

Age at Gluten Introduction and Risk of Celiac Disease

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OBJECTIVES: The goal of this study was to determine whether age at introduction to gluten was associated with risk for celiac disease (CD) in genetically predisposed children.

abstract

METHODS: TEDDY (The Environmental Determinants of Diabetes in the Young) is a prospective birth cohort study. Newborn infants ($N = 6436$) screened for high-risk HLA-genotypes for CD were followed up in Finland, Germany, Sweden, and the United States. Information about infant feeding was collected at clinical visits every third month. The first outcome was persistent positive for tissue transglutaminase autoantibodies (tTGA), the marker for CD. The second outcome was CD, defined as either a diagnosis based on intestinal biopsy results or on persistently high levels of tTGA.

RESULTS: Swedish children were introduced to gluten earlier (median: 21.7 weeks) compared with children from Finland (median: 26.1 weeks), Germany, and the United States (both median: 30.4 weeks) ($P < .0001$). During a median follow-up of 5.0 years (range: 1.7–8.8 years), 773 (12%) children developed tTGA and 307 (5%) developed CD. Swedish children were at increased risk for tTGA (hazard ratio: 1.74 [95% CI: 1.47–2.06]) and CD (hazard ratio: 1.76 [95% CI: 1.34–2.24]) compared with US children, respectively ($P < .0001$). Gluten introduction before 17 weeks or later than 26 weeks was not associated with increased risk for tTGA or CD, adjusted for country, HLA, gender, and family history of CD, neither in the overall analysis nor on a country-level comparison.

CONCLUSIONS: In TEDDY, the time to first introduction to gluten introduction was not an independent risk factor for developing CD.



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WHAT'S KNOWN ON THIS SUBJECT: Both early and late introduction to gluten has been associated with increased risk for celiac disease (CD) and being breastfed at time of gluten introduction has been associated with a lower risk for CD.

WHAT THIS STUDY ADDS: In this prospective multinational study, time to first introduction to gluten-containing cereals is not an independent risk factor for developing CD, by a 5-year follow-up, neither on an overall level nor on country-level comparison.

Gluten is a food component found in cereals such as wheat, rye, or barley that are commonly used in the human diet worldwide. Gluten proteins (prolamines) are also the triggering antigen that is necessary for celiac disease (CD) to develop.¹ The incidence of CD is increasing in the Western world.^{2–5} The optimal age at first introduction to gluten to avoid development of CD has been rigorously debated. Several studies hypothesized that the age at first introduction to gluten could influence the onset of the disease.^{6–11} Others claim that breastfeeding and its interaction with gluten during weaning could reduce the risk for CD.^{12,13} Today, the general recommendation is to introduce small amounts of gluten while the infant is still breastfed, preferably between 4 and 6 months of age.¹⁴ However, the trials on which the recommendations are based are few and have not yet been evaluated in longitudinal studies to confirm whether these infant feeding recommendations are valid in different populations.

In TEDDY (The Environmental Determinants of Diabetes in the Young),¹⁵ an ongoing multinational

cohort study, children from Sweden had a twofold increased risk for CD compared with children in the United States despite adjusting for HLA genotypes, suggesting that environmental factors may be influencing the development of CD during early childhood.¹⁶

The goal of the present study was to confirm whether timing of gluten introduction was an independent risk factor for CD in children followed up prospectively in a multinational birth cohort study.

METHODS

Study Population

The TEDDY study is a prospective cohort study with the primary goal of identifying environmental determinants of type 1 diabetes mellitus (T1DM). The study comprised 6 clinical research centers located in Finland, Germany, Sweden, and the states of Colorado, Georgia/Florida, and Washington in the United States.^{15,17} Infants are followed up from birth to 15 years of age or until the diagnosis of T1DM is established. Between September 2004 and February 2010, a total of 424 788

newborns were screened for T1DM-associated HLA genotypes.¹⁸ Infants were eligible for initial study contact if they had 1 of the following HLA genotypes: DR3-DQ2/DR4-DQ8, DR4-DQ8/DR4-DQ8, DR4-DQ8/DR8-DQ8, DR3-DQ2/DR3-DQ2, DR4/DR4b, DR4/DR1, DR4/DR13, DR4/DR9, and DR3/DR9. The last 4 genotypes were only applicable for infants with a first-degree relative (ie, mother, father, sibling) with T1DM.¹⁷

The initial screening identified 21 589 eligible infants; 8677 were enrolled in the follow-up study before the age of 4 months, after informed consent from parents or the primary caregiver was obtained.¹⁸ Characteristics of the TEDDY cohort have been described previously.¹⁹ Children were screened annually from the age of 24 months for celiac disease autoimmunity (CDA) with tissue transglutaminase autoantibodies (tTGA) by using radiobinding assays as described elsewhere.²⁰ Children testing positive for tTGA before 36 months were retested after 3 months and children testing positive for tTGA at ≥ 48 months were retested after 6 months. In children positive for tTGA at 24 months, previous blood samples

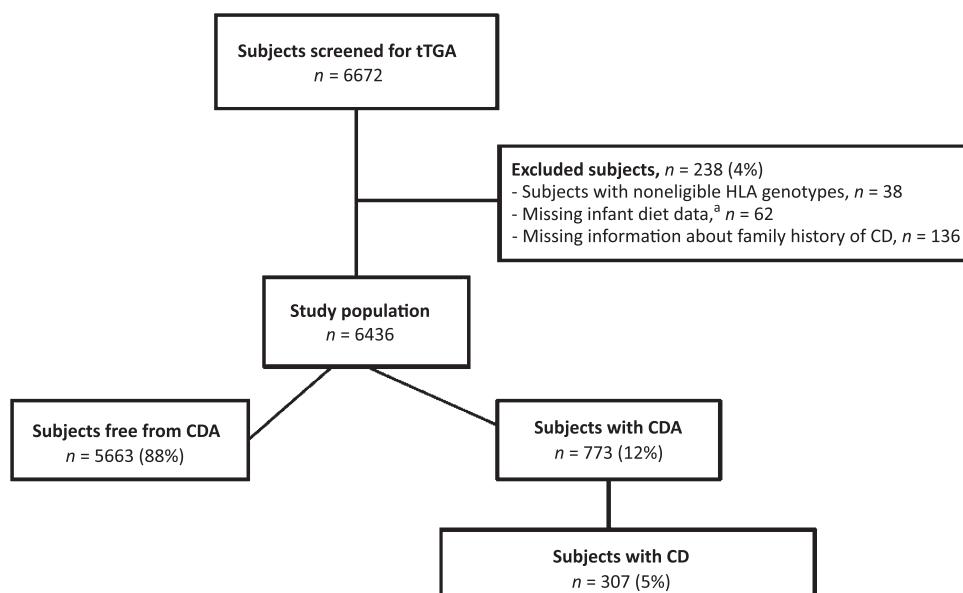


FIGURE 1
Flowchart describing the TEDDY study population

collected every 3 months from birth were analyzed to determine the time of seroconversion to tTGA positivity. Children testing positive for tTGA in 2 consecutive samples were defined as having CDA and were referred to a pediatric gastroenterologist to confirm diagnosis. The decision to perform an intestinal biopsy was outside the TEDDY protocol and was decided by a pediatric gastroenterologist at the local hospital.

Biopsy-proven CD was defined as having a Marsh score ≥ 2 .²¹ If a confirmatory intestinal biopsy had not been performed, children with a mean tTGA level of 2 consecutive samples > 100 U (cutoff for a positive test is 1.3) were also included as having CD in our analysis.

As of July 31, 2013, a total of 6672 children had been tested at least once for tTGA; the median age at follow-up

was 5.0 years (range: 1.7–8.8 years). After excluding children with missing questionnaire data (238 of 6672), the study population comprised 6436 children. A total of 773 (12%) of 6436 children developed CDA; 307 of these (5%) were diagnosed with CD, of whom 20 children were considered to have CD based on high tTGA levels (Fig 1). Of the 773 children who tested positive for tTGA, 283 (37%) were positive at 24 months, 536 (68%) at 36 months, 658 (85%) at 48 months, and 185 (24%) children were tested positive in samples collected before the age of 24 months.

Written informed consent was obtained for all study children from a parent or primary caretaker for the genetic screening and participation in a prospective follow-up. The study was approved by local institutional review boards and is

monitored by an external advisory board formed by the National Institutes of Health.

Questionnaires

Information about early infant feeding practices were collected every third month by using a booklet that was given to the parents or primary caregiver at study entry. Parents were instructed to record in the booklet when a new food was introduced, with the goal of ensuring accurate recall between visits. The booklet was reviewed at each visit (at 6, 9, 12, 15, 18, 21, and 24 months of age) by the clinical staff. Introduction to gluten-containing foods was defined as the infant's age when first introduced to foods containing gluten (follow-up formulas, cereals, porridges, bread, biscuits, or pasta containing wheat, rye, or barley), regardless of amount.

TABLE 1 Nondietary Factors and Risk of CDA (Primary End Point) and CD (Secondary End Point)

	Median (range) age at end point, y	CDA (n = 773)			CD (n = 307)		
		3.0 (0.9–7.5)		P	3.8 (1.2–8.8)		P
		n (%) ^a	HR (95% CI) ^b		n (%) ^a	HR (95% CI) ^b	
Country							
United States	228 (9)	1	—	93 (4)	1	—	
Sweden	353 (16)	1.74 (1.47–2.06)	<.0001	151 (7)	1.73 (1.34–2.24)	<.0001	
Finland	171 (12)	1.22 (1.00–1.49)	.05	52 (4)	0.84 (0.60–1.18)	.31	
Germany	41 (11)	1.21 (0.87–1.69)	.26	11 (3)	0.75 (0.40–1.40)	.37	
Gender							
Boys	317 (10)	1	—	107 (3)	1	—	
Girls	456 (14)	1.55 (1.34–1.79)	<.0001	200 (6)	2.02 (1.59–2.55)	<.0001	
HLA genotype							
TEDDY other ^c	430 (8)	1	—	146 (3)	1	—	
DR3-DQ2/DR3-DQ2	343 (26)	3.56 (3.09–4.11)	<.0001	161 (12)	4.58 (3.66–5.74)	<.0001	
First degree relative with celiac disease							
No	732 (12)	1	—	282 (4)	1	—	
Yes	41 (28)	2.60 (1.90–3.57)	<.0001	25 (17)	3.83 (2.55–5.77)	<.0001	
Season of birth							
Winter (December – February)	185 (11)	1	—	63 (4)	1	—	
Spring (March – May)	212 (14)	1.18 (0.97–1.44)	.10	95 (6)	1.55 (1.13–2.13)	.007	
Summer (June – August)	194 (12)	1.06 (0.87–1.30)	.55	75 (5)	1.19 (0.85–1.68)	.30	
Fall (September – November)	182 (11)	1.03 (0.84–1.26)	.77	74 (5)	1.16 (0.83–1.63)	.38	
Maternal smoking during pregnancy							
No	710 (12)	1	—	275 (5)	1	—	
Yes	63 (10)	0.85 (0.65–1.09)	.20	28 (5)	0.98 (0.67–1.45)	.92	
Maternal education							
Basic primary	129 (11)	0.89 (0.74–1.08)	.25	54 (5)	0.94 (0.70–1.27)	.70	
Higher education	640 (12)	1	—	253 (5)	1	—	
Maternal age at delivery, y							
Mean \pm SD	30.9 \pm 4.7	1.0 (0.98–1.01)	.85	30.8 \pm 4.5	1.0 (0.97–1.02)	.75	

^a Proportion of exposed children with CDA or CD in each category.

^b Unadjusted hazard ratio (HR) with 95% confidence interval (CI).

^c DR3-DQ2/DR4-DQ8 (39%), DR4-DQ8/DR4-DQ8 (20%), DR4-DQ8/DR8-DQ8 (17%), types only applicable on subjects with family history of T1DM (3%).

TABLE 2 Background Characteristics of Age at Introduction to Gluten and Breastfeeding Duration, by Country

Variable	United States (<i>n</i> = 2542)			Finland (<i>n</i> = 1472)			Germany (<i>n</i> = 380)			Sweden (<i>n</i> = 2042)		
	<i>n</i> (%)	Mean ± SD	Median (Q1, Q3)	<i>n</i> (%)	Mean ± SD	Median (Q1, Q3)	<i>n</i> (%)	Mean ± SD	Median (Q1, Q3)	<i>n</i> (%)	Mean ± SD	Median (Q1, Q3)
Time to gluten introduction, wk	2542	30.1 ± 8.4	30.4 (26.1, 34.9)	1472	27.8 ± 8.1	26.1 (23.9, 30.4)	380	32.8 ± 10.4	30.4 (26.1, 37.0)	2042	21.6 ± 4.5	21.7 (17.4, 23.9)
Category of age at gluten introduction												
Early (<17 wk) ^a	98 (4)	11.6 ± 3.9	13.0 (11.0, 14.0)	47 (3)	7.8 ± 4.1	7.0 (4.3, 10.0)	18 (5)	14.5 ± 1.9	14.0 (14.0, 16.0)	233 (11)	15.0 ± 1.6	15.3 (14.0, 16.0)
Before (17–26 wk) ^a	447 (18)	21.0 ± 2.2	21.7 (19.6, 21.7)	463 (32)	22.1 ± 1.8	21.7 (21.7, 23.9)	53 (14)	22.0 ± 1.9	21.7 (19.6, 23.9)	1330 (65)	20.6 ± 2.3	21.7 (18.0, 21.7)
Late (>26 wk) ^a	1997 (78)	33.0 ± 6.6	30.4 (26.1, 34.9)	962 (65)	31.5 ± 6.7	30.4 (26.1, 34.9)	309 (81)	35.7 ± 9.2	32.6 (29.3, 39.1)	479 (24)	27.7 ± 2.9	26.1 (26.1, 28.3)
Duration of exclusive breastfeeding, wk ^b	2542	5.4 ± 8.3	1.0 (0.07, 8.0)	1472	7.2 ± 8.6	3.0 (0.07, 13.0)	380	10.1 ± 11.1	4.0 (0.07, 21.7)	2042	7.5 ± 7.8	4.0 (0.07, 16.0)
Duration of any breastfeeding, wk ^b	2542	38.4 ± 34.0	34.6 (10.0, 56.6)	1472	39.4 ± 24.7	39.1 (21.7, 54.6)	380	36.5 ± 27.2	34.7 (14.1, 49.3)	2042	32.7 ± 22.7	31.9 (17.4, 43.4)

^a Mean ± SD and median (Q1, Q3) are presented for each category of age at gluten introduction.

^b Children who were not breastfed were assigned a duration of 0. A total of 124 children in the United States, 0 children in Finland, 7 children in Germany, and 9 children in Sweden were not breastfed.

Categorical variables were created to identify children introduced early versus late to gluten-containing foods. Cut-points for early and late introduction of gluten were defined as before 17 weeks of age (<4 months) and after 26 weeks (>6 months) respectively, according to the recommendations by the World Health Organization²² and by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition's Committee on Nutrition.¹⁴ Introduction to gluten in the 4- to 6-month window was considered as the referent group. Breastfeeding duration was defined as the period of time (in weeks) when infants were exclusively or partially breastfed. Breastfeeding at time of gluten introduction has been associated with a lower risk of CD.¹³ Therefore, we created a variable examining whether the child was breastfed at time of introduction to gluten with continued breastfeeding for >1 month (long-term), the child was breastfed at time of gluten introduction with continued breastfeeding for ≤1 month (short-term), or breastfeeding had been discontinued before the time of gluten introduction (discontinued [referent group]).

Statistical Analyses

Time to developing CDA was defined as age when the first tTGA-positive blood sample was drawn, and the right-censored time was the age when the last blood sample was collected for testing of tTGA. Time to diagnosis of CD was the age of intestinal biopsy, and the right-censored time was age of the last TEDDY clinic visit that was confirmed to be CD-free. In children considered to have CD based on their high tTGA level, the time of diagnosis was defined as age when the first tTGA positive blood sample was drawn. A Cox proportional hazards model was used for the analysis after adjusting for confounders (HLA, country of residence, gender and family history of CD, and age at gluten introduction where appropriate). The selection

of confounding variables was based on the criteria of having a *P* value <.05 in the unadjusted analysis. In a Cox proportional hazards model, analyses between exposure and outcome are conducted in "risk sets," which include all subjects in follow-up at each age an outcome (CDA and CD) occurs. In our analyses, if a subject in the risk set had not yet been introduced to gluten by that age, he or she was assigned to the reference group for the categorized age at introduction variable (reference = introduced at 17.0–26.0 weeks). Likewise, these subjects were assigned to the reference group for the breastfed at time of introduction to gluten variable (reference = breastfeeding discontinued before the time of gluten introduction).

P values <.05 were considered to be statistically significant. All analyses were performed by using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Risk factors associated with development of CDA and CD were HLA-DR3-DQ2, Sweden as country of residence, female gender, and having a family history of CD. No significant associations were found with maternal education level, maternal age at delivery, season of birth, or smoking during pregnancy (Table 1).

Timing of Gluten Introduction and Risk for CDA and CD

Median age at introduction to gluten-containing cereals was 26.1 weeks (6 months). Age at gluten introduction differed between countries. Children in Sweden were introduced earliest, at a median age of 21.7 weeks (interquartile range [IQR]: 17.4–23.9) compared with children from Finland (26.1 weeks [IQR: 23.9–30.4]), Germany (30.4 weeks [IQR: 26.1–37.0]), and the United States (30.4 weeks [IQR: 26.1–34.9]) (*P* < .0001) (Table 2). Overall, 396 (6%) of the children were introduced to gluten-containing cereals before the

TABLE 3 Time to First Introduction to Gluten-Containing Cereals and Risk for CDA and CD

Gluten Introduction	CDA			CD		
	n (%) ^a	HR (95% CI) ^b	P	n (%) ^a	HR (95% CI) ^b	P
<17 wk	52 (13)	1.06 (0.79–1.42)	.71	13 (3)	0.59 (0.33–1.04)	.07
17–26 wk	315 (14)	1	—	141 (6)	1	—
>26 wk	406 (11)	0.97 (0.82–1.15)	.76	153 (4)	0.90 (0.69–1.18)	.45

^a Proportion of exposed children with CDA and CD in each time period.^b After adjusting for country, HLA, gender, and family history of CD.

age of 17 weeks (4 months), and 3747 (58%) were introduced to gluten-containing cereals after 26 weeks of age (>6 months).

Introduction to gluten before 17 weeks or after 26 weeks was not associated with increased risk for CDA or CD, compared with introduction between 17 and 26 weeks (4–6 months of age), adjusting for country, HLA, gender, and family history of CD (Table 3). Stratifying for country and gluten introduction before 17 weeks or after 26 weeks were not associated with increased risk for CDA or CD, adjusted for HLA, gender, and family history of CD (Supplemental Table 5).

Breastfeeding and Its Protective Association on CDA and CD

Duration of breastfeeding (exclusive and any) by each participating country is given in Table 2. The median duration of any breastfeeding in this population was 34.7 weeks (8 months). To further investigate the duration of breastfeeding and its association with CD, infants who continued breastfeeding for >1 month after first introduction of gluten were studied (Table 4). In total, 3553 (55%) of 6436 infants were breastfed for >1 month after gluten introduction, whereas 2384

(37%) of 6436 stopped breastfeeding before the first introduction of gluten. In the overall analysis, the risk for developing tTG antibodies was increased if the child was breastfed for >1 month after gluten introduction (hazard ratio: 1.23 [95% confidence interval: 1.05–1.44]) but not for CD (hazard ratio: 1.13 [95% confidence interval: 0.88–1.46]), adjusting for country, HLA, gender, family history of CD, and age of gluten introduction. On a country level, Sweden and Finland had the largest proportion of children who were breastfed >1 month after gluten introduction (63% and 60%, respectively) compared with 48% in the United States and 43% in Germany. Analysis stratified according to country showed that the association was not due to a specific country (Supplemental Table 6).

DISCUSSION

In TEDDY, we had previously confirmed that Swedish children are at a twofold increased risk for CD compared with US children.¹⁶ Sweden is by tradition a country where infants are served gluten-containing cereal-based foods such as porridge, follow-up formulas, and bread. Therefore, it is tempting to speculate that the factors

related to gluten introduction (eg, amount, source of gluten, type of food) may affect the risk for developing CD during early childhood. Despite differences in timing of gluten introduction between participating countries,²³ the time to first introduction to gluten-containing cereals was not found to be a risk factor for CDA or CD in the present study. Instead, we found a significantly increased risk for CDA, but not for CD, among children being breastfed for >1 month after gluten introduction, in the overall analysis. In a previous meta-analysis,¹³ breastfeeding duration has been associated with a lower risk for CD, although not confirmed in newer studies.²⁴ A recent study from Norway using biopsy-proven CD as an outcome reported a nonsignificant increased risk for CD among children who were breastfed for >1 month after gluten introduction with a similar categorization.¹⁰ These findings are in line with our results.

In our study, timing of gluten introduction was not associated with risk for CDA and CD. Our results do not support previous findings which suggest that avoiding either early (ie, before 4 months) or late (ie, after 6 months) gluten introduction reduces the risk for disease development.^{12,16,25} The Norwegian study presented a modest increased risk for CD when gluten was introduced at the age of ≥6 months.¹⁰ However, 2 other studies from Sweden and Germany found no association between timing and risk for CD, suggesting that there might be differences in the risk factors by country of residence.^{7,24} Because our study cohort comprised children from

TABLE 4 Gluten Introduction Under Conditions of Long-Term Continued Breastfeeding (>1 Mo), Short-Term Continued Breastfeeding (Continued ≤1 Mo After Gluten Introduction), and Discontinued Breastfeeding Before Gluten Introduction and the Risk for CDA and CD

Continued Breastfeeding at Time of Gluten Introduction	CDA (n = 773)			CD (n = 307)		
	n (%) ^a	HR (95% CI) ^b	P	n (%) ^a	HR (95% CI) ^b	P
Long-term (continued >1 mo)	474 (13)	1.23 (1.05–1.44)	.0107	186 (5)	1.13 (0.88–1.46)	.3249
Short-term (continued ≤1 mo)	62 (12)	1.08 (0.82–1.44)	.5729	25 (5)	1.07 (0.69–1.67)	.7571
Discontinued previous gluten introduction	231 (10)	1	—	93 (4)	1	—

CI, confidence interval; HR, hazard ratio.

^a Proportion of exposed children with CDA or CD in each time period.^b Adjusted for country, HLA, gender, family history of CD, and age at gluten introduction.

4 different countries, we tested for this heterogeneity by applying a model that included the interaction between age at gluten introduction and country, and it was not statistically significant (data not shown), suggesting that the associations did not vary by country. We adjusted for country of residence in our analyses to remove possible effects such as country-specific infant feeding practices.

The strength of our study is its large, multinational prospective design. All centers shared a uniform protocol, including detailed data on infant feeding collected every third month and standardized questioning to maximize recall. By 2 years of age (when screening for CDA started), the majority of the children had stopped being breastfed, and gluten-containing foods were already introduced to the child's diet; knowledge of tTGA positivity would therefore not have influenced family decisions regarding early infant feeding.

Although tTGA measurements are performed through a strict uniform protocol, the diagnosis of CD by intestinal biopsy result is a clinical decision point. Therefore, one weakness of this study is that the CD outcome

may vary depending on clinical decisions outside of the protocol.

The main reason for not performing an intestinal biopsy was due to low levels of tTGA in absence of clinical symptoms. However, only 27% of the participants diagnosed with CD in TEDDY reported related symptoms before diagnosis by 5 years of age.¹⁶ The prevalence of CD in this study may therefore be underestimated.

Furthermore, although children with only a single copy of DR3-DQ2 were included (in the form of DR3-DQ2/DR4-DQ8), we were unable to assess the pure effect of DR3-DQ2 alone because that information is not included in TEDDY. However, it is unclear how the addition of DR4-DQ8 might affect the outcome.

We are aware that our finding (ie, continued breastfeeding at the time of gluten introduction may increase CDA risk) is in contradiction to the recommendations of World Health Organization and that it is controversial.²² However, this risk was not seen for children who developed CD, suggesting that the associative risk of breastfeeding on CDA should be interpreted with caution.

CONCLUSIONS

There is a remarkable variation when gluten-containing cereals is first introduced into the infants diet as well as marked differences in risk of developing CDA and CD between participating countries in TEDDY. However, time to first introduction of gluten is not an independent risk factor for developing CD by 5 years of age, neither on an overall level nor on a country level comparison. We speculate that the increased risk of CD among Swedish children compared with children from other countries could be caused by a higher intake of gluten-containing cereals at time of weaning, although this assumption needs to be explored in future studies.

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Members of the TEDDY Study Group are listed in the Supplemental Appendix.

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