Early-life antibiotic exposure and type 1 diabetes risk: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND
Early-life antibiotic exposure directly impacts the gut microbiota and may affect the developing immune system. These interactions have implications for the evolution of immune disorders such as type 1 diabetes (T1D). Evidence for the effect of early-life antibiotic exposure on T1D is conflicting but critical to clarify as antibiotic prescribing practices could influence T1D risk. To address this question, we performed a systematic review and meta-analysis to examine the association between antibiotic exposure throughout early-life (12 months before conception, prenatal, neonatal and postnatal up to 24 months) and T1D.

METHODS
Eligibility Criteria: Observational studies reporting the association between early-life antibiotic exposure and T1D were included.
Information Sources: Medline, Embase, Web of Science Core Collection, and Scopus were searched from inception to August 28, 2024.
Study Selection: All records were imported into Covidence for automated deduplication, abstract screening and full-text screening by two independent reviewers.
Data Extraction and Synthesis: Data from 20 studies were extracted and analysed using a random-effects meta-analysis. Pooled odds ratios (ORs) and hazard ratios (HRs) with associated 95% confidence intervals (CIs) were calculated.

RESULTS
In the preconception period, Macrolide (OR = 1.23 [95% CI: 1.02–1.48]), Sulfonamide/Trimethoprim (OR = 1.34 [95% CI: 1.07–1.69]) and Tetracycline (OR = 1.26 [95% CI: 1.11–1.44]) use were associated with an increased odds of T1D. Prenatal antibiotic exposure was not significantly associated with T1D (OR = 1.00 [95% CI: 0.93–1.08]). Similarly, no significant associations were observed for antibiotic use during the neonatal and postnatal periods, including 0–6 months, 0–12 months and 0–24 months after birth.

DISCUSSION
The overall certainty of evidence is low to moderate due to the observational nature of the included studies and their variability in data collection.

REGISTRATION
The protocol was pre-registered on PROSPERO (CRD42024589374) and follows PRISMA guidelines.

1. INTRODUCTION

1.1 Rationale

Type 1 diabetes (T1D) is an autoimmune disease characterised by the progressive destruction of pancreatic β-cells (1). It increases the risk of diabetic ketoacidosis, cardiovascular disease, kidney disease, and stroke while also impacting quality of life through daily disease management and psychological stress (2, 3). Additionally, T1D places a significant economic burden on healthcare systems due to the lifelong need for insulin therapy, glucose monitoring, and complication management (4). Despite decades of research aimed at identifying modifiable risk factors, delaying onset, and preserving β-cell function, T1D incidence continues to rise (5).

Several immunotherapies have been investigated to delay T1D progression by preserving β-cell function. Currently, Teplizumab, a humanized anti-CD3 monoclonal antibody, is the only FDA-approved therapy for delaying the onset of Stage 3 T1D (6). In a phase 3 trial, Teplizumab treatment significantly preserved β-cell function at 78 weeks (7). However, its effects were temporary, and it did not improve metabolic outcomes or insulin requirements. Despite advancements like Teplizumab, no therapy achieves long-term remission. It is important to focus on disease prevention and identify modifiable environmental risk factors to alleviate its burden of disease.

Early-life antibiotic exposure has been identified as a potential risk factor for T1D, with conflicting findings on its effects. In NOD mouse models, continuous exposure to Vancomycin or Neomycin from birth was shown to accelerate diabetes onset, increase serum insulin autoantibodies, and alter gut effector T cells, including higher interferon-γ+ CD4+ T cells and lower interleukin-17+ CD4+ T cells (8). In contrast, neonatal Vancomycin treatment until weaning was shown to reduce diabetes incidence, lower bacterial diversity and increase pro-inflammatory CD4+ T cell activity in the small intestine (9). Conflicting results may suggest that both the antibiotic class and the timing of exposure influence T1D risk.

Maternal protection refers to the phenomenon where mothers with T1D have a significantly lower odds of transmitting T1D to their offspring compared to fathers with T1D (10). There is no strong evidence to suggest a genetic basis for this effect. Instead, the association between maternal age at diagnosis and the duration of diabetes before pregnancy on offspring T1D risk suggests that in-utero exposure to maternal diabetes shapes disease susceptibility (11). Women with T1D have a more inflammatory gut microbiota during pregnancy than those without T1D, characterised by increased fecal calprotectin and serum I-FABP (12). Early-life antibiotic exposure may increase T1D risk by altering the gut microbiota and consequently decreasing protective inflammation. Without this protection, perhaps there is a greater susceptibility to diabetogenic insults.

1.2 Knowledge Gap & Need for a Systematic Review

The absence of effective and sustained immunotherapies highlights the need to explore the modifiable risk factors that contribute to T1D onset. Early-life antibiotic exposure seems to be a promising factor. Despite many cohort studies investigating the effect of early-life antibiotic use on T1D risk, there is yet to be a comprehensive systematic review and meta-

analysis on preconception, prenatal, neonatal, and postnatal periods to synthesise existing evidence and resolve discrepancies.

1.3 Objectives

This systematic review aims to examine the association between early-life antibiotic exposure and T1D. Findings may clarify which antibiotic interventions, and at what developmental stages, influence T1D risk. Conclusions could guide future research on antibiotic-microbiota interactions in T1D and inform clinical decision-making on the appropriateness of early-life antibiotic use.

Exposure windows of interest:

- Preconception: 12 months before conception
- Prenatal: During pregnancy
- Neonatal: First two weeks of life
- Postnatal: 0–6 months, 0–12 months, 0–24 months

Antibiotic interventions of interest:

- Any antibiotic use
- Specific antibiotic classes (e.g., Macrolides, Tetracyclines, Sulfonamides)
- Antibiotic spectrum (broad spectrum, narrow spectrum)
- Number of antibiotic courses

2. RESEARCH DESIGN AND METHODS

2.1 Registration

The protocol for this systematic review and meta-analysis was pre-registered on PROSPERO (CRD42024589374) and follows PRISMA guidelines.

2.2 Information Sources and Search Strategy

A systematic literature search was conducted in Medline, Embase, Web of Science Core Collection, and Scopus from database inception to August 28, 2024. No language restrictions were applied. The search strategy was developed using key terms, MeSH terms, and Emtree terms, and was reviewed by librarians at the University of Melbourne. The full search strategies are available in the Supplementary Materials.

2.3 Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria:

- Study design: Cohort or case-control observational studies
- Population: Pregnant women and children under 2 years of age
- Intervention: Antibiotic exposure during early-life (12 months preconception, prenatal, neonatal, postnatal up to 24 months)
- Comparator: No antibiotic exposure
- Outcome: T1D diagnosis

2.4 Study Selection and Screening

All records retrieved from the database searches were imported into Covidence as RIS files for automated deduplication, abstract screening, and full-text screening. Two independent reviewers screened titles and abstracts for study relevance, followed by full-text assessment of studies. Conflicts at both the abstract and full-text screening stages were resolved through discussion. Only published studies were included. The RIS files are available in the Supplementary Materials.

2.5 Data Collection and Extraction

Data extraction was conducted by one reviewer. The following data were extracted from each study:

- Study details: Author, year, country, study design
- Population characteristics: Number of cases, total cohort size, number of cases with/without antibiotic exposure, percentage female
- Intervention details: Period of antibiotic exposure, specific antibiotic classes, number of courses
- Data sources: Source of antibiotic exposure data (e.g., prescription records, parental self-report)
- Outcome details: T1D definition (e.g., clinical diagnosis, antibody positivity), age at outcome assessment
- Confounders: Adjustments made (e.g., age, sex, delivery mode)

2.6 Statistical Analysis

2.6.1 Meta-Analysis Model

A random-effects model was used for meta-analysis, implemented using the meta package in R.

2.6.2 Effect Measures

The primary effect measure was ORs with 95% CIs. Some studies reported HRs, which were analysed separately and not pooled with ORs.

2.6.3 Heterogeneity Assessment

Heterogeneity was assessed using the I^2 statistic, τ^2, and p-value. Only the prenatal OR meta-analysis included heterogeneity measures, as it had the largest number of contributing studies, n = 8.

2.6.4 Subgroup Analysis

Subgroup analyses were conducted when at least two studies reported data on the same intervention and period. These included:

- Any antibiotic use
- Specific antibiotic classes (e.g., Macrolides, cephalosporins, quinolones)
- Number of antibiotic courses (1–2 courses vs. ≥3 courses)
- Broad vs. narrow-spectrum antibiotics

3. RESULTS

3.1 Study selection

1,071 records were retrieved across Embase, Scopus, Medline, and Web of Science Core Collections. After automated duplicate removal in Covidence (n = 442) and manual removal of two additional duplicates, 627 unique records remained for abstract screening. Following abstract screening, 596 irrelevant records were excluded, leaving 31 studies for full-text screening. After full-text screening, 14 studies were excluded, resulting in 17 eligible studies. Additionally, 3 studies meeting the inclusion criteria were identified outside the search and manually included. Thus, 20 studies were included in the systematic review. The study selection process is illustrated in Figure 1. All conflicts between the two independent screeners during screening were resolved through discussion.

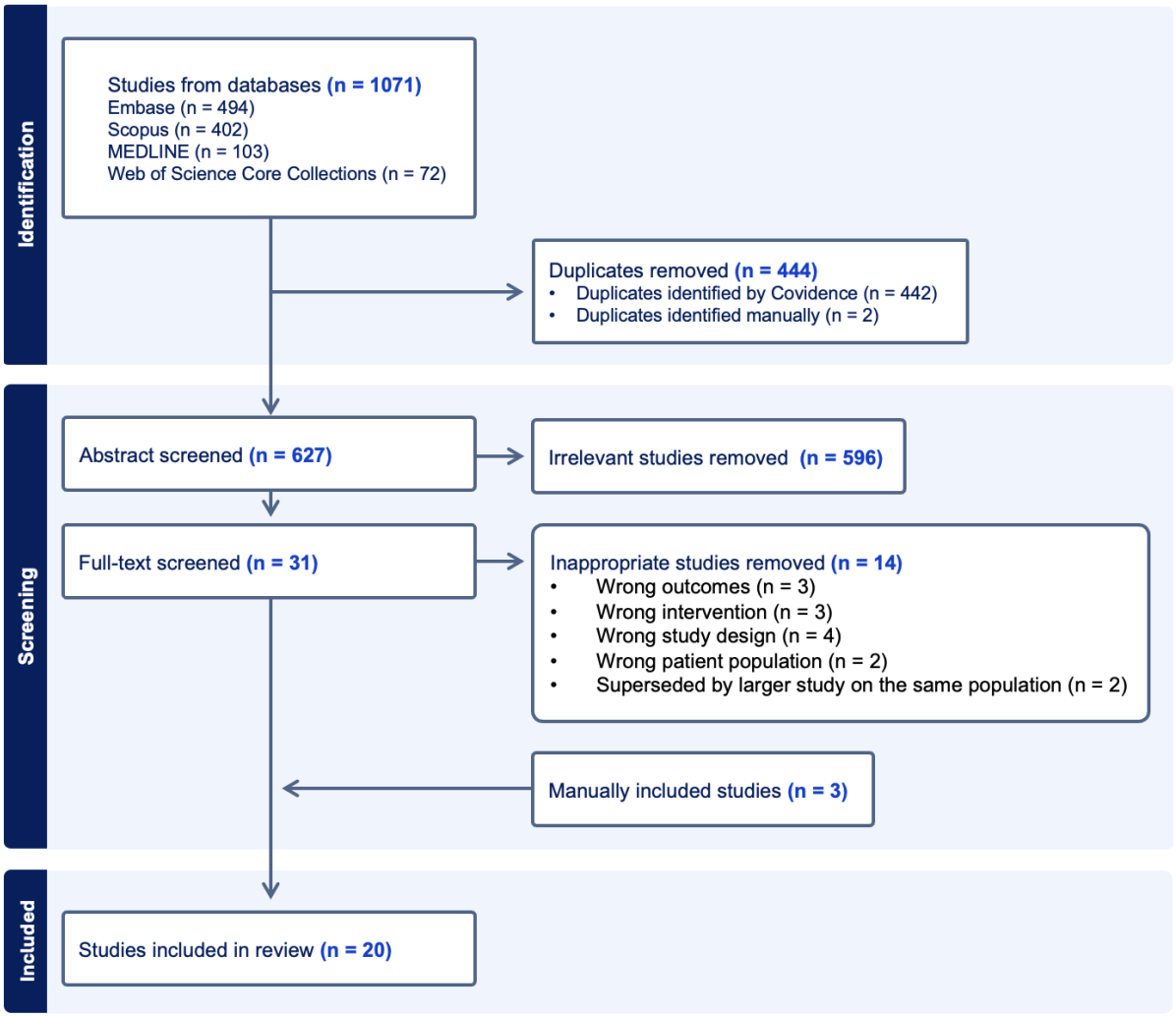

Fig. 1: PRISMA flow diagram illustrating the study selection process for the systematic review and meta-analysis.

3.2 Characteristics of included studies

The characteristics of the included studies are summarised in Table 1, with additional details available in the Supplementary Material. The 20 included studies span 14 countries, with the majority conducted in Europe (United Kingdom, Germany, Luxembourg, Latvia, Lithuania, Romania, Malta, Sweden, Finland, Denmark, Norway), alongside studies from Israel, South Korea and the USA.

All studies were observational and examined the association between early-life antibiotic exposure (12 months preconception, prenatal, up to 24 months postnatal) and T1D risk. Collectively, these studies included over 3 million participants and 10,960 T1D cases.

Most studies adjusted their effect sizes for key confounders. Most commonly, age, sex, country and mode of delivery. Many studies did not report effect sizes and CIs for all exposure periods and interventions. In such cases, effect sizes and CIs were independently calculated using the data provided in the studies. These independently derived estimates do not account for additional confounders beyond those considered in the original matching of controls to cases.

Table.1: Characteristics of included studies.

Author	Year	Country	No Cases: Cohort Size	Age (years) at diagnosis	Percentage female	Confounders accounted for
Blom (13)	1991	Sweden	339:867	0-14	47.2	Age, sex, country
McKinney (14)	1997	UK	196:521	<16	NR*	Age, sex
EURODIAB (15)	2000	Latvia Lithuania Luxemburg Romania England Northern Ireland	1028:4072	<15	NR	Age, site, breast feeding, birth weight, maternal age, jaundice at birth, asthma before disease diagnosis, vitamin D supplementation
Kilkkinen (16)	2006	Finland	437:2185	2.7 mean	50.1	Age, sex, hospital district
Cardwell (17)	2008	UK	367:4579	5.9 mean	54.5	Age, sex, region, non-infection related GP consultations
Hviid (18)	2009	Denmark	454:606420	4.4 mean	NR	Age, calendar period, maternal ethnicity
Virtanen (19)	2014	Finland	223:6242	<15	47.6	Sex, genetic risk (HLA-DQB1), family history, delivery mode, birthplace, parental asthma/allergic rhinitis, maternal education, maternal age, home municipality urbanisation level, asthma/atopic eczema in the child by age 5 years
Mikkelsen (20)	2016	Denmark	250:2236	<16	49.8	Sex, age
Clausen (21)	2016	Denmark	1503:858201	<15	48.7	Sex, birth year, parity, delivery mode
Kemppainen (22)	2017	Finland, Germany, Sweden, USA	463:8495	<4.1	49	Sex, country, T1D/CD family history, HLA-DR genotype, Caesarean delivery, probiotic use before age 90 days,

						breastfeeding, prenatal antibiotic use, season of birth
Haupt-Jørgensen (23)	2018	Denmark	336:75629	<18.4	NR	Maternal BMI, paternal BMI, maternal age, socioeconomic status, parity, etc
Tapia (24)	2018	Norway	835:537458	4.4 mean	51	Sex, maternal age and parity, maternal T1D, prenatal smoking, education level, pre-pregnancy BMI, birthweight
Antvorskov (25)	2020	Denmark	NR:50931	<18.4	NR	Socioeconomic status, parity, maternal diabetes, smoking during pregnancy, delivery mode, etc
Wernroth (26)	2020	Sweden	1238:760907	4.2 mean	48.5	Sex, parity, prenatal smoking, maternal T1D, maternal age, parental birthplace, parental education, disposable income, birth year, birth season, region of residence, population density, maternal BMI, delivery mode, gestational age, paternal T1D, birth weight
Belteky (27)	2020	Sweden	126:14910	<18	47	Sex, T1D in the father, maternal autoimmune disease
Zargari (28)	2022	Israel	52:184	8.2 median	50	Maternal illness, birth weight, neonatal intravenous glucose infusion, neonatal feeding method
Abela (29)	2022	Malta	89:178	11 mean	46.1	Gestational age, birth weight, delivery mode, infant feeding, number of household siblings, parental smoking, parental age
Lee (30)	2022	South Korea	53:63434	<8	48.3	Age, sex, household income, and overweight
Raisanen (31)	2023	Finland	102:959	11 mean	40.2	Age, sex, residential area, gestational age, delivery mode
Hakola (32)	2024	Finland	2869:74263	5.2 mean	46	Sex, delivery mode, gestational age, birth weight

*NR = not reported

3.3 Impact of antibiotic use on T1D risk throughout early-life

This meta-analysis examined the association between early-life antibiotic exposure and T1D, with pooled estimates calculated for different exposure periods: 12 months preceding conception, prenatal, neonatal, and postnatal periods (0–6 months, 0–12 months, 0–24 months).

3.3.1 Preconception antibiotic use (12 months preceding conception)

For antibiotic use in the 12 months preceding conception, three antibiotic classes were significantly associated with a increased odds of T1D:

- Macrolide: OR = 1.23 [95% CI: 1.02–1.48]
- Sulfonamide/Trimethoprim: OR = 1.34 [95% CI: 1.07–1.69]

- Tetracycline: OR = 1.26 [95% CI: 1.11–1.44]

Other antibiotic categories showed no significant association with T1D:
- Any antibiotic use: OR = 1.05 [95% CI: 0.98–1.13]
- Cephalosporin: OR = 0.97 [95% CI: 0.75–1.26]
- Phenoxymethylpenicillin: OR = 1.28 [95% CI: 0.80–2.03]
- Quinolone: OR = 1.58 [95% CI: 0.84–2.98]

3.3.2 Prenatal antibiotic use

Any antibiotic use during the prenatal period showed no significant association with T1D (OR = 1.00 [95% CI: 0.93–1.08]). Additionally, no specific antibiotic class or number of courses was associated T1D.

3.3.3 Postnatal antibiotic use (0–6, 0–12, 0–24 months postnatal)

No significant associations were observed for antibiotic use during the first two years of life, including:
- 0–6 months postnatal
- 0–12 months postnatal
- 0–24 months postnatal

3.3.4 Heterogeneity Assessment

Heterogeneity was most meaningfully assessed for the prenatal period, where eight studies (eight ORs and 95% CIs) contributed to the pooled estimate. The calculated heterogeneity statistics were:
- $I^2 = 4.4\%$
- $\tau^2 = 0$
- $p = 0.3962$

These values suggest that the variability in effect sizes across studies is minimal, and differences in study results are likely due to random variation rather than systematic differences between the studies.

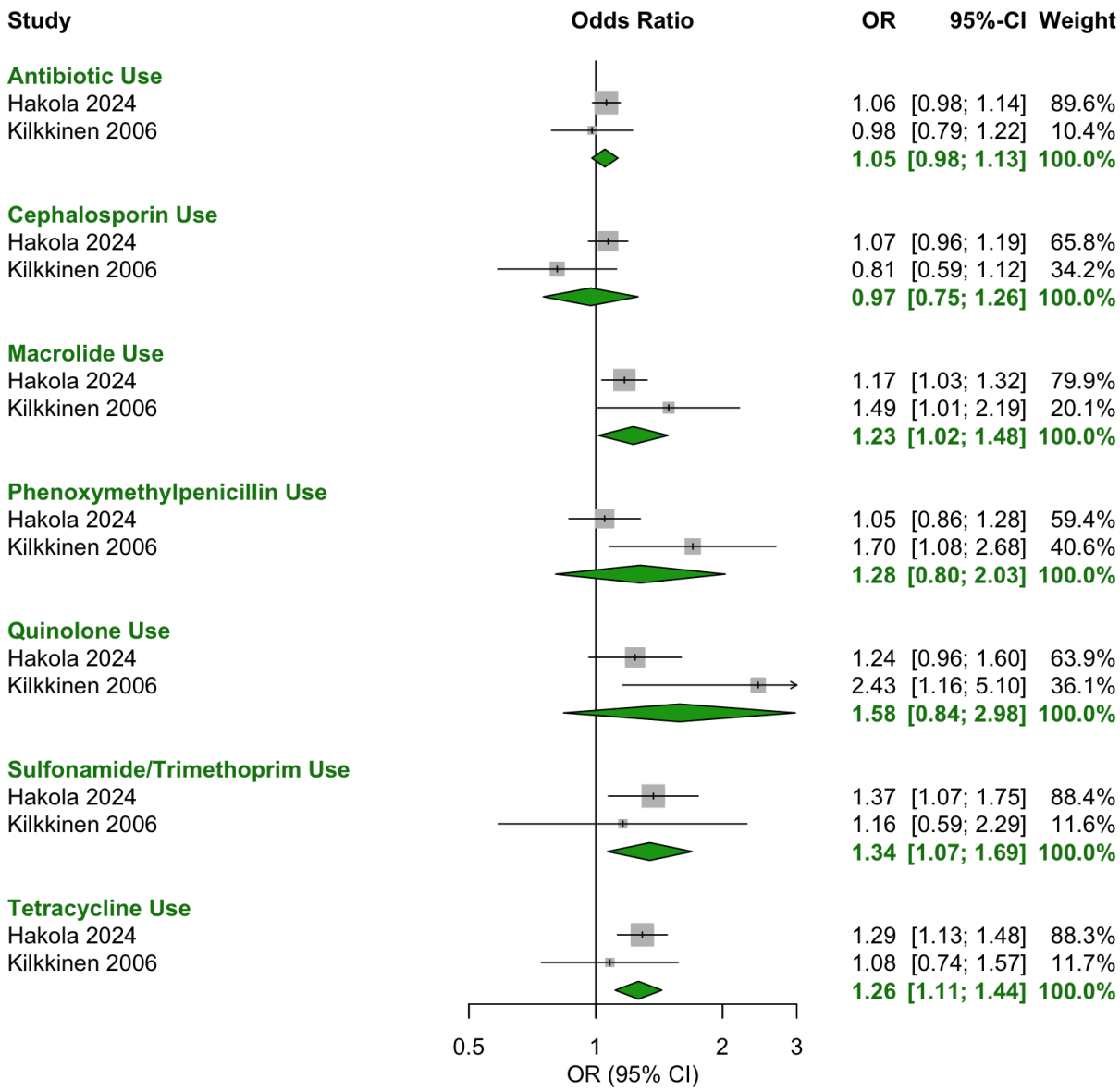

Fig. 2: Forest plot of OR estimates and 95% CIs for the association between antibiotic use in the year before conception and T1D. Pooled estimates were calculated using a random-effects model. The diamond represents the pooled effect estimate, with its width indicating the 95% CI. Study weightings in the meta-analysis are shown in the far-right column and visually represented by the size of the squares.

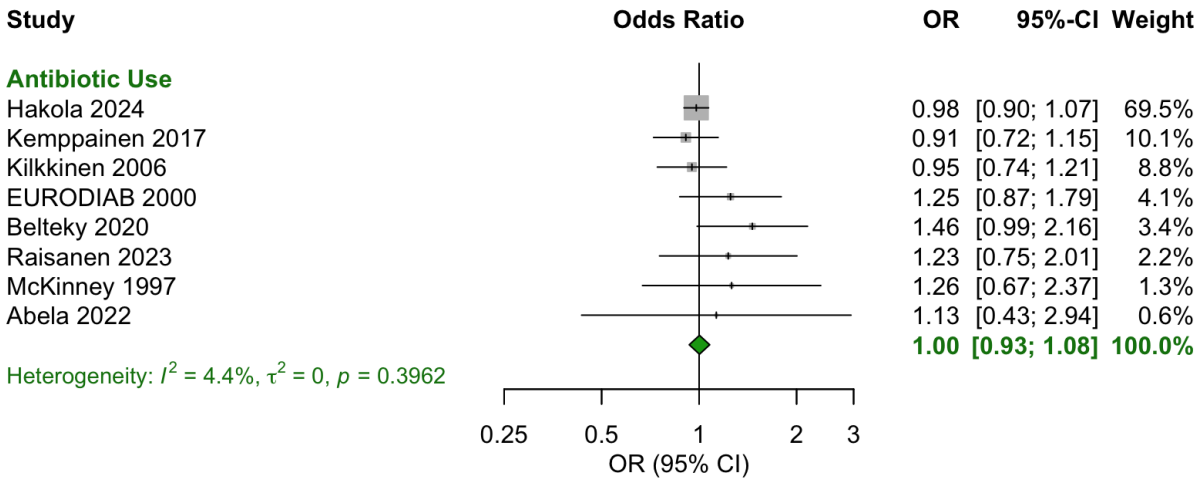

Fig. 3: Forest plot of OR estimates and 95% CIs for the association between prenatal antibiotic and T1D.

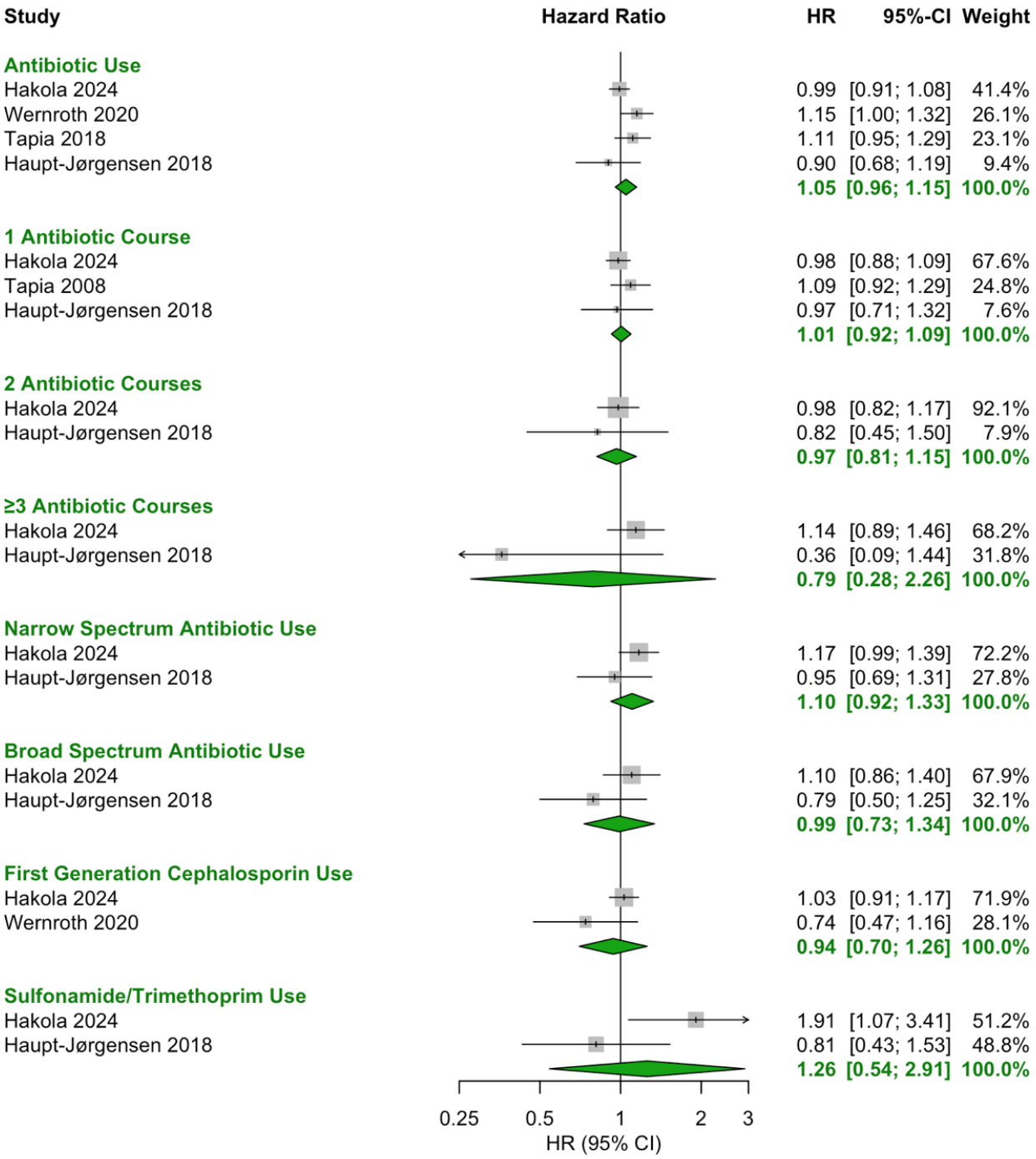

Fig. 4: Forest plot of HR estimates and 95% CIs for the association between prenatal antibiotic and T1D.

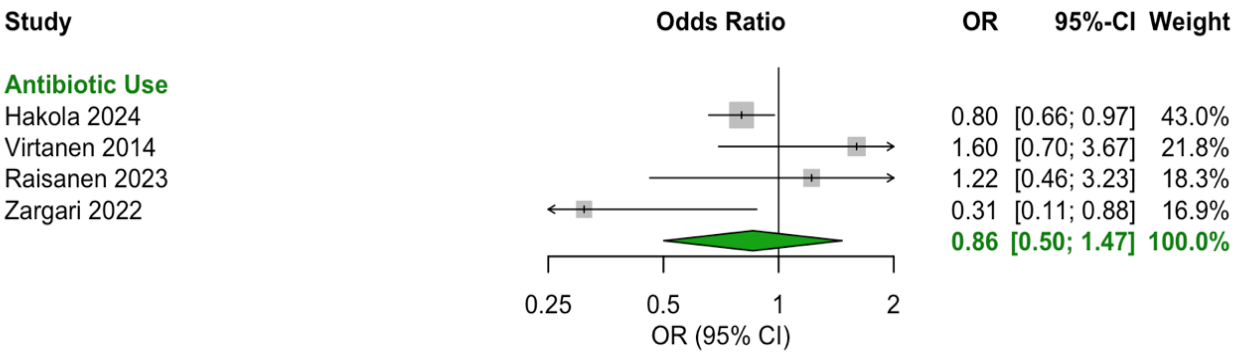

Fig. 5: Forest plot of OR estimates and 95% CIs for the association between neonatal antibiotic and T1D.

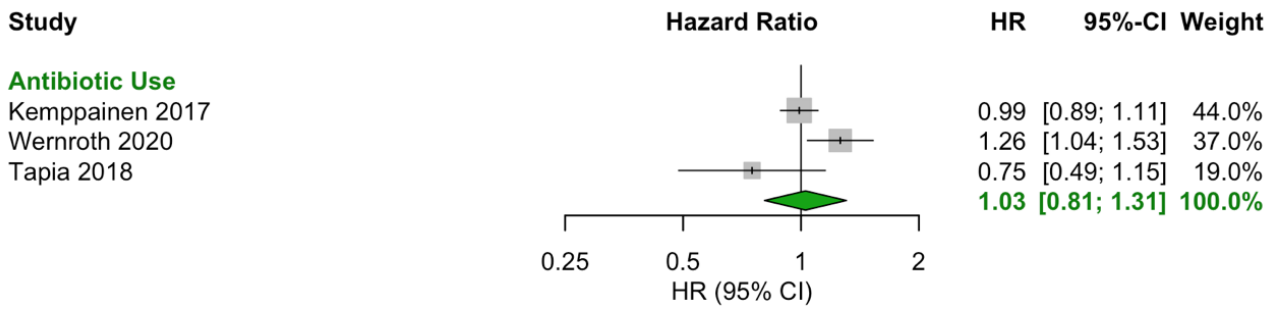

Fig. 6: Forest plot of HR estimates and 95% CIs for the association between antibiotic use in the first 6 months after birth and T1D.

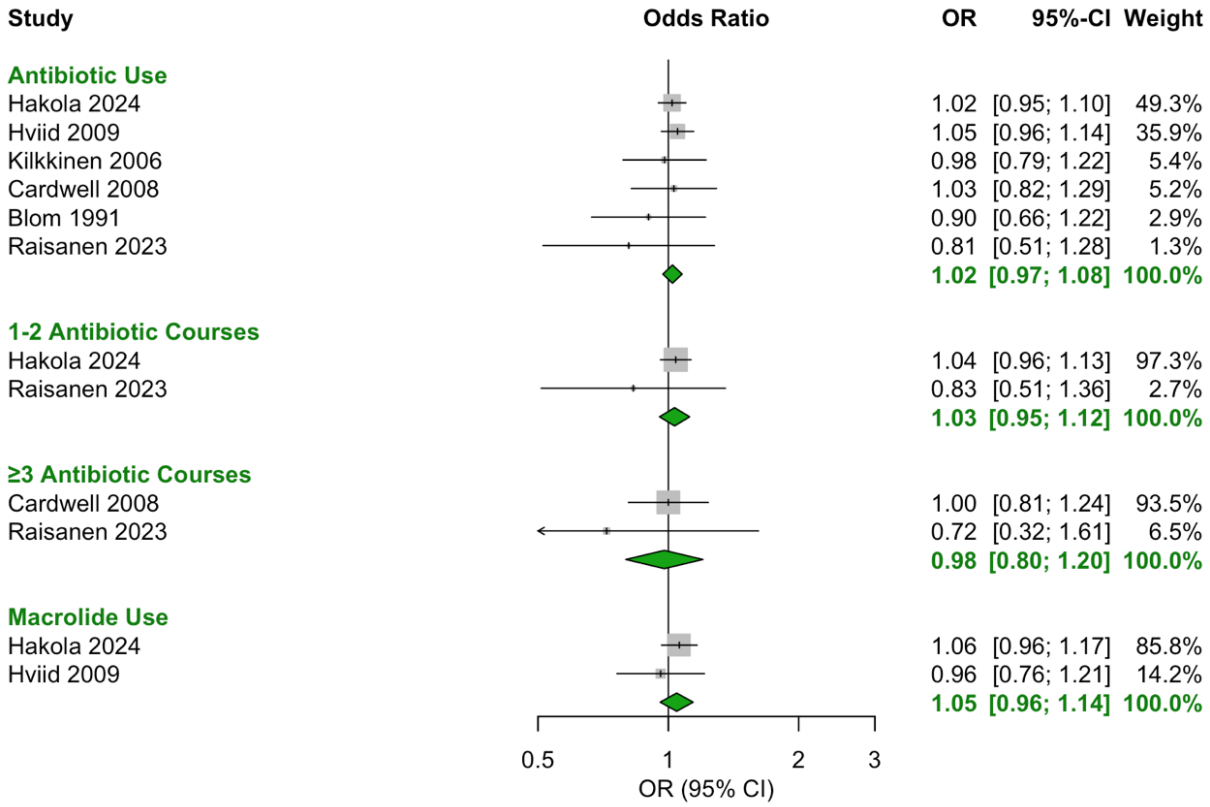

Fig. 7: Forest plot of OR estimates and 95% CIs for the association between antibiotic use in the first year of life and T1D.

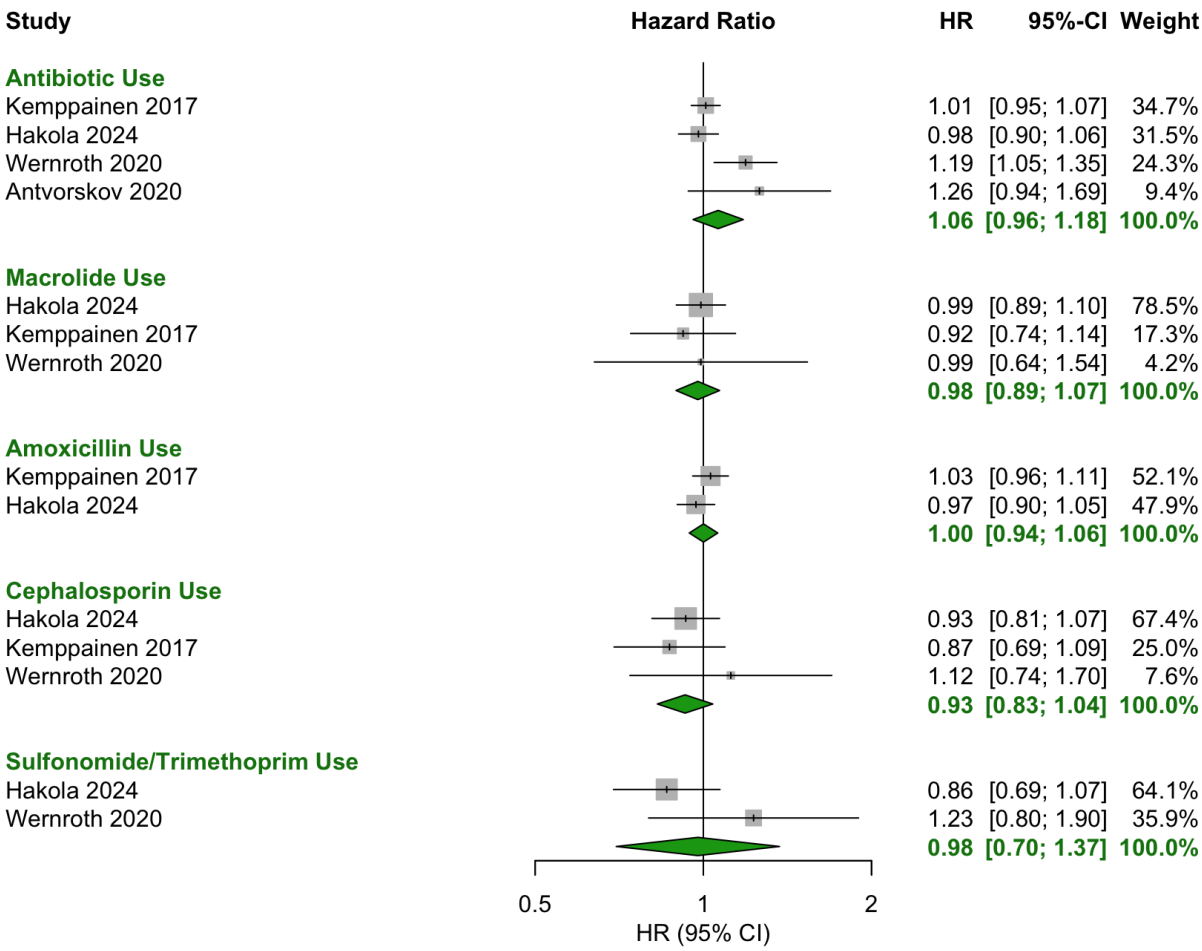

Fig. 8: Forest plot of HR estimates and 95% CIs for the association between antibiotic use in the first year of life and T1D.

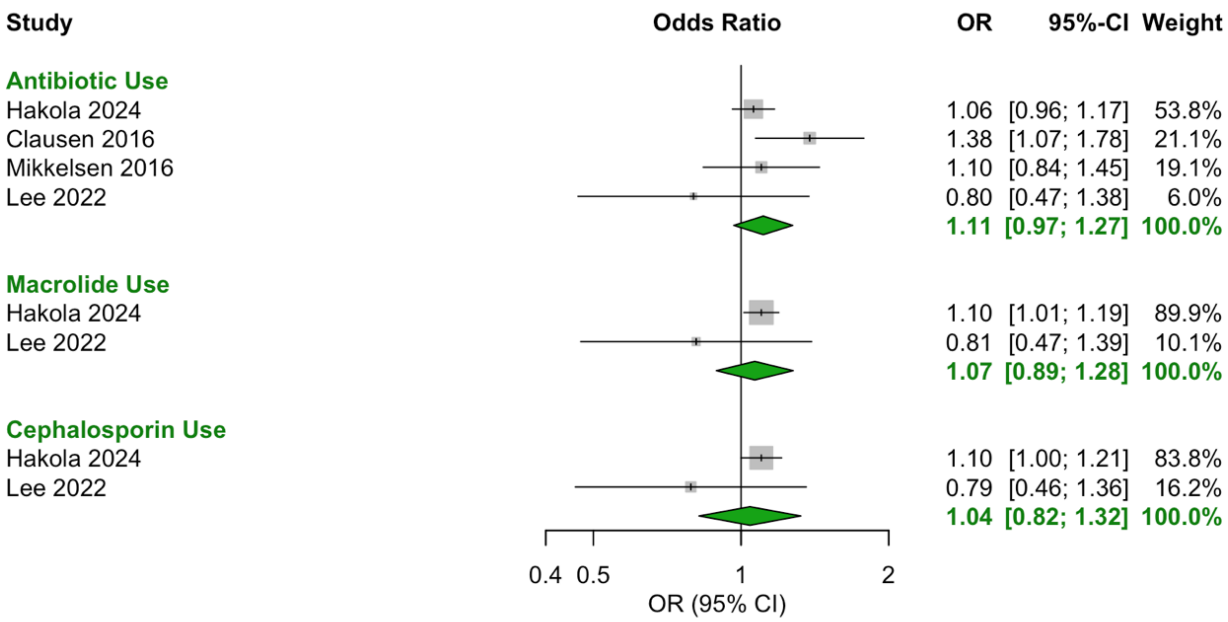

Fig. 9: Forest plot of OR estimates and 95% CIs for the association between antibiotic use in the first two years of life and T1D.

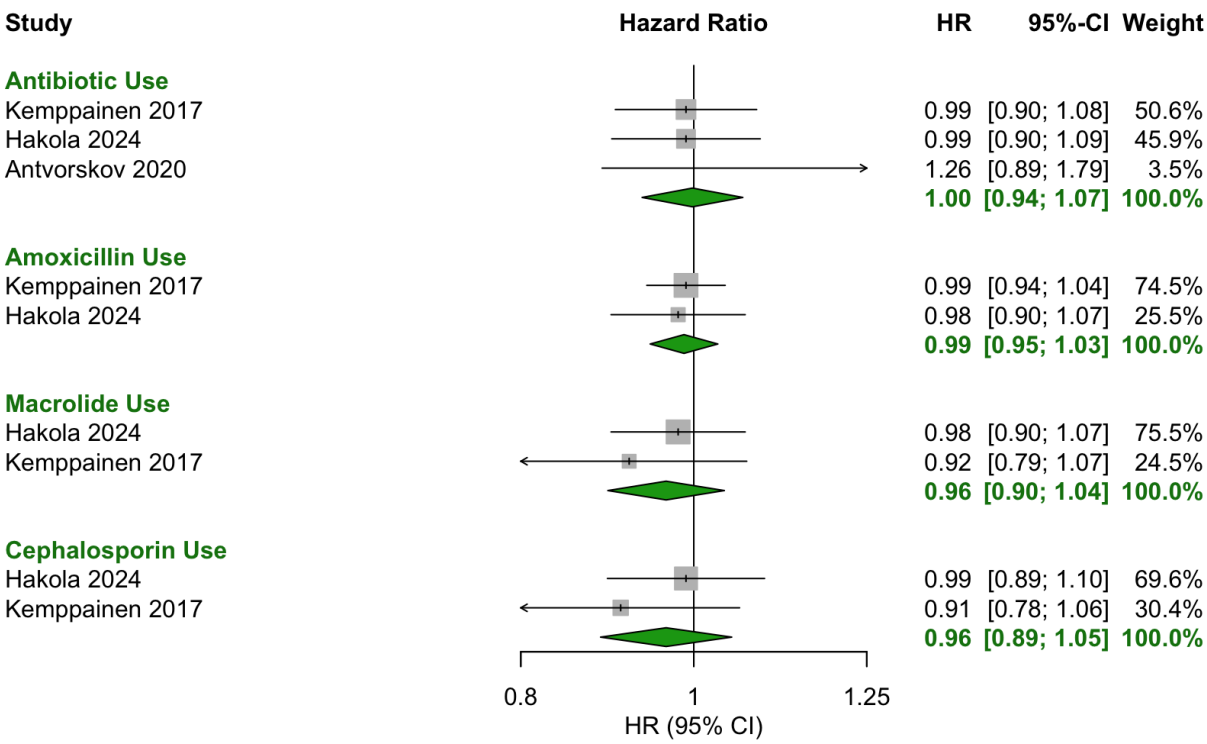

Fig. 10: Forest plot of HR estimates and 95% CIs for the association between antibiotic use in the first two years of life and T1D.

4. DISCUSSION

4.1 Summary and Interpretation of Findings

This meta-analysis found that preconception use of Macrolides was associated with 23% increased odds of T1D development, Sulfonamides/Trimethoprim with a 34% increase, and Tetracyclines with a 26% increase (OR = 1.23 [1.02–1.48], 1.34 [1.07–1.69], 1.26 [1.11–1.44]). In contrast, preconception use of any antibiotic and Cephalosporins was not associated with significantly altered odds (OR = 1.05 [0.98–1.13], 0.97 [0.75–1.26]). Similarly, Phenoxymethylpenicillin and Quinolones showed no significant association, though their wide confidence intervals suggest substantial uncertainty (OR = 1.28 [0.80–2.03], 1.58 [0.84–2.98]). Across the two preconception studies, only 140 cases were exposed to Phenoxymethylpenicillin and 77 to Quinolones, limiting statistical power. A true association may exist but was not detected due to the small sample size. Additionally, there was no significant pooled effect of antibiotic class, spectrum, and number of courses on T1D development for prenatal, neonatal, and postnatal periods.

Though pooled ORs indicate a significantly increased odds of developing T1D following preconception use of Macrolides, Sulfonamides/Trimethoprim, and Tetracyclines, individual study results provide important context. In the Hakola 2023 study, preconception Macrolide use was associated with both increased odds of T1D (OR = 1.17 [1.03–1.32]) and increased rate (adjusted HR = 1.17 [1.02–1.33]), strengthening confidence in this association. In contrast, Sulfonamides/Trimethoprim and Tetracyclines had significant ORs (1.37 [1.07–1.75] and 1.29 [1.13–1.48], respectively) but non-significant adjusted HRs (1.1 [0.86–1.42] and 1.02 [0.89–1.17]), weakening the certainty of their association with T1D. This discrepancy may stem from limited statistical power in the Hakola study, where only 68 cases were exposed to Sulfonamides/Trimethoprim and 236 to Tetracyclines, compared to 270 for Macrolides. The meta-analysis increases the sample size from 68 to 79 for Sulfonamides/Trimethoprim and from 236 to 275 for Tetracyclines, but it lacks adjustment for confounders beyond case matching for age and sex, unlike the adjusted HRs in Hakola. Given that the Hakola study's adjusted HRs did not identify a significant association for preconception Sulfonamides/Trimethoprim and Tetracyclines use with T1D, larger, well-powered studies with robust confounder adjustment are needed to clarify these relationships.

4.2 Related Research

Given the high confidence of the association between preconception use of Macrolides and T1D, it is important to consider its mechanisms of effect in the context of T1D.

Macrolides exhibit anti-inflammatory effects independent of their antibacterial properties, which may be relevant to T1D. Ianaro et al. (2000) demonstrated that three types of Macrolides: Roxithromycin, Clarithromycin, and Erythromycin, significantly reduced inflammation in a rat carrageenan pleurisy model, with Roxithromycin showing the strongest effect. These Macrolides lowered prostaglandin E2, nitric oxide, and TNF-α levels, suggesting they have a net anti-inflammatory effect. In LPS-stimulated murine macrophages, Macrolides suppressed TNF-α, IL-1β, IL-6, nitric oxide, and prostaglandins in a dose-

dependent manner, likely by inhibiting inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression, again suggesting an anti-inflammatory effect.

Further supporting these immunomodulatory properties, Domon et al. (2023) found that Azithromycin and Erythromycin suppressed inflammation triggered by Macrolide-resistant Streptococcus pneumoniae (MRSP). Macrolides downregulated bacterial genes involved in peptidoglycan, lipoteichoic acid (LTA), and lipoprotein synthesis, reducing activation of Toll-like receptor 2 (TLR2) and nucleotide-binding oligomerisation domain 2 (NOD2), which drive inflammatory responses. In macrophage models, Macrolide treatment reduced TNF-α, IL-6, and IL-8 secretion, while in mouse models, Macrolides dampened pneumolysin-mediated lung inflammation without significantly affecting bacterial load. These findings suggest that Macrolides modulate inflammation at both the host immune level and bacterial transcriptional level, reinforcing the idea of their broad immunoregulatory effect.

Since inflammation could be the mechanism underlying maternal protection, perhaps Macrolides, which undermine inflammation through multiple pathways, offset the protection of inflammation. Without this protection, perhaps there is a greater susceptibility to diabetogenic insults, which manifests as the observed association between preconception use of Macrolides and T1D in the child. Unfortunately, the two preconception studies included in this review did not divide Macrolides into further categories such as Roxithromycin, Clarithromycin, and Erythromycin. More comprehensive categorisation could help ascertain the specific pathways that alter protection. Similarly, they did not report more precise periods beyond 0-12 months before conception. Future studies could build on these significant findings by pinpointing a specific window within the 0-12 preconception period that is associated with increased T1D odds when specific Macrolides are taken.

4.3 Limitations of the Evidence

Despite the inclusion of large, cross-country cohorts and adherence to strict eligibility criteria, several limitations reduce the confidence of these findings.

First, antibiotic exposure windows in the included studies were often broad. For example, the 0-12-month preconception period likely includes periods that are irrelevant to T1D risk. It is plausible that only a narrower window, such as the 0-6 months before conception, is biologically relevant. Broad exposure windows may dilute meaningful signals and contribute to statistically non-significant findings despite the presence of a true effect in a critical subperiod. Second, the measurement of antibiotic exposure in the included studies was inconsistent and biased. Some studies relied on prescription records, which do not confirm actual consumption and do not consider non-prescribed use. Others used parental questionnaires, which are prone to recall bias. Both approaches risk exposure misclassification, potentially resulting in antibiotic-exposed individuals being included in the control group or unexposed individuals in the case group. These misclassifications could shift estimates towards null. Third, there are limitations inherent to study design. The included studies were observational and cannot determine causality. Moreover, potential publication bias, where null findings are less likely to be published and hence included in this review, may inaccurately shift results towards false significance.

Taken together, these factors contribute to an overall certainty of evidence that is best described as low to moderate.

4.4 Implications for Practice, Policy, and Future Research

There is a significant association between T1D and preconception use of Macrolides, Sulfonamides/Trimethoprim, and Tetracyclines. However, given the low to moderate quality of this evidence, it is unclear whether these findings should inform clinical decision-making and public health policy. Future research is needed to clarify whether early-life antibiotic use represents a modifiable risk factor for T1D.

Future research should aim to increase confidence in these findings and address key methodological limitations identified in this review. First, studies should explore narrower preconception exposure periods, such as 0-3 months and 3-6 months, and investigate antibiotic subclasses, especially for Macrolides, Sulfonamides/Trimethoprim, and Tetracyclines. Second, where possible, prescription data, pharmacy dispensing records, and self-reported adherence logs should all be considered to reduce the misclassification of cases and controls. Additionally, comparing the gut microbiota of antibiotic-exposed and unexposed women may clarify whether disruption of maternal microbial communities and the resulting inflammatory pathways contribute to altered T1D risk in the offspring.

This review and meta-analysis can readily be adjusted to account for the results of future studies

5. REFERENCES

1. Mannering SI, Pathiraja V, Kay TW. The case for an autoimmune aetiology of type 1 diabetes. Clinical & Experimental Immunology. 2015;183(1):8-15.
2. Lucier J, Mathias PM. Type 1 Diabetes. StatPearls. NCBI: StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2024.
3. Cox DJ, Gonder-Frederick L. Major developments in behavioral diabetes research. J Consult Clin Psychol. 1992;60(4):628-38.
4. Sussman M, Benner J, Haller MJ, Rewers M, Griffiths R. Estimated Lifetime Economic Burden of Type 1 Diabetes. Diabetes Technology & Therapeutics. 2020;22(2):121-30.
5. Gong B, Yang W, Xing Y, Lai Y, Shan Z. Global, regional, and national burden of type 1 diabetes in adolescents and young adults. Pediatric Research. 2024;97(2):568-76.
6. FDA. FDA approves first drug that can delay onset of type 1 diabetes. AAP News; 2023. p. 1-2.
7. Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A, et al. Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes. New England Journal of Medicine. 2023;389(23):2151-61.
8. Brown K, Godovannyi A, Ma C, Zhang Y, Ahmadi-Vand Z, Dai C, et al. Prolonged antibiotic treatment induces a diabetogenic intestinal microbiome that accelerates diabetes in NOD mice. The ISME Journal. 2015;10(2):321-32.
9. Hansen CH, Krych L, Nielsen DS, Vogensen FK, Hansen LH, Sørensen SJ, et al. Early life treatment with vancomycin propagates Akkermansia muciniphila and reduces diabetes incidence in the NOD mouse. Diabetologia. 2012;55(8):2285-94.
10. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR. Differences in Risk of Insulin-Dependent Diabetes in Offspring of Diabetic Mothers and Diabetic Fathers. New England Journal of Medicine. 1984;311(3):149-52.
11. Allen LA, Taylor PN, Gillespie KM, Oram RA, Dayan CM. Maternal type 1 diabetes and relative protection against offspring transmission. The Lancet Diabetes & Endocrinology. 2023;11(10):755-67.
12. Roth-Schulze AJ, Penno MAS, Ngui KM, Oakey H, Bandala-Sanchez E, Smith AD, et al. Type 1 diabetes in pregnancy is associated with distinct changes in the composition and function of the gut microbiome. Microbiome. 2021;9(1):167.
13. Blom L, Nystriim L, Dahlquist G. The Swedish childhood diabetes study Vaccinations and infections as risk determinants for diabetes in childhood. Diabetologia. 1991;34(3):176-81.
14. McKinney PA, Parslow R, Gurney1 K, Law G, Bodansky HJ, Williams D, R, R. Antenatal risk factors for childhood diabetes mellitus; a case-control study of medical record data in Yorkshire, UK. Diabetologia. 1997;40:933-9.
15. Group ESS. Infections and vaccinations as risk factors for childhood Type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. Diabetologia. 2000;43(1):47-53.
16. Kilkkinen A, Virtanen SM, Klaukka T, Kenward MG, Salkinoja-Salonen M, Gissler M, et al. Use of antimicrobials and risk of type 1 diabetes in a population-based mother-child cohort. Diabetologia. 2005;49(1):66-70.
17. Cardwell CR, Carson DJ, Patterson CC. 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. 2007;25(3):261-7.
18. Hviid A, Svanstrom H. Antibiotic use and type 1 diabetes in childhood. Am J Epidemiol. 2009;169(9):1079-84.
19. Virtanen SM, Takkinen HM, Nwaru BI, Kaila M, Ahonen S, Nevalainen J, et al. Microbial exposure in infancy and subsequent appearance of type 1 diabetes mellitus-associated autoantibodies: a cohort study. JAMA Pediatr. 2014;168(8):755-63.
20. Mikkelsen KH, Knop FK, Vilsboll T, Frost M, Hallas J, Pottegard A. Use of antibiotics in childhood and risk of Type 1 diabetes: a population-based case-control study. Diabetic Medicine. 2017;34(2):272-7.
21. Clausen TD, Bergholt T, Bouaziz O, Arpi M, Eriksson F, Rasmussen S, et al. Broad-Spectrum Antibiotic Treatment and Subsequent Childhood Type 1 Diabetes: A Nationwide Danish Cohort Study. PLoS One. 2016;11(8):e0161654.
22. Kemppainen KM, Vehik K, Lynch KF, Larsson HE, Canepa RJ, Simell V, et al. Association Between Early-Life Antibiotic Use and the Risk of Islet or Celiac Disease Autoimmunity. JAMA Pediatr. 2017;171(12):1217-25.
23. Haupt-Jorgensen M, Morgen CS, Jess T, Buschard K, Josefsen K, Allin KH, et al. Maternal Antibiotic Use During Pregnancy and Type 1 Diabetes in Children-A National Prospective Cohort Study. Diabetes Care. 2018;41(12):e155-e7.
24. Tapia G, Stordal K, Marild K, Kahrs CR, Skrivarhaug T, Njolstad PR, et al. Antibiotics, acetaminophen and infections during prenatal and early life in relation to type 1 diabetes. International Journal of Epidemiology. 2018;47(5):1538-48.
25. Antvorskov JC, Morgen CS, Buschard K, Jess T, Allin KH, Josefsen K. Antibiotic treatment during early childhood and risk of type 1 diabetes in children: A national birth cohort study. Pediatr Diabetes. 2020;21(8):1457-64.
26. Wernroth ML, Fall K, Svennblad B, Ludvigsson JF, Sjolander A, Almqvist C, 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. 2020;43(5):991-9.
27. Belteky M, Wahlberg J, Ludvigsson J. Maternal respiratory infections in early pregnancy increases the risk of type 1 diabetes. Pediatr Diabetes. 2020;21(7):1193-201.
28. Zargari I, Adar A, Morag I, Pinhas-Hamiel O, Eyal O, Keidar R, et al. Early exposures and inherent factors in premature newborns are associated with type 1 diabetes. Pediatr Res. 2023;94(4):1516-22.
29. Abela AG, Fava S. Prenatal and early life factors and type 1 diabetes. Endocrine. 2022;77(1):48-56.
30. Lee D, Choi S, Chang J, Park YJ, Kim JH, Park SM. Association of antibiotics exposure within the first 2 years after birth with subsequent childhood type 1 diabetes. Endocrine. 2022;77(1):21-9.
31. Raisanen LK, Kaariainen SE, Sund R, Engberg E, Viljakainen HT, Kolho KL. Antibiotic exposures and the development of pediatric autoimmune diseases: a register-based case-control study. Pediatr Res. 2023;93(4):1096-104.
32. Hakola L, Lundqvist A, Gissler M, Virta LJ, Virtanen SM, Metsala J. Prenatal and Postnatal Exposure to Antibiotics and the Risk of Type 1 Diabetes in Finnish Children: A Registry-based Study. The Journal of Pediatrics. 2024;276:114292.