Infectious Disease and Risk of Later Celiac Disease in Childhood

WHAT’S KNOWN ON THIS SUBJECT: Genetic and environmental factors affect the risk of developing CD. Results of earlier research suggested that breastfeeding during gluten introduction protects against future CD, but the role of infection in the pathogenesis of CD is unknown.

WHAT THIS STUDY ADDS: Through prospectively collected, population-based data, we assessed the risk of CD in relation to early infections and infant feeding patterns. Children with any infection or gastroenteritis at the time of gluten introduction were at no increased risk of later CD.

abstract

OBJECTIVE: The goal was to examine whether parent-reported infection at the time of gluten introduction increases the risk of future celiac disease (CD).

METHODS: Through the population-based All Infants in Southeast Sweden study, parents recorded data on feeding and infectious disease prospectively. Complete data on gluten introduction and breastfeeding duration were available for 9408 children. Those children had 42 826 parent-reported episodes of infectious disease in the first year of life (including 4003 episodes of gastroenteritis). We identified 44 children with biopsy-verified CD diagnosed after 1 year of age, and we used Cox regression to estimate the risk of future CD for children with infection at gluten introduction.

RESULTS: Eighteen children with CD (40.9%) had an infection at the time of gluten introduction, compared with 2510 reference individuals (26.8%; \( P = .035 \)). Few children had gastroenteritis at the time of gluten introduction (1 child with CD [2.3%] vs 166 reference individuals [1.8%]; \( P = .546 \)). With adjustment for age at gluten introduction and breastfeeding duration, we found no association between a future diagnosis of CD and either any infection (adjusted hazard ratio: 1.8 [95% confidence interval: 0.9–3.6]) or gastroenteritis (adjusted hazard ratio: 2.6 [95% confidence interval: 0.2–30.8]) at the time of gluten introduction. We found no associations between breastfeeding duration, age at gluten introduction, and future CD.

CONCLUSION: These results indicate that parent-reported infection at the time of gluten introduction is not a major risk factor for CD. *Pediatrics* 2010;125:e530–e536
Celiac disease (CD) is an immune-mediated disease that occurs in ~1% of the Western population. Although almost all individuals with CD are HLA-DQ2- or DQ8-positive, twin studies imply that environmental factors affect the risk of developing CD.

Several studies have investigated the effect of breastfeeding on the risk of CD. Although most studies suggested a greater risk of CD for infants with short breastfeeding duration, research findings were inconsistent. There is no consensus on the role of environmental factors with respect to the risk of CD. Altogether, studies have suggested that breastfeeding at gluten introduction protects against CD. The majority of earlier studies were based on retrospectively collected feeding data, however.

Gastroenteritis is common among infants and young children. Through increased mucosal permeability, gastrointestinal infection may allow absorption of intact gliadin molecules, leading to an immune response that initiates CD. This might explain the finding of frequent rotavirus infections in children with future CD autoimmunity. We used prospectively collected data from the population-based All Infants in Southeast Sweden (ABIS) study to evaluate the independent associations of breastfeeding and childhood infections with the risk of developing CD.

**METHODS**

**Participants**

Between October 1, 1997, and October 1, 1999, all infants born in southeast Sweden were invited to participate in the ABIS cohort project. This project examines the role of environmental factors in the development of immune-mediated diseases. Of the 21,700 infants born during the study period, the parents of 17,055 children gave their informed consent for participation. The mothers received a birth questionnaire in the maternity ward, which was completed by 16,286 mothers in the maternity ward or at home. Participating parents were asked to maintain a diary (distributed in the maternity ward) regarding diet and infectious diseases in the child’s first year of life, including dates of introduction and cessation of breastfeeding, dates of first gluten-containing foods, and dates of all infections the child experienced during the first year of life (Fig 1, which is published as supporting information). The diaries were completed prospectively at home and were collected at the child health center after 1 year. In total, diary data were collected for 9,849 children.

The majority of children with CD were identified through a study on symptoms of CD. In 2007–2008, the same 8 pediatric departments that participated in the study published in 2004 were contacted again and were asked to report on children in the ABIS study with biopsy-verified CD (villus atrophy). CD-consistent symptoms and antibody markers were required for the diagnosis of CD (additional details were reported previously). The onset of CD was defined as the date of the first positive small-intestinal biopsy findings. The ABIS study child population was not screened actively for CD.

The control group in our analyses consisted of all children included in the ABIS project for whom we had diary data on breastfeeding and the date of gluten introduction and who had not received a diagnosis of CD. We restricted this study to individuals with prospective data on both breastfeeding duration and date of gluten introduction. The rationale for this restriction was that gluten exposure is a prerequisite for later CD and short breastfeeding duration is a likely risk factor for later CD.

**Statistical Analyses**

To avoid potential recall bias, we excluded individuals with a diagnosis of CD before the age of 1 year. Therefore, follow-up monitoring began at 1 year of age. The risk of CD was estimated through Cox regression analysis in which the time scale was time (in years) from 1 year of age until the end of the study (December 1, 2006), death, or the date of CD. Our a priori main analyses addressed the risk of CD in children with (1) any parent-reported infection, including gastroenteritis, or (2) parent-reported gastroenteritis at the time of gluten introduction. Children whose parents reported repeated vomiting, diarrhea, or stomach flu for the child were defined as having gastroenteritis. After a discussion regarding the incubation periods of different infectious diseases and their potential effects on the immune system (A. Ternhag, MD, PhD, personal verbal communication, 2008), we defined infection onset at the time of gluten introduction as the reported onset of any infection (or gastroenteritis) occurring ≤21 days before gluten introduction or ≤7 days after gluten introduction (ie, an infection occurring within 28 days around gluten introduction) (Fig 2, which is published as supporting information).

Because the numbers of infections were not normally distributed, we used the Mann-Whitney U test to compare infectious disease load during the first year for children with and without a diagnosis of CD. We calculated the risk of CD according to the age at gluten introduction, the age at the end of breastfeeding, and the presence of infections (any infection or gastroenteritis). Because only 0.5% of children received gluten before 60 days of age and <5% from day 240 onward, we estimated the risk of CD only for children who received their first
portions of gluten between month 3 and month 8.

It is possible that infection at the time of gluten introduction constitutes a risk factor for CD only at certain sensitive ages during the first year of life. Therefore, we examined the interactions between ages at gluten introduction and the end of breastfeeding and infectious disease.

In a final model, we tested the association between future CD and infection at the time of gluten introduction, with adjustment for age at gluten introduction, presence of infection during the first year of life, and age at the end of breastfeeding. A similar model was used to examine the association between future CD and gastroenteritis at the time of gluten introduction.

We did not adjust for maternal age, maternal education, or first-degree relative with type 1 diabetes mellitus/CD because these factors were not associated with the risk of infection (Table 5). We did not adjust for maternal age and month of birth because month of birth is likely to be a marker for exposure to infectious disease and therefore cannot be confounders. We did not adjust for month of birth because month of birth is likely to be a marker for exposure to infectious disease and not a true confounder. Confidence intervals (CIs) not including 1 and

**RESULTS**

**Background Data**

Diary data were collected for 9849 children 1 year of age. There were data on breastfeeding duration for 9644 infants (97.9%). According to diary data, 9529 children (96.8%) had received gluten before 1 year of age. We had data on both breastfeeding duration and date of gluten introduction for 9414 children (95.6%). At the end of the follow-up study, children were 8 years of age and there were 50 cases of CD (Table 1), which corresponded to a prevalence of diagnosed CD of 1 case per 188 children (0.53%).

In the first year of life, 92.4% of the children (8702 of 9414 children) had ≥1 parent-reported infectious disease; the average number of infections between 0 and 12 months was 4.6 (Table 2). In total, we had data on 42,826 episodes of infectious disease reported with date of onset (Table 6), which is published as supporting information. Of those infections, 239 episodes occurred in children with CD. Of 9414 children, 3214 (34.1%) had ≥1 episode of gastroenteritis in the first year of life.

Raw data on the exact ages at all reported infections, gluten introduction, and the end of breastfeeding for individuals who had a diagnosis of CD after 1 year of age are presented in Fig 1. Six of the children with CD had a diagnosis of CD before 1 year of age and were excluded from the main analyses, which therefore included data for 9408 children (CD, n = 44, not CD, n = 9364). The follow-up time for the 9408 children (starting at 1 year of age) was 68,206 person-years. Except where explicitly stated, all analyses were restricted to data for those 9408 children.

Risk factors for future CD included having a first-degree relative with type 1 diabetes mellitus or CD (Table 1). Also, female gender was associated with increased risk of CD (Table 1).

**Breastfeeding Duration, Introduction of Gluten, and Risk of CD**

No individual with CD had received gluten in the first 3 months of life, compared with 1.1% of reference individuals. Almost one half of participating children were breastfed for >10 months (Table 2). Gluten was most often introduced during months 5 and 6. Ages at the introduction of gluten and the end of breastfeeding were not associated with future CD (Table 2).

**Any Infection, Gastroenteritis, and Risk of CD**

Infection at the time of gluten introduction was associated with increased risk of future CD (hazard ratio [HR]: 1.9 [95% CI: 1.0–3.4]; P = .056), whereas gastroenteritis at the time of gluten introduction was not (HR: 1.3 [95% CI:

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**TABLE 1** Background Characteristics According to Presence of Future CD

<table>
<thead>
<tr>
<th></th>
<th>Reference (N = 9364)</th>
<th>CD (N = 44)</th>
<th>Unadjusted HR for CD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>4534 (48.4)</td>
<td>31 (70.5)</td>
<td>2.5 (1.3–4.8)</td>
</tr>
<tr>
<td>Age on December 1, 2006, mean, y</td>
<td>8.3</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with type 1 diabetes mellitus, n (%)</td>
<td>225 (2.4)</td>
<td>6 (13.6)</td>
<td>6.3 (2.6–15.0)</td>
</tr>
<tr>
<td>First-degree relative with CD, n (%)</td>
<td>119 (1.3)</td>
<td>2 (4.5)</td>
<td>3.7 (0.9–15.2)</td>
</tr>
<tr>
<td>Maternal education of &gt;12 y (university education), n (%)</td>
<td>3136 (34.1)</td>
<td>19 (44.3)</td>
<td>1.6 (0.9–3.1)</td>
</tr>
<tr>
<td>Mother’s age at child’s birth, mean ± SD, y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.8 ± 4.5</td>
<td>29.0 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>Mother’s age at child’s birth, mean ± SD, y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4576 (48.8)</td>
<td>16 (39.0)</td>
<td>0.6 (0.3–1.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>For maternal education, 8197 reference mothers and 41 mothers with children with CD had available data.

<sup>b</sup>For maternal age, 9182 reference mothers and 41 mothers with children with CD had available data.

<sup>c</sup>P = .290.
**TABLE 2** Infant Feeding Patterns, Infections, and Risk of Future CD

<table>
<thead>
<tr>
<th>Age initially exposed to gluten, n (%)</th>
<th>Reference (N = 9364)</th>
<th>CD (N = 44)</th>
<th>Unadjusted HR for CD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 mo (0–59 d)</td>
<td>44 (0.5)</td>
<td>0 (0.0)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>3–4 mo (60–119 d)</td>
<td>630 (6.7)</td>
<td>3 (6.8)</td>
<td>1.0 (0.3–3.3)</td>
</tr>
<tr>
<td>5–6 mo (120–179 d)</td>
<td>5599 (59.8)</td>
<td>27 (61.4)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>7–8 mo (180–239 d)</td>
<td>2691 (28.7)</td>
<td>14 (31.8)</td>
<td>1.1 (0.6–2.0)</td>
</tr>
<tr>
<td>9–10 mo (240–319 d)</td>
<td>384 (4.1)</td>
<td>0 (0.0)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>11–12 mo (320–365 d)</td>
<td>16 (0.2)</td>
<td>0 (0.0)</td>
<td>Not estimated</td>
</tr>
<tr>
<td>End of breastfeeding, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 mo (0–59 d)</td>
<td>620 (6.6)</td>
<td>2 (4.5)</td>
<td>0.7 (0.2–3.1)</td>
</tr>
<tr>
<td>3–4 mo (60–119 d)</td>
<td>592 (6.3)</td>
<td>2 (4.5)</td>
<td>0.7 (0.2–3.2)</td>
</tr>
<tr>
<td>5–6 mo (120–179 d)</td>
<td>743 (7.9)</td>
<td>1 (2.3)</td>
<td>0.3 (0.0–2.1)</td>
</tr>
<tr>
<td>7–8 mo (180–239 d)</td>
<td>1527 (16.3)</td>
<td>10 (22.7)</td>
<td>1.4 (0.7–3.1)</td>
</tr>
<tr>
<td>9–10 mo (240–319 d)</td>
<td>1712 (18.3)</td>
<td>10 (22.7)</td>
<td>1.3 (0.6–2.8)</td>
</tr>
<tr>
<td>11–12 mo (320–365 d)</td>
<td>4170 (44.5)</td>
<td>19 (43.2)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

**TABLE 3** Age at Gluten Exposure, Infectious Diseases, and Risk of CD

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>HR (95% CD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11–12</td>
<td>1.5 (0.3–3.2)</td>
</tr>
<tr>
<td>9–10</td>
<td>2.0 (0.4–9.5)</td>
</tr>
<tr>
<td>7–8</td>
<td>4.0 (0.8–19.2)</td>
</tr>
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</tr>
<tr>
<td>3–4</td>
<td>0.8 (0.2–2.9)</td>
</tr>
</tbody>
</table>

**TABLE 4** End of Breastfeeding, Infectious Diseases, and Risk of CD

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11–12</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>9–10</td>
<td>2.0 (0.4–9.5)</td>
</tr>
<tr>
<td>7–8</td>
<td>4.0 (0.8–19.2)</td>
</tr>
<tr>
<td>5–6</td>
<td>2.8 (1.1–7.0)</td>
</tr>
<tr>
<td>3–4</td>
<td>0.8 (0.2–2.9)</td>
</tr>
</tbody>
</table>

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0.2–9.4]) (Table 2). However, in none of these analyses did we adjust for the main effects (ages at gluten introduction and at infection/gastroenteritis). Among the 2528 children with infection at the time of gluten introduction, there were 18 individuals with future CD (expected number: 11.8), compared with 26 among the 6880 children without infection at the time of gluten introduction (P = .035, $\chi^2$ test). One (0.60%) of 167 children with gastroenteritis at the time of gluten introduction developed CD (expected number: 0.8), as opposed to 43 (0.47%) of 9241 children without gastroenteritis at gluten introduction (P = .546, Fisher’s exact test). Individuals with and without CD had otherwise similar numbers of infections and episodes of gastroenteritis during the first year of life (Table 2). The association between any infection at the time of gluten introduction and future CD remained statistically significant when we included the 6 individuals with CD diagnosed before 1 year of age (HR: 1.8 [95% CI: 1.0–3.2]; P = .038). In that analysis, we started follow-up monitoring at the time of gluten introduction.

To discriminate further between the increased risk of CD attributable to any infection and dietary practice, we studied age at gluten introduction, duration of any breastfeeding, and the relationship between infectious disease and future CD separately. Tables 3 and 4 show that the highest risk estimates for CD were seen when parents reported infections just after gluten introduction or coinciding with the end of breastfeeding. Age at infection was not statistically significantly associated with future CD, although children with a reported infection at 7 to 8 months of age were at 1.8-fold increased risk of CD (Table 2).
In a final model, we adjusted for age at gluten introduction, age at the end of breastfeeding, and age at infection (or gastroenteritis). In this model, with main effects taken into consideration, we found no statistically significant association between infection at the time of gluten introduction (adjusted HR: 1.8 [95% CI: 0.9–3.6]; P = .111) or gastroenteritis at the time of gluten introduction (adjusted HR: 3.6 [95% CI: 0.2–30.8]; P = .439) and future CD (Table 7, which is published as supporting information).

**DISCUSSION**

This study is part of a population-based cohort study including nearly 10 000 children. The prevalence of CD in our cohort was 0.53%. Mäki et al reported CD prevalence rates of 0.3% in children before screening and 1% in children after screening. The follow-up period and the identification method limited our study to clinically detected childhood cases.

Having a first-degree relative with type 1 diabetes mellitus or CD was a risk factor for future CD (Table 1). This is consistent with previous work performed by our group, which showed an association between CD and type 1 diabetes mellitus. In addition, our results showed that female gender was a risk factor for CD (Table 1). This finding is consistent with previous results and implies gender-specific risk factors.

We found no statistically significant associations between breastfeeding duration, age at gluten introduction, and future CD (Table 2). However, this could be attributable to insufficient study power and, because several previous studies suggested that breastfeeding duration affects the risk of future CD, we included this variable in our final analysis (we also adjusted for the main effects, namely, age at gluten introduction and age at infection). In this analysis, we found no association between infection at the time of gluten introduction and risk of future CD.

Stene et al suggested that a high frequency of rotavirus infections increases the risk of CD autoimmunity in childhood. In contrast to Stene et al, we estimated not the overall rotavirus infectious load in childhood but instead gastroenteritis or any infection at the time of gluten introduction. A majority of the children with parent-reported gastroenteritis or any infection at the time of gluten introduction did not develop CD. Therefore, our results indicate that recent or ongoing infection is no absolute obstacle to introducing gluten in the diet of small children.

Rotavirus is the most common cause of pediatric gastroenteritis worldwide. A drawback of the current study is the lack of data on specific pathogens and severity. We cannot rule out the possibility that gastroenteritis attributable to rotavirus, or other specific pathogens, constitutes an independent risk factor for CD or that the severity of infection might have an effect on the risk of future CD. The mean number of infections per child and the mean number of episodes of gastroenteritis per child in the first year of life did not differ between case and control subjects (Table 2). Here our study had great statistical power, because it was based on >40 000 prospectively recorded episodes of infections during the first year of life.

With adjustment for age at gluten introduction and breastfeeding duration, we found no association between gastroenteritis at the time of gluten introduction and risk of future CD. Inasmuch as only 167 children had gastroenteritis at the time of gluten introduction and only 1 child received a diagnosis of CD before the end of the follow-up period, we had low power to detect differences, although nearly 4000 episodes of gastroenteritis were reported.

Our prospectively recorded data showed no increased risk of future CD for children introduced to gluten before 3 months of age (Table 2). It should be noted that early gluten introduction is very unusual in Sweden and it is difficult to examine the effects of early gluten introduction with adequate power in a Swedish population. Previous research was inconclusive. Some studies showed no association between age at gluten introduction and risk of future CD and others did.

We found no association between duration of breastfeeding and risk of future CD (Table 2). A number of previous studies found increased risk for CD among children with short breastfeeding duration, with significantly increased risk for CD among children breastfed for <2 months, 90 days, or <30 days. However, results were inconsistent and, in contrast to several earlier studies, our feeding data were collected prospectively. In the present study, only 4 children with CD were breastfed for <4 months. It is possible that the changing infant feeding patterns in Sweden seen in the past 15 to 20 years explain why we found no independent effect of breastfeeding on the risk of CD in the ABIS study cohort, born after the end of the Swedish epidemic of CD, in contrast to, for example, the study by Ivarsson et al, in which the majority of subjects were born during the epidemic. Faith-Magnusson et al investigated the effects of partial and exclusive breastfeeding on CD and found that children with CD were breastfed for a significantly shorter time, with significant differences in partial and exclusive breastfeeding rates. We did not discriminate between partial and exclusive breastfeeding.
We measured infections through concurrent parent reporting. It is unusual for Swedish parents to seek medical advice when their child experiences minor infections, including minor infections during the infancy period. Therefore, we did not collect data from patient charts. By excluding patients who received their CD diagnoses before 1 year of age, we eliminated the risk of recall bias. An additional strength of the current study is that data on infections and infant feeding were collected prospectively.

A limitation of the current study is the lack of data on type of infection. Stene et al. measured rotavirus infection frequencies in early childhood through serological testing. We did not have the ability to acquire blood samples for serological testing to evaluate infectious loads in our study. In addition, it should be noted that we studied parent-reported infections and not subclinical infections, which further limits this study.

The study population included in our main analyses was restricted to children whose parents chose to participate in the study and to complete the diary and children for whom diary data on gluten introduction and the end of breastfeeding were available. The symptoms of CD are unlikely to arise during the period of the child’s life in which gluten is introduced and breastfeeding is weaned; therefore, gluten introduction is highly unlikely to have an effect on the parents’ decision-making, in terms of diary completion. Furthermore, because breastfeeding and gluten introduction data were available in >95% of the diaries, we consider the risk of selection bias very low. This study identified CD diagnosed in childhood but, because CD is increasingly diagnosed in adulthood, screening for CD and a longer follow-up period would be required for complete elucidation of the possible relationship between infections and CD.

CONCLUSIONS

This study adds valuable information to the current discussion regarding environmental risk factors and the pathogenesis of CD. We conclude that parent-reported infectious load during the time of gluten introduction, as measured in the current study, is not a major risk factor for future CD. However, we cannot rule out the possibility that specific pathogens constitute risk factors for CD, because risk estimates for infection at the time of gluten introduction were of borderline statistical significance. We found no association between age at gluten introduction or breastfeeding duration and future CD.

REFERENCES


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http://pediatrics.aappublications.org/content/125/3/e530.full.html