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Effect of extensively hydrolyzed casein vs. conventional formula on the risk of asthma and allergies: The TRIGR randomized clinical trial

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Abstract

Background: The role of hydrolyzed infant formulas in the prevention of asthma and allergies remains inconsistent. We tested whether extensively hydrolyzed casein formula compared to conventional cow's milk–based formula prevented asthma, allergic rhinitis, or atopic eczema.

Methods: In the randomized double-blind Trial to Reduce IDDM in Genetically at Risk (TRIGR), comparing extensively hydrolyzed to standard cow's milk–based infant formula during the first 6-8 months of life, we assessed the effect of the intervention on the incidence of asthma, allergic rhinitis, and eczema when the children were 9- to 11-years old. The asthma, allergic rhinitis, and eczema occurrence was assessed using online standardized and validated ISAAC questionnaire. Of the 1106 children who participated in this Ancillary study, 560 had been randomized to the experimental (extensively hydrolyzed casein formula) and 546 to the control arm (cow's milk–based formula).

Results: The risk of persistent asthma, allergic rhinitis, or atopic eczema did not differ by treatment, the hazard ratios (95% CI) being 1.00 (0.66-1.52), 0.95 (0.66-1.38), and 0.89 (0.70-1.15), respectively, in the intention-to-treat analysis. Neither were there any differences in the per-protocol analysis.

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Conclusions: Extensively hydrolyzed casein formula did not protect from asthma, rhinitis, or eczema in this population carrying genetic risk for type 1 diabetes.

KEYWORDS
asthma, daycare, eczema, extensively hydrolyzed casein formula, infant feeding, rhinitis, weaning

1 | INTRODUCTION

Asthma and allergic diseases represent the most prevalent chronic disease group in children.[1] Environmental factors and diet have been implicated to play a role in the disease etiology.[2] The nutritional factors identified in prospective studies as possibly protecting from or causing asthma and allergic diseases include breastfeeding, age at introduction of new foods in infancy, prenatal or postnatal dietary exposure to n-3 long-chain fatty acids, dietary antioxidants, vitamin D, probiotics, and fish intake, and obesity.[2-5] Also, higher diversity of the infant diet may be associated with lower risk of atopic asthma and allergic diseases.[6-8] Early introduction of complex proteins in infancy has been suspected to increase the risk of asthma and allergies. Hydrolyzed infant formulas have been developed to postpone exposure to intact cow's milk proteins. Recent systematic reviews and meta-analyses, however, do not support that extensively or partially hydrolyzed infant formulas as compared to conventional cow's milk–based ones would prevent atopic disease.[9,10] Still, large randomized clinical trials on extensively hydrolyzed infant formulas are few in this field.

We aimed to study whether weaning to an extensively hydrolyzed casein formula, as compared to conventional cow's milk–based one, delays or prevents the development of persistent asthma, allergic rhinitis, and atopic eczema in the Trial to Reduce Insulin Dependent Diabetes in the Genetically at Risk (TRIGR), a study population with genetic susceptibility to type 1 diabetes, but not selected for asthma or allergy risk. TRIGR was planned to examine whether extensively hydrolyzed infant formula, as compared to conventional formula based on cow's milk, delays or prevents the development of beta-cell autoimmunity and/or type 1 diabetes in children at increased genetic risk of type 1 diabetes.[11] We also studied associations of infant feeding and some environmental factors with the risk of asthma, rhinitis, and eczema.

Key Message

We performed an Asthma, Atopic Eczema and Allergy Ancillary study in the randomized double-blind Trial to Reduce IDDM in Genetically at Risk (TRIGR). The trial compared extensively hydrolyzed to standard cow's milk–based infant formula feeding during the first 6-8 months of life. The asthma, allergic rhinitis, and eczema occurrence was assessed using validated ISAAC questionnaire. Extensively hydrolyzed casein formula did not protect from asthma or allergies in this population unselected for asthma and allergy risk but carrying genetic risk for type 1 diabetes.

2 | RESEARCH DESIGN AND METHODS

2.1 | Participants

TRIGR is a double-blind randomized trial which enrolled newborn infants who had a first-degree relative with type 1 diabetes and carried defined HLA risk genotypes in 2002-2007 from 15 countries[11] and followed them until the diagnosis of type 1 diabetes or until the youngest participant reached 10 years of age in 2017. Randomization of the infants took place before or immediately after birth. Altogether, 2159 newborn infants with an eligible HLA genotype (41.9% of the genotyped infants) were randomized to the TRIGR intervention study. The affected first-degree relative was the mother in 1055 infants (48.9%), the father in 723 (33.5%), and a sibling in 308 (14.3%), and 73 participants (3.4%) had multiple affected relatives. Written informed consent was obtained from the family before enrollment. The study was approved by the ethics committees of all participating centers.

This TRIGR Asthma, Eczema, and Allergy Ancillary study (Ancillary study) was performed between 2013 and 2016 when the children were 9 to 11 years old. Among Swedish and Canadian sites participating in TRIGR, eight sites did not participate in this Ancillary study, meaning that 133 children were not invited to participate. The 1106 children recruited to the Ancillary study represent 47% of the original cohort and 55% of those invited (n = 2026).

2.2 | Dietary intervention

Infants were randomly assigned weaning to either the intervention or control formula. The intervention formula was an extensively hydrolyzed casein formula (Nutramigen®), while the control formula composed of 80% intact cow's milk protein and 20% hydrolyzed milk protein (Enfamil®) (Mead Johnson Nutrition). Newborn infants requiring supplemental feeding before randomization received banked breastmilk or an extensively hydrolyzed casein formula. Breastfeeding was practiced at the discretion of the participating mothers, and maternal diets were unmodified. Breastfeeding was encouraged and exceeded national averages in both groups.[12] The dietary intervention period lasted until the infant reached the age

TABLE 1 Demographic and Clinical Characteristics and Dietary Exposure of the Trial Participants: the Whole Original TRIGR Cohort and the Asthma, Eczema, and Allergy Ancillary study Sub Cohort

	Whole TRIGR Cohort			Ancillary study Sub Cohort			Comparison of those in and not in Ancillary study Sub Cohort
Characteristic	Casein hydrolysate (n = 1081[a])	Control formula (n = 1078 [a])	*P*-value	Casein hydrolysate (n = 560[a])	Control formula (n = 546[a])	*P*-value	*P*-value
Region, No. (%)							
Australia	51 (4.7)	50 (4.6)	.998	19 (3.4)	21 (3.9)	.936	<.001
Canada	265 (24.5)	263 (24.4)		122 (21.8)	124 (22.7)		
Europe	566 (52.4)	569 (52.8)		350 (62.5)	338 (61.9)		
United States	199 (18.4)	196 (18.2)		69 (12.3)	63 (11.5)		
Female infants, No. (%)	505 (46.7)	516 (47.9)	.592	250 (44.6)	253 (46.3)	.572	.084
Older siblings, No. (%)	13 (1.2)	11 (1.0)	.686	10 (1.8)	6 (1.1)	.339	.128
Cesarean section, No. (%)	466 (43.1)	477 (44.3)	.593	241 (43.0)	230 (42.1)	.759	.295
Cow's milk allergy, No. (%)	61 (5.6)	63 (5.8)	.841	23 (4.1)	25 (4.6)	.700	.004
Breastfeeding duration, median (Q1-Q3), mo	7.8 (2.2-9.0)	7.1 (2.1-9.0)	.098	9.0 (3.4-9.0)	8.3 (3.2-9.0)	.394	<.001
No. of infants	1071	1066		558	545		
Exclusive breastfeeding duration, median (Q1-Q3), wk	0.29 (0.14-10.0)	0.29 (0.14-7.0)	.892	0.43 (0.14-13.0)	0.43 (0.14-13.0)	.914	<.001
No. of infants	1071	1065		558	545		
Age at introduction of study formula, mean (SD), mo	2.0 (2.3)	1.8 (2.2)	.050	2.1 (2.4)	2.0 (2.4)	.276	<.001
No. of infants	865	872		458	461		
Study formula duration, median (Q1-Q3), wk	9.0 (0.4-18)	10.0 (1.0-22)	.007	9.0 (1.0-16.0)	9.5 (2.3-21.0)	.068	.411
No. of infants	1071	1065		558	544		
Exposed to study formula, No. (%)	869 (81.3)	874 (82.1)	.611	461 (82.6)	461 (84.7)	.340	.016
No. of infants	1069	1064		558	544		
Duration of follow-up, mean (SD), y	10.9 (2.8)	11.0 (2.7)	.628	11.6 (1.7)	11.7 (1.7)	.205	<.001

[a]Sample sizes are reported when they differ from the overall sample sizes.

of 6 months, and if by that time the child had not received the study formula for at least 60 days, study formula feeding was continued until 60 days of study formula exposure was reached, but not beyond 8 months of age. Parents were asked not to feed the children any commercial or other baby foods containing bovine protein during the intervention period. Adherence to the protocol including use of study formulas and the frequency of use of allowed and non-recommended foods and breastfeeding was monitored by means of validated regular family nutrition interviews (at the age of 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 months)[13] and by the analysis of cow's milk antibodies in serum samples.

For the statistical analysis, the amount of extensively hydrolyzed formula and of all study formulas together (intervention and control one) were used as continuous variables.

2.3 | HLA genotyping

HLA genotyping for the selected DQB1 and DQA1 alleles was performed using sequence-specific oligonucleotide hybridization. The following genotypes were eligible: (1) HLA DQB1*02/DQB1*03:02 (high risk); (2) HLA DQB1*03:02/x (x not DQB1*02, DQB1*03:01 or DQB1*06:02 (moderate risk); (3) HLA DQA1*05-DQB1*02/y (y not DQA1*02:01-DQB1*02, DQB1*03:01, DQB1*06:02 or DQB1*06:03 (mild risk); and (4) HLADQA1*03-DQB1*02/y (y not DQA1*02:01-DQB1*02, DQB1*03:01, DQB1*06:02 or DQB1*06:03 (rare mild risk)).

2.4 | Asthma and allergic disease measurements

The incidence of persistent asthma, allergic rhinitis, and atopic eczema was assessed using the standardized and validated ISAAC core questionnaire presented online to the parents of the participating children[14] including additional questions related to the child's use of asthma medications, whether the child was ever diagnosed by a physician with certain diseases and food allergies, and other factors related to asthma and/or allergies. Persistent asthma was defined as doctor-diagnosed asthma plus either any wheezing symptom or use of asthma medication during the preceding 12 months. Age at onset of asthma was determined by the question: "at what age did the symptom of asthma start or at what age the child first wheezed?" Wheezing was defined as any of the following during the past 12 months: wheezy sound in respiration; wheezy sound during respiration in association with physical activity; difficulties in respiration in the morning on waking up; and wheezy respiration without having sniffles or respiratory infection. Allergic rhinitis was defined as doctor-diagnosed hay fever or allergic rhinoconjunctivitis during the preceding 12 months. Age at onset of allergic rhinitis was based on child's age at the onset of symptoms including sneezing, nasal congestion, or rhinitis other than with respiratory infections, accompanied by itching of the eye and tearing. Atopic eczema was defined as ever doctor-diagnosed atopic eczema. Age at onset of atopic eczema was based on the question. "At what age did the child first have atopic eczema?" In addition to persistent asthma, allergic rhinitis, and atopic eczema outcomes, we analyzed disease ever, doctor-diagnosed disease, and disease in the last 12 months outcomes for asthma, rhinitis, and eczema. All online questionnaires, including ISAAC, were available in local languages. Information on suspected cow's milk allergy came from study doctors and nurses and from interviews conducted during the intervention period.

2.5 | Statistical analyses

The cumulative incidence of onset of each end-point from birth was estimated using the Kaplan-Meier survival function. The difference between assigned treatment groups in the cumulative incidence functions was tested using the logrank test (Tables 1 and 2). The relative risk of disease onset between the treatment groups was estimated from the Cox proportional hazard model[15] and adjustments are presented in the footnotes of Table 3. The per-protocol analysis was defined to include those on the hydrolyzed formula arm who were not exposed to any non-allowed food containing cow's milk and had exposure to study formula for at least 60 days.

The adjustments used in Cox proportional hazard analysis on dietary and environmental risk determinants of asthma and allergies are presented in the footnotes of Tables S1 and S2.

Data were analyzed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, NC). Two-tailed *P*-values <.05 were considered to be statistically significant. No adjustment in type 1 error was made for multiple comparisons except in the context of the multiple Cox regression model.

3 | RESULTS

Of the 1106 children who participated in the Ancillary study, 560 had been randomized to the experimental (extensively hydrolyzed casein formula) and 546 to the control (cow's milk–based formula) arm. Compared to those TRIGR subjects who did not participate in the Ancillary study, a larger proportion of the Ancillary study participants were European, had suspected cow's milk allergy, and had received study formula. Duration of any and exclusive breastfeeding and duration of follow-up were longer and age at introduction of study formula feeding later in the Ancillary study (Table 1). The demographic, clinical, feeding, and allergic background characteristics did not differ between the hydrolysate and control formula arms in the Ancillary study (Tables 1 and 2).

The risk of persistent asthma, allergic rhinitis, or atopic eczema did not differ by treatment (intention-to-treat analysis): HR (95% CI) 1.00 (0.66-1.52), 1.05 (0.64-1.73), and 0.79 (0.56-1.13), respectively (Table 3). During follow-up, persistent asthma developed in 46 children in the casein hydrolysate group (8.2%) and in 43 children in

TABLE 2 Characteristics[a] of the participants of the TRIGR Asthma, Eczema, and Allergy Ancillary study by treatment group: extensively hydrolyzed casein and conventional cow's milk–based control formula

Characteristic	Casein hydrolysate (n = 560[b])	Control formula (n = 546 [b])	*P*-value
Parental asthma, No. (%)	126 (23.6)	127 (24.8)	.660
No. of infants	533	512	
Parental rhinitis, No. (%)	242 (46.9)	216 (42.5)	.159
No. of infants	516	508	
Parental eczema, No. (%)	162 (32.0)	154 (31.4)	.825
No. of infants	506	491	
Maternal smoking in pregnancy, No. (%)	40 (7.3)	29 (5.4)	.211
No. of infants	549	534	
Smoking exposure during 1. y, No. (%)	125 (22.8)	114 (21.5)	.607
No. of infants	548	530	
Eczema during first 6 mo, No. (%)	48 (8.6)	55 (10.1)	.390
No. of infants	560	546	

[a]Characteristics collected in the TRIGR Asthma, Eczema, and Allergy Ancillary study presented in this table.

[b]Sample sizes are reported when they differ from the overall sample sizes.

the control group (7.9%) (difference, 0.3% [95% CI, −2.9% to 3.5%], *P* = .999; Figure 1A); allergic rhinitis developed in 85 children in the casein hydrolysate group (15.2%) and in 82 children in the control group (15.0%) (difference, 0.2% [95% CI, −4.1% to 4.4%], *P* = .801; Figure 1B); and atopic eczema developed in 121 children in the casein hydrolysate group (21.6%) and in 130 children in the control group (23.8%) (difference, −2.2% [95% CI, −7.1% to 2.7%], *P* = .364; Figure 1C). Neither were there any differences by treatment according to the per-protocol analysis (Table 3). Neither were there any differences by treatment when using less strict outcome definitions: disease ever, doctor-diagnosed disease, disease in the last 12 months (Table 3).

Feeding during the first 3 days of life was associated with asthma risk (unadjusted *P* = .019 and adjusted *P* = .012): extensively hydrolyzed formula (including the intervention study formula) and the use of more than one type of milk (cow's milk formula, hydrolyzed formula, breastmilk, or other formula) were associated with higher risk of asthma as compared to those exclusively breastfed (Table S1). Duration of any or exclusive breastfeeding was not associated with the disease end-points (Table S1). Neither was the amount of extensively hydrolyzed formula or the amount of both study formulas together associated with the outcomes (data not shown). Introducing vegetables and potatoes; fruits and fruit juices; oat, wheat, rye, and barley cereals; or cow's milk by the age of 6 months was not associated with the risk of asthma, rhinitis, or eczema (Table S1). Egg exposure by 6 months of age was associated (*P* = .035) with increased risk of eczema (Table S1). Using variables with three categories for vegetables and potatoes (< 4 mo, 4-5.9 mo, ≥ 6 mo), fruits and fruit juices (< 4 mo, 4-5.9 mo, ≥ 6 mo), and cereals (oats, wheat, barley, and rye) (< 5 mo, 5-5.9 mo, ≥ 6 mo) did not change the results (data not shown). Neither was the type of milk feeding at 3 months of age or the number of foods introduced by 6 months of age associated with the risk of the atopic diseases. The pet or farm animal exposure during the first year of life was not associated with the risk of asthma, rhinitis, or eczema (Table S2). Daycare exposure during the first year of life was inversely associated with the risk of eczema (HR 0.57 [95% CI 0.35-0.91], *P* = .019) (Table S2).

4 | DISCUSSION

In this international randomized double-blind trial in children with increased genetic risk for type 1 diabetes, weaning to extensively hydrolyzed casein formula compared to conventional cow's milk–based control formula did not affect the incidence of asthma, allergic rhinitis, or atopic eczema whether analyzed according to intension to treat or per protocol.

We observed few associations between infant feeding during the first 6 months of life and subsequent development of persistent asthma, allergic rhinitis, or atopic eczema among children participating in a randomized infant feeding trial. Due to several comparisons carried out, the weak associations found of hydrolyzed formulas or several types of milks in first days with asthma, and of egg in the first 6 months with eczema, may be chance findings. Of environmental exposures, only daycare attendance during the first year of life was associated with a marginally decreased risk of eczema.

The trial was conducted under a carefully constructed protocol that resulted in a double-blinded intervention of dietary intake.[16] Also, the compliance with the intervention [11] as well as the participation in this Ancillary study was good. There are few other studies with such a long follow-up.[17] The current study is one of the largest trials in terms of number of participants and number of outcomes in the casein hydrolysate arm. The strengths of the study include also

TABLE 3 Hazard ratios of extensively hydrolyzed casein formula as compared with conventional cow's milk–based control formula, for development of Persistent Asthma, Allergic Rhinitis, and Atopic Eczema in the TRIGR Asthma, Eczema, and Allergy Ancillary study according to intention-to-treat (n = 1106) and per-protocol (n = 639) analysis

Disease	No. with the disease	HR (95% CI)	*P*-Value	Adjusted[a] HR (95% CI)	*P*-Value
Intention to treat					
Persistent asthma	89	1.00 (0.66-1.52)	1	0.99 (0.64-1.52)	.95
Ever	133	0.93 (0.65-1.33)	.69	0.90 (0.63-1.30)	.58
Doctor diag	122	0.92 (0.65-1.32)	.66	0.90 (0.62-1.29)	.56
Within Last 12 M	237	1.04 (0.68-1.58)	.87	1.05 (0.68-1.62)	.81
Allergic rhinitis	167	0.95 (0.66-1.38)	.8	0.87 (0.60-1.27)	.47
Ever	390	1.01 (0.77-1.32)	.94	0.95 (0.72-1.25)	.72
Doctor diag	130	0.94 (0.67-1.33)	.73	0.89 (0.63-1.26)	.51
Within Last 12 M	362	1.02 (0.78-1.33)	.88	0.96 (0.73-1.26)	.76
Atopic eczema	251	0.89 (0.70-1.15)	.38	0.92 (0.71-1.18)	.49
Ever	390	0.99 (0.80-1.23)	.94	1.04 (0.83-1.29)	.76
Doctor diag	251	0.89 (0.70-1.15)	.38	0.92 (0.71-1.18)	.49
Within Last 12 M	182	1.07 (0.78-1.47)	.69	1.16 (0.84-1.62)	.37
Per protocol					
Persistent asthma	51	1.17 (0.68-2.03)	.58	1.30 (0.74-2.28)	.36
Ever	83	1.01 (0.64-1.58)	.98	1.03 (0.65-1.65)	.89
Doctor diag	77	1.01 (0.64-1.58)	.98	1.03 (0.65-1.64)	.91
Within Last 12 M	146	1.21 (0.70-2.10)	.49	1.37 (0.78-2.41)	.27
Allergic rhinitis	92	1.29 (0.78-2.12)	.32	1.18 (0.71-1.96)	.53
Ever	224	1.16 (0.81-1.66)	.41	1.12 (0.77-1.63)	.54
Doctor diag	72	1.14 (0.72-1.80)	.59	0.95 (0.59-1.52)	.82
Within Last 12 M	202	1.19 (0.84-1.71)	.33	1.15 (0.79-1.66)	.47
Atopic eczema	142	1.21 (0.87-1.68)	.25	1.18 (0.84-1.65)	.35
Ever	228	1.20 (0.91-1.59)	.2	1.16 (0.87-1.54)	.32
Doctor diag	142	1.21 (0.87-1.68)	.25	1.18 (0.84-1.65)	.35
Within Last 12 Ms	100	1.22 (0.79-1.88)	.38	1.20 (0.76-1.88)	.43

Note: Also, the outcomes ever, doctor-diagnosed, and having disease within last 12 mo are shown for asthma, rhinitis, and eczema.

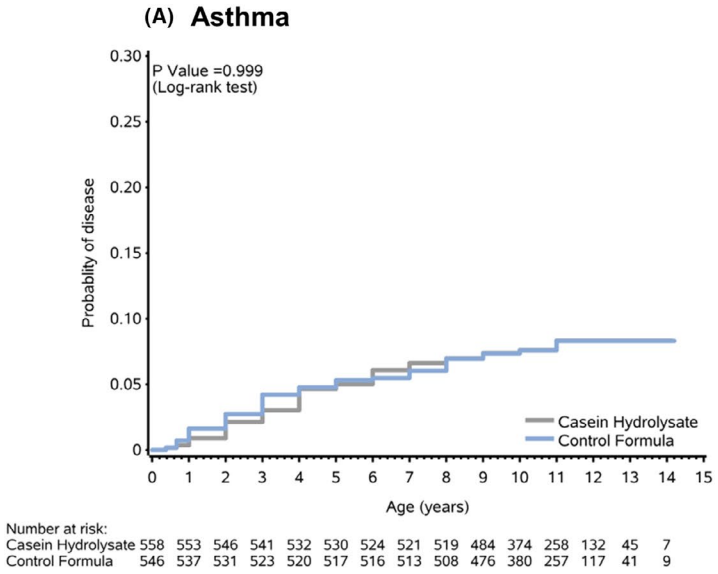
[a]Adjusted for breastfeeding duration, duration of study formula consumption, sex, mode of delivery (cesarean section vs other), maternal smoking during pregnancy and smoking exposure during the first year, older siblings (yes vs no), suspected cow's milk allergy, and region, while treating study center as a random effect. In addition asthma adjusted for parental asthma, rhinitis for parental rhinitis, and eczema for parental asthma, rhinitis, and eczema.

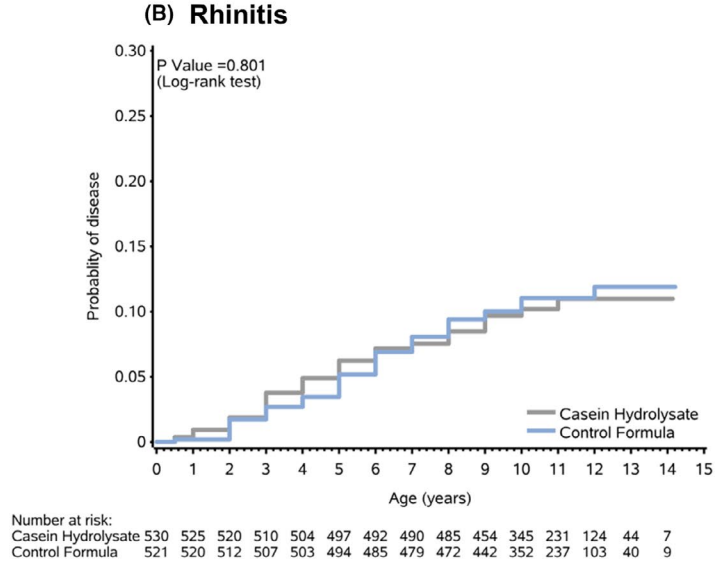
the use of strictly standardized and validated dietary data collection methods, and frequent prospective collection of dietary data.[13]

In this study, the incidence of asthma and allergic diseases was self-reported using the modified ISAAC instrument. No medical record confirmation was available. While this is a population selected for HLA genotypes conferring increased risk for type 1 diabetes, there is no evidence that HLA contributes to increased risk for these diseases. In the current study population, the risk of asthma, allergic rhinitis, and atopic eczema did not differ by HLA genotypes.[18] The limitation of the current study is that information on infant feeding was available only for the first 6 months of life. As the duration of breastfeeding was longer and age at introduction of complementary feeding later in the current subject series compared to other studies carried out in these populations, relatively few of the infants were exposed to complementary feeding by the age of 6 months.[12,19]

One of the largest randomized, double-blind trials in this field with strictly defined end-points,[20] the German Infant Nutritional Intervention Study (GINI), reports variable beneficial effects of extensively hydrolyzed casein and whey formulas on asthma, allergic rhinitis, and atopic eczema up to adolescence.[21] Several expert bodies, however, have concluded that there is lack of evidence that extensively or partially hydrolyzed infant formulas prevent atopic disease [5,10,22] and showed that there is evidence of publication bias, methodological biases, and/or conflict of interest in many studies reporting allergic outcomes including GINI.[10]

Exclusive breastfeeding during the first 3 to 4 months of life protects from atopic eczema during the first 2 years of life.[5] Increasing evidence is accumulating on the preventive effect of longer breastfeeding on asthma.[5] We did not observe any association between exclusive or any breastfeeding and development of asthma and





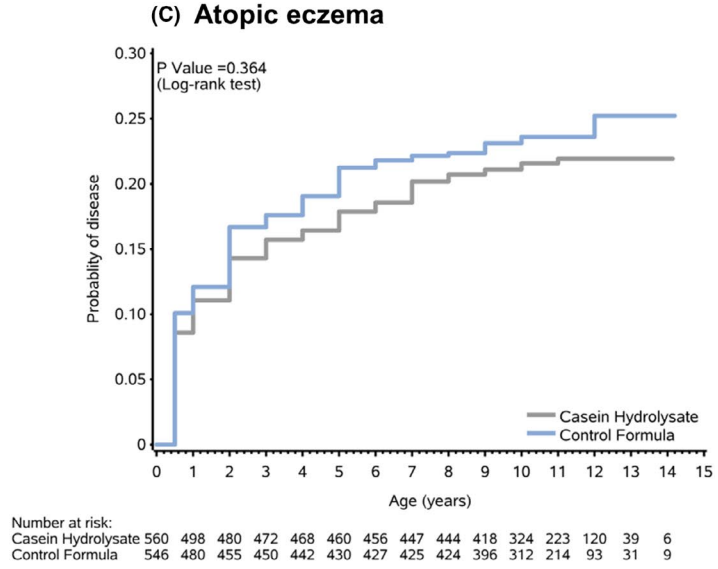


FIGURE 1 Cumulative survival (A) without persistent asthma; (B) without allergic rhinitis; and (C) without atopic eczema in the TRIGR Asthma, Eczema, and Allergy Ancillary study by Treatment: extensively hydrolyzed casein formula compared to control formula [Colour figure can be viewed at wileyonlinelibrary.com]

allergies. In our study, half of the mothers had type 1 diabetes and most of them had cesarean delivery, which may explain partly the low frequency of exclusive breastfeeding [12] and discrepancy of our findings with other studies.

Prospective cohort studies are inconsistent whether age at introduction of complementary foods affects the risk of allergic diseases and asthma in childhood [eg.23-29] Clinical randomized trials have shown that peanut and egg allergies can be prevented by oral tolerance induction.[3,4] These effects may be allergen-specific.[30] Also, higher number of foods introduced during infancy, that is, higher diversity of the diet, may be associated with lower risk of atopic asthma and allergic diseases in pre-school children.[6-8] In accordance with another study with long-term follow-up to 10 years of age,[17] we did find very few relationships between age at introduction of new foods or dietary diversity during the first 6 months of life and development of asthma or allergies.

Evidence whether early feeding in the maternity hospital could influence the development of asthma and allergies is controversial and few. Findings from a randomized trial suggest that cow's milk–based formula could increase the risk of cow's milk allergy compared to other feeding.[31] On the other hand, in another maternity ward study, cow's milk–based formula was not associated with later atopic disease risk.[32] In the current study, early introduction of extensively hydrolyzed formula showed a marginal association with increased risk of asthma.

4.1 | Conclusions

These findings add to the growing literature that weaning to an extensively hydrolyzed formula does not protect from asthma, rhinitis, or eczema.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Suvi Virtanen: Conceptualization (lead); Data curation (supporting); Investigation (equal); Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal). **David Cuthbertson:** Data curation (equal); Formal analysis (lead); Methodology (equal); Writing-review & editing (equal). **Marisa Couluris:** Conceptualization (supporting); Writing-review & editing (supporting). **Erkki Savilahti:** Writing-review & editing (supporting). **Mikael Knip:** Conceptualization (equal); Funding acquisition (equal); Writing-review & editing (equal). **Jeffrey P. Krischer:** Conceptualization (lead); Data curation (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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