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Association of gluten intake in the first 5 years with incidence of celiac disease autoimmunity and celiac disease among children at increased risk

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Key Points

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

Findings: In this multinational prospective birth cohort consisting of 6,605 genetically predisposed children, higher gluten intake was associated with a statistically significant increase of celiac disease autoimmunity (HR 1.30, 95% CI 1.22-1.38) and celiac disease (HR 1.50, 95% CI 1.35-1.66), 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 of celiac disease autoimmunity and celiac disease in genetically predisposed children.

Abstract

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 Environmental Determinants of Diabetes in the Young (TEDDY), a prospective observational birth cohort designed to identify environmental triggers of type 1 diabetes and celiac disease. Participants were followed at six clinical centers in Finland, Germany, Sweden and the US. Between 2004 and 2010, 8,676 newborns carrying HLA-genotypes associated with type 1 diabetes and celiac disease, were enrolled into a longitudinal observational study. In 6,757 children, screening for celiac disease with tissue transglutaminase (tTG) autoantibodies was performed annually from age 2 years. Data on gluten intake were available in 6,605 (98%) children.

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

Main Outcomes: The primary endpoint was celiac disease autoimmunity, defined as positive tTG autoantibodies in two consecutive serum samples. The secondary endpoint was celiac disease confirmed by intestinal biopsy or persistently high tTG autoantibody levels.

Results: Of the 6,605 children (49% females, median follow-up 9.0 years [interquartile range 8.0 to 10.0 years]), 1,216 (18%) developed celiac disease autoimmunity and 447 (7%) developed celiac disease by September 30, 2017. The incidence for both endpoints peaked at age 2 to 3 years. Daily gluten intake was associated with higher risk of celiac disease autoimmunity (HR 1.30, 95% CI 1.22-1.38) and celiac disease (HR 1.50, 95% CI 1.35-1.66) for every 1-gram/day increase. The absolute risk increases corresponding to HR were 6.1% for celiac disease autoimmunity and 7.2% for celiac disease, respectively.

Conclusions and Relevance: Higher gluten intake in the first 5 years was associated with

increased risk of celiac disease autoimmunity and celiac disease among genetically predisposed children.

Introduction

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 attributable to both genetic and environmental factors[2]. While gluten consumption and certain human leukocyte antigen (HLA) genes 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 pathophysiologic factors[4,5].

Celiac disease commonly presents early in childhood[6], highlighting the importance of studying early life events for identifying 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]. Importantly, 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 from genetically at-risk children followed in the multinational prospective birth cohort the Environmental Determinants of Diabetes in the Young (TEDDY) 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 to inform feeding recommendations to minimize disease burden.

Methods

Study population

This prospective cohort study follows children from birth up to 15 years of age at clinical research centers in Colorado, Georgia, Florida, and Washington state in the U.S., as well as Finland, Germany, and Sweden[16]. The final date of follow-up for the present study 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 genotypes associated with type 1 diabetes and celiac disease[17]. Distribution of the HLA-genotypes in the study is shown in **Table 1.** For all study participants separate written informed consents for genetic screening and participation in the prospective follow-up beginning at birth were obtained from a parent or primary caretaker. Local institutional or regional ethics review boards in all participating countries approved the study. Full details of study design, eligibility and methods have been published previously[16,18-20].

Dietary assessment

Gluten intake was estimated from 3-day food records collected at ages 6, 9, and 12 months and biannually (i.e. at 18, 24, 30, 36 months) thereafter until 5 years of age. Parents were asked to keep a food record documenting all foods and drinks consumed by the child over the 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 in detail elsewhere[15,21].

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

Measurement of tissue transglutaminase (tTG) autoantibodies

Testing for serum tTG autoantibodies started from the 24 months clinic visit and continued yearly thereafter. Radiobinding assays were used to measure tTG autoantibody levels in two laboratories as previously described[19]. Briefly, samples from US centers were screened for IgA-tTG autoantibodies at the Barbara Davis Center for Childhood Diabetes, University of Colorado (Denver laboratory)[24]. Samples from European centers were tested at the University of Bristol, UK, (Bristol laboratory), using an assay that detected both IgA and IgG autoantibodies against tTG[25]. To harmonize results, all samples with tTG autoantibody index >0.01 in the Denver laboratory were sent for quantification of tTG autoantibodies in the Bristol laboratory, the reference laboratory for the study[19]. Results were expressed in arbitrary units derived from a standard curve consisting of dilutions of serum taken from a patient with celiac disease. If a sample tested positive from the Bristol laboratory (≥1.3 units)[25], the child's earlier blood samples were retrospectively analyzed in the Bristol laboratory to determine the age at which tTG autoantibodies first became detectable. Persistence of tTG autoantibodies

was confirmed by finding positive results in two consecutive samples at least 3 months apart[26].

Outcomes

The primary outcome was celiac disease autoimmunity, defined as positive tTG autoantibodies measured in the Bristol laboratory in two consecutive 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 TEDDY study protocol. The secondary endpoint was celiac disease, which was defined as an intestinal biopsy showing a Marsh score ≥2 or, if biopsy was not performed, non-biopsy proven celiac disease was defined by the average of two samples ≥100 units[26].

Statistical analyses

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

To address concerns regarding missing data and variability in dietary data, joint modeling was selected as the pre-specified analysis, 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 the intake over time. Based on

the patterns seen in **eFigure 1** and **eFigure 2**, a linear trajectory was assumed for the longitudinal model and the incidence peak in the beginning was considered for the baseline hazard estimation assuming piecewise constant. Seven intervals without weighting were applied per the best model fit based on ΔAIC[30]. The longitudinal model was adjusted for energy intake (kcal/day) at the same time, and the time to event model was adjusted for HLA-genotype, sex, country of residence and family history (mother, father, or sibling) of celiac disease. SAS macro JMFit was used for the analyses[31]. From the log-hazard model fitted by joint modeling, absolute risk by 3 years old was estimated as the cumulative hazard, in relation to the average daily gluten intake at 2 years of age. The hazard ratios and absolute risk increases were assessed at 1 unit increase of gluten intake, conditioned on energy intake (kcal/day) at the same time, HLA-genotype, sex, country of residence and family history of celiac disease.

In addition, two Cox regression analyses including the most recent intake prior to the event and energy intake at the same time as time dependent covariates were performed as sensitivity analyses: 1) all children, and 2) 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.

As a post-hoc analysis, we examined the effects of age-specific gluten intake. 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 TEDDY 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 reported at the specific age 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 needs to be controlled to assess the effects of the intake reported at the specific age (i.e., the primary

interest). In order 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 hazard assumption was examined using martingale residual analysis with the supremum test. The functional form in the martingale residual plot, as well as change-point analysis based on 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 <0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Between September 2004 and February 2010, 424,788 newborn infants were screened for HLA and 21,589 (5%) HLA-eligible infants were identified, of whom 8,676 (40%) were enrolled in this study before the age of 4 months. The most common reasons for failing to enroll to this 15-year follow-up study were related to protocol characteristics (e.g. blood draw, demanding protocol) or family circumstances (e.g. changing contact information)[33]. At time of analysis, 6,757 children had been screened for tTG autoantibodies, and 6,605 (97.8%) had submitted at least one 3-day food record during the first 5 years of life or prior to detection of tTG autoantibody positivity (**eFigure 3**). Descriptive characteristics of the study population are presented in **Table 1**. Of 6,605 children in the study, 3,233 (49%) were girls. Data on gluten intake were missing or of inadequate quality in 4,465 visits (8%) of the 52,952 visits for which parallel tTG results were available. In total, 204 (3%) subjects completed at only one food record. Among children with celiac disease autoimmunity, 20 (1.6%) subjects completed one food record more than 3 months prior to their seroconversion.

As of September 30, 2017, among the 6,605 children included in the analysis, 1,411 (21%) had tested positive for tTG autoantibodies on at least one occasion. During a median follow up of 9.0 years (range 1.0 – 13.0, interquartile range 8.0 – 10.0) 1,216 (18%) children with celiac disease autoimmunity had seroconverted to positive tTGA autoantibodies at a median age of 3.3 years (range 0.9 - 11.5), and 447 (7%) children fulfilling the criteria for celiac disease had their seroconversion at a median age of 3.0 years (range 0.9 – 11.2). The incidence of seroconversion for both endpoints peaked around 2 to 3 years of age (**eFigure 1**).

Children homozygous for 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 endpoints (**eTable 1**).

Gluten consumption linearly increased with age with some national differences (**eFigure 2, eTable 2**). Higher intake of gluten during the first 5 years of life was associated with increased risk of both celiac disease autoimmunity and celiac disease (**Table 2**). Absolute intake of gluten was associated with higher risk of celiac disease autoimmunity (HR 1.30, 95% CI 1.22 -1.38; p= <0.001) and celiac disease (HR 1.50, 95% CI 1.35 -1.66; p= <0.001) for every per 1-gram/day increase in gluten consumption. Age- and energy adjusted gluten intake was associated with higher risk of celiac disease autoimmunity (HR 1.40, 95% CI 1.30 -1.52; p= <0.001) and celiac disease (HR 1.43, 95% CI 1.23 -1.68; p= <0.001) for every per 1-gram/day increase in gluten consumption. In addition, gluten intake per 10 kg bodyweight was associated with higher risk of celiac disease autoimmunity (HR 1.87, 95% CI 1.66 -2.11; p= <0.001) and celiac disease (HR 2.18, 95% CI 1.75 -2.71; p= <0.001) for every per 1-gram/day/10kg increase in gluten consumption. Sensitivity analysis using Cox regression models supported the statistical significance found from the joint modeling analysis (**Table 2**).

In the country-specific analyses, a higher gluten intake was associated with an increased risk of celiac disease autoimmunity in all countries (**eTable 3**). Absolute gluten intake and age- and energy adjusted intake were associated with increased risk for celiac disease in the U.S. and Sweden.

Finally, the absolute risks by 3 years of age in relation to the average daily gluten intake at 2 years of age were assessed. The absolute risk difference suggests the risk increase if gluten was 1 unit higher than the average daily gluten intake at 2 years of age. The absolute risk increases were 6 to 18% for celiac disease autoimmunity and 3 to 20% celiac disease, respectively (**Table 3**).

Post-hoc analysis

In view of the early peak incidence of seroconversion to later celiac disease autoimmunity and celiac disease, we focused on the intake reported at 2 and 3 years of age, respectively. Gluten intake reported at the 2-year visit was available for 833 children with celiac disease autoimmunity and intake reported at the 3-year visit was available for 526 children with celiac disease autoimmunity. The analysis showed that gluten intake at 2 years of age had an independent effect on the risk of celiac disease autoimmunity and celiac disease, in addition to the current intake during the first 5 years of life (**eTable 4**).

The supremum test showed no indication of violating the proportional hazard assumption, but there was a deviation at >2g gluten intake per day in the martingale residual plot (**eFigure 4**). In addition, the change point analysis showed a significance risk difference between >2 and ≤ 2g/day. Based on these analyses, we dichotomized the gluten intake reported at 2 years as >2 and ≤2 g/day and examined the adjusted HRs with the endpoints (**Table 4**). Children who consumed gluten >2g/day at 2 years of age had a 50% higher risk of celiac disease autoimmunity (HR 1.49, 95% CI 1.16 – 1.91; p= <0.002) and a 75% higher risk of celiac disease (HR 1.75, 95% CI 1.10 – 2.81; p= <0.019), compared with those who consumed ≤2g

gluten per day. When analyzing absolute gluten intake reported at the 2-year visit and risk for developing celiac disease autoimmunity and celiac disease, using a subsequent increase in gluten intake, a linear increase in hazard ratios were seen for higher intakes (**Table 5**).

Discussion

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

The incidence of both endpoints peaked around 2 to 3 years of age. In the post-hoc analysis, the association with gluten intake on these risks was significantly increased if the child consumed more than 2 g/day at around 2 years of age, which corresponds to approximately one slice (35 g) of white bread or 1 portion of cooked pasta (150g). Also, hazard ratios increased with subsequent higher gluten intake at the 2 year visit suggesting that higher intakes were associated with higher risk of celiac disease autoimmunity and celiac disease.

These findings are in line with a previous retrospective case-control study of gluten intake in Swedish children born during the mid-1980s, which 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 furthermore addressed in a randomized placebo-controlled intervention trial, though with 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-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 previously found 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, compared with children with lower gluten intake. This nested case-control study on 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 have been harmonized which enabled us to do longitudinal analysis of the full birth cohort. In addition, we have extended the data with gluten intake up to 5 years of age and included another 301 children diagnosed with celiac disease and performed time to event analyses. This extended data set yields credible power to do country-specific analysis for celiac disease autoimmunity and celiac disease, except for the German site, which had only 16 cases with celiac disease. In these 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 intake were only associated with increased risk for celiac disease in the U.S. and Sweden.

Despite similar dietary assessment methods and calculation of gluten intake, discrepancies in results between the studies are likely attributed to study design and population size. In the randomized controlled study, the gluten introduction was overlooked and gluten amounts were fixed[11], which indeed 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[5], which partly could explain why Swedish children are more prone to develop celiac disease as compared to children from other countries.

A major strength of this study as compared to the aforementioned the randomized controlled study [11], is its prospective study design, enrolling a large cohort of children with the same

genetic risk, from four 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 at time food records were collected. Our analyses were also adjusted for known confounders for celiac disease (HLA, country, gender, and having a family member with celiac disease)[26]. Moreover, potential confounders such as socioeconomic status in terms of maternal smoking (during pregnancy), maternal education, and maternal age had previously already been analyzed and were not associated with risk of celiac disease[34] and therefore considered less likely to confound the results.

Limitations

This study has several limitations. First, the lack of information of analyzed gluten content in foods in national food composition databases. Therefore, the same conversion factor for estimation of gluten content in wheat, rye and barley was chosen because this method has been used in several previous 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 as they are 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. Conclusions should therefore be taken with care. A randomized trial of different amounts during early childhood in genetically at-risk individuals would therefore be warranted to confirm our findings.

Conclusions

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

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494 **Table 1.** Descriptive characteristics of the study population, by study endpoint.

	Children always negative for tTG autoantibodies (n = 5,194)	Children with celiac disease autoimmunity (n = 1,216)	Children with celiac disease (n = 447)
Country	**n (%)**	**n (%)**	**n (%)**
USA	**2108 (40.5)**	**444 (36.5)**	**131 (29.3)**
- HLA DR3-DQ2/DR3-DQ2[a]	391 (18.5)	194 (43.7)	69 (52.7)
- HLA DR3-DQ2/DR4-DQ8[b]	849 (40.3)	183 (41.2)	50 (38.2)
- HLA others[c]	868 (41.2)	67 (15.1)	12 (9.1)
Finland	**1218 (23.5)**	**251 (20.6)**	**78 (17.4)**
- HLA DR3-DQ2/DR3-DQ2[a]	124 (10.2)	79 (31.5)	36 (46.2)
- HLA DR3-DQ2/DR4-DQ8[b]	376 (30.9)	120 (47.8)	30 (38.5)
- HLA others[c]	718 (58.9)	52 (20.7)	12 (15.4)
Germany	**314 (6.1)**	**57 (4.7)**	**16 (3.6)**
- HLA DR3-DQ2/DR3-DQ2[a]	50 (15.9)	22 (38.6)	9 (56.2)
- HLA DR3-DQ2/DR4-DQ8[b]	131 (41.7)	19 (33.3)	4 (25.0)
- HLA others[c]	133 (42.4)	16 (28.1)	3 (18.8)
Sweden	**1554 (29.9)**	**464 (38.2)**	**222 (49.7)**
- HLA DR3-DQ2/DR3-DQ2[a]	225 (14.5)	202 (43.5)	108 (48.6)
- HLA DR3-DQ2/DR4-DQ8[b]	690 (44.4)	152 (32.8)	66 (29.7)
- HLA others[c]	639 (41.1)	110 (23.7)	48 (21.6)
First degree relative with celiac disease			
Yes	129 (2.5)	126 (10.4)	77 (17.2)
No	5065 (97.5)	1090 (89.6)	370 (82.8)
Sex			
Female	2453 (47.3)	693 (57.0)	281 (62.9)
Male	2741 (52.7)	523 (43.0)	166 (37.1)
Breastfeeding duration, months, median (q1, q3)	7.8 (3.5, 12.0)	8.3 (5.0, 12.0)	8.1 (5.0, 12.0)
Age at gluten introduction, months, mean (SD)	6.2 (1.9)	6.1 (1.8)	5.9 (1.9)

Footnote: Detailed description of human leukocyte antigen (HLA) genotypes followed in TEDDY.

[a] DR3-DQA1*05:01-DQB1*02:01 / DR3-DQA1*05:01-DQB1*02:01

[b] DR4-DQA1*03:0X-DQB1*03:02 / DR3-DQA1*05:01-DQB1*02:01

[c] 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.

Table 2. Daily gluten intake and risk for developing celiac disease autoimmunity and celiac disease in the TEDDY study.

		Celiac disease autoimmunity		Celiac disease	
Analysis [a]	**Measurements of gluten**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Joint modeling, n=1,216	Absolute intake (g/day)	1.30 (1.22 to 1.38)	<0.001	1.50 (1.35 to 1.66)	<0.001
	Residual intake (g/day) [b]	1.40 (1.30 to 1.52)	<0.001	1.43 (1.23 to 1.68)	<0.001
	Intake/10kg body weight	1.87 (1.66 to 2.11)	<0.001	2.18 (1.75 to 2.71)	<0.001
Cox regression, n=1,216	Absolute intake (g/day)	1.14 (1.11 to 1.17)	<0.001	1.14 (1.09 to 1.20)	<0.001
	Residual intake (g/day) [b]	1.12 (1.09 to 1.15)	<0.001	1.07 (1.02 to 1.13)	0.011
	Intake/10kg body weight	1.19 (1.14 to 1.23)	<0.001	1.14 (1.07 to 1.22)	<0.001
Cox regression including only those with gluten consumption available within 1 year prior to time of event, n=905	Absolute intake (g/day)	1.12 (1.08 to 1.16)	<0.001	1.07 (1.02 to 1.13)	0.009
	Residual intake (g/day) [b]	1.09 (1.05 to 1.13)	<0.001	1.04 (0.99 to 1.10)	0.140
	Intake/10kg body weight	1.15 (1.10 to 1.20)	<0.001	1.12 (1.05 to 1.21)	0.002

[a] Adjusting for HLA-type, country, sex, FDR with celiac disease, and energy intake

[b] Age- and energy adjusted intake using the residual method (ref 27).

n = Number of children with celiac disease autoimmunity included in each analysis.

Table 3. Absolute risk for developing celiac disease autoimmunity and celiac disease in the TEDDY study, conditioned on HLA-type, country, sex, FDR with celiac disease, and energy intake. Cumulative hazard from the log-hazard model fit by the joint modeling in Table 2.

		Celiac disease autoimmunity			Celiac disease		
Measurements of gluten	**Gluten intake (Reference [a])**	**Absolute risk by 3 years of age if gluten was consumed at reference amount (%)**	**Absolute risk by 3 years of age if 1 unit higher than reference was consumed (%)**	**Absolute risk difference (%)**	**Absolute risk by 3 years of age if gluten was consumed at reference amount (%)**	**Absolute risk by 3 years of age if 1 unit higher than reference was consumed (%)**	**Absolute risk difference (%)**
Absolute intake (g/day)	3.71	28.1	34.2	6.1	20.7	27.9	7.2
Residual intake (g/day) [b]	0.48	18.7	24.6	5.9	7.8	10.7	2.9
Intake/10kg body weight	2.91	51.9	70.2	18.3	35.0	55.0	20.0

[a] Average gluten intake reported at the 2-year visit was considered as reference

[b] Age- and energy adjusted intake using the residual method (ref 27).

Abbreviation: FDR; First degree relative

Table 4. Daily absolute gluten intake reported at the 2-year visit and risk for developing celiac disease autoimmunity and celiac disease in the TEDDY study.

		Celiac disease autoimmunity		Celiac disease	
Model		**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
A	≤ 2g/day	1		1	
	>2 g/day	1.49 (1.16 to 1.91)	0.002	1.75 (1.10 to 2.81)	0.019
B	≤ 2g/day	1		1	
	>2 g/day	1.62 (1.29 to 2.03)	<0.001	1.71 (1.12 to 2.60)	0.012

A: Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake and the most recent gluten intake prior to the event as time dependent covariates

B: Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake at 2 year TEDDY visit.

Table 5. Daily absolute gluten intake reported at the 2-year visit and risk for developing celiac disease autoimmunity and celiac disease in the TEDDY study.

	Celiac disease autoimmunity		Celiac disease	
Model[a]	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
≤ 2 g/day	1		1	
> 2 and ≤ 4 g/day	1.52 (1.20 to 1.93)	<0.001	1.57 (1.02 to 2.41)	0.041
> 4 and ≤ 6 g/day	1.77 (1.37 to 2.29)	<0.001	1.96 (1.24 to 3.11)	0.004
> 6 and ≤ 8 g/day	2.43 (1.76 to 3.36)	<0.001	2.69 (1.53 to 4.71)	<0.001
> 8 g/day	1.54 (0.81 to 2.93)	0.70	2.04 (0.68 to 6.08)	0.20

[a]Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake at 2 year TEDDY visit

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Access to Data and Data Analysis

Dr. Hye-Seung Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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