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Antibiotics, acetaminophen and infections during prenatal and early life in relation to type 1 diabetes

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Background: Infections in early life have been linked to type 1 diabetes (T1D) risk, but no previous study has comprehensively analysed exposure to antibiotics, acetaminophen and infections during pregnancy and early childhood in relation to offspring risk of T1D.

Methods: Participants in the Norwegian Mother and Child Cohort Study (n=114 215 children, of whom 403 children were diagnosed with T1D) reported infections and medication use through repeated questionnaires from pregnancy until the children were 18 months old. Adjusted hazard ratios (aHR) for offspring T1D were estimated through Cox regression adjusted for child's sex, maternal age and parity, maternal T1D, smoking in pregnancy, education level, pre-pregnancy BMI and birth weight. Antibiotic use was also analysed in a population-based register cohort of 541 036 children of whom 836 developed T1D.

Results: Hospitalization for gastroenteritis during the first 18 months of life was associated with increased risk (aHR 2.27, 95% CI 1.21 – 4.29, p = 0.01) of T1D. Childhood infections not requiring hospitalization, or any kind of maternal infection during pregnancy, did not predict offspring risk of T1D. Antibiotic or acetaminophen use in pregnancy, or child`s use in early childhood, was not associated with risk of T1D.

Conclusions: Our study, which is population-based and the largest of its kind, did not find support for general early life infections, infection frequency nor use of antibiotics or acetaminophen to play a major role in childhood T1D. Hospital admission for gastroenteritis was associated with T1D risk, but must be interpreted cautiously due to few cases.

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Keywords: Antibiotics, Acetaminophen, Paracetamol, Infection, Type 1 diabetes, Pregnancy, Childhood, Norwegian Mother and Child Cohort

MESH terms: Diabetes Mellitus, Type 1; Pregnancy; Human; Antibiotics; Acetaminophen; Infection

Key Messages

- Antibiotic or acetaminophen (paracetamol) use during pregnancy was not associated with offspring type 1 diabetes risk.
- Infections during pregnancy were not associated with offspring type 1 diabetes risk.
- Antibiotic or acetaminophen use in early life was not associated with type 1 diabetes risk.
- General infections during early life was not associated with type 1 diabetes risk, but there was a possible association between hospitalization for gastroenteritis in early childhood and higher risk of type 1 diabetes.

Introduction

Genetic studies in type 1 diabetes (T1D) have revealed multiple risk loci, but environmental risk factors are essentially unknown. Childhood infections have long been suspected (for a brief overview see Online- only Supplement and Supplementary Figure 1), but it is unclear whether specific or general infections, or infection severity, could be associated with type 1 diabetes. Previous studies have not simultaneously considered antibiotics and acetaminophen (paracetamol), which are commonly used for infections, and could be mediators in observed associations.

Antibiotics in early life influence microbiota composition, a factor proposed in type 1 diabetes development [1]. The maternal gut microbiota influence postnatal immune development in mice [2], including diabetes development [3]. Maternal antibiotic use has been associated with offspring asthma risk in epidemiologic studies, but is suspected to be an indicator for infection propensity [4].There are few studies of antibiotics and type 1 diabetes, and they have not simultaneously considered infections as potential confounders. Use of acetaminophen during pregnancy has been linked to offspring asthma [5, 6], but to our knowledge, use during pregnancy and offspring risk of type 1 diabetes has not previously been studied. It is also conceivable acetaminophen use during febrile infections may influence immunity and possibly immune-mediated diseases in childhood. A recent study of analgesic antipyretics use found no association with islet autoimmunity, a surrogate endpoint for type 1 diabetes [7]. Other earlier studies on analgesic use [8-11] might include other medications, are retrospective or use medical records, which indicates an underlying condition.

We aimed to study prenatal and early life exposure to antibiotics, acetaminophen or infections, and type 1 diabetes risk in a large, prospective population-based birth cohort. Antibiotics were also studied in a nationwide register-based cohort. We further assessed

whether a possible association between infections and type 1 diabetes would be influenced by adjustment for antibiotic or acetaminophen use.

Research Design and Methods

Participants, design and outcome: Prospective pregnancy cohort study

We analysed two cohorts (Supplementary Figure 2). The primary cohort is the Norwegian Mother and Child Cohort Study (MoBa), a Norwegian nationwide population-based pregnancy cohort that recruited ~114 000 born children (114 215 in the present study) [12]. Participants (41% of eligible pregnancies) were recruited around pregnancy week 17 during 1999-2008. Maternal pregnancy exposures were assessed by questionnaires (available at www.fhi.no/moba) administered at pregnancy week 17 and 30, and at child's age six months (covering pregnancy weeks 0-17, 18-30 and 30 until delivery, respectively). The child`s exposures were collected from parent-recorded questionnaires administered at ages six and 18 months. Follow-up in MoBa is ongoing; in this sub-study we included cases diagnosed with type 1 diabetes by 31st May 2017.

Children with type 1 diabetes (n=403) were identified through the Norwegian Childhood Diabetes Registry (data capture until 31st May 2017) [13], and the Norwegian Patient Register (NPR). Reporting to the NPR is mandatory and the International Classification of Diseases, Tenth revision (ICD-10) diagnosis E10 (type 1 diabetes) was available from all government-owned hospitals and outpatient clinics in Norway, which covers virtually all paediatric care, from January 1st 2008 until December 31st 2013. Data were linked using the Norwegian 11-digit personal identification number. The study included live-born children who survived their first year of life, with questionnaire data from pregnancy up to six (n = 84 418; 336 cases) and 18 months (n = 70 440; 286 cases).

Participants, design and outcome: Register-based cohort study

To complement our analyses between antibiotics and type 1 diabetes, we obtained a partially independent register based cohort, with only antibiotic data. All children born between January 1, 2004 (start of follow–up) and December 31, 2012, as registered in the Medical Birth Registry of Norway (MBRN) (n=541 036, including 836 type 1 diabetes cases) formed the cohort (Supplementary Figure 2), with follow-up until January 2015. The Norwegian prescription database (NorPD) provided antibiotic prescription data during pregnancy or early childhood, and insulin prescriptions to mother or child, dispensed at Norwegian pharmacies. Type 1 diabetes diagnosis was identified using ICD-10 code E10 from the NPR by latest end of 2013, with the first dispensed insulin prescription from NorPD used as a proxy for diagnosis date. We identified 726 children from the NPR (2008-13) with any registered E10 code, and 665 children had an insulin prescription, yielding 656 with both. Children with only insulin prescription (n = 9) or E10 diagnosis (n = 70) were likely misclassifications, as sourcing insulin outside health services is unlikely and children have regular check-ups which necessitates a diagnosis, and excluded. Additionally 181 had insulin prescriptions in 2014, (data unavailable for 2014 from the NPR), which we included as cases. Children with first insulin prescription <six months of age (n = 1) were excluded, leaving 836 cases.

Highest attained maternal education by 2014 was obtained from the government agency Statistics Norway. No information on maternal BMI, infections or acetaminophen was available in this cohort, but this cohort has no self-selection and a larger sample size than MoBa. Children in MoBa born 2004-2009 were also part of the register-based cohort.

Exposures

Our specified primary exposure for analysis was the number of parent-reported exposures (antibiotics, acetaminophen, and infections), each measured separately as described below, during the whole pregnancy, or first 18 months of life. Exposures were divided into groups, with the lowest category as reference. Secondary analyses considered specific time periods (first six months of life, only before or after pregnancy week 17, or both) and specific categories as described below. Additionally, analyses to replicate earlier reported findings were done.

In Norway, antibiotics are only available through prescription, while acetaminophen is freely available at pharmacies and general stores. All medication use was coded using the anatomical therapeutic chemical (ATC) pharmaceutical classification system. Medication use was counted irrespective of indication. Antibiotics were grouped into penicillin V, extended-spectrum penicillins, other specified systemic antibiotics, or unspecified if no ATC code could be identified (Supplementary Table 1). We assessed potential dose-response effects by considering repeated use of antibiotics (≥2 vs. 1 vs. 0 courses), and number of days of acetaminophen usage. Children with very high frequency of reported acetaminophen use (>60 days the first six months, n = 10) were excluded from analysis due to potential comorbidities.

Our primary analysis considered the total number of infections, while secondary analyses considered specific groups/categories of infections. Type of infection (yes/no) was specified as common cold, throat infection, sinusitis/ear infection, lower respiratory tract infections (pneumonia/bronchitis in mothers, and additionally RS-virus in the children), urinary tract infections (pyelonephritis/acute cystitis in mothers) and gastroenteritis. Additionally, mothers reported influenza during pregnancy and child's croup. Infections were grouped by type: respiratory tract infections (pneumonia/acute bronchitis, common cold, influenza, throat,

sinusitis/ear infections), gastroenteritis, and urinary tract infections during pregnancy, upper respiratory tract infections (common cold, throat infection, ear infection and croup), lower respiratory tract infections, and gastroenteritis in childhood. Additional groups were febrile infections in pregnancy (>38.5 °C, compared with no infections) and infections requiring medical care in early childhood (the participants were asked if the child had been hospitalized during 0 - 6 or 6 - 18 months of life, and doctor/clinic visits the first six months of life).

A priori, we decided to count separate reports of common cold/influenza, pneumonia/acute bronchitis and throat infection/sinusitis/ear infection as a single episode if reported within the same period of pregnancy. Children with an implausibly high infection frequency (≥10 specific infections in a six-month period) were excluded from analysis.

Other variables

Based on previous literature[14, 15] and available data we selected the following adjustment variables, which were covariates in the adjusted analysis: maternal age, pregnancy smoking, type 1 diabetes, education, pre-pregnancy body mass index (BMI), parity, child's sex, birth weight, gestational age and mode of delivery (categorized as shown in Table 1). Infections, antibiotic and acetaminophen use were included in the adjusted models, and mutually adjusted for each other (e.g. when analysing infections, variables of antibiotic and acetaminophen use were included as covariates). BMI was unavailable in the register cohort. As a sensitivity analysis, we included breastfeeding (any versus no breastfeeding) in the childhood analyses. Variable data were retrieved from pregnancy questionnaires and MBRN [16]. Maternal type 1 diabetes was ascertained from the NPR (ICD-10 code E10) in MoBa and from NorPD in the register cohort. We investigated the unadjusted association between each exposure (infections, antibiotic or acetaminophen use) and offspring type 1 diabetes. We then adjusted

for covariates listed above, and lastly additionally adjusted for other exposures (e.g when analysing infections, we adjusted for antibiotic and acetaminophen use in addition to covariates). We present unadjusted estimates, and estimates adjusted for other exposures and covariates. To illustrate the assumed relationships between these variables, directed acyclic graphs (DAGs) were drawn (Supplementary Figure 3).

Statistical analyses

We used Cox proportional-hazard regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), after confirmation that the models did not violate the proportional-hazards assumption by assessment of Schönfeld residuals. Several models were fit on the same exposure: exposure as a continuous variable (which gives maximum statistical power under the log-linearity assumption), as a categorical variable (to assess linearity and possible threshold effects), and as a binary variable (yes/no, to compare with other studies). Robust variance estimator was used to account for potentially correlated data among siblings. In analyses of pregnancy exposures, we counted time from birth to diagnosis of type 1 diabetes. To ensure exposures occurred before type 1 diabetes in childhood analyses, we excluded cases with diagnosis before six and 18 months of age in these time-periods. Therefore, we counted time from 6 or 18 months to type 1 diabetes diagnosis for exposures in the first six and 18 months of life, respectively. Children were followed until diagnosis or administrative censoring (May 2017 in MoBa, January 2015 in the register-based cohort), whichever occurred first. To investigate possible effects of misclassification a bias analysis was conducted using the episens package.[17] As a sensitivity analysis, a conditional logistic regression using mother as grouping variable (sibling-matched design) was done in the

register-based cohort. Stata version 14 (StataCorp LP Texas, USA) was used for the statistical analyses.

Ethics

Written informed consent was obtained from all MoBa participants. The establishment and data collection in MoBa has obtained a license from the Norwegian Data Protection Authority, and the present study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway (REK). The register-based cohort study was approved by REK, and has an independent license from the Norwegian Data Protection Authority.

Results

Distributions of covariates for the cohorts are shown in Table 1. The prevalence of exposures in the MoBa cohort are shown in Supplementary Table 2.

Among children in MoBa (n = 84 407), median age attained at study end (May 2017) was 12.3 years (range 8.4 - 17.9), and 403 (204 girls, 51%) were diagnosed with type 1 diabetes, with median diagnosis age 7.4 years (range 0.7 – 15.2 years). In the register-based cohort (n = 537 460), median age attained at study end (January 2015) was 6.4 years (range 2.0 - 11.0), and 836 (391 girls, 46.7%) were classified as type 1 diabetes cases, with a median diagnosis age 4.4 years (range 0.5 – 10.5 years).

Antibiotic use during pregnancy, the first six or 18 months of life, did not seem to be associated to offspring risk of type 1 diabetes in either cohort, and we observed no dose-dependent associations (Figure 1). To investigate previous reports that children taking ≥5 or >7 antibiotic courses had increased risk we tested both these cut-offs but failed to replicate these findings (data not shown). Sibling-matched analysis of antibiotic use gave similar results (Supplementary Table 5).

Acetaminophen exposure in pregnancy or in the first 18 months of life did not show an increased type 1 diabetes risk (Table 2), although estimates for use in pregnancy were increased (aHR 1.22, 95% CI 0.97 - 1.53, p= 0.08). Using acetaminophen ≥3 days the first six months of life showed an association with type 1 diabetes (aHR 0.65, 95% CI 0.43 – 0.98, p = 0.04 Supplementary Table 3).

Infections during pregnancy did not seem to be associated with offspring type 1 diabetes risk (Table 3). Children hospitalized for gastrointestinal infections the first 18 months of life had increased type 1 diabetes risk (aHR 2.27, 95% CI 1.21 – 4.29, p = 0.01), while hospitalization for upper and lower respiratory tract infections were not associated with type 1 diabetes (Table 3). Results were similar when restricting analyses to infections in the first six months of life (Supplementary Table 3), except that admission to hospital for any infection was associated with type 1 diabetes risk. Overall number of infections or other specific infections were not associated with type 1 diabetes in the first 18 (Table 3) or six months of life (Supplementary Table 3). Adjusting for breastfeeding did not appreciably change our estimates.

We present unadjusted estimates and estimates where exposures are mutually adjusted for each other (e.g when analysing infections, the estimates are adjusted for acetaminophen and antibiotic use). Estimates where the exposures were not mutually adjusted for each other were not appreciably different (data not shown). As the estimates did not change appreciably after adjustment, potential effects of infections, antibiotic and acetaminophen use do not seem to be mediated nor confounded by each other, or adjusting variables. The bias analysis (see online supplementary) shows extensive misclassification is necessary to appreciably change reported estimates (Supplementary Table 4).

Conclusions

In this large-scale pregnancy cohort, general infections, acetaminophen and antibiotic use during pregnancy and early life did not seem to be associated with offspring type 1 diabetes. Increased type 1 diabetes risk was observed after hospitalization for gastroenteritis in early childhood.

Strengths and limitations of the study

Strengths include study size, population-based design and prospective, comprehensive questionnaire data collected during pregnancy and childhood. Findings are likely generalizable to the population. Our study covers a wide infection range with self-reported infections, visits to a clinic/doctor or hospitalization. As common infections are generally self-limited, self-reported infections might better capture symptomatic infections compared with medical records, as it is uncommon in Norway to seek medical care during non-severe infections. Likewise, self-reported use capture better typical use compared to prescribed acetaminophen, as acetaminophen is available prescription-free at general stores and a prescription indicates an underlying condition. We were able to adjust for possible confounders, and investigated if exposures mediated or confounded each other. Comparing unadjusted and adjusted results rules out strong confounding by studied variables. We regard the risk of misclassification of type 1 diabetes as minimal. Diagnostic criteria are clear, we have data from two nationwide registers and other conditions, such as MODY or insulin-dependent type 2 diabetes, are very rare in young children and are screened for at the Norwegian Childhood Diabetes Register [16]. The endpoint studied is type 1 diabetes, not islet autoantibodies which is a commonly used surrogate endpoint, but not everyone with islet autoantibodies progress to type 1 diabetes.

Limitations include potential self-selection to MoBa (but not in the register based cohort), exposure misclassification and lack of data on infectious agents. Participating mothers in MoBa are slightly older, with a healthier life-style than the general population, and the same applies to those who continued to participate. Self-selection is more likely to impact on disease incidences, which in our study are similar to national type 1 diabetes data [13]. Potential misclassifications cannot be ruled out as participants might misunderstand or make errors, but this is expected to be randomly distributed and should be non-differential. Grouping infections minimize possible misclassifications between similar infections. While we cannot entirely exclude possible errors, short recall period likely minimizes potential information bias. We are unable to validate the self-reported data, but believe parents would accurately report rare exposures (e.g hospitalizations) as these are memorable, and common exposures should be easily identified. An earlier study comparing parental-reported hospitalization in MoBa with one major hospital found 197 of 212 admissions correctly reported [18]. The bias analysis shows estimates do not appreciably change unless there is implausible high misclassification.

This study is unsuitable to capture specific, asymptomatic or subclinical infections given our restriction to questionnaire data not confirmed by clinicians or laboratory test results. We cannot refute that a specific infectious agent, or asymptomatic infections, could influence type 1 diabetes risk. We have not investigated short time periods of antibiotic use, or use of specific antibiotics, as this could easily lead to spurious results due to small numbers. We also cannot be certain that antibiotics were necessary, or that courses were fully followed. Antibiotics given at a hospital are not registered in the NorPD, but most intravenous courses are completed with oral administration (which would be registered), and use in new-borns is registered in the MBRN. Antibiotic prescriptions in the register-based cohort were dispensed, but we cannot confirm usage. Antibiotics require prescription in Norway, which is restrictive

in their usage [19]. This makes it unlikely that antibiotics are prescribed or used needlessly, and makes it probable that courses are used.

Comparison with other studies in the field

There are important inter-study differences in exposure data. Prospective studies tend to use medical records, while retrospective studies tend to use questionnaires. Registry studies tend to be larger, but often lack data on confounders. There are also exposure differences, such as hospitalization vs self-reported symptoms. An exposure might be a risk factor for islet autoimmunity, or for progression from islet autoimmunity to clinical type 1 diabetes.

Our findings of no association with general antibiotic use are consistent with previous studies in pregnancy [8, 10, 20-22] and childhood [20, 21, 23-26]. Similar observations in both cohorts strongly suggest that antibiotic use in general does not influence type 1 diabetes risk. This does not exclude that antibiotic types infrequently used, repeated use or use in specific populations could be associated with later type 1 diabetes, or potential time window effects. A recent study linked broad-spectrum antibiotic use in the first 2 years of life with type 1 diabetes risk in children delivered with caesarean section [26]. Kilkinnen et al. [22] and Mikkelsen et al. [25] show increased risk in children with repeated courses (>7 and ≥ 5, respectively), but we did not replicate these findings. This could be due to few children taking so many courses, using broad-spectrum antibiotics or caesarean section. A Dutch study reported that children (<19 years) were prescribed more antibiotics prior to type 1 diabetes diagnosis [27], but this study investigated a different period and is not directly comparable.

Studies covering over-the-counter medications as acetaminophen require a prospective design and are not possible to study in register-based studies. Clinical trials do not usually include pregnant women or young children, which makes observational studies necessary to elucidate

possible risks. With a high proportion of participants using acetaminophen, our study indicates that acetaminophen use in pregnancy does not influence offspring type 1 diabetes risk. Earlier studies on pregnancy analgesic use report somewhat higher risk estimates for type 1 diabetes [8, 10]. The differences in risk might be due to a different exposure or recall bias. Nevertheless, as our study found a slightly increased estimate (HR 1.22, 95% CI 0.98 - 1.53, p = 0.08) after acetaminophen exposure, and increased risk for offspring type 1 diabetes has been observed after analgesic use in prior studies, further studies are recommended. We found that using acetaminophen ≥3 days the first six months of life had a protective effect in a sub-analysis, which must be interpreted with caution and replicated independently. A recent study found no association between analgesic antipyretic use and development of islet autoimmunity [7], which is in line with our results, but do not report on number of days used.

Earlier studies on general infections in pregnancy and early life, and childhood type 1 diabetes, have published seemingly contradicting results (for an overview, see Online-only supplement and Supplementary Figure 1). Retrospective studies are susceptible to recall bias, so we compare our results on infections only with other prospective studies. Most studies tend to show no increased risk after infections in pregnancy [10, 20, 28], which fits our results. Two studies have reported increased risk in early childhood after infections noted in hospital records [20], and viral infections during the first six months of life using medical insurance claims data [29]. There is also a recent study using inpatient claims on infections during childhood that report increased risk [28]. These findings fits well with our results on hospitalization, although the studies are heterogeneous in nature. Two studies found essentially no increase in risk using medical records from primary care [23] and prospective diaries [21], which is similar to our results on general infections. Two smaller studies found decreased risk after at least one infection the first six months [30] and first year of life [31], but we did not replicate these findings (data not shown). These differences could be due to

differences in exposure, age, adjustment for different confounding variables or differences between countries.

Infections could trigger autoimmunity, increase progression of autoimmunity or act as a precipitating factor for clinical diagnosis. All cases but one were diagnosed with type 1 diabetes >5 years of age, which suggests hospitalization for gastroenteritis is not a precipitating factor for clinical type 1 diabetes diagnosis. Infection severity could be important for later type 1 diabetes as only hospitalization was associated, and only the most serious cases would be hospitalized. This represents strong inflammation, which could predispose to later type 1 diabetes. More severe gastroenteritis could also increase intestinal permeability, which could lead to infectious agents infiltrating the pancreas and, if not cleared, persistent inflammation which could increase type 1 diabetes risk. Hospitalization for gastroenteritis could also be linked to changes in the microbiota, which could predispose towards later autoimmunity and type 1 diabetes. Few children were hospitalized, which makes estimates uncertain and these findings should be replicated, as this association could be due to chance or uncontrolled bias. We also cannot exclude the possibility that hospitalization resulted from an excessive immune response or infection susceptibility due to an underlying, already present subclinical autoimmunity.

To conclude, use of antibiotics, acetaminophen and general infections in pregnancy or early childhood did not predict childhood type 1 diabetes. Hospital admission for gastroenteritis in early childhood was associated with increased risk for type 1 diabetes, but must be interpreted cautiously due to few cases.

Conflicts of interest

No potential conflict of interest relevant to this article was reported. The authors alone are responsible for the content and writing of the paper.

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Table 1: Characteristics of children in MoBa pregnancy cohort and population based-cohort

	MoBa; pregnancy, and until 6 months of age (n, %)	MoBa; until 18 months of age (n, %)	Register-based cohort
Participants with exposure data	84 407 (100.0%)	70 430 (100.0%)	537 460 (100.0%)
Girls	41 224 (48.8%)	34 429 (48.9%)	261 583 (48.7%)
Maternal diabetes	454 (0.5%)	379 (0.5%)	6 510 (1.2%)*
Maternal education†			
Low	29 939 (35.5%)	23 983 (34.1%)	87 878 (16.4%)
Medium	34 887 (41.3%)	29 648 (42.1%)	153 954 (28.6%)
High	19 226 (22.8%)	16 528 (23.5%)	274 010 (51.0%)
Missing	355 (0.4%)	271 (0.4%)	21 618 (4.0%)
Maternal smoking in pregnancy			
No	76 351 (90.5%)	64 185 (91.1%)	385 688 (71.8%)
Yes	6 747 (8.0%)	5 232 (7.4%)	61 524 (11.5%)
Missing	1 309 (1.6%)	1 013 (1.4%)	90 248 (16.8%)
Maternal parity			
0	39 528 (46.8%)	33 592 (47.7%)	226 465 (42.1%)
1	29 318 (34.7%)	24 047 (34.1%)	191 902 (35.7%)
≥2	15 561 (18.4%)	12 791 (18.2%)	119 093 (22.2%)
Maternal pre-pregnancy BMI			
< 25	56 602 (67.1%)	47 566 (67.5%)	-
25-29.9	17 968 (21.3%)	14 898 (21.2%)	-
≥ 30	7 662 (9.1%)	6 250 (8.9%)	-
Missing	2 175 (2.6%)	1 716 (2.4%)	537 460 (100%)‡
Birthweight (grams)			
<2500 g	3 756 (4.4%)	3 154 (4.5%)	26 140 (4.9%)
2500-3499 g	32 108 (38.0%)	26 847 (38.1%)	227 094 (42.3%)
3500-4499 g	44 795 (53.1%)	37 315 (53.0%)	265 635 (49.4%)
≥4500 g	3 748 (4.4%)	3 114 (4.4%)	18 591 (3.5%)
Maternal age (years)			
≤ 24	8 487 (10.1%)	6 541 (9.3%)	88 739 (16.5%)
25-34	61 114 (72.4%)	51 379 (73.0%)	346 882 (64.5%)
≥ 35	14 806 (17.5%)	12 510 (17.8%)	101 839 (19.0%)
Gestational age			
<37 weeks	4 774 (5.7%)	3 981 (5.7%)	35 397 (6.6%)
≥37 weeks	79 276 (93.9%)	66 149 (93.9%)	498 263 (92.7%)
Missing	357 (0.4%)	300 (0.4%)	3 800 (0.7%)
Caesarean section	12 271 (14.5%)	10 172 (14.4%)	90 128 (16.8%)
Breastfeeding	-		-
Never	945 (1.1%)	778 (1.1%)	-
Yes	83 462 (98.9%)	69 652 (98.9%)	-
Missing	-	-	537 460 (100%)‡
Age at end of follow-up among non-cases (median, range)	12.3 (8.4 - 17.9)	12.3 (8.4 - 17.9)	6.4 (2.0 – 11.0)

*: in the register-based cohort this is defined as maternal insulin use, which would include gestational diabetes and type 2 diabetes.

†: characterized as ≤12 years, 13-15 years, ≥16 years in the MoBa cohort and 9 years, 10-12 years, ≥13 years in the register cohort. This is maternal education at ~week 18 of pregnancy in the MoBa cohort, and highest attained education in the register-based cohort. This is due to differences in how the data is provided from Statistics Norway and how the questions are asked in the MoBa questionnaires.

‡: Not available in the register-based cohort

Table 2: Risk of type 1 diabetes in offspring according **to acetaminophen use during pregnancy and early childhood** in the MoBa cohort.

Use during Pregnancy	Cases n= 336*	Incidence Rate / 100 000 †	Unadjusted HR	95 % CI	P-value	Adjusted‡ aHR	95 % CI	P-value
No	165	30.9	Ref.			Ref.		
Yes	171	37.4	1.22	0.98 - 1.51	0.08	1.22	0.97 - 1.53	0.08
Number of days								
No days	160	31.2	Ref.			Ref.		
One day	43	36.1	1.16	0.83 - 1.63	0.38	1.21	0.86 - 1.71	0.27
2-4 days	43	35.9	1.16	0.82 - 1.63	0.40	1.23	0.87 - 1.74	0.25
5 or more days	36	32.6	1.05	0.73 - 1.52	0.77	1.02	0.70 - 1.50	0.92
Per day of use			1.00	0.99 - 1.01	0.93	1.00	0.98 - 1.01	0.31
Period of use								
Early (<17 weeks)	61	38.1	1.24	0.92 - 1.67	0.17	1.27	0.93 - 1.73	0.13
Late (>17 weeks)	40	36.0	1.17	0.83 - 1.66	0.37	1.13	0.79 - 1.62	0.51
Both periods	70	37.5	1.22	0.92 - 1.63	0.17	1.23	0.92 - 1.66	0.17
Use 0-18 months	**n = 286**							
No	109	36.3	Ref.			Ref.		
Yes	217	38.4	1.02	0.78 - 1.33	0.88	0.98	0.74 - 1.28	0.86
Number of								
No use	79	37.6	Ref.			Ref.		
1 episode	43	37.2	0.99	0.68 - 1.44	0.95	0.95	0.65 - 1.40	0.80
2 episodes	52	38.1	1.01	0.71 - 1.44	0.94	0.99	0.69 - 1.41	0.94
3 episodes	42	39.5	1.05	0.72 - 1.53	0.79	1.02	0.69 - 1.49	0.93
4 or more	60	38.2	1.03	0.73 - 1.44	0.87	0.96	0.67 - 1.37	0.82
Per episode			1.01	0.93 - 1.09	0.96	0.99	0.92 - 1.06	0.78
Period of use								
No use	103	34.9	Ref.			Ref.		
0-6 months of age	47	41.3	1.15	0.72 - 1.82	0.56	1.15	0.72 - 1.82	0.57
6-18 months of	111	41.1	1.14	0.85 - 1.54	0.38	1.09	0.80 - 1.48	0.58
Both periods	65	34.9	0.98	0.70 - 1.37	0.90	0.93	0.66 - 1.32	0.70

aHR, adjusted hazard ratio; 95% CI, 95% confidence interval.

* Not all participants had complete data on all exposures, so totals in the groups do not necessarily add up 336.

† Risk presented as incidence proportion (cumulative incidence) of type 1 diabetes during follow-up.

‡ Hazard ratios estimated through Cox regression adjusted for child's sex, maternal age and parity, maternal type 1 diabetes, smoking in pregnancy, education level, pre-pregnancy BMI, prematurity, birth weight, infections and antibiotic use.

§ Range 0 – 280, Missing = 9297. The estimates presented are days of use as a categorical variable (one day, two to four days or ≥5 days) and as a continuous variable (Per day of use), with no use as reference.

|| a count of child's reported acetaminophen use (reported at 0-6, 6-8, 9-11, 12-14 and 15-18 months of life), irrespective of days used. The estimates presented are number of episodes as a categorical variable (one, two, three, ≥4 episodes) and as a continuous variable (Per episode), with no episodes as reference.

Table 3. Risk of type 1 diabetes in offspring according to infections during pregnancy and early life in the MoBa cohort.

Infections during pregnancy	Cases n=336*	Incidence rate/100 000†	Unadjusted			Adjusted ‡		
			HR	95% CI	P-value	aHR	95% CI	P-value
Any infection §								
No	88	30.6	Ref.			Ref.		
1 episode	122	38.6	1.26	0.96 - 1.66	0.10	1.29	0.97 – 1.71	0.08
2 or more episodes	126	32.4	1.06	0.81 - 1.40	0.66	0.98	0.73 - 1.33	0.92
Per infection			1.01	0.93 - 1.09	0.84	0.98	0.90 - 1.07	0.65
Any infection with fever								
No	88	30.6	Ref.			Ref.		
Yes	39	29.9	0.98	0.67 - 1.43	0.91	0.80	0.52 – 1.24	0.32
Infection Period								
No	88	30.6	Ref.			Ref.		
Early (<17 weeks)	80	37.6	1.23	0.91 - 1.67	0.18	1.26	0.92 - 1.72	0.16
Late (≥17 weeks)	68	32.2	1.05	0.77 - 1.45	0.75	1.06	0.76 - 1.47	0.73
Both periods	100	35.6	1.17	0.88 - 1.56	0.29	1.10	0.81 - 1.50	0.55
Gastroenteritis‖								
No	257	33.4	Ref.			Ref.		
Yes	79	35.5	1.07	0.83 - 1.38	0.62	1.05	0.81 - 1.37	0.70
Respiratory tract infection **								
No	122	31.6	Ref.			Ref.		
1 episode	133	38.9	1.23	0.96 - 1.58	0.09	1.23	0.95 - 1.58	0.12
2 or more episodes	81	30.7	0.98	0.74 - 1.30	0.87	0.91	0.67 - 1.23	0.55
Urinary tract infection††								
No	297	33.5	Ref.			Ref.		
Yes	39	37.2	1.10	0.79 - 1.54	0.56	1.04	0.70 - 1.55	0.85
Infections during early life	**n=286***							
Any infection§								
0-4 infections	70	37.3	Ref.			Ref.		
5-6 infections	58	39.3	1.06	0.75 - 1.51	0.74	1.00	0.70 - 1.43	1.00
7-9 infections	76	41.0	1.11	0.80 - 1.54	0.82	1.12	0.80 - 1.60	0.52
≥10 infections	71	34.8	0.95	0.68 - 1.32	0.76	0.92	0.64 - 1.30	0.62
per infection episode			0.98	0.96 - 1.01	0.18	0.98	0.95 - 1.01	0.95
Hospital admission								
No	247	37.4	Ref.			Ref.		
Yes	29	45.1	1.20	0.82 - 1.77	0.35	1.24	0.82 - 1.87	0.31
Gastroenteritis‖‖								
No infections	115	39.9	Ref.			Ref.		
One infection	95	41.7	1.05	0.80 - 1.38	0.72	1.04	0.78 - 1.37	0.81
Two or more infections	65	31.4	0.80	0.59 - 1.09	0.15	0.78	0.57 - 1.07	0.13
per infection episode			0.93	0.84 - 1.02	0.12	0.92	0.83 - 1.02	0.13
Hospital admission								
No	266	37.3	Ref.			Ref.		
Yes	10	81.1	2.19	1.16 - 4.10	0.02	2.27	1.21 - 4.29	0.01
Upper respiratory tract **								
0-3 infections	67	37.9	Ref.			Ref.		
4-5 infections	64	36.6	0.97	0.69 - 1.38	0.88	0.93	0.65 - 1.33	0.70

6-7 infections	55	37.2	0.99	0.69 - 1.42	0.97	1.00	0.70 - 1.45	0.99
≥8 infections	89	39.5	1.06	0.77 - 1.45	0.72	1.05	0.75 - 1.47	0.78
per infection episode			0.99	0.96 - 1.02	0.50	0.99	0.96 - 1.02	0.47
Hospital admission								
No	260	37.3	Ref.			Ref.		
Yes	16	56.6	1.51	0.91 - 2.50	0.11	1.55	0.93 - 2.56	0.09
Lower respiratory tract								
No	240	38.8	Ref.			Ref.		
Yes	34	33.1	0.85	0.59 - 1.21	0.36	0.82	0.56 - 1.21	0.31
per infection episode			0.88	0.71 - 1.09	0.25	0.87	0.69 - 1.09	0.22
Hospital admission								
No	270	38.8	Ref.			Ref.		
Yes	6	21.1	0.54	0.24 - 1.21	0.14	0.54	0.23 - 1.24	0.14

aHR, adjusted hazard ratio; 95% CI, 95% confidence interval.

* Not all participants had complete data on infections, so the totals in the groups do not necessarily add up total number of cases

† Risk presented as incidence proportion (cumulative incidence) of type 1 diabetes during follow-up.

‡ Hazard ratios estimated through Cox regression adjusted for child's sex, maternal age and parity, maternal type 1 diabetes, smoking in pregnancy, education level, pre-pregnancy BMI, prematurity, birth weight, acetaminophen and antibiotic use during the relevant time period (pregnancy, or 0-18 months of life). Children with complete data on covariates (n=81 341 for infections in pregnancy and n = 67 693 in 0 – 18 months of life) were included in adjusted model.

§ Includes gastroenteritis, respiratory tract infections, and urinary tract infections. Range 0 – 11 infections during pregnancy and 0 – 58 infections during early life. The estimates presented are maternally reported infections as a categorical variable (none, one or ≥two infection episodes during pregnancy, and 0-4, 5-6, 7-9 and ≥10 infections during early life) with the lowest category as reference, and as a continuous variable (Per infection episode), with no infections as reference. ‖ Range 0 – 3 infections during pregnancy and 0 – 17 infections during early life.

** Includes common cold/influenza, throat infection/sinusitis/ear infection and pneumonia/acute bronchitis during pregnancy (range 0 – 9 infections). Includes common cold/influenza, throat infection/sinusitis/ear infection during 0 – 18 months of life (range 0 – 49 infections).

†† Defined as acute cystitis or pyelonephritis. Range 0 – 3 infections during pregnancy.

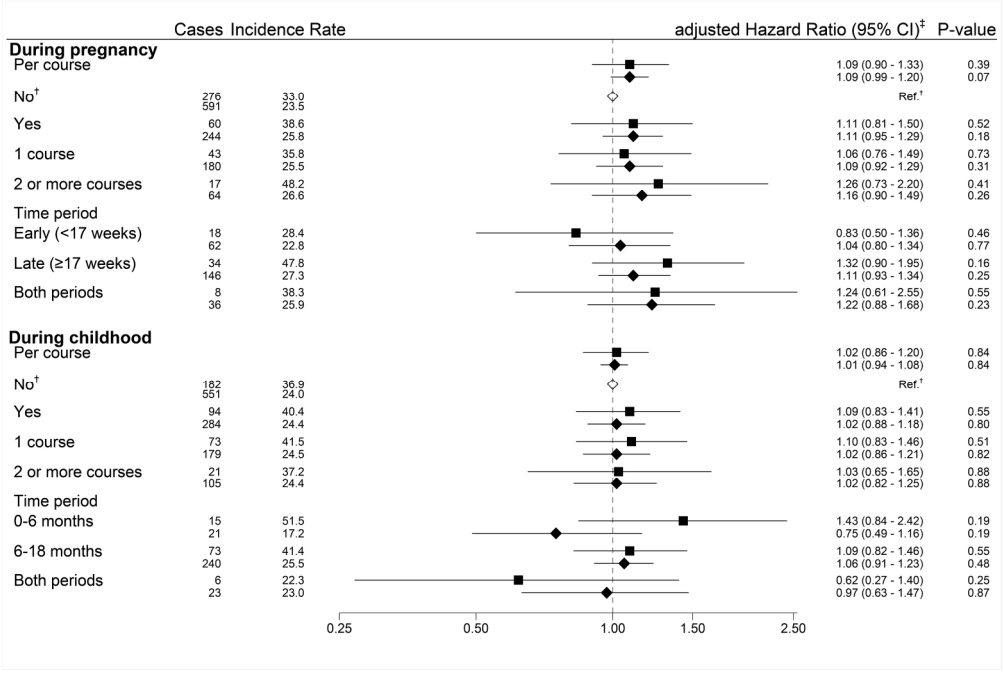
‡‡ Defined as pneumonia/acute bronchitis. Range 0 – 16 infections during 0 – 18 months of life.

Figure 1: Forest plot of antibiotic use and type 1 diabetes risk in both cohorts*.

*Results from the MoBa cohort (n = 84 407) are in the top lines, marked with a square, and results from the register cohort (n = 537 460) are in the bottom line, marked with a diamond.

† Common reference for all exposure categories in the relevant time period

‡ Hazard ratios estimated through Cox regression adjusted for child's sex, maternal age and parity, maternal type 1 diabetes, smoking in pregnancy, education level, pre-pregnancy BMI, prematurity, birth weight, mode of delivery, infections and acetaminophen use during the relevant time period (pregnancy, or first six or 18 months of life) in the MoBa cohort. The register cohort was adjusted for the same variables, with the exception of maternal pre-pregnancy BMI, smoking, acetaminophen use and infections. Adjusting for maternal smoking in the register-based cohort did not appreciably change our estimates; we present data not adjusted for maternal smoking as there was a high proportion with missing data in the register-based cohort. Children with complete data on covariates (n = 67 718 for analysis in 0-18 months of age) were included in adjusted model for the MoBa cohort.



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204x136mm (300 x 300 DPI)