Original Investigation

Infant Exposures and Development of Type 1 Diabetes Mellitus
The Diabetes Autoimmunity Study in the Young (DAISY)

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IMPORTANCE The incidence of type 1 diabetes mellitus (T1DM) is increasing worldwide, with the most rapid increase among children younger than 5 years of age.

OBJECTIVE To examine the associations between perinatal and infant exposures, especially early infant diet, and the development of T1DM.

DESIGN The Diabetes Autoimmunity Study in the Young (DAISY) is a longitudinal, observational study.

SETTING Newborn screening for human leukocyte antigen (HLA) was done at St. Joseph's Hospital in Denver, Colorado. First-degree relatives of individuals with T1DM were recruited from the Denver metropolitan area.

PARTICIPANTS A total of 1835 children at increased genetic risk for T1DM followed up from birth with complete prospective assessment of infant diet. Fifty-three children developed T1DM.

EXPOSURES Early (<4 months of age) and late (≥6 months of age) first exposure to solid foods compared with first exposures at 4 to 5 months of age (referent).

MAIN OUTCOME AND MEASURE Risk for T1DM diagnosed by a physician.

RESULTS Both early and late first exposure to any solid food predicted development of T1DM (hazard ratio [HR], 1.91; 95% CI, 1.04-3.51, and HR, 3.02; 95% CI, 1.26-7.24, respectively), adjusting for the HLA-DR genotype, first-degree relative with T1DM, maternal education, and delivery type. Specifically, early exposure to fruit and late exposure to rice/oat predicted T1DM (HR, 2.23; 95% CI, 1.14-4.39, and HR, 2.88; 95% CI, 1.36-6.11, respectively), while breastfeeding at the time of introduction to wheat/barley conferred protection (HR, 0.47; 95% CI, 0.26-0.86). Complicated vaginal delivery was also a predictor of T1DM (HR, 1.93; 95% CI, 1.03-3.61).

CONCLUSIONS AND RELEVANCE These results suggest the safest age to introduce solid foods in children at increased genetic risk for T1DM is between 4 and 5 months of age. Breastfeeding while introducing new foods may reduce T1DM risk.

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Type 1 diabetes mellitus (T1DM) is increasing worldwide, with the most rapid increase among children younger than 5 years of age.[1-6] Perinatal factors, such as birth delivery type, birth weight, infant growth, neonatal jaundice, and maternal age have been associated with T1DM and islet autoimmunity (IA), the preclinical stage of T1DM.[7-15]

Exposures in the infant diet have been of particular interest in the etiology of T1DM.[16,17] Of the retrospective studies, 2 reports found T1DM cases had been exposed to solid foods earlier than control subjects,[18,19] while 2 reports found no association[20,21] and 1 report showed T1DM cases had been exposed to solid foods later than control subjects.[22] Prospective studies examining the development of IA have been more consistent. We found early (0-3 months of life) and late (≥7 months of life) introduction of cereals, compared with the introduction in the 4th to 6th month of life, to predict IA.[23] Ziegler et al[24] found a similar increased risk for IA with early (<3 months of age) introduction of gluten-containing foods. Recently, Virtanen et al[25] found early introduction to root vegetables (≤4 months of age) to be associated with an increased risk for IA.

The purpose of this prospective study was to examine infant exposures, with a particular focus on infant diet, and their association with development of T1DM in a birth cohort of children at increased genetic risk for T1DM. While many of these exposures have been previously examined for association with IA in this cohort, to our knowledge, this is the first time these infant exposures have been examined prospectively for the risk for T1DM.

Methods

Study Population

The Diabetes Autoimmunity Study in the Young (DAISY) is a prospective study following up 2 groups of children at increased genetic risk for developing T1DM. One group consists of babies born at St. Joseph's Hospital in Denver, Colorado, and screened by umbilical cord blood for diabetes-susceptibility alleles in the human leukocyte antigen (HLA) region.[26,27] The details of the newborn screening have been published elsewhere.[28]

The second group consists of unaffected children with a first-degree relative (either a mother, father, or sibling) with T1DM identified and recruited between birth and 8 years of age. Only children followed up from birth were included in these analyses. DAISY subjects enrolled at birth completed clinic visits at 9, 15, and 24 months, and annually thereafter. The Colorado Multiple Institutional Review Board approved all study protocols. Informed consent was obtained from the parents/legal guardians of all children. Assent was obtained from children age 7 years and older.

We examined the following descriptive and perinatal variables: HLA genotype (HLA-DR3/4, DQB1*0302 vs other), first-degree relative with T1DM (mother vs father or sibling vs none), maternal age at child's birth, maternal education (>12 years vs ≤12 years), sex (female vs male), race/ethnicity (non-Hispanic white vs other race/ethnicity), birth weight, birth season (September-February vs March-August), type of delivery (cesarean delivery vs complicated vaginal delivery vs uncomplicated vaginal delivery), and maternal smoking during pregnancy (yes vs no).

Weight Measurement

Weight in kilograms was measured at study visits at 9, 15, and 24 months, and annually thereafter on a scale with a precision of ±0.1 kg. The infant growth rate was calculated for 0 to 9 months and 0 to 24 months as (weight at 9 months − birth weight)/(age at 9-month clinic visit) and (weight at 24 months − birth weight)/(age at 24-month clinic visit) to represent how rapidly the child grew (kg/y) in the first year and 2 years of life, respectively.

The first measurement of height was not taken until the child was able to stand cooperatively, at around 2 years of age; therefore, height was not taken into consideration in these analyses.

Infant Diet Measurement

Data for infant diet were collected during telephone or face-to-face interviews at 3, 6, 9, 12, and 15 months of age. At each interview, mothers were asked to report the date of introduction and frequency of exposure (ie, number of servings per day) of all milks, formulas, and foods the infants consumed during the previous 3 months. Exclusive breastfeeding duration was determined by the reported age at which the infant was exposed to any foods or liquids other than breast milk or water. Breast-milk months is a novel breastfeeding variable we created to examine whether relative amounts of breast milk, rather than simply timing, are important in T1DM risk. Breast-milk months is a relative quantity of breast milk based on the proportion of breast milk to formula over the first 9 months of life. For example, for infants exclusively breastfed for the first 9 months, the proportion of breast milk to formula for each month was 1.0 and the number of breast-milk months summed to 9.0 breast-milk months. For infants who received both breast milk and formula, the total number of servings of breast milk for each month was divided by the total number of servings of formula and breast milk for that month, and these were summed over the first 9 months to arrive at the number of breast-milk months. Based on previous work showing a protective effect of breastfeeding when introducing cereals (for IA)[23] or gluten (for celiac disease),[29] we created 3 additional breastfeeding variables to represent whether the child was breastfed at the time of the introduction to any solid foods, cereals, and food containing wheat/barley.

We created an overall variable of age at first exposure to any solid foods, as well as variables that were components of this solid-foods variable, such as age at exposure to cereal (wheat/barley/oats/rice), wheat/barley, rice/oat, fruit (not including fruit juice), vegetables, and meat. There were no reports of introducing rye in the infant diet in DAISY children. Juices were not included in the fruit variable because we were interested in solid-food introductions. The study was an observational study; therefore, no dietary advice was given to the participating families.

Diagnosis of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus was diagnosed by a physician and defined as typical symptoms of polyuria and/or polydipsia and a random glucose level of 200 mg/dL or greater or an oral glu-

cose tolerance test with a fasting plasma glucose of 126 mg/dL or greater or a 2-hour glucose of 200 mg/dL or greater.

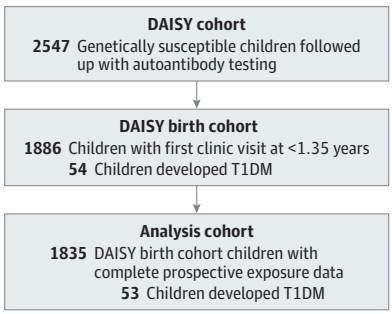
Analysis Population

Of the 2547 children followed up by DAISY, 1886 (74.0%) had a clinic visit before the age of 1.35 years, and of these, 1835 children (97.3%) had complete prospectively collected solid-food exposure data. Our analysis population comprised these 1835 children, 53 of whom developed T1DM during follow-up, as shown in **Figure 1**.

Statistical Analysis

The SAS version 9.3 (SAS Institute Inc) statistical software package was used for all statistical analyses. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards regression to account for right-censored data. A clustered time-to-event analysis was performed treating siblings from the same family as clusters, and robust sandwich variance estimates[30] were used for statistical inference. Calculations of follow-up time began at birth. When modeling the association between T1DM and perinatal and infant dietary exposures, we adjusted for HLA, first-degree relative with T1DM, and delivery type because these were associated with T1DM. We also evaluated maternal age, maternal education, sex, and race/ethnicity as potential confounders. Only the inclusion of maternal education changed the hazard ratio of the perinatal or infant diet variable by more than 10% and therefore was included in the final models. The significance threshold was defined as $\alpha < 0.05$. Because our analyses were based on a priori hypotheses and because we were interested in analyzing a complete diet in which the timing of introductions is highly correlated (ie, not independent) among foods, *P* values were not corrected for multiple testing.

Figure 1. Study Participants



Flowchart illustrating formation of analysis cohort from the Diabetes Autoimmunity Study in the Young (DAISY) population. T1DM indicates type 1 diabetes mellitus.

Results

Children who developed T1DM were more likely to have the HLA-DR3/4, DQB1*0302 genotype and to have a father or sibling with T1DM (**Table 1**). Children who experienced a complicated vaginal delivery (ie, breech or use of forceps or vacuum) were more likely to develop T1DM than those with an uncomplicated vaginal delivery, adjusting for HLA, first-degree relative with T1DM, and maternal education. The risk for T1DM was not predicted by birth weight, weight

Table 1. Demographic and Perinatal Characteristics of DAISY Birth Cohort By T1DM Status

	No. (%)			
	Developed T1DM (n = 53)	Did Not Develop T1DM (n = 1782)	HR (95% CI)	*P* Value
Demographic factors				
HLA-DR3/4, DQB1*0302	30 (56.6)	421 (23.6)	3.69 (2.12-6.40)	<.001
First-degree relative with T1DM				
None	22 (41.5)	1193 (67.0)	1.0 [Reference]	
Mother	3 (5.7)	182 (10.2)	0.89 (0.27-2.96)	.85
Father or sibling	28 (52.8)	407 (22.8)	3.32 (1.85-5.97)	<.001
Maternal age, mean (SD), y	30.9 (6.0)	30.0 (5.7)	1.01 (0.95-1.06)	.79
Maternal education, >12 y	37 (69.8)	1294 (75.9)	0.60 (0.33-1.09)	.09
Female	26 (49.1)	867 (48.7)	1.02 (0.58-1.80)	.94
Race/ethnicity, non-Hispanic white	45 (84.9)	1241 (69.8)	1.80 (0.78-4.15)	.17
Perinatal factors				
Birth weight, mean (SD), kg[a]	3.3 (0.6)	3.3 (0.6)	0.90 (0.53-1.55)	.70
9-mo weight growth rate, mean (SD), kg/y[a]	7.0 (1.4)	7.0 (1.3)	1.02 (0.84-1.24)	.86
2-y weight growth rate, mean (SD), kg/y[a]	4.4 (0.7)	4.4 (0.7)	0.97 (0.62-1.52)	.89
Birth season, September-February[a]	20 (37.7)	838 (47.0)	0.71 (0.40-1.24)	.22
Delivery type[b]				
Uncomplicated vaginal delivery	32 (60.4)	1133 (66.5)	1.0 [Reference]	
Complicated vaginal delivery	12 (22.6)	192 (11.3)	1.93 (1.03-3.61)	.04
Cesarean delivery	9 (17.0)	380 (22.3)	0.83 (0.37-1.89)	.66
Exposure to maternal cigarette smoke in utero[a]	5 (9.4)	178 (10.5)	1.19 (0.46-3.06)	.72

Abbreviations: DAISY, Diabetes Autoimmunity Study in the Young; HLA, human leukocyte antigen; HR, hazard ratio; T1DM, type 1 diabetes mellitus.

[a] HRs are adjusted for HLA genotype, first-degree relative with T1DM, maternal education, and delivery type.

[b] HR is adjusted for HLA genotype, first-degree relative with T1DM, and maternal education.

Table 2. Infant Dietary Exposure Characteristics of DAISY Birth Cohort By T1DM Status

Characteristic	No. (%) Developed T1DM (n = 53)	No. (%) Did Not Develop T1DM (n = 1782)	Adjusted HR[a] (95% CI)	P Value
Exclusive breastfeeding duration, mean (SD), mo	1.4 (2.0)	1.3 (1.7)	0.97 (0.83-1.14)	.73
Breastfeeding duration, mean (SD), mo	5.8 (7.0)	6.4 (6.9)	0.97 (0.92-1.01)	.17
Breast-milk mo, mean (SD)	3.7 (3.3)	4.2 (3.4)	0.92 (0.84-1.01)	.08
Breastfeeding at introduction of solid foods, yes vs no	28 (52.8)	980 (55.0)	0.70 (0.38-1.28)	.25
Breastfeeding at introduction of cereals (wheat/barley /oats/rice), yes vs no	27 (50.9)	976 (54.8)	0.66 (0.36-1.21)	.18
Breastfeeding at introduction of wheat/barley, yes vs no	17 (32.1)	765 (42.9)	0.47 (0.26-0.86)	.01
Age at first exposure to cow's milk, mean (SD), mo	4.4 (4.0)	3.5 (3.3)	1.01 (0.93-1.10)	.79
Age at first exposure to any solid food, mo[b]				
<4	28 (52.8)	763 (42.8)	1.91 (1.04-3.51)	.04
≥6	7 (13.2)	115 (6.5)	3.02 (1.26-7.24)	.01
Age at first exposure to any cereal (wheat/barley/oats/rice)[b]				
<4	25 (47.2)	715 (40.1)	1.72 (0.95-3.12)	.08
≥6	9 (17.0)	137 (7.7)	3.33 (1.54-7.18)	.002
Age at first exposure to foods containing wheat/barley[b]				
<4	6 (11.3)	124 (7.0)	2.08 (0.76-5.68)	.15
≥6	34 (64.2)	1049 (58.9)	1.26 (0.67-2.38)	.48
Age at first exposure to foods containing rice/oat, mo[b]				
<4	24 (45.3)	696 (39.1)	1.62 (0.90-2.92)	.11
≥6	9 (17.0)	159 (8.9)	2.88 (1.36-6.11)	.01
Age at first exposure to fruit, excluding fruit juice, mo[b]				
<4	15 (28.3)	265 (14.9)	2.23 (1.14-4.39)	.02
≥6	14 (26.4)	533 (29.9)	1.03 (0.51-2.09)	.94
Age at first exposure to vegetables, mo[b]				
<4	7 (13.2)	189 (10.6)	1.19 (0.49-2.89)	.70
≥6	16 (30.2)	544 (30.5)	1.06 (0.55-2.01)	.87
Age at first exposure to meat, mo[b]				
<4	2 (3.8)	13 (0.7)	2.52 (0.44-14.49)	.30
≥6	42 (79.3)	1527 (85.7)	0.63 (0.31-1.28)	.20

Abbreviations: DAISY, Diabetes Autoimmunity Study in the Young; HR, hazard ratio; T1DM, type 1 diabetes mellitus.

[a] Adjusted HRs are adjusted for human leukocyte antigen genotype, first-degree relative with T1DM, maternal education, and delivery type.

[b] Reference = 4 or 5 months old.

growth at 9 months or 2 years, exposure to smoking in utero, or season of birth.

Based on American Academy of Pediatrics guidelines that recommend introduction of solid foods between 4 and 6 months of age,[31] we categorized age at first exposure to foods as younger than 4 months (early, introduced prior to the 4-month birthday) and 6 months of age or older (late, introduced on the 6-month birthday or later) and compared them to 4 to 5 months of age (referent) (**Table 2**). Adjusting for HLA, first-degree relative with T1DM, maternal education, and delivery type, both early (<4 months) and late (≥6 months) exposure to any solid food predicted T1DM. We then examined individual components of the solid-foods variable to determine whether certain foods were driving this association. We first tested whether age at first exposure to any cereals predicted T1DM because this variable has previously been found to predict IA in our cohort.[23] In the current analysis, early (<4 months) and late (≥6 months) exposure to any cereal (wheat/barley/oats/rice) increased the risk for T1DM. We then divided this variable into foods containing wheat/barley (ie, gluten containing) and foods containing rice/oat (nongluten containing). Late (≥6 months) first exposure to rice/oat increased the risk for T1DM, while early (<4 months) first exposure did not predict T1DM. First exposure to wheat/barley did not predict the development of T1DM. Early, but not late, exposure to fruits increased the risk for T1DM. The timing of introduction of vegetables or meat did not predict T1DM.

Children who were still breastfed when wheat/barley were introduced had a significantly lower risk for T1DM than children who were not breastfed at the time when wheat/barley were introduced, adjusting for HLA, first-degree relative with T1DM, maternal education, and delivery type (Table 2). More breast-milk months marginally decreased the risk for T1DM. Partial and exclusive breastfeeding duration and age at first exposure to cow's milk did not predict T1DM.

As many food introductions happen together and therefore may not be independent, we placed all food-introduction and breastfeeding variables found to either marginally or significantly predict T1DM in the same model to evaluate the

Table 3. Investigation of Independent Effects of Infant Diet Exposures on Risk for T1DM in DAISY Birth Cohort

Variable	Adjusted HR (95% CI)	*P* Value
HLA-DR3/4,DQB1*0302	5.59 (3.07-10.19)	<.001
First-degree relative with T1DM		
None	1.0 [Reference]	
Mother	1.75 (0.53-5.85)	.36
Father or sibling	5.86 (3.15-10.90)	<.001
Maternal education, >12 y	0.89 (0.42-1.87)	.75
Delivery type		
Uncomplicated vaginal delivery	1.0 [Reference]	
Complicated vaginal delivery	1.89 (0.98-3.65)	.06
Cesarean delivery	0.82 (0.34-1.96)	.66
Breastfeeding at introduction of wheat/barley, yes vs no	0.46 (0.26-0.80)	.01
Age at first exposure to foods containing wheat/barley, mo[a]		
<4	2.03 (0.71-5.80)	.18
≥6	1.17 (0.61-2.22)	.64
Age at first exposure to foods containing rice/oat, mo[a]		
<4	0.92 (0.44-1.93)	.82
≥6	3.32 (1.46-7.51)	.004
Age at first exposure to fruit, excluding fruit juice, mo[a]		
<4	1.99 (0.88-4.51)	.10
≥6	0.67 (0.31-1.46)	.31

Abbreviations: DAISY, Diabetes Autoimmunity Study in the Young; HLA, human leukocyte antigen; HR, hazard ratio; T1DM, type 1 diabetes mellitus.

[a] Reference = 4 or 5 months old.

independent effects of each (**Table 3**). Adjusting for HLA, first-degree relative with T1DM, maternal education, and delivery type, the association between T1DM and early (<4 months) exposure to fruit was attenuated with the inclusion of the other food variables, while breastfeeding at the time of first exposure to foods containing wheat/barley and late (≥6 months) exposure to rice/oat remained significantly predictive of T1DM.

As rice/oat is the most common first solid food introduced in DAISY children (**Figure 2**), it was important to understand the differences, demographically and dietwise, between mothers who waited until after 6 months of age to introduce rice/oat compared with mothers who introduced it earlier (**Table 4**). Mothers who introduced rice/oat late (≥6 months) were more likely to be older, more educated, and have T1DM than mothers who introduced rice/oat earlier. Mothers who introduced rice/oat late (≥6 months) were also more likely to breastfeed (both partially and exclusively) for a longer duration and introduce all other solid foods later than mothers who introduced rice/oat earlier.

We explored the distribution of ages at first exposure to rice/oat in the late (≥6 months) category and found 71 children (42.3%) were introduced to rice/oat on their 6-month birthday (ie, the first day of the late category), perhaps reflecting the propensity to use benchmarks such as birthdays in decisions about diet. To explore the sensitivity of the age cutoff for this late category, we placed the 71 children introduced to rice/oat on their birthday into the previous category of 4 to 5 months (a difference of 1 day) and reexamined the risk for T1DM. The adjusted hazard ratio for the late introduction of rice/oat when placing those children introduced to rice/oat on the 6-month birthday in the reference category (4-5 months) increased to 4.28 (95% CI, 1.90-9.66) from 2.88 (95% CI, 1.36-6.11) (Table 2), suggesting T1DM predicted by late introduction to rice/oat was most likely driven by even later introduction of rice/oat than on the 6-month birthday.

Discussion

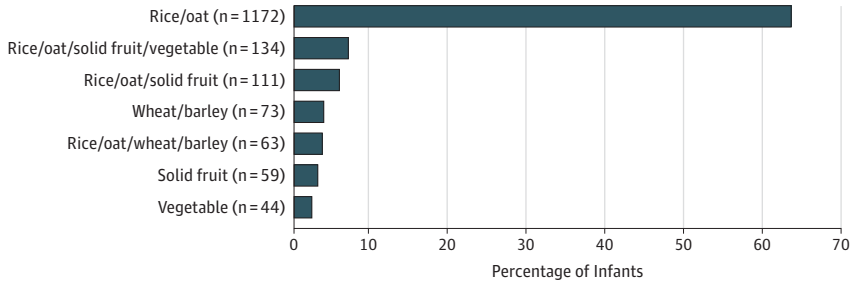
DAISY now has a sufficient number of T1DM cases to investigate risk factors for development of T1DM. The findings reported here are consistent with our previous report, in which we had found a window of time for introduction of cereals, 4 to 6 months, outside of which risk for development of IA increased.[23] Our current data suggest the increased risk for T1DM found with early (<4 months) and late (≥6 months) introduction of solid foods appears to be driven by late first exposure to rice/oat and early first exposure to wheat/barley and fruit.

Our previous report defined the categories of time for introduction in terms of months of life rather than months of age, with first exposure to foods in the 0 to 3 months of life (ie, prior to 3 months of age) and 7 months or more of life (ie, at or after 6 months of age) with the reference being the 4 to 6 months of life.[23] Given the recommendation by the American Academy of Pediatrics to introduce solid foods between 4 and 6 months of age, we chose on or after the 4-month birthday and before the 6-month birthday as the reference group for the current analysis, which more accurately reflects the way mothers and pediatricians would interpret this recommendation. Moreover, instead of referring to the categories in terms of months of life, in the present study, we refer to these in terms of months of age, which is how we believe mothers tend to report the age of their child when describing milestones such as introducing new foods, first sitting, and first crawling.

The relation between late (≥6 months) introduction of rice/oat and development of T1DM is of particular interest. Rice/oat is the most common first solid food introduced in DAISY children, reflecting US practices. While there were many differences between children who were exposed to cereals after 6 months compared with before, an increased T1DM risk remained after adjustment for these variables. It is possible late (≥6 months) introduction of rice/oat represents an unmeasured set of variables/behaviors that increases T1DM risk.

Our findings align with the American Academy of Pediatrics recommendation to introduce solid foods between 4 and 6 months of age[31]; although recently, the American Academy of Pediatrics Section on Breastfeeding reaffirmed its recommendation of exclusive breastfeeding for about 6 months.[32] These apparently conflicting recommendations can result in confusion over the best practice. Our sensitivity analysis showing T1DM predicted by late introduction to rice/oat was mostly driven by later introduction of rice/oat than 6 months suggests there is some leeway in the timing of the introduction

Figure 2. First Solid Food Introduced to 1835 Diabetes Autoimmunity Study in the Young Infants



As shown, solid foods may be introduced individually or in combination with other solid foods.

Table 4. Characteristics of Timing of Rice/Oat Introduction

Characteristic	Mean (SD)		
	<4 mo	4-5 mo	≥6 mo
HLA-DR3/4, DQB1*0302, %	25.4	24.6	20.8
First-degree relative with T1DM, %[a]			
None	70.0	64.2	61.3
Mother	8.5	10.7	13.7
Father or sibling	21.5	25.1	25.0
Mean maternal age, y[a]	28.5 (5.6)	30.9 (5.5)	31.8 (5.4)
Maternal education, >12 y, %[a]	68.8	79.4	85.0
Race/ethnicity, non-Hispanic white, %	67.7	71.9	71.9
Exclusive breastfeeding, mo[a]	0.7 (1.2)	1.4 (1.8)	2.5 (2.6)
Breastfeeding duration, mo[a]	4.3 (5.9)	7.3 (6.8)	10.4 (8.9)
Breast-milk mo[a]	2.9 (3.0)	4.9 (3.4)	6.0 (3.3)
Age at first exposure to dairy, mo[a]	3.0 (3.0)	3.7 (3.3)	5.4 (4.4)
Age at first exposure to wheat/barley, mo[a]	6.5 (2.0)	7.2 (1.6)	8.2 (1.8)
Age at first exposure to fruit, mo[a]	5.1 (1.4)	6.1 (1.2)	7.3 (1.6)
Age at first exposure to vegetables, mo[a]	5.4 (1.4)	6.2 (1.2)	7.4 (1.6)
Age at first exposure to meat, mo[a]	8.7 (3.1)	9.3 (2.7)	10.3 (2.8)

Abbreviations: HLA, human leukocyte antigen; T1DM, type 1 diabetes mellitus.

[a] $P < .05$ for comparisons across groups.

of cereals, such that women who choose to exclusively breastfeed their child for 6 months may not have to worry they are increasing their child's risk for T1DM by waiting until this time to introduce cereals.

The risk predicted by early exposure to solid foods might suggest a mechanism involving an abnormal immune response to solid food antigens in an immature gut immune system in susceptible individuals. As the increased risk is not limited to a specific food, it is possible many solids, including cereals and fruits, contain a common component that triggers an immature response. The increased risk predicted by late exposure to solid foods may be related to the larger amounts given at initial exposure to older children.[23,29,33] Also, if solid foods are introduced too late, when breast milk alone no longer meets the infant's energy and nutrient needs, nutrient deficiencies may occur,[34] which may play a role in increasing T1DM risk. Additionally, the increased risk predicted by late exposure to solid foods may be related to the cessation of breastfeeding before solid foods are introduced, resulting in a loss of the protective effects of breast milk at the introduction of foreign food antigens.

Breastfeeding is thought to reduce T1DM risk by protecting against infections through secretory immunoglobulin A antibodies and enhancement of the infant's immune response via increased β-cell proliferation,[35] as well as delayed exposure to foreign milk antigens. However, to our knowledge, prospective studies in genetically at-risk children have not found an association[23-25] between breastfeeding duration or timing of exposure to cow's milk and development of IA. The most strongly associated breastfeeding variable in our analyses was breastfeeding at wheat/barley introduction, suggesting that breast milk may protect against an abnormal immune response to new antigens in an immature gut. Previously, we found a significant reduction in IA risk if cereals were introduced while the child was still breastfeeding, independent of the age at first exposure to cereals.[23] Similarly, Ivarsson et al[29] reported a reduced celiac disease risk in children who had been breastfed when gluten was introduced.

Our findings suggesting an increased risk for T1DM predicted by complicated vaginal delivery but not cesarean delivery are similar to what we found previously with the outcome of IA.[7] A recent report, which suggested cesarean delivery

may predict a faster progression to T1DM after the appearance of IA, did not differentiate between complicated and uncomplicated vaginal delivery.[36] Perhaps the stress of a complicated vaginal delivery affecting the fetal immune system, or other unknown factors complicating the birth or leading to a decision to not have a cesarean delivery, may be related to T1DM risk.

In this prospective study, we examined infant exposures as risk factors for the development of T1DM in children at increased genetic risk. While much of the focus of infant diet and T1DM research has been on the timing of the introduction of a single antigen (ie, milk or gluten), our data suggest multiple foods/antigens play a role and that there is a complex relationship between the timing and type of infant food exposures and T1DM risk. In summary, there appears to be a safe window in which to introduce solid foods between 4 and 5 months of age; solid foods should be introduced while continuing to breastfeed to minimize T1DM risk in genetically susceptible children. These findings should be replicated in a larger cohort for confirmation.

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