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

Carin Andrén Aronsson,*Hye-Seung Lee,‡Sibylle Koletzko,§Ulla Uusitalo,‡Jimin Yang,‡ Suvi M. Virtanen,k,¶,#Edwin Liu,**Åke Lernmark,*Jill M. Norris,‡‡Daniel Agardh,*and theTEDDY Study Group

*Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden;
‡
Health Informatics Institute,
Morsani College of Medicine, University of South Florida, Tampa, Florida;
§
Dr. von Hauner Children
’
s Hospital, Ludwig
Maximilians University, Munich, Germany;
k
National Institute for Health and Welfare, Nutrition Unit, Helsinki, Finland;
¶
School of Health Sciences,
#
Research Center for Child Health, Tampere University and University Hospital, Science Center of Pirkanmaa Hospital District, University of Tampere, Finland; **Digestive Health Institute, Children
’
s Hospital Colorado,
‡‡
Department of Epidemiology, Colorado School of Public Campus, University of Colorado Denver, Aurora, Colorado

Email the author Daniel Agardh the show TEDDY Study Group

Abstract

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

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

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 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.

Table 1Matching 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)		
2005	366 (18)	37 (25)	28 (18, 48)	.066[b]

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.

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).

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

Characteristic	Celiac disease (N = 146)	Controls (N = 436)	OR (95% CI)	*P* value
	Median (Q1, Q3)	Median (Q1, Q3)		
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

a Gluten-containing cereals (wheat, rye, or barley).

b Total energy intake (kcal) at the visit before the cases first positive tTGA test.

Table 3Daily 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.

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).

Table 4Daily 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.

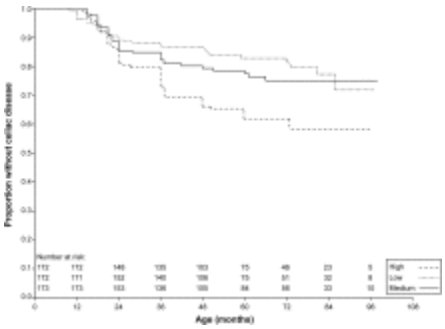

Figure 1

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]).

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), 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. 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 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.

Acknowledgments

The authors express their gratitude to the families who participated in the study. Members of the TEDDY Study Group are listed in the Supplementary Appendix.

Supplementary Appendix 1

The Teddy Study Group

The following were members of the Colorado Clinical Center: Marian Rewers, MD, PhD, Principal Investigator,[1,4–6,10,11] Kimberly Bautista,[12] Judith Baxter,[9,10,12,15] Ruth Bedoy,[2] Daniel Felipe-Morales, Brigitte I. Frohnert, MD,[14] Patricia Gesualdo,[2,6,12,14,15] Michelle Hoffman,[12–14] Rachel Karban,[12] Edwin Liu, MD, PhD,[13] Jill Norris, PhD,[2,3,12] Adela Samper-Imaz, Andrea Steck, MD,[3,14] Kathleen Waugh,[6,7,12,15] and Hali Wright[12] (University of Colorado, Anschutz Medical Campus, Barbara Davis Center for Childhood Diabetes).

The following were members of the Georgia/Florida Clinical Center: Jin-Xiong She, PhD, Principal Investigator,[1,3,4,11] Desmond Schatz, MD, PhD (University of Florida),[4,5,7,8] Diane Hopkins,[12] Leigh Steed,[12–15] Jamie Thomas (University of Florida),[6,12] Janey Adams (University of Florida),[12] Katherine Silvis,[2] Michael Haller, MD, PhD (University of Florida),[14] Melissa Gardiner, Richard McIndoe, PhD, Ashok Sharma, Joshua Williams, Gabriela Foghis, Stephen W. Anderson, MD (Pediatric Endocrine Associates, Atlanta), and Richard Robinson (Center for Biotechnology and Genomic Medicine, Georgia Regents University).

The following were members of the Germany Clinical Center: Anette G. Ziegler, MD, PhD, Principal Investigator,[1,3,4,11] Andreas Beyerlein, PhD,[2] Ezio Bonifacio, PhD (Center for Regenerative Therapies, TU Dresden),[5] Michael Hummel, MD, PhD,[13] Sandra Hummel, PhD,[2] Kristina Foterek (Research Institute for Child Nutrition, Dortmund),[2] Mathilde Kersting, PhD (Research Institute for Child Nutrition, Dortmund),[2] Annette Knopff,[7] Sibylle Koletzko, MD, PhD (Dr. von Hauner Children's Hospital, Department of Gastroenterology, Ludwig Maximillians University Munich),[13] Claudia Peplow,[12] Roswith Roth, PhD,[9] Joanna Stock,[9,12] Elisabeth Strauss,[12] Katharina Warncke, MD,[14] and Christiane Winkler, PhD[2,12,15] (Forschergruppe Diabetes e.V. and Institute of Diabetes Research, Helmholtz Zentrum München, and Klinikum rechts der Isar, Technische Universität München).

The following were members of the Finland Clinical Center: Jorma Toppari, MD, PhD, Principal Investigator (University of Turku, Turku University Hospital, Hospital District of Southwest Finland),[1,4,11,14] Olli G. Simell, MD, PhD (University of Turku, Turku University Hospital, Hospital District of Southwest Finland),[1,4,11,13] Annika Adamsson, PhD (Turku University Hospital, Hospital District of Southwest Finland),[12] Heikki Hyöty, MD, PhD (University of Tampere, Tampere University Hospital),[6] Jorma Ilonen, MD, PhD (University of Turku, University of Kuopio),[3] Sanna Jokipuu (Turku University Hospital, Hospital District of Southwest Finland), Tiina Kallio (Turku University Hospital, Hospital District of Southwest Finland), Miia Kähönen (University of Oulu, Oulu University Hospital), Mikael Knip, MD, PhD (University of Tampere, Tampere University Hospital),[5] Annika Koivu (University of Turku, Turku University Hospital, Hospital District of Southwest Finland), Mirva Koreasalo (University of Tampere, Tampere University Hospital, National Institute for Health and Welfare, Finland),[2] Kalle Kurppa, MD, PhD (University of Tampere, Tampere University Hospital),[13] Maria Lönnrot, MD, PhD (University of Tampere, Tampere University Hospital),[6] Elina Mäntymäki (University of Turku, Turku University Hospital, Hospital District of Southwest Finland), Katja Multasuo (University of Oulu, Oulu University Hospital), Juha Mykkänen, PhD (University of Turku, Turku University Hospital, Hospital District of Southwest Finland),[3] Tiina Niininen (University of Tampere, Tampere University Hospital),[12] Mia Nyblom (University of Tampere, Tampere University Hospital), Petra Rajala (Turku University Hospital, Hospital District of Southwest Finland), Jenna Rautanen (Tampere University Hospital, National Institute for Health and

Welfare, Finland), Anne Riikonen (University of Tampere, Tampere University Hospital), Minna Romo (University of Turku, Turku University Hospital, Hospital District of Southwest Finland), Satu Simell, MD, PhD (Turku University Hospital, Hospital District of Southwest Finland, Tampere University Hospital),[13] Tuula Simell, PhD (University of Turku, Turku University Hospital, Hospital District of Southwest Finland), Ville Simell (University of Turku, Turku University Hospital, Hospital District of Southwest Finland),[13] Maija Sjöberg (University of Turku, Turku University Hospital, Hospital District of Southwest Finland),[12,14] Aino Stenius (University of Oulu, Oulu University Hospital),[12] Maria Särmä (Turku University Hospital, Hospital District of Southwest Finland), Sini Vainionpää (Turku University Hospital, Hospital District of Southwest Finland), Eeva Varjonen (University of Turku, Turku University Hospital, Hospital District of Southwest Finland),[12] Riitta Veijola, MD, PhD (University of Oulu, Oulu University Hospital),[14] Suvi M. Virtanen, MD, PhD (University of Tampere, Tampere University Hospital, National Institute for Health and Welfare, Finland),[2] Mari Vähä-Mäkilä (Turku University Hospital, Hospital District of Southwest Finland), and Mari Åkerlund (University of Tampere, Tampere University Hospital, National Institute for Health and Welfare, Finland).

The following were members of the Sweden Clinical Center: Åke Lernmark, PhD, Principal Investigator,[1,3–6,8,10,11,15] Daniel Agardh, MD, PhD,[13] Carin Andrén Aronsson,[2,13] Maria Ask, Jenny Bremer, Ulla-Marie Carlsson, Corrado Cilio, PhD, MD,[5] Emelie Ericson-Hallström, Lina Fransson, Thomas Gard, Joanna Gerardsson, Rasmus Bennet, Monica Hansen, Gertie Hansson,[12] Cecilia Harmby, Susanne Hyberg, Fredrik Johansen, Berglind Jonasdottir, MD, Helena Elding Larsson, MD, PhD,[6,14] Sigrid Lenrick Forss, Markus Lundgren, MD,[14] Maria Månsson-Martinez, Maria Markan, Jessica Melin,[12] Zeliha Mestan, Kobra Rahmati, Anita Ramelius, Anna Rosenquist, Falastin Salami, Sara Sibthorpe, Birgitta Sjöberg, Ulrica Swartling, PhD,[9,12] Evelyn Tekum Amboh, Erika Trulsson, Carina Törn, PhD,[3,15] Anne Wallin, Åsa Wimar,[12,14] and Sofie Åberg (Lund University).

The following were members of the Washington Clinical Center: William A. Hagopian, MD, PhD, Principal Investigator,[1,3–7,11,13,14] Michael Killian,[6,7,12,13] Claire Cowen Crouch,[12,14,15] Jennifer Skidmore,[2] Stephen Ayres, Kayleen Dunson, Rachel Hervey, Corbin Johnson, Rachel Lyons, Arlene Meyer, Denise Mulenga, Elizabeth Scott, Joshua Stabbert, Alexander Tarr, Morgan Uland, and John Willis (Pacific Northwest Diabetes Research Institute).

The following were members of the Pennsylvania Satellite Center: Dorothy Becker, MD, Margaret Franciscus, MaryEllen Dalmagro-Elias Smith,[2] Ashi Daftary, MD, Mary Beth Klein, and Chrystal Yates (Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center).

The following were members of the Data Coordinating Center: Jeffrey P. Krischer, PhD, Principal Investigator,[1,4,5,10,11] Michael Abbondondolo, Sarah Austin-Gonzalez, Sandra Baethke, Rasheedah Brown,[12,15] Brant Burkhardt, PhD,[5,6] Martha Butterworth,[2] Joanna Clasen, David Cuthbertson, Christopher Eberhard, Steven Fiske,[9] Dena Garcia, Jennifer Garmeson, Veena Gowda, Kathleen Heyman, Francisco Perez Laras, Hye-Seung Lee, PhD,[1,2,13,15] Shu Liu, Xiang Liu, PhD,[2,3,9,14] Kristian Lynch, PhD,[5,6,9,15] Jamie Malloy, Cristina McCarthy,[12,15] Wendy McLeod, Steven Meulemans, Chris Shaffer, Laura Smith, PhD,[9,12] Susan Smith,[12,15] Noah Sulman, PhD, Roy Tamura, PhD,[1,2,13] Ulla Uusitalo, PhD,[2,15] Kendra Vehik, PhD,[4–6,14,15] Ponni Vijayakandipan, Keith Wood, and Jimin Yang, PhD, RD[2,15]; and past staff included Lori Ballard and David Hadley, PhD (University of South Florida).

The project scientist was Beena Akolkar, PhD[1,3–7,10,11] (National Institutes of Diabetes and Digestive and Kidney Diseases).

The following were other contributors: Kasia Bourcier, PhD[5] (National Institutes of Allergy and Infectious Diseases), Thomas Briese, PhD[6,15] (Columbia University), Suzanne Bennett Johnson, PhD[9,12] (Florida State University) and Eric Triplett, PhD[6] (University of Florida).

The committees were as follows: [1]Ancillary Studies, [2]Diet, [3]Genetics, [4]Human Subjects/Publicity/Publications, [5]Immune Markers, [6]Infectious Agents, [7]Laboratory Implementation, [8]Maternal Studies, [9]Psychosocial, [10]Quality

Assurance, [11]Steering, [12]Study Coordinators, [13]Celiac Disease, [14]Clinical Implementation, and [15]Quality Assurance Subcommittee on Data Quality.

Supplementary Figure 1

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

References

1. Ludvigsson, J.F. and Green, P.H. Clinical management of coeliac disease. J Intern Med. 2011; 269: 560–571
2. Catassi, C., Gatti, S., and Fasano, A. The new epidemiology of celiac disease. J Pediatr Gastroenterol Nutr. 2014; 59: S7–S9
3. Sollid, L.M. and Thorsby, E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology. 1993; 105: 910–922
4. Hunt, K.A., Zhernakova, A., Turner, G. et al. Newly identified genetic risk variants for celiac disease related to the immune response. Nat Genet. 2008; 40: 395–402
5. Ivarsson, A., Persson, L.A., Nyström, L. et al. Epidemic of coeliac disease in Swedish children. Acta Paediatr. 2000; 89: 165–171
6. Ivarsson, A., Myléus, A., Norström, F. et al. Prevalence of childhood celiac disease and changes in infant feeding. Pediatrics. 2013; 131: e687–e694
7. Stördal, K., White, R.A., and Eggesbö, M. Early feeding and risk of celiac disease in a prospective birth cohort. Pediatrics. 2013; 132: e1202–e1209
8. Aronsson, C.A., Lee, H., Liu, E. et al. Age at gluten introduction and risk for celiac disease. Pediatrics. 2015; 135: 239–245
9. Vriezinga, S.M., Auricchio, R., Bravi, E. et al. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med. 2014; 371: 1304–1315
10. Lionetti, E., Castellaneta, S., Francavilla, R. et al. Introduction of gluten, HLA status and the risk of celiac disease in children. N Engl J Med. 2014; 371: 1295–1303
11. Ivarsson, A., Hernell, O., Stenlund, H. et al. Breast-feeding protects against celiac disease. Am J Clin Nutr. 2002; 75: 914–921
12. TEDDY Study group. The Environmental determinants of Diabetes in The Young (TEDDY) study: study design. Pediatr Diabetes. 2007; 8: 286–298
13. Liu, E., Lee, H., Aronsson, C.A. et al. HLA Haplotype and country and the risk of celiac disease in early childhood. N Engl J Med. 2014; 371: 42–49
14. Weile, B., Cavell, B., Nivenius, K. et al. Striking differences in the incidence of childhood celiac disease between Denmark and Sweden: a plausible explanation. J Pediatr Gastroenterol Nutr. 1995; 21: 64–68
15. TEDDY Study group. The Environmental Determinants of Diabetes in The Young (TEDDY) study. Ann N Y Acad Sci. 2008; 1150: 1–13
16. Hagopian, W.A., Erlich, H., Lernmark, Å. et al. The Environmental Determinants of Diabetes in The Young (TEDDY): genetic criteria and international diabetes risk screening of 410 000 infants. Pediatr Diabetes. 2011; 12: 733–743
17. Vehik, K., Fiske, S.W., Logan, C.D. et al. Methods, quality control and specimen management in an international multi-center investigation of type 1 diabetes: TEDDY. Diabetes Metab Res Rev. 2013; 29: 557–567
18. Yang, J., Lynch, K.F., Uusitalo, U. et al. Factors associated with longitudinal food record compliance in a paediatric cohort study. Public Health Nutr. 2015; 19: 1–10

19. Koskinen, O., Villanen, M., Korponay-Szabo, I. et al. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. J Pediatr Gastroenterol Nutr. 2009; 48: 559–565
20. Uusitalo, U., Kronberg-Kippilä, C., Andren Aronsson, C. et al. Food composition database harmonization for between-country comparisons of nutrient data in the TEDDY study. J Food Compost Anal. 2011; 24: 494–505
21. National Food Agency, Uppsala, Sweden. The Swedish Food Composition Database. Available: http://www.slv.se/en-gb/Group1/Food-and-Nutrition/The-Food-Database/. Assessed: November 20, 2014.
22. van Overbeek, F.M., Uil-Dieterman, I.G., Mol, I.W. et al. The daily gluten intake in relatives of patients with coeliac disease compared with that of the general Dutch population. Eur J Gastroenterol Hepatol. 1997; 9: 1097–1099
23. Arentz-Hansen, H., McAdam, S.N., Molberg, Ö. et al. Celiac lesion T cells recognize epitopes that cluster in regions of gliadines rich in proline residues. Gastroenterology. 2002; 123: 803–809
24. Mearin, M.L., Biemond, I., Peña, A.S. et al. HLA-DR phenotypes in Spanish coeliac children: their contribution to the understanding of the genetics of the disease. Gut. 1983; 24: 532–537
25. Tjon, J., van Bergen, J., and Koning, F. Celiac disease: how complicated can it get?. Immunogenetics. 2010; 62: 641–651
26. Vader, W., Stepniak, D., Kooy, Y. et al. The HLA-DQ2 gene dose effect in celiac disease is directly related to the magnitude and breadth of gluten-specific T cell responses. Proc Natl Acad Sci U S A. 2003; 100: 12390–12395
27. Andrén Aronsson, C., Uusitalo, U., Vehik, K. et al. Age at first introduction to complementary foods is associated with sociodemographic factors in children with increased genetic risk of developing type 1 diabetes. Matern Child Nutr. 2015; 11: 803–814
28. Ascher, H., Holm, K., Kristiansson, B. et al. Different features of coeliac disease in two neighbouring countries. Arc Dis Child. 1993; 69: 375–380
29. Almquist-Tangen, G., Dahlgren, J., Rosvall, J. et al. Milk cereal drink increases BMI risk at 12 and 18 months, but formula does not. Acta Paediatr. 2013; 102: 1174–1179