Infant Feeding in Relation to Islet Autoimmunity and Type 1 Diabetes in Genetically Susceptible Children: The MIDIA Study

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OBJECTIVE

We aimed to study the association of breast-feeding duration and age at the introduction of solid foods with the risk of islet autoimmunity and type 1 diabetes in genetically susceptible children.

RESEARCH DESIGN AND METHODS

Newborns were recruited from the Norwegian general population during 2001–2007. After genetic screening of nearly 50,000 newborns, 908 children with the high-risk HLA genotype were followed up with blood samples and questionnaires at age 3, 6, 9, and 12 months and then annually. Complete infant diet data were available for 726 children.

RESULTS

Any breast-feeding for 12 months or longer predicted a decreased risk of developing type 1 diabetes compared with any breast-feeding for less than 12 months before and after adjusting for having a first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education, sex, and delivery type (hazard ratio 0.37 [95% CI 0.15–0.93]). Any breast-feeding for 12 months or longer was not associated with islet autoimmunity but predicted a lower risk of progression from islet autoimmunity to type 1 diabetes (hazard ratio 0.35 [95% CI 0.13–0.94]). Duration of full breast-feeding was not significantly associated with the risk of islet autoimmunity or type 1 diabetes nor was age at introduction of solid foods or breast-feeding at the time of introduction of any solid foods.

CONCLUSIONS

These results suggest that breast-feeding for 12 months or longer predict a lower risk of progression from islet autoimmunity to type 1 diabetes among genetically predisposed children.

Type 1 diabetes is one of the most common chronic diseases in childhood and results from the autoimmune destruction of the insulin-producing β-cells in the pancreas after a subclinical period of variable length where autoantibodies against β-cell antigens are present (1). Recent studies from Sweden, Finland, and Norway indicate that the incidence has ceased to increase in the past few years (2–4). Still, the incidence of type 1 diabetes has changed during the past two to three decades (5). Because the genetic background is stable, the change in incidence suggests a role for environmental factors in the development of type 1 diabetes. Infant feeding may contribute to the development of islet autoimmunity and type 1 diabetes, but few

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prospective studies have investigated this in humans (6). Potential protective mechanisms of breast-feeding, such as decreased gut permeability, decreased frequency of early enterovirus infections, and postponed exposure to dietary antigens, have been suggested (6).

A meta-analysis of studies published up to 1996 indicated that the risk of type 1 diabetes was lower among breast-fed children compared with children receiving infant formulas before 6 months of age, but all of the studies included were retrospective and thus susceptible to recall bias (7). A recent meta-analysis suggested an association between breast-feeding in the early weeks of life and a lower risk of developing type 1 diabetes but provided little evidence of an association with breast-feeding over a longer period, and nearly all of the studies were retrospective (8).

Results from studies that have investigated the association between breast-feeding duration and the development of type 1 diabetes and islet autoimmunity are inconsistent (9–12). Most of the studies are retrospective, and are thus susceptible to recall bias. Prospective studies can minimize the risk of recall and selection bias and, preferably, also include measures of preclinical islet autoantibodies.

The objective of this study was to investigate the association of breast-feeding duration and age at introduction of solid foods with the risk of islet autoimmunity and type 1 diabetes in genetically susceptible children.

RESEARCH DESIGN AND METHODS

Subjects and Design

The MIDIA (Norwegian acronym for "Environmental Triggers of Type 1 Diabetes") study recruited newborns from the Norwegian general population during 2001–2007. After genetic screening of nearly 50,000 newborns, 908 children with the high-risk HLA genotype (DRB1*0401-DQA1*03-DQB1*0302/DRB1*03-DQA1*05-DQB1*02) were followed up with blood samples at age 3, 6, 9, and 12 months and then annually (Fig. 1). Questionnaires were administered at the same time points (13).

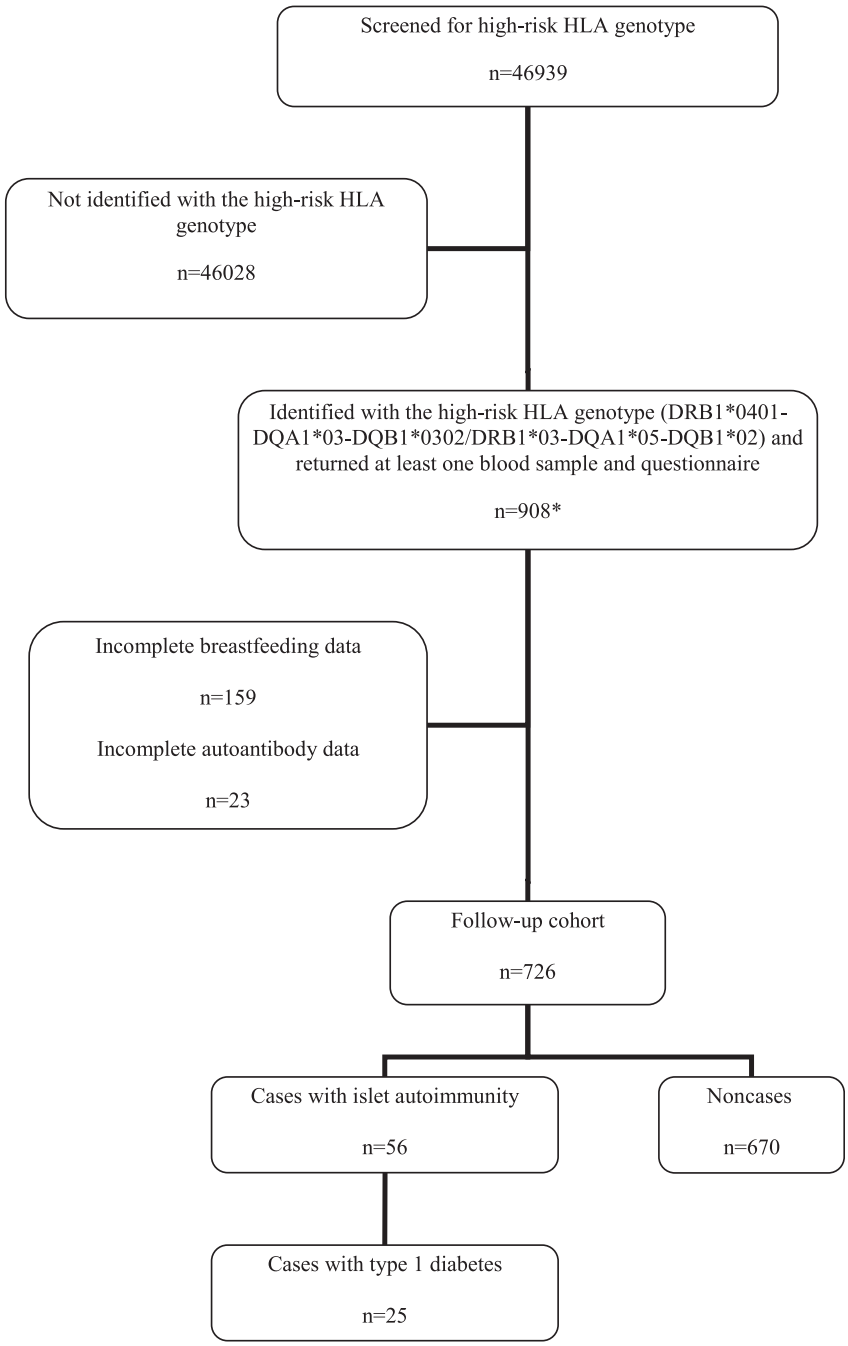

Figure 1—Flowchart shows MIDIA participants included in the cohort analysis. *3 of 911 subjects later withdrew and requested their data deleted.

Assessment of Breast-Feeding and Infant Diet

Information about infant diet was derived from three main questions in questionnaires administered at age 3, 6, 9, and 12 months: *1*) what type of milk the child consumed at specific ages, reported in 2-week intervals in the questionnaire administered at 3 months of age and in 2-month intervals in the other questionnaires (the alternatives were breast milk, different types of infant formulas, and other milk; *2*) frequency intake of the milk consumed; and *3*) whether solid or semisolid foods were regularly given to the child. The intake of milk and solid foods was not quantified. Parents were asked to keep records of breast-feeding and other food intake as a help to complete the questionnaires.

The World Health Organization definitions (14,15) were used to categorize breast-feeding as "full breast-feeding" and "any breast-feeding." The category "full breast-feeding" includes children who received breast milk, water, water-based drinks or fruit juices, and not solid or semisolid food, daily or weekly. The

category "any breast-feeding" includes infants who received breast milk, regardless of introduction to other drinks and complementary foods.

Information on vitamin D supplementation was derived from one main question included in the questionnaires used at all age levels. The alternatives included five supplements containing vitamin D in addition to an open text field where the participants could report intake of supplements that were not listed as an alternative. Supplementation was reported as frequencies (times per week). The mean frequency of vitamin D supplement intake from 3 to 12 months of age was calculated and combined into three categories: <3 times/week, 3–6 times/week, and daily.

Categorization was based on current recommendations and ensuring a sufficient number of cases in each category. Full breast-feeding duration was categorized into <4, 4–5.9, and ≥6 months and into ≤2 and >2 weeks. Any breast-feeding duration was categorized into <12 and ≥12 months. Age at introduction of maize/rice cereal, oat cereal, or wheat cereal was categorized into <5, 5–5.9, and ≥6 months. An overall variable for age at introduction of any solid foods and variables for age at introduction of cereals, gluten, and nongluten cereals were created from the different solid food variables mentioned above. Variables for breast-feeding at introduction of the different solid foods were also created.

Covariates

Demographic variables and family history of type 1 diabetes were obtained from the questionnaire administered

Table 1—Characteristics of the MIDIA cohort and risk of islet autoimmunity and type 1 diabetes

Characteristic	All infants *n* = 726 *n* (%)	Developed autoimmunity *n* = 56 *n* (%)	Hazard ratio (95% CI)*	Developed type 1 diabetes *n* = 25 *n* (%)	Hazard ratio (95% CI)†
First-degree relative with type 1 diabetes					
No	656 (92.1)	39 (73.6)	1	16 (66.7)	1
Yes	56 (7.9)	14 (26.4)	4.56 (2.48–8.41)	8 (33.3)	5.67 (2.42–13.3)
Sex					
Female	359 (49.4)	32 (57.1)	1	18 (72.0)	1
Male	367 (50.6)	24 (42.9)	0.74 (0.44–1.25)	7 (28.0)	0.38 (0.16–0.92)
Maternal education level‡					
Low/medium	570 (78.8)	44 (78.6)	1	21 (84.0)	1
High	153 (21.2)	12 (21.4)	0.95 (0.50–1.79)	4 (16.0)	0.66 (0.23–1.93)
Maternal age at delivery, years					
≤31	401 (56.1)	35 (62.5)	1.40 (0.81–2.40)	17 (68.0)	1.87 (0.81–4.32)
>31	314 (43.9)	21 (37.5)	1	8 (32.0)	1
Maternal smoking in pregnancy					
No	605 (83.9)	49 (87.5)	1	22 (88.0)	1
Yes	116 (16.1)	7 (12.5)	0.76 (0.34–1.67)	3 (12.0)	0.73 (0.22–2.44)
Preeclampsia					
No	661 (93.9)	50 (90.9)	1	23 (95.8)	1
Yes	43 (6.1)	5 (9.1)	1.70 (0.68–4.27)	1 (4.2)	0.71 (0.10–5.23)
Number of siblings					
0	266 (36.6)	17 (30.4)	1	7 (28.0)	1
1	302 (41.6)	24 (42.9)	1.21 (0.65–2.25)	12 (48.0)	1.33 (0.52–3.38)
≥2	158 (21.8)	15 (26.8)	1.53 (0.76–3.05)	6 (24.0)	1.39 (0.47–4.15)
Birth weight, g					
≤3,500	278 (38.5)	20 (35.7)	1.10 (0.64–1.90)	7 (28.0)	1.50 (0.63–3.58)
>3,500	444 (61.5)	36 (64.3)	1	18 (72.0)	1
Gestational age, completed weeks					
<37	39 (5.5)	3 (5.7)	1.17 (0.36–3.74)	2 (8.3)	1.76 (0.41–7.49)
≥37	666 (94.5)	50 (94.3)	1	22 (91.7)	1
Delivery type					
Elective cesarean delivery	36 (5.0)	3 (5.4)	1.14 (0.36–3.66)	3 (12.0)	2.65 (0.79–8.94)
Emergency cesarean delivery	76 (10.5)	5 (8.9)	0.87 (0.34–2.17)	2 (8.0)	0.79 (0.19–3.40)
Vaginal delivery	614 (84.6)	48 (85.7)	1	20 (80.0)	1
Vitamin D supplementation					
<3 times/week	211 (29.1)	18 (32.1)	1	4 (16.0)	1
3–6 times/week	400 (55.1)	31 (55.4)	0.88 (0.49–1.57)	16 (64.0)	2.13 (0.71–6.38)
Daily	115 (15.8)	7 (12.5)	0.71 (0.30–1.70)	5 (20.0)	2.28 (0.61–8.51)

*Unadjusted hazard ratio for islet autoimmunity. The hazard ratio for the reference category is set to 1. †Unadjusted hazard ratio for type 1 diabetes. The hazard ratio for the reference category is set to 1. ‡Low/middle maternal education level is defined as primary, secondary, and comprehensive school, academy/college/university up to 4 years. High maternal education level is defined as academy/college/university more than 4 years.

when the child was 3 months old. Information on delivery type, gestational age, and birth weight was obtained from The Medical Birth Registry of Norway (16). Potential confounders were included as covariates in the regression models and categorized as shown in Table 1.

Outcome Measures

Blood samples were tested at the Oslo University Hospital Hormone Laboratory for diabetes-associated autoantibodies against insulin (IAA), GADA, and the protein tyrosine kinase–related protein IA-2 (IA-2A) using radiobinding assays, as described in detail (13). Islet autoimmunity was defined as high titers of one autoantibody or titers above the cutoff for two or three autoantibodies in two or more consecutive samples. The disease specificities of our assays in Diabetes Antibody Standardization Program/Islet Autoantibody Standardization Program year 2005–2012 ranged between 93 and 100% for GADA, 94 and 100% for IA2A, and 94 and 99% IAA, whereas the disease sensitivities ranged between 50 and 80% for GADA, 58 and 70% for IA2A, and 4 and 18% for IAA. Data from the Norwegian Childhood Diabetes Registry, with samples from 217 children, has shown an estimated specificity of 100% and sensitivity of 32% for IAA (Peter A. Torjesen, personal communication). Clinical diagnosis of type 1 diabetes was also used as an outcome.

Data Analysis

Statistical analyses were performed with IBM SPSS Statistics 20.0 software (IBM Corp., Armonk, NY) and STATA 13 software. Cox regression analysis was used to estimate hazard ratios with 95% CIs compared with reference categories. We also estimated the probability of islet autoimmunity or type 1 diabetes by breast-feeding duration as 1-survival, using the Kaplan-Meier method.

Follow-up time was counted from birth to the midpoint between the last autoantibody-negative and the first antibody-positive sample for those with islet autoimmunity and to the time of the most recent blood sample in those who did not develop islet autoimmunity. For analyses of type 1 diabetes as the end point, follow-up time was counted to the time of diagnosis for those with type 1 diabetes and to the time of the most recent blood sample in those who did not develop type 1 diabetes.

Participants who were excluded due to missing data about breast-feeding practices (n = 159) did not differ from the included participants with regard to development of type 1 diabetes and autoimmunity, but their mothers were more likely to be smokers ($P < 0.01$) and lower educated ($P < 0.01$) (data not shown).

RESULTS

During the mean follow-up time of 7.70 (SD 1.58) years, 7.7% developed islet autoimmunity, and 3.4% developed type 1 diabetes. GADA only was the first islet autoantibody combination to appear in 44.4%, IAA only in 20.4%, both GADA and IAA in 18.5%, IA-2 only in 1.9%, and other combinations in 14.8% of the islet autoimmunity cases. Other characteristics of the cohort are reported in Table 1, with characteristics stratified by family history reported in Supplementary Table 1. The prevalence of full and any breast-feeding by age are shown in Fig. 2.

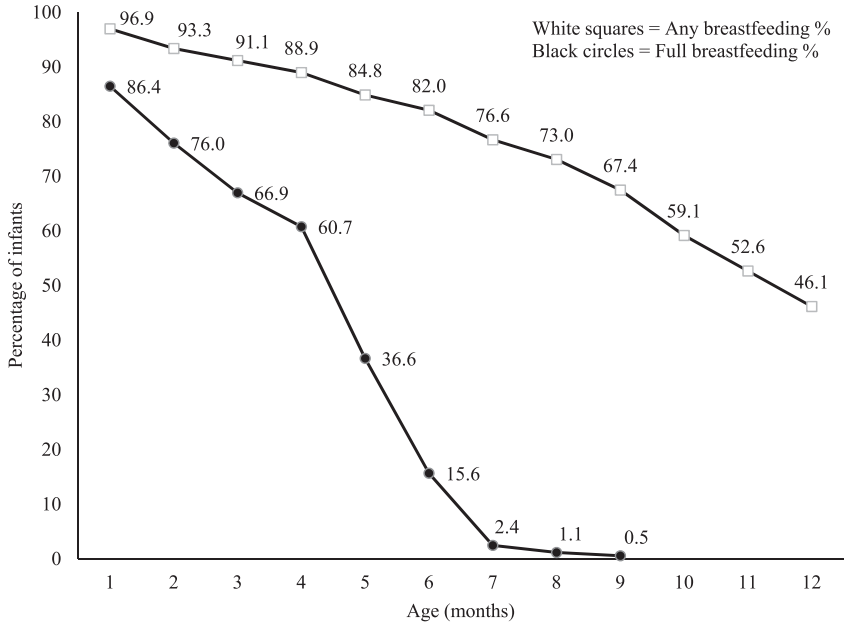

Figure 2—Full breast-feeding and any breast-feeding during the first year of life of MIDIA infants (n = 726).

The duration of any breast-feeding did not differ significantly between those who developed type 1 diabetes and those who did not (Mann-Whitney test, P = 0.44). However, a lower risk of developing type 1 diabetes was predicted by any breast-feeding for 12 months or longer compared with any breast-feeding for less than 12 months, before and after adjusting for having a first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education, sex, and delivery type (Table 2 and Fig. 3*A*). The risk of islet autoimmunity was not predicted by any breast-feeding for 12 months or longer (Table 2 and Fig. 3*B*).

To further investigate this, we analyzed the relation between duration of any breast-feeding and progression from islet autoimmunity (n = 56) to type 1 diabetes. In this analysis, follow-up time was counted from the midpoint between the last autoantibody-negative and the first antibody-positive sample to the time of diagnosis for those with type 1 diabetes and to the time of the most recent blood sample in those who did not develop type 1 diabetes. We found that any breast-feeding for 12 months or longer predicted a lower risk of progressing to type 1 diabetes (hazard ratio 0.35 [95% CI 0.13–0.94]). Duration of full breast-feeding was not associated with risk of islet autoimmunity or type 1 diabetes (Table 2).

There were no associations between early or late introduction of any solid foods and development of islet autoimmunity or type 1 diabetes (Table 2 and Supplementary Table 2). The most common (solid) weaning food that was introduced first was maize/rice cereal. There was no association between breast-feeding or not at the time of introduction of solid foods and development of islet

Table 2—Infant dietary exposure characteristics of the MIDIA cohort and risk of islet autoimmunity and type 1 diabetes

Characteristic	All infants *N* = 726	Developed autoimmunity *n* = 56	Hazard ratio (95% CI)*†	Developed type 1 diabetes *n* = 25	Hazard ratio (95% CI)‡†
Full breast-feeding duration, mean (SD) months	3.4 (1.9)	3.5 (1.8)	1.03 (0.89–1.20)	3.2 (1.8)	0.96 (0.78–1.18)
Full breast-feeding duration, *n* (%)					
<4 months	290 (39.9)	21 (37.5)	1	11 (44.0)	1
4–5.9 months	326 (44.9)	25 (44.6)	0.98 (0.53–1.81)	10 (40.0)	0.79 (0.32–1.94)
≥6 months	110 (15.2)	10 (17.9)	1.23 (0.57–2.66)	4 (16.0)	0.84 (0.26–2.73)
Full breast-feeding duration, *n* (%)					
≤2 weeks	100 (13.8)	7 (12.5)	0.93 (0.41–2.11)	4 (16.0)	1.10 (0.36–3.41)
>2 weeks	626 (86.2)	49 (87.5)	1	21 (84.0)	1
Any breast-feeding duration, mean (SD) months	10.3 (5.2)	10.3 (4.1)	1.01 (0.93–1.09)	9.9 (3.6)	0.99 (0.88–1.11)
Any breast-feeding duration, *n* (%)					
<12 months	391 (53.9)	32 (57.1)	1	18 (72.0)	1
≥12 months	335 (46.1)	24 (42.9)	0.74 (0.43–1.30)	7 (28.0)	0.37 (0.15–0.93)
Age at introduction of					
Other milk, mean (SD) months	4.9 (3.8)	5.5 (3.8)	1.02 (0.94–1.10)	5.1(3.8)	0.97 (0.87–1.08)
Any solid food, mean (SD) months	4.7 (1.2)	4.5 (1.0)	0.92 (0.71–1.18)	4.3 (0.9)	0.74 (0.49–1.11)
Any solid foods, *n* (%)					
<5 months	350 (48.5)	30 (53.6)	1.31 (0.67–2.56)	15 (60.0)	1.89 (0.67–5.36)
5–5.9 months	221 (30.6)	14 (25.0)	1	5 (20.0)	1
≥6 months	151 (20.9)	12 (21.4)	1.33 (0.61–2.94)	5 (20.0)	1.37 (0.39–4.78)
Any cereal, *n* (%)					
<5 months	334 (47.4)	27 (48.2)	1.17 (0.60–2.31)	13 (52.0)	1.31 (0.48–3.56)
5–5.9 months	208 (29.5)	14 (25.0)	1	6 (24.0)	1
≥6 months	163 (23.1)	15 (26.8)	1.44 (0.68–3.03)	6 (24.0)	1.20 (0.38–3.75)
Maize/rice					
<5 months	304 (51.0)	26 (56.5)	1.29 (0.64–2.60)	13 (59.1)	1.30 (0.48–3.52)
5–5.9 months	185 (31.0)	13 (28.3)	1	6 (27.3)	1
≥6 months	107 (18.0)	7 (15.2)	0.98 (0.38–2.49)	3 (13.6)	0.83 (0.20–3.36)
Oat					
<5 months	76 (12.6)	5 (10.9)	1.20 (0.38–3.73)	2 (10.5)	2.91 (0.39–21.9)
5–5.9 months	120 (19.9)	10 (21.7)	1	3 (15.8)	1
≥6 months	407 (67.5)	31 (67.4)	1.21 (0.55–2.67)	14 (73.7)	2.36 (0.52–10.7)
Wheat					
<5 months	72 (13.7)	4 (10.3)	1.24 (0.32–4.79)	3 (18.8)	6.82 (0.64–72.6)
5–5.9 months	114 (21.6)	6 (15.4)	1	2 (12.5)	1
≥6 months	341 (64.7)	29 (74.4)	1.93 (0.74–5.03)	11 (68.8)	4.10 (0.52–32.4)
Gluten					
<5 months	92 (13.3)	5 (9.4)	0.89 (0.28–2.76)	3 (12.5)	5.83 (0.58–58.6)
5–5.9 months	121 (17.5)	9 (17.0)	1	2 (8.3)	1
≥6 months	477 (69.1)	39 (73.6)	1.24 (0.58–2.69)	19 (79.2)	5.76 (0.76–43.7)

*Adjusted hazard ratio for islet autoimmunity. The hazard ratio for the reference category is set to 1. †Hazard ratios were adjusted for first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education level, sex, and delivery type. Unadjusted hazard ratio estimates were very similar to the adjusted ones (data not shown). ‡Adjusted hazard ratio for type 1 diabetes. The hazard ratio for the reference category is set to 1.

autoimmunity or type 1 diabetes (Supplementary Table 3).

Finally we did sensitivity analyses where those with only one autoantibody no longer were included. This analysis included 45 children, and results were essentially unchanged (data not shown).

CONCLUSIONS

Our key finding was that any breast-feeding for 12 months or longer predicted a lower risk of type 1 diabetes and a lower risk of progressing from islet autoimmunity to type 1 diabetes.

Previous population-based studies provide little evidence for an association between full breast-feeding or any

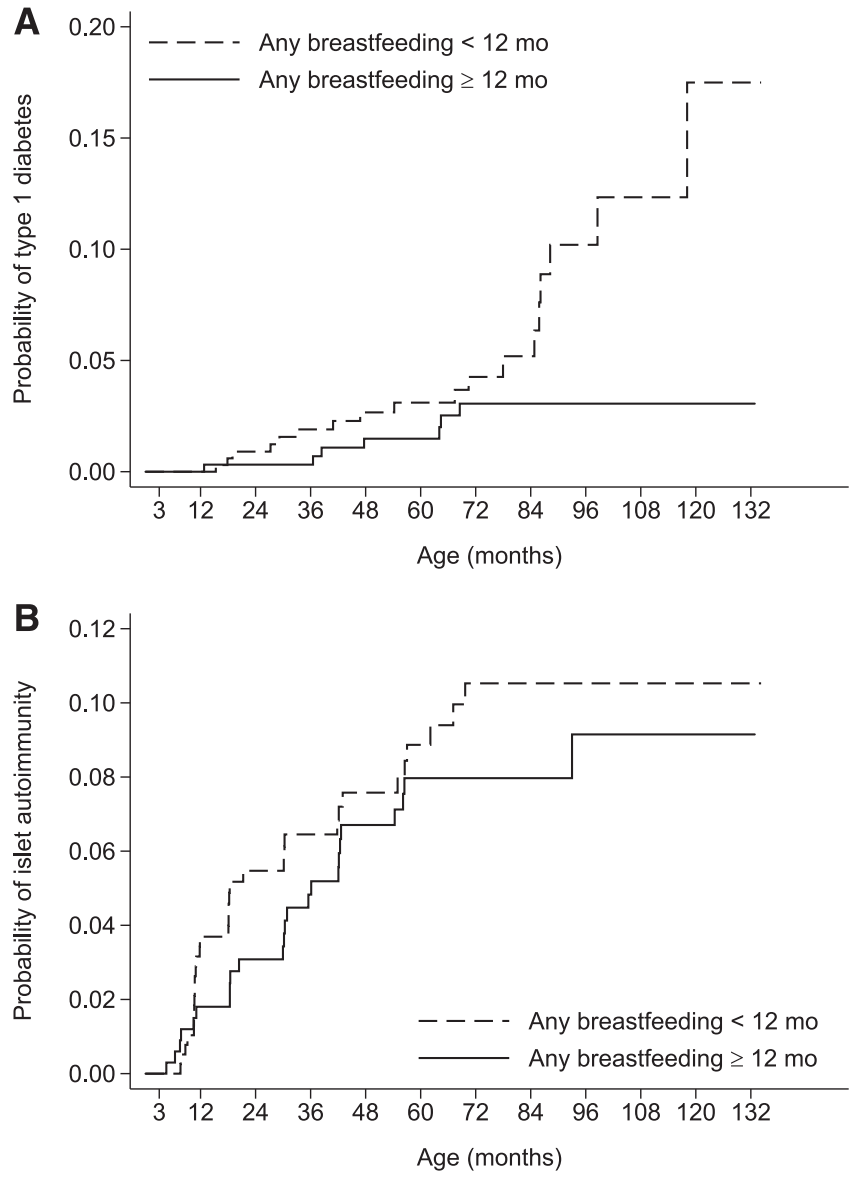

Figure 3—Risk of type 1 diabetes (*A*) and islet autoimmunity (*B*) by duration of any breast-feeding in the MIDIA study. Risk (probability) of end point by age was estimated as 1-survival, using the Kaplan-Meier method.

breast-feeding over a longer period and development of type 1 diabetes (8). The Diabetes Autoimmunity Study in the Young (DAISY) did not find any association with type 1 diabetes for exclusive breast-feeding duration or for any breast-feeding duration when other dietary exposures were not taken in to consideration (12). DAISY included 1,835 children from Colorado with high or moderate HLA genotypes or with first-degree relatives with type 1 diabetes, of which 53 developed type 1 diabetes. Our data might be more suitable to detect the effect of breast-feeding duration on type 1 diabetes given the relatively high prevalence of 46.1% at 12 months of age. The high prevalence of children being breast-fed in this study is similar to that in the Norwegian Infant Nutrition Survey of children born in 2006 (17–19) and The Norwegian Mother and Child Cohort Study (20).

The risk of developing islet autoimmunity was not predicted by full breast-feeding or any breast-feeding duration. This is in line with results from other similar prospective studies, including Diabetes Prediction and Prevention (DIPP), with more than 3,000 Finnish children with high- and moderate-risk HLA genotypes, of whom ~100 developed islet autoimmunity, and German BABYDIAB, with 1,460 offspring of mothers or fathers with type 1 diabetes, of whom 81 developed islet autoimmunity (9,10). A prospective study from Sweden that reported a positive association between short total and exclusive breast-feeding duration and islet autoimmunity lacked repeated measurements of autoantibodies, and the cutoff points were set to the 95th percentile in the cohort, which likely included many false-positives (11). Data from Trial to Reduce IDDM in the Genetically at Risk (TRIGR), a randomized controlled trial including genetically susceptible children, suggests that weaning to a highly hydrolyzed formula compared with a regular cow's milk formula was not associated with a decreased risk of developing autoimmunity (21). The intervention in the TRIGR study does not directly address the effect of breast-feeding or intake of other foods.

A hypothesis of a critical window effect for introduction of food antigens, most likely between 4 and 6 months of age, has been suggested (22). DAISY recently reported that both early and late first exposure to any solid food predicted development of type 1 diabetes (12). An increased risk of islet autoimmunity if cereals were introduced before 4 months and after 6 months of age, compared with those who were introduced to cereals from 4 to 6 months, has also been reported (23). We found no association between early or late introduction of any solid foods and development of islet autoimmunity or type 1 diabetes. Relatively high hazard ratios for type 1 diabetes were observed for early introduction of wheat and gluten, but these were not statistically significant and should be interpreted with caution. Few of the infants in our study were introduced to any solid foods before 4 months, in line with the national recommendations for infant feeding (24). Cultural differences in infant feeding practices could influence the ability to detect differences between the groups. Although directly comparing all aspects of infant diet among published studies is difficult (9,10,12), there was, for instance, a higher proportion of infants introduced to any solid foods before age 4 months in DAISY compared with our study.

A protective effect of breast-feeding while introducing solid foods has been suggested, and studies from DAISY have reported a protective effect on type 1 diabetes of breast-feeding while introducing wheat/barley (12) and a reduced risk of islet autoimmunity if cereal was introduced while breast-feeding was maintained (23). We found no association between breast-feeding and not breast-feeding at the time of introduction of solid foods and development of islet autoimmunity or type 1 diabetes. There might be a masking of a potential negative effect on type 1 diabetes or islet autoimmunity of early or late introduction of solid foods by the high rate of breast-feeding from birth through 12 months of age, and thus the low rate of children not being breast-fed at introduction of solid foods.

The main strengths of the study are the prospective design, with questionnaires completed close to the time of exposure and frequent assessment of islet autoantibodies. We have studied a high-risk group, and the results cannot necessarily be generalized, but the group amounts to a large share of those who develop type 1 diabetes in the population.

A limitation of the study is the limited number of children who developed type 1 diabetes. Although we have studied biologically plausible hypotheses, we cannot rule out the possibility that our statistically significant association was a chance finding. Adjusting for variables that previously have been thought to influence islet autoimmunity or type 1 diabetes did not affect our results. The study is observational, which means that we cannot exclude unmeasured confounding as an explanation for our findings. Although only a randomized trial design can eliminate confounding, a randomized controlled trial of breast-feeding duration is hard to imagine for ethical reasons. In the continued absence of randomized studies on this topic, our study adds to a small pool of prospective cohort studies that can form the basis for recommendations. In conclusion, breast-feeding for 12 months or longer predicted a lower risk of progression from islet autoimmunity to type 1 diabetes in genetically susceptible children.

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