



Early Infant Diet and Islet Autoimmunity in the TEDDY Study

Diabetes Care 2018;41:522–530 | <https://doi.org/10.2337/dc17-1983>

Ulla Uusitalo,¹ Hye-Seung Lee,¹
Carin Andrén Aronsson,² Kendra Vehik,¹
Jimin Yang,¹ Sandra Hummel,³
Katherine Silvis,⁴ Åke Lernmark,²
Marian Rewers,⁵ William Hagopian,⁶
Jin-Xiong She,⁴ Olli Simell,⁷
Jorma Toppari,⁸ Anette-G. Ziegler,³
Beena Akolkar,⁹ Jeffrey Krischer,¹
Suvi M. Virtanen,^{10,11,12} Jill M. Norris,¹³
and the TEDDY Study Group*

OBJECTIVE

To examine duration of breastfeeding and timing of complementary foods and risk of islet autoimmunity (IA).

RESEARCH DESIGN AND METHODS

The Environmental Determinants of Diabetes in the Young (TEDDY) study prospectively follows 8,676 children with increased genetic risk of type 1 diabetes (T1D) in the U.S., Finland, Germany, and Sweden. This study included 7,563 children with at least 9 months of follow-up. Blood samples were collected every 3 months from birth to evaluate IA, defined as persistent, confirmed positive antibodies to insulin (IAAs), GAD, or insulinoma antigen-2. We examined the associations between diet and the risk of IA using Cox regression models adjusted for country, T1D family history, HLA genotype, sex, and early probiotic exposure. Additionally, we investigated martingale residuals and log-rank statistics to determine cut points for ages of dietary exposures.

RESULTS

Later introduction of gluten was associated with increased risk of any IA and IAA. The hazard ratios (HRs) for every 1-month delay in gluten introduction were 1.05 (95% CI 1.01, 1.10; $P = 0.02$) and 1.08 (95% CI 1.00, 1.16; $P = 0.04$), respectively. Martingale residual analysis suggested that the age at gluten introduction could be grouped as <4, 4–9, and >9 months. The risk of IA associated with introducing gluten before 4 months of age was lower (HR 0.68; 95% CI 0.47, 0.99), and the risk of IA associated with introducing it later than the age of 9 months was higher (HR 1.57; 95% CI 1.07, 2.31) than introduction between 4 and 9 months of age.

CONCLUSIONS

The timing of gluten-containing cereals and IA should be studied further.

The interplay between genes and environmental factors, such as diet, has been hypothesized to play an important role in triggering type 1 diabetes (T1D) (1,2), the incidence of which continues to increase globally (3).

The ability of breast milk to provide the required nutrients becomes limited among older infants. Therefore, timely introduction of complementary foods is essential for the baby's well-being and growth (4). To examine certain infant feeding practices, several studies have been carried out in populations with genetically increased T1D risk by focusing on an arbitrary chosen age range in relation to islet autoimmunity (IA) and/or T1D. It has been reported that a shorter duration of breastfeeding (5–7), certain “age windows” (≤ 3 and ≥ 7 months vs. 4–6 months) for introducing cereals (8,9), as well as early (<3–4 months) exposure to cow's milk (10,11), gluten-containing cereals

¹Health Informatics Institute, Department of Pediatrics, Morsani College of Medicine, University of South Florida, Tampa, FL

²Department of Clinical Sciences, Lund University, Malmö, Sweden

³Institute of Diabetes Research, Helmholtz Zentrum München and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München and Forschergruppe Diabetes e.V., Munich, Germany

⁴Medical College of Georgia, Augusta University, Augusta, GA

⁵Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, Aurora, CO

⁶Pacific Northwest Diabetes Research Institute, Seattle, WA

⁷Department of Pediatrics, University of Turku, Turku, Finland

⁸Department of Physiology, Institute of Biomedicine, University of Turku; Department of Pediatrics, Turku University Hospital, Turku, Finland

⁹National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

¹⁰Nutrition Unit, National Institute for Health and Welfare, Helsinki, Finland

¹¹Faculty of Social Sciences and Center for Child Health Research, University of Tampere and Tampere University Hospital, Tampere, Finland

¹²The Science Center of Pirkanmaa Hospital District, Tampere, Finland

¹³Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO

Corresponding author: Ulla Uusitalo, ulla.uusitalo@epi.usf.edu.

Received 22 September 2017 and accepted 8 December 2017.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1983/-/DC1>.

S.M.V. and J.M.N. share last authorship.

*A complete list of the TEDDY Study Group can be found in the Supplementary Data online.

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

(12,13), fruits and berries (9,14), and potatoes and root vegetables (14,15) may increase the risk of IA and/or T1D. However, a recent study (16) showed that this association between age at introduction of complementary foods and IA may decrease/disappear when the follow-up is extended, including older children. The association between the timing of food introduction and IA remains inconclusive because of inconsistent results (17). Types of early foods linked to IA/T1D seem to vary at least partly by country.

The mechanisms linking early feeding practices and the development of IA/T1D are not very well known, but those suggested to play a crucial role include immature and adverse immunological responses of the gut to complementary food (18,19), mucosal inflammation, and increased gut permeability (20,21).

This study aims to examine breastfeeding duration and the timing of initiating infant formula, regular cow's milk, and solid food in relation to the risk of IA in The Environmental Determinants of Diabetes in the Young (TEDDY) study. We investigated the overall association between those dietary exposures and the risk of IA. To our knowledge, this is the first attempt to analyze these dietary exposures without a predetermined categorization. Additionally, we examined whether a categorization of breastfeeding duration or age at initiating a food is statistically justified based on the association with the risk of IA in TEDDY.

RESEARCH DESIGN AND METHODS

Study Population

TEDDY is a prospective observational cohort with the primary aim to identify environmental causes of T1D. The study includes the following six clinical research centers: three in the U.S. (Colorado, Georgia/Florida, and Washington) and three in Europe (Finland, Germany, and Sweden). A total of 424,788 newborns were screened in hospitals affiliated with the study centers between September 2004 and February 2010, identifying 21,589 HLA-eligible infants. The HLA typing has been previously described in detail (22–24). Of the 8,676 enrolled subjects, 8,263 singleton babies were identified carrying one of the eligible HLA types with determined IA status. Of those, we included 7,572 subjects who were followed for at least 9 months to obtain complete information on the duration of

breastfeeding and the timing of the introduction of complementary foods. After excluding nine subjects who lacked information on early feeding, a total of 7,563 children were analyzed in this study. Their median (Q_3 – Q_1) follow-up time was 92 months (114–54).

Written informed consent was obtained for all children in the study from a parent or primary caretaker, separately, for genetic screening and participation in prospective follow-up. The study was approved by local institutional review or ethics boards and was monitored by an External Evaluation Committee formed by the National Institutes of Health.

IA

Blood samples using serum separation tubes were drawn every 3 months between 3 and 48 months of age and every 6 months thereafter, unless the autoantibodies developed in the child, in which case the child continued to be followed, including blood draws every 3 months. Serum was stored in two 0.5-mL cryovials for autoantibody measurements and were frozen within 2 h from collection. Persistent IA (any IA) was defined as confirmed positive insulin autoantibodies (IAAs), GAD antibody (GADA), specifically to isoform GAD₆₅, or insulinoma antigen-2 autoantibody, which were analyzed by radiobinding assays (25,26) on at least two consecutive study visits. All positive and 5% of negative islet autoantibodies were confirmed in the following central autoantibody laboratories: Barbara Davis Center for Childhood Diabetes, University of Colorado, in the U.S. and University of Bristol in the U.K., which both previously have found high sensitivity and specificity (27) and concordance. Positive results due to maternal IgG transmission when defining the child's IA status were omitted from the IA-positive group. The date of persistent IA was defined as the draw date of the first of two consecutive samples confirmed positive for a specific autoantibody, with which the child was deemed persistent. In addition to any IA, we separately studied children who had either IAAs alone or GADAs alone as their first appearing autoantibody. The median age (Q_3 – Q_1) of children at IA seroconversion was 33 months (62–16) ($n = 703$). The median (Q_3 – Q_1) values were 21 months (40–11) for IAAs ($n = 272$) and 46 months (77–25) for GADAs ($n = 299$), respectively.

Characteristics, Diet, and Health Monitoring of the Study Population

Demographic characteristics, family history of diabetes, and infant feeding practices were obtained from various questionnaires and have been explained previously (28). Information about infant feeding (breastfeeding and food introductions) was recorded by parents in a diary ("TEDDY Book") at home and collected every 3 months during the clinic visits or over the phone starting at 3 months of age. This information was recorded in the TEDDY Book until the clinic visit at 24 months except for any breastfeeding, which was followed up to 5 years of age. If the breastfeeding duration was >5 years, the child was not introduced to a complementary food by 24 months of age, or the correct timing of food introduction was not available, the information was regarded as unknown. The duration of breastfeeding that corresponded to the age when breastfeeding ended (exclusive and any) and the ages at which consumption of infant formula and solid foods started were examined in relation to IA. A baby was considered to be exclusively breastfed when his/her diet included only breast milk and possibly small amounts of non-nutritious drinks (e.g., water). Any breastfeeding could also be accompanied by other foods in the diet. The infant formula in this study included the following: commercial infant formulas that contain intact cow's milk proteins or cow's milk proteins hydrolyzed to any degree, soy formula, elemental formula, regular cow's milk and other animals' milks, and vegetarian "milks." The solid foods that were studied separately in this study included the following: any type of cereal (wheat, rye, barley, oat, rice, or any other nongluten cereal), gluten-containing cereals (wheat, rye, and barley), rice, potatoes, root vegetables, fruits and berries, meat (beef, pork, game, and/or poultry), eggs, fish, and other seafood (Table 1). In addition to these foods, the "any solid food" included milk products (e.g., cheese, yogurt), sausages, and various vegetables. The age at the introduction of any solid food was defined as the earliest time when any of the aforementioned solid foods were introduced. "Selected foods" included foods found to be associated with IA/T1D in the earlier studies, as follows: cereals (IA), including rice/oat (T1D) and gluten-containing cereals (IA); potatoes (IA); root

Table 1—Description of foods and food groups studied in relation to the risk of IA

Dietary Exposures		
Breastfeeding and food exposures that were each studied separately	Selected foods: foods associated with IA in previous studies; they were studied as one combined variable	Any solid food: all solid foods that were studied as one combined variable
Exclusive breastfeeding		
Any breastfeeding		
Infant formula		
Cow's milk (any cow's milk exposure)		
All cereals	All cereals	All cereals
Gluten-containing cereals	Gluten-containing cereals	Gluten-containing cereals
Rice	Rice	Rice
Fruits and berries	Fruits and berries	Fruits and berries
Potatoes	Potatoes	Potatoes
Root vegetables	Root vegetables	Root vegetables
Meat (beef, pork, poultry, game)		Meat (beef, pork, poultry, game)
Fish and seafood		Fish and seafood
Egg	Egg	Egg Milk products (yogurt, sour cream, cheese, commercial baby foods containing yogurt, cottage cheese) Spinach Peas, green beans Cabbages (Chinese cabbage, red cabbage, cauliflower, broccoli, kale, cabbage turnip, collard, mustard green, turnip greens) Squash, pumpkin Tomato, tomato sauce Corn Other vegetable Sausage, hot dogs

Variables studied are shown in bold.

vegetables (IA); fruits and berries (IA/T1D); and eggs (IA) (8,9,12,14,15).

Statistical Analysis

Cox proportional hazards models were used to study the association between dietary exposures (duration of breastfeeding and age of initiating a food, as defined above) and the risk of IA, after adjusting for country, T1D family history (first-degree relative [FDR]), sex of the child, HLA (DR3/4 vs. other genotypes), and exposure to probiotics at <28 days of age. Time of seroconversion was the age when the first blood sample for persistent IA was drawn. Time for right censoring was the age when the last blood sample in the follow-up was determined to be negative for IA. A proportional cause-specific hazard model for first-appearing IAA or first-appearing GADA was used by treating events other than the one of interest as censored observations. In each risk set, including those who experienced the event of interest and those who were

event free by a certain age, the age of initiating consumption of a food was analyzed in those who had initiated consumption of the food at an age younger than that of the risk set.

The functional form of each dietary exposure and IA association was explored by plotting martingale residuals with a loess smoothing parameter of 0.4. Additionally, we applied the change-point method, based on the log-rank statistic, in order to find a cut point for each dietary exposure dichotomization in relation to the risk of IA (29).

Two-sided *P* values <0.05 were considered to determine a statistical significance. All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Characteristics and potential confounders associated with risk of any IA are presented in Table 2. After adjusting for those factors, we found that later introduction

of gluten-containing cereals was associated with increased risk of any IA (hazard ratio [HR] for 1-month delay 1.05; 95% CI 1.01, 1.10; *P* = 0.02) and with increased risk of IAA (HR for 1-month delay 1.08; 95% CI 1.00, 1.16; *P* = 0.04) (Table 3). When examining the durations of exclusive breastfeeding and any breastfeeding, the timing of any infant formula, the timing of single foods other than gluten-containing cereals, or any solid food introduction as a combined variable of exposures of solid foods, we could not detect any association between them and the risk of outcomes (Table 3). There were 959 children (12.7%) who moved straight from breast milk to solid food (e.g., milk-based thin porridges) and therefore had no values for age of introduction of infant formula.

The martingale residual analysis showed changes in the association between age of introduction of gluten-containing cereals and the risk of any IA. There was an increasing trend of risk between 0 and 4 months,

Table 2—Characteristics associated with any IA

	Study population, N			Any IA (N = 703)			IAA (N = 272)			GADA (N = 299)		
	N	N (%)	HR (95% CI)	P value	N (%)	HR (95% CI)	P value	N (%)	HR (95% CI)	P value		
Country												
Finland	1,654	180 (25.6)	1.40 (1.15, 1.71)	<0.001	89 (32.7)	2.28 (1.67, 3.11)	<0.001	110 (36.8)	1.00 (0.72, 1.39)	0.999		
Germany	510	54 (7.7)	1.30 (0.96, 1.76)	0.092	20 (7.4)	1.36 (0.82, 2.25)	0.234	60 (20.1)	0.82 (0.47, 1.42)	0.471		
Sweden	2,283	240 (34.1)	1.30 (1.08, 1.56)	0.005	83 (30.5)	1.38 (1.02, 1.89)	0.039	15 (5.0)	1.25 (0.96, 1.62)	0.103		
U.S.	3,116	229 (32.6)	1		80 (29.4)	1		114 (38.1)	1			
High-risk HLA genotype (DR3/4)												
Yes	2,956	344 (48.9)	1.61 (1.38, 1.88)	<0.001	128 (47.1)	1.54 (1.21, 1.96)	<0.001	150 (50.2)	1.65 (1.31, 2.07)	<0.001		
No	4,607	359 (51.1)	1		144 (52.9)	1		149 (49.8)	1			
FDR with T1D												
Yes	857	136 (19.4)	1.99 (1.64, 2.43)	<0.001	58 (21.3)	2.32 (1.71, 3.15)	<0.001	52 (17.4)	1.85 (1.36, 2.53)	<0.001		
No	6,706	567 (80.6)	1		214 (78.7)	1		247 (82.6)	1			
Sex of the child												
Female	3,698	322 (45.8)	0.87 (0.75, 1.00)	0.056	152 (44.1)	0.81 (0.64, 1.03)	0.079	144 (48.2)	0.95 (0.76, 1.19)	0.661		
Male	3,865	381 (54.2)	1		120 (55.9)	1		155 (51.8)	1			
Probiotics, age at first exposure												
<28 days	538	41 (5.8)	0.70 (0.50, 0.97)	0.022	15 (5.5)	0.53 (0.31, 0.91)	0.021	15 (5.0)	0.72 (0.42, 1.24)	0.237		
≥28 days	7,025	662 (94.2)	1		257 (94.5)	1		284 (95.0)	1			

a plateau from 4 to 9 months, and increasing risk again at introductions from 9 months on (Supplementary Fig. 1). The application of the change-point method revealed a significant dichotomization in the duration of any breastfeeding (at 7 months of age with any IA and at 6 months of age with GADA), age of introducing cow's milk (at 5 months of age with any IA), cereals (at 4 months of age with any IA), rice (at 7 months of age with any IA and at 6 months of age with GADA), fruits and berries (at 4 months of age with any IA), potato (at 4 months of age with any IA), meat (at 8 months of age with any IA), egg (at 9 months of age with any IA), and fish and seafood (at 9 months of age with GADA).

We applied the data-driven categorizations of dietary exposures in evaluating the risk of IA. When compared with the introduction at 4–9 months of age (Supplementary Fig. 1), introduction of gluten-containing cereals before 4 months of age showed decreased risk of any IA (HR 0.68; 95% CI 0.47, 0.99) but increased risk of any IA (HR 1.57; 95% CI 1.07, 2.31) if introduced after 9 months of age. The HRs remained similar in the introduction of gluten-containing cereals before 4 months of age when adjusted for country of residence, HLA, FDR with T1D, sex of the child, and early exposure to probiotics (HR 0.67; 95% CI 0.54, 0.98; *P* = 0.04). When the dichotomizations were applied, the risk difference between the two timing categories of duration of breastfeeding and food introductions was not very noticeable. However, the introduction of egg at or before 9 months of age showed consistently lower risk of any IA compared with introduction after 9 months of age both in the unadjusted analysis (HR 0.86; 95% CI 0.74, 0.99) and in the adjusted analysis (HR 0.84; 95% CI 0.72, 0.99) (Table 4).

CONCLUSIONS

Data from the multinational prospective TEDDY Study suggests that later introduction of gluten-containing cereals is associated with increased risk of any IA and IAA. The residual plot suggested a plateau in risk at introduction between 4 and 9 months of age, and the results from categorized analysis supported that, as well as the overall finding that later introduction of gluten-containing cereals is associated with increased risk of IA.

The major strength of the study was its consistently collected data using the same

Table 3—Association of timing of dietary exposures with the risk of IA (any IA, IAA, or GADA)

Dietary exposure	IA	Duration of breastfeeding or age at introduction of food (months)				Among those who developed autoantibodies				Among those who did not develop autoantibodies			
		N	Not breastfed or food was not introduced by the end of follow-up (%)		N	Not breastfed or food was not introduced by the end of follow-up (%)		N	Not breastfed or food was not introduced by the end of follow-up (%)		Mean (SD)	HR (95% CI)*	P value*
			Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)						
Exclusive breastfeeding	Any IA	703	0	1.3 (1.9)	6,860	0	1.2 (1.8)	1.00 (0.96, 1.04)	0.980				
	IAA	272		1.4 (1.9)	7,291		1.2 (1.8)	1.01 (0.95, 1.07)	0.763				
	GADA	299		1.3 (1.9)	7,264		1.2 (1.8)	1.01 (0.95, 1.07)	0.810				
Any breastfeeding	Any IA	694	1.3	8.4 (7.3)	6,617	3.5	7.4 (6.4)	1.01 (1.00, 1.02)	0.118				
	IAA	270		8.5 (6.7)	7,041		7.5 (6.5)	1.01 (0.99, 1.03)	0.205				
	GADA	294		8.6 (8.2)	7,017		7.4 (6.5)	1.01 (1.00, 1.03)	0.123				
Any infant formula	Any IA	598	14.9	1.2 (2.5)	6,006	12.4	1.2 (2.3)	0.99 (0.96, 1.02)	0.522				
	IAA	235		1.4 (2.7)	6,369		1.2 (2.3)	1.02 (0.96, 1.05)	0.574				
	GADA	257		1.3 (2.5)	6,347		1.2 (2.3)	1.01 (0.96, 1.06)	0.696				
Cow's milk	Any IA	701	0.3	2.1 (3.1)	6,824	0.5	1.8 (2.8)	1.01 (0.98, 1.04)	0.474				
	IAA	270		2.2 (3.2)	7,255		1.8 (2.8)	1.02 (0.98, 1.07)	0.301				
	GADA	299		2.0 (3.0)	7,226		1.9 (2.8)	1.01 (0.97, 1.05)	0.613				
Any solid food	Any IA	701	0.3	3.6 (1.4)	6,839	0.3	3.5 (1.4)	1.03 (0.97, 1.09)	0.384				
	IAA	272		3.5 (1.4)	7,268		3.5 (1.4)	0.99 (0.90, 1.08)	0.757				
	GADA	297		3.7 (1.3)	7,243		3.5 (1.4)	1.07 (0.97, 1.17)	0.159				
Selected foods	Any IA	701	0.3	3.7 (1.3)	6,838	0.3	3.6 (1.4)	1.03 (0.97, 1.09)	0.368				
	IAA	272		3.6 (1.3)	7,267		3.6 (1.4)	1.01 (0.91, 1.11)	0.873				
	GADA	297		3.7 (1.3)	7,242		3.6 (1.4)	1.00 (1.00, 1.01)	0.118				
Cereals, any	Any IA	699	0.6	4.4 (1.4)	6,810	0.7	4.2 (1.4)	1.03 (0.97, 1.10)	0.330				
	IAA	271		4.4 (1.4)	7,238		4.2 (1.4)	1.01 (0.91, 1.14)	0.789				
	GADA	296		4.3 (1.3)	7,213		4.2 (1.4)	1.03 (0.94, 1.14)	0.525				
Gluten-containing cereals	Any IA	699	0.6	5.8 (2.1)	6,708	2.2	5.7 (2.0)	1.05 (1.01, 1.10)	0.023				
	IAA	271		5.9 (2.1)	7,136		5.7 (2.0)	1.08 (1.00, 1.16)	0.038				
	GADA	296		5.8 (2.0)	7,111		5.7 (2.0)	1.06 (0.99, 1.13)	0.121				
Rice	Any IA	699	0.6	5.0 (1.9)	6,755	1.5	4.8 (1.8)	1.02 (0.97, 1.07)	0.445				
	IAA	271		5.1 (2.0)	7,183		4.8 (1.8)	1.01 (0.93, 1.10)	0.779				
	GADA	296		4.8 (1.7)	7,158		4.8 (1.8)	1.00 (0.93, 1.08)	0.936				
Root vegetables	Any IA	701	0.3	4.3 (1.2)	6,806	0.8	4.3 (1.3)	1.03 (0.96, 1.10)	0.464				
	IAA	272		4.2 (1.2)	7,235		4.3 (1.3)	1.00 (0.90, 1.12)	0.942				
	GADA	297		4.4 (1.3)	7,210		4.3 (1.3)	1.05 (0.95, 1.16)	0.352				
Potatoes	Any IA	699	0.6	5.2 (2.2)	6,698	2.4	5.3 (2.4)	1.05 (1.00, 1.10)	0.051				
	IAA	271		5.1 (2.1)	7,126		5.3 (2.4)	1.05 (0.97, 1.14)	0.200				
	GADA	296		5.4 (2.4)	7,101		5.3 (2.3)	1.06 (0.99, 1.13)	0.116				

Continued on p. 527

Table 3—Continued

Dietary exposure	Duration of breastfeeding or age at introduction of food (months)									
	Among those who developed autoantibodies					Among those who did not develop autoantibodies				
	IA	N	Not breastfed or food was not introduced by the end of follow-up (%)	Mean (SD)	N	Not breastfed or food was not introduced by the end of follow-up (%)	Mean (SD)	HR (95% CI)*	P value*	
Fruits or berries	Any IA	700	0.4	4.3 (1.4)	6,806	0.8	4.2 (1.5)	1.04 (0.98, 1.10)	0.167	
	IAA	272		4.3 (1.5)	7,234		4.2 (1.5)	1.04 (0.95, 1.14)	0.372	
	GADA	296		4.4 (1.4)	7,210		4.2 (1.5)	1.05 (0.96, 1.14)	0.315	
Meat	Any IA	692	1.6	6.0 (1.8)	6,676	2.7	6.1 (2.0)	1.02 (0.97, 1.08)	0.457	
	IAA	269		6.0 (1.7)	7,099		6.1 (2.0)	1.03 (0.94, 1.12)	0.564	
	GADA	292		6.1 (2.0)	7,076		6.1 (2.0)	1.04 (0.96, 1.12)	0.364	
Egg	Any IA	684	2.7	8.9 (2.5)	6,458	5.9	8.7 (2.5)	1.02 (0.99, 1.05)	0.288	
	IAA	266		8.9 (2.7)	6,876		8.7 (2.5)	1.00 (0.95, 1.06)	0.878	
	GADA	290		8.9 (2.4)	6,852		8.7 (2.5)	1.04 (0.99, 1.09)	0.140	
Fish or other seafood	Any IA	662	5.8	8.6 (3.6)	6,210	9.5	8.6 (3.6)	1.01 (0.98, 1.04)	0.537	
	IAA	256		8.5 (3.8)	6,616		8.6 (3.6)	0.99 (0.94, 1.05)	0.810	
	GADA	280		8.7 (3.6)	6,592		8.6 (3.6)	1.03 (0.98, 1.08)	0.258	

*HR and corresponding P value were obtained from the Cox regression model adjusted for country, HLA genotype, FDR status, sex of the child, and probiotic use <28 days. HRs reflect the change in the risk with 1-month longer breastfeeding or 1-month delay in food introduction.

protocol and questionnaires across four TEDDY countries. Including larger geographical areas in the study made it possible to consider the importance of varying feeding habits. Additionally, both continuous and statistically derived categorized exposures were used in the investigation of associations. As a limitation, we did not record the amounts of the introduced food or count the initial frequency of feeding the new food. Thus, the cumulative exposure of a new food or foods was not possible to study.

When studying introductions of solid foods, we found that later introduction of gluten-containing cereals was associated with increased risk of IA. Later introduction of foods into a diet overall may be associated with larger initial amounts of food given to the children. Larger amounts can be challenging to their immature immune system and can therefore hamper the development of tolerance to foreign antigens. Very few studies have investigated the amounts of food at early age and a risk of disease. Aronsson et al. (30) suggested that a larger amount of gluten consumed during the first 2 years of life was associated with increased risk of celiac disease. However, we did not study the amounts of foods given in this study. A positive association between the early introduction of gluten-containing foods (<3 months vs. later introduction with exclusive breastfeeding until 3 months of age) (12), as well as early (≤ 3 months vs. 4–6 months) and late (≥ 7 months vs. 4–6 months) introductions of any cereals (8), and the risk of IA has been reported among children with increased risk of T1D. Our results did not support the finding related to early gluten introduction and the risk of IA by Ziegler et al. (12).

The preferred first solid foods varies among the countries, for example, cereals in the U.S. and fruits, potato, and root vegetables in Finland (28). It appears that the first solid food a child consumed was most often associated with IA risk (8,14,15). This could be interpreted in a way that the type of complementary food first introduced may be of less importance to the disease risk than the timing of introduction of any first solid food. However, we did not observe an association between any first solid food consumed, as defined in Table 1, and IA in the TEDDY cohort.

The finding related to early introduction (≤ 9 months vs. at a later age) of egg and

Table 4—Categorized duration of breastfeeding and timing of introduction of complementary foods and risk of IA (any IA or GADA)

IA	Dietary exposure*	Timing in months*	Number of children who developed any IA or GADA, N (%)	Number of children who did not develop any IA or GADA, N (%)	Unadjusted HR (95% CI)	P value	Adjusted† HR (95% CI)	P value
Any IA	Gluten-containing cereals	<4	28 (6)	445 (94)	0.68 (0.47, 0.99)	0.047	0.67 (0.54, 0.98)	0.037
		4–9	637 (10)	6,048 (90)	1		1	
	Any breastfeeding	>9	31 (14)	185 (86)	1.57 (1.07, 2.31)	0.022	1.44 (0.97, 2.16)	0.074
		≤7	334 (9)	3,575 (91)	0.93 (0.80, 1.08)	0.326	0.94 (0.81, 1.09)	0.426
		>7	360 (11)	3,042 (89)	1		1	
	Cow's milk	≤5	584 (10)	5,922(91)	0.83 (0.68, 1.00)	0.055	0.85 (0.69, 1.04)	0.115
		>5	117 (11)	902 (89)	1		1	
	Cereals	≤4	483 (9)	4,765 (91)	0.99 (0.85, 1.17)	0.945	1.09 (0.92, 1.30)	0.309
		>4	216 (10)	2,045 (90)	1		1	
	Rice	≤7	618 (9)	6,196 (91)	0.79 (0.63, 0.99)	0.046	0.87 (0.69, 1.10)	0.233
		>7	75 (13)	502 (87)	1		1	
	Fruit and berries	≤4	460 (9)	4,552 (91)	0.99 (0.85, 1.15)	0.868	1.00 (0.85, 1.18)	0.999
		>4	240 (10)	2,254 (90)	1		1	
	Potato	≤7	578 (10)	5,345 (90)	1.19 (0.98, 1.45)	0.077	0.98 (0.77, 1.25)	0.898
		>7	121 (8)	1,353 (92)	1		1	
Meat	≤8	615 (10)	5,762 (90)	1.27 (1.01, 1.59)	0.040	1.13 (0.88, 1.45)	0.344	
	>8	77 (8)	914 (92)	1		1		
Egg	≤9	282 (9)	3,002 (91)	0.86 (0.74, 0.99)	0.045	0.84 (0.72, 0.99)	0.035	
	>9	402 (10)	3,456 (90)	1		1		
GADA	Any breastfeeding	≤6	120 (3)	3,476 (97)	1.20 (0.95, 1.52)	0.126	1.17 (0.92, 1.49)	0.196
		>6	174 (5)	3,541 (95)	1		1	
	Rice	≤6	264 (4)	6,435 (96)	1.25 (0.87, 1.78)	0.224	1.10 (0.76, 1.58)	0.623
		>6	28 (4)	664 (96)	1		1	
	Fish and seafood	≤9	188 (4)	4,538 (96)	0.88 (0.70, 1.12)	0.290	1.11 (0.81, 1.53)	0.507
		>9	92 (4)	2,054 (96)	1		1	

*Dietary exposure: timing of breastfeeding or food; categorization of timing of gluten-containing cereals' introductions was based on martingale residuals whereas dichotomizations of timing of other dietary exposures in relation to the risk of any IA or GADA were based on change-point methods using log-rank test (28); only statistically significant ($P < 0.05$) cut points are shown. No statistically significant cut point of timing of a dietary exposure for IAA was detected. †The Cox regression model was adjusted for country, HLA genotype, FDR status, sex of the child, and probiotic use <28 days.

decreased risk of IA contradicted the finding by Virtanen et al. (15), who suggested that the early introduction of egg (<8 months vs. later) was linked to increased risk of IA during the first 3 years of life. In a recent study in the same population (16), this association was no longer found after children older than 3 years of age were included in the analysis. However, the association in the current study was quite weak, and no association was observed when the egg exposure was investigated as a continuous variable.

Our findings related to the timing of gluten-containing cereals and egg are not consistent with the findings from earlier studies, and the reasons for that can be speculated. Previous studies have been carried out in populations within small geographical areas. The type and timing of first complementary foods as well as the length of the follow-up have varied between the study populations. Moreover, timing has been studied using arbitrary categorization of dietary exposures. There have been differences in the use of dietary supplements (28,31) as well as in types of infant formula (32). Variations in HLA genotype eligibility between the studies may also have contributed to the discrepant findings. It is important to recognize that infant feeding habits change over time. New types of processed foods and dietary supplements are continuously adopted. Use of probiotics during the first year of life has become more common among children in the TEDDY study (31), and they are often given concurrently with new solid foods. Wheat is the main source of gluten in an infant diet (30) and is also an important source of prebiotics (9). Early exposure of both probiotics and prebiotics in gluten-containing cereals like wheat may provide a favorable base for beneficial gut microbiota. However, the role of dietary gluten and wheat in the etiology of T1D remains controversial in animal models (33–35). It has been suggested that wheat may result in mimicry-induced autoimmune disorders given that its peptide sequence is similar to that of human tissue, such as human islet cell tissue (36).

This was the first international study where duration of breastfeeding and timing of the introduction of new foods and their relationship with T1D-related autoantibodies were studied. Overall, we could not confirm the previously published findings between early infant feeding and the risk of IA. Nevertheless, the timing of gluten-

containing cereals and the appearance of islet autoantibodies should be studied further. New dietary recommendations for early infant feeding cannot be made based on the current results.

Funding. The TEDDY Study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases grants U01-DK-63829, U01-DK-63861, U01-DK-63821, U01-DK-63865, U01-DK-63863, U01-DK-63836, U01-DK-63790, UC4-DK-63829, UC4-DK-63861, UC4-DK-63821, UC4-DK-63865, UC4-DK-63863, UC4-DK-63836, UC4-DK-95300, UC4-DK-100238, and UC4-DK-106955, and Contract No. HHSN267200700014C; the National Institute of Allergy and Infectious Diseases; the National Institute of Child Health and Human Development; the National Institute of Environmental Health Sciences; JDRF; and the Centers for Disease Control and Prevention. This work was supported in part by the National Institutes of Health/National Center for Advancing Translational Sciences Clinical and Translational Science Awards to the University of Florida (UL1-TR-000064) and the University of Colorado (UL1-TR-001082).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. U.U. contributed to the study design and the acquisition, analysis, and interpretation of data and drafted the article. H.-S.L. performed statistical analysis and contributed to the interpretation of data and the drafting of the manuscript. C.A.A., K.V., J.Y., S.H., and K.S. contributed to the acquisition and interpretation of the data and critically reviewed the manuscript. Å.L., M.R., W.H., J.-X.S., O.S., J.T., A.-G.Z., B.A., J.K., S.M.V., and J.M.N. contributed to the study concept and design and the acquisition and interpretation of data and critically reviewed the manuscript. U.U. and H.-S.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

- Pociot F, McDermott MF. Genetics of type 1 diabetes mellitus. *Genes Immun* 2002;3:235–249
- Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? *Diabetes Metab Res Rev* 2011;27:3–13
- Tuomilehto J. The emerging global epidemic of type 1 diabetes. *Curr Diab Rep* 2013;13:795–804
- Agostoni C, Decsi T, Fewtrell M, et al.; ESPGHAN Committee on Nutrition. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110
- Kimpimäki T, Erkkola M, Korhonen S, et al. Short-term exclusive breastfeeding predisposes young children with increased genetic risk of Type 1 diabetes to progressive beta-cell autoimmunity. *Diabetologia* 2001;44:63–69
- Holmberg H, Wahlberg J, Vaarala O, Ludvigsson J; ABIS Study Group. Short duration of breast-feeding as a risk-factor for beta-cell autoantibodies in 5-year-old children from the general population. *Br J Nutr* 2007;97:111–116
- Lund-Blix NA, Stene LC, Rasmussen T, Torjesen PA, Andersen LF, Rønningen KS. Infant feeding in relation to islet autoimmunity and type 1 diabetes

in genetically susceptible children: the MIDIA Study. *Diabetes Care* 2015;38:257–263

8. Norris JM, Barriga K, Klingensmith G, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA* 2003;290:1713–1720

9. François IE, Lescroart O, Veraverbeke WS, et al. Effects of a wheat bran extract containing arabinoxylan oligosaccharides on gastrointestinal health parameters in healthy adult human volunteers: a double-blind, randomised, placebo-controlled, cross-over trial. *Br J Nutr* 2012;108:2229–2242

10. Virtanen SM, Räsänen L, Ylönen K, et al.; The Childhood in Diabetes in Finland Study Group. Early introduction of dairy products associated with increased risk of IDDM in Finnish children. *Diabetes* 1993;42:1786–1790

11. Wahlberg J, Vaarala O, Ludvigsson J; ABIS-study group. Dietary risk factors for the emergence of type 1 diabetes-related autoantibodies in 2½-year-old Swedish children. *Br J Nutr* 2006;95:603–608

12. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003;290:1721–1728

13. Chmiel R, Beyerlein A, Knopff A, Hummel S, Ziegler AG, Winkler C. Early infant feeding and risk of developing islet autoimmunity and type 1 diabetes. *Acta Diabetol* 2015;52:621–624

14. Virtanen SM, Kenward MG, Erkkola M, et al. Age at introduction of new foods and advanced beta cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes. *Diabetologia* 2006;49:1512–1521

15. Virtanen SM, Takkinen HM, Nevalainen J, et al. Early introduction of root vegetables in infancy associated with advanced β-cell autoimmunity in young children with human leukocyte antigen-conferred susceptibility to type 1 diabetes. *Diabet Med* 2011;28:965–971

16. Hakola L, Takkinen HM, Niinistö S, et al. Infant feeding in relation to the risk of advanced islet autoimmunity and type 1 diabetes in children with HLA-conferred disease susceptibility to type 1 diabetes: a cohort study. *Am J Epidemiol* 2018;187:34–44

17. Nucci AM, Virtanen SM, Becker DJ. Infant feeding and timing of complementary foods in the development of type 1 diabetes. *Curr Diab Rep* 2015;15:62

18. Westerholm-Ormio M, Vaarala O, Pihkala P, Ilonen J, Savilahti E. Immunologic activity in the small intestinal mucosa of pediatric patients with type 1 diabetes. *Diabetes* 2003;52:2287–2295

19. Savilahti E, Akerblom HK, Tainio VM, Koskimies S. Children with newly diagnosed insulin dependent diabetes mellitus have increased levels of cow's milk antibodies. *Diabetes Res* 1988;7:137–140

20. Morris G, Berk M, Carvalho AF, Caso JR, Sanz Y, Maes M. The role of microbiota and intestinal permeability in the pathophysiology of autoimmune and neuroimmune processes with an emphasis on inflammatory bowel disease type 1 diabetes and chronic fatigue syndrome. *Curr Pharm Des* 2016;22:6058–6075

21. Li X, Atkinson MA. The role for gut permeability in the pathogenesis of type 1 diabetes—a solid or leaky concept? *Pediatr Diabetes* 2015;16:485–492

22. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design. *Pediatr Diabetes* 2007;8:286–298
23. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) Study. *Ann N Y Acad Sci* 2008;1150:1–13
24. Hagopian WA, Erlich H, Lernmark A, et al.; TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY): genetic criteria and international diabetes risk screening of 421 000 infants. *Pediatr Diabetes* 2011;12:733–743
25. Bonifacio E, Yu L, Williams AK, et al. Harmonization of glutamic acid decarboxylase and islet antigen-2 autoantibody assays for National Institute of Diabetes and Digestive and Kidney Diseases consortia. *J Clin Endocrinol Metab* 2010;95:3360–3367
26. Babaya N, Yu L, Miao D, et al. Comparison of insulin autoantibody: polyethylene glycol and micro-IAA 1-day and 7-day assays. *Diabetes Metab Res Rev* 2009;25:665–670
27. Törn C, Mueller PW, Schlosser M, Bonifacio E, Bingley PJ; Participating Laboratories. Diabetes Antibody Standardization Program: evaluation of assays for autoantibodies to glutamic acid decarboxylase and islet antigen-2. *Diabetologia* 2008; 51:846–852
28. Andrén Aronsson C, Uusitalo U, Vehik K, et al.; TEDDY Study Group. 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
29. Contal C, O’Quigley J. An application of change-point methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal* 1999;30:253–270
30. Andrén Aronsson C, Lee HS, Koletzko S, et al.; TEDDY Study Group. Effects of gluten intake on risk of celiac disease: a case-control study on a Swedish birth cohort. *Clin Gastroenterol Hepatol* 2016; 14:403–409.e3
31. Uusitalo U, Liu X, Yang J, et al.; TEDDY Study Group. Association of early exposure of probiotics and islet autoimmunity in the TEDDY Study. *JAMA Pediatr* 2016;170:20–28
32. Hummel S, Beyerlein A, Tamura R, et al.; TEDDY Study Group. First infant formula type and risk of islet autoimmunity in The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Diabetes Care* 2017;40:398–404
33. Funda DP, Kaas A, Bock T, Tlaskalová-Hogenová H, Buschard K. Gluten-free diet prevents diabetes in NOD mice. *Diabetes Metab Res Rev* 1999;15:323–327
34. Funda DP, Kaas A, Tlaskalová-Hogenová H, Buschard K. Gluten-free but also gluten-enriched (gluten+) diet prevent diabetes in NOD mice; the gluten enigma in type 1 diabetes. *Diabetes Metab Res Rev* 2008;24:59–63
35. Gorelick J, Yarmolinsky L, Budovsky A, et al. The impact of diet wheat source on the onset of type 1 diabetes mellitus—lessons learned from the non-obese diabetic (NOD) mouse model. *Nutrients* 2017;9:482
36. Vojdani A. Molecular mimicry as a mechanism for food immune reactivities and autoimmunity. *Altern Ther Health Med* 2015;21(Suppl. 1): 34–45