Original Investigation

Respiratory Infections in Early Life and the Development of Islet Autoimmunity in Children at Increased Type 1 Diabetes Risk
Evidence From the BABYDIET Study

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IMPORTANCE There is evidence for a role of infections within the pathogenesis of islet autoimmunity and type 1 diabetes mellitus (T1D), but previous studies did not allow assessment of potential critical time windows in this context.

OBJECTIVE To examine whether early, short-term, or cumulative exposures to episodes of infection and fever during the first 3 years of life were associated with the initiation of persistent islet autoimmunity in children at increased T1D risk.

DESIGN Prospective cohort study with daily infection records and regular assessment of islet autoimmunity.

SETTING Diabetes Research Institute, Munich, Germany.

PARTICIPANTS A total of 148 children at high T1D risk with documentation of 1245 infectious events in 90 750 person-days during their first 3 years of life.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for seroconversion to persistent islet autoantibodies were assessed in Cox regression models with numbers of respiratory, gastrointestinal, and other infections, adjusting for sex, delivery mode, intervention group, season of birth, and antibiotic use.

RESULTS An increased HR of islet autoantibody seroconversion was associated with respiratory infections during the first 6 months of life (HR = 2.27; 95% CI, 1.32-3.91) and ages 6.0 to 11.9 months (HR = 1.32; 95% CI, 1.08-1.61). During the second year of life, no meaningful effects were detected for any infectious category. A higher number of respiratory infections in the 6 months prior to islet autoantibody seroconversion was also associated with an increased HR (HR = 1.42; 95% CI, 1.12-1.80).

CONCLUSIONS AND RELEVANCE Respiratory infections in early childhood are a potential risk factor for the development of T1D.

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The incidence of type 1 diabetes mellitus (T1D) is increasing worldwide,[1] but its etiology is still not well understood. Infections have been discussed as important environmental determinants in the pathogenesis of T1D.[2-4] Retrospective case-control studies showed that patients with newly diagnosed T1D had higher titers of enterovirus antibodies[5] and were more likely to be positive for enterovirus RNA[6,7] compared with healthy controls. Prospective studies from Finland confirmed the potential association between enterovirus infections and islet autoimmunity,[8,9] while others from Germany and the United States did not.[10-12]

These studies were based on a nested case-control design, which has only a limited ability to control for potential confounding factors. Furthermore, the approaches used did not allow detailed analyses on whether there are critical time windows in which infections might have a particularly strong influence on the development of islet autoimmunity. Moreover, infectious agents other than enteroviruses, eg, rotaviruses, have been reported to be related to T1D.[13-15]

The occurrence of fever is also of interest in this context, as fever indicates a strong immune response and therefore a potentially sufficient and fast removal of the possibly autoimmunity-triggering pathogen.[16,17] However, fever might also indicate a severe infection and excessive immune response leading to tissue damage and activation of autoreactive cells.[18,19] Therefore, it is not yet known whether fever is a favorable or unfavorable prognostic factor in the pathogenesis of autoimmune diseases.

The aim of this study was to examine whether infections and fever episodes during the first 3 years of life were associated with the risk of developing islet autoimmunity. We hypothesized 3 scenarios to explain how infectious diseases might be involved in this context. First, early exposure, eg, in the first months of life, may be instrumental in inducing a state of susceptibility for future seroconversion. Alternatively, infections may have a short-term effect, causing islet autoantibody seroconversion in the following few months. Third, infections might have a cumulative effect such that the frequency of infectious events would increase the likelihood of islet autoimmunity irrespective of when they occur. To study this, we took advantage of data from children at high risk for T1D who had been followed up from 3 months of age within the BABYDIET study.

Methods

Data Collection

The BABYDIET study is an intensively monitored German dietary intervention study testing the potential effect of delayed gluten exposure on the development of islet autoimmunity in children at increased risk for diabetes. The study cohort is still followed up and has been described in detail elsewhere.[20,21] In brief, 150 children younger than 3 months with at least 1 first-degree relative with T1D and 1 of 3 specific T1D-associated HLA genotypes were recruited between August 2000 and August 2006 (participation rate, 88.8%) and randomized to exposure to dietary gluten in the first year of life. After inclusion, children were followed up in 3-monthly intervals until age 3 years and yearly thereafter for efficacy (persistent islet autoantibodies) and safety assessment, including intensive monitoring with 3-monthly sample collections of venous blood, urine, and stool.

The BABYDIET study was conducted at the Diabetes Research Institute, Munich, Germany, and approved by the ethics committee of the Ludwig-Maximilian University, Munich.

Assessment of Infectious Episodes

At the child's age of 3 months, parents completed a detailed questionnaire on their children's history of infections, fever, and medication. Specifically, they were asked about fever, infectious symptoms (such as diarrhea, vomiting, constipation, and allergies), and the names of administered pharmaceutical agents or their active ingredients with starting date and duration of infections and medication. The questionnaire additionally addressed the occurrence of diabetes and other autoimmune diseases in the child or his or her family and lifestyle habits such as smoking during pregnancy. All families then received a BABYDIET book in which they were asked to record all infections and fever events (temperature >38°C) together with medication and health visits of their children on a daily basis until age 3 years. Parents were instructed to report disease-free days in the BABYDIET book as well. The diseases were classified using the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) code from 2011 based on the physicians' diagnosis (if medical care had been sought) or on parental reports of symptoms.

Infectious disease was defined as an acute event according to the *ICD-10* code or by a symptom indicating an infectious genesis. Infectious events were assigned to a specific time interval by their date of onset. We defined 3 categories of infectious diseases: (1) infections of the respiratory tract, of the ear, nose, and throat, and of the eye (if inflammatory symptoms of the respiratory tract were reported); (2) gastrointestinal tract infections (if the main symptoms were diarrhea and/or vomiting); and (3) other infections (eg, with symptoms of skin or mucosa lesions). Other disease events such as allergies or accidents were not considered as infectious diseases. Separate infectious diseases of 1 category were defined as 1 infectious event if there were less than 6 days of potential remission between the respective infections, as these seemed likely to be caused by the same infectious agent. Additionally, we defined a category of "any infections" in which infectious diseases of different categories were considered as 1 infectious event if their time intervals overlapped.

Assessment of Islet Autoantibody Seroconversion

Seroconversion was defined as the development of persistent autoantibodies to 1 or more of the following antigens: insulin, glutamic acid decarboxylase 65, insulinoma antigen 2, or zinc transporter 8. Only the first event of seroconversion in each subject was taken into account. Measurement of autoantibodies has been described elsewhere.[21] The upper limits of normal were determined using quantile-quantile plots, corresponded to the 99th percentile of control children, and were 1.5 local units/mL for insulin autoantibodies, 35 World Health

Organization units/mL for glutamic acid decarboxylase antibodies, 5 World Health Organization units/mL for insulinoma antigen 2 antibodies, 16 units/mL for zinc transporter 8-arginine antibodies, and 30 units/mL for zinc transporter 8-tryptophan antibodies. Using these thresholds for positivity, the assays had respective sensitivities and specificities of 70% and 99% (insulin autoantibodies), 86% and 93% (glutamic acid decarboxylase antibodies), 72% and 100% (insulinoma antigen 2 antibodies), and 84% and 100% for multiple islet autoantibodies in the Diabetes Antibody Standardization Program proficiency workshop.[22] Persistence was defined as being positive in at least 2 consecutive samples and in the last available sample. Islet autoantibodies were measured in venous blood samples from all scheduled visits and therefore every 3 months. Diabetes development was monitored and diagnosed according to the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus criteria.[23]

Table 1. Total Documented Days and Numbers of Infectious and Fever Events in 148 Participants in the BABYDIET Study

Events and Days	No.
Events of islet autoantibody seroconversion	26
Total documented days	90 750
Infections, d	12 910
Fever, d	1137
Infectious events, total No.	
Any[a]	843
Respiratory	669
Gastrointestinal	257
Other	319
Fever events, total No.	431

[a] In the category of any infections, the respiratory, gastrointestinal, and other infections were considered as 1 infectious event if their time intervals overlapped. Therefore, the total number of infections recorded in this category was lower than the total number of infections summed over the 3 categories of respiratory, gastrointestinal, and other infections.

Statistical Analysis

From the daily records in the BABYDIET books, which also covered disease-free days, it was possible to distinguish between documented days (with or without disease) and undocumented days. To avoid potential bias due to variation in the number of documented days between subjects and time periods, we calculated the numbers of infectious disease and fever events per 100 documented days for each child as a measure of incidence. Due to the detailed questionnaire at the child's age of 3 months, we considered all days from birth to this visit as being documented. The analyses were restricted to observations based on at least 20 documented days in the respective time interval.

To address the early-exposure hypothesis, we calculated hazard ratios (HRs) of time until seroconversion to islet autoantibodies with respective 95% CIs by the number of infectious events per 100 documented days in the intervals of 0 to 5.9 months, 6.0 to 11.9 months, and 12.0 to 23.9 months of age using Cox proportional hazard regression model. For any time point, we calculated 4 models, using total number of infectious events as predictor in the first model, numbers of respiratory, gastrointestinal, and other infections as separate predictors in the second model, number of any fever events (recorded with or without an infectious episode) as predictor in the third model, and number of fever events without infection in the fourth model. In total, the data set included 26 events of islet autoantibody seroconversion, which occurred at ages 0.59 to 7.90 years. There were no observations with reported islet autoantibody seroconversion in the first 6 months of life; those with seroconversion at ages 6.0 to 11.9 months were excluded from the analysis of ages 12.0 to 23.9 months.

To examine the short-term effect hypothesis, we calculated Cox regression models with numbers of infectious and fever events per 100 documented days in the last 6 months before autoantibody seroconversion within the first 3 years of life as time-varying predictors.[24]

Table 2. Description of the BABYDIET Study Population[a]

Variable	Median (Range)		*P* Value[b]
	Seroconversion	No Seroconversion	
Male, No. (%)	12 (46)	54 (44)	.86
Mother smoking during pregnancy, No. (%)[c]	0	13 (9)	.13
Follow-up, y	5.76 (0.75-9.18)	5.09 (0.26-10.01)	.38
No. of dd/child	484 (145-1098)	535 (95-1110)	.89
First year of life	309.5 (123-366)	357.5 (94-366)	.86
Any infections/100 dd	2.20 (1.30-5.15)	1.70 (0.00-5.42)	.02
First year of life	1.94 (0.82-4.88)	1.37 (0.00-3.84)	.002
Respiratory infections/100 dd	1.55 (0.64-4.64)	1.30 (0.00-4.90)	.02
First year of life	1.66 (0.00-4.88)	1.04 (0.00-3.62)	.002
Gastrointestinal infections/100 dd	0.38 (0.00-1.03)	0.13 (0.00-2.29)	.01
First year of life	0.30 (0.00-1.63)	0.00 (0.00-1.79)	.006
Other infections/100 dd	0.33 (0.00-1.64)	0.27 (0.00-1.84)	.22
First year of life	0.00 (0.00-1.31)	0.27 (0.00-1.84)	>.99
Fever events/100 dd	1.00 (0.27-3.51)	0.60 (0.00-2.53)	.001
First year of life	0.83 (0.00-3.51)	0.55 (0.00-2.47)	.04

Abbreviation: dd, documented days.

[a] Infections and fever were documented up to age 3 years.

[b] Determined by χ^2 test and Mann-Whitney *U* test as appropriate.

[c] Three missing values in each group.

To disentangle potential early-exposure and short-term effects, we performed 2 sensitivity analyses. In the first, we restricted the models with infectious or fever events during the first half year of life to those seroconversion events that occurred after the first year of life. In the second, we restricted the models with time-varying predictors to those seroconversion events that happened between ages 1.5 and 3 years.

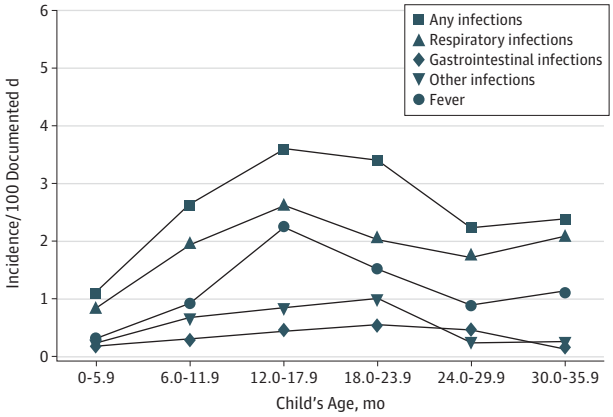
All Cox regression models were adjusted for sex, delivery mode (cesarean or vaginal), intervention group, season of birth (March-May; June-August; September-November; December-February), and frequency of antibiotic use and were tested for interaction with the virus-sensing interferon induced with helicase C domain 1 (*IFIH1*) gene polymorphism.[25]

With respect to the cumulative-exposure hypothesis, we compared the distributions of the recorded numbers of infectious events in children with and without autoantibody seroconversion during their first 2 years of life in 3-monthly intervals.

One subject dropped out of the study after the first visit, and another one had less than 20 documented days in every age interval examined. Both children were therefore excluded from the sample, leaving a final sample size of 148 subjects.

The level of significance was set to .05 in all analyses. All calculations were carried out with SAS version 9.2 statistical software (SAS Institute, Inc). Plotting was done using R version 2.14.1 statistical software (http://cran.r-project.org).

Figure 1. Incidences of Infectious and Fever Events



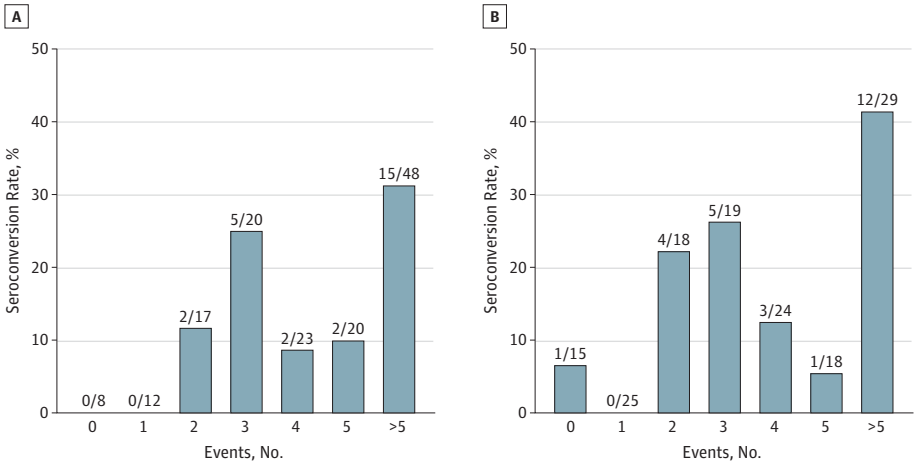
Mean incidences of infectious and fever events per 100 documented days in the first 3 years of life in the BABYDIET data.

Table 3. Islet Autoantibody Seroconversion at Any Time During Follow-up by Number of Infectious Diseases and Fever Events per 100 Documented Days During Ages 0 to 5.9 Months and 6.0 to 11.9 Months

	Hazard Ratio (95% CI)			
	0-5.9 mo		6.0-11.9 mo	
Events	Crude	Adjusted[a]	Crude	Adjusted[a]
Infections				
Any	1.60 (1.06-2.42)	1.68 (1.04-2.72)	1.11 (0.998-1.24)	1.25 (1.06-1.47)
Respiratory	1.95 (1.18-3.22)	2.27 (1.32-3.91)	1.10 (0.97-1.25)	1.32 (1.08-1.61)
Gastrointestinal	1.38 (0.53-3.60)	1.29 (0.48-3.46)	1.46 (0.97-2.18)	1.37 (0.90-2.09)
Other	0.52 (0.15-1.73)	0.41 (0.12-1.47)	1.06 (0.77-1.45)	1.07 (0.75-1.52)
Fever				
Any	1.83 (0.84-3.96)	1.81 (0.77-4.26)	1.38 (0.93-2.05)	1.50 (0.99-2.28)
Without infection	1.56 (0.34-7.05)	2.04 (0.43-9.72)	1.30 (0.57-3.00)	1.44 (0.53-3.95)

[a] Adjustment was made for sex, delivery mode, intervention group, season of birth, and antibiotic use.

Figure 2. Rates of Islet Autoantibody Seroconversion



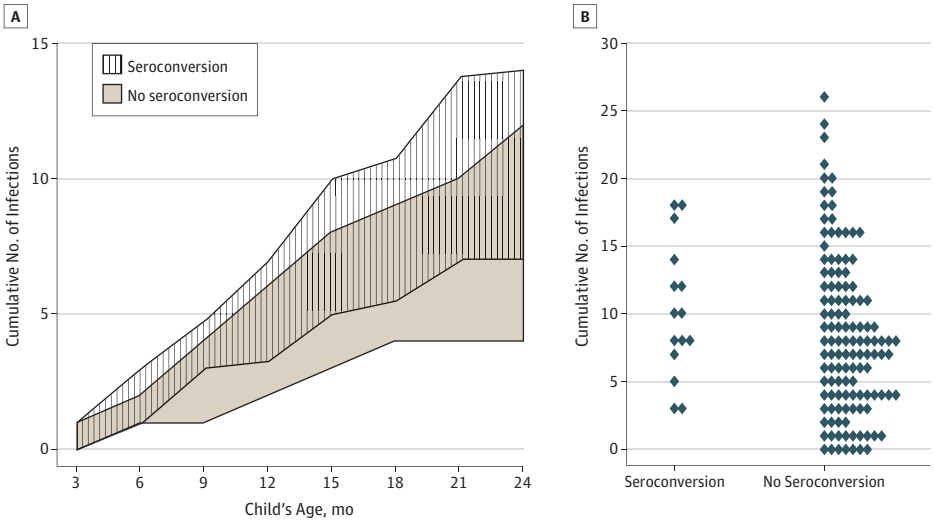
Rates of islet autoantibody seroconversion by total number of infectious events, including any infections (A) and respiratory infections (B), in the first year of life as recorded in the BABYDIET data.

Table 4. Islet Autoantibody Seroconversion at Ages 0 to 3 Years and 1.5 to 3 Years, by Number of Infectious Diseases and Fever Events per 100 Documented Days in the 6 Months Prior to Seroconversion

	Hazard Ratio (95% CI)			
	Seroconversion at 0-3 y		Seroconversion at 1.5-3 y	
Event	Crude	Adjusted[a]	Crude	Adjusted[a]
Infections				
Any	1.17 (1.03-1.34)	1.17 (1.03-1.32)	1.21 (0.91-1.61)	1.29 (0.93-1.78)
Respiratory	1.25 (1.04-1.51)	1.42 (1.12-1.80)	1.25 (0.93-1.67)	1.32 (0.95-1.82)
Gastrointestinal	0.94 (0.51-1.74)	0.98 (0.53-1.81)	1.05 (0.63-1.75)	1.08 (0.64-1.82)
Other	1.08 (0.79-1.47)	0.94 (0.68-1.30)	0.33 (0.03-3.75)	0.31 (0.03-3.70)
Fever				
Any	1.15 (1.07-1.24)	1.15 (1.07-1.23)	1.33 (0.99-1.78)	1.35 (1.01-1.82)
Without infection	1.29 (1.05-1.58)	1.27 (1.03-1.57)	1.53 (0.56-4.17)	1.48 (0.53-4.14)

[a] Adjustment was made for sex, delivery mode, intervention group, season of birth, and antibiotic use.

Figure 3. Total Cumulative Numbers of Any Infections in Children With and Without Islet Autoantibody Seroconversion



A, Interquartile ranges of cumulative number of infections are depicted in 3-monthly intervals up to age 24 months. For each time point, subjects with prior seroconversion were excluded from the respective calculations. B, Cumulative numbers of infections at age 24 months are shown in detail.

Results

Descriptive Statistics

In total, our data comprised 90 750 documented days (**Table 1**). Overall, 1245 events (8.41 per child) and 431 events (2.91 per child) had been reported with respect to infections and fever, respectively. Children with islet autoantibody seroconversion during follow-up were significantly more exposed to respiratory and gastrointestinal infections as well as to fever, both during the first year of life and overall (**Table 2**). The median number of documented days decreased from 350.5 in the first year of life to 177.5 in the second year and 12.5 in the third year. The median number of documented days and median follow-up time per child were similar in both groups.

While there were no islet autoantibody seroconversion events observed in the first 6 months of life, the incidence rates of seroconversion per 100 person-years were 8.51 in the second half year, 4.07 in the second year, and 3.67 in the third year of life. The mean incidences of the 3 infection categories also increased considerably after the first 6 months of life and remained relatively constant thereafter, with a slight decline in the third year of life (**Figure 1**). The same tendency was observed for the incidence of fever. Respiratory infections constituted the majority of the infections recorded.

Addressing the Early-Exposure Hypothesis

Despite the overall lower incidence of infections in the first 6 months of life, the number of infections during this age period per 100 documented days was associated with an increase in the HR for islet autoantibody seroconversion in both crude and adjusted analyses (**Table 3**). The effect size was particularly high for respiratory infections (adjusted HR = 2.27; 95% CI, 1.32-3.91), while there were no significant associations with gastrointestinal and other infections in this early period. The results were similar when we excluded all seroconversion events that happened during the first year of life (data not shown).

In the following 6 months of life, any infections and respiratory infections were again significantly associated with

islet autoantibody seroconversion. However, the effect size was much lower than in the preceding period (eg, respiratory infections: adjusted HR = 1.32; 95% CI, 1.08-1.61). There were no significant associations with fever events in any of the 2 periods. During the second year of life, no meaningful effects were detected for infections or fever (data not shown). We did not detect significant interactions with *IFIH1* genotype in any model (data not shown).

When we explored the associations observed in the Cox regression analyses in further detail (**Figure 2**), we found that the rate of islet autoantibody seroconversion was highest in children with more than 5 recorded events of respiratory infections in the first year of life. For all seroconverters, at least 2 infections had been reported in this period, including respiratory infections for all except 1 case.

Addressing the Short-term Effect Hypothesis

Calculations with time-dependent covariates indicated that the HR for seroconversion was significantly increased by a higher number of respiratory infections per 100 documented days within the preceding 6 months (adjusted HR = 1.42; 95% CI, 1.12-1.80) (**Table 4**). Again, gastrointestinal and other infections did not have a positive association with the seroconversion rate. However, we detected significant associations with any fever events and fever events without infection. When we restricted these analyses to seroconversion events after 1.5 years of life to disentangle potential effects of the first year of life and the preceding 6 months, the results were similar but not significant, with the exception of any fever events. Again, we found no interactions with *IFIH1* genotype (data not shown). For all seroconverters, at least 1 infection had been reported within 6 months prior to the seroconversion event, including respiratory infections for all except 2 cases (data not shown).

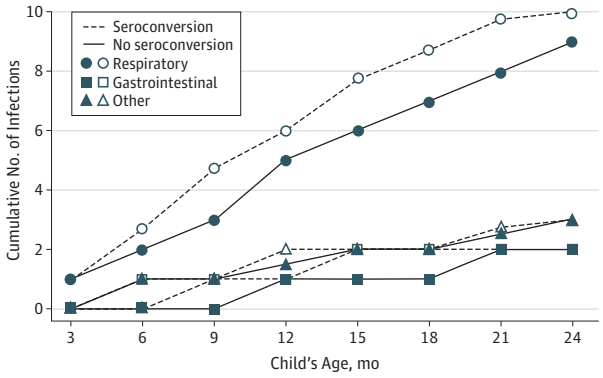
Addressing the Cumulative-Exposure Hypothesis

Between 9 and 18 months of life, subjects with later islet autoantibody seroconversion had on average a higher total number of infectious events recorded than their peers without seroconversion as determined by Mann-Whitney *U* tests (data not shown). The respective interquartile ranges of their number of cumulative infections differed accordingly, although the highest exposures were observed in children without seroconversion (**Figure 3**). The upper quartiles (75th percentiles) of the distributions of the cumulative numbers of respiratory infections increased considerably faster in seroconverters compared with healthy peers during the first year of life, but this difference remained relatively constant thereafter (**Figure 4**). There were no meaningful results with respect to gastrointestinal and other infections. Therefore, the average higher cumulative infection number in children with later seroconversion (as concluded from higher interquartile ranges) reflected mainly a higher exposure to respiratory infections during the first year of life. All these findings were similar when we compared numbers of events per 100 documented days (data not shown).

Additional Analyses

In an attempt to identify specific infectious diseases that might be mainly responsible for the increased rate of seroconversion by respiratory infections, we compared infection rates between children with and without seroconversion. We observed significantly higher rates of infections of the upper respiratory tract (Mann-Whitney *U* test, $P = .005$) and among these of acute rhinopharyngitis (*ICD-10* code J00, $P = .001$). When we used infections of the upper respiratory tract as predictor variable in the Cox regression models, we found significant associations at ages 0 to 5.9 months, at ages 6.0 to 11.9 months, and for 6 months before seroconversion (**Table 5**). We observed no significant associations with infections of the lower respiratory tract (Table 5), of ear, nose, and throat, and of the eye (data not shown).

Figure 4. Seventy-fifth Percentiles of Distributions of Total Cumulative Numbers of Infections



Seventy-fifth percentiles of the distributions of total cumulative numbers of respiratory, gastrointestinal, and other infections in children with and without islet autoantibody seroconversion in 3-monthly intervals up to age 24 months. For each time point, subjects with prior seroconversion were excluded from the respective calculations.

Table 5. Islet Autoantibody Seroconversion by Number of Infections in the Upper and Lower Respiratory Tract and of Acute Rhinopharyngitis per 100 Documented Days

	Hazard Ratio (95% CI)[a]		
Event	0-5.9 mo	6.0-11.9 mo	6 mo Before Seroconversion
Infections			
Upper respiratory tract	2.02 (1.10-3.72)	1.41 (1.09-1.82)	1.57 (1.26-1.95)
Lower respiratory tract	0.88 (0.17-4.64)	2.12 (0.96-4.69)	1.28 (0.51-3.17)
Acute rhinopharyngitis	1.77 (0.88-3.53)	1.34 (1.02-1.75)	1.31 (0.90-1.90)

[a] All analyses were adjusted for sex, delivery mode, intervention group, season of birth, and antibiotic use as well as for other respiratory, gastrointestinal, and other infections.

Discussion

Through the daily documentation of illnesses and fever in children with a family history of T1D during the first 3 years of life, we could demonstrate that exposure to infectious diseases, and in particular to respiratory infections, in early life predicted the development of islet autoimmunity. Primarily, we found strong associations with infections occurring in the first year of life, confirming the early-exposure hypothesis.

There was also some evidence for the short-term effect hypothesis, as infections and fever events within 6 months prior to islet autoantibody seroconversion were also associated with an increased risk of islet autoimmunity. Notably, all children who developed islet autoimmunity had at least 2 infections in the first year of life and at least 1 infection within 6 months before islet autoantibody seroconversion. However, cumulative exposure alone seemed not to be instrumental, as potential differences in the cumulative disease numbers between children with and without islet autoantibody seroconversion mainly reflected different exposure to infections in the first year of life only. Fever seemed to be associated with a detrimental rather than protective effect, particularly with respect to short-term effects, but these findings were not conclusive.

These results are novel. To our knowledge, this study for the first time prospectively assessed infectious diseases together with their starting date and duration in children at risk for T1D. Overall, only few data exist about the incidence of infections and fever in infancy. Our finding that the infection rates increased largely after the first 6 months of life and remained relatively stable thereafter is comparable to results from another study[26] and appears likely to reflect protection by maternal passive immunity, which is known to decline during the first year of life.[27-29] Extrapolated to yearly rates, our incidences of respiratory infections were comparable to those observed in another German population.[30] Other strengths of our study lie in the frequent 3-monthly measurement of all 4 relevant islet autoantibodies and in the fact that parents reported disease-free days as well, so that we were able to estimate disease frequencies without reporting bias. Accompanied collection of medication data even enabled us to rule out that our results were confounded by antibiotic use.

A potential limitation is the sample size, but such frequent follow-up of study subjects, detailed phenotyping, and daily documentation of infectious events constitute a challenge for both investigators and participants, so that it appears difficult to obtain a larger population size with such a study design. As a consequence, our data did not allow us to finally exclude that infections other than upper respiratory tract infections might also have a potential effect on development of islet autoimmunity, as the statistical power might simply have been too low to detect such associations. Apparently for the same reason, we were not able to finally exclude that potential short-term associations observed in our data might be due to early-exposure effects. Although we performed a number of sensitivity analyses, it appears unlikely that this has resulted in a multiple-testing problem. The results of these analyses were only used to assess the validity of the main analyses (which had been performed beforehand) and were not interpreted otherwise.

Various mechanisms have been discussed to explain how infectious diseases might induce autoreactivity in T1D. Results from animal studies indicate that different viruses can affect the development of islet autoimmunity via various mechanisms such as direct beta-cell lysis, bystander activation of autoreactive T cells, loss of regulatory T cells, and molecular mimicry,[31,32] which might therefore also be relevant in humans.[33-36]

The period between ages 6 months and 3 years has been identified as the peak incidence period of islet autoimmunity in the BABYDIET data as well as in other studies,[37-39] implying that most of the relevant causative events occur at or before this time. Our results indicate that early exposure to infections increases the susceptibility for developing islet autoantibodies. Although it might appear plausible that such a state of susceptibility would soon lead to islet autoantibody seroconversion, we found that exposure to infections in the first 6 months of life was also associated with seroconversion after the first year of life, thus also indicating longer-term effects by early exposure.

Potential prevention strategies against T1D derived from studies like this might address early vaccination against specific infectious agents. Unfortunately, we were not able to identify a single infectious agent that might be instrumental in the development of T1D. Our results point to a potential role of infections in the upper respiratory tract and specifically of acute rhinopharyngitis. These results are partly supported by the MIDIA study,[40] which also indicated that respiratory infections are associated with the development of islet autoimmunity. In general, our findings are in accordance with other previous studies that showed associations with enterovirus infections,[5,6,8,9] as rhinoviruses—an enterovirus species—are known to be the major causative agents of respiratory infections.[41-43]

In conclusion, our study identified respiratory infections in early childhood, especially in the first year of life, as a risk factor for the development of T1D. We also found some evidence for short-term effects of infectious events on development of autoimmunity, while cumulative exposure alone seemed not to be causative.

ARTICLE INFORMATION

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Author Contributions: Beyerlein had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ziegler is the principal investigator of the BABYDIET study.
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Acquisition of data: Ziegler, Pflueger.
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