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Brief Original Contribution

Infections in Early Life and Development of Celiac Disease

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It has been suggested that early infections are associated with increased risk for later celiac disease (CD). We analyzed prospective claims data of infants from Bavaria, Germany, born between 2005 and 2007 ($n = 295{,}420$), containing information on medically attended infectious diseases according to *International Classification of Diseases, Tenth Revision*, codes in quarterly intervals. We calculated hazard ratios and 95% confidence intervals for time to CD diagnosis by infection exposure, adjusting for sex, calendar month of birth, and number of previous healthcare visits. CD risk was higher among children who had had a gastrointestinal infection during the first year of life (hazard ratio = 1.32, 95% confidence interval: 1.12, 1.55) and, to a lesser extent, among children who had had a respiratory infection during the first year of life (hazard ratio = 1.22, 95% confidence interval: 1.04, 1.43). Repeated gastrointestinal infections during the first year of life were associated with particularly increased risk of CD in later life. These findings indicate that early gastrointestinal infections may be relevant for CD development.

celiac disease; gastrointestinal infections; respiratory infections

Abbreviations: CD, celiac disease; ICD-10, *International Classification of Diseases, Tenth Revision*.

Recent studies have shown that infections in the first year of life are associated with increased risk for later celiac disease (CD) but have not been consistent as to whether respiratory or gastrointestinal infections are more relevant (1, 2). We investigated associations between types of medically attended infectious diseases and CD in a large population-based cohort. The main focus of our analyses was on infections during the first year of life, but we additionally explored associations of CD with infections up to age 2 years.

METHODS

We used claims data provided by the Kassenärztliche Vereinigung Bayerns of all ($n = 295{,}420$) statutorily insured infants born alive between 2005 and 2007 in Bavaria, Germany (92.6% of all live-born children during this period in Bavaria), from birth to a median age of 8.5 years. These data covered diagnoses from both primary care and specialized physicians (e.g., general practitioners, pediatricians, gastroenterologists, and internal medicine specialists). Diagnoses of medically attended infectious diseases and CD were obtained using *International Classification of Diseases, Tenth Revision* (ICD-10), codes recorded in quarterly calendar intervals (3). Development of CD was defined by first occurrence of the ICD-10 code K90.0. The selection and classification of relevant infection diagnoses was done as previously described for the Environmental Determinants of Diabetes in the Young (TEDDY) study (4). We distinguished infections by symptoms (mainly respiratory and gastrointestinal) and causes (mainly viral and bacterial) according to their ICD-10 codes (see Web Table 1 (available at https://academic.oup.com/aje) for details). Infections with unknown causes were classified according to their symptoms only. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals for time to CD diagnosis according to infection exposure, adjusting for sex, calendar month of birth, and the number of previous healthcare visits (as a proxy for comorbidities). Infections were treated as separate, individual binary covariates with nonexposure to a specific infection as the referent: 1) during the whole first year of life and 2) in quarterly intervals during the first 2 years of life (i.e., we calculated

a separate Cox model for each infection type—including "any" infections, i.e., irrespective of symptoms or causes—and exposure interval). In sensitivity analyses, we: 1) adjusted all Cox models for the number of previous quarterly intervals with infections of the same type, 2) excluded children with CD diagnoses recorded in only 1 quarterly interval in order to reduce the number of potential false-positive cases, and 3) excluded infections occurring within 12 months prior to CD diagnosis, to exclude potential bias by symptoms of undiagnosed CD. Cumulative risks of CD after age 12 months were compared according to the number of quarterly intervals with respiratory or gastrointestinal infections during the first year of life, using Kaplan-Meier analysis and log-rank tests.

To avoid reverse-causation bias, time at risk for CD was measured after the respective infection exposure period in each analysis. Terms for interaction of the respective predictor variables with time were calculated to check the proportional hazards assumption. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and R, version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was determined at the 5% level (2-sided). Data release was approved by the data protection officer in accordance with the German Guidelines for Secondary Data Analysis (5).

RESULTS

In total, 853 children (0.29%; 415 (48.7%) boys) were diagnosed with CD at a median age of 5.0 years, of which 820 (95.5%) developed CD after the first year of life (see Web Table 2 for detailed characteristics of study subjects by infection exposure). In 488 cases (57.2%), CD diagnosis was recorded in more than 1 quarterly interval. CD risk was higher in children who had had a medically attended gastrointestinal infection during the first year of life (hazard ratio = 1.32, 95% confidence interval: 1.12, 1.55), accounting for an incidence rate of 46/100,000 person-years compared to a rate of 34/100,000 person-years in children without a gastrointestinal infection. The association was slightly weaker in children who had had a medically attended respiratory infection during the first year (hazard ratio = 1.22, 95% confidence interval: 1.04, 1.43), with incidence rates of 38/100,000 person-years and 32/100,000 person-years in children with and without respiratory infections, respectively. The proportional hazards assumption was not rejected for either of the models. These associations were relatively constant across all quarterly age intervals during the first 2 years of life and thereafter, but they could not be attributed to either viral or bacterial infections only (Figure 1) and were very similar when we adjusted for previous infections of the same type (Web Figure 1) or restricted the analysis to CD diagnoses recorded in more than 1 quarterly interval (Web Figure 2) or to infections occurring more than 12 months prior to CD diagnosis (data not shown). Repeated respiratory and, particularly, gastrointestinal infections during the first year of life were associated with increased cumulative risk of CD in later life (Figure 2).

DISCUSSION

Medically attended gastrointestinal and respiratory infections were associated with CD development by age 8 years in a large, population-based sample. Particularly strong associations were observed for repeated gastrointestinal infections in the first year of life. Early gastrointestinal infections may therefore be relevant for CD development rather than for type 1 diabetes development, for which early respiratory infections have been found to be more relevant in the same data (3).

Our data are consistent with a similar prospective study that interrogated infection records, which showed strong associations of CD with gastrointestinal infections during

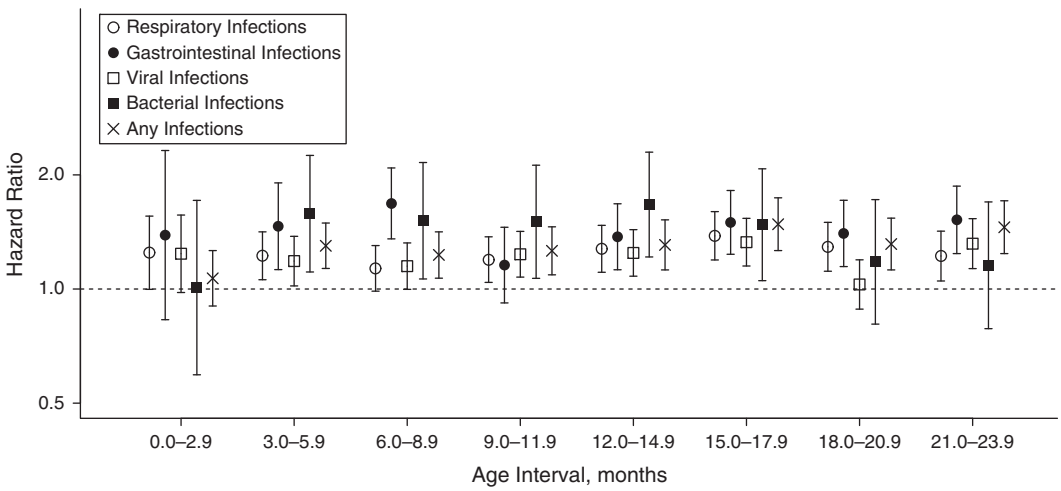

Figure 1. Hazard ratios (dots) and 95% confidence intervals (bars) for celiac disease development according to types of medically attended infectious diseases, Bavaria, Germany, 2005–2015. Estimates were based on data on 295,420 infants born between 2005 and 2007, with adjustment for sex, month of birth, and number of previous healthcare visits. Time at risk for celiac disease was measured after the respective infection exposure period for each model.

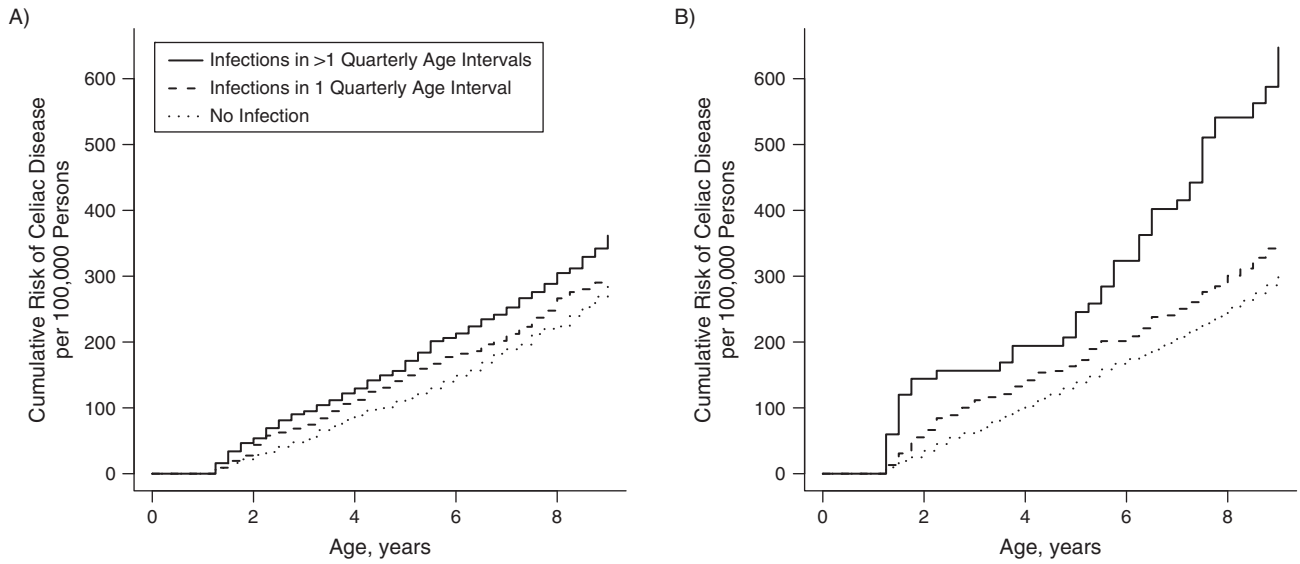

Figure 2. Cumulative risk of celiac disease development after age 12 months according to number of quarterly intervals with a medically attended infection during the first year of life, Bavaria, Germany, 2005–2015. A) Respiratory infection (log-rank $P = 0.006$); B) gastrointestinal infection (log-rank $P < 0.001$). Estimates were based on data on 295,420 infants born between 2005 and 2007.

the first 12 months of life (2) and partly also with another in which a positive association with respiratory infections was observed (1). It should be mentioned, however, that in these studies infections were defined based on parental reports (1) or hospitalization records (2), respectively, indicating different levels of infection severity compared with our data. Further, our CD diagnoses could not be validated with data from other sources, such as questionnaires (1) or pathology reports (2), but we assume their validity is relatively high, because the diagnoses were coded by physicians for the purpose of remuneration (e.g., to support fees claimed for diagnostic testing). Neither of the previous studies had data on onset of CD-associated autoantibodies, so it remains unclear from these findings whether early infections trigger the disease or rather contribute to susceptibility. Several mechanisms have been suggested for early infections to potentially cause CD, including alterations of the microbiome or induction of specific immune responses, such as type I interferons (6). Our data do support further investigation of these potential pathways; however, given that we observed the strongest associations for repeated gastrointestinal infections—but no major role for either viral or bacterial infections—our results might suggest that it is a persistent state of inflammation in the gastrointestinal tract in early life rather than a specific infectious agent that leads to increased CD risk.

Unfortunately, our data do not contain information about whether CD diagnosis was based on clinical, serological, and/or histopathologic findings or about socioeconomic status, infant feeding, or antibiotic use. These might be potential confounders in this context. Further, we investigated several infection types with different exposure ages, potentially introducing multiple testing errors.

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