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Research: Epidemiology

Use of antibiotics in childhood and risk of Type 1 diabetes: a population-based case–control study

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Abstract

Aims To investigate whether the use of antibiotics from infancy to adolescence influences the risk of Type 1 diabetes.

Methods We conducted a population-based case–control study, including all Type 1 diabetes cases in Denmark among children born between 1997 and 2012 (n = 1578). Odds ratios associating Type 1 diabetes with use of antibiotics were calculated using conditional logistic regression.

Results Overall, we found no association between the use of antibiotics and risk of Type 1 diabetes. Furthermore, no associations were seen specifically for broad-spectrum, narrow-spectrum, bactericidal or bacteriostatic types of antibiotics or for the most frequently used individual classes of antibiotics. No differences were observed in subgroups defined by sex or by age at time of diagnosis. However, filling five or more antibiotic prescriptions in the first 2 years of life specifically was associated with a higher odds ratio of 1.35 (95% CI 1.10–1.64). This association appeared to be driven by exposure to broad-spectrum antibiotics within the second year of life.

Conclusion Antibiotic exposure in childhood is generally not associated with the risk of developing Type 1 diabetes. Future studies should investigate the effects of multiple exposures to broad-spectrum antibiotics during the second year of life.

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Introduction

Type 1 diabetes is a chronic immune-mediated disease characterized by the selective destruction of pancreatic β cells [1]. The autoimmune reaction is believed to be triggered by environmental factors in genetically disposed individuals, although the causes of the rapid increase in Type 1 diabetes incidence remain poorly understood [2]. Several cross-sectional studies have found an altered gut bacteria composition in people with Type 1 diabetes as well as in those en route to developing the disease [3,4]. Furthermore, experiments in mice have shown a modulatory role of gut bacteria on diabetes progression, along with changes in immune cell differentiation, inflammatory level or sex hormone levels [5–7]. As such, changes in the human intestinal bacteria composition constitute a putative contributing factor to the increasing incidence of Type 1 diabetes [4].

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Antibiotics treatment has marked short-term effects on the composition and function of intestinal bacteria in adults [8], and a recent study showed more persisting changes in preschool children [9]. Based on evidence from non-obese diabetic mice, prolonged antibiotics treatment may induce a pro-diabetogenic intestinal bacteria composition that accelerates disease progression [10,11]. The exact effects of antibiotics on Type 1 diabetes development, however, seem to depend on the timing of the antibiotic exposure, the type of antibiotics used and the host immune system [5,10–13].

We conducted a nationwide case–control study to investigate whether the use of antibiotics in childhood influences risk of developing Type 1 diabetes.

Methods

The present study was a population-based case–control study of incident cases of Type 1 diabetes among children born in Denmark (population 5.5 million) during the period 1 January 1997 to 31 December 2012 (1.0 million children).

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What's new?

- Using data from three Danish registers we performed a nationwide case–control study of the association between antibiotic exposure in childhood and development of Type 1 diabetes in Danish children and adolescents.
- Overall, no association was seen between use of antibiotics and risk of Type 1 diabetes, irrespective of type of antibiotic used.
- A positive association was, however, seen between Type 1 diabetes and exposure to broad-spectrum antibiotics in the first 2 years of life.

Data sources

We used data from three sources: the Danish National Registry of Patients [14], the Danish National Prescription Registry [15] and the Danish Person Registry [16]. Data sources were linked by use of the Central Person Registry Number [11]. The Danish National Prescription Registry [15] contains data on all prescription drugs redeemed by Danish citizens since 1995. In order to obtain data on antibiotic exposure in the first years of life for the entire study cohort, we chose not to include people born before 1995. In addition, for some children in the 1995–1996 cohort, use of antibiotics was occasionally registered to the parents' Central Person Registry number instead of the child's own and we therefore decided to include only people born after 1996. The Danish National Registry of Patients contains data on all secondary care contacts in Denmark since 1977, and the combined use of the Danish National Registry of Patients and the Danish National Prescription Registry has been validated previously to identify people with diabetes and to separate Type 1 from Type 2 diabetes [14]. Further information about the Danish health registries can be found elsewhere [17].

Cases

Cases were defined as all Danish children born after 1 January 1997 who developed Type 1 diabetes before 31 December 2012. Type 1 diabetes was defined as a hospital diagnosis of Type 1 diabetes or insulin-dependent diabetes [International Classification of Diseases (ICD)10 code E10] and having filled at least one prescription for insulin [Anatomical Therapeutic Chemical (ATC) code A10A*) < 180 days after this diagnosis. The date of diagnosis was denoted as the index date.

We excluded cases with any history of other diagnoses related to diabetes (ICD-10 codes E11–14 and H360) or prior use of any non-insulin antidiabetic (ATC code A10B*) and children who at any time before the index date had lived outside of Denmark. Furthermore, children with primary adrenal insufficiency (ICD-10 code E271) were excluded because of the association of primary adrenal insufficiency with Type 1 diabetes and with increased risk of infection [18,19]. Lastly, we excluded children with a history of autoimmune thyroiditis (ICD10 codes E06*), acute or chronic pancreatitis (ICD10 codes K85* and K86*) and any cancer except non-melanoma skin cancer (ICD10 codes C00-C97 excluding C44).

Controls

For each case, we selected eight control children randomly from those born in Denmark between 1997 and 2012. Controls were matched by gender and birth calendar quarter, assigning an index date identical to the corresponding case and applying the same exclusion criteria as those described for cases.

Exposure definition

We obtained information on the use of systemic antibiotics (ATC codes J01*) for cases and controls. Use of antibiotics was quantified according to number of antibiotic courses taken before the index date, categorized as 0 (reference), 1–4 and ≥5. Repeat prescriptions filled for the same antibiotic within 20 days of the first dispensing were considered as belonging to the same course of treatment.

Antibiotic prescriptions filled <1 month before the index date were disregarded in order to avoid reverse causation bias; for example, if the polyuria of a yet undiagnosed Type 1 diabetes was interpreted as a urinary tract infection and treated with antibiotics.

Data analysis

The odds ratios (ORs) for developing Type 1 diabetes associated with antibiotic exposure were estimated using conditional logistic regression. In the main analysis, we estimated the association for 1–4 and ≥5 prescriptions, respectively. In all analyses, 0 prescriptions was used as a reference. We also estimated associations with 1–2, 3–4, 5–8, 9–15, 16–24 and ≥25 prescriptions in order not to overlook a potential dose–response effect outside of common exposure levels. We tested for associations with individual classes of commonly prescribed antibiotics: β-lactamase-sensitive penicillins; β-lactamase-resistant penicillins; sulphonamides and trimethoprim; macrolides; penicillins with extended spectrum; and combinations of penicillins [20]. Similar analyses were conducted for different types of antibiotics: narrow-spectrum; broad-spectrum; bactericidal; and bacteriostatic antibiotics (categorized as previously described [21]). Any confounding effect from age, sex and calendar time was handled by the matching procedure and the conditional analysis. No other confounders were included in the analysis.

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We conducted subgroup analyses by sex, by age at time of diagnosis (0–2 years, 2–5 years, 5–8 years and 8–16 years) and after restricting the data to cases without a history of hospital admission for infectious disease (a complete list of diagnoses can be found in Appendix S1) or cases without any history of a hospital diagnosis of atopic dermatitis (ICD10 codes L208-209), as this condition may be linked to both Type 1 diabetes and an increased risk of antibiotic exposure.

For the sensitivity analyses we considered only antibiotic prescriptions occurring within the 5 years preceding the index date, disregarded all antibiotic prescriptions occurring up to 12 months before the index date in order to assess the risk of reverse causation bias, and specifically considered the potential effects of antibiotic exposure in early life (within age 0–1, 1–2 or 0–2 years).

Ethics

The study was approved by the scientific board of Statistics Denmark. Approval from an ethics committee is not required according to Danish law [22].

Results

In the period from 1 January 1997 to 31 December 2012 we identified 1578 incident cases of Type 1 diabetes, which were matched to 12 610 controls (children without diabetes; Table 1).

Compared with no use of antibiotics, 1–4 or ≥5 courses of antibiotics were not associated with Type 1 diabetes, with ORs of 1.02 (95% CI 0.85–1.22) and 1.01 (95% CI 0.82–1.24), respectively (Table 1). No dose–response effect was observed for antibiotics overall or for broad-spectrum, narrow-spectrum, bactericidal or bacteriostatic types of antibiotics (Fig. 1). Lastly, none of the six most-used individual classes of antibiotics were found to have any association with Type 1 diabetes (Table S1).

Table 1 Baseline characteristics of children with Type 1 diabetes (cases) and control children, and use of antibiotics with odds ratios and 95% CIs for Type 1 diabetes according to antibiotic exposure

	Cases (N = 1578)	Controls (N = 12 610)	OR
Sex, *n* (%)			
Boys	792 (50.2)	6328 (50.2)	
Girls	786 (49.8)	6282 (49.8)	
Median (IQR) age	7 (4–10)	7 (4–10)	
Age range	0–15	0–15	
Age group, *n (%)*			
0–2 years	250 (15.8)	1986 (15.7)	
3–5 years	406 (25.7)	3248 (25.8)	
6–9 years	515 (32.6)	4120 (32.7)	
10–16 years	407 (25.8)	3256 (25.8)	
Exposure to antibiotics			
Any, *n* (%)			
0 prescriptions	212 (13.4)	1737 (13.8)	1.00 (reference)
1–4 prescriptions	723 (45.8)	5971 (47.4)	1.02 (0.85–1.22)
≥5 prescriptions	643 (40.7)	4902 (38.9)	1.01 (0.82–1.24)
Narrow-spectrum antibiotics, *n* (%)			
0 prescriptions	389 (24.7)	2955 (23.4)	1.00 (reference)
1–4 prescriptions	878 (55.6)	7317 (58.0)	0.90 (0.78–1.03)
≥5 prescriptions	311 (19.7)	2338 (18.5)	0.98 (0.80–1.21)
Broad-spectrum antibiotics, *n* (%)			
0 prescriptions	538 (34.1)	4590 (36.4)	1.00 (reference)
1–4 prescriptions	827 (52.4)	6431 (51.0)	1.11 (0.98–1.24)
≥5 prescriptions	213 (13.5)	1589 (12.6)	1.15 (0.95–1.39)

IQR, interquartile range; OR, odds ratio.
Table shows the number of children receiving 0, 1–4 or ≥5 antibiotic prescriptions and the OR for Type 1 diabetes given this specific exposure, using redemption of 0 antibiotic prescriptions as reference.

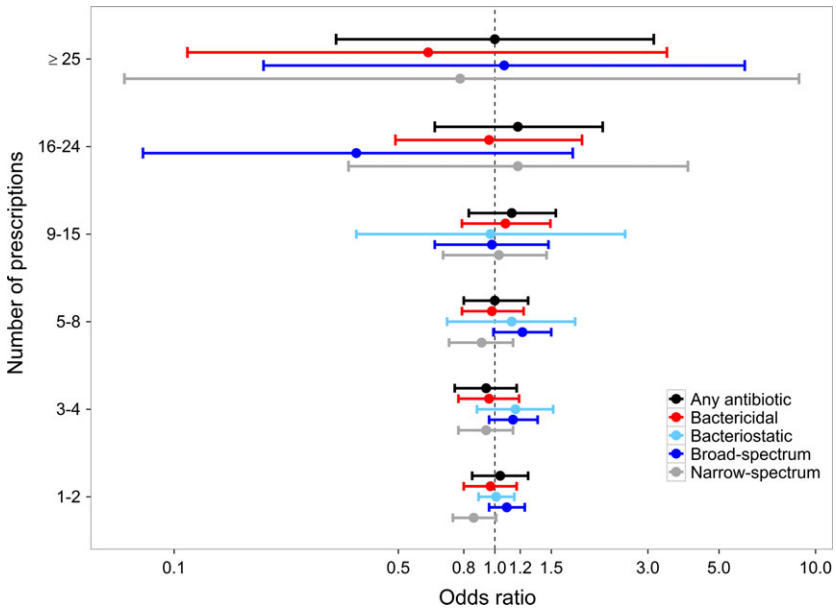

FIGURE 1 Odds ratios for Type 1 diabetes as a function of the number of antibiotic (overall and specified by type of antibiotic) prescriptions before diagnosis of Type 1 diabetes. Redemption of 0 prescriptions on antibiotics was used as reference.

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Subgroup analyses did not show any sex-specific effects or dependency on age at time of diagnosis of Type 1 diabetes (Table S2). Results were not affected by restricting the population to children free of hospital admissions for infectious diseases or diagnosis of atopic dermatitis (Table S2).

Considering only antibiotic prescriptions occurring within the 5 years preceding the index date did not change the results (data not shown). Disregarding antibiotic prescriptions in the period from 0–12 months before diagnosis did not significantly alter the results (data not shown).

A statistically significant OR of 1.35 (95% CI 1.10–1.64) was found for exposure before 2 years of age to ≥5 courses of antibiotics compared with 0 courses. A similar association was seen for broad-spectrum antibiotics (OR 1.39; 95% CI 1.04–1.85) and for bactericidal antibiotics alone (OR 1.26; 95% CI 1.01–1.58). When only considering antibiotic exposure occurring in the second year of life, there was an increased OR for Type 1 diabetes with redemption of 1–4 vs 0 prescriptions of broad-spectrum antibiotics (OR 1.14; 95% CI 1.02–1.27), and a tendency (although not statistically significant) towards a higher OR was observed with ≥ 5 courses of broad-spectrum antibiotics in this period (OR 1.52; 95% CI 0.94–2.48). No association was observed between development of Type 1 diabetes and the number of narrow-spectrum antibiotic courses in the first 2 years of life or the use of antibiotics in the first year of life (OR 0.97; 95% CI 0.56–1.67 for any antibiotic; Table 2).

Finally, two *post hoc* sensitivity analyses were performed. We excluded cases diagnosed within the first 6 months of life ($n < 5$), as these children probably had monogenic neonatal diabetes with a different aetiology from that of Type 1 diabetes [23]. Secondly, we required at least two insulin prescriptions for case inclusion, which reduced the total number of cases from 1578 to 1524. None of these sensitivity analyses changed our results (data not shown).

Table 2 Use of antibiotics and odds ratios with 95% CIs for Type 1 diabetes in sensitivity analyses, taking into account only antibiotic prescriptions in the period from 0–1 years or 1–2 years of age

	Use within 0–1 years OR	Use within 1–2 years OR
Any antibiotic		
0 prescriptions	1.00 (reference)	1.00 (reference)
1–4 prescriptions	0.98 (0.87–1.09)	1.11 (0.99–1.25)
≥5 prescriptions	0.97 (0.56–1.67)	1.13 (0.84–1.53)
Narrow-spectrum antibiotics		
0 prescriptions	1.00 (reference)	1.00 (reference)
1–4 prescriptions	1.04 (0.91–1.18)	1.02 (0.91–1.14)
≥5 prescriptions	1.31 (0.14–11.96)	1.30 (0.64–2.64)
Broad-spectrum antibiotics		
0 prescriptions	1.00 (reference)	1.00 (reference)
1–4 prescriptions	1.03 (0.91–1.17)	1.14 (1.02–1.27)
≥5 prescriptions	0.61 (0.14–2.63)	1.52 (0.94–2.48)
Bactericidal antibiotics		
0 prescriptions	1.00 (reference)	1.00 (reference)
1–4 prescriptions	0.99 (0.88–1.11)	1.08 (0.96–1.20)
≥5 prescriptions	0.61 (0.27–1.38)	1.19 (0.84–1.69)
Bacteriostatic antibiotics		
0 prescriptions	1.00 (reference)	1.00 (reference)
1–4 prescriptions	1.13 (0.90–1.41)	1.07 (0.90–1.28)
≥5 prescriptions	–	1.82 (0.51–6.45)

OR, odds ratio.
Table shows ORs for Type 1 diabetes with redemption of 1–4 or ≥5 antibiotic prescriptions, using redemption of 0 antibiotic prescriptions as reference.

Discussion

In this nationwide register-based study we found no overall association between development of Type 1 diabetes and exposure to antibiotics in childhood.

The primary strength of the study was the use of the nationwide Danish health registries, allowing the capture of all Danish Type 1 diabetes cases over a 16-year period and complete registration of their use of antibiotics.

As for any observational study, the impact of bias and confounding must be considered carefully. Type 1 diabetes is a risk factor for bacterial infection [24], which means that any delays in diagnosis of cases could lead to reverse causation bias. Also, initial symptoms of as yet undiagnosed Type 1 diabetes could lead to increased healthcare contacts and possibly also increased use of antibiotics (protopathic bias). Based on the largely neutral findings in the present analysis, using varying lag-times and when excluding children with hospital diagnoses of infection, we would not expect reverse causation bias or lack time bias to have significantly biased our results.

A limitation of the study was the low rate of use of some antibiotics, which meant that we were unable to test for associations with the full spectrum of antibiotics used for children. We could have overlooked diabetes-promoting effects of individual and less-used classes of antibiotics; however, we found low ORs and low upper CI (when disregarding exposure levels redeemed by very few cases) for all of the six most commonly used antibiotic classes as well as the four overall types of antibiotics. Notably, this lack of association with Type 1 diabetes was also true for macrolides, a class of antibiotics known to have a particularly strong and long-acting impact on gut bacteria composition and function [9,25].

Two other observational studies have previously tested the association between antibiotics and Type 1 diabetes. A Danish study from 2008 found no association between exposure to antibiotics and subsequent development of Type 1 diabetes in a cohort of children born in 1995–2003, of whom 454 developed Type 1 diabetes. Extensive adjustment for potential confounders had no apparent effect on the results in that study [26]. It should be noted that some of the underlying data in that study were also included in the present study. A strength of the present study, however, was that we included three times as many cases, and cases had a longer mean observation period and an age distribution closer to that of the general population with Type 1 diabetes.

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A recent case–control study using a UK database, THIN, reported an association between exposure to particular antibiotic groups and development of diabetes of either Type 1 or Type 2 [27]. In an analysis restricted to cases with Type 1 diabetes, there was a significant association with >5 prescriptions of penicillin (OR 1.41; 95% CI 1.11–1.78) or 2–5 prescriptions of cephalosporins (OR 1.63; 95% CI 1.26–2.11), but the interpretation of these results is limited by the fact that there was no estimate of the association between overall antibiotics use and Type 1 diabetes and no analysis of the effect of timing of antibiotic exposure was performed.

Although the main analyses and subgroup analyses in the present study showed no association between Type 1 diabetes and antibiotics in childhood, we did observe a statistically significant association between development of Type 1 diabetes and exposure to broad-spectrum antibiotics before 2 years of age. A tendency towards a dose–response relationship between Type 1 diabetes and the number of exposures to broad-spectrum antibiotics in the second year and the first 2 years of life was observed, while this tendency was not seen for narrow-spectrum antibiotics in the same period.

As gut bacteria shape the immune system during infancy and early childhood [28], a true biological effect of antibiotic perturbation in the first years of life does seem biologically plausible. It also seems plausible that a more widespread eradication of gut bacteria by broad-spectrum antibiotics, compared with narrow-spectrum antibiotics, could result in a less complete education of the developing intestinal immune system. Several studies using the non-obese diabetic mice model have found modulatory effects of antibiotics on diabetes development, but mainly when treatment was initiated early in life and when broad-spectrum antibiotics were given [10,12,13]. The lack of association between antibiotics exposure in the first year of life and development of Type 1 diabetes reported in the present study seemingly challenges the hypothesis that antibiotic perturbation of the developing microbiome increases the risk of Type 1 diabetes; however, the majority of children in Denmark are breastfed [29] and a previous cohort study of Danish children found that significant changes in gut microbiota occurred particularly from age 9 to 18 months on cessation of breastfeeding and introduction of complimentary foods [30]. As such, in a Danish setting, the second year of life might be the time window during which the infant's microbiome is most susceptible to the effects of antibiotic exposure.

We conclude that Type 1 diabetes development does not seem to be associated with general antibiotic exposure in childhood, but the possibility exists that multiple courses of broad-spectrum antibiotics in the second year of life may be a risk factor for Type 1 diabetes development.

Funding sources

None.

Competing interests

K.H.M. holds stocks in Chr. Hansen. F.K.K. has received personal honoraria for consulting, lectures and/or for advisory board participation within the last 36 months from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Zealand Pharma, and has received unrestricted research grants from the Novo Nordisk and Sanofi-Aventis. T.V. has received lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Novartis and Sanofi, and is a member of the advisory boards of AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi. M.F. has received fees for teaching from Amgen, Genzyme and Eli Lily. J.H. has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, Nycomed, Astellas and Alkabello with grants paid to the institution where he was employed. He has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers and from Nycomed, Pfizer, Novartis, Astra Zeneca, Menarini, Leo Pharmaceuticals and Ferring. A.P. has received funding from AstraZeneca, Astellas, Almirall, Servier, Boehringer Ingelheim and Alcon; all with grants paid to the institution where he is employed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Use of antibiotics in cases and controls and odds ratios (with 95% CIs) for Type 1 diabetes according to antibiotic exposure (categorized by classes of antibiotics) before diagnosis of Type 1 diabetes.
Table S2. Use of antibiotics and odds ratios (with 95% CIs) for Type 1 diabetes according to subgroups.
Appendix S1. Diagnoses used in subgroup analysis 3.

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