



Effects of Gluten Intake on Risk of Celiac Disease: A Case-Control Study on a Swedish Birth Cohort

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BACKGROUND & AIMS: Early nutrition may affect the risk of celiac disease. We investigated whether amount of gluten in diet until 2 years of age increases risk for celiac disease.

METHODS: We performed a 1-to-3 nested case-control study of 146 cases, resulting in 436 case-control pairs matched for sex, birth year, and HLA genotype generated from Swedish children at genetic risk for celiac disease. Newborns were annually screened for tissue transglutaminase autoantibodies (tTGA). If tested tTGA positive, time point of seroconversion was determined from frozen serum samples taken every 3 months. Celiac disease was confirmed by intestinal biopsies. Gluten intake was calculated from 3-day food records collected at ages 9, 12, 18 and 24 months. Odds ratios (OR) were calculated through conditional logistic regression.

RESULTS: Breastfeeding duration (median, 32 wk) and age at first introduction to gluten (median, 22 wk) did not differ between cases and tTGA-negative controls. At the visit before tTGA seroconversion, cases reported a larger intake of gluten than controls (OR, 1.28; 95% confidence interval [CI], 1.13–1.46; $P = .0002$). More cases than controls were found in the upper third tertile (ie, >5.0 g/d) before they tested positive for tTGA seroconversion than controls (OR, 2.65; 95% CI, 1.70–4.13; $P < .0001$). This finding was similar in children homozygous for DR3-DQ2 (OR, 3.19; 95% CI, 1.61–6.30; $P = .001$), heterozygous for DR3-DQ2 (OR, 2.24; 95% CI, 1.08–4.62; $P = .030$), and for children not carrying DR3-DQ2 (OR, 2.43; 95% CI, 0.90–6.54; $P = .079$).

CONCLUSIONS: The amount of gluten consumed until 2 years of age increases the risk of celiac disease at least 2-fold in genetically susceptible children. These findings may be taken into account for future infant feeding recommendations.

Keywords: Pediatric; TEDDY Study; Diet; Wheat.

See editorial on page 410.

Celiac disease (CD) is an emerging public health disorder affecting 1% to 3% of the general population, with variations between ethnic groups and geographic regions.¹ Both gluten exposure and carrying any of the HLA-risk haplotypes DR3-DQ2 and DR4-DQ8 are necessities for the risk of CD.^{2,3} However, gluten is a universally consumed food antigen and half of the Caucasian population possesses at least 1 of these 2 risk haplotypes,⁴ suggesting that additional environmental factors determine whether lifelong gluten intolerance develops in an individual at genetic risk.

Age at first introduction to gluten or the risk of CD has long been debated. Retrospective data generated in Sweden have indicated that introducing gluten in small amounts between 4 and 6 months of age while being breastfed reduces the risk of celiac disease compared with introducing gluten in larger amounts at older ages.^{5,6} The hypothesis of an optimal time window for

Abbreviations used in this paper: CD, celiac disease; TEDDY, The Environmental Determinants of Diabetes in the Young; tTGA, tissue transglutaminase autoantibodies.

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inducing tolerance to gluten recently was questioned by results of prospective cohort studies.^{7,8} Furthermore, 2 recent randomized controlled intervention studies failed to show an effect of timing of gluten introduction on risk of CD, and neither study directly examined the impact of the quantity of gluten intake.^{9,10} Although retrospective data from Sweden pointed to the importance of quantity of gluten intake for risk of CD,¹¹ no prospective studies free of recall bias have been performed to date.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is an international prospective birth cohort study following up genetically susceptible children in search of environmental factors associated with type 1 diabetes and CD.¹² TEDDY has previously confirmed that the risk for celiac disease by 5 years of age is dependent on HLA genotype, and that children with the highest-risk group (ie, homozygous for DR3/DQ2) develop CD-associated autoantibodies to tissue transglutaminase (tTGA) much earlier compared with children carrying a single or no DR3-DQ2 haplotype.¹³ In addition, Swedish TEDDY participants are at the highest risk for CD at an early age compared with participants in other TEDDY countries.¹³ Swedish infants traditionally receive gluten-containing follow-up formulas and porridge during the first 2 years of life.¹⁴ Although Swedish TEDDY participants are introduced to gluten earlier than children in the other countries, the age at which gluten was introduced did not explain why Swedish children were at increased risk for CD in the TEDDY study.⁸ In this study, we investigated if the amount of gluten intake during the first 2 years of life is a risk factor for CD.

Patients and Methods

Study Population

The TEDDY study was conducted in 6 clinical centers in Finland, Germany, Sweden, and the United States, and was approved by local Institutional Review Boards and monitored by an External Advisory Board formed by the National Institutes of Health.¹⁵ Between September 2004 and February 2010, a total of 424,788 newborns were HLA genotyped at 1 of these 6 sites and were eligible if they had one of the following HLA genotypes: DR3-DQ2/DR4-DQ8, DR4-DQ8/DR4-DQ8, DR4-DQ8/DR8, DR3-DQ2/DR3-DQ2, DR4-DQ8/DR4b, DR4-DQ8/DR1, DR4-DQ8/DR13, DR4-DQ8/DR9, or DR3-DQ2/DR9.¹⁶ Of the screened newborns, 48,140 were from the Swedish site, of whom 3723 (7.7%) were HLA-eligible and invited to participate in a 15-year follow-up period. Written informed consent was obtained from parents or primary caretakers in 2525 of the 3723 (68%).¹⁶

Annual screening for CD starts from the age of 2 years with tTGA using radiobinding assays as described elsewhere.¹⁷ Earlier blood samples collected from birth and onward were analyzed retrospectively to determine the age of seroconversion in cases with tTGA positivity.¹³

Children who tested positive for tTGA in 2 consecutive samples were defined as persistently tTGA positive and referred to their health care provider for evaluation of CD with an intestinal biopsy. A biopsy showing a Marsh score of 2 or greater in tTGA-positive children proved CD.¹³ At time of this study, 2062 of the Swedish children had been screened for tTGA, of whom 330 were persistently tTGA positive and 147 were diagnosed with CD (Supplementary Figure 1).

Study Design

A 1-to-3 matched nested case-control study was conducted on Swedish children screened for tTGA. Cases were defined as children with biopsy-confirmed CD. All controls were tTGA negative within 45 days of the case's age of seroconversion of tTGA and free of biopsy-confirmed CD within 45 days of the cases age at biopsy. Age at seroconversion of tTGA was set as the age when the first positive sample was drawn. Sex and HLA genotype (ie, the number of DR3-DQ2 alleles) were chosen as matching factors.¹³ Controls also were matched to the cases for birth year to control for changes in nutrient and food composition in commercial baby foods available on the Swedish market during the follow-up period. Three controls per case were selected randomly from subjects who met these matching criteria. Among the 147 children who were diagnosed with CD, 1 child did not have any eligible controls and another child had only 1 eligible control. In all, the analysis included 436 case-control pairs from 146 cases. Six cases (4%) and 13 (3%) controls had a first-degree relative with CD. The median age of seroconversion to tTGA was 24 months (range, 10–86 mo), and the median age at diagnosis was 38 months (range, 15–102 mo).

Dietary Assessment

Information about breastfeeding duration (exclusive and total breastfeeding) and timing of introduction of gluten-containing cereals were collected every 3 months through a booklet given to the parents at study entry, which has been described in detail elsewhere.⁸ Data on overall food consumption were collected by a 24-hour recall at the first clinic visit (age, 3–4.5 mo) and by 3-day food records at clinic visits at 6, 9, 12, 18, and 24 months of age.¹⁸ Parents were asked to keep a food record covering all foods and drinks consumed by the child for the given 3 days (ideally, 2 weekdays and 1 weekend day) before the scheduled visit. Parents were given instructions on how to fill out the records by trained study personnel. They were advised not to change the eating habits of the child during the time they were completing the food record. Written instructions and guidance were provided to the families. If the primary caregiver indicated that the child had started attending daycare, separate food records were provided for the daycare

personnel to complete. At each clinical visit, the food records were reviewed by a study nurse. Probing about missing or unclear information was obtained by face-to-face interview during the visit. Brand names were requested for all commercial baby foods. Portion sizes were estimated using household measures, drawings, and pictures from a booklet. Each set of photographs of foods and dishes contained 4 to 5 portion sizes in increasing order. Drawings and shapes of other types of foods such as bread, cakes, and pizza also were included. For soft bread, drawings of actual size of bread slices and thicknesses were provided. The booklet was handed out to the families at study entry and used at home when keeping the food records.

Gluten-containing foods included products and composite dishes (such as pizza and sandwiches) with wheat, rye, and barley, but not oats. Oats consists of proteins that will not lead to the same intestinal damage as wheat, rye, and barley, and therefore were treated as a non-gluten-containing cereal.¹⁹ The food database and connected software enables the summarization of intake of each food and food group.²⁰ Recipes were created to describe ingredients in dishes. For commercial baby foods containing gluten, specific recipes were created for each brand name based on the ingredient list. The Swedish National Food Composition Database was used as a source for nutrient content and standard recipes of foods such as bread, sweet bakery, pancakes, pizza, and so forth.²¹ Unique user recipes provided by the parents were added and used in the local database. All recipes were broken down to ingredients, and intake of gluten-containing flours was summarized and the mean intake of the 3-day recording period was calculated as grams per day. The daily gluten intake was calculated from the amount of vegetable protein in gluten-containing flours and then multiplied by a factor of 0.8.²² At the age of 6 months, 97% of the children's families had submitted complete food records, and 84% of the food records were submitted at the age of 24 months.

Statistical Analyses

The Kruskal–Wallis test was used to compare the age of tTGA seroconversion in the cases by sex, birth year, and HLA. Conditional logistic regression was used to compare characteristics in cases with those in matched controls. Gluten intake was estimated from the 3-day food records at the visit before the cases seroconverted to tTGA. The estimate at the visit before the tTGA seroconversion was analyzed, as well as total intake, which was defined as the sum of the estimates from all visits up to the visit before the tTGA seroconversion. For cases whose age of seroconversion was older than 24 months, the visit at 24 months of age was used as the visit before seroconversion. The estimated amount of gluten intake at the visit before the tTGA seroconversion was analyzed both as a continuous

variable (g/d) and as a trichotomous variable based on tertiles of quantity (ie, low [<3.4 g/d], medium [3.4 – 5.0 g/d], and high [>5.0 g/d]). The Kaplan–Meier estimates of time to tTGA seroconversion for cases, stratified by tertile of amount of gluten intake, were plotted. For controls currently negative for tTGA, the censored time was the age at collection of the last sample negative for tTGA. For controls currently positive for tTGA, the censored time was the age at collection of the initial sample positive for tTGA. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC). All reported P values were 2-sided without multiple testing correction, and P values less than .05 were considered to represent statistical significance.

Results

Age at first introduction to gluten, breastfeeding duration, or having a first-degree relative with CD were considered as potential confounders, but none of the variables had an impact on the results and therefore were not included in the final analysis. Matching factors and age of seroconversion are described in [Table 1](#).

Gluten Intake in Cases and Controls

Total and exclusive breastfeeding duration and age at first introduction to gluten-containing cereals (wheat, rye, or barley) did not differ between cases and controls ([Table 2](#)). Cases reported a higher gluten intake than the matched controls ([Table 3](#)). If cases and controls with a first-degree relative with CD were excluded, the results were in the same direction (data not shown).

One unit (g/d) increase of gluten before seroconversion of tTGA was associated with a 28% increase in risk of CD ($P = .0002$). Because 14 cases were missing gluten intake data at the visit before seroconversion (2 cases at the 18-month visit and 12 cases at the 24-month visit), 385 pairs from 132 cases were analyzed for the gluten intake before seroconversion of tTGA ([Table 4](#)). Gluten intake reported by cases was higher at all ages beginning at 12 months, continuing with a trend toward higher intake at 18 months, and again significantly higher intake was seen at the age of 24 months. Moreover, children who received amounts of gluten in the upper tertile (ie, high gluten intake) were at more than a 2-fold higher risk for CD than those who consumed less (OR, 2.65; 95% CI, 1.70–4.13; $P < .0001$). [Figure 1](#) shows the Kaplan–Meier plot by 3 groups categorized by tertiles (low, medium, high intake).

Gluten Intake in Cases According to HLA Genotype

Gluten intake at the visit before seroconversion of tTGA was not different among cases homozygous for DR3-DQ2 (median, 4.8 g; quartile 1 (Q1), 3.2; Q3, 5.9),

Table 1. Matching Factors and Age of tTGA Seroconversion in the TEDDY Swedish Birth Cohort and in Children With Celiac Disease

Matching factor	Birth cohort (N = 2062) N (%)	Celiac disease (N = 146) N (%)	Age of tTGA seroconversion Median, mo (Q1, Q3)	P value ^a
Sex				
Boys	1055 (51)	49 (34)	29 (21, 48)	.066
Girls	1007 (49)	97 (66)	24 (18, 36)	
Birth year				
2004	91 (4)	8 (6)		.066 ^b
2005	366 (18)	37 (25)	28 (18, 48)	
2006	377 (18)	22 (15)	30 (21, 59)	
2007	412 (20)	31 (21)	24 (20, 37)	
2008	363 (18)	25 (17)	30 (22, 36)	
2009	385 (19)	19 (13)	21 (17, 24)	
2010	68 (3)	4 (3)		
HLA genotype				
DR3-DQ2/DR3-DQ2	438 (21)	70 (48)	21.5 (17, 28)	<.0001
DR3-DQ2/DR4-DQ8	868 (42)	48 (33)	36 (22.5, 48.5) ^c	
DR3-DQ2/DR9	1 (<1)			
DR4-DQ8/DR4-DQ8	455 (22)	26 (18)	35 (21.5, 37) ^d	
DR4-DQ8/DR8	268 (13)	2 (1)		
DR4-DQ8/DR1	18 (1)			
DR4-DQ8/DR13	13 (<1)			
DR4-DQ8/DR9	1 (<1)			

^aKruskal–Wallis test P value.

^b2004 and 2010 were not included because of the small number of observations.

^cIncluding DR3-DQ2/DR4-DQ8 and DR3-DQ2/DR9.

^dIncluding DR4-DQ8/DR4-DQ8, DR4-DQ8/DR8, DR4-DQ8/DR1, DR4-DQ8/DR13, and DR4-DQ8/DR9.

heterozygous for DR3-DQ2 (median, 5.1 g; Q1, 3.8; Q4, 6.3), or in those without DR3-DQ2 (median, 4.9 g; Q1, 3.5; Q3, 5.9) ($P = .49$). To examine whether the association between increased gluten intake and CD risk differed by genetic susceptibility to CD, we examined this association separately in case-control pairs that were homozygous for the matching variable DR3-DQ2, pairs that were heterozygous for DR3-DQ2, and pairs without DR3-DQ2. In DR3-DQ2 homozygotes, children who received gluten in the upper tertile (high gluten intake) had a 3-fold higher risk for celiac disease than those who received less (OR, 3.19; 95% CI, 1.61–6.30; $P = .001$). A similar association was seen in DR3-DQ2 heterozygotes (OR, 2.24; 95% CI, 1.08–4.62; $P = .030$) and in children negative for DR3-DQ2 (OR, 2.43; 95% CI,

0.90–6.54; $P = .079$), albeit the latter did not reach statistical significance.

Discussion

In this nested case-control study, we showed that a high overall intake of gluten during the first 2 years of life, and in particular at 12 months of age, was associated with an increased risk for CD during childhood. More importantly, this association did not differ between children at very high or increased genetic risk for the disease; a high quantity of gluten still was associated with CD in children with no, 1, or 2 copies of the major celiac disease risk HLA-DR3-DQ2 haplotype.

Table 2. Infant Feeding Characteristics in Children With Celiac Disease and Matched Controls

Characteristic	Celiac disease (N = 146) Median (Q1, Q3)	Controls (N = 436) Median (Q1, Q3)	OR (95% CI)	P value
Breastfeeding duration, wk				
Total	31 (20, 40)	33 (18, 43)	0.99 (0.99–1.00)	.361
Exclusive	4 (1, 14)	6 (1, 16)	0.98 (0.96–1.00)	.124
Age at first introduction, wk				
Gluten-containing cereals ^a	22 (18, 24)	22 (18, 24)	0.99 (0.95–1.04)	.866
Wheat	22 (20, 25)	22 (18, 25)	1.00 (0.96–1.05)	.888
Energy intake, kcal ^b	1019 (840, 1164)	1009 (858, 1156)	1.00 (1.00–1.00)	.450

^aGluten-containing cereals (wheat, rye, or barley).

^bTotal energy intake (kcal) at the visit before the cases first positive tTGA test.

Table 3. Daily Gluten Intake in Children With Celiac Disease and Matched Controls

Gluten intake	Celiac disease (N = 146) Median (Q1, Q3)	Controls (N = 436) Median (Q1, Q3)	OR (95% CI)	P value
Total gluten (g) intake before tTGA seroconversion ^a	10.5 (7.6, 14.2)	9.9 (5.9, 13.8)	1.05 (1.01–1.10)	.030
Gluten (g) intake at the visit before tTGA seroconversion	4.9 (3.5, 5.9)	3.9 (2.9, 5.2)	1.28 (1.13–1.46)	.0002

^aIntake from all visits (sum of all visits) up to the visit before the cases first positive tTGA test.

These findings may contribute to a better understanding of why some, but not all, children at genetic risk develop CD.

Gluten-derived peptides are able to induce immune responses in individuals with DR3-DQ2 as well as with DR4-DQ8.²³ The disease risk is modified further by genotype, DR3-DQ2 homozygous individuals develop CD at an early age.²⁴ It has been hypothesized that the threshold of tolerance to gluten is dependent on the HLA genotype.²⁵ However, this proposed threshold model is supported only by in vitro studies showing that the strongest T-cell response is seen among DR3-DQ2 homozygous individuals who need only a small quantity of stimulatory gluten peptides to activate an immune response.²⁶ In this study, time to seroconversion of tTGA occurred a median of 12 months earlier among the high-risk group (DR3-DQ2 homozygous) than among the remaining cases with standard risk. It thus is tempting to speculate that the gluten intake needed for triggering CD was dependent on HLA risk genotype in this study. However, we found no indication that the gluten intake according to tertile distribution differed among cases carrying different HLA risk genotypes, indicating that the amount was an independent risk factor for CD to develop.

Only 2 important studies have reported on the amount of gluten intake and subsequent risk for CD. In the European PreventCD study, the mean daily intake (after dose escalation) was not associated with an increased risk for CD.⁹ In contrast, another study indicated that the risk of CD was increased in Swedish children before 2 years of age who were introduced to gluten in large amounts during weaning.¹¹ Swedish feeding practices differ from other European countries and the United States, which also was confirmed in the

TEDDY cohort.²⁷ It is traditional to feed infants with cereal-based foods in Sweden. Moreover, Swedish infants are first introduced to gluten-containing foods at an earlier age and in larger amounts compared with other Nordic countries.^{8,14,28} By tradition, most common cereal-based foods given to Swedish infants are cereal in milk formulations (gruel) or spoon-fed porridges, which are nutritionally similar products. At the age of 6 months, 60% of Swedish children were bottle-fed with 250 to 500 mL of gruel per day and almost all infants were given porridge.²⁹ The major source of gluten in gluten-containing commercial baby foods comes from wheat and rye flour. In Sweden, gruels and porridges are available in numerous brands and for different age groups. The gluten-content in these types of products is between 0.3 and 0.7 g gluten per 100 g of prepared product (data based on the recipes created in the Swedish nutrient database). In our study, we showed a sharp increase in the reported amount of gluten between 9 and 12 months of age. This is typically the time when many infants are given gluten-containing commercial feeding products in Sweden. This could suggest that porridges and gruel given in large amounts modulate the risk of CD during early childhood in Sweden after controlling for HLA risk genotype.¹³

The strength of the present study was the prospective design with the use of a 3-day food record for the dietary assessment of early childhood food consumption. This method provides a more accurate estimation about gluten intake compared with dietary assessment methods using standard portions such as food frequency questionnaires. During the first year of life, parents kept a food record frequently and with a very high compliance rate. The face-to-face visits made it possible to probe about missing portion sizes, which maximized the efforts

Table 4. Daily Gluten Intake at the Clinical Visit Before tTGA Seroconversion in Children With Celiac Disease and Matched Controls

Age at 3-day food record, mo	Celiac disease (N = 132) ^a		Controls (N = 385)		OR (95% CI)	P value
	N ^a	Median, g/d ^b (Q1, Q3)	N	Median, g/d ^b (Q1, Q3)		
9	6	1.6 (1.4, 1.8)	17	1.9 (1.1, 2.4)	0.63 (0.19–2.05)	.444
12	32	4.9 (3.5, 5.6)	89	3.2 (2.5, 4.5)	1.58 (1.17–2.13)	.003
18	37	4.9 (3.9, 5.9)	103	3.9 (3.2, 5.2)	1.22 (0.99–1.51)	.077
24	57	5.1 (3.7, 6.2)	176	4.3 (3.3, 5.7)	1.23 (1.01–1.49)	.043

^aChildren with data missing at the clinic visit before tTGA seroconversion were excluded (N = 14).

^bReported gluten intake before age of tTGA seroconversion in children.

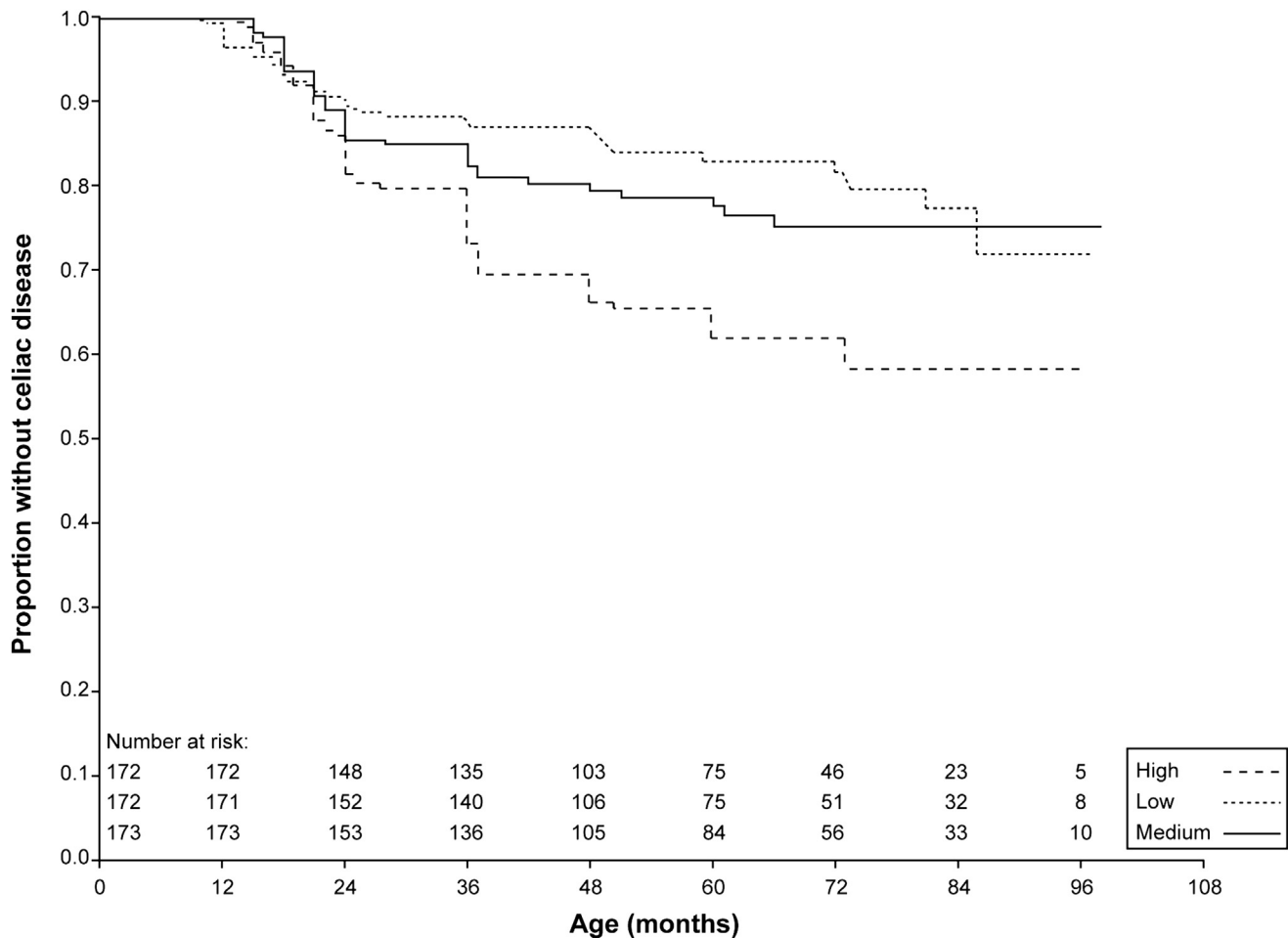


Figure 1. Time to tTGA positivity by gluten intake (g) at the visit closest before tTGA seroconversion. Gluten intake was categorized by tertiles of quantity (ie, low [<3.4 g/d], medium [3.4 – 5.0 g/d], and high [>5.0 g/d]).

of collecting complete data. The prospective design of this birth cohort study enabled us to obtain the diet information before seroconversion of tTGA as a marker of CD. This eliminated the risk of reporting biases or a change in feeding habits because of the knowledge of serology results or disease status. A potential weakness of the study was that we did not analyze information about the number of servings of gluten-containing foods per day. We cannot exclude the possibility, for example, that the number of portions given frequently during the course of the day may have different effects on disease risk.

In conclusion, this study showed that a high intake of gluten during the first 2 years of life is associated with an increased risk of CD. This association was similar in children carrying any of the major HLA risk genotypes for CD. Because these HLA risk genotypes also are widely distributed in the general population, our findings therefore may have consequence for future infant feeding recommendations. Future studies from other countries are warranted to confirm if gluten intake during infancy triggers celiac disease in young children.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2015.09.030>.

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Conflicts of interest

The authors disclose no conflicts.

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Supplementary Appendix 1

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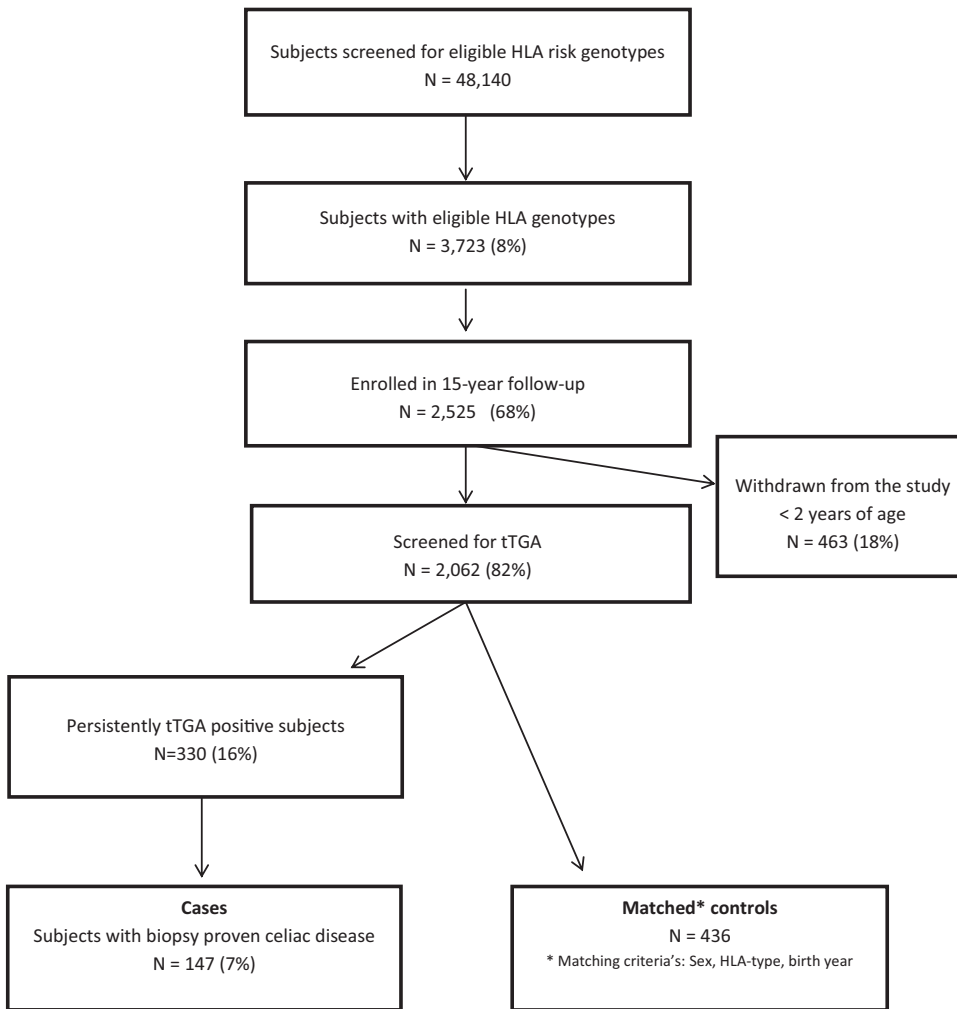
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Supplementary Figure 1. Flow chart of study enrollment and participation in the Swedish TEDDY birth cohort.