Check for updates

Diabetes, Obesity and Metabolism

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Antibiotic Exposure in Early Life and Risk of Type 1 Diabetes: A Meta-Analysis

Sharan Ram[1] | Marine Corbin[1] | Andrea 't Mannetje[1,†] | Jeroen Douwes[1] | Amanda Kvalsvig[2] | Amanda Eng[1]

[1]Centre for Public Health Research, Massey University, Wellington, New Zealand | [2]Department of Public Health, University of Otago, Wellington, New Zealand

Correspondence: Sharan Ram (s.ram@massey.ac.nz)

Received: 12 October 2025 | **Revised:** 20 February 2026 | **Accepted:** 22 February 2026

Keywords: antibiotic-use | childhood type 1 diabetes | early life | meta-analysis | microbiome dysbiosis

ABSTRACT

Background: Early-life antibiotic use may increase the risk of childhood type 1 diabetes (T1D), potentially through gut microbiota dysbiosis and associated effects on immune development. This meta-analysis evaluated associations between early-life antibiotic use and T1D.

Methods: A systematic search of PubMed, MEDLINE, Scopus and Web of Science was conducted up to June 2025, which focused on studies reporting associations between antibiotic use in the pre- and postnatal periods and childhood T1D. Pooled effect sizes were assessed using random effects models separately for prenatal and postnatal antibiotic exposure, with subgroup analyses by antibiotic course, class and spectrum. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS).

Results: The analysis included 20 studies (11 cohort, 9 case-control), encompassing > 1.5 million participants for prenatal and over 4 million for postnatal antibiotic exposure. A pooled effect size of 1.05 (95% CI 0.98–1.11) for prenatal exposure was found. Further analysis by antibiotic spectrum yielded no significant associations, likely due to the small number of studies. For postnatal antibiotic exposure, a pooled effect size of 1.07 (95% CI 1.01–1.14) was found, with estimates increasing with increased number of antibiotic courses: ≥ 2 courses, 1.11, 95% CI 1.02–1.20; and ≥ 5 courses, 1.14, 95% CI 1.00–1.30. Associations were stronger for broad-spectrum (1.13, 95% CI 1.03–1.23) than for narrow-spectrum antibiotics (1.08, 95% CI 0.93–1.26) but no significant associations were observed by antibiotic class. The impact of mode of obstetric delivery remained inconclusive across studies. The quality of the evidence was high.

Conclusion: This meta-analysis suggests that early-life antibiotic use is associated with an increased risk of T1D, particularly with repeated courses and broad-spectrum agents. However, confidence in these findings is constrained by variability in study design and exposure definitions, as well as the potential for confounding by indication. While the observed associations are modest, they highlight the importance of judicious antibiotic prescribing in early life. Further large, well-designed prospective cohort studies are needed to clarify causality and better disentangle the effects of antibiotics from those of underlying infections.

1 | Introduction

Type 1 diabetes (T1D) is the second most common autoimmune disease among children and adolescents and its incidence has increased significantly over the past few decades [1, 2], although substantial variability exists by age, geographic region and country-income classification [3]. In the 0–14-year age group, the highest incidence is observed in Northern Europe (23.96/100 000), Australia/New Zealand (22.8/100 000) and North America (18.02/100 000), whilst the lowest is

†Deceased 30 August 2023.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2026 The Author(s). *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

observed in Melanesia, Western Africa and South America (all < 1/100 000) [3].

The pathogenesis of T1D is complex and involves both genetic and environmental factors such as lifestyle, air pollution, microbial factors and diet in early-life [4–6]. In particular, there is increasing evidence that the gut microbiome in early life and the downstream effects on immune system development and homeostasis, may play a critical role in the development of autoimmune related conditions such as T1D [7], as shown in both human studies [8] and animal models [2, 9]. However, as the infant and child microbiome is shaped by multiple external factors, including the maternal gut microbiome [10, 11], mode of delivery [12], breastfeeding practices [13] and maternal and child antibiotic consumption [14], causal pathways are likely complex and, as a result, they remain poorly understood.

The role of rapidly increasing antibiotic consumption rates, which increased by 39%–65% between 2000 and 2015 [15, 16], as a significant driver of gut microbiome disruption has received considerable attention, with several epidemiological studies showing associations between early-life antibiotic exposure and T1D [17, 18]. An indication of a dose–response has also been reported in some studies [18, 19]. However, results have not always been consistent, with some large-scale register-based studies showing no associations between early-life antibiotic use and T1D [20–22]; also, although biologically plausible, reverse causation cannot be excluded. Maternal antibiotic use during pregnancy may also increase this risk of T1D [17] as resulting microbial dysbiosis in the mother may delay or prevent the transmission of beneficial microflora to the child [14], but the evidence is mixed [22, 23].

Thus, given the conflicting findings of individual studies and concerns regarding residual confounding, it remains unclear whether increasing antibiotic-consumption may be involved in the increased incidence of T1D observed in the past few decades, as hypothesised [17, 24]. An improved understanding of associations between antibiotic-use and T1D is important as it may guide the development of interventions to halt the worrying increase in T1D observed in many parts of the world. This paper presents a meta-analysis of reported associations between maternal and early-life antibiotic-use and subsequent childhood T1D.

2 | Methods

2.1 | Data Sources and Search Strategy

For this meta-analysis we used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [25]. A literature search was completed on 15 December 2025 on PubMed, MEDLINE, Scopus and Web of Science using the search terms:

pregnan* OR gestation* OR labor* OR labour* OR childbirth* OR peripartum OR postpartum OR preterm* OR prematur* OR postmatur* OR pre-nat* OR prenat* OR "post-nat*" OR postnat* OR perinat* OR neonat* OR newborn* OR "new born*" OR infan* OR baby* OR babies OR toddler* OR preschool* OR child* OR "early life" OR "early-life" OR pediat* OR paediat* (Topic) and antibiotic* OR anti-biotic* OR antimedic* OR anti-medic* OR "anti medic*" OR antibacterial* OR anti-bacterial* OR "anti bacterial*" OR antimicrobial* OR anti-microbial* OR "anti microbial*" OR antimycobacterial* OR anti-mycobacterial* OR "anti mycobacterial*" OR bacteriocid* OR bacteriostat* (Topic) and T1D OR T1DM OR "type 1 diabet*" OR "diabet* mellitus type 1" OR "diabet* type1" (Topic).

All databases were searched from inception through to June 2025. The search was limited to English-language publications involving human participants. Bibliographies of eligible articles and relevant review articles were also screened.

2.2 | Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met all of the following criteria: (i) populations of pregnant women, or children; (ii) included a control or reference group; (iii) reported on exposure to any antibiotics during early life (pre-natal or post-natal) prior to T1D diagnosis; and (iv) reported effect estimates such as odds ratios (OR), relative risks (RR), or hazard ratios (HR), with 95% confidence intervals (CI). Further, we excluded studies focused solely on sub-populations with specific health outcomes (e.g., pre-term infants) or disease predispositions (e.g., genetic risk for T1D).

2.3 | Study Selection

Study selection was conducted independently by MC and AE, who each screened 50% of the titles and abstracts, while SR screened all records. Following this initial stage, all three reviewers met to discuss any discrepancies and to reach consensus on the studies to include or exclude. Subsequently, the full text for each study considered potentially relevant after abstract screening was retrieved. A list of all studies excluded after full-text assessment, with the specific reasons for their exclusion, is provided in Table S1.

2.4 | Data Extraction and Management

For all studies selected for data extraction, SR extracted data from every paper. In parallel, MC and AE each independently extracted data from 50% of the papers, such that all studies underwent double data extraction. A standardised data extraction form was used to ensure consistency. The following information was extracted: author; year of publication; study location; study design; control source (for case-control studies); sample size; timing of antibiotic exposure; antibiotic exposure (yes vs. no, and where available, the number of courses prescribed or taken; antibiotic spectrum and classes); data source for exposure; follow-up period; source/methods of T1D case identification (e.g., pharmaceutical prescriptions, self-reports, hospitalisation data or a combination); covariates; and effect sizes with 95% CIs. Any discrepancies between extractors were discussed collectively among SR, MC and AE until consensus was reached. When multiple effect estimates

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

were reported, we prioritised those adjusted for the largest set of covariates.

2.5 | Risk of Bias and Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of studies according to the recommendation from the Cochrane collaboration [26]. NOS has eight criteria, and the scores range from 0 (high risk of bias) to 9 (low risk of bias). A total star rating of ≤ 5 was considered a high risk of bias, a star rating between 6 and 7 intermediate risk and a star rating ≥ 8 low risk. Two authors completed the quality assessment independently. Discrepancies were resolved by consensus. Publication bias was assessed using visual inspection of funnel plots.

2.6 | Statistical Analysis

For the meta-analysis, we treated reported risk estimates OR, HR and RR as equivalent, as the outcome was rare, all case-control studies used density (or incidence density) sampling and therefore the ORs and HRs approximated RRs. Meta-analyses were performed separately for the prenatal and post-natal early childhood periods if at least two studies reported an adjusted risk/crude estimate for the same exposure. Random effects models were used to pool risk estimates using STATA/BE 17.0. Between-study heterogeneity was assessed using I^2 and the p-value for heterogeneity (Cochrane's Q statistic). We conducted subgroup analyses for study design, antibiotic class and spectrum and course categories. We also conducted leave-one-out sensitivity analyses and repeated the analysis using the MoBa cohort estimate instead of the register-based estimate from Tapia et al. [20] to assess robustness for both the exposure assessment methods. For analysis of the number of antibiotic courses, we selected the highest course category compared to never exposed (unless stated otherwise).

3 | Results

3.1 | Search Results

We identified 837 records through database searches and one additional record through reference screening. After excluding duplicates, 529 abstracts were screened, which led to 35 full text articles being retrieved and evaluated for eligibility (Figure 1). Fifteen studies were excluded (a list of all studies excluded after full-text assessment, with the specific reasons for their exclusion is provided in Table S1), leaving 20 articles that met the inclusion criteria for the meta-analysis.

3.2 | Study Characteristics

Information about the 20 eligible publications is presented in Table 1; of these, five examined prenatal (during pregnancy) antibiotic exposure only, 11 examined postnatal exposure only and four assessed both prenatal and postnatal antibiotic exposure. Eleven publications were cohort studies and nine case-control studies. All were published between 2000 and 2025, and all conducted in high-income countries. Nineteen studies were of high quality and the mean quality assessment score of the 20 studies was 8.05 (see Table S2 for breakdown of scores).

Twelve studies specifically focussed on antibiotic exposure and T1D, whilst the remainder reported on antibiotic exposure as one of several risk factors for T1D, including four that focussed on infections. One study [20] examined two partially overlapping cohorts: (i) a large, prospective, population-based Mother and Child Cohort Study (MoBa); and (ii) a nationwide register-based cohort. For the meta-analyses, risk estimates from the register-based cohort were selected due to the larger size as well as the use of routinely collected data, in contrast to self-reported data in the MoBa cohort.

3.3 | Prenatal Antibiotic-Use and Type 1 Diabetes

Eight studies (Table 1) assessed associations between prenatal antibiotic use and T1D in childhood, including four cohort studies [17, 20, 27, 28] and four case-control studies [24, 29–31]. These studies were conducted in Sweden (2 studies), Italy, Norway, Denmark, Malta, Finland (1 study) and multiple additional European regions, comprising a total of 1 513 872 participants.

Among the studies included, only one [17] reported a borderline statistically significant increased risk. The pooled effect size was 1.05 (95% CI 0.98–1.11; Figure 2), with low heterogeneity ($p = 0.433$, $I^2 = 0.0\%$). Subgroup analysis by study design indicated an association for cohort studies: pooled effect size 1.11 (95% CI 1.01–1.21) but not for case-control studies: 1.00 (95% CI 0.92–1.09). In a sensitivity analysis replacing the register-based estimate with the MoBa cohort estimate from Tapia et al. [20], the pooled effect estimate remained materially unchanged (1.04; 95% CI 0.97–1.13), indicating that the overall association was not sensitive to exposure ascertainment method.

Evidence of publication bias was not observed as shown by the funnel plot (Figure S1).

Given the limited number of studies, subgroup analyses were restricted to antibiotic spectrum (three studies) and course categories (two studies; see Figures S2 and S3). One study [17] reported a greater risk for narrow spectrum (HR 1.17; 95% CI 0.99–1.39) compared to broad spectrum (HR 1.10; 95% CI 0.86–1.40) but this did not reach statistical significance. A study by Haupt-Jørgensen et al. [28] did not observe significant associations by spectrum, but only a relatively small number of cases ($n = 336$) were included. The two studies [20, 28] that examined the number of prescribed courses showed no evidence of an association. The same two studies examined specific time windows during pregnancy [28]: trimester-specific antibiotic exposure [20]; early- (< 17 weeks); and late-term (≥ 17 weeks) but these showed no significant associations with T1D.

In the study by Wernroth et al. [17], the authors assessed whether the type of infection for which antibiotics were prescribed influenced the associations with T1D. Prescriptions for

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

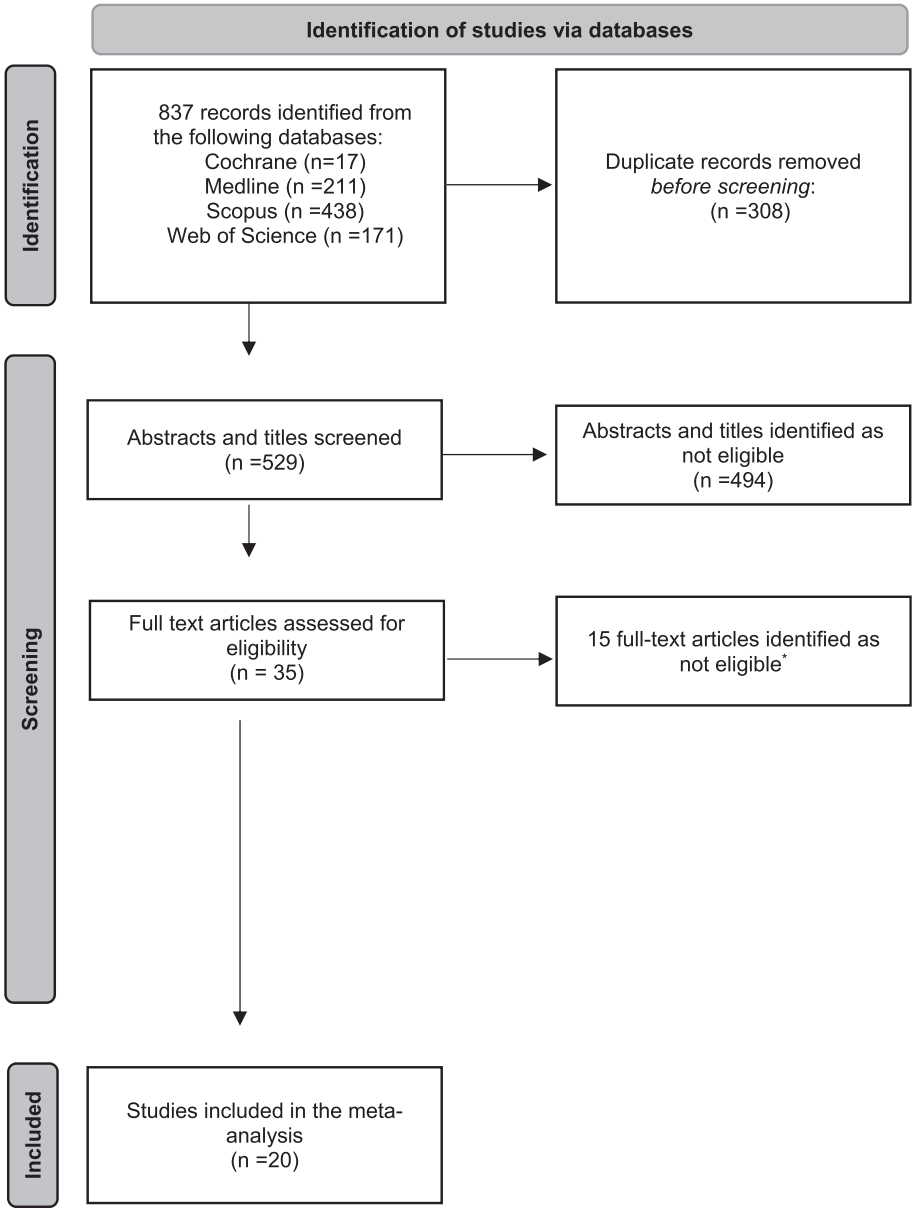

FIGURE 1 | Flow chart of study selection. *A list of all studies excluded after full-text assessment, with the specific reasons for their exclusion, is provided in Table S1.

urinary tract or skin infections were associated with a higher risk of T1D compared to no antibiotics (1.29; 95% CI 1.05–1.60), whereas prescriptions for otitis media and respiratory tract infections showed a weaker and non-significant association (1.12; 95% CI 0.93–1.33). Mother's prescribed antibiotics for both types of infections showed no increased risk (0.82; 95% CI 0.54–1.24). None of the included studies assessed whether the association between prenatal antibiotic exposure and T1D risk differed by mode of delivery.

3.4 | Postnatal Antibiotic-Use and Type 1 Diabetes

Fifteen studies (Table 1) assessed associations with early childhood antibiotics, including nine cohort studies [17, 20–23, 32–35] and six case-control studies [18, 19, 24, 36–38]. Together, these studies included a total of 4 672 362 participants and were conducted in Denmark [5], Finland [3], Sweden [2], United Kingdom [2], Norway [1], Wales [1] and South Korea [1]. As with the analysis of prenatal antibiotic exposure, we only included the register-based cohort for the study conducted by Tapia et al. [20].

The risk estimates from individual studies varied from 0.81 to 1.39; 12 reported positive associations; however, only two were statistically significant [17, 18]. The primary pooled effect estimate was 1.07 (95% CI 1.01–1.14; Figure 3), with moderate heterogeneity across studies ($p = 0.032$, $I^2 = 44.6\%$). Subgroup analysis by study design showed similar results for cohort (1.06; 95% CI 0.98–1.15) and case-control studies (1.09; 95% CI 0.97–1.23). Leave-one-out sensitivity analysis showed that sequential exclusion of each study yielded pooled estimates ranging from 1.05 to 1.09, with no material change in statistical significance or heterogeneity (Figure S4). This indicates that the overall association was not driven by any single study.

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | Summary of included studies.

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Tapia et al. (2018) (MoBa cohort) Norway *Note:* Not included in meta-analysis Tapia et al. (2018) Register based cohort Norway	Cohort (A)	403/114 215	49% Boys & 51% Girls Median age: 12.3 years	Prenatal-Maternal Infancy (Child) (0–18 months)	2–11 years	Medical Records Yes/No	Child sex, maternal age, parity, maternal T1D, smoking in pregnancy, education level, pre-pregnancy body mass index (BMI), birthweight, prematurity, mode of delivery, infections, acetaminophen use and antibiotic use	(ICD-10) diagnosis E10 with the first dispensed insulin prescription	Antibiotic use during pregnancy, or by the child during the first 6 or 18 months of life, was not associated with the risk of T1D.
	Cohort (B) [1 Jan 2004–31 Dec 2012]	836/541 036	51.3% Boys & 48.7% Girls Median age: 6.4 years	Prenatal (Maternal) Early (< 17 weeks); Late (≥ 17 weeks) Infancy (Child) (0–6; 6–18 & 0–18 months)	2–11 years	Parental interview No	Child sex, maternal age, parity, maternal T1D, education level, birthweight, prematurity, mode of delivery and antibiotic use	(ICD-10) diagnosis E10 with the first dispensed insulin prescription	The results were consistent with MoBa, showing no association between antibiotic prescriptions and T1D risk
Hviid et al. (2009) Denmark	Prospective Cohort study [Born between 1995 and 2003]	454/606 420	NR (Broken down by person-years of follow-up) Followed from 1 year of age	Infancy (Child) 0–2 months 3–11 months 1 year ≥ 2 years	2–10 years	Medical Records Yes	Adjusted for age, calendar period and ethnicity of mother. Other investigated confounders included: child's sex, birth order, place of birth, ethnicity of the mother, mother's age at birth, birth weight, gestational age, socioeconomic category of the father, educational level of the mother	T1D [Diagnostic codes DE10 and DE14]	No statistically significant association

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70536 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Cardwell et al. (2008) United Kingdom	Matched case–control [Born between 1987 and 2005]	367; 4579	46% Male, 54% Female NR	Infancy (Child) (0–1 year)	≤15 years	Medical records No	Matched on year of birth, sex, region of residence.	Infections: T1D [T1D cases based on insulin prescription prior to their 15th birthday & validated against clinical diagnoses].	There was no evidence of an association between antibiotic prescriptions in the first year or first 2 years of life and the risk of childhood-onset T1D
Antvorskov et al. (2020) Denmark	Cohort [Born between 1996 and 2002]	322/75 615	NR for both	Infancy (Child) (0–2 years)	11.5–18.4 years	Medical records Yes	Parental BMI, maternal age at conception, socioeconomic status, parity, smoking during pregnancy, gestational weight gain, caesarean section and duration of breastfeeding.	T1D [ICD-10 diagnoses DE10 and DE14 with onset after 24 months of age]	Modest increased risk but not statistically significant
Mikkelsen et al. (2017) Denmark	Matched Case–control [Born between 1997 and 2012]	1578; 12 610	50.2% Males & 49.8% Females	Infancy (Child) 0–1 and 0–2 years	≤15 years	Medical records Yes (Spectrum only)	Age, sex and calendar time—matching variables and adjusted for in the analysis	(ICD)10: E10 and having filled at least one prescription for insulin	Identified an increased risk, specifically finding that five or more antibiotic prescriptions within the first 2 years of life were associated with a higher odds ratio (1.35) for T1D.

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Townson et al. (2019) Wales	Matched Case–control study [Born between 2000 and 2015]	1345; 4035	53.3% Males & 46.7% Females NR	Infancy (Child): Day of diagnosis, 1–30 days prior, 31–90 days prior, 91–180 days prior, 181–366 days prior	<15 years	Medical records No	Matched on age, sex, primary care practice	T1D	Antibiotic prescriptions within 1 month prior to diagnosis were associated with a higher likelihood of children presenting with diabetic ketoacidosis (DKA).
Raisanen et al. (2022) Finland	Case–control study [Born between 2000 and 2005]	102; 280	59.8% Males & 40.2% Females is (for T1D/DM). Median age: 16 years	Infancy (Child): From birth until date of diagnosis or 2 months prior to index date for controls	13–18 years	Medical records Yes	Matched on age, sex, residential area, gestation age, mode of delivery.	Autoimmune diseases (ADs) including T1D	The total number of antibiotic purchases throughout childhood was not related to the onset of T1D, and penicillin-group antibiotics were found to be safe.
Visalli et al. (2003) Rome, Italy	Case–control study [Born between 1977 and 1989]	150; 750	Cases: 50.7% Males & 49.3% females; Controls: 378 males 50.4% males & 49.6% females Age: 6–18 years	Prenatal (Maternal)	6–18 years	Medical records No	Matched on age.	T1D and were ascertained through a registry of T1D cases	Maternal antibiotic use during pregnancy showed no significant difference between T1D cases and control subjects.

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Wernroth et al. (2020) Sweden	Cohort [Cohort were born from pregnancies estimated to be conceived on or after 1 July 2005]	1297/797 318	NR Follow-up: 10 years (median: 4 years)	Prenatal (Maternal) Infancy (Child) (0–1 years)	1 day–8.3 years	Medical records Yes	Parity, smoking during pregnancy, maternal T1D, maternal age at delivery, parental country of birth, parental education, disposable income, birth year, birth season, region of residence, population density. Additional adjustment for prenatal exposure: Maternal BMI Additional adjustment for early childhood exposure: Mode of delivery, sex, gestational age, paternal type 1 diabetes and small or large for gestational age Sibling analysis also performed.	T1D (ascertained through validated health registers that track diabetes diagnoses in the population)	Antibiotic prescriptions in the first year of life are associated with an increased risk of T1D, with the strongest effect observed in children delivered by caesarean section.
Bélteky et al. (2020) Sweden	Prospective cohort study [Born between October 1997 and October 1999]	137; 16 292	53% males & 47% females NR	Prenatal (Maternal)	1–17 years	Parent Interviews No	Sex, heredity of T1D in the father, T2D in the mother, maternal autoimmune disease (hypothyroidism, hyperthyroidism, IBD, pernicious anaemia, SLE, Addison's disease, T1D, Celiac disease and rheumatism), gestational diabetes, vaginal birth, neonatal intensive care. Respiratory infection gestational Month 3 (model 1)/respiratory infection pregnancy trimester 1 (model 2).	T1D [Validated again clinical diagnosis].	Antibiotic use during pregnancy was not generally associated with T1D, though it may increase risk in children with specific 'neutral' HLA genotypes.

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70536 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Clausen et al. (2016) Denmark	Retrospective cohort study [Born between 1 January 1997 and 31 December 2010]	1503/858 201	Males—51.3% males & 48.7% females Follow-up from age 2–14 years	Infancy (Child) (0–2 years)	2–15 years	Medical records Yes (Spectrum only)	Birth year (1997–2010), sex (male or female), parity (primiparous or multiparous) and mode of delivery (vaginal delivery, intrapartum caesarean section or prelabour caesarean section), maternal or paternal diabetes status at childbirth, as well as maternal and paternal educational level, maternal age at childbirth, maternal redemption of antibiotics during pregnancy (Trimester 1, 2 or 3) and during the first 6 months after delivery, Birth weight, gestational age	The date of onset of T1D was defined as the first of either the date of the first diabetes-related hospital admission or the date for the second redemption of insulin/insulin analogues	Reported that broad-spectrum antibiotics administered during the first 2 years of life were associated with an increased risk of T1D, but specifically in children delivered by caesarean section.
Haupt-Jørgensen et al. (2018) Denmark	Prospective cohort study [Pregnant women recruited between 1996 and 2002 and their children born between 1997 and 2003]	336/75 629	NR Mean follow-up time of 14.3 years	Prenatal (Maternal)	11.5–18.4 years	Medical records Yes	Maternal prepregnancy BMI, paternal BMI, maternal age at conception, socioeconomic status, parity, maternal diabetes, smoking during pregnancy, birth weight and gestational weight gain.	T1D [Diagnostic codes DE10 and DE14]	Antibiotics during pregnancy is not associated with the risk of T1D in the offspring.

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Kilkkinen et al. (2006) Finland	Matched case-control [Born between 1996 and 2000]	437; 1748		Pre-pregnancy (1 year) Prenatal (Maternal) Infancy (Child) (0—Index date, i.e., T1D diagnosis date)	47 days–5.7 years	Medical record Yes	Maternal smoking, maternal T1D, gestational age and mode of delivery	T1D (Based on reimbursement for drug costs).	While overall use showed no association, high childhood exposure (> 7 purchases) and specific patterns (maternal quinolones or penicillins before pregnancy and joint maternal-child macrolide use) were linked to a higher risk of T1D.
Lee et al. (2022) South Korea	Retrospective Cohort study [Born between 2008 and 2012]	53/63 434	58.3% males & 41.8% females NR	Infancy (Child) (0–2 years)	2–7 years	Medical record Yes	Age, sex, income and overweight	Outcome measure was the diagnosis of type 1 diabetes, which was ascertained using ICD-10 codes (specifically E10, E11 and E14).	Antibiotics exposure within the first 2 years of life was not associated with subsequent T1D risk, regardless of dose or antibiotic class.

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Beier et al. (2025) UK	Retrospective cohort study with a secondary sibling-matched analysis	1 091 449	Exposed group: 52.3% male & 47.7% females. Unexposed group: 46.6% male & 53.4% female Age: 27 months	Infancy (Child) (0–2 years)	From age 27 m (the 'index date') until the 12th birthday	Medical record Yes	Maternal comorbidities, concomitant medications, prenatal/perinatal factors, infections (pregnancy and early childhood), healthcare utilisation, birth era, maternal smoking and area-based socioeconomic status (Index of Multiple Deprivation)	T1D identified using Read Codes; where possible, secondary outcomes combined diagnoses and treatments	Early childhood antibiotic exposure was not consistently associated with the risk of developing T1D.
EURODIAB Substudy 2 Study Group. (2000) Multicentre study across seven European centres: Austria (Vienna), Latvia, Lithuania, Luxemburg, Romania (Bucharest), UK (Leeds) and UK (Northern Ireland)	Case-control study	900/2302	NR Study focused on children diagnosed with T1D under 15 years of age	Prenatal (Maternal)	Not applicable (case-control design); cases were obtained from population-based registers	Parental (maternal) recall and hospital records/notes	Centre, age-group (< 5, 5–9, ≥ 10 years), breastfeeding (< 2, ≥ 2 months), birth weight (< 2500, ≥ 2500 g), maternal age (≤ 25, > 25 years), jaundice at birth, asthma before diagnosis and vitamin D supplementation	Association of T1D risk with maternal antibiotic treatment (recall/notes) and child antibiotic treatment (recall/notes)	Antibiotic treatment for the mother during pregnancy or for the newborn child was not associated with an increased risk of diabetes.
Abela et al. (2022) Malta	Retrospective case-control study	89/89	Among the 89 T1D patients, 54% male & 46% female Age: 23 years	Prenatal (Maternal)	The study was retrospective, covering the time period from birth up to the time of diagnosis for cases and up to the same age for matched controls	Parent Interviews No		Maternal use of antibiotics during pregnancy was compared between cases and controls.	No significant association was found between childhood antibiotic use and the development of T1D.

(Continues)

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70536 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Author (year), and country	Study design (case control OR cohort) [Birth period of the children]	Study sample size (Cohort: cases/cohort size; case-control: cases & controls)	Sex Age metrics for follow-up	Timing of antibiotic exposure Prenatal (maternal)/ postnatal (child)	Time of follow-up Baseline time	Ascertainment of antibiotic exposure Antibiotic specified (yes/no)	Covariates adjusted for	Outcome measures (e.g., overall, specific antibiotics, dosage)	Study conclusion
Hakola et al. (2025). Finland	Case-cohort study	2869/74 263	Among T1D cases: 54.0% male & 46.0% female Follow-up age: 7.5 years	One-year preceding pregnancy, during pregnancy (Maternal), neonatal (child) ward, 0–1, 0–2 years	Children born between January 1, 1996 and December 31, 2008, followed until December 31, 2009, death, or diagnosis	Medical record Yes	Maternal exposure models: Maternal age, smoking, diabetes, asthma, previous deliveries, child's year of birth and season of birth Child exposure models: All maternal factors plus mode of delivery, sex, gestational age, birth size and childhood asthma	Overall exposure (0 vs. ≥1 purchase), specific antibiotic classes/ agents and dose–response (number of purchases: 0, 1, 2, 3, 4, or ≥5)	While overall prenatal and postnatal exposure did not increase risk, specific antibiotics (macrolides before pregnancy and sulphonamides/ trimethoprim during pregnancy) were linked to higher T1D risk.
Brandt et al. (2025) Denmark	Cohort study	Total population: 518 483 children; Sibling population: 272 753 children (126 632 sibships)	50.0% male & 50% female Follow-up: 18 years	Postnatal (Child) 0–1 year	Mean follow-up of 13.2 years (SD 3.12), ranging from 0 to 17 years after the first year of life	Medical record Yes	Sex, birth weight, gestational age, mode of delivery, parity, maternal smoking during pregnancy, socioeconomic status at birth and maternal systemic antibiotic use during pregnancy	Any antibiotic exposure before age one, dose–response (number of courses), antibiotic type and timing of use	Use of antibiotics in the first year of life was not associated with type 1 diabetes in either the total population or a sibling-matched cohort.
Belteky et al. (2025) Sweden	Cohort study	16 428 children followed from birth. As of December 2023, 168 individuals developed T1D, while the remaining individuals served as the reference group	Among T1D cases: 56.0% male & 44.0% female	Postnatal (Child) 0–1, 1–3 and 3–5 years	A mean follow-up of 25 years (range 1–24.5 years)	Parental/ caregiver questionnaires collected at 1, 3 and 5 years of age	Sex, family history of type 1 diabetes (heredity) and socioeconomic status (defined as maternal education level at birth)	Reported as any antibiotic use and frequency of treatments (binned into intervals: 1–2, 3–5, or 6 or more treatments) for each age period	The study found no significant difference in the use of antibiotics between children βwho developed type 1 diabetes and those who did not.

Note: Prenatal/maternal: Exposure occurs via the mother during pregnancy. *Postnatal/child*: Exposure occurs via direct prescription to the child, typically in the first 1–5 years of life.
Abbreviation: NR, not reported.

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

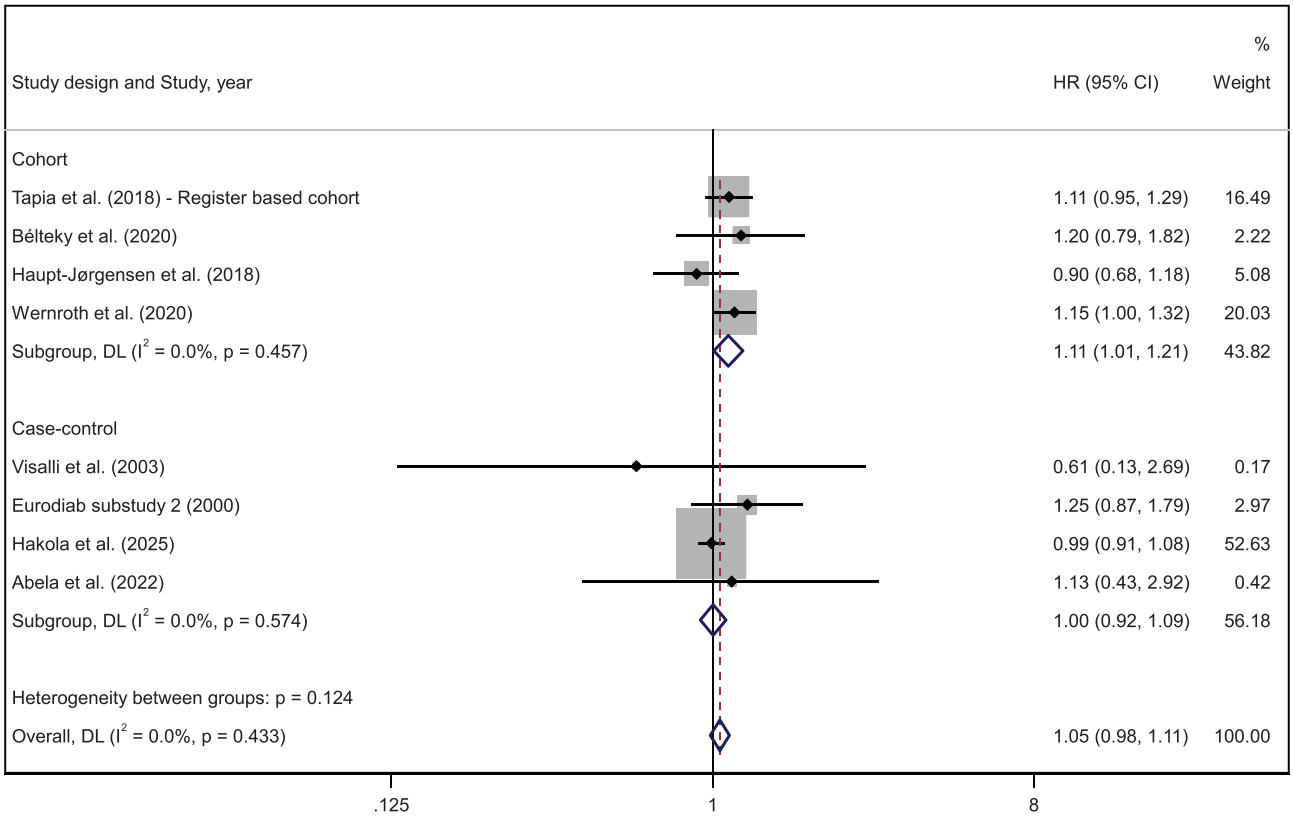

FIGURE 2 | Meta-analysis of prenatal antibiotic exposure (vs. no exposure) and T1D risk, by study design.

Excluding the five studies that did not report 'ever versus never' exposure did not affect the result: 1.06 (95% CI 0.99–1.13), nor did replacing the register-based estimate with the MoBa cohort estimate from Tapia et al. [20]: (1.08; 95% CI 1.01–1.12). Four studies applied sibling matched designs to account for confounding (e.g., shared genetics and breastfeeding) and none of the studies found any association between antibiotic use in the first year of life and T1D in the sibling-matched analysis [17, 20, 22, 34]. Evidence of publication bias was not observed as shown by the funnel plot (Figure S5).

Subgroup analyses showed no significant association for narrow-spectrum antibiotics (pooled effect size: 1.08; 95% CI 0.93–1.26; $I^2 = 67.2\%$) while broad-spectrum antibiotic-use was significantly associated with T1D (1.13; 95% CI 1.03–1.23; $I^2 = 0\%$; Figure S6). Only one study [17] reported a higher risk for narrow spectrum antibiotics (1.26; 95% CI 1.09–1.47) but no statistically significant associations was found for broad spectrum antibiotics (1.06; 95% CI 0.80–1.40). The authors attributed the non-significant association of broad-spectrum antibiotics to the fact that these are not as commonly used in this Swedish cohort. The other two studies [18, 23] reported a modest increased risk for broad spectrum antibiotics; however narrow- and broad-spectrum antibiotics exposure were not reported as mutually exclusive categories. In the subgroup analysis by antibiotic class, no statistically significant association with T1D risk was observed for any specific class (Figure S7). Specifically, the pooled HRs were: penicillins (1.06; 95% CI 0.99–1.14), macrolides (1.03; 95% CI 0.98–1.09), extended-spectrum penicillins (1.07; 95% CI 0.98–1.16), cephalosporins (1.00; 95% CI 0.92–1.09) and sulphonamides and trimethoprim (1.11; 95% CI 0.75–1.64). Children in many of the included studies were frequently exposed to multiple antibiotic types, and it is therefore difficult to examine the independent effect of each specific class.

Of the 13 studies that examined associations with ≥2 courses, 11 reported positive associations, although only one was statistically significant. The pooled estimate was 1.11 (95% CI 1.02–1.20). The studies reporting on ≥5 antibiotic courses yielded a pooled estimate of 1.14 (95% CI 1.00–1.30) (see Figures S8 and S9). All studies that focused on post-natal exposure and examined course-response associations used 'no exposure' as the reference except for the study by Räisänen et al. [38] that used '<4 courses' as the reference and the study by Lee et al. [33] that used a 'cumulative defined daily dose' (cDDD) of 0–29 as the reference. Kilkkinen et al. [19] also examined 7+ versus <7 antibiotic courses, which resulted in an OR of 1.66 (95% CI 1.24–2.24).

Three studies [17, 34, 36] focused on antibiotic exposure during the first year of life (0–1 year), whilst three others [22, 23, 32] examined exposures between 0 and 2 years. The remaining studies encompassed a broader range of antibiotic exposure periods, including, but not limited to, 0–3, 3–6, 6–12, 0–18 months and exposures extending until the diagnosis of T1D. Townson et al. [37] focussed on different time periods within 1 year prior to T1D diagnosis.

Three studies conducted detailed analyses of the timing of post-natal antibiotic exposure to identify potential 'critical windows' of vulnerability during infancy. Brandt et al. [34] examined age of first antibiotic use at 0 to <3, 3 to <6, 6 to <9 and 9–12 months

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

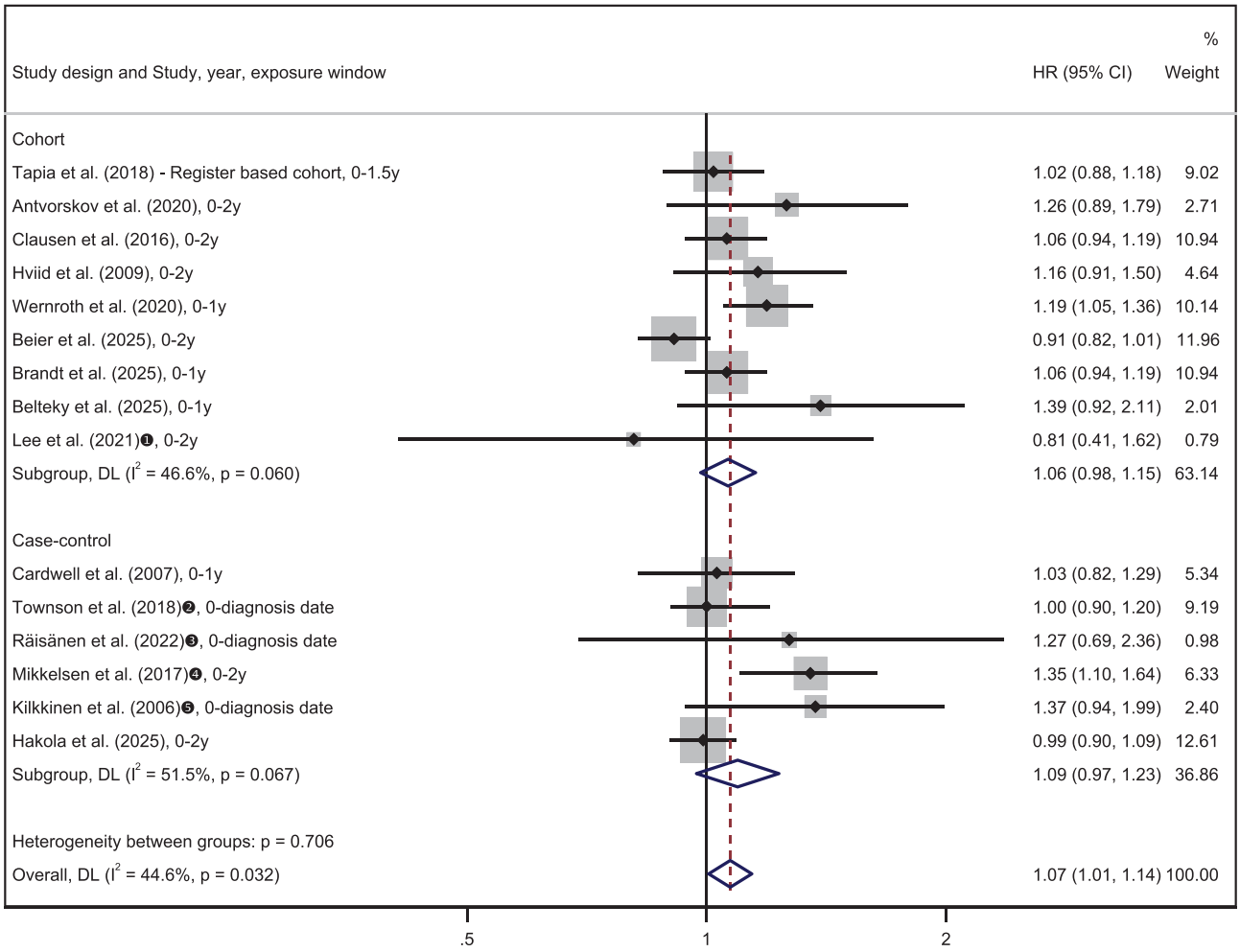

FIGURE 3 | Meta-analysis of studies on postnatal antibiotic exposure and T1D risk, stratified by study design. (1) Lee et al. (2021): Exposure to highest Cumulative Daily Defined Doses (cDDD) of ≥60. (2) Townson et al. (2018): Used OR for antibiotic prescription for symptoms during 181–366 days prior to T1D diagnosis. (3) Räisänen et al. (2021): <4 courses (ref) versus >8 courses. (4) Mikkelsen et al. (2016): 0 (ref) versus ≥5 courses for 0–2-year period. (5) Kilkkinen et al. (2004): 0 (ref) versus >7 purchases. (6) For all other studies: No antibiotics (ref) versus Exposed. For studies with multiple exposure windows, we used 0–1 year when it was the only early-life estimate and 0–2 years when both 0–1 and 0–2 were available. For Hakola et al. (2005) (0–1, 1–3, and 3–5), we selected 0–1 year to align with early-life windows used in other studies.

for children who received only one course of antibiotic; Lee et al. [33] assessed exposure at 0–119, 120–239 and ≥240 days; and Hviid and Svanstrom [21] evaluated exposure during 0–2 and 3–11 months in infancy, as well as additional windows at 1 and ≥2 years. None of these studies identified a specific time window within which antibiotic exposure was associated with a higher risk of T1D. When restricting the analysis to studies that focussed on 0–1 year, the pooled effect estimate was 1.06 (95% CI: 0.99–1.13) (Figure S10).

Four studies [17, 23, 24, 32] assessed whether mode of obstetric delivery affected associations between postnatal antibiotic-use and T1D. Clausen et al. [23] showed that the association between antibiotic-use in the first 2 years of life and T1D was strongly modified by mode of obstetric delivery (*p*-value for interaction: 0.0023). In particular, broad-spectrum antibiotics were associated with an increased risk of T1D in children delivered by either intrapartum caesarean section (HR 1.70; 95% CI 1.15–2.51) or prelabour caesarean section (1.63; 95% CI 1.11–2.39), but not in vaginally delivered children (1.05; 95% CI 0.94–1.18). In a Swedish nationwide cohort, Wernroth et al. [17] likewise reported evidence of interaction between antibiotic exposure in the first year of life and mode of delivery (*p* for interaction = 0.016), with an elevated risk of T1D among children delivered by caesarean section (1.60; 95% CI 1.22–2.08) but not among those delivered vaginally (1.10; 95% CI 0.96–1.28). In contrast, both Antvorskov et al. [32] and Hakola et al. [24] showed no difference in association when comparing different modes of obstetric delivery.

4 | Discussion

In this meta-analysis, we found that antibiotic exposure was associated with a modest increase in the risk of childhood T1D both prenatally (pooled effect size 1.06, 95% CI 0.98–1.21) and postnatally (pooled effect size 1.07, 95% CI 1.01–1.15); however, the associations reached statistical significance for postnatal exposure only. Stronger summary estimates were observed at higher exposure levels, suggesting a possible dose–response relationship and subgroup analyses indicated a significant association for postnatal broad-spectrum antibiotics.

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

A central challenge in interpreting these findings is the possibility of confounding by indication. Infections themselves may influence immune development and T1D risk, making it difficult to disentangle the effects of antibiotics from those of the underlying infection. Two studies examined the reason for antibiotic prescriptions [17, 20]. Wernroth et al. [17] reported an increased risk for antibiotics in early childhood recommended for otitis media and other respiratory tract infections (HR 1.19, 95% CI 1.04–1.36) but not for antibiotics recommended for urinary tract or skin and soft tissue infection (HR 1.06, 95% CI 0.70–1.62). This suggests that the observed association between early-life antibiotic use and T1D may differ by infection type; however, their classification relied partly on anatomical therapeutic chemical (ATC) codes and indication data were incomplete, raising concerns about misclassification and selection bias. Results of the Mother and Baby (MoBa) cohort [20] were adjusted for infections, with risk estimates showing a similar non-significant modestly increased risk (HR 1.11; 95% CI 0.81–1.50) when compared to results of the register-based cohort (included in our meta-analysis) that were not adjusted for infections, thus suggesting that the effects of antibiotic use may be independent of the infection. In addition, findings from the MoBa study also showed that early life infections were generally not associated with T1D (when adjusted for antibiotic use), except for hospitalisation for gastroenteritis (aHR 2.27, 95% CI 1.21–4.29). Taken together, these findings suggest that infection alone is unlikely to fully account for the observed associations, although residual confounding cannot be excluded. Reverse causation is another concern, as early symptoms of undiagnosed T1D could increase infection risk and subsequent antibiotic prescribing. Two studies addressed this by introducing lag periods or excluding prescriptions close to diagnosis [17, 18]. Associations persisted despite these approaches, indicating that reverse causation is unlikely to fully explain the findings.

4.1 | Potential Mechanisms

Several biologically plausible mechanisms may underlie the observed associations. Antibiotic-associated gut microbial dysbiosis and resultant effects on the developing immune system, including autoimmune diseases, could explain why antibiotics may increase the risk of T1D [39, 40]. Limited evidence is provided by studies that have shown altered gut microbiota in T1D patients [41], although this may also be the result of treatment or a consequence of the condition. Alternative explanations include the effect antibiotics may have on pancreatic beta cells in susceptible individuals [42], and a lower abundance of beneficial butyrate-producing bacteria such as *Lachnospiraceae*, which have been associated with impaired intestinal barrier function and increased autoimmune activity [40].

The reason why maternal antibiotic-use may affect childhood T1D is unknown, but likely involves a change in maternal microbiota, which in turn affects the colonisation of the infant's gut after birth [42]. Although largely speculative, animal models have shown that maternal antibiotic treatment during pregnancy can alter the offspring's gut microbiota and increase T1D susceptibility [43–46]. Alternatively, maternal antibiotic-use may affect pancreatic islet development and subsequent immune system development in the offspring [42], potentially triggering an autoimmune response, including T1D [47].

4.2 | Timing of Exposure

Most included studies focused on pregnancy and the first 2 years of life, which reflects the assumption that the gut microbiome undergoes significant development and maturation during this time, making it more susceptible to perturbations from antibiotics [48]. The few studies that examined specific time windows during the first 2 years of life did not identify a specific window within which antibiotic exposure was associated with a higher risk of T1D. Three studies examined associations beyond the 0–2 years time window [19, 35, 38] and observed modest associations although these were not statistically significant. Additionally, restricting the meta-analysis to studies that considered only the first year of life (0–1 year) did not significantly alter the pooled effect size, suggesting that effects are not limited to early-life antibiotic exposure. Pooling of data for narrower windows during the prenatal period, such as by trimesters or smaller intervals for the postnatal period, was not feasible due to high heterogeneity in the timing of exposure across studies.

Among the three studies that examined both prenatal and postnatal exposure, none reported associations for cumulative exposure across both periods. Also, they did not explicitly indicate that postnatal exposure was adjusted for prenatal exposure, or vice versa: thus, the potential interactions between pre- and postnatal antibiotic exposures in relation to T1D risk remain unclear and this is an important consideration for future research.

4.3 | Antibiotics Spectrum and Class

Subgroup analysis revealed a positive and statistically significant association between postnatal broad-spectrum antibiotics and T1D. In contrast, prenatal broad-spectrum antibiotics did not show a significant association, although this finding is based on three studies only. Broad-spectrum antibiotics likely lead to greater disruption of the microbial ecosystem, potentially having a stronger impact on immune dysregulation and resultant autoimmunity responses [49, 50]. No consistent associations were observed according to antibiotic class; however, studies varied on how antibiotic use was defined for specific classes or spectra of antibiotics [23] and it is therefore difficult to disentangle the independent effects, particularly as patients often use multiple classes of antibiotics over time.

4.4 | Mode of Obstetric Delivery

Two out of four studies [17, 23] showed a greater risk of T1D for antibiotic exposure in children who were delivered by Caesarean section (CS) compared to those delivered vaginally. This is believed to be attributed to differences in the initial gut colonisation and subsequent microbiome development in CS-delivered infants [51]. CS-delivered infants lack exposure to maternal vaginal and faecal microbiota during birth, which may lead to an altered gut microbiota composition characterised by lower diversity and a reduced abundance of beneficial bacteria, such as

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Bacteroides and *Bifidobacterium* species [52]. This, as noted before, may impair early immune system programming, increasing susceptibility to autoimmune conditions like T1D [53, 54].

4.5 | Strength and Limitations

The main strength of this meta-analysis is its novelty, as no previous meta-analysis has focussed on the association between early life exposure and T1D. Half of the studies were cohort studies, which utilised routine records for both assessment of antibiotic exposure and T1D case ascertainment, which reduces the possibility of recall bias. In addition, data linkage reduces the risk of loss to follow-up or response bias. Overall, the studies generally had high quality scores.

There are several limitations. First, only twenty studies were included in the meta-analysis and most included < 500 cases. There was also heterogeneity in reporting of antibiotic type, number of courses prescribed, reference categories and timing of antibiotic exposure, which made a pooled analysis more challenging. Although subgroup analyses were conducted on antibiotic spectra, analyses fully examining the independent effects of antibiotic class or trimesters of exposure were not feasible due to insufficient data; also, it was not possible with the limited number of studies available to explore course-response associations in more detail. Another limitation is that, as discussed above, no studies considered the combined effect of prenatal and postnatal exposure or at the very least, mutually adjusted for pre- and postnatal antibiotic use to assess whether associations were independent of one another. The studies also varied widely in their adjustment for covariates, particularly the reason for antibiotic prescription. Finally, all studies were conducted in high-income countries, and therefore our results may not be applicable to populations in low- and middle-income countries or to sub-populations with different economic, ethnic, or healthcare-access characteristics. In addition, our search was limited to English-language publications, which may introduce language bias and result in the exclusion of potentially relevant non-English studies.

4.6 | Quality of Evidence

Although a formal GRADE assessment was not undertaken, the included studies generally demonstrated good methodological quality, with a high mean Newcastle–Ottawa Scale score. The average scores for the selection and exposure/outcome domains were 3.9 and 2.85, respectively (Table S1), further supporting the methodological quality of the evidence base.

The pooled estimate for prenatal exposure was not statistically significant, whereas postnatal exposure was associated with a statistically significant effect with relatively narrow confidence intervals. This association was consistent across both cohort and case-control study designs, suggesting limited inconsistency. Funnel plots did not reveal clear evidence of publication bias; however, the modest number of eligible studies limits the power to detect small-study effects. Indirectness was likely minimal, as most studies specifically examined antibiotic exposure in relation to T1D diabetes risk. Additionally, stronger summary effect estimates were observed for higher exposure levels (> 2 and > 5 doses), supporting a possible dose–response relationship.

Overall, the available evidence appears to be of at least moderate certainty, characterised by low risk of bias, consistency across designs, minimal indirectness and suggestive dose–response effects, while some uncertainty remains due to the limited number of studies.

5 | Conclusion

In conclusion, this meta-analysis suggests that early-life antibiotic exposure, particularly postnatal exposure, is associated with a modestly increased risk of childhood T1D. The associations appeared stronger for multiple courses and for broad-spectrum antibiotics. However, confidence in these findings is tempered by variability in study design, exposure definitions and outcome ascertainment across studies, as well as the potential for residual confounding by indication, particularly where underlying infections may influence prescribing patterns.

Although the observed effect sizes are modest, the high frequency of antibiotic use in early life means that the population-level impact could be considerable. If these associations are causal, they further reinforce the importance of judicious antibiotic prescribing and strengthened antimicrobial stewardship, especially during critical windows of immune development. Future research should more clearly disentangle the role of infections, address reverse causation, examine potential interactions with mode of obstetric delivery and clarify the independent effects of broad- versus narrow-spectrum and specific antibiotic classes.

Acknowledgments

Open access publishing facilitated by Massey University, as part of the Wiley - Massey University agreement via the Council of Australasian University Librarians

Funding

This work was supported by Health Research Council of New Zealand (HD21/053).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70636.

References

1. G. A. Gregory, T. I. Robinson, S. E. Linklater, et al., "Global Incidence, Prevalence, and Mortality of Type 1 Diabetes in 2021 With Projection to

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2040: A Modelling Study," *Lancet Diabetes & Endocrinology* 10, no. 10 (2022): 741–760.

2. P. Jamshidi, S. Hasanzadeh, A. Tahvildari, et al., "Is There Any Association Between Gut Microbiota and Type 1 Diabetes? A Systematic Review," *Gut Pathogens* 11, no. 1 (2019): 49.

3. A. Gomber, Z. J. Ward, C. Ross, et al., "Variation in the Incidence of Type 1 Diabetes Mellitus in Children and Adolescents by World Region and Country Income Group: A Scoping Review," *PLOS Global Public Health* 2, no. 11 (2022): e0001099.

4. S. Dedrick, B. Sundaresh, Q. Huang, et al., "The Role of Gut Microbiota and Environmental Factors in Type 1 Diabetes Pathogenesis," *Frontiers in Endocrinology* 11 (2020): 78.

5. A. C. Fenneman, E. Rampanelli, Y. S. Yin, et al., "Gut Microbiota and Metabolites in the Pathogenesis of Endocrine Disease," *Biochemical Society Transactions* 48 (2020): 915–931.

6. A. C. Fenneman, M. Weidner, L. A. Chen, M. Nieuwdorp, and M. J. Blaser, "Antibiotics in the Pathogenesis of Diabetes and Inflammatory Diseases of the Gastrointestinal Tract," *Nature Reviews. Gastroenterology & Hepatology* 20, no. 2 (2023): 81–100.

7. H. Neuman, P. Forsythe, A. Uzan, O. Avni, and O. Koren, "Antibiotics in Early Life: Dysbiosis and the Damage Done," *FEMS Microbiology Reviews* 42, no. 4 (2018): 489–499.

8. S. M. Virtanen, H.-M. Takkinen, B. I. Nwaru, et al., "Microbial Exposure in Infancy and Subsequent Appearance of Type 1 Diabetes Mellitus-Associated Autoantibodies: A Cohort Study," *JAMA Pediatrics* 168, no. 8 (2014): 755–763.

9. N. Fernandez Trigo, C. Kalbermatter, B. Yilmaz, and S. C. Ganal-Vonarburg, "The Protective Effect of the Intestinal Microbiota in Type-1 Diabetes in NOD Mice Is Limited to a Time Window in Early Life," *Frontiers in Endocrinology* 15 (2024): 2024.

10. K. Korpela, P. Costea, L. P. Coelho, et al., "Selective Maternal Seeding and Environment Shape the Human Gut Microbiome," *Genome Research* 28, no. 4 (2018): 561–568.

11. Y. Vandenplas, V. P. Carnielli, J. Ksiazyk, et al., "Factors Affecting Early-Life Intestinal Microbiota Development," *Nutrition* 78 (2020): 110812.

12. X. Shi, Y. Liu, T. Ma, H. Jin, F. Zhao, and Z. Sun, "Delivery Mode and Maternal Gestational Diabetes Are Important Factors in Shaping the Neonatal Initial Gut Microbiota," *Frontiers in Cellular and Infection Microbiology* 14 (2024): 1397675.

13. J. Penders, "Early Diet and the Infant Gut Microbiome: How Breastfeeding and Solid Foods Shape the Microbiome," in *Microbiota in Health and Disease: From Pregnancy to Childhood* (Wageningen Academic, 2017), 105–118.

14. J. Miyoshi and T. Hisamatsu, "The Impact of Maternal Exposure to Antibiotics on the Development of Child Gut Microbiome," *Immunological Medicine* 45, no. 2 (2022): 63–68.

15. G. Ternák, "Antibiotic-Modified Microbiome Might Be Responsible for Non-Contagious World-Wide Epidemics," *American Journal of Bioscience and Bioengineering* 7, no. 2 (2019): 34–39.

16. E. Y. Klein, T. P. Van Boeckel, E. M. Martinez, et al., "Global Increase and Geographic Convergence in Antibiotic Consumption Between 2000 and 2015," *Proceedings of the National Academy of Sciences of the United States of America* 115, no. 15 (2018): E3463–E3470.

17. M. Wernroth, K. Fall, B. Svennblad, et al., "Early Childhood Antibiotic Treatment for Otitis Media and Other Respiratory Tract Infections Is Associated With Risk of Type 1 Diabetes: A Nationwide Register-Based Study With Sibling Analysis," *Diabetes Care* 43, no. 5 (2020): 991–999.

18. K. Mikkelsen, F. Knop, T. Vilsbøll, M. Frost, J. Hallas, and A. Pottegård, "Use of Antibiotics in Childhood and Risk of Type 1 Diabetes: A Population-Based Case–Control Study," *Diabetic Medicine* 34, no. 2 (2017): 272–277.

19. A. Kilkkinen, S. M. Virtanen, T. Klaukka, et al., "Use of Antimicrobials and Risk of Type 1 Diabetes in a Population-Based Mother-Child Cohort," *Diabetologia* 49, no. 1 (2006): 66–70.

20. G. Tapia, K. Stordal, K. Marild, et al., "Antibiotics, Acetaminophen and Infections During Prenatal and Early Life in Relation to Type 1 Diabetes," *International Journal of Epidemiology* 47, no. 5 (2018): 1538–1548.

21. A. Hviid and H. Svanstrom, "Antibiotic Use and Type 1 Diabetes in Childhood," *American Journal of Epidemiology* 169, no. 9 (2009): 1079–1084.

22. M. A. Beier, S. Setoguchi, T. Gerhard, et al., "Early Childhood Antibiotics and Chronic Pediatric Conditions: A Retrospective Cohort Study," *Journal of Infectious Diseases* 232 (2025): jiaf191.

23. T. D. Clausen, T. Bergholt, O. Bouaziz, et al., "Broad-Spectrum Antibiotic Treatment and Subsequent Childhood Type 1 Diabetes: A Nationwide Danish Cohort Study," *PLoS One* 11, no. 8 (2016): e0161654.

24. L. Hakola, A. Lundqvist, M. Gissler, L. J. Virta, S. M. Virtanen, and J. Metsala, "Prenatal and Postnatal Exposure to Antibiotics and the Risk of Type 1 Diabetes in Finnish Children: A Registry-Based Study," *Journal of Pediatrics* 276 (2025): 114292.

25. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *International Journal of Surgery* 88 (2021): 105906.

26. W. Ga, B. Shea, D. O'Connell, et al., "The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses," 2011, https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

27. M. Bélteky, J. Wahlberg, and J. Ludvigsson, "Maternal Respiratory Infections in Early Pregnancy Increases the Risk of Type 1 Diabetes," *Pediatric Diabetes* 21, no. 7 (2020): 1193–1201.

28. M. Haupt-Jørgensen, C. S. Morgen, T. Jess, et al., "Maternal Antibiotic Use During Pregnancy and Type 1 Diabetes in Children—A National Prospective Cohort Study," *Diabetes Care* 41, no. 12 (2018): e155–e157.

29. N. Visalli, L. Sebastiani, E. Adorisio, A. Conte, A. L. De Cicco, and R. D'Elia, "Environmental Risk Factors for Type 1 Diabetes in Rome and Province," *Archives of Disease in Childhood* 88, no. 8 (2003): 695–698.

30. A.-G. Abela and S. Fava, "Association of Incidence of Type 1 Diabetes With Mortality From Infectious Disease and With Antibiotic Susceptibility at a Country Level," *Acta Diabetologica* 50, no. 6 (2013): 859–865.

31. EURODIAB Substudy 2, "Infections and Vaccinations as Risk Factors for Childhood Type I (Insulin-Dependent) Diabetes Mellitus: A Multicentre Case-Control Investigation," *Diabetologia* 43, no. 1 (2000): 47–53.

32. J. C. Antvorskov, C. S. Morgen, K. Buschard, T. Jess, K. H. Allin, and K. Josefsen, "Antibiotic Treatment During Early Childhood and Risk of Type 1 Diabetes in Children: A National Birth Cohort Study," *Pediatric Diabetes* 21, no. 8 (2020): 1457–1464.

33. D. Lee, S. Choi, J. Chang, Y. J. Park, J. H. Kim, and S. M. Park, "Association of Antibiotics Exposure Within the First 2 Years After Birth With Subsequent Childhood Type 1 Diabetes," *Endocrine* 77, no. 1 (2022): 21–29.

34. S. Brandt, J. Thorsen, M. A. Rasmussen, et al., "Use of Antibiotics in Early Life and Development of Diseases in Childhood: Nationwide Registry Study," *BMJ Medicine* 4, no. 1 (2025): e001064.

35. M. Bélteky, J. Wahlberg, and J. Ludvigsson, "Infections and Antibiotic Use in Early Childhood Have Limited Importance in Developing Manifest Type 1 Diabetes—The ABIS Cohort Study," *Frontiers in Endocrinology* 16 (2025): 1529447.

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

36. C. R. Cardwell, D. Carson, and C. Patterson, "No Association Between Routinely Recorded Infections in Early Life and Subsequent Risk of Childhood-Onset Type 1 Diabetes: A Matched Case-Control Study Using the UK General Practice Research Database," *Diabetic Medicine* 25, no. 3 (2008): 261–267.

37. J. Townson, R. Cannings-John, N. Francis, D. Thayer, and J. W. Gregory, "Presentation to Primary Care During the Prodrome of Type 1 Diabetes in Childhood: A Case-Control Study Using Record Data Linkage," *Pediatric Diabetes* 20, no. 3 (2019): 330–338.

38. L. K. Räisänen, S. E. Kääriäinen, R. Sund, E. Engberg, H. T. Viljakainen, and K.-L. Kolho, "Antibiotic Exposures and the Development of Pediatric Autoimmune Diseases: A Register-Based Case-Control Study," *Pediatric Research* 93, no. 4 (2022): 1096–1104.

39. L. M. Quinn, F. S. Wong, and P. Narendran, "Environmental Determinants of Type 1 Diabetes: From Association to Proving Causality," *Frontiers in Immunology* 12 (2021): 737964.

40. Z. Xu, X. X. Yuan, R. M. Chen, et al., "Association Between New Onset Type 1 Diabetes and Real-World Antibiotics and Neonicotinoids' Exposure-Related Gut Microbiota Perturbation," *World Journal of Pediatrics* 18, no. 10 (2022): 671–679.

41. P. Zheng, Z. Li, and Z. Zhou, "Gut Microbiome in Type 1 Diabetes: A Comprehensive Review," *Diabetes/Metabolism Research and Reviews* 34, no. 7 (2018): e3043.

42. X. S. Zhang, J. Li, K. A. Krautkramer, et al., "Antibiotic-Induced Acceleration of Type 1 Diabetes Alters Maturation of Innate Intestinal Immunity," *eLife* 7 (2018): e37816.

43. M. Gomez de Agüero, S. C. Ganal-Vonarburg, T. Fuhrer, et al., "The Maternal Microbiota Drives Early Postnatal Innate Immune Development," *Science* 351, no. 6279 (2016): 1296–1302.

44. Y. Hu, J. Peng, N. Tai, et al., "Maternal Antibiotic Treatment Protects Offspring From Diabetes Development in Nonobese Diabetic Mice by Generation of Tolerogenic APCs," *Journal of Immunology* 195, no. 9 (2015): 4176–4184.

45. C.-M. Chen, H.-C. Chou, and Y.-C. S. Yang, "Maternal Antibiotic Treatment Disrupts the Intestinal Microbiota and Intestinal Development in Neonatal Mice," *Frontiers in Microbiology* 12 (2021): 684233.

46. W. Liang, E. Enée, C. Andre-Vallee, M. Falcone, J. Sun, and J. Diana, "Intestinal Cathelicidin Antimicrobial Peptide Shapes a Protective Neonatal Gut Microbiota Against Pancreatic Autoimmunity," *Gastroenterology* 162, no. 4 (2022): 1288–1302.e16.

47. C. H. F. Hansen, M. Haupt-Jorgensen, K. Buschard, B. Pakkenberg, L. Krych, and A. K. Hansen, "Maternal Antibiotic Exposure Increases Total Islet Number and Volume in the Neonatal Pancreas and Reduces HbA1c and Insulitis in Adult Female Non-Obese Diabetic Mice," *Clinical and Translational Discovery* 3, no. 2 (2023): e188.

48. H. Huang, J. Jiang, X. Wang, K. Jiang, and H. Cao, "Exposure to Prescribed Medication in Early Life and Impacts on Gut Microbiota and Disease Development," *EClinicalMedicine* 68 (2024): 102428.

49. F. De Luca and Y. Shoenfeld, "The Microbiome in Autoimmune Diseases," *Clinical and Experimental Immunology* 195, no. 1 (2019): 74–85.

50. K. M. Felix, S. Tahsin, and H. J. Wu, "Host-Microbiota Interplay in Mediating Immune Disorders," *Annals of the New York Academy of Sciences* 1417, no. 1 (2018): 57–70.

51. M. Selma-Royo, M. Calatayud Arroyo, I. García-Mantrana, et al., "Perinatal Environment Shapes Microbiota Colonization and Infant Growth: Impact on Host Response and Intestinal Function," *Microbiome* 8, no. 1 (2020): 167.

52. E. Rutayisire, K. Huang, Y. Liu, and F. Tao, "The Mode of Delivery Affects the Diversity and Colonization Pattern of the Gut Microbiota During the First Year of Infants' Life: A Systematic Review," *BMC Gastroenterology* 16, no. 1 (2016): 86.

53. C. Zhang, L. Li, B. Jin, et al., "The Effects of Delivery Mode on the Gut Microbiota and Health: State of Art," *Frontiers in Microbiology* 12 (2021): 724449.

54. F. Inchingolo, A. D. Inchingolo, I. Palumbo, et al., "The Impact of Cesarean Section Delivery on Intestinal Microbiota: Mechanisms, Consequences, and Perspectives—A Systematic Review," *International Journal of Molecular Sciences* 25, no. 2 (2024): 1055.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Full-text articles excluded from meta-analysis. **Table S2:** Assessment of methodological quality of studies, scored according to the Newcastle-Ottawa Scale for cohort studies & case-control studies. **Figure S1:** Funnel plot for studies examining the association between prenatal antibiotic exposure and risk of T1D in the offspring. **Figure S2:** Meta-analysis of prenatal narrow- and broad-spectrum antibiotic exposure and risk of T1D. **Figure S3:** Meta-analysis of antibiotic exposure (≥ 2 courses vs. none) during prenatal period and T1D risk. **Figure S4:** Influence (leave-one-out) analysis of the association between postnatal antibiotic exposure and risk of T1D. **Figure S5:** Funnel plot of studies examining the association between postnatal antibiotic exposure and risk of T1D in the offspring. **Figure S6:** Meta-analysis of antibiotic exposure by spectrum during postnatal period and T1D risk. **Figure S7:** Meta-analysis of antibiotic exposure by class during postnatal period and T1D risk. **Figure S8:** Meta-analysis of antibiotic exposure to (≥ 2 courses) during postnatal period and T1D risk. **Figure S9:** Meta-analysis of antibiotic exposure to (≥ 5 courses) during postnatal period and T1D risk. **Figure S10:** Meta-analysis of antibiotic exposure for 0–1-year period and T1D risk.

14631326, 0, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.70636 by Massey University Library, Wiley Online Library on [22/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License