Letters

RESEARCH LETTER

Infections in Early Life and Development of Type 1 Diabetes

Viral infections, particularly enteroviruses,[1] have been hypothesized to cause type 1 diabetes (T1D).[2] Recent studies suggest that respiratory tract infections are associated with increased T1D risk if they are encountered within the first 6 months.[3] We explored associations between infection types during the first 2 years and between respiratory tract infections in the first 6 months and T1D in a population-based cohort.

Methods | The Kassenärztliche Vereinigung Bayern processes claims data for all statutorily insured patients in Bavaria, Germany (approximately 85% of the total Bavarian population). Infants born between 2005 and 2007 were included and observed until March 2015 or last contact with a physician. Diagnoses of infection, T1D, and juvenile idiopathic arthritis (JIA, as a control autoimmune disease) were obtained using *International Classification of Diseases, Tenth Revision*, codes recorded in 3-month age intervals over 2 years (eg, birth to 2.9 months). Infections were categorized by symptoms (respiratory, gastrointestinal, dermal, and eye) and causes (viral, bacterial, and mycoses). Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals of time to T1D diagnosis by infection event, adjusting for sex and calendar month of birth. Infections were treated as binary time-varying covariates with nonexposure to a specific infection in a quarterly interval as reference category.

Kaplan-Meier analysis was used to estimate cumulative risks of T1D and JIA by respiratory tract infections or viral respiratory tract infections in the first 6 months. Differences were assessed by the log-rank test. Statistical analyses were conducted using SAS (SAS Institute), version 9.3, and R (R Foundation), version 3.0.3. Statistical significance was determined at the 5% level (2-sided). Data release was approved by the data protection officer according to German Guidelines for Secondary Data Analysis.[4]

Results | Of the 295 420 infants included (male, 55.0%), 720 were diagnosed with T1D over a median follow-up of 8.5 years (interquartile range, 7.5-9.3), for an incidence of 29 diagnoses per 100 000 children annually. At least 1 infection was reported during the first 2 years of life in 92.9% of all children, and in 96.7% of children with T1D (χ^2 $P < .001$). Most children experienced respiratory (87.1%) and viral (83.5%) infections.

Respiratory tract infections between birth and 2.9 months of age or between 3 and 5.9 months occurred in 278 children who developed T1D (38.6%) and 100 693 children who did not develop T1D (34.2%). T1D risk was increased in children who had a respiratory tract infection compared with children who had no respiratory tract infections in these age intervals (HR, 1.17 [95% CI, 1.00-1.37]) (**Figure 1**).

Viral infections occurred between birth and 5.9 months of age in 243 children who developed T1D (33.8%) and 86 758 children who did not develop T1D (29.4%). An increased T1D risk was observed compared with children without viral infections (HR, 1.19 [95% CI, 1.01-1.39]).

Respiratory tract infections occurring in both age intervals (birth to 2.9 months and 3 to 5.9 months) were reported for 56 children with T1D (7.8%). Having respiratory tract infections in both age intervals was associated with an increased T1D risk compared with having infections in only 1 age interval or having no infections (cumulative 5-year risk per 100 000: 206 for infections in both intervals, 142 for infection in 1 age interval, 118 for no infections, $P = .01$). Risk was particularly increased if the infections were caused by viruses (cumulative 5-year risk per 100 000: 270 for infections in both age intervals, 145 for infection in 1 age interval, 120 for no infections; $P < .001$, **Figure 2**). No association was found between respiratory tract infections in the first 6 months and JIA (cumulative 5-year risk per 100 000: 102 for infections in both age intervals, 99 for infection in 1 age interval, 89 for no infections; $P = .78$).

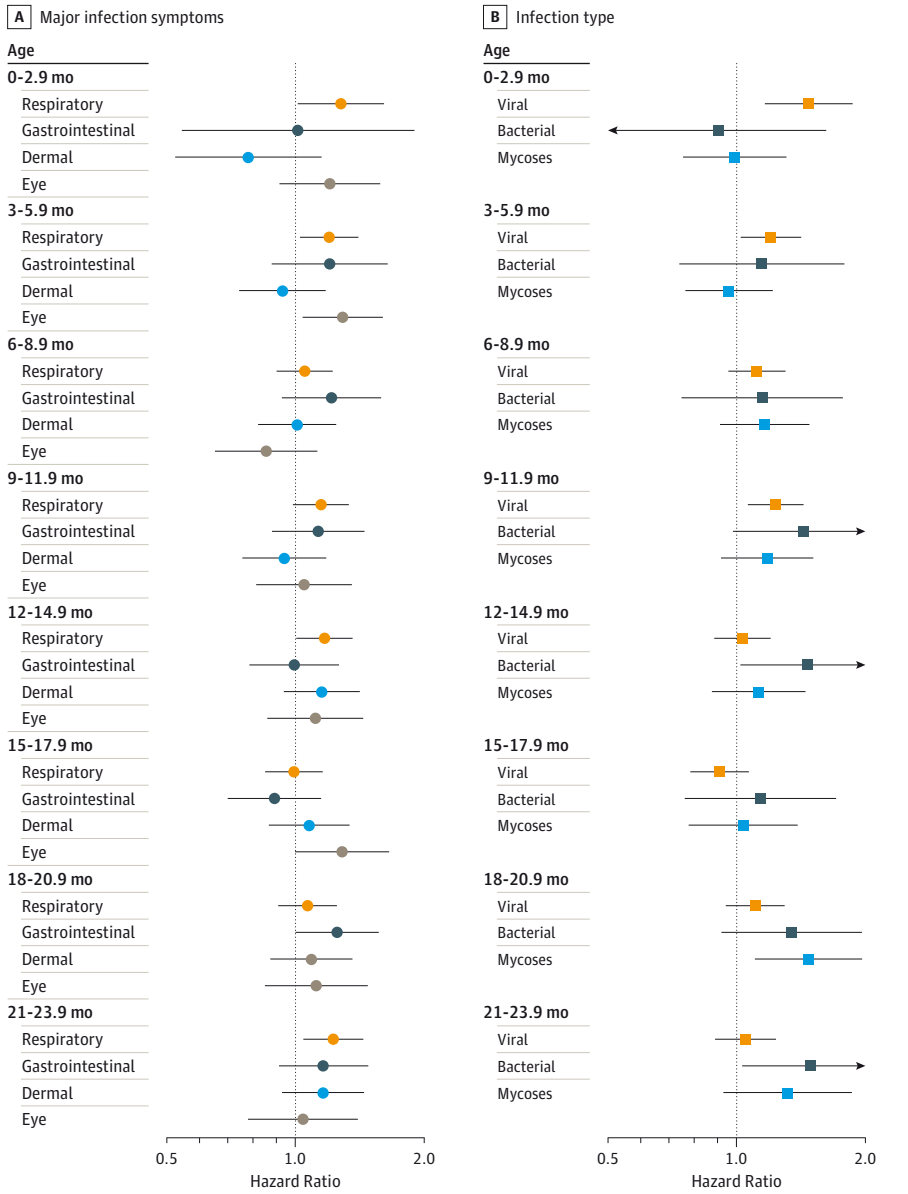
Discussion | Recurrent viral respiratory tract infections during the first 6 months were associated with T1D development by age 8 years in a large, population-based sample. It is unknown whether the association with early infections reflects increased exposure to virus or an impairment of the immune system response, perhaps due to genetic susceptibility. A similar study from Taiwan found that enterovirus infections were associated with increased T1D risk but was unable to investigate different time windows for infection exposure.[5]

We were unable to adjust for potential confounding factors such as family history of T1D or delivery mode as these data were unavailable. We did not have data on specific viral infections. Furthermore, we investigated several infection types with different exposure ages, potentially introducing multiple testing errors. However, the association of respiratory tract infections in the first 6 months with T1D is consistent with smaller studies assessing autoantibody development,[3,6] suggesting that the first half-year of life is crucial for the development of the immune system and autoimmunity.

Andreas Beyerlein, PhD
Ewan Donnachie, MSc
Sibille Jergens, MSc
Anette-Gabriele Ziegler, MD

Author Affiliations: Institute of Diabetes Research, Helmholtz Zentrum München, Munich, Germany (Beyerlein, Jergens, Ziegler); Kassenärztliche Vereinigung Bayern (Bavarian Association of Statutory Health Insurance Physicians), Munich, Germany (Donnachie).

Figure 1. Type 1 Diabetes Development Risk by Major Infection Symptoms and Infection Type Across Age Intervals Among Children



Error bars indicate 95% confidence intervals. Values adjusted for sex and month of birth.

Corresponding Author: Anette-G. Ziegler, MD, Institute of Diabetes Research, Helmholtz Zentrum München, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany (anette-g.ziegler@helmholtz-muenchen.de).

Author Contributions: Drs Beyerlein and Donnachie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Beyerlein, Ziegler.
Acquisition, analysis, or interpretation of data: Beyerlein, Donnachie, Jergens, Ziegler.
Drafting of the manuscript: Beyerlein, Ziegler.
Critical revision of the manuscript for important intellectual content: Donnachie, Jergens, Ziegler.
Statistical analysis: Beyerlein, Donnachie.
Administrative, technical, or material support: Donnachie, Jergens.
Study supervision: Ziegler.

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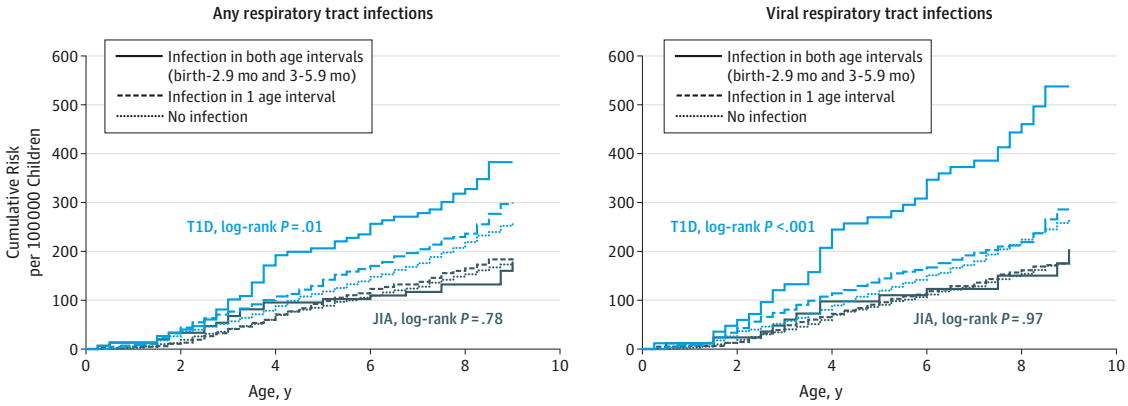
Figure 2. Type 1 Diabetes Development Risk by No. of 3-Month Age Intervals With a Respiratory Tract Infection During the First 6 Months of Life[a]



T1D										
No. at risk										
Both age intervals	15159	14825	14271	13827	10550	8499	8303	8000	7748	5874
1 Age interval	85811	83436	79889	77047	57634	63758	61988	59382	57327	43057
No infection	194449	188419	176873	166741	125600	223163	216389	203651	192540	144853
J1A										
No. at risk										
Both age intervals	15160	14892	14338	13844	10569	8499	8387	8041	7763	5892
1 Age interval	85811	83453	79920	77082	57678	63758	62001	59406	57353	43084
No infection	194449	188446	176911	166808	125679	223163	216418	203697	192618	144950

T1D indicates type 1 diabetes; JIA, juvenile idiopathic arthritis.

[a] Diagnoses of infection, T1D and JIA (as a control autoimmune disease) were obtained using *International Classification of Diseases, Tenth Revision*, codes recorded in 3-month age intervals over 2 years.

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COMMENT & RESPONSE

Noninvasive Ventilation and Outcomes Among Immunocompromised Patients

To the Editor The use of noninvasive ventilation as first-line therapy for immunocompromised patients with acute respiratory failure remains controversial.[1,2] Dr Lemiale and colleagues[3] reported the largest randomized clinical trial to date (374 immunocompromised patients) with the aim of assessing whether noninvasive ventilation could improve outcomes. No difference was found between patients treated with oxygen therapy alone or with noninvasive ventilation.

However, nearly 40% of patients in both groups received high-flow oxygen through nasal cannula. The reason for using high-flow oxygen in place of standard oxygen could be either more severe respiratory disease or changes in clinical practice in the participating centers leading to routine use of high-flow oxygen as standard therapy. A recent randomized clinical trial including 310 patients admitted to the intensive care unit for acute respiratory failure found a lower mortality rate when patients were treated with high-flow oxygen alone compared with standard oxygen or noninvasive ventilation.[4] The beneficial effects of high-flow oxygen were even more pronounced in the patients with severe hypoxemia, with a significantly reduced intubation rate. In the present study, high-flow oxygen may have masked the potential beneficial or deleterious effects of noninvasive ventilation or oxygen therapy alone.

Furthermore, the relatively low severity of respiratory distress of the patients included in the study might attenuate the importance of the findings. Nearly half had a respiratory rate below 25/min at randomization, contrasting with a low ratio of Pao_2 to fraction of inspired oxygen (Fio_2).[3] This contrast raises a question about the accuracy of the Pao_2:Fio_2 ratio estimated during spontaneous breathing. The calculation of the ratio was not described in the article and could have overestimated respiratory severity. The authors performed a post hoc subgroup analysis based on the delivered oxygen flow rate at inclusion (≤9 L/min vs >9 L/min) that did not show any difference in mortality between patients treated with noninvasive ventilation or oxygen alone. A subgroup analysis by respiratory rate might have been more discriminating.

The results of the study by Lemiale et al stand in contrast to recent findings suggesting that the use of high-flow oxygen with noninvasive ventilation could be the best strategy for immunocompromised patients.[5] The increasing use of high-flow oxygen among patients with acute respiratory failure raises questions about the most effective treatment and about what control group should be used in future