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HLA Genotype and Probiotics Modify the Association Between Timing of Solid Food Introduction and Islet Autoimmunity in the TEDDY Study

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IA, islet autoimmunity; T1D, type 1 diabetes.

ARTICLE HIGHLIGHTS

- Children with the HLA-DR3/4 genotype demonstrated increased risk of islet autoimmunity if solid food was introduced before 6 months of age.
- The association was not present in children who were exposed to probiotics at an early age.
- It is important to investigate the function and immune responses to the host microbiome when studying early diet, including probiotics and islet autoimmunity in genetically high-risk children.





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OBJECTIVE

To study the interaction among HLA genotype, early probiotic exposure, and timing of complementary foods in relation to 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. We used a Cox proportional hazards regression model adjusting for potential confounders to study early feeding and the risk of IA in a sample of 7,770 children.

RESULTS

Any solid food introduced early (<6 months) was associated with increased risk of IA if the child had the HLA DR3/4 genotype and no probiotic exposure during the 1st year of life. Rice introduced at 4–5.9 months compared with later in the U.S. was associated with an increased risk of IA.

CONCLUSIONS

Timing of solid food introduction, including rice, may be associated with IA in children with the HLA DR3/4 genotype not exposed to probiotics. The microbiome composition under these exposure combinations requires further study.

Class II HLA haplogenotypes account for about one-half of the genetic risk for islet autoimmunity (IA) and the later progression to type 1 diabetes (1). In addition to genes, environmental factors, including early diet, have been shown to be associated with the risk of IA (2). Probiotic use any time during the first 27 days of life was inversely associated with IA among children with the high-risk HLA DR3/4 genotype for type 1 diabetes in The Environmental Determinants of Diabetes in the Young (TEDDY) study (3). The objective of the current study was to investigate the interaction among timing of introduction of complementary foods, HLA genotype, and timing of first probiotic exposure in relation to IA in the TEDDY cohort.

RESEARCH DESIGN AND METHODS

TEDDY is a prospective cohort study involving three clinical centers in the U.S. (Colorado, Georgia/Florida, Washington State), and three in Europe (Finland, Germany,

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or multiple autoantibodies appearing

simultaneously. We also conducted three-

way interaction models to examine

whether the association between tim-

and Sweden). The detailed study design and methods have been described previously (4-6). The study population is presented in Supplementary Fig. 1, and population characteristics in Supplementary Table 2. The final sample size was 7,770. The food exposures and categorization of timing are described in Table 1.

Infant gut microbiota goes through significant changes over the 1st year of life (7). Therefore, we also studied the timing of the initial probiotic exposure either from dietary supplements or from infant formula during the first 52 weeks. We also considered only early exposures before 26 weeks of age. We did not analyze findings during the first 4 weeks of life, as reported earlier (3), because these subgroup numbers were insufficient. Probiotics mainly included Lactobacillus reuteri and Lactobacillus rhamnosus. The length of probiotic use was not examined in this observational study.

IΑ

Persistent confirmed IA was defined by the presence of one or several autoantibodies against GAD (GADA), IA-2 antigen determined as negative for IA.

Statistical Analysis

A Cox proportional hazards regression model was used to investigate the association between timing of food exposures and the risk of IA in the TEDDY cohort. Interactions between timing of food exposure and HLA genotype (DR3/4 compared with any other genotype than DR3/4) and between timing of food exposure and first probiotics were studied while controlling for country, whether any first-degree relative had type 1 diabetes, and sex of the child. Response variables included the risk of developing IA overall, IAA only as the first-appearing autoantibody (IAA-first), GADA only as the first-appearing autoantibody (GADA-first),

(IA-2A), or insulin (IAA) at each of the two TEDDY laboratories on two or more consecutive visits. The detailed study design and methods have been previously published (4,5). The timing of seroconversion was defined as the age of the first persistent confirmed autoantibody sample and the right-censored time as the age when the last blood sample available was

ing of selected foods and the risk of IA was modified by HLA DR3/4 and by the first exposure to probiotics. All statistical analyses were done using SAS 9.4 software (SAS/STAT 15.2).

RESULTS

Main Effects

Early introduction of gluten-containing cereals was associated with a decreased risk of any IA, GADA-first, and multiple autoantibodies (Supplementary Tables 3-6). Wheat (consumed alone or with another cereal) accounted for 90% of the first exposures to gluten-containing cereals before 6 months of age.

Subgroups

There was an interaction between timing of introduction of fruit and berries and HLA genotype (DR3/4 vs. other) when multiple autoantibodies were studied as an outcome. Similarly, an interaction between timing of any solid food and first probiotics within the first 52 weeks in relation to multiple autoantibodies was observed. Furthermore, the interactions between timing of egg introduction and first probiotics in relation to IAA-first and GADA-first were found (Table 2).

Both HLA genotype and probiotic exposure together modified the association between timing of any solid food introduction and risk of the outcomes (Fig. 1 and Supplementary Table 7). Among children who carried HLA DR3/4 and who were not exposed to probiotics during their first 52 weeks of life, early introduction of any solid food was associated with an increased risk of any IA, IAA-first, and multiple autoantibodies. However, if probiotics were introduced before 52 weeks, none of these associations were present in the subgroup of children with HLA DR3/4 (Fig. 1). The change in direction in the association by probiotics at <52 weeks was found only among children carrying a DR3 allele. Duration of breastfeeding was not associated with the risk of IA.

Gluten-Containing Cereals, Nongluten-Containing Cereals, and Cereals Overall

Both HLA DR3/4 genotype and exposure to probiotics modified the association

Table 1—Food exposures			
	Categorization of timing of foo	d introduction	n by age (months)
Food	Early or short duration		Late (reference)
Exclusive breastfeeding	<4		≥4
Any breastfeeding	<4		≥4
Any infant formula	<4	4 to <6	≥6
Any solid food†	<4	4 to <6	≥6
All cereals	<4	4 to <6	≥6
Gluten-containing cereals	<4	4 to <6	≥6
Nongluten-containing cereals	<4	4 to <6	≥6
Fruits and berries	<4	4 to <6	≥6
Root vegetables	<4	4 to <6	≥6
Other vegetables than roots	<4	4 to <6	≥6
Regular cow's milk	<4	4 to <6	≥6
Any meat‡	<4	4 to <6	≥6
Egg	≤9		>9
Rice*	<4	4 to <6	≥6
Oat*	<4	4 to <6	≥6

†All cereals (including gluten and nongluten), fruits and berries, all vegetables (including roots), milk products, eggs, any meat (including red meat, poultry, fish and seafood, processed meats). ‡Including all red meat, poultry, fish, and seafood. *Preliminary analyses suggested that nongluten cereals played a role in the associations between any solid food and the outcomes, and therefore, we additionally studied two of the most commonly consumed nongluten baby cereals, rice and oat, and their timing of introduction in relation to outcomes separately by country.

			HLA g	HLA genotype					Use of probiotics during the first 52 weeks***	g the firs	st 52 weeks	***
Timing of first food exposure (months) and outcome	и	Affected,	ed, Other than HLA DR3/4 HR (95% CI), <i>P*</i>	u	Affected, n	HLA DR3/4 HR (95% CI), P*	u	Affected, n	No probiotic exposure before 52 weeks of age HR (95% CI), P**	u	Affected, n	Probiotic exposure before or at 52 weeks of age HR (95% CI), <i>p**</i>
Any solid foods Any IA	1 840	145	0 93 (0 66 1 30) 0 656	1 192	159	131 (090 191) 0153	7 367	23.0	1 20 (0 88 1 62) 0 245	565	6	0 91 (0 57 1 44) 0 678
0 0 0 1 7	2,040	24.5			100	1 21 (0.01, 1.01), 0.153	2,70	770	1 21 (0 08 1 76) 0 060	0 0	2 2	0.01 (0.57, 1.44), 0.676
4 (0 < 0	2,393	243			213	1.51 (0.91, 1.89), 0.151	3,070	505 1	1.51 (0.98, 1.76), 0.069	407	0 6	0.91 (0.39, 1.42), 0.688
9	495	4 8	-1	377	36	7	179	55	T	196	67	-1
Interaction P			0.	0.209					0.154	54		
IAA-first												
<4	1,840	26	0.96 (0.54, 1.69), 0.880		09	1.78 (0.90, 3.53), 0.098	2,367	88	1.45 (0.85, 2.46), 0.174	999	28	0.90 (0.42, 1.93), 0.777
4 to <6	2,393	95	1.13 (0.65, 1.94), 0.670	1,528	92	1.70 (0.86, 3.34), 0.126	3,070	131	1.55 (0.92, 2.60), 0.101	851	38	0.90 (0.43, 1.87), 0.769
9<	495	17	1	322	10	Н	621	17	П	196	10	П
Interaction P			0.	0.290					0.3	968.0		
GADA-first												
<4 4	1,840	55	0.84 (0.48, 1.46), 0.543	1,192	89	1.09 (0.64, 1.86), 0.754	2,367	94	0.93 (0.60, 1.44), 0.749	999	59	1.17 (0.53, 2.59), 0.692
4 to <6	2,393	118	1.28 (0.76, 2.15), 0.350		101	1.12 (0.66, 1.89), 0.667	3,070	174	1.22 (0.80, 1.86), 0.358	851	43	1.22 (0.57, 2.60), 0.609
9<	495	18		322	18	1	621	27	1	196	6	Н
Interaction P			0	307					0.732	32		
Multiple autoantibodies												
. 4>	1,840	69	0.86 (0.54, 1.38), 0.531	1,192	66	1.28 (0.81, 2.03), 0.289	2,367	122	1.29 (0.85, 1.95), 0.234	999	46	0.77 (0.45, 1.34), 0.358
4 to <6	2,393	129		1,528	142	1.37 (0.87, 2.14), 0.172	3,070	212	1.61 (1.08, 2.41), 0.020	851	29	0.73 (0.43, 1.23), 0.234
9/1	495	27		322	24		621	59	, ,	196	22	, ,
Interaction P			0.	0.236					0.028	28		
Cereals (24 missing)												
Any IA												
·	1,101	81	0.86 (0.63, 1.19), 0.371	762	89	1.03 (0.74, 1.45), 0.844	1,501	135	1.06 (0.80, 1.40), 0.689	362	35	0.76 (0.48, 1.19), 0.224
4 to <6	2.807	273		1.744	262	1.22 (0.91, 1.63), 0.184	3,585	428	1.25 (0.98, 1.59), 0.072	996	107	0.84 (0.59, 1.20), 0.335
9<	802	82		527	62		952	89	1	380	55	
Interaction P			ò	0.447					0.051	51		
IAA-first												
<4	1,101	32	0.88 (0.52, 1.47), 0.617	762	33	1.26 (0.71, 2.25), 0.435	1,501	49	1.05 (0.67, 1.66), 0.820	362	16	1.02 (0.50, 2.07), 0.960
4 to <6	2,807	101		1,744	94	1.50 (0.90, 2.52), 0.121	3,585	154	1.24 (0.84, 1.85), 0.277	996	41	0.96 (0.53, 1.73), 0.891
9<	802	32	н		19	₩	952	33		380	18	, ,
Interaction P			0.0	402					0.522	22		
GADA-first												
<4	1,101	31	0.79 (0.47, 1.32), 0.364	762	34	0.89 (0.53, 1.50), 0.252	1,501	52	0.93 (0.61, 1.44), 0.756	362	13	0.69 (0.33, 1.43), 0.315
4 to <6	2,807	130	1.16 (0.76, 1.77), 0.502	1,744	125	1.29 (0.83, 2.00), 0.697	3,585	207	1.38 (0.96, 1.99), 0.085	996	48	0.94 (0.53, 1.66), 0.832
9<	802	30		527	27		952	37		380	20	
Interaction P			0.	0.957					0.368	89		

Timing of first food exposure (months) and outcome			HLA genotype	notype					Use of probiotics during the first 52 weeks***	ng the fire	st 52 weeks	* * *
	c	Affected,	Other than HLA DR3/4 HR (95% CI), <i>P*</i>	c c	Affected,	HLA DR3/4 HR (95% CI), <i>P*</i>	2	Affected,	No probiotic exposure before 52 weeks of age HR (95% CI), P**	c	Affected,	Probiotic exposure before or at 52 weeks of age HR (95% CI), P**
Multiple autoantibodies <4 4 to <6 ≥6 Interaction P	1,101 2,807 805	40 137 48	0.82 (0.52, 1.27), 0.371 0.97 (0.68, 1.39), 0.877 1 0.43	762 1,744 527 130	53 169 43	0.91 (0.60, 1.38), 0.660 1.21 (0.85, 1.72), 0.298	1,501 3,585 952	70 238 55	0.95 (0.66, 1.37), 0.782 1.24 (0.90, 1.69), 0.184 1	2 362 4 966 380 0.240	23 68 36	0.76 (0.44, 1.33), 0.337 0.84 (0.54, 1.29), 0.420
Gluten-containing cereals (134 missing) Any IA <44 4 to <6 ≥6 ≥6	294 1,624 2,723	14 162 259	0.49 (0.28, 0.84), 0.010 0.97 (0.77, 1.21), 0.765	213 1,057 1,725	22 160 230	0.81 (0.52, 1.27), 0.359 1.01 (0.80, 1.27), 0.918	410 2,116 3,421	31 254 365	0.68 (0.46, 0.99), 0.042 0.95 (0.79, 1.14), 0.580	2 97 0 565 1,027	5 68 124	0.52 (0.21, 1.28), 0.155 1.13 (0.82, 1.56), 0.454
$ AA-first < 4$ < 4 $4 \text{ to } < 6$ ≥ 6 $ Africal first < 6$	294 1,624 2,723	7 58 100	0.65 (0.295, 1.43), 0.281 0.88 (0.61, 1.28), 0.509 1	213 1,057 1,725	7 52 86	0.73 (0.33, 1.62), 0.442 0.92 (0.63, 1.36), 0.670	410 2,116 3,421	14 83 138	0.84 (0.47, 1.48), 0.539 0.84 (0.61, 1.14), 0.255 1	97 5 565 1,027 0.798	0 27 48	_ 1.15 (0.70, 1.91), 0.578 1
GADA-first <4 <4 to <6 ≥ 6 Interaction P	294 1,624 2,723	4 82 105	0.33 (0.12, 0.90), 0.030 1.18 (0.84, 1.66), 0.330 1 0.33	213 1,057 1,725	9 75 102	0.73 (0.36, 1.47), 0.377 1.04 (0.74, 1.46), 0.823 1	410 2,116 3,421	10 128 158	0.51 (0.26, 0.98), 0.042 1.12 (0.86, 1.48), 0.404 1	2 97 4 565 1,027 0.804	3 29 49	0.67 (0.20, 2.21), 0.505 1.09 (0.65, 1.82), 0.748
Multiple autoantibodies <4 4 to <6 ≥ 6 Interaction P	294 1,624 2,723	3 74 147	0.19 (0.06, 0.59), 0.004 0.78 (0.57, 1.07), 0.127 1	213 1,057 1,725 063	12 106 147	0.76 (0.41, 1.38), 0.365 1.16 (0.87, 1.53), 0.317	410 2,116 3,421	12 136 214	0.46 (0.25, 0.83), 0.010 0.91 (0.71, 1.16), 0.429 1	97 9 565 1,027 0.916	80 80	0.52 (0.16, 1.67), 0.271 1.16 (0.78, 1.72), 0.465
Nongluten-containing cereals (29 missing) Any IA < 4 4 to <6 ≥ 6 Interaction P	1,029 2,830 850	79 270 87	0.89 (0.65, 1.23), 0.486 0.98 (0.75, 1.27), 0.870 1	712 1,759 561 523	83 261 69	0.99 (0.71, 1.38), 0.948 1.15 (0.87, 1.53), 0.323	1,415 3,601 1,018	128 424 100	1.01 (0.77, 1.32), 0.946 1.17 (0.93, 1.47), 0.192 1	6 326 2 988 393 0.092	34 107 56	0.83 (0.53, 1.31), 0.418 0.84 (0.59, 1.19), 0.326
A to <6 ≥6	1,029 2,830 850	28 99 28	0.90 (0.54, 1.50), 0.675 0.93 (0.61, 1.41), 0.723 1	712 1,759 561 886	35 107 26	1.08 (0.61, 1.89), 0.796 1.29 (0.79, 2.08), 0.307	1,415 3,601 1,018	31 100 34	0.91 (0.59, 1.42), 0.696 1.09 (0.75, 1.58), 0.648 1	5 326 8 988 393 0.475	32 106 20	1.19 (0.58, 2.43), 0.927 0.97 (0.54, 1.76), 0.773

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Thing of first book	Table 2—Continued												
Afficience Aff				HLA ge	notype					Use of probiotics during	g the first	52 weeks	**
1,029 30 080 (0.88, 135), 0.406 712 32 0.93 (0.25, 1.86), 0.776 1,415 50 0.94 (0.62, 1.45), 0.786 376 12 0.03 (0.25, 1.26), 0.776 1,415 0.036 123 (0.95, 1.95), 0.039 988 49 0.98 122 0.38 12 0.39 12	Timing of first food exposure (months) and outcome	c	Affected,	Other than HLA DR3/4 HR (95% CI), <i>P*</i>	u	Affected, n	HLA DR3/4 HR (95% CI), P*	c	Affected, n	No probiotic exposure before 52 weeks of age HR (95% CI), P**		Affected,	Probiotic exposure before or at 52 weeks of age HR (95% CI), P**
1,023 20 0.00 (0.48, 1.28), 0.455 1.759 1.759 1.26 1.34 (0.87, 1.26), 0.776 1.415 5.0 0.54 (0.67, 1.34), 0.786 3.26 1.2 0.770 1.816 3.601 2.05 1.35 (0.95, 1.94), 0.785 9.88 3.26 1.2 0.770 1.20	GADA-first												
2820 123 112 (0.74, 1.69), 0.555 128 128 128 1207, 0.186 3.601 2 0 135 (0.95, 1.93), 0.055 288 49 0.080 architecture 2.020 2.021 2 0.088 0.054 2.07, 0.186 3.07 1.018 40 1.35 (0.95, 1.93), 0.054 2.05 1.008 0.054 2.05 1.018 40 0.91 (0.67, 1.93), 0.944 2.05 0.051 2.0	<4	1,029	30	0.80 (0.48, 1.35), 0.406	712	32	0.93 (0.55, 1.56), 0.776	1,415	20	0.94 (0.62, 1.45), 0.788	326	12	0.72 (0.34, 1.52), 0.386
SSO 32 1 0.888 1.2 1 1.018 40 1 0.451 233 20	4 to <6	2,830	129	1.12 (0.74, 1.69), 0.595	1,759	126	1.34 (0.87, 2.07), 0.186	3,601	506	1.35 (0.95, 1.93), 0.095	886	49	0.98 (0.56, 1.73), 0.943
1,029 40 0.91 (0.58, 1.41), 0.660 712 49 0.88 (0.58, 1.33), 0.543 1,415 67 0.96 (0.67, 1.39), 0.844 326 22 0.83 (0.58, 1.41), 0.396 1,170 (0.31, 1.65), 0.386 3,631 3,0543 1,415 67 0.96 (0.67, 1.39), 0.844 326 22 0.83 (0.58, 1.41), 0.396 1,170 (0.31, 1.65), 0.385 1,471 1,139 1	9∧	850	32	1	561	28	П	1,018	40	1	393	20	1
1,023 40 0.91 (0.58, 1.41), 0.066 712 49 0.88 (0.58, 1.13) 0.543 1415 67 0.96 (0.67, 1.39) 0.844 226 22 0.88 (0.58, 1.13) 0.248 1.17 (0.83, 1.65), 0.376 3601 237 1.23 (0.91, 1.66), 0.198 68 0.88 (0.58, 1.13) 0.248 1.17 (0.83, 1.65), 0.376 3601 3.038 3.049 1.11 1.008 1.12 (0.91, 1.69), 0.199 40.2 37 0.88 37 0.88	Interaction P			3.0	388					0.4	51		
1,023 40 0.91 (0.58, 1.41), 0.666 712 49 0.88 (0.58, 1.33) 0.543 1415 67 0.56 (10.57, 1.39), 0.844 22 6 0.08 (1.58, 1.41), 0.656 712 49 1.17 (0.83, 1.65), 0.375 3.601 237 1.23 (1.91, 1.66), 0.188 98 66 0.233 859 49 1.17 (0.83, 1.65), 0.375 6 1.23 (1.91, 1.66), 0.189 98 66 0.233 1.24 1.248 1.248 0.56 (0.57, 1.02), 0.751 1.584 230 1.09 (0.85, 1.40), 0.514 3.124 3.67 1.03 (0.85, 1.25), 0.759 941 1.11 1.00 0.00 0.05, 0.751 1.254 0.254 0.051 1.25, 0.751 1.584 230 1.09 (0.85, 1.40), 0.514 3.124 3.67 1.03 (0.85, 1.25), 0.759 941 1.11 1.00 0.051 1.15 0	Multiple autoantibodies												
850 49 136 0.99 (0.63 1.41), 0.936 1.759 169 1.17 (0.83 1.65), 0.376 3.50 123 (0.91, 1.66), 0.188 98 68 0.89 (0.64) 1.41), 0.936 1.759 169 1.17 (0.83 1.65), 0.376 3.50 123 (0.91, 1.66), 0.198 98 68 0.89 (0.83 0.83 1.41), 0.936 1.756 98 1.13 (0.83 0.83 1.34 1.84 2.80 1.03 (0.77, 1.39), 0.835 1.341 1.56 167 1.03 (0.85, 1.26), 0.199 402 37 0.83 (0.76, 1.22), 0.751 1.584 2.80 1.09 (0.85, 1.40), 0.554 3.124 3.67 1.03 (0.85, 1.22), 0.751 1.584 2.80 1.09 (0.85, 1.40), 0.554 3.124 3.67 1.03 (0.85, 1.22), 0.755 94 1.11 1.00 (0.85, 1.40), 0.655 1.341 3.2 0.96 (0.64, 1.44), 0.843 40.2 14 0.811 1.10 (0.80, 1.77), 0.397 1.584 8.9 1.12 (0.73, 1.72), 0.653 1.341 3.2 0.96 (0.64, 1.44), 0.843 40.2 14 0.811 1.10 (0.80, 1.77), 0.397 1.584 8.9 1.12 (0.73, 1.72), 0.391 1.566 3.1 1.16 (0.83, 1.62), 0.054 6.90 3.1 1.12 (0.82, 1.75), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.348 1.12 (0.75, 1.26), 0.848 1.12 (0.75, 1.26), 0.848 1.12 (0.75, 1.26), 0.848 1.12 (0.75, 1.26), 0.851 1.12 (0.82, 1.12),	< 4	1,029	40	0.91 (0.58, 1.41), 0.660	712	49	0.88 (0.58, 1.33), 0.543	1,415	29	0.96 (0.67, 1.39), 0.844	326	22	0.81 (0.46, 1.42), 0.456
850 49 1 551 47 1 1 1010	4 to <6	2,830	136	0.99 (0.69, 1.41), 0.936	1,759	169	1.17 (0.83, 1.65), 0.376	3,601	237	1.23 (0.91, 1.66), 0.188	886	89	0.82 (0.53, 1.27), 0.380
(a) 1,053 69 0.69 (0.51, 0.94), 0.017 690 84 1,03 (0.77, 1.39), 0.835 1,341 116 0.85 (0.67, 1.09), 0.199 402 37 0.83 1,342 1248 0.96 (0.76, 1.22), 0.751 1,584 230 1.09 (0.85, 1.40), 0.514 3,124 367 1.03 (0.85, 1.25), 0.759 941 111 1.00 1.20 1.20 1.20 1.20 1.20 1.20	9 (1	850	49	1	561	47	1	1,018	29	1	393	37	1
1,053 69 0.69 (0.51, 0.94), 0.017 690 84 1.03 (0.77, 1.39), 0.835 1,341 116 0.85 (0.67, 1.09), 0.199 402 37 0.83 1,341 126 118 248 0.96 (0.76, 1.22), 0.751 1,884 230 1.09 (0.85, 1.40), 0.514 3,124 367 1.03 (0.85, 1.25), 0.759 941 111 1.00 0.617 1.056 118 0.056 (0.76, 1.22), 0.751 1,884 230 1.09 (0.85, 1.40), 0.514 3,124 86 167 1.03 (0.85, 1.25), 0.759 941 111 1.00 0.617 1.059 2.68 1.02 (0.86, 1.28), 0.303 690 32 1.12 (0.68, 1.83), 0.665 1.341 32 0.96 (0.64, 1.44), 0.843 402 14 0.83 1.146 0.83 (0.59, 1.77), 0.397 1,884 89 1.12 (0.73, 1.72), 0.603 3,124 80 1.16 (0.83, 1.62), 0.375 941 45 1.111 1.00 0.83 (0.59, 1.18), 0.303 1,884 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.121 1.169 56 1 1 0.283 1.884 144 1.09 (0.80, 1.24), 0.607 0.641 1.07), 0.397 1.884 144 1.09 (0.80, 1.24), 0.607 0.601 1.10), 0.514 0.607 0.607 0.601 1.10), 0.515 0.515 1.189 0.511 0.515 0.533 1.884 144 1.09 (0.80, 1.24), 0.607 0.601 1.10), 0.515 0.515 0.515 1.189 0.515 0	Interaction P			0.4	180					0.2	13		
1053 69 0.66 (0.75, 0.94), 0.017 690 84 1.03 (0.77, 1.39), 0.835 1.341 116 0.85 (0.67, 1.09), 0.199 402 37 0.83 1.469 118 1.06 (0.76, 1.22), 0.751 1.584 230 1.09 (0.85, 1.40), 0.514 3.124 367 1.03 (0.85, 1.25), 0.759 941 111 1.00 1.106 118 1.107 0.120 0.33 1.29 1.248 1.12 (0.85, 1.28), 0.76 (0.46, 1.28), 0.393 6.90 32 1.12 (0.68, 1.83), 0.665 1.341 32 0.96 (0.64, 1.44), 0.843 402 1.4 0.83 1.12 (0.75, 1.77), 0.397 1.584 89 1.12 (0.73, 1.72), 0.603 3.124 80 1.16 (0.83, 1.62), 0.375 3.4 1 46 0.76 (0.49, 1.02), 0.375 3.1 1 0.220 0.25 (0.80, 1.51), 0.834 1.341 46 0.70 (0.49, 1.02), 0.865 941 47 1.12 0.39 1.16 0.33 (0.59, 1.18), 0.303 1.584 10 1.20 (0.82, 1.75), 0.348 3.124 1.69 0.98 (0.74, 1.30), 0.865 941 47 1.12 0.30 1.16 0.33 (0.55, 1.25), 0.333 1.24 1.26 81 1.20 (0.82, 1.15), 0.384 1.24 1.26 81 1.20 (0.82, 1.15), 0.384 1.24 1.20 (0.82, 1.15), 0.384 1.24 1.20 (0.82, 1.12), 0.394 1.25 (0.80, 1.23), 0.394 1.25 (0.80, 1.23), 0.394 1.25 (0.80, 1.24), 0.905 (Fruits and berries												
1,1053 69 0.669 (0.51, 0.94), 0.017 690 84 103 (0.77, 1.39), 0.835 1,341 116 085 (0.67, 1.09), 0.199 402 37 0.088 1 1.11 1.00 1.169 118 0.96 (0.76, 1.22), 0.751 1,584 230 1.09 (0.85, 1.40), 0.514 3,124 367 103 (0.85, 1.25), 0.759 941 111 1.00 1.10	(37 missing)												
1,053 69 069 (0.51,0.94), 0.017 690 84 103 (0.77,139), 0.835 1,341 116 0.85 (0.67,1.09), 0.199 402 37 0.83 2,481 248 0.96 (0.76,1.22), 0.751 1,544 290 10.85,1.40), 0.554 357 1.34 367 1.03 (0.85,1.25), 0.759 941 111 1.00 0.120 1,169 118 0.96 (0.76,1.22), 0.321 1,524 290 1.03 (0.85,1.43), 0.663 13,124 367 1.03 (0.85,1.25), 0.759 941 111 1.00 0.120 1,169 38 1 1.19 (0.80,1.77), 0.397 1,524 89 1.12 (0.73,1.72), 0.603 3,124 80 1.16 (0.83,1.62), 0.375 941 45 1.11 1.00 0.290 1,053 29 0.61 (0.38,0.96), 0.034 690 32 1.12 (0.73,1.72), 0.603 3,124 80 1.16 (0.83,1.62), 0.375 941 45 1.11 1.00 0.83 (0.55,1.18), 0.303 1,524 89 1.12 (0.73,1.72), 0.548 31 1.26 89 1.12 (0.73,1.72), 0.548 31 1.26 89 1.12 (0.73,1.72), 0.548 31.24 80 1.16 (0.83,1.62), 0.375 941 45 1.11 1.00 0.83 (0.55,1.18), 0.303 1,524 10 1.20 (0.82,1.15), 0.348 31.24 46 0.70 (0.49,1.02), 0.061 402 16 1.01 0.289 1,053 30 0.54 (0.34,0.84), 0.066 690 57 1.08 (0.75,1.156), 0.602 1.341 60 0.98 (0.74,1.30), 0.865 941 47 1.12 0.248 1.16 0.99 (0.80,1.23), 0.347 2.032 28 1.00 (0.80,1.24), 0.974 400 0.99 (0.80,1.13), 0.355 64 1.00 (0.80,1.24), 0.974 400 0.99 (0.80,1.13), 0.515 1.26 81 1.26 81 1.26 89 1.26 81 1.26 89 1.26 8	Any IA												
1,169 118	. >	1.053	69	0.69 (0.51, 0.94), 0.017	069	84	1.03 (0.77, 1.39), 0.835	1.341	116	0.85 (0.67, 1.09), 0.199	402	37	0.83 (0.53, 1.30), 0.413
1,169 118 1 756 98 1 1 1,566 167 1 1,566 167 1 0.617 1,053 26 0.76 (0.46, 1.28), 0.303 690 32 11.2 (0.68, 1.83), 0.665 1,341 32 0.96 (0.64, 1.44), 0.843 402 14 0.81 1,169 38 1.19 (0.80, 1.77), 0.397 1,584 89 11.2 (0.73, 1.72), 0.603 3,124 80 11.6 (0.83, 1.62), 0.375 941 45 11.1 1,169 56 0.61 (0.34, 0.84), 0.006 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 1,169 56 0.94 (0.34, 0.84), 0.006 690 57 10.8 (0.82, 1.75), 0.583 1,246 89 1.14 1.09 (0.80, 1.49), 0.687 1.13 1.14 1.14 1.14 1.14 1.14 1.14 1.14	4 to <6	2.481	248	0.96 (0.76, 1.22), 0.751	1.584	230	1.09 (0.85, 1.40), 0.514	3.124	367	1.03 (0.85, 1.25), 0.759	941	111	1.00 (0.69, 1.44), 0.987
1,053 26 0.76 (0.46, 1.28), 0.303 690 32 1.12 (0.68, 1.83), 0.665 1,341 32 0.96 (0.64, 1.44), 0.843 402 14 0.81 1.11 (0.80, 1.77), 0.397 1,584 89 1.12 (0.73, 1.72), 0.603 3,124 80 1.16 (0.83, 1.62), 0.375 911 45 1.11 1.19 (0.80, 1.77), 0.397 1,584 89 1.12 (0.73, 1.72), 0.603 3,124 80 1.16 (0.83, 1.62), 0.375 911 45 1.11 1.11	9 . Al	1.169	118	1	756	86	1	1.566	167	1	359	49	1
1,053 26 0.76 (0.46, 1.28), 0.303 690 32 112 (0.68, 1.83), 0.665 1,341 32 0.96 (0.64, 1.44), 0.843 402 14 0.81 2,481 101 1.19 (0.80, 1.77), 0.397 1,584 89 1.12 (0.73, 1.72), 0.603 3124 80 1.16 (0.83, 1.62), 0.375 941 45 1.11 1,063 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.00 1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.00 1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.00 1,053 30 0.54 (0.34, 0.84), 0.006 690 57 1.08 (0.75, 1.56), 0.682 1,341 64 0.84 (0.61, 1.17), 0.305 402 23 0.65 1,169 67 1 2,56 64 1.44 1.09 (0.80, 1.49), 0.602 3,124 202 1.04 (0.80, 1.35), 0.756 941 69 0.86 1,353 450 1 886 126 126 126 126 126 126 126 126 126 12	Interaction P				120					9.0	17		
1,053 26 0.76 (0.46, 1.28), 0.303 690 32 1.12 (0.68, 1.83) 0.665 1,341 32 0.96 (0.64, 1.44), 0.843 402 14 0.81 111 2,481 101 1.19 (0.80, 1.77), 0.397 1,584 89 1.12 (0.73, 1.72), 0.603 3,124 80 1.16 (0.83, 1.62), 0.375 941 45 1.11 1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.01 2,481 106 0.83 (0.59, 1.18), 0.303 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1,169 56 0.84 (0.44, 0.84), 0.006 690 57 1.08 (0.75, 1.56), 0.682 1,341 64 0.84 (0.61, 1.17), 0.305 402 23 0.65 2,481 127 0.90 (0.65, 1.25), 0.533 1,584 144 1.09 (0.80, 1.49), 0.602 3,124 202 1.04 (0.80, 1.35), 0.756 941 69 0.88 2,481 127 0.90 (0.65, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 3,098 286 0.99 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 69 123 1.16 0.80 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 1 127 0.94 (0.79, 1.12), 0.515 1,036 69 123 1.16 0.80 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 1 1 1,663 192 1 1,036 1,035 1,036 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,466 69 1 1,469 1,	IAA-first										i		
1,159 20 0.01 (0.30, 1.77), 0.397 1,384 89 1,112 (0.73, 1.72), 0.063 1,314 80 1,116 (0.84, 1.74), 0.043 1,023 1,034 1,341 46 0.70 (0.49, 1.02), 0.054 1,039 1,030 1,380	35 11 20	1 052	26	5050 (85 1 36 0) 350		,,	117 (0 68 1 83) 0 665	1 2 4 1	,,	0.06 (0.64 1.44) 0.843	707	7	0 81 (0 38 1 31) 0 575
1,169 38 1.11 (0.34, 1.27), 0.397 1,284 89 1.12 (0.34, 1.27), 0.603 3, 1.24 80 1.15 (0.85, 1.62), 0.375 941 45 1.11 (0.85, 1.62), 0.375 941 45 1.12 (0.85, 1.62), 0.380 16 1.01 (0.88) 1,039 0.64 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.01 (0.82, 1.25), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 (0.283 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 (0.283 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 (0.283 1,584 144 1.09 (0.80, 1.24), 0.662 3,124 202 1.04 (0.80, 1.35), 0.355 1.18 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 (0.80, 1.23), 0.946 (0.80, 1.23), 0.946 (0.80, 1.23), 0.946 (0.80, 1.23), 0.946 (0.80, 1.23), 0.946 (0.80, 1.23), 0.946 (0.80, 1.23), 0.946 (0.80, 1.23), 0.940 (0.80, 1.23), 0.974 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 (0.80, 1.23), 0.946 (0.80, 1.23), 0.940 (0.80, 1.23), 0.940 (0.80, 1.24), 0.974 4,082 445 (0.94 (0.79, 1.12), 0.515 1,036 (0.80, 1.23), 0.801	4	1,053	70,	0.76 (0.46, 1.28), 0.303	690	37	1.12 (0.68, 1.83), 0.663	1,341	37	0.96 (0.64, 1.44), 0.843	402	1 t	0.81 (0.38, 1./1), 0.5/5
1,169 38 1 756 33 1 1,156 33 1 0.880 1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.01 2,481 106 0.83 (0.59, 1.18), 0.303 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1,169 56 1 0.54 (0.34, 0.84), 0.06 690 57 1.08 (0.75, 1.56), 0.682 1,341 64 0.84 (0.61, 1.17), 0.305 402 23 0.68 2,481 127 0.90 (0.65, 1.25), 0.533 1,584 144 1.09 (0.80, 1.49), 0.602 3,124 202 1.04 (0.80, 1.35), 0.756 941 69 0.88 1,169 67 1 1,756 64 1.09 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 3,098 286 0.99 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 0.80 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 0.80 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 0.80 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16	4 to <6	2,481	101	1.19 (0.80, 1.77), 0.397	1,584	68	1.12 (0.73, 1.72), 0.603	3,124	S 1	1.16 (0.83, 1.62), 0.375	941	45	1.11 (0.60, 2.05), 0.746
1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.01 2,481 106 0.83 (0.59, 1.18), 0.303 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1.12 1.169 56 1 1.033 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1.12 1.12 1.12 1.12 1.12 1.12 1.1	9	1,169	38	1	756	33	Н	1,566	33	\leftarrow 1	329	16	₩.
1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.01 2,481 106 0.83 (0.59, 1.18), 0.303 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1,169 56 1,028 (0.34, 0.34), 0.006 690 57 1.08 (0.75, 1.56), 0.682 1,341 64 0.84 (0.61, 1.17), 0.305 402 23 0.69 2,481 127 0.90 (0.65, 1.25), 0.533 1,584 144 1.09 (0.80, 1.49), 0.602 3,124 202 1.04 (0.80, 1.35), 0.756 941 69 0.86 1,169 67 1 0.0035 1.20 0.000 (0.80, 1.20), 0.900 1.000 1.0	Interaction P			0.2	290					0.8	80		
1,053 29 0.61 (0.38, 0.96), 0.034 690 33 0.95 (0.60, 1.51), 0.834 1,341 46 0.70 (0.49, 1.02), 0.061 402 16 1.01 2,481 106 0.83 (0.59, 1.18), 0.303 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1,169 56 1	GADA-first												
2,481 106 0.83 (0.59, 1.18), 0.303 1,584 10 1.20 (0.82, 1.75), 0.348 3,124 169 0.98 (0.74, 1.30), 0.865 941 47 1.12 1,169 56 1	<4	1,053	53	0.61 (0.38, 0.96), 0.034	069	33	0.95 (0.60, 1.51), 0.834	1,341	46	0.70 (0.49, 1.02), 0.061	402	16	1.01 (0.50, 2.07), 0.970
1,169 56 1 1 756 43 1 1 1,566 81 1 1,566 81 1 1,566 81 1 1,566 81 1 1,566 81 1 1,566 81 1 1,566 81 1 1,565 18 0.283 1,053 30 0.54 (0.34, 0.84), 0.006 690 57 1.08 (0.75, 1.56), 0.682 1,341 64 0.84 (0.61, 1.17), 0.305 402 23 0.86 2,481 127 0.90 (0.65, 1.25), 0.533 1,584 144 1.09 (0.80, 1.49), 0.602 3,124 202 1.04 (0.80, 1.35), 0.756 941 69 0.86 1,169 67 1 756 64 1.09 (0.80, 1.24), 0.576 96 1 0.035 3,098 286 0.99 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 1,353 450 1 886 126 126 1 1,066 126 1 1,066 126 1 1,066 126 126 126 126 126 126 126 126 126 1	4 to <6	2,481	106	0.83 (0.59, 1.18), 0.303	1,584	10	1.20 (0.82, 1.75), 0.348	3,124	169	0.98 (0.74, 1.30), 0.865	941	47	1.12 (0.62, 2.03), 0.710
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1,169 67 1 756 64 1 1 1,566 96 1 35 35 35 35 35 35 35 35 36 36 0.035 0.0	4 to <6	2,481	127	0.90 (0.65, 1.25), 0.533	1,584	144	1.09 (0.80, 1.49), 0.602	3,124	202	1.04 (0.80, 1.35), 0.756	941	69	0.86 (0.55, 1.34), 0.504
0.507 3,098 286 0.99 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 1,353 450 1 886 126 1 1,663 192 1 576 69 0.801	9 ≳	1,169	29	1	756	64	1	1,566	96	1	359	35	1
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3,098 286 0.99 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 1,353 450 1 886 126 1 1,663 192 1 5 576 69 0.801	Egg (470 missing)												
3,098 286 0.99 (0.80, 1.23), 0.947 2,020 282 1.00 (0.80, 1.24), 0.974 4,082 445 0.94 (0.79, 1.12), 0.515 1,036 123 1.16 1.353 450 1 2 2.00 1 886 126 126 126 126 126 126 126 126 126 12	Any IA												
1,353 450 1 886 126 1 1,663 192 1 576 69 action <i>P</i> 0.801	. ∀∣	3,098	286	0.99 (0.80, 1.23), 0.947	2,020	282	1.00 (0.80, 1.24), 0.974	4,082	445	0.94 (0.79, 1.12), 0.515	1,036	123	1.16 (0.85, 1.58), 0.350
action P	6	1.353	450		886	126	1	1,663	192	1	576	69	1
	Interaction P	/-		0.8	301	i	1		1	0.4	99	;	í

			HLA 8	HLA genotype					Use of probiotics during the first 52 weeks***	g the firs	st 52 weeks	* * *
Timing of first food exposure (months) and outcome	c	Affected,	Affected, Other than HLA DR3/4 n HR (95% CI), P*	c	Affected,	HLA DR3/4 HR (95% CI), P*	c	Affected,	No probiotic exposure before 52 weeks of age HR (95% CI), P**	c	Affected,	Probiotic exposure before or at 52 weeks of age HR (95% CI), P**
IAA-first												
6 ∀I	3,098	107	0.93 (0.66, 1.31), 0.682	2,020	97	0.96 (0.67, 1.37), 0.811	4,082	166	1.09 (0.81, 1.47), 0.554 1,036	1,036	38	0.63 (0.40, 1.01), 0.053
6<	1,353	54	1	988	47	1	1,663	64	1	216	37	1
Interaction P			0.9	.911					0.0	0.038		
GADA-first												
6∀	3,098	130	1.02 (0.74, 1.42), 0.898	2,020	132	1.08 (0.78, 1.50), 0.651	4,082	200	0.86 (0.67, 1.11), 0.245 1,036	1,036	62	2.26 (1.29, 3.97), 0.004
6<	1,353	22	1	988	23	1	1,663	91	1	216	17	1
Interaction P			0.9	904					0.0	0.004		
Multiple autoantibodies												
6 VI	3,098	135	0.83 (0.63, 1.11), 0.210	2,020	176	0.95 (0.72, 1.23), 0.677	4,082	236	0.85 (0.68, 1.06), 0.153 1,036	1,036	75	1.01 (0.6, 1.48), 0.942
6<	1,353	81	1	988	98	1	1,663	119	П	216	48	1
Interaction P			0.	.321					0.4	0.475		

Boldface indicates significance at P < 0.05. *Adjusted for country, first-degree family member with type 1 diabetes status, sex of the child, and probiotic exposure during the 1st year of life (52 weeks). **Adjusted for country, first-degree family member with type 1 diabetes status, sex of the child, and high-risk genotype (HLA DR3/4). ***When the timing of first probiotic exposure was studied in cateinterpretation of the results did not affect but they found, or none, slightly stronger associations were weeks, weeks, gories < 26

between early introduction of glutencontaining cereals and the outcomes (i.e., IA, GADA-first, and multiple autoantibodies) (Table 2). Children with the HLA DR3/4 genotype exposed to probiotics before the age of 52 weeks had an increased risk of IA and GADA-first if gluten-containing cereals were introduced between age 4 and 6 months compared with later (three-way interaction) (Fig. 1). However, among children with other HLA genotypes, early introduction of glutencontaining cereals was inversely associated with the risk of any IA if no probiotics were given before age of 52 weeks.

Country-Specific Analyses

There was an interaction between timing of rice introduction and country (P =0.036) but not between timing of oat introduction and country. Only the U.S. and Sweden had a sufficient number of children in the subgroups to study the interaction. Timing of first rice cereal between age 4 and 6 months compared with later was associated with an increased risk of IA in the U.S. (hazard ratio [HR] 1.74; 95% CI 1.27, 2.38; P < 0.0005) but not in other countries (Table 3). U.S. children without probiotic exposure during the first 52 weeks, regardless of the HLA genotype, had an HR of 1.69 (1.22, 2.34; P = 0.0017) for the risk of any IA and 1.76 (1.10, 2.82; P = 0.019) for GADA-first when timing of rice introduction was between age 4 and 6 months compared with later.

CONCLUSIONS

As published before, early introduction of gluten-containing cereals overall was linked to a decreased risk of IA in the geographically diverse population of TEDDY (8). We also confirmed that the risk of IA related to early introduction of any solid food among children with the highest level of HLA genetic risk (DR3/4) may be modified by probiotics, although the association was not as strong as previously observed in the younger cohort of TEDDY participants (9). A novel finding was that early exposure to egg (age < 9 months) is associated with an increased risk of GADA-first only in those who were exposed to probiotics.

Immune or microbiota responses to gluten-containing cereals may depend on both the HLA genotype and probiotic diabetesjournals.org/care Uusitalo and Associates 1845

HLA-DR3/4	Any IA		IAA-first		GADA-first		Multiple AAB	
Timing of food introduction	No probiotics	Probiotics	No probiotics	Probiotics	No probiotics	Probiotics	No probiotics	Probiotics
Any solid food								
< 4 months	HR 1.61 (1.01, 2.56), p=0.044		HR 2.79 (1.10, 7.08) p=0.031					
4-<6 months	HR 1.71 (1.08, 2.70), p=0.021		HR 2.79 (1.11, 7.03) p=0.030				HR 1.95 (1.10, 3.45) p=0.021	
Cereals, any								
< 4 months								
4-<6 months	HR 1.50 (1.05,2.14) p=0.028		HR 2.05 (1.07, 3.93) p=0.031					
Gluten cereals								
< 4 months								
4-<6 months		HR 1.64 (1.04, 2.61) p=0.035				HR 2.13 (1.09, 4.18) p=0.027		HR 1.66 (0.95, 2.91) p=0.076
Egg								
≤ 9 months						HR 2.69 (1.20, 6.01) p=0.016		
Other than	Any IA		IAA-first		GADA-first	,	Multiple AAB	
HLA-DR3/4								
Timing of food introduction	No probiotics	Probiotics	No probiotics	Probiotics	No probiotics	Probiotics	No probiotics	Probiotics
Gluten cereals								
< 4 months	HR 0.51 (0.28, 0.93) p=0.029				HR 0.33 (0.10, 1.06) p=0.063		HR 0.22 (0.07, 0.72) p=0.012	
4-<6 months					HR 1.50 (1.02, 2.19) p=0.038	HR 0.46 (0.20,1.05) p=0.065		
Fruit & berries								
< 4 months	HR 0.69 (0.49, 0.98) p=0.040				HR 0.56 (0.33, 0.95) p=0.033		HR 0.60 (0.35, 1.01) p=0.052	HR 0.42 (0.18, 0.99) p=0.048
4-<6 months								

Figure 1—Timing of the introduction of foods and the risk of developing any IA, IAA-first, GADA-first, and multiple autoantibodies by HLA genotype and by probiotic exposure by 52 weeks of age, showing only the statistically significant associations. The HR from the Cox proportional hazard model (with 95% CI) uses the reference of \geq 6 months, except >9 months for egg. Dark-colored arrows flag P < 0.05, and light-colored arrows flag 0.05 < P < 0.09. Statistically significant three-way interactions between HLA genotype, timing of probiotic exposure, and timing of gluten cereals introduction: P = 0.034 for any IA and P = 0.019 for GADA-first, and between HLA genotype, timing of probiotic exposure, and timing of egg introduction: P = 0.023 for multiple autoantibodies.

exposure, and they could interact with each other. Molecular mechanisms that drive probiotic effects that may interact with genotype and food are not well understood (10). Nevertheless, gluten in cereals can act as a doubleedged sword in its connection to the risk of type 1 diabetes (11,12). Gluten in wheat, barley, and rye are suggested to increase the risk of IA by promoting gut permeability and dysbiosis and to increase proinflammatory cytokines (13). Whole-grain wheat also contains several bioactive compounds promoting overall health, such as prebiotic oligosaccharides, which are linked to healthy gut microbiota (14).

The Infant Feeding Practices study (15) concluded that introduction of solid complementary foods before 4–6 months of age poses a greater risk to infant

health than does infant formula. In our study, we noticed an increased risk of any IA and IAA-first with early introduction of any solid foods but only among those who were carrying the HLA DR3/4 (DR3) genotype and who did not have probiotic exposure.

The association between early timing of rice and increased risk of any IA in U.S. TEDDY children was intriguing. A somewhat toxic form of inorganic arsenic is found in relatively large quantities in rice of U.S. origin, especially if grown in southern states (16). Arsenic is a toxic trace element that can affect $\beta\text{-cell}$ function and increase the risk of type 1 diabetes in youth (17) and may possibly interact with the gut microbiome (18). To decrease the potential of adverse health effects, the U.S. Food and Drug Administration has recently given

guidelines for industry to reduce the arsenic content of infant rice cereals to the of level 100 parts per billion, which should be achievable under current good manufacturing practices (19). The association with the outcome was found with rice exposure between age 4 and 6 months but not earlier. During this time, children are introduced to larger quantities of solid foods. Therefore, the exposure effect of possible contaminants may be stronger than with small tastings provided earlier.

It will be important to investigate the function and immune responses of the host microbiome when studying early diet, including probiotic usage in children with a genetically increased risk of type 1 diabetes. Rice as an early food also requires further attention. The results of this study do not impose any

		U.S.			Finland	pu		Germany	yuk		Sweden	ne
Timing of first food exposure (months)	Developed IA, n (%)	No IA, n (%)	HR (95% CI), <i>P*</i>	Developed IA, n (%)	No IA, n (%)	HR (95% CI), P*	Developed IA, n (%)	No IA, n (%)	HR (95% CI), P*	Developed IA, n (%)	No IA, n (%)	HR (95% CI), P*
Any solid food <4 4 to <6 ≥ 6	112 (8.7) 150 (10.3) 28 (5.8)	1,169 (91.3) 1,301 (89.7) 452 (94.2)	1.78 (1.17, 2.69), 0.0066 1.97 (1.32, 2.96), 0.001	82 (11.6) 100 (11.8) 26 (19.0)	627 (88.4) 751 (88.2) 111 (81.0)	0.67 (0.43, 1.03), 0.070 0.64 (0.41, 0.98), 0.039	9 (6.3) 28 (12.4) 23 (13.9)	133 (93.7) 197 (87.6) 142 (86.1)	0.68 (0.31, 1.50), 0.340 1.07 (0.61, 1.870, 0.813	101 (11.2) 184 (13.2) 7 (20.0)	799 (88.8) 1,210 (86.8) 28 (80.0)	0.75 (0.34, 1.62), 0.460 0.82 (0.38, 1.76), 0.608
Gluten-containing cereals <4 4 to <6 >6 Missing	8 (6.2) 47 (8.4) 234 (9.6) 85	122 (93.8) 512 (91.6) 2,204 (90.4) 5	0.74 (0.36, 1.49), 0.392 0.91 (0.67, 1.25), 0.565	3 (5.3) 71 (13.0) 133 (12.5) 24	54 (94.7) 477 (87.0) 935 (87.5)	0.42 (0.13, 1.31), 0.132 1.07 (0.80, 1.42), 0.665	1 (2.6) 6 (6.7) 53 (13.5)	38 (97.4) 83 (93.3) 340 (86.4)	0.30 (0.04, 2.22), 0.240 0.66 (0.28, 1.54), 0.331	24 (8.5) 198 (13.3) 69 (12.6)	257 (91.5) 1,287 (86.7) 480 (87.4)	0.73 (0.46, 1.16), 0.179 1.05 (0.80, 1.38), 0.740
Nongluten-containing cereals <4 4 to <6 ≥6 Missing	66 (7.7) 176 (10.4) 48 (7.3) 6	787 (92.3) 1,523 (89.6) 606 (92.7)	1.19 (0.82, 1.73), 0.363 1.55 (1.13, 2.14), 0.007	40 (11.9) 118 (11.6) 50 (15.0) 6	296 (88.1) 903 (88.4) 284 (85.0)	0.86 (0.57, 1.31), 0.486 0.78 (0.56, 1.09), 0.149	2 (4.3) 16 (9.4) 42 (13.6) 5	45 (95.7) 154 (90.6) 268 (86.5)	0.47 (0.11, 1.95) 0.298 0.75 (0.42, 1.33), 0.323	54 (10.7) 221 13.0) 16 (14.2)	451 (89.3) 1,478 (87.0) 97 (85.8)	0.89 (0.51, 1.56) 0.690 0.99 (0.59, 1.65), 0.962
Rice	61 (7.8) 178 (10.7) 51 (6.8)	720 (92.2) 1,480 (89.3) 705 (93.2)	1.29 (0.89, 1.87), 0.185 1.74 (1.27, 2.38), 0.0005	1 (2.2) 89 (12.3) 117 (13.2) 40	44 (97.8) 634 (87.7) 772 (86.8)	0.20 (0.03, 1.40), 0.104 0.97 (0.73, 1.28), 0.815	1 (2.6) 15 (10.3) 44 (13.2)	37 (97.4) 131 (89.7) 289 (86.8)	0.26 (0.04, 1.90), 0.185 0.86 (0.48, 1.55), 0.614	23 (9.0) 176 (13.1) 92 (12.9) 21	233 (91.0) 1,164 (86.9) 620 (87.1)	0.77 (0.49, 1.21), 0.259 1.03 (0.80, 1.33), 0.824
Oat	12 (6.9) 84 (9.0) 190 (9.5)	163 (93.1) 849 (91.0) 1,816 (90.5) 8	0.82 (0.46, 1.46), 0.494 0.96 (0.74, 1.24), 0.736	4 (14.8) 103 (11.4) 100 (13.4) 21	23 (85.2) 798 (88.6) 648 (86.6)	1.31 (0.48, 3.59), 0.596 0.89 (0.67, 1.17), 0.402	0 4 (8.5) 55 (12.7) 45	7 (100.0) 43 (91.5) 378 (87.3)	0 0.87 (0.31, 2.43), 0.988 1	20 (8.4) 197 (13.3) 74 (12.6)	218 (91.6) 1,286 (86.7) 513 (87.4)	0.78 (0.48, 1.28), 0.327 1.04 (0.79, 1.35), 0.796
Fruits and berries** <4 4 to <6 ≥6 Missing	59 (8.0) 137 (10.5) 93 (8.0) 15	680 (92.0) 1,161 (89.5) 1,067 (92.0) 5	1.16 (0.84, 1.61), 0.368 1.42 (1.09, 1.85), 0.0087	50 (11.4) 112 (11.4) 45 (17.1) 8	389 (88.6) 874 (88.6) 219 (82.9)	0.72 (0.48, 1.08), 0.1114 0.70 (0.49, 0.98), 0.040	4 (5.1) 15 (8.3) 41 (15.4) 7	75 (94.9) 165 (91.7) 225 (84.6)	0.47 (0.17, 1.33), 0.157 0.64 (0.35, 1.17), 0.147	40 (8.2) 214 (13.4) 37 15.7)	446 (91.8) 1,387 (86.6) 198 (84.3)	0.61 (0.39, 0.95), 0.029 0.91 (0.64, 1.29), 0.597

Boldface indicates significance at P < 0.05. *Adjusted for first-degree family member with type 1 diabetes status, sex of the child, probiotic exposure during the 1st year of life (52 weeks), and high-risk genotype (HLA DR3/4). **Fruits and berries are often served together with baby porridge.

diabetesjournals.org/care Uusitalo and Associates 1847

changes in the current recommendations on infant feeding.

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