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Original Article



Association Between Antibiotic Exposure and Type 2 Diabetes Risk: A Meta-Analysis

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Abstract

Type 2 diabetes mellitus (T2DM) is a significant contributor to morbidity and mortality globally and more than 500 million people are already affected. It has been estimated that almost 800 million may be living with T2DM by 2045. This review evaluated the association between antibiotic exposure and the risk of type 2 diabetes mellitus (T2DM). A systematic search of PubMed, Dimensions, Google Scholar and ScienceDirect was conducted on 5th June, 2025 and four (4) eligible studies were identified, that are all cohort studies. Data synthesis was performed using RevMan version 5.4.1, employing a fixed-effects model to pool hazard ratios (HR) with 95% confidence intervals (CI). Heterogeneity and publication bias were assessed using I^2 statistics, Chi^2 tests, and funnel plots. The pooled HR identified was 1.31 (95% CI: 1.12-1.53), corresponding to a 31% increase in diabetes risk among individuals with longer antibiotic exposure compared to those unexposed. However, the overall effect was statistically significant (Z = 3.44, P < 0.0001). Moreover, substantial heterogeneity was observed across the four (4) studies ($Chi^2 = 24.94$, $Chi^2 = 24.94$, Ch

Keywords: Antibiotics exposure, Type 2 diabetes mellitus, Meta-analysis.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major contributor to worldwide morbidity and mortality, with its incidence increasing at an alarming rate. More than 500 million people are already affected, and forecasts indicate that almost 800 million may be living with the disease by 2045 [1]. The repercussions transcend individual health, including heightened risks of cardiovascular disease, renal failure, neuropathy, and untimely mortality, with significant economic and societal challenges. Obesity, eating choices, and physical inactivity are well-known causes of type 2 diabetes. However, researchers are now looking into environmental and drug exposures that may possibly play a role in the disease's emergence [2].

Antibiotic exposure has been a significant element of interest. Antibiotics are among the most commonly given treatments worldwide, frequently utilised repeatedly throughout an individual's life. In addition to their primary therapeutic activity, antibiotics have significant and enduring impacts on the gut microbiota, an ecosystem acknowledged as a crucial regulator of host metabolism, immune response, and glucose homeostasis [2,3]. Dysbiosis, or

changes in the diversity and function of microbes, can make it harder for the body to make short-chain fatty acids, change how bile acids are broken down, and cause low-grade inflammation throughout the body. Most of these conditions are directly related to insulin resistance and the onset of type 2 diabetes [4,5].

Different results have been obtained from epidemiological studies. While some large cohort and case-control studies revealed that frequent exposure to antibiotic exposure relates with high risk of Type 2 Diabetes Mellitus (T2DM) occurrence [6,7]. On the other hand, some studies revealed that there is no existing relationship upon adjustment for potential confounders [8]. A significant challenge is distinguishing genuine causal effects from reverse causality; individuals with early, undiagnosed diabetes may experience increased infections, resulting in heightened antibiotic usage prior to diagnosis.

Because antibiotic prescriptions are so common and T2DM is becoming more common, it is very important for both doctors and the public to understand what this connection means. If antibiotic exposure is an independent risk factor, it may signify a novel and

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potentially alterable predictor of diabetes risk, with impacts reaching beyond infectious illness management to chronic disease prevention.

To resolve these concerns, we performed a meta-analysis to consolidate existing information regarding the correlation between antibiotic exposure and the risk of T2DM. We aimed to (1) estimate the aggregated risk of T2DM linked to antibiotic exposure; (2) examine variations by duration or course of exposure; and (3) pinpoint deficiencies in the evidence base to enhance future research and improve clinical and policy decision-making.

Objective and Research Question

The objective of this systematic review was to synthesize current evidence from Cohort studies on the association between duration of antibiotics exposure and the risk of T2DM. However, the review aimed to specifically address the primary research question guiding this review: Is duration or increased course of antibiotic exposure associated with an increased risk of developing type 2 diabetes, in cohort studies investigations? This research question was developed using PICOS framework as shown in the breakdown below [9];

P - Population of interest: Individuals at risk of or with type 2 diabetes

I - Intervention: Antibiotic Exposure

C - Comparison: Individuals who were not exposed to antibiotics

O - Outcome: Increased risk of developing type 2 diabetes

S - Study Design: Cohort study

2. Methodology

Study Design

This study followed the guidelines for meta-analysis outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] to investigate the association between antibiotic exposure and the risk of developing type 2 diabetes. The review synthesis was based on evidence from Cohort Studies. Cohort studies often involve large, diverse populations, which is beneficial for generalizability and establishing temporal relationships between exposure and outcomes. By focusing on cohort studies, we aimed to ensure more robust and consistent findings with a larger sample size and more reliable outcome measures, thus studies such as case-control studies were excluded.

This study was not registered in PROSPERO or any other database for systematic reviews.

Literature Search and Search Strategy

The literature search was conducted in four databases: PubMed, Dimensions, Google Scholar and ScienceDirect and it focused on research articles Published from 1st January 2010 to 31st May 2025. The search terms featured "antibiotic exposure", and "type 2 diabetes" related terms. These search results were refined with the application of Boolean operators "AND" and "OR" [11]. The details of the search strategy employed in the databases are presented in Table 1.

Database	Compiled search term	Search yield	Filters	Yield after applying filters
PubMed	(antibiotics[Title/Abstract] OR antibiotic[Title/Abstract] OR tetracycline[Title/Abstract] OR doxycycline[Title/Abstract] OR cephalosporin[Title/Abstract] OR penicillin[Title/Abstract] OR metronidazole[Title/Abstract] OR fluoroquinolone[Title/Abstract] OR sulfonamide[Title/Abstract] OR macrolide[Title/Abstract] AND (Type 2 diabetes[Title/Abstract] OR Type 2 diabetes mellitus[Title/Abstract] OR Diabetes mellitus type 2[Title/Abstract] OR Non-insulin-dependent diabetes mellitus[Title/Abstract] OR Type 2 DM[Title/Abstract] OR T2DM[Title/Abstract] OR Diabetes type 2[Title/Abstract] OR Non-insulin-dependent diabetes[Title/Abstract] OR Diabetes mellitus[Title/Abstract])		2010-2025, Free full text, Clinical Trial, Multicenter Study, Observational Study, English, Humans.	99
Google Scholar	(antibiotics OR antibiotic OR tetracycline OR doxycycline OR cephalosporin OR penicillin OR metronidazole OR fluoroquinolone OR sulfonamide OR macrolide) AND (Type 2 diabetes OR Type 2 diabetes mellitus OR Diabetes mellitus type 2 OR Non-insulin-dependent diabetes mellitus OR Type 2 DM OR T2DM OR Diabetes type 2 OR Non-insulin-dependent diabetes OR Diabetes mellitus)	927,000	2010-2025	18,200
Dimensions	(antibiotics OR antibiotic OR tetracycline OR doxycycline OR cephalosporin OR penicillin OR metronidazole OR fluoroquinolone OR sulfonamide OR macrolide) AND (Type 2 diabetes OR Type 2 diabetes mellitus OR Diabetes mellitus type 2 OR Non-insulin-dependent diabetes mellitus OR Type 2 DM OR T2DM OR Diabetes type 2 OR Non-insulin-dependent diabetes OR Diabetes mellitus)	2,396	2010-2025, article, all open access	1,127
Science Direct	(antibiotics OR antibiotic) AND (Type 2 diabetes OR Type 2 diabetes mellitus OR Diabetes mellitus type 2 OR Non-insulin-dependent diabetes mellitus OR T2DM OR Diabetes type 2)	124,371	2010-2025, Research articles, English, open access,	15,248

Eligibility Criteria

The studies considered for inclusion were those that reported the incidence of type 2 diabetes in populations exposed to antibiotics, with clear reports on the duration or course of antibiotic exposure. Only cohort studies involving human subjects, published in English,

in peer-reviewed journals, and reported statistical outcome measures (hazard ratios) were included. Studies not published in English, without clear definitions of antibiotic exposure or those not measuring diabetes incidence were excluded.

Study Selection

After screening the titles and abstracts of the retrieved studies, the full-text articles were assessed for eligibility. Two independent reviewers performed the screening to ensure consistency and minimization of bias. Disagreements between reviewers were resolved through consensus. Studies that met the eligibility criteria were included for data extraction.

Data Extraction

A data collection form was developed to systematically extract relevant information from the selected studies. This was conducted independently by two researchers and discrepancies were resolved through discussion. The primary outcome, risk of type 2 diabetes, was extracted as hazard ratio (HR). Data on the duration of antibiotic exposure were also extracted, as these factors are central to understanding the long-term impacts of exposures.

Quality Assessment

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies for observational studies [12].

Data Synthesis and Statistical Analysis

A narrative synthesis was conducted to summarize the findings from the included studies characteristics and key findings. A metaanalysis was conducted using RevMan software (version 5.4.1) and this involved statistical pooling of effect estimates by determination of log risk ratios (LogHR) at 95% confidence intervals (CI) using a random effects model due to anticipated heterogeneity across studies and the I² statistic. Sensitivity analyses were conducted to test the robustness of the results and funnel plots were used to visually map publication bias.

3. Results

Literature selection

The initial database search identified 1058684 records (4917 from PubMed, 2396 from Dimensions, 927000 from Google Scholar and 124371 from ScienceDirect). After removing duplicates and applying appropriate filters, 34760 articles remained which were subjected to title and abstract screening. 34514 articles were excluded from studies at this stage that did not meet the inclusion criteria and the full text of 208 articles were not retrieved for screening. Following detailed eligibility assessment of the full text of 38 articles, four (4) studies met the inclusion criteria [13-16]. The literature selection process is illustrated in the PRISMA flow diagram as shown in Figure 1.

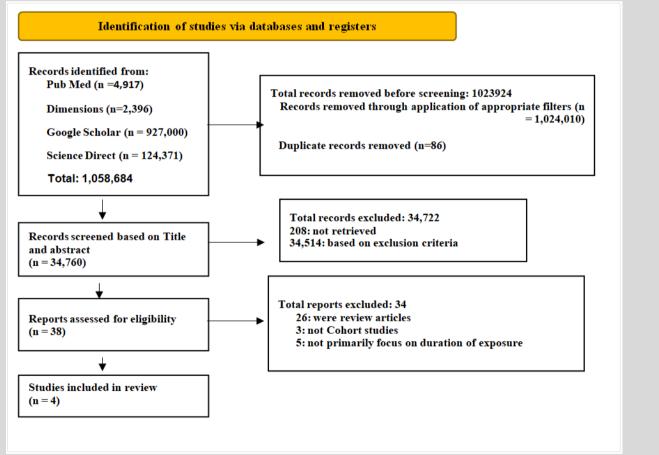


Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [This diagram illustrates the selection process of studies, from initial screening to final inclusion in the meta-analysis]

Study Characteristics

There were four studies included in this review [13-16] and they were all recent studies as they were published between 2020 and 2025. The sample size of the involved participants ranged from 24,674 to 201,459 and of the four studies, one study featured women, another featured children and adolescents while the remaining two studies

featured adults and they were all cohort studies. Interventions and comparators were consistent across studies. The duration of antibiotic exposure in the included studies ranged from days into months and then into a period of one (1) year. The characteristics of included studies are shown in Table 2.

Table 2: The key characteristics of the included studies

Study ID	Study	Antibiotic Exposure	Effect Measure	Study Population	Study	Summary of Key
	Design	(Highest Duration)	(HR, CI)		Information	Findings
Yuan et	Cohort	>2 months	(HR 1.20, 95%	Women, 114,210	Published in Longer antibiotic use (>2	
al. (2020)	study		CI 1.02 - 1.38)		International months) associated with	
[13]					Journal of	increased risk of type 2
					Epidemiology	diabetes
Nuotio et	Cohort	> 5 antibiotic courses in	(HR 1.73;	Adults, 24,674	Published in	Antibiotic exposure (>5
al. (2022)	study	a year	95%CI 1.51-	participants,	BMC	courses) linked to
[14]			1.99).		Endocrine	increased risk of type 2
					Disorders	diabetes
Park et	Cohort	90+ days antibiotic use	(HR 1.16, 95%	Adults, 201,459	Published in	Recurrent antibiotic use
al. (2021)	Study		CI 1.07-1.26)		Scientific	(≥ 90 days) increases type
[15]					Reports	2 diabetes risk
Li et al.	Cohort	Long-term or recurrent	(HR, 1.26; 95%	UK Biobank cohort	Published in	Long-term or recurrent
(2025) ^[16]	study	exposure (three or more	CI, 1.16–1.37)	(childhood and	Journal of	use in early life increases
		times in 1 year)		adolescence), 147,010	Diabetes	risk of type 2 diabetes

[Data adapted from Yuan et al. 2020 [13], Nuotio et al. 2022 [14], Park et al. 2021 [15], and Li et al. 2025 [16]]

Confounding Variables

The studies included in our meta-analysis controlled for several confounders to ensure a valid assessment of the relationship between antibiotic use and type 2 diabetes risk. For instance, Park et al. (2021) [15] adjusted for BMI, smoking, alcohol consumption, physical activity, and family history of diabetes. Li et al. (2025) [16] controlled for demographic factors, lifestyle factors, and BMI.

Nuotio et al. (2022) [14] accounted for early-life BMI and socioeconomic status. Yuan et al. (2020) [13] also adjusted for similar lifestyle factors. These adjustments minimized the potential influence of confounders, such as obesity and lifestyle factors, allowing for a clearer understanding of the impact of antibiotic exposure on diabetes risk.

Summary of Confounders Controlled in the Included Studies on Antibiotic Exposure and Type 2 Diabetes Risk

Study	Confounders Controlled	
Park et al.	BMI, ethnicity, location of residence, parental history of diabetes, diet, physical activity, Charlson comorbidity index (CCI)	
(2021)		
Li et al.	Age, sex, ethnicity, BMI, physical activity, alcohol consumption, smoking, fruit intake, red and processed meat intake, family	
(2025)	history of diabetes, cardiovascular disease, hypertension, hyperlipidemia, statin use, aspirin use, NSAID use, corticoid use	
Nuotio et al.	Age, sex, childhood family income, parental smoking, early life BMI, insulin, systolic blood pressure, physical activity	
(2022)		
Yuan et al.	Demographic factors, family history of diabetes, BMI, physical activity, smoking, alcohol consumption	
(2020)		

Quality Assessment

According to the quality assessment of the four (4) included studies that were assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies all studies were rated to be of good quality as shown in Table 3. They all had similar scores for each domain

except for Nuotio et al. (2022) [14] study with a score of three (3) in the selection domain while others scored 4. This is because in Nuotio et al. (2022) study, there was no demonstration that outcome of interest was not present at start of study.

Table 3: The Quality Assessment of the included studies Based on New Ottawa Scale (NOS) for Cohort studies Study ID Selection (Max 4) Comparability (Max 2) Outcome (Max 3) Total Score (Max 9) Yuan et al. (2020) [13] 4 3 8 Nuotio. (2022) [14] 3 3 7 1 Park et al. (2021) [15] 4 3 8 1 Li et al. (2025) [16] 4 3 1 8

Meta-analysis Findings

In the quantitative synthesis of cohort studies evaluating the association between duration of antibiotic exposure and the risk of developing type 2 diabetes, the pooled hazard ratio (HR) was 1.31 (95% CI: 1.12-1.53), corresponding to a 31% increase in diabetes risk among individuals with longer antibiotic exposure compared to those unexposed. The overall effect was statistically significant (Z = 3.44, P < 0.0006). Substantial heterogeneity was observed across

studies (Chi² = 24.94, df = 3, P < 0.0001; $I^2 = 88\%$), suggesting variability in effect sizes that may be attributable to differences in study populations, antibiotic classes assessed, or exposure duration definitions. Despite this heterogeneity, the consistency of direction across individual study estimates reinforces the robustness of the pooled effect. The forest plot summarising individual study hazard ratios and the pooled estimate is presented in Figure 2.

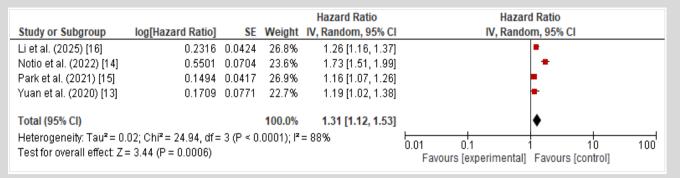
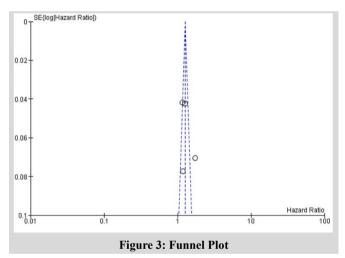


Figure 2: The forest plot illustrating the individual and pooled effect sizes across studies

Publication Bias

Assessment of publication bias was conducted using a funnel plot of the studies included in the meta-analysis (Figure 3). The plot displayed four (4) visible points, each corresponding to an individual cohort study. The distribution of these points appeared relatively symmetrical around the pooled effect size line, with no marked clustering on one side. This suggests an absence of strong small-study effects or substantial publication bias. However, given the limited number of included studies, the visual assessment of symmetry should be interpreted with caution, as funnel plots have low power to detect asymmetry when fewer than ten studies are analyzed [17]. Overall, the funnel plot did not provide evidence of systematic bias that could significantly affect the validity of the pooled hazard ratio.



4. Discussion

Summary of Findings

This meta-analysis identified a correlation between extended and recurrent antibiotic exposure and an elevated risk of acquiring Type 2 Diabetes Mellitus (T2DM). The pooled hazard ratio (HR) was 1.31(95% CI: 1.12–1.53), signifying a 31% elevated risk of T2DM in those with prolonged antibiotic exposure vs to those without exposure.

Comparison with Previous Studies

Our findings align with prior cohort studies indicating a correlation between antibiotic exposure and the incidence of diabetes. Boursi et al. (2015) [18] discovered that those subjected to various antibiotic regimens exhibited an elevated risk of developing Type 2 Diabetes Mellitus (T2DM). Mikkelsen et al. (2015) [19] identified a connection between frequent antibiotic use and heightened diabetes risk. Nonetheless, the processes that underpin this connection remain ambiguous. Prior research has indicated that antibiotics may

influence the gut flora, resulting in insulin resistance, a recognised precursor to type 2 diabetes mellitus (T2DM). Notwithstanding these findings, many studies, notably Chu et al. (2023)^[20], have posited that environmental sources of antibiotic exposure, such as contaminated food or water, may also augment the risk of T2DM. This indicates that the impact of antibiotics on diabetes risk may transcend therapeutic application.

Strengths and Limitation

This meta-analysis employs a rigorous search method, quality evaluation via the Newcastle-Ottawa Scale, and utilises a fixed-effects model to aggregate effect estimates. A significant advantage is the utilisation of cohort studies, which offer more robust evidence of causality compared to case-control studies. Nonetheless, the search was narrow; due to language limited antibiotics, and no grey literature search was performed. The limited number of research considered (merely four cohort studies) constrains the generalisability of the findings. The studies in this review exhibited considerable heterogeneity ($I^2 = 88\%$), indicating that the results may be affected by variations in study populations, antibiotic classes, and exposure durations.

Implications

Our data indicate that extended and repeated antibiotic usage may elevate the risk of T2DM, which carries significant implications for clinical practice and public health policy. Clinicians must exercise caution when prescribing antibiotics, especially for extended periods, and evaluate the potential long-term hazards of Type 2 Diabetes Mellitus (T2DM). Policymakers should contemplate advancing antibiotic stewardship programs to reduce superfluous antibiotic consumption and diminish the risk of chronic diseases such as Type 2 Diabetes Mellitus.

Future Research

Future research should seek to elucidate the molecular pathways connecting antibiotic exposure to type 2 diabetes mellitus, including the influence of the gut microbiota on insulin resistance. Subsequent studies should investigate the impact of antibiotic exposure in early life, as multiple studies indicate that such exposure may have enduring consequences on metabolic health. Furthermore, extensive cohort studies are essential for a more comprehensive evaluation of the long-term effects of antibiotic usage, whereas randomised controlled trials may aid in determining causality.

Conclusion

This meta-analysis highlights the potential link between prolonged and recurrent antibiotic exposure and an increased risk of developing Type 2 Diabetes. The findings underscore the need for clinicians and patients to be cautious about prolonged antibiotic use, particularly in individuals at risk of diabetes.

Declarations

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Conflict of Interest

The authors declare no conflict of interest related to the content of this study.

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