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Association of Gluten Intake During the First 5 Years of Life With Incidence of Celiac Disease Autoimmunity and Celiac Disease Among Children at Increased Risk

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IMPORTANCE High gluten intake during childhood may confer risk of celiac disease.

OBJECTIVES To investigate if the amount of gluten intake is associated with celiac disease autoimmunity and celiac disease in genetically at-risk children.

DESIGN, SETTING, AND PARTICIPANTS The participants in The Environmental Determinants of Diabetes in the Young (TEDDY), a prospective observational birth cohort study designed to identify environmental triggers of type 1 diabetes and celiac disease, were followed up at 6 clinical centers in Finland, Germany, Sweden, and the United States. Between 2004 and 2010, 8676 newborns carrying HLA antigen genotypes associated with type 1 diabetes and celiac disease were enrolled. Screening for celiac disease with tissue transglutaminase autoantibodies was performed annually in 6757 children from the age of 2 years. Data on gluten intake were available in 6605 children (98%) by September 30, 2017.

EXPOSURES Gluten intake was estimated from 3-day food records collected at ages 6, 9, and 12 months and biannually thereafter until the age of 5 years.

MAIN OUTCOMES AND MEASURES The primary outcome was celiac disease autoimmunity, defined as positive tissue transglutaminase autoantibodies found in 2 consecutive serum samples. The secondary outcome was celiac disease confirmed by intestinal biopsy or persistently high tissue transglutaminase autoantibody levels.

RESULTS Of the 6605 children (49% females; median follow-up: 9.0 years [interquartile range, 8.0-10.0 years]), 1216 (18%) developed celiac disease autoimmunity and 447 (7%) developed celiac disease. The incidence for both outcomes peaked at the age of 2 to 3 years. Daily gluten intake was associated with higher risk of celiac disease autoimmunity for every 1-g/d increase in gluten consumption (hazard ratio [HR], 1.30 [95% CI, 1.22-1.38]; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 28.1%; absolute risk if gluten intake was 1-g/d higher than the reference amount, 34.2%; absolute risk difference, 6.1% [95% CI, 4.5%-7.7%]). Daily gluten intake was associated with higher risk of celiac disease for every 1-g/d increase in gluten consumption (HR, 1.50 [95% CI, 1.35-1.66]; absolute risk by age of 3 years if the reference amount of gluten was consumed, 20.7%; absolute risk if gluten intake was 1-g/d higher than the reference amount, 27.9%; absolute risk difference, 7.2% [95% CI, 6.1%-8.3%]).

CONCLUSIONS AND RELEVANCE Higher gluten intake during the first 5 years of life was associated with increased risk of celiac disease autoimmunity and celiac disease among genetically predisposed children.

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Gluten is a food antigen found in wheat, rye, and barley. It has a high content of proteins rich in gliadin peptides, which are resistant to complete digestion by gastrointestinal enzymes, and may cause an inflammatory response leading to celiac disease in genetically predisposed individuals.[1] Celiac disease is an autoimmune enteropathy affecting approximately 1% of the Western population and is attributable to both genetic and environmental factors.[2] Although gluten consumption and certain HLA antigen genotypes are key factors for celiac disease development, not all individuals with a predisposing genetic background develop lifelong intolerance to gluten,[3] and the risk is likely to be modified by the timing or quantities of gluten consumed as well as other potential pathophysiological factors.[4,5]

Celiac disease commonly presents during early childhood,[6] highlighting the importance of studying early life events to identify triggers of the disease.[7] It was initially reported that early or late introduction of gluten to infants increased the risk of celiac disease.[8,9] The timing of infant gluten exposure has not been consistently associated with celiac disease risk,[10,11] and this has led to changing recommendations for infant feeding.[12] It remains unclear whether the amount of gluten consumed triggers celiac disease.[11,13-15]

Gluten intake during the first 5 years of life was assessed in genetically at-risk children followed up in The Environmental Determinants of Diabetes in the Young (TEDDY), a multinational prospective birth cohort study. The aim was to investigate whether the amount of gluten in the diet was associated with development of celiac disease autoimmunity and celiac disease to allow better understanding of the pathogenesis and inform feeding recommendations to minimize disease burden.

Key Points

Question Is the amount of gluten intake during the first 5 years of life associated with the risk of celiac disease autoimmunity and celiac disease in at-risk children?

Findings In this multinational prospective birth cohort consisting of 6605 genetically predisposed children, higher gluten intake was associated with a statistically significant increase in celiac disease autoimmunity (absolute risk difference, 6.1%) and celiac disease (absolute risk difference, 7.2%) for every gram increase of gluten intake per day.

Meaning Increased intake of gluten during the first 5 years of life was an independent risk factor for celiac disease autoimmunity and celiac disease in genetically predisposed children.

Methods

Study Population

This prospective cohort study was designed to follow up children from birth up to 15 years of age at 6 clinical research centers in Finland, Germany, Sweden, and the United States (one center in Colorado, one center for Florida and Georgia, and one center in Washington state).[16] The enrollment period was from September 2004 through February 2010 and the final date of follow-up was September 30, 2017.

The primary goal was to identify genetic and environmental factors associated with increased risk of type 1 diabetes, celiac disease, or both. Newborn infants were screened for HLA antigen genotypes associated with type 1 diabetes and celiac disease.[17] Distribution of the HLA antigen genotypes in the study appear in **Table 1**.

For all study participants, separate written informed consent was obtained from a parent or primary caretaker for genetic screening and participation in the prospective follow-up beginning at birth. Local institutional or regional ethics review boards in all participating countries approved the study. Details of the study design, eligibility, and methods have been published.[16,18-20]

Dietary Assessment

Gluten intake was estimated from 3-day food records collected at ages 6, 9, and 12 months and biannually (ie, at 18, 24, 30, and 36 months) thereafter until the age of 5 years. Parents were asked to keep a food record documenting all foods and drinks consumed by the child over 3-day periods (2 weekdays and 1 weekend day) before the scheduled clinic visit. Normal food habits were encouraged during the time of food record collection. Portion sizes were estimated using household measurements, food models, pictures, drawings, and shapes of foods as references. A specific booklet was developed and used in all countries to facilitate estimation of food portion sizes. The dietary assessment method used in the study has been described elsewhere.[15,21]

Dietary intake was analyzed using the food composition databases from each participating country. For the analyses at the food-group level, a harmonized food-grouping system was developed with comparable food groups and quantification of food intakes among the databases used in the individual countries.[22] Composite foods and recipes were broken down to ingredients. Mean intake (grams/day) was calculated from total intake of gluten-containing flours (wheat, rye, and barley) reported during the 3-day recording period. Vegetable protein content (using country-specific values) was obtained from the daily intake of gluten-containing flours and converted to the amount of gluten using a conversion factor of 0.8 (the gluten content in wheat protein).[23] The converted amount was analyzed as absolute gluten intake (grams/day).

Measurement of Tissue Transglutaminase Autoantibodies

Testing for serum tissue transglutaminase (tTG) autoantibodies started at the 24-month clinic visit and was continued yearly thereafter. Radiobinding assays were used to measure tTG autoantibody levels at 2 laboratories as described.[19] Briefly, serum samples from US centers were screened for IgA-tTG autoantibodies at the Barbara Davis Center for Childhood Diabetes, University of Colorado (Denver laboratory).[24]

Serum samples from the European centers were tested at the University of Bristol (Bristol laboratory) using an assay that detected both IgA and IgG autoantibodies against tTG.[25]

Table 1. Descriptive Characteristics of the Children by Study Outcome

	No. (%) of Children[a]		
	Always Negative for tTG Autoantibodies (n = 5194)	Celiac Disease Autoimmunity (n = 1216)	Celiac Disease (n = 447)
Sex			
Male	2741 (52.8)	523 (43.0)	166 (37.1)
Female	2453 (47.2)	693 (57.0)	281 (62.9)
Finland			
Total	1218 (23.5)	251 (20.6)	78 (17.4)
HLA DR3-DQ2/DR3-DQ2[b]	124 (10.2)	79 (31.5)	36 (46.2)
HLA DR3-DQ2/DR4-DQ8[c]	376 (30.9)	120 (47.8)	30 (38.5)
Other HLA antigen genotypes[d]	718 (58.9)	52 (20.7)	12 (15.4)
Germany			
Total	314 (6.1)	57 (4.7)	16 (3.6)
HLA DR3-DQ2/DR3-DQ2[b]	50 (15.9)	22 (38.6)	9 (56.2)
HLA DR3-DQ2/DR4-DQ8[c]	131 (41.7)	19 (33.3)	4 (25.0)
Other HLA antigen genotypes[d]	133 (42.4)	16 (28.1)	3 (18.8)
Sweden			
Total	1554 (29.9)	464 (38.2)	222 (49.7)
HLA DR3-DQ2/DR3-DQ2[b]	225 (14.5)	202 (43.5)	108 (48.6)
HLA DR3-DQ2/DR4-DQ8[c]	690 (44.4)	152 (32.8)	66 (29.7)
Other HLA antigen genotypes[d]	639 (41.1)	110 (23.7)	48 (21.6)
United States			
Total	2108 (40.5)	444 (36.5)	131 (29.3)
HLA DR3-DQ2/DR3-DQ2[b]	391 (18.5)	194 (43.7)	69 (52.7)
HLA DR3-DQ2/DR4-DQ8[c]	849 (40.3)	183 (41.2)	50 (38.2)
Other HLA antigen genotypes[d]	868 (41.2)	67 (15.1)	12 (9.2)
First-degree relative with celiac disease	129 (2.5)	126 (10.4)	77 (17.2)
Breastfeeding duration, median (IQR), mo	7.8 (3.5-12.0)	8.3 (5.0-12.0)	8.1 (5.0-12.0)
Age at gluten introduction, mean (SD), mo	6.2 (1.9)	6.1 (1.8)	5.9 (1.9)

Abbreviations: IQR, interquartile range; tTG, tissue transglutaminase.

[a] Unless otherwise indicated.

[b] Detailed description of HLA antigen genotypes: DR3-DQA1*05:01-DQB1*02:01/DR3-DQA1*05:01-DQB1*02:01.

[c] Detailed description of HLA antigen genotypes: DR4-DQA1*03:0X-DQB1*03:02/DR3-DQA1*05:01-DQB1*02:01.

[d] Detailed description of HLA antigen genotypes: DR4-DQA1*03:0X-DQB1*03:02/DR4-DQA1*03:0X-DQB1*03:02 or DR3-DQA1*05:01-DQB103:02/DR8-DQA1*04:01-DQB1*04:02, DR4-DQA1*03-DQB1*03:02/DR3-DQA1*05:01-DQB1*02:01, DR4-DQA1*03-DQB1*03:02/DR4-DQA1*03-DQB1*03:02, DR4-DQA1*03-DQB1*03:02/DR8-DQA1*04:01-DQB1*04:02, DR3-DQA1*05:01-DQB1*02:01/DR3-DQA1*05:01-DQB1*02:01, DR4-DQA1*03-DQB1*03:02/DR4-DQA1*03-DQB1*02, DR4-DQA1*03-DQB1*03:02/DR1-DQA1*01:01-DQB1*05:01, DR4-DQA1*03-DQB1*03:02/DR13-DQA1*01:02-DQB1*06:04, DR4-DQA1*03-DQB1*03:02/DR9-DQA1*03-QB1*03:03, or DR3-DQA1*05:01-DQB1*02:01/DR9-DQA1*03-DQB1*03:03.

To harmonize the results, all samples with a tTG autoantibody index greater than 0.01 at the Denver laboratory were sent for quantification at the Bristol laboratory, which was the reference laboratory for the study.[19]

The results were expressed in arbitrary units derived from a standard curve consisting of dilutions of serum samples taken from a patient with celiac disease. If a sample tested positive from the Bristol laboratory (≥1.3 U),[25] the child's earlier serum samples were retrospectively analyzed at the Bristol laboratory to determine the age at which the tTG autoantibodies first became detectable. Persistence of tTG autoantibodies was confirmed if positive results were found for 2 consecutive serum samples collected at least 3 months apart.[26]

Primary and Secondary Outcomes

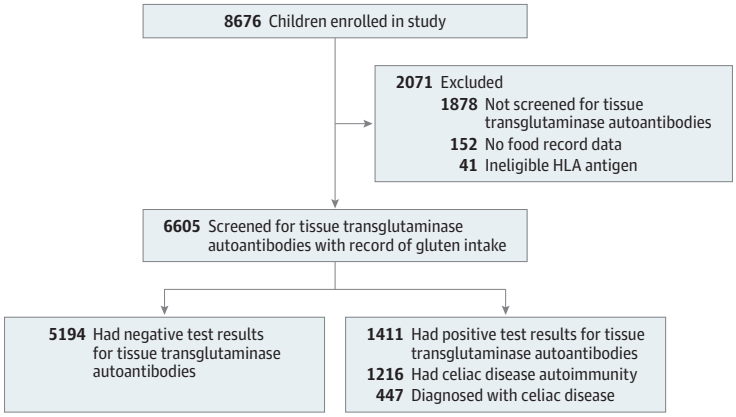
The primary outcome was celiac disease autoimmunity (defined as positive tTG autoantibodies found at the Bristol laboratory for 2 consecutive serum samples). Children meeting the criteria for persistence of tTG autoantibodies were referred to a gastroenterologist at the clinical discretion of their usual physician. The decision whether to perform a biopsy was not determined by the study protocol.

The secondary outcome was celiac disease (defined as an intestinal biopsy showing a Marsh score of ≥2 or, if biopsy was not performed, when the average of 2 samples was ≥100 U).[26]

Statistical Analyses

The time to an event was defined as the age of the first positive tTG autoantibody sample for children who later fulfilled the criteria for both celiac disease autoimmunity and celiac disease. The right-censored time for celiac disease autoimmunity was the age at the last negative tTG autoantibody sample and for celiac disease was the age at the last clinic visit when

Figure 1. Flowchart of The Environmental Determinants of Diabetes in the Young Population Cohort



celiac disease had not been diagnosed. To control for differences in age or body size, we analyzed energy and age-adjusted gluten intake using the residual method,[27] as well as gluten intake per 10 kg of body weight at a given age, in addition to absolute daily intake of gluten.

To address concerns regarding missing data and variability in dietary data, joint modeling was selected as the prespecified analysis and was chosen to assess the association between gluten intake over time and the risk of celiac disease autoimmunity and celiac disease.[28,29] Joint modeling assesses the association by fitting an individual trajectory for gluten intake over time. Based on the patterns detected, a linear trajectory for gluten intake was assumed for the longitudinal model, and the incidence peak during the beginning of the study was considered for the baseline hazard estimation, assuming a piecewise constant. Seven intervals without weighting were applied per the best model fit based on the difference in the Akaike information criterion.[30] The longitudinal model was adjusted for energy intake (kilocalories/day) at the same time, and the time-to-event model was adjusted for HLA antigen genotype, sex, country of residence, and family history of celiac disease (mother, father, or sibling). The SAS macro JMFit was used for the analyses.[31] From the log-hazard model fitted by joint modeling, absolute risk by the age of 3 years was estimated as the cumulative hazard in relation to the mean daily gluten intake at 2 years of age. The hazard ratios (HRs) and absolute risk differences were assessed at a 1-g/d or 1-g/d/10 kg (of body weight) increase of gluten intake.

In addition, 2 Cox regression analyses were performed as sensitivity analyses that included the most recent gluten intake prior to the event and energy intake as time-dependent covariates. One analysis included all children, and the other analysis included children with gluten intake available within 1 year prior to each risk set to control for various lag times between gluten exposure and the event. Because an early peak incidence of seroconversion was found, we examined the effects of age-specific gluten intake as a post hoc analysis. The association with subsequent incidence of celiac disease autoimmunity and celiac disease was assessed using Cox regression, focusing on absolute intake reported at the age of each study visit. For children whose gluten intake at the specific age was the most recent data prior to the event, the standard Cox regression model assessed the effects of gluten intake as a time constant covariate. For children who had additional gluten intake data available after the specific age, the most recent gluten intake prior to the event needed to be controlled for to assess the effects of the intake. To assess the effects of age-specific gluten intake in addition to the effect of current intake, the model considered the most recent intake prior to the event as a time-dependent covariate and the intake at the specific age as a time-constant covariate.

The proportional hazards assumption was examined using the martingale residual analysis with the supremum test. The functional form in the martingale residual plot, as well as a change-point analysis based on the log-rank test,[32] suggested a dichotomization for absolute gluten intake at 2 years of age. Two-sided *P* values are reported. Statistical significance was determined when the *P* value was <.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

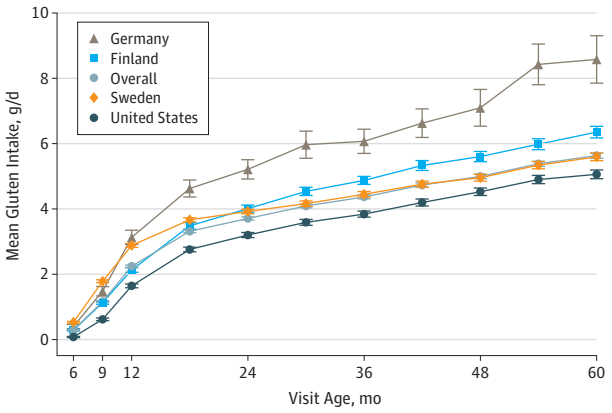
Results

Between September 2004 and February 2010, 424 788 newborn infants were screened for HLA antigens. Of those screened, there were 21 589 infants (5%) identified as being eligible for study inclusion and 8676 (40%) were enrolled before the age of 4 months. The most common reasons for not enrolling were related to protocol characteristics (eg, blood draw, demanding protocol) or family circumstances (eg, changing contact information).[33]

There were 6757 children screened for tTG autoantibodies and 6605 (97.8%) submitted at least one 3-day food record during the first 5 years of life or prior to detection of tTG autoantibody positivity (**Figure 1**). Descriptive characteristics of the study population appear in Table 1.

Of 6605 children included in the study, 3233 (49%) were girls. Gluten consumption linearly increased with age, but there were some national differences (**Figure 2**). Mean daily gluten

Figure 2. Mean Daily Gluten Intake up to the Age of 5 Years by Country and Overall



Error bars indicate 95% CIs.

intake per visit and country is presented in eTable 1 in the Supplement. Of the 52 952 visits for which parallel tTG autoantibody results were available, data on gluten intake were missing or of inadequate quality at 4465 visits (8%). In total, 204 (3%) participants completed only 1 food record. Among children with celiac disease autoimmunity, 20 (1.6%) completed only 1 food record more than 3 months prior to their seroconversion.

Primary and Secondary Outcome Analyses

As of September 30, 2017, among the 6605 children included in the analysis, 1411 (21%) tested positive for tTG autoantibodies on at least 1 occasion. During a median follow up of 9.0 years (range, 1.0-13.0 years; interquartile range, 8.0-10.0 years), 1216 children (18%) developed celiac disease autoimmunity (seroconverted to positive tTG autoantibodies at a median age of 3.3 years [range, 0.9-11.5 years]). There were 447 children (7%) who developed celiac disease (seroconverted at a median age of 3.0 years [range, 0.9-11.2 years]). The incidence of seroconversion for both outcomes peaked at 2 to 3 years of age (eFigure 1 in the Supplement).

Children homozygous for HLA DR3-DQ2 were at the highest risk of celiac disease autoimmunity and celiac disease. Swedish residence, female sex, and family history of celiac disease were also associated with increased risk for both outcomes (eTable 2 in the Supplement).

Higher intake of gluten during the first 5 years of life was associated with increased risk and absolute risk by the age of 3 years in relation to mean daily gluten intake at the age of 2 years for both celiac disease autoimmunity and celiac disease (**Table 2** and **Table 3**). Daily (absolute) gluten intake was associated with higher risk of celiac disease autoimmunity for every 1-g/d increase in gluten consumption (HR, 1.30 [95% CI, 1.22-1.38], $P < .001$; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 28.1%; absolute risk if the gluten amount consumed was 1-g/d higher than the reference amount, 34.2%; absolute risk difference, 6.1% [95% CI, 4.5%-7.7%]). Daily (absolute) gluten intake was associated with higher risk of celiac disease for every 1-g/d increase in gluten consumption (HR, 1.50 [95% CI, 1.35-1.66], $P < .001$; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 20.7%; absolute risk if the gluten amount consumed was 1-g/d higher than the reference amount, 27.9%; absolute risk difference, 7.2% [95% CI, 6.1%-8.3%]).

Age- and energy-adjusted (residual) gluten intake was associated with higher risk of celiac disease autoimmunity for every per 1-g/d increase in gluten consumption (HR, 1.40 [95% CI, 1.30-1.52], $P < .001$; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 18.7%; absolute risk if the gluten amount consumed was 1-g/d higher than the reference amount, 24.6%; absolute risk difference, 5.9% [95% CI, 4.4%-7.4%]). Age- and energy-adjusted (residual) gluten intake was associated with higher risk of celiac disease for every per 1-g/d increase in gluten consumption (HR, 1.43 [95% CI, 1.23-1.68], $P < .001$; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 7.8%; absolute risk if the gluten amount consumed was 1-g/d higher than the reference amount, 10.7%; absolute risk difference, 2.9% [95% CI, 1.9%-3.8%]).

In addition, gluten intake per 10 kg of body weight was associated with a higher risk of celiac disease autoimmunity for every 1-g/d/10 kg increase in gluten consumption (HR, 1.87 [95% CI, 1.66-2.11], $P < .001$; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 51.9%; absolute risk if the gluten amount consumed was 1-g/d/10 kg higher than the reference amount, 70.2%; absolute risk difference, 18.3% [95% CI, 16.7%-19.9%]). Gluten intake per 10 kg of body weight was associated with a higher risk of celiac disease for every 1-g/d/10 kg increase in gluten consumption (HR, 2.18 [95% CI, 1.75 -2.71], $P < .001$; absolute risk by the age of 3 years if the reference amount of gluten was consumed, 35.0%; absolute risk if the gluten amount consumed was 1-g/d/10 kg higher than the reference amount, 55.0%; absolute risk difference, 20.0% [95% CI, 19.0%-21.0%]).

Sensitivity Analyses

The sensitivity analyses using Cox regression models generally supported the statistical significance found from the joint modeling analysis (Table 2). In the country-specific analyses, higher gluten intake was associated with an increased risk of celiac disease autoimmunity in all countries and at all sites (eTable 3 in the Supplement). Absolute gluten intake and age- and energy-adjusted intake were associated with increased risk for celiac disease in the United States (specifically, in Colorado and Washington State) and in Sweden. The analyses could not be performed in Germany because there were only 16 cases of celiac disease.

Post Hoc Analysis

Gluten intake reported at the 2-year visit was available for 833 children with celiac disease autoimmunity. Gluten intake reported at the 3-year visit was available for 526 children with celiac disease autoimmunity. The post hoc analysis showed that gluten intake at 2 years of age had an independent association with the risk of celiac disease autoimmunity and celiac disease, in addition to the current intake during the first 5 years of life (eTable 4 in the Supplement).

Table 2. Daily Gluten Intake and Risk for Developing Celiac Disease Autoimmunity and Celiac Disease

Type of Analysis[a]	No. of Children With Celiac Disease Autoimmunity	Measurements of Gluten	Celiac Disease Autoimmunity		Celiac Disease	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Joint modeling	1216	Absolute intake, g/d	1.30 (1.22-1.38)	<.001	1.50 (1.35-1.66)	<.001
		Residual intake, g/d[b]	1.40 (1.30-1.52)	<.001	1.43 (1.23-1.68)	<.001
		Intake/10 kg of body weight	1.87 (1.66-2.11)	<.001	2.18 (1.75-2.71)	<.001
Cox regression	1216	Absolute intake, g/d	1.14 (1.11-1.17)	<.001	1.14 (1.09-1.20)	<.001
		Residual intake, g/d[b]	1.12 (1.09-1.15)	<.001	1.07 (1.02-1.13)	.01
		Intake/10 kg of body weight	1.19 (1.14-1.23)	<.001	1.14 (1.07-1.22)	<.001
Cox regression including only those with gluten consumption available within 1 y prior to time of event	905	Absolute intake, g/d	1.12 (1.08-1.16)	<.001	1.07 (1.02-1.13)	.01
		Residual intake, g/d[b]	1.09 (1.05-1.13)	<.001	1.04 (0.99-1.10)	.14
		Intake/10 kg of body weight	1.15 (1.10-1.20)	<.001	1.12 (1.05-1.21)	.002

Abbreviation: HR, hazard ratio.

[a] Adjusted for HLA antigen genotype, country, sex, first-degree relative with celiac disease, and energy intake.

[b] Adjusted for age and energy intake using the residual method.[27]

The supremum test showed no indication of violating the proportional hazards assumption, but there was a deviation with gluten intake greater than 2 g/d in the martingale residual plot (eFigure 2 in the Supplement). In addition, the change point analysis showed a significant risk difference between gluten intake greater than 2 g/d and gluten intake of 2 g/d or less. Based on these analyses, we dichotomized the gluten intake reported at 2 years as greater than 2 g/d and 2 g/d or less and examined the adjusted HRs with the outcomes (eTable 5 in the Supplement).

Gluten consumption greater than 2 g/d at 2 years of age was associated with a higher risk of celiac disease autoimmunity (HR, 1.49 [95% CI, 1.16-1.91], *P* = .002) and celiac disease (HR, 1.75 [95% CI, 1.10-2.81], *P* = .02) compared with those who consumed 2 g/d or less. When analyzing absolute gluten intake reported at the 2-year visit and risk for developing celiac disease autoimmunity and celiac disease, a linear increase in HRs were seen with higher intake of gluten (eTable 6 in the Supplement).

Discussion

Higher gluten intake during the first 5 years of life was associated with statistically significantly increased risks of celiac disease autoimmunity and celiac disease among genetically predisposed children. The incidence of both outcomes peaked at 2 to 3 years of age. If gluten intake was 1-g/d higher than the mean at 2 years of age (corresponding to a half slice of white bread), the absolute risk differences for the respective outcome were 6% and 7% higher by 3 years of age. The 6% to 7% increase in risk for a small 1-g/d increase in gluten intake appears clinically important.

In addition, the finding of a cut point at which gluten intake was associated with an increased risk is relevant for gluten feeding recommendations in at-risk children; however, this conclusion was based on a post hoc analysis and should be confirmed. The association of gluten intake with these risks was significantly increased if the child consumed more than 2 g/d of gluten at around 2 years of age, which corresponds to approximately 1 slice (35 g) of white bread or 1 portion of cooked pasta (150 g). The HR increased with subsequent higher gluten intake at the 2-year visit, further supporting the results that higher intakes of gluten were associated with higher risks of celiac disease autoimmunity and celiac disease.

The findings from a previous case-control study of gluten intake among Swedish children born during the mid-1980s showed that children subsequently diagnosed with celiac disease had been introduced to larger amounts of gluten-containing foods compared with children who did not develop celiac disease.[13] The hypothesis that gluten given in small amounts at 5 to 6 months of age would protect at-risk children from developing celiac disease was addressed in a randomized placebo-controlled intervention trial; however, that study produced null results.[11] In the same study population, mean daily gluten intake (from 10 months of age when unrestricted gluten consumption was allowed) was not associated with celiac disease up to 3 years of age, except in children carrying the HLA antigen genotype HLA-DQ2.2/-DQ7.[14]

In contrast to the randomized placebo-controlled intervention trial, gluten consumption during the first 2 years of life was found to be associated with increased risk of celiac disease in a subset of Swedish children from the present cohort, and furthermore, children in the upper tertile of gluten intake were at a 2-fold increased risk of celiac disease vs children with lower gluten intake. This nested case-control study including 146 children with biopsy-confirmed celiac disease and 436 matched controls indicated that the amount of gluten consumed could be a risk factor for celiac disease.[15]

For the current study, food record data from all the participating countries were harmonized, which made it feasible to perform a longitudinal analysis of the full birth cohort. In addition, the current analysis included gluten intake up to 5 years of age and another 301 children diagnosed with celiac disease, which made it possible to do country-specific analyses using time-to-event analyses. In the country-specific analyses, a higher gluten intake was associated with an increased risk of celiac disease autoimmunity in all countries, whereas absolute gluten intake and age- and energy-adjusted

Table 3. Absolute Risk for Developing Celiac Disease Autoimmunity and Celiac Disease[a]

Measurements of Gluten	Reference Gluten Intake, Mean (SD)[b]	Absolute Risk for Developing Celiac Disease Autoimmunity by Age of 3 y			Absolute Risk for Developing Celiac Disease by Age of 3 y		
		If Reference Amount of Gluten Was Consumed, %[c]	If Amount of Gluten Consumed Was 1-U Higher Than Reference Amount, %	Absolute Risk Difference, % (95% CI)[d]	If Reference Amount of Gluten Was Consumed, %[c]	If Amount of Gluten Consumed Was 1-U Higher Than Reference Amount, %	Absolute Risk Difference, % (95% CI)[d]
Absolute intake, g/d	3.71 (1.75)	28.1	34.2	6.1 (4.5-7.7)	20.7	27.9	7.2 (6.1-8.3)
Residual intake, g/d[e]	0.48 (1.67)	18.7	24.6	5.9 (4.4-7.4)	7.8	10.7	2.9 (1.9-3.8)
Intake/10 kg of body weight	2.91 (1.39)	51.9	70.2	18.3 (16.7-19.9)	35.0	55.0	20.0 (19.0-21.0)

[a] Analysis was conditioned on HLA antigen genotype, country, sex, first-degree relative with celiac disease, and energy intake. Cumulative hazard from the log-hazard model fit by joint modeling in Table 2.

[b] Average amount reported at the 2-year visit.

[c] Assessed in relation to the average daily gluten intake at 2 years of age.

[d] Implies the risk increase if the gluten intake was 1-g/d higher than the average gluten intake at 2 years of age.

[e] Adjusted for age and energy intake using the residual method.[27]

intake were only associated with increased risk for celiac disease in the United States and Sweden.

Despite similar dietary assessment methods and calculation of gluten intake, discrepancies in results among the studies are likely attributable to study design and population size. In the randomized clinical trial, the time of gluten introduction was not accounted for and gluten amounts were fixed,[11] which differed from the present observational study consisting of a larger population that reflected the natural variations of gluten intake in real life. Other contributing factors may be differences in exposures to various triggering environmental factors, such as gastrointestinal infections or rotavirus vaccination status,[4,5] which could partly explain why Swedish children are more prone to develop celiac disease compared with children from other countries.

Because gluten intake was measured as the mean from 3-day food records, there were missing data and day-to-day variation. The joint modeling method simultaneously models longitudinal data and time-to-event data. By fitting the longitudinal pattern through modeling, missing gluten intake was imputed by the fit, and variability also was considered. However, Cox regression includes observed data only and assumes covariates without any variability. Therefore, joint modeling was considered as the primary analytic method, but various sensitivity analyses were conducted using Cox regression. Joint modeling tends to produce greater effect sizes.[28]

A major strength of this study is its prospective design, enrolling a large cohort of children with the same genetic risk from 4 countries with different infant feeding habits and following the same study protocol. Another strength is the dietary assessment method that allowed repeated measurements to capture changes in dietary habits in growing infants and young children over time prior to disease onset. The prospective design also reduced the effect of changes in dietary habits because parents were unaware of their child's autoantibody status when the food records were collected. The analyses also were adjusted for known confounders for celiac disease (HLA antigen, country, sex, and having a family member with celiac disease).[26] Moreover, potential confounders such as socioeconomic status, maternal smoking during pregnancy, maternal education, and maternal age had previously been analyzed and were not associated with risk of celiac disease,[34] and are therefore considered less likely to confound the results.

Limitations

This study has several limitations. First, information on analyzed gluten content in foods in national food composition databases was lacking. Due to variability in protein content in different types, cultivars, and crops of wheat, the accuracy of gluten intake would improve if gluten content were available in food composition databases. The same conversion factor for estimation of gluten content in wheat, rye, and barley was chosen because this method has been used in several studies.[10,14,15,35] Other studies have used cereal-specific conversion factors for the estimation of gluten content.[36]

Second, calculations of gluten content are approximate because they were based on self-reported dietary data. Different

dietary assessment methods together with differences in methods of estimating gluten content are challenging when comparing results from previous studies. A randomized clinical trial of different amounts of gluten during early childhood in genetically at-risk individuals would be warranted to confirm our findings.

Conclusions

Higher gluten intake during the first 5 years of life was associated with increased risk of celiac disease autoimmunity and celiac disease among genetically predisposed children.

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