Early Infant Diet and Islet Autoimmunity in the TEDDY Study

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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

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

(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 GAD_{65}, 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 nonnutritious 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 (%)	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)

		Duration of breastfeeding or age at introduction of food (months)							
		Among those who developed autoantibodies			Among those who did not develop autoantibodies				
Dietary exposure	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*
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

		Duration of breastfeeding or age at introduction of food (months)							
		Among those who developed autoantibodies			Among those who did not develop autoantibodies				
Dietary exposure	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 (≥7months 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	
		>9	31 (14)	185 (86)	1.57 (1.07, 2.31)	0.022	1.44 (0.97, 2.16)	0.074
	Any breastfeeding	≤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.

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