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DIABETIC Medicine

SYSTEMATIC REVIEW OR META-ANALYSIS

Parental smoking, type 1 diabetes, and islet autoantibody positivity in the offspring: A systematic review and meta-analysis

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Abstract

Aims: Our aim was to synthesize current evidence on the association between parental smoking and incidence of type 1 diabetes and islet autoantibody positivity (IA) in the offspring by conducting a systematic review and meta-analysis.

Methods: We searched Medline, Embase, and Cochrane Library until January 21, 2021, for human studies with parental tobacco use as exposure, type 1 diabetes or IA as outcome, and hazard, risk, or odds ratios as effect estimates. Summary relative risks (RR) and 95% confidence intervals (CI) were estimated with random-effects models. Heterogeneity was quantified with the I^2 statistic, bias with the ROBINS-I tool, and the certainty of evidence with the GRADE tool.

Results: We identified 535 records of which 23 were eligible including 25 927 cases of type 1 diabetes. Maternal smoking during pregnancy was associated with a reduced risk of type 1 diabetes ($n = 22$, RR 0.78, CI 0.71–0.86, I^2=69%). Including only studies with low to moderate risk of bias indicated similar results with less heterogeneity ($n = 14$, RR 0.73, CI 0.68–0.79, $I^2 = 44\%$). The certainty of evidence was graded as high. There was no clear association between type 1 diabetes and neither maternal ($n = 6$, RR 0.95, CI 0.78–1.14, $I^2 = 0\%$) nor paternal ($n = 6$, RR 0.90, 0.70–1.17, $I^2 = 68\%$) smoking during childhood. Furthermore, the association between maternal smoking during pregnancy and IA was weak ($n = 4$, RR 0.86, CI 0.44–1.65, $I^2 = 71\%$).

Conclusions: Maternal smoking during pregnancy may reduce the risk of type 1 diabetes in the offspring. Further studies are needed to elucidate potential mechanisms underlying this association.

Registration: Prospero CRD42021236717.

KEYWORDS

incidence, islet autoimmunity, maternal, paternal, prenatal, smoking, tobacco, type 1 diabetes

Twitter @SofiaEJCarlsson, @karolinskainst, @Jessica_eds, @EstridStudy, @AMLampousi: Smoking during pregnancy but not childhood is associated with a reduced risk of type 1 diabetes. Could nicotine play a role in prevention?

1 | INTRODUCTION

Smoking is associated with an increased risk of type 2 diabetes,[1] but its influence on autoimmune forms of diabetes such as type 1 diabetes and latent autoimmune diabetes in adults (LADA) is less clear. Studies in LADA have yielded conflicting results with indications of increased[2] as well as reduced risk[3] in smokers. Regarding type 1 diabetes, two previous meta-analyses reported a reduced risk in children of mothers who smoked during pregnancy.[4,5] However, these studies were limited to population-based studies[4] or studies without children at high genetic risk.[5] No previous attempts have been made to summarize the entire literature on parental smoking, including both maternal and paternal smoking during pregnancy and childhood, and risk of type 1 diabetes in the offspring. In addition, no study has summarized results regarding parental smoking and development of islet autoantibody positivity (IA).

To fill this knowledge gap, we aimed to systematically synthesize the entire literature on parental smoking and type 1 diabetes, including prenatal exposure and exposure to maternal as well as paternal smoking during childhood, and considering both type 1 diabetes and IA as outcomes.

Novelty Statement

What is already known?

- It has been suggested that fetal exposure to smoking is associated with a reduced risk of type 1 diabetes.
- The influence of childhood exposure to smoking on type 1 diabetes risk is not clear.
- The totality of evidence regarding these associations has not been systematically synthesized.

What this study has found?

- Evidence of high certainty supports that maternal smoking during pregnancy is associated with a reduced risk of childhood type 1 diabetes.
- Neither maternal nor paternal smoking during childhood is associated with a reduced risk of type 1 diabetes.

What are the implications of the study?

These findings highlight the need for mechanistic investigations into the link between fetal exposure to smoking and type 1 diabetes.

2 | METHODS

2.1 | Literature search

We conducted a systematic review and meta-analysis according to a predefined protocol registered in the International Prospective Register for Systematic Reviews (PROSPERO) on March 19th, 2021 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=236717) and followed the PRISMA guidelines. Medline (Ovid), Embase, and Cochrane Library (Wiley) were searched from inception until January 21, 2021, by librarians at the Karolinska Institutet University Library (complete search strategy presented in Tables S1–S3). Eligible studies had (1) type 1 diabetes or IA (Autoantibodies against insulin [IAA], Glutamic acid decarboxylase antibodies [GADA], Tyrosine phosphatase-related islet antigen 2 [IA-2A], or Islet cell antibodies [ICA]) as outcome; (2) maternal or paternal tobacco use as exposure, including prenatal exposure to tobacco; (3) cohort, case-cohort, case-control, or randomized controlled trial (RCT) design; and (4) hazard ratios, risk ratios, or odds ratios with 95% confidence intervals (CI), as measures of association. We also retrieved relevant papers from the reference lists of the eligible articles. All identified studies were initially screened based on the title and abstract and articles that seemed to fulfil the eligibility criteria were fully examined. Conference/congress papers, reviews, editorials, letters, and animal studies were excluded and only articles in English were considered.

From the studies deemed to be eligible, we extracted the following: the name of first author, year of publication, country, name of the cohort (when applicable), study design, sample size, number of cases, age at diagnosis, type of exposure, exposure categorization, exposure and outcome assessment, outcome (type 1 diabetes or IA), effect estimate (HR/RR/OR) with 95% CI, choosing the most adjusted estimate, and finally information on which covariates were included in the models. If a paper included data from several cohorts, each cohort was treated as a separate study. Study selection, data extraction, and risk of bias assessment was performed independently by two reviewers (JE and SC) and disagreements were resolved by consultation with a third reviewer (AML). Exposure in the included studies was primarily cigarette smoking but could also include smoking pipe, cigars, or cigarillos and will therefore be referred to as "smoking". It did not include marijuana, e-cigarettes, or smokeless tobacco products.

2.2 | Assessing bias and quality of evidence

Eligible studies were assessed for risk of bias using the Revised Cochrane risk-of-bias tool for Non-randomized

Studies of Interventions (ROBINS-I).[6] ROBINS-I grades bias as low, moderate, serious, or critical in seven domains: confounding, selection of participants, classification of intervention (exposure), deviation from intended intervention (change of exposure category), missing data, measurement of the outcome and selection of reported results. The overall grade of a study is based on the domain with the highest risk of bias. To assess the overall certainty of evidence for each meta-analysis, we used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool[7]. For each meta-analysis, we assessed risk of bias, inconsistency of results, indirectness of evidence, imprecision and reporting bias (when it was possible to assess). Based on this assessment, the overall certainty of evidence was 'very low', 'low', 'moderate' or 'high'.

2.3 | Statistical analysis

Statistical analysis was performed with Review Manager (RevMan) version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata Statistical Software release 16 (StataCorp, College Station, TX: StataCorp LLC). Random-effects models were used for estimating pooled relative risks (RR) and 95% CI of type 1 diabetes and IA separately in relation to maternal smoking during pregnancy, maternal smoking during childhood and paternal smoking during childhood (yes vs. no). We pooled odds ratios and hazard ratios since according to the rare disease assumption, they will be similar if the outcome is rare. Weights were assigned to each study based on the inverse variance of their estimate. When effect estimates were given for different exposure levels, they were pooled to get an overall estimate of the RR associated with smoking to include in the meta-analysis. Cochran´s Q test was used to estimate heterogeneity across studies and the I^2 statistic indicated the percentage of variance due to such heterogeneity ($I^2 > 50\%$ indicates substantial heterogeneity). We could assess small study effects with the Egger´s test for meta-analyses with at least 10 studies. Finally, we used contour-enhanced funnel plots with critical regions at 1%, 5% and 10% significance levels to elucidate if small study effects were attributed to publication bias. Sensitivity analyses were conducted where we restricted the meta-analyses to (a) prospective studies, (b) studies with low or moderate bias and (c) studies of children with high genetic risk.

3 | RESULTS

3.1 | Characteristics

The literature search identified 535 records, and out of 40 fully screened articles, 17 were excluded and 23 were eligible[4,8-29] (Figure 1). Two of the papers[16,26] included data from more than one cohort, and each cohort was treated as a separate study yielding 26 studies to be included in the meta-analyses. These studies were primarily based on European populations, but there were also three from the US[11,12,23] and two Australian studies.[4,13] In total, there were 15 cohort[4,8,12-16,19,23,26,27,29] and 11 case-control studies.[9-11,17,18,20-22,24,25,28] Details of these studies together with our bias assessment are summarized in Tables S4–S8.

3.2 | Maternal smoking during pregnancy and type 1 diabetes

The association between maternal smoking during pregnancy and type 1 diabetes was addressed in 22 studies,[4,8-21,23-27] and the pooled analysis showed a reduced risk of type 1 diabetes in children of smoking mothers (RR 0.78, CI 0.71–0.86), with some heterogeneity across studies ($I^2 = 68\%$) (Figure 2). The Egger's test did not indicate the presence of small study effects ($p = 0.1427$) and visual inspection of the funnel plot did not suggest publication bias (Figure S1). When the analysis was restricted to prospective cohort studies, results were similar (RR 0.75, CI 0.71–0.80, $n = 12$), with less heterogeneity ($I^2 = 7\%$) (Figure S2). Results were also similar (RR 0.73, CI 0.68–0.79, $I^2 = 44\%$, $n = 14$) when only studies with low or moderate risk of bias that adjusted for a range of confounders including socioeconomic status, breastfeeding, birth weight, parental diabetes, mode of delivery, and maternal body mass index were included in the analysis (Figure 3). Similar results were seen when only the eight studies with low risk of bias were included in the analysis (Figure S3). One study included data on the risk of offspring type 1 diabetes in relation to cord blood cotinine, an indicator of prenatal smoking exposure[30]; the odds ratios were 0.82 (CI 0.42–1.6) for ≤30 nmol/L and 0.42 (CI 0.17–1.0) for >30 nmol/L compared to having undetectable cotinine levels.[16] Overall, the level of certainty regarding the meta-results was deemed to be high (Table S9).

3.3 | Paternal smoking during pregnancy and type 1 diabetes

The association between paternal smoking during pregnancy and offspring type 1 diabetes was assessed in two Scandinavian cohorts[16] (Table S5), with a pooled estimate of 0.97 (CI 0.81–1.15) (Figure S5). Neither study was adjusted for maternal smoking, and the overall level of certainty was low (Table S9).

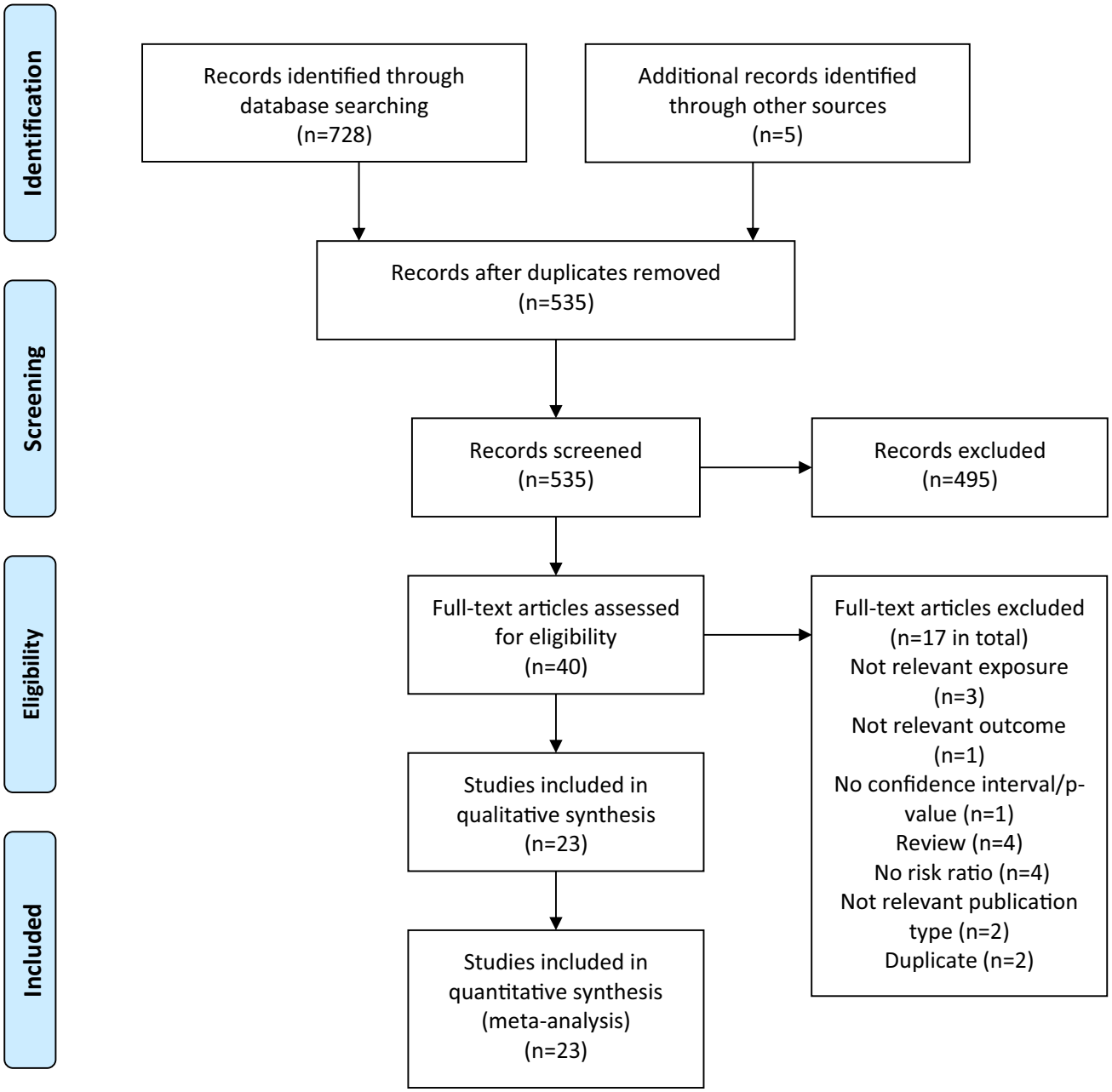

FIGURE 1 Flow diagram of study selection

3.4 | Parental smoking during childhood and type 1 diabetes

Six studies[16,21,22,26] addressed maternal smoking during childhood and type 1 diabetes risk (Table S7), and overall, the association was weak (RR 0.95, CI 0.78–1.14, $I^2 = 0\%$) (Figure 4). When we restricted the analysis to prospective studies (Figure S7), the RR was lower but CIs wide (RR 0.81, CI 0.59–1.11, $I^2 = 0\%$, $n = 4$). For paternal smoking during childhood, RR was estimated at 0.90 (CI 0.70–1.17, $I^2 = 68\%$) (Figure 5), based on the same six studies[16,21,22,26] (Table S8), and 0.78 (CI 0.55–1.09, $I^2 = 63\%$, $n = 4$) when only prospective cohort studies were included in the analysis (Figure S9). Two of the cohorts with data on parental (maternal or paternal) smoking and type 1 diabetes had low risk of bias[16] (Figures S8 and S10) and the remaining four[21,22,26] had serious risk of bias. The evidence from the meta-analyses of childhood exposure to smoking (maternal or paternal) and type 1 diabetes risk was assessed as being of low certainty (Table S9).

3.5 | Parental smoking and IA

The association between maternal smoking during pregnancy and development of IA in the offspring was assessed in four studies[15,23,27,29] (Table S6). IA was defined as repeated

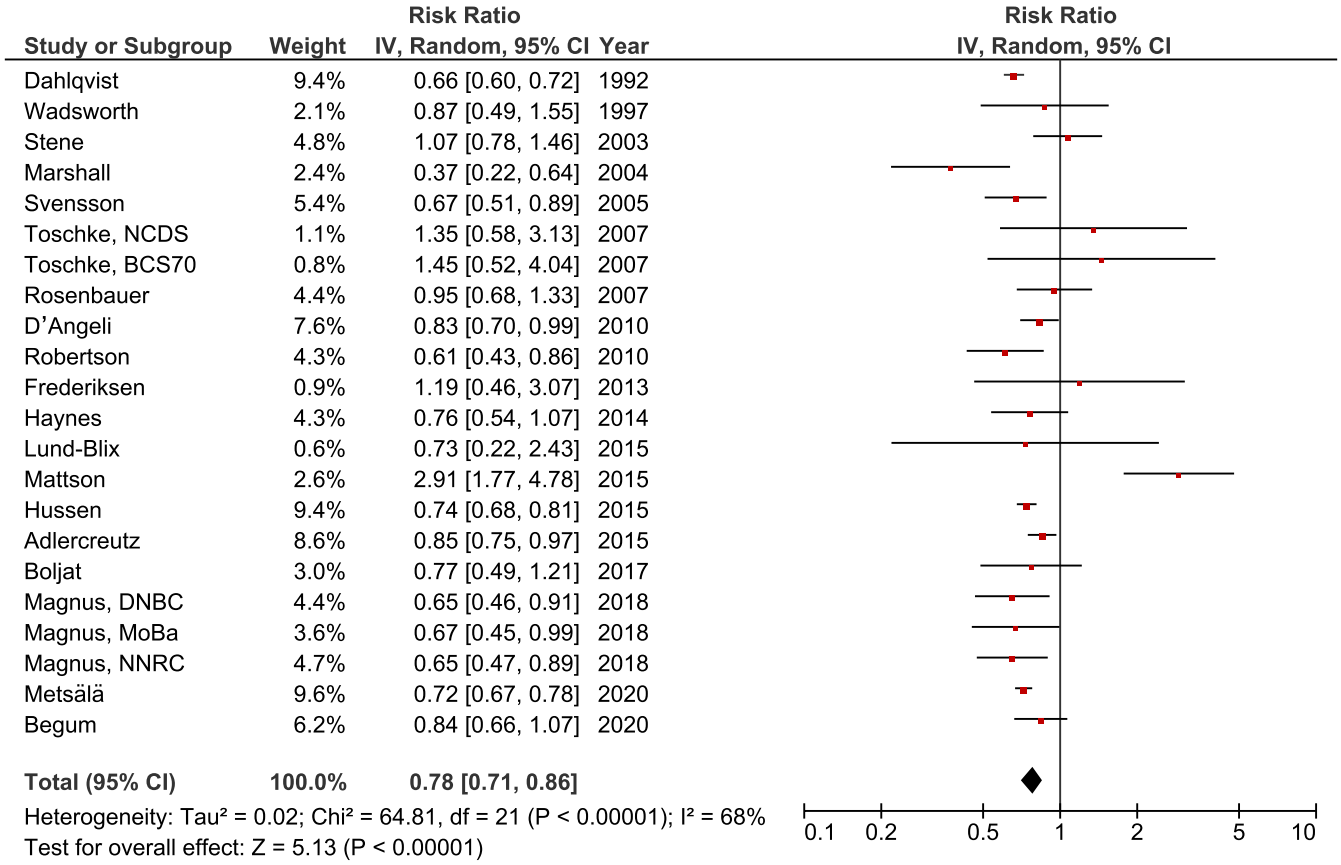

FIGURE 2 Maternal smoking during pregnancy and incidence of type 1 diabetes in the offspring. Study-specific and pooled risk ratios and 95% confidence intervals

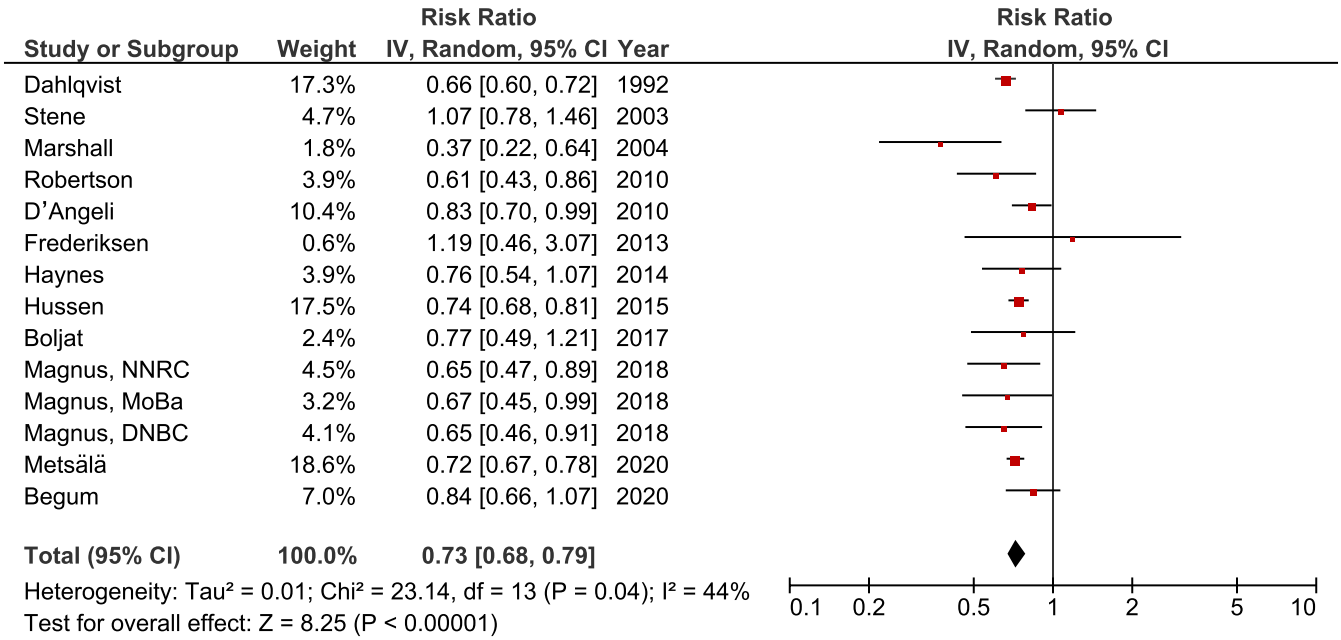

FIGURE 3 Maternal smoking during pregnancy and incidence of type 1 diabetes in the offspring, studies with low or moderate risk of bias. Study-specific and pooled risk ratios and 95% confidence intervals

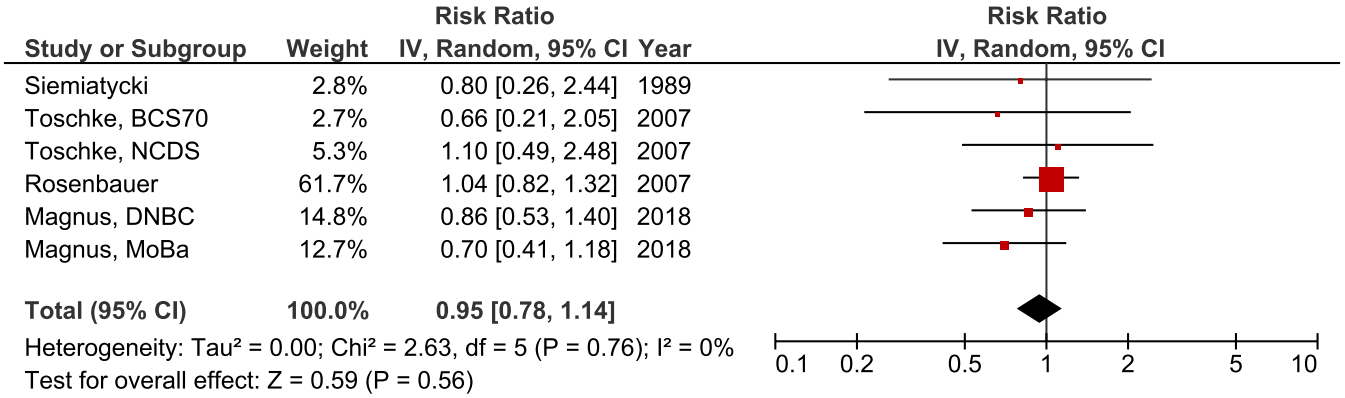

FIGURE 4 Maternal smoking during childhood and incidence of type 1 diabetes in the offspring. Study-specific and pooled risk ratios and 95% confidence intervals

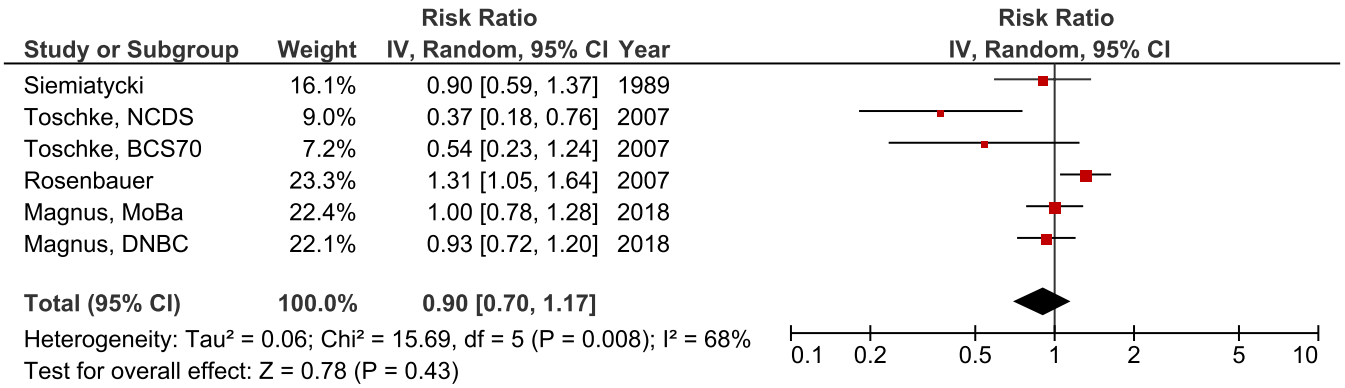

FIGURE 5 Paternal smoking during childhood and incidence of type 1 diabetes in the offspring. Study-specific and pooled risk ratios and 95% confidence intervals

positivity for one or more autoantibodies (IAA, GADA, IA-2A),[15,23] or two or more (ICA and at least one of the above mentioned),[27] or as positivity to either GADA or IA-2A at a single measurement at age 2.5 years.[29] Measurements were taken repeatedly up to 12 months of age and then annually[15] or repeatedly up to 24 months of age.[23,27]

No association was detected between maternal smoking and IA, and there was high heterogeneity across studies (OR 0.86, CI 0.44–1.65, $I^2 = 71\%$) (Figure S6). All but one[23] of these studies had serious risk of bias, primarily due to the lack of adjustment for potential confounders. The certainty of evidence regarding the results of this meta-analysis was deemed to be very low (Table S9). There were no studies assessing IA in relation to paternal smoking during pregnancy, and only one in relation to parental smoking during childhood.[29] This study was deemed to have serious risk of bias, and the results were not conclusive (Table S6).

3.6 | Children with high genetic risk

Four studies were based on children with high genetic risk, either with diabetes associated human leukocyte antigen genotypes or family history of type 1 diabetes.[12,15,23,27] When these studies were pooled, the RR associated with maternal smoking during pregnancy was 0.72 (CI 0.47–1.10, $I^2 = 0\%$) for the composite outcome of IA or type 1 diabetes (Figure S4).

4 | DISCUSSION

4.1 | Principal findings

These meta-analyses were based on 26 individual studies[4,8-29] and the results revealed a 22% reduced risk of childhood type 1 diabetes in the offspring of mothers who smoke during pregnancy. The association remained in sensitivity analyses and there was no indication of publication bias, while the certainty of this evidence was deemed to be high. The findings are in line with previous meta-analyses based on five[4] to 10 studies.[5] Maternal smoking during pregnancy was not associated with a reduced risk of IA; however, there were few studies and most of them did not adjust for any potential confounders. Our findings did not suggest that

childhood exposure to maternal or paternal smoking reduces the risk of type 1 diabetes, but the level of certainty regarding this evidence was low.

The mechanism linking prenatal smoking exposure to a reduced risk of type 1 diabetes remains to be elucidated. Animal studies suggest that smoking may inhibit the development of autoimmune diabetes by preserving the pancreatic insulin content and promoting anti-inflammatory processes.[31] Nicotine, the major active component of cigarettes, activates nicotinic acetylcholine receptors (nAChRs), expressed on the surface of most immune cells, and this activation is linked to suppression of autoreactivity and inflammation.[32,33] It is possible that the association between smoking and type 1 diabetes is mediated through such a "nicotinic anti-inflammatory pathway".[34] In support hereof, pancreatic ß-cells express nAChRs and an increase in both ß-cell mass and survival, induced by nAChR-signalling, has been observed.[35] Moreover, there is support for inverse associations of nicotine/smoking with other inflammatory and autoimmune diseases such as ulcerative colitis[36,37] and autoimmune hypothyroidism.[38] In both ulcerative colitis and autoimmune thyroiditis, the activation of alpha7 nAChRs, or treatment with such agonists, has been proposed to be involved in the underlying suppressive mechanism.[39,40] Our findings suggest that potentially protective effects of nicotine are restricted to prenatal exposure since we did not find an association between childhood exposure to parental smoking and type 1 diabetes. The mechanisms remain to be elucidated but it is noteworthy that nicotine has been shown to pass to the fetus through the placenta,[41] which may lead to higher exposure than environmental smoking. It should also be noted that the first autoantibody often presents during the first two years of life in children who subsequently develop diabetes.[42] This indicates that early life factors may play an important role in the aetiology of type 1 diabetes. On the other hand, few studies assessed the influence of parental smoking and several of them had serious methodological problems, which precludes any firm conclusions regarding the association between type 1 diabetes and fetal vs. childhood exposure to smoking. Moreover, cigarette smoke contains thousands of chemicals and any of these mixtures may be implicated besides nicotine.

4.2 | Strengths and weaknesses

The strengths of this study include the use of a predefined protocol, a broad literature search conducted by a librarian and the use of recommended tools for the assessment of bias of individual studies, and the overall certainty of evidence. Literature review, data extraction and bias assessment was done by two independent reviewers to increase reliability. Furthermore, we performed sensitivity analyses to address the influence of study design, risk of bias and genetic susceptibility, which pointed in the same direction as the main analysis. Still, we cannot rule out that confounding explains the association between maternal smoking and the child´s type 1 diabetes risk. Importantly, the inverse association was observed in studies that had adjusted for a range of factors including socioeconomic status, maternal diabetes,[4] both paternal and maternal diabetes,[14] maternal BMI, parity[16] and breast feeding.[20] It should also be noted that adjustment for confounders appeared to have minor influence on the effect estimates. As an example, Begum et al. observed an HR of 0.80 associated with maternal smoking in their crude model and 0.84 in their fully adjusted model.[4] Self-reported information on maternal smoking during pregnancy is another problem, e.g., mothers may underreport their smoking due to social desirability. Fortunately, there were several prospective studies where underreporting can be expected to be independent of whether the child eventually develops diabetes. Such non-differential misclassification will lead to dilution of exposure-outcome associations and is unlikely to explain the observed risk reduction. It should also be noted that results were similar when prenatal exposure to smoking was estimated through cotinine levels, a valid biomarker of nicotine exposure,[30] measured in cord blood.[16] A strength in several of the included studies is the use of registers for the assessment of incident type 1 diabetes, which should preclude loss to follow-up. One limitation is that we could not perform dose-response analysis since only three studies provided effect estimates for different exposure levels, and all three were judged to have serious risk of bias.[18,21,28] The role of timing of smoking during pregnancy also remains to be explored to elucidate whether smoking during early vs late pregnancy affects offspring type 1 diabetes risk. A final limitation was the small number of studies on childhood exposure to smoking, which precluded conclusion regarding the absence of a potential effect. In terms of generalizability, it is important to note that the data primarily came from European and US studies, and it remains to be seen whether the results apply to other populations that may have different susceptibility to type 1 diabetes. The association between maternal smoking and IA was weaker than with type 1 diabetes; this could reflect that IA is a less specific outcome than type 1 diabetes. Not all children with IA progress to type 1 diabetes,[43] and furthermore, the definition of IA in terms of the type and number of autoantibodies varied across studies.

In conclusion, this study indicates that maternal smoking during pregnancy is associated with a reduced risk of type 1 diabetes in the offspring. The significance of these findings lies in their contribution to a better understanding

of the aetiology of type 1 diabetes, which in terms of risk and protective factors is largely unknown. By no means do the findings diminish the profoundly harmful effects of smoking during pregnancy on fetal development and childhood health.[44]

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CONFLICT OF INTEREST

SC declares shareholding in Swedish Match AB to a value of 3000 euro. These were received as a gift at birth and were originally shares in Volvo Cars Corporation. Through investments and spin offs made by Volvo Cars, part of the shares was transferred into shares in Swedish Match by Volvo in 1996. SC has had no active management of these shares.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and provided final approval of the version to be published. SC is the guarantor of this work.

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SUPPORTING INFORMATION

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