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Infections in Early Life and Development of Celiac Disease

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Am J Epidemiol. 2017;186(11):1277-1280.

Abstract and Introduction

Abstract

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.

Introduction

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 (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.

Web Table 1. Infections were categorized by symptoms (respiratory, gastrointestinal, dermal, eye, and other) and causes (viral, bacterial, mycoses, parasites, or unknown) based on their ICD-10 code as tabulated below. For each child, the presence of infections (binary variable) from a specific category – but not their frequency – was reported in quarterly intervals. For example, if a child was diagnosed with a gastrointestinal infection in January, March and November of the same year, respectively, it would have a gastrointestinal infection record in the first and fourth quarter, but not in the second and third quarter of this particular year.

ICD-10 code	Categorization by symptoms	Categorization by causes
A00	gastrointestinal	bacterial
A01	gastrointestinal	bacterial

A02	gastrointestinal	bacterial
A03	gastrointestinal	bacterial
A04	gastrointestinal	bacterial
A05	gastrointestinal	bacterial
A06	gastrointestinal	parasites
A07	gastrointestinal	parasites
A08.0	gastrointestinal	viral
A08.1	gastrointestinal	viral
A08.2	gastrointestinal	viral
A08.3	gastrointestinal	viral
A08.4	gastrointestinal	viral
A08.5	gastrointestinal	unknown
A09	gastrointestinal	unknown
A16	other	bacterial
A21	other	bacterial
A28	other	bacterial
A37	other	bacterial
A38	respiratory	bacterial
A40	other	bacterial
A41	other	bacterial
A42	other	bacterial
A49	other	bacterial
A52	other	bacterial
A54	other	bacterial
A66	other	bacterial
A68	other	bacterial
A69	other	bacterial
A87	other	viral
A90	other	viral
A93	other	viral
A94	other	viral
A98	other	viral
B00	other	viral
B01	other	viral
B02	other	viral
B05	other	viral
B06	other	viral
B07	other	viral
B08	other	viral
B09	other	viral
B19	other	viral

B26	other	viral
B27	other	viral
B30	other	viral
B33	other	viral
B34	other	viral
B35	other	mycoses
B36	other	mycoses
B37	other	mycoses
B43	other	mycoses
B48	other	mycoses
B49	other	mycoses
B50	other	parasites
B65	other	parasites
B68	other	parasites
B80	other	parasites
B82	other	parasites
B85	other	parasites
B86	other	parasites
B89	other	parasites
B95	other	bacterial
B97	other	viral
B99	other	unknown
G00	other	bacterial
H00	eye	unknown
H01	eye	unknown
H04	eye	unknown
H10.0	eye	unknown
H10.2	eye	unknown
H10.3	eye	unknown
H10.4	eye	unknown
H10.5	eye	unknown
H10.8	eye	unknown
H10.9	eye	unknown
H60.0	other	unknown
H60.3	other	unknown
H60.9	other	unknown
H65	respiratory	unknown
H66	respiratory	unknown
H70.0	respiratory	unknown
H70.9	respiratory	unknown
H73.0	respiratory	unknown

H92	respiratory	unknown
I30.1	other	unknown
I88.0	other	unknown
I88.9	other	unknown
I89.1	other	unknown
J00	respiratory	viral
J01	respiratory	unknown
J02.0	respiratory	bacterial
J02.8	respiratory	viral
J02.9	respiratory	viral
J03.0	respiratory	bacterial
J03.8	respiratory	viral
J03.9	respiratory	viral
J04	respiratory	viral
J05	respiratory	viral
J06	respiratory	viral
J09	respiratory	viral
J10	respiratory	viral
J11	respiratory	viral
J12	respiratory	viral
J13	respiratory	bacterial
J14	respiratory	bacterial
J15	respiratory	bacterial
J18	respiratory	unknown
J20.0	respiratory	bacterial
J20.1	respiratory	bacterial
J20.2	respiratory	bacterial
J20.3	respiratory	viral
J20.4	respiratory	viral
J20.5	respiratory	viral
J20.6	respiratory	viral
J20.7	respiratory	viral
J20.8	respiratory	unknown
J20.9	respiratory	unknown
J21	respiratory	unknown
J22	respiratory	unknown
J32.0	respiratory	unknown
J32.2	respiratory	unknown
J32.8	respiratory	unknown
J32.9	respiratory	unknown
J35.9	respiratory	unknown

J38.5	respiratory	unknown
J40	respiratory	unknown
J41	respiratory	unknown
J42	respiratory	unknown
J44.8	respiratory	unknown
J45.1	respiratory	unknown
J45.8	respiratory	unknown
J45.9	respiratory	unknown
J46	respiratory	unknown
J85.1	other	bacterial
J98	respiratory	unknown
K04.6	other	unknown
K05	other	unknown
K12	other	unknown
K13.7	other	unknown
K14.1	other	unknown
L00	dermal	bacterial
L01	dermal	bacterial
L02.1	dermal	bacterial
L02.2	dermal	bacterial
L02.3	dermal	bacterial
L02.4	dermal	bacterial
L02.9	dermal	bacterial
L03	dermal	bacterial
L04	dermal	unknown
L08	dermal	bacterial
M30.3	other	unknown
M72.6	other	bacterial
N10	other	unknown
N11.9	other	unknown
N30	other	unknown
N34.1	other	unknown
N39	other	unknown
N45.9	other	unknown
N48.1	other	unknown
N48.2	other	unknown
N51.2	other	unknown
N61	other	bacterial
N76.2	other	unknown
N77.1	other	unknown
P36	other	unknown

P39.0	other	unknown
P39.1	eye	unknown
P39.2	other	unknown
P39.3	other	unknown
P39.4	dermal	unknown
P39.8	other	unknown
P39.9	other	unknown
P58.2	other	unknown
R05	respiratory	unknown
R06.2	respiratory	unknown
R06.7	respiratory	viral
R07.0	respiratory	unknown
R11	gastrointestinal	unknown
R21	dermal	unknown
R50	fever	unknown
R56.0	other	unknown
R59	other	unknown
T88.0	other	unknown

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 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).

Web Table 2. Characteristics of study subjects according to records of medically attended infections during the first year of life.

	All children (n=295,420)	**Children with ≥ 1 respiratory infections (n=203,160)**	**Children with ≥ 1 gastrointestinal infections (n=54,581)**
Total follow-up, years (median)	2,349,386 (8.5)	1,640,579 (8.5)	440,595 (8.5)
Celiac disease, n (%)	853 (0.29 %)	626 (0.31 %)	203 (0.37 %)
Sex, n (%)			
Males	162,448 (55.0	115,103 (56.7 %)	31,470 (57.6 %)

	%)		
Females	132,972 (45.0 %)	88,057 (43.3 %)	23,111 (42.3 %)
Season of birth, n (%)			
March to May	73,639 (24.9 %)	51,422 (25.3 %)	13,353 (24.5 %)
June to August	77,996 (26.4 %)	55,336 (27.2 %)	15,361 (28.1 %)
September to November	73,218 (24.8 %)	49,470 (24.4 %)	13,716 (25.1 %)
December to February	70,567 (23.9 %)	46,932 (23.1 %)	12,151 (22.3 %)
Number of previous healthcare visits, n (%)			
0–3 visits	85,333 (28.9 %)	38,829 (19.1 %)	7,850 (14.4 %)
4–6 visits	146,733 (49.7 %)	109,846 (54.1 %)	27,560 (50.5 %)
7–9 visits	51,980 (17.6 %)	44,086 (21.7 %)	14,634 (26.8 %)
≥ 10 visits	11,374 (3.8 %)	10,399 (5.1 %)	4,537 (8.3 %)

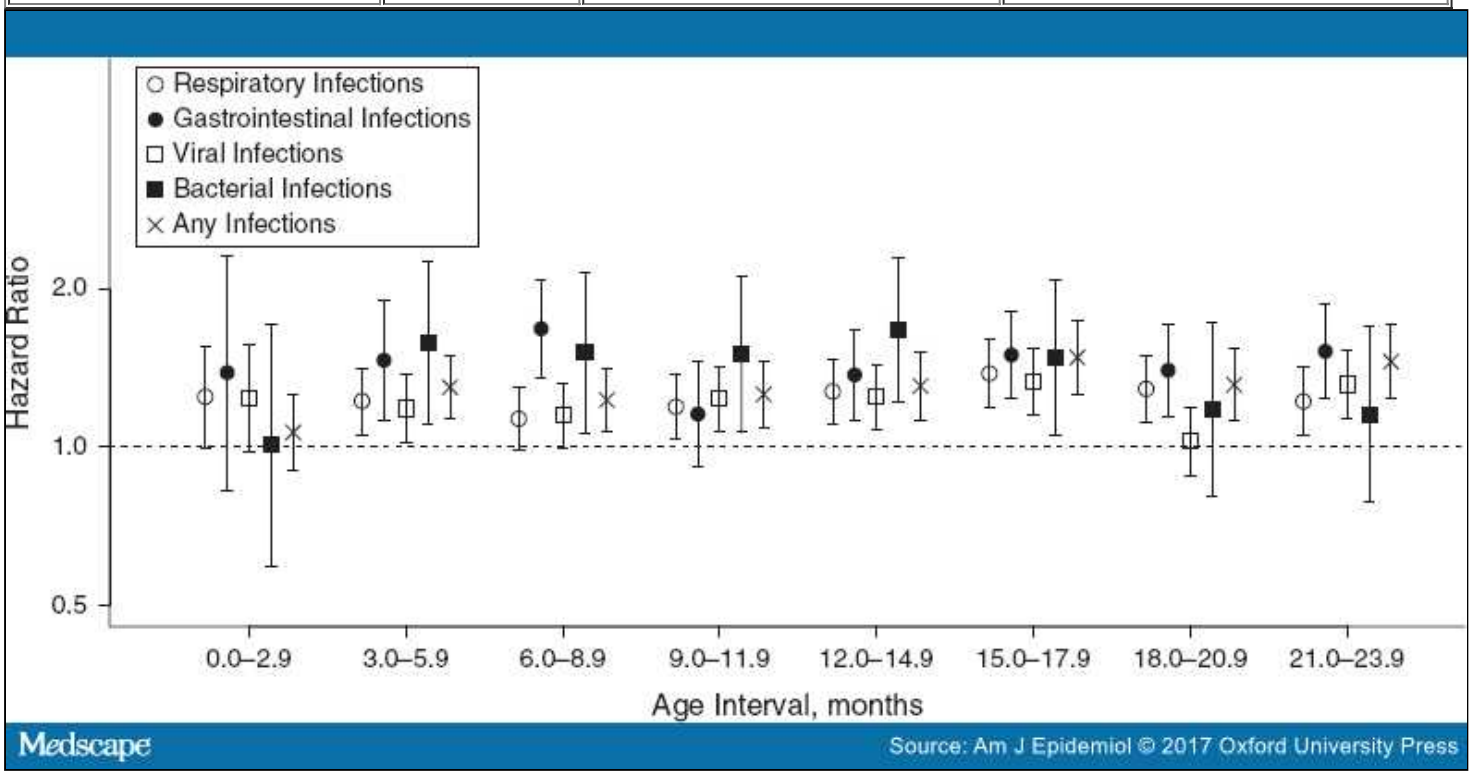


Figure 1.

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.

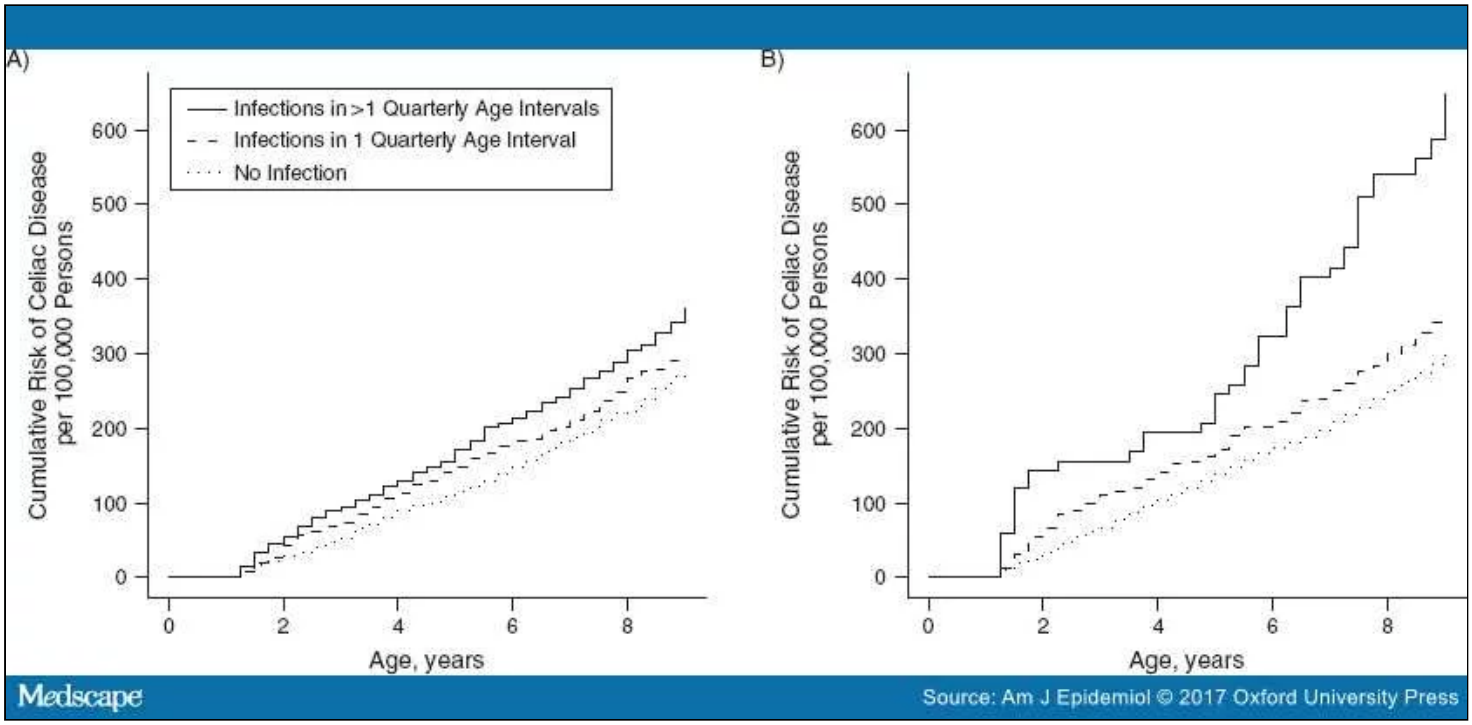
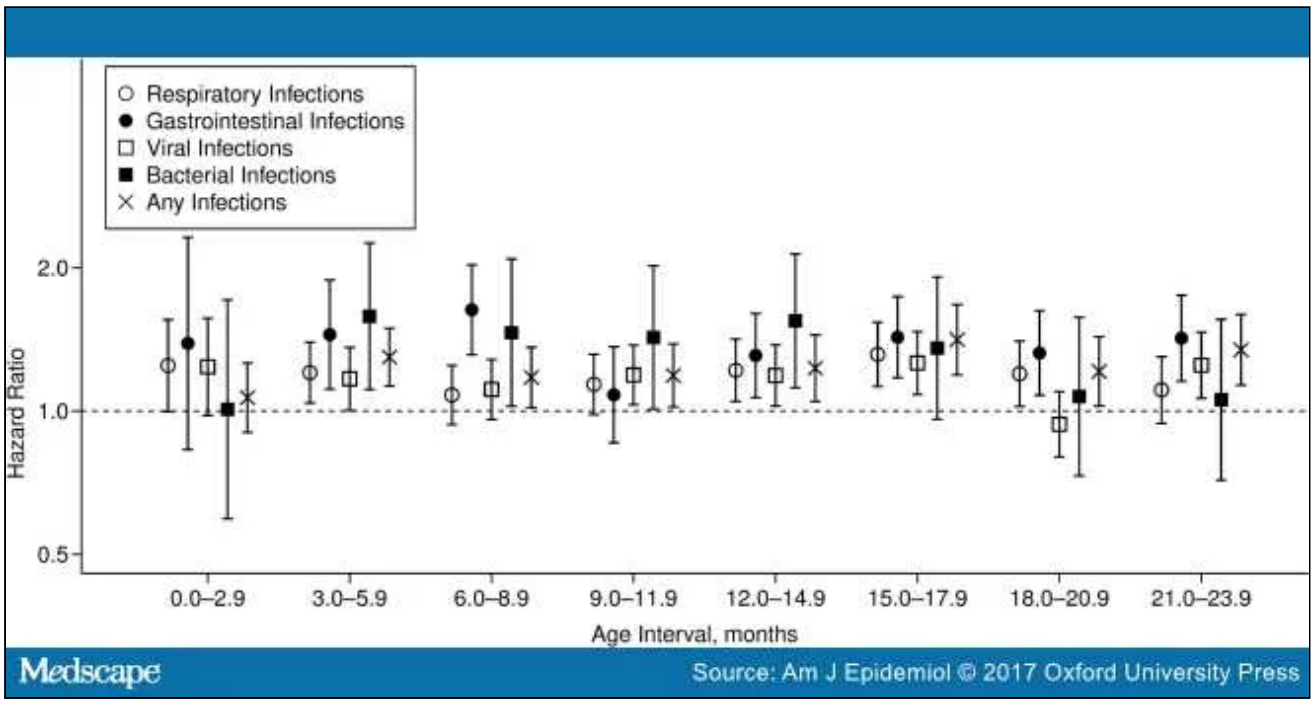


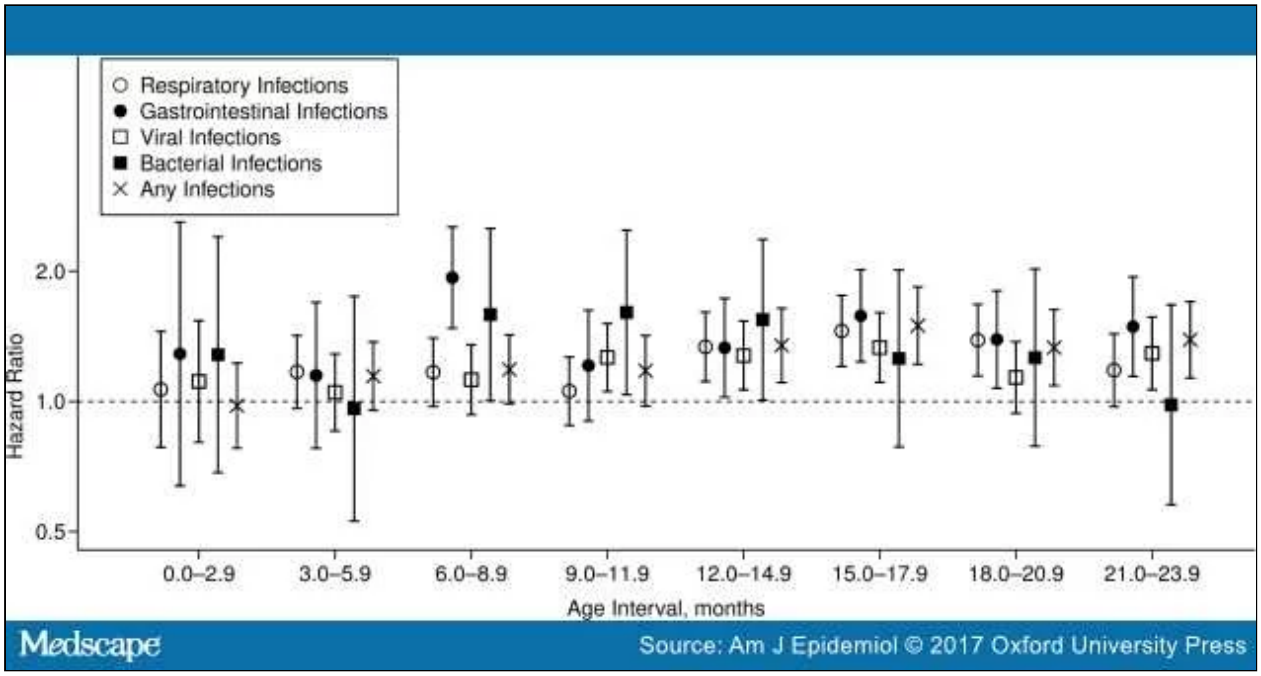
Figure 2.

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.



Web Figure 1.

Hazard ratios (dots) and 95% confidence intervals for celiac disease development by types of medically attended infectious diseases, adjusted for sex, month of birth, number of previous healthcare visits, and number of previous quarterly intervals with infections of the same type, based on data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007. Time at risk for CD was measured after the respective infection exposure period for each model.



Web Figure 2.

Hazard ratios (dots) and 95% confidence intervals for celiac disease development as recorded in at least two quarterly intervals by types of medically attended infectious diseases, adjusted for sex, month of birth and number of previous healthcare visits, based on data of n=295,420 infants from Bavaria, Germany, born between 2005 and 2007. Time at risk for CD was measured after the respective infection exposure period for each model.

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 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.

References

1. Mårild K, Kahrs CR, Tapia G, et al. Infections and risk of celiac disease in childhood: a prospective nationwide cohort study. *Am J Gastroenterol*. 2015;110(10):1475–1484.

2. Canova C, Zabeo V, Pitter G, et al. Association of maternal education, early infections, and antibiotic use with celiac disease: a population-based birth cohort study in northeastern Italy. *Am J Epidemiol*. 2014;180(1):76–85.

3. Beyerlein A, Donnachie E, Jergens S, et al. Infections in early life and development of type 1 diabetes. *JAMA*. 2016;315(17): 1899–1901.

4. Lönnrot M, Lynch K, Larsson HE, et al. A method for reporting and classifying acute infectious diseases in a prospective study of young children: TEDDY. *BMC Pediatr*. 2015;15:24.

5. Swart E, Gothe H, Geyer S, et al. [Good Practice of Secondary Data Analysis (GPS): guidelines and recommendations]. *Gesundheitswesen*. 2015;77(2):120–126.

6. Sollid LM, Jabri B. Triggers and drivers of autoimmunity: lessons from coeliac disease. *Nat Rev Immunol*. 2013;13(4): 294–302.

Acknowledgments
This work was supported by the JDRF (grant JDRF-No 2-SRA-2015-13-Q-R), funding from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.), by the Leona M. and Harry B. Helmsley Charitable Trust (grant 2015PG-T1D072), and by iMed—the Helmholtz Initiative on Personalized Medicine.

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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

Am J Epidemiol. 2017;186(11):1277-1280.