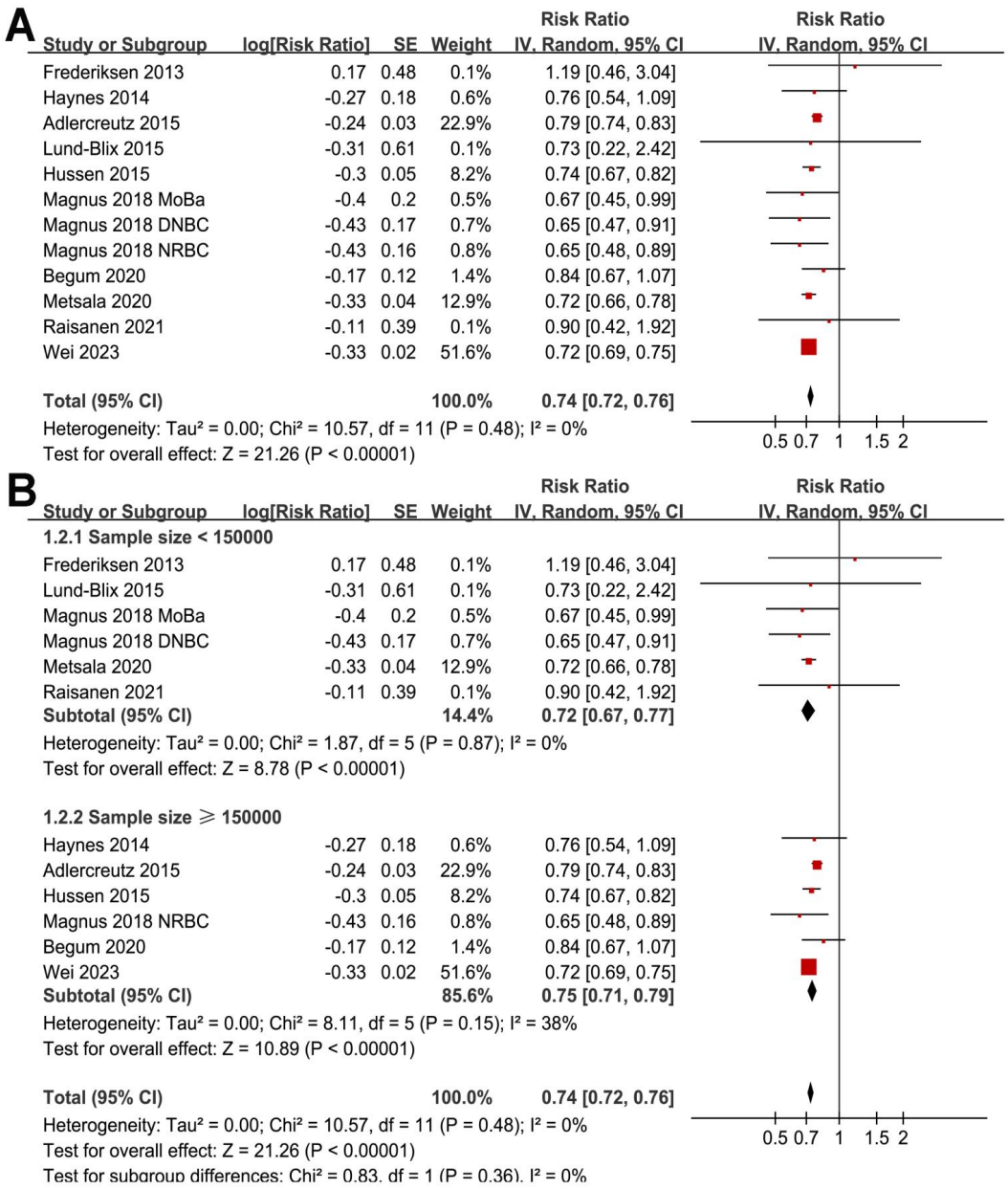

Figure 2. Forest plots for the meta-analysis of the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. (A) Overall meta-analysis; (B) Subgroup analysis according to sample of the included studies. RRs with 95% CIs are shown for each study. Weights are derived from inverse-variance random-effects models. Abbreviations: T1D: Type 1 diabetes; RR: Risk ratio; CI: Confidence interval; SE: Standard error; df: Degrees of freedom; τ^2: between-study variance; I^2: percentage of total variation due to heterogeneity; Chi^2: Cochran's Q statistic.

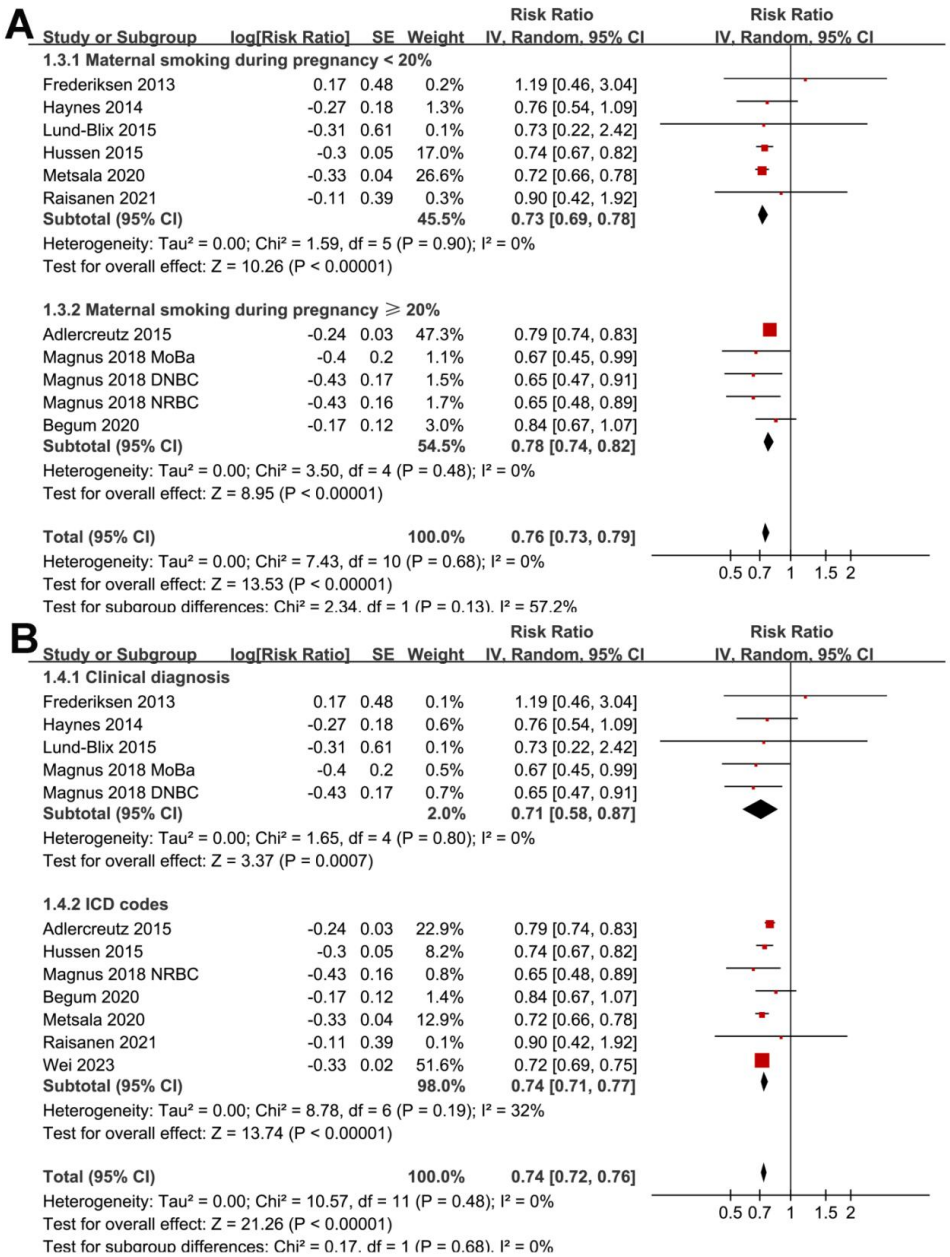

Figure 3. Forest plots for the subgroup analyses of the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. (A) Subgroup analysis according to the prevalence of maternal smoking during pregnancy in each study; (B) subgroup analysis according to the methods for the diagnosis of T1D. RRs with 95% CIs are shown for each study. Weights are derived from inverse-variance random-effects models. Abbreviations: T1D: Type 1 diabetes; RR: Risk ratio; CI: Confidence interval; SE: Standard error; df: Degrees of freedom; τ^2: Between-study variance; I^2: Percentage of total variation due to heterogeneity; Chi^2: Cochran's Q statistic.

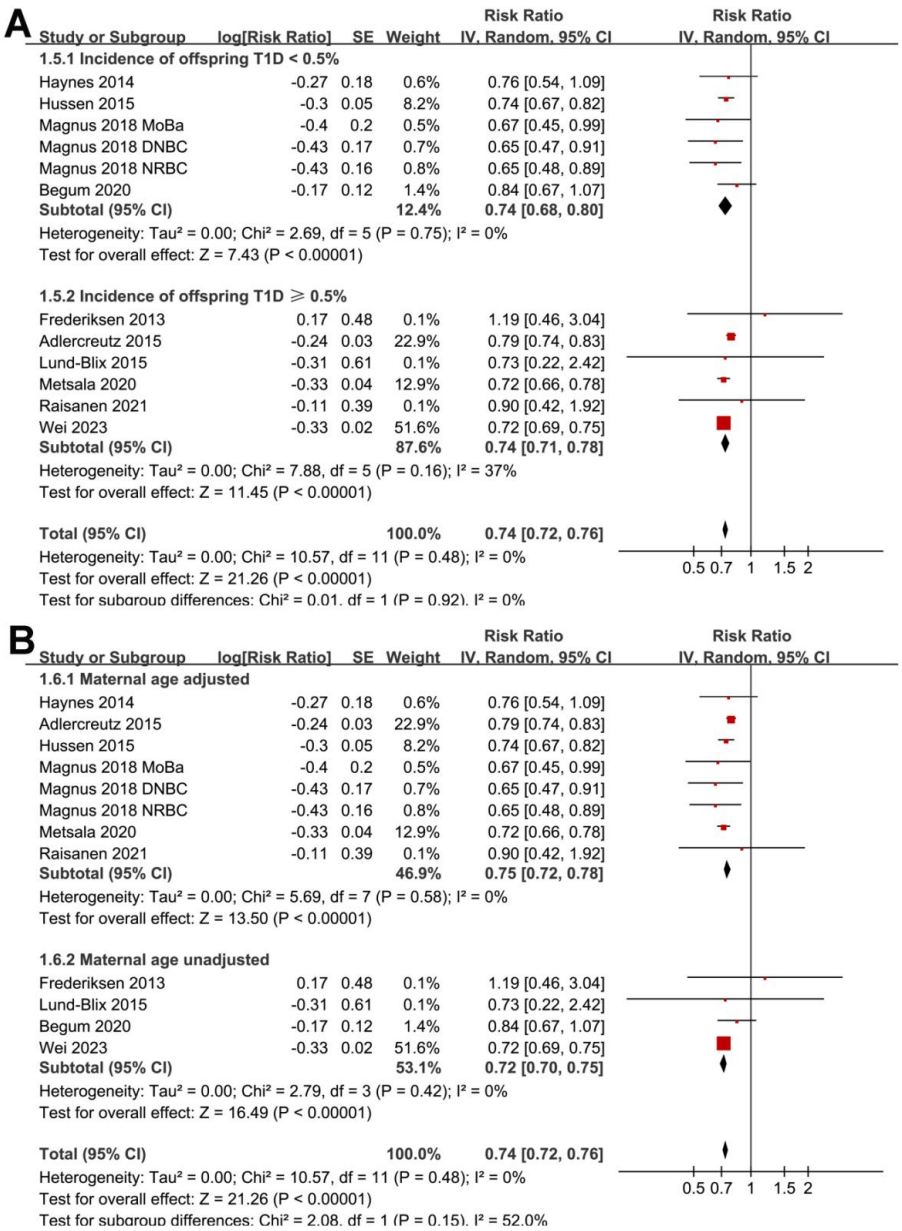

Figure 4. Forest plots for the subgroup analyses of the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. (A) Subgroup analysis according to the incidence of offspring T1D in each study; (B) Subgroup analysis according to whether maternal age was adjusted in each study. RRs with 95% CIs are shown for each study. Weights are derived from inverse-variance random-effects models. Abbreviations: T1D: Type 1 diabetes; RR: Risk ratio; CI: Confidence interval; SE: Standard error; df: Degrees of freedom; τ^2: Between-study variance; I^2: Percentage of total variation due to heterogeneity; Chi^2: Cochran's Q statistic.

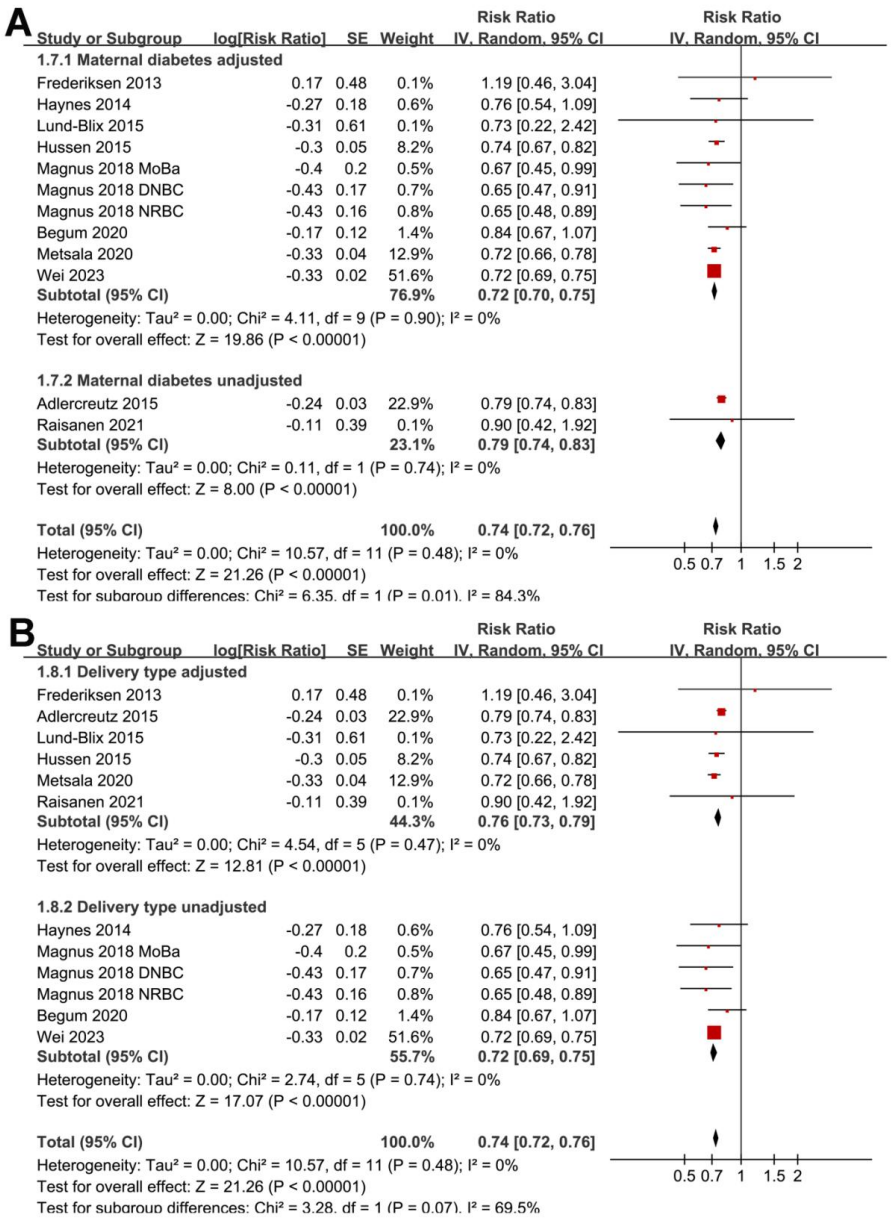

Figure 5. Forest plots for the subgroup analyses of the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. (A) Subgroup analysis according to whether maternal diabetes was adjusted in each study; (B) subgroup analysis according to whether delivery type was adjusted in each study. RRs with 95% CIs are shown for each study. Weights are derived from inverse-variance random-effects models. Abbreviations: T1D: Type 1 diabetes; RR: Risk ratio; CI: Confidence interval; SE: Standard error; df: Degrees of freedom; τ^2: Between-study variance; I^2: Percentage of total variation due to heterogeneity; Chi^2: Cochran's Q statistic.

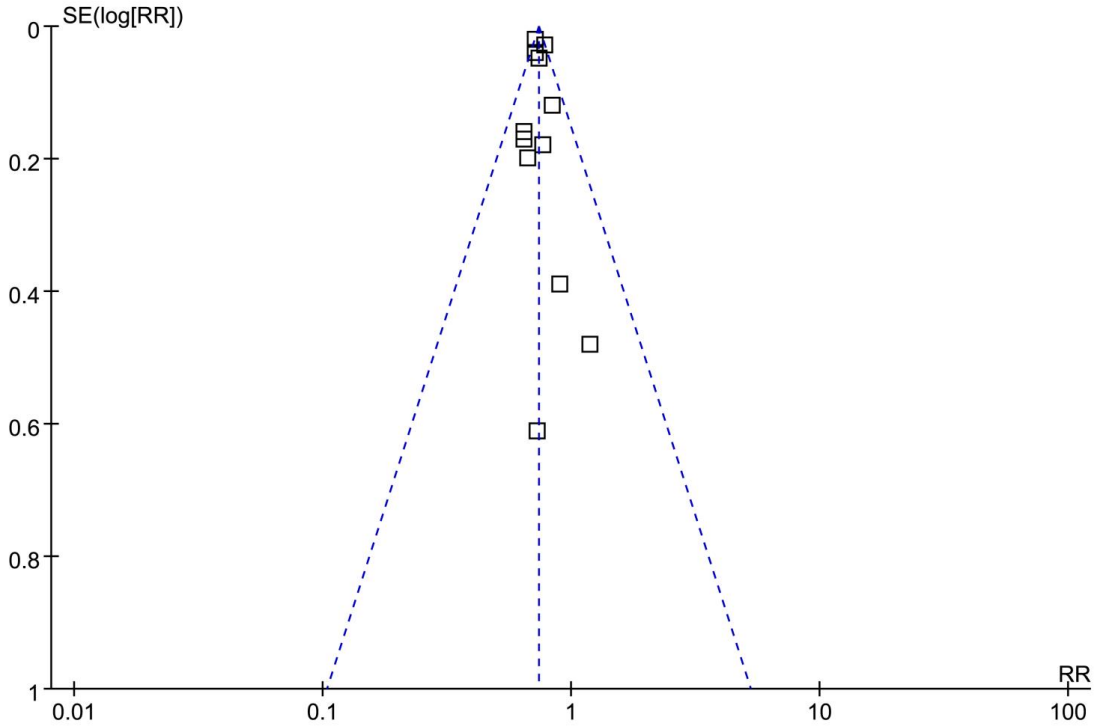

Figure 6. Funnel plots for estimating the potential publication biases underlying the meta-analyses of the association between maternal smoking during pregnancy and the risk of childhood-onset T1D in offspring. Each dot represents an individual dataset. The vertical line indicates the pooled effect estimate. Symmetry suggests absence of small-study effects, though formal tests are underpowered with 12 datasets. All 12 studies are represented; some markers overlap due to nearly identical coordinates of effect estimates and standard errors. Abbreviation: T1D: Type 1 diabetes.

SUPPLEMENTAL DATA

Supplemental File 1. Detailed search strategy for each database

PubMed

("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR pregnancy[tiab] OR pregnant[tiab] OR prenatal[tiab] OR pre-natal[tiab]) AND ("Smoking"[Mesh] OR "Tobacco Use"[Mesh] OR smoking[tiab] OR smoke[tiab] OR cigarette[tiab] OR cigarettes[tiab] OR nicotine[tiab] OR tobacco[tiab]) AND ("Diabetes Mellitus, Type 1"[Mesh] OR "type 1 diabetes"[tiab] OR T1D[tiab] OR T1DM[tiab] OR diabetic[tiab] OR diabetes[tiab]) AND ("Child"[Mesh] OR "Adolescent"[Mesh] OR "Pediatrics"[Mesh] OR child[tiab] OR children[tiab] OR adolescent[tiab] OR adolescents[tiab] OR pediatric[tiab] OR paediatric[tiab] OR offspring[tiab] OR childhood[tiab] OR adolescence[tiab]) AND (humans[Filter]) AND ("journal article"[Publication Type])

Embase

('pregnancy'/exp OR 'pregnant woman'/exp OR pregnancy:ti,ab OR pregnant:ti,ab OR prenatal:ti,ab OR pre-natal:ti,ab) AND ('smoking'/exp OR 'tobacco use'/exp OR smoking:ti,ab OR smoke:ti,ab OR cigarette:ti,ab OR cigarettes:ti,ab OR nicotine:ti,ab OR tobacco:ti,ab) AND ('type 1 diabetes mellitus'/exp OR 'diabetes mellitus':ti,ab OR 'type 1 diabetes':ti,ab OR T1D:ti,ab OR T1DM:ti,ab OR diabetic:ti,ab) AND ('child'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR child:ti,ab OR children:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR pediatric:ti,ab OR paediatric:ti,ab OR offspring:ti,ab OR childhood:ti,ab OR adolescence:ti,ab) AND [humans]/lim AND [article]/lim

Web of Science

TS=("pregnancy" OR "pregnant" OR "prenatal" OR "pre-natal") AND TS=("smoking" OR "smoke" OR "cigarette" OR "cigarettes" OR "nicotine" OR

"tobacco") AND TS=("type 1 diabetes" OR "diabetes" OR "diabetic" OR "T1D" OR "T1DM") AND TS=("child" OR "children" OR "adolescent" OR "adolescents" OR "pediatric" OR "paediatric" OR "offspring" OR "childhood" OR "adolescence") AND DT=(Article) AND LA=(English)