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The association between stressful life events and respiratory infections during the first 4 years of life: The Environmental Determinants of Diabetes in the Young study

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Abstract

The aim of this study was to conduct a prospective analysis of the association between negative life events (NLEs) and respiratory infections in children genetically at risk for islet autoimmunity (IA) and type 1 diabetes (T1D). Long- and short-term temporal associations between NLEs and rate of respiratory infection episodes (RIEs) in 5,618 children in The Environmental Determinants of Diabetes in the Young study for at least 1 up to 4 years were analysed. All models were adjusted for demographic, day care, season of infection, and psychosocial factors associated with the rate of child RIEs between study visits. The rate of child RIEs was 26% higher in Europe (Sweden, Finland, Germany) than in the United States (rate ratio [*RR*] = 1.26, $p < 0.001$). However, the percentage of child NLEs (odds ratio [*OR*] = 1.18, $p < 0.001$) and mother NLEs (*OR* = 1.83, $p < 0.001$) was higher in the United States compared with Europe. In both continents (Europe, *RR* = 1.12, $p < 0.001$; United States, *RR* = 1.07, $p = 0.006$), high child cumulative NLEs (>1 NLE per year since study inception) was significantly associated with an increased rate of child RIEs. This large-scale prospective study confirms observations that stress may increase the susceptibility for infections in paediatric populations and suggests at least one mechanism by which stress could increase risk for IA and T1D in genetically at risk children.

KEYWORDS
autoimmunity, longitudinal study, negative life events, respiratory childhood infections, stress, type 1 diabetes

The datasets generated and analysed during the current study will be made available in the NIDDK Central Repository at https://www.niddkrepository.org/studies/teddy

1 | INTRODUCTION

The incidence of type 1 diabetes (T1D) among children has increased globally during recent decades with an annual rate of increase of 3.9% reported in Europe (Patterson, Dahlquist, Gyürüs, Green, Soltész, & the EURODIAB Study Group, 2009) and 5.3% in North America (The Diamond Study Group, 2006). The rate of increase is of particular concern among children younger than 5 years in whom the number of affected individuals is expected to double by 2020 (Patterson et al., 2009).

T1D is an autoimmune disorder in genetically predisposed individuals (Castano & Eisenbarth, 1990) and is characterized by destruction of the insulin-producing cells of the pancreas. The disease onset is preceded by a preclinical period of islet autoimmunity (IA; Atkinson & Eisenbarth, 2001; Ziegler & Nepom, 2010). Both IA and T1D onset have been associated with respiratory infections and certain specific viruses, such as enteroviruses. Evidence from epidemiological studies; biomedical studies detecting enteroviruses from the blood, pancreas, and gut of T1D patients; and animal studies suggests that enterovirus infections may accelerate the pathogenesis of T1D in susceptible individuals (Beyan, Wen, & Leslie, 2012; Beyerlein, Wehweck, Ziegler, & Pflueger, 2013; Christen, Bender, & von Herrath, 2012; Christen & von Herrath, 2005; Davis-Richardson & Triplett, 2015; de Beeck & Eizirik, 2016; Dotta & Sebastiani, 2014; Hober et al., 2012; Laitinen et al., 2014; Peng & Hagopian, 2006; Salvatoni et al., 2013; Yeung, Rawlinson, & Craig, 2011). The molecular mimicry theory suggests that epitope mimicry between a virus and human proteins can activate autoimmune diseases like T1D (de Oliveira Andrade et al., 2016). Respiratory infections were reported to increase the risk for T1D autoimmunity in the BABYDIET (Beyerlein et al., 2013; de Beeck & Eizirik, 2016), MIDIA (Rasmussen, Witso, Tapia, Stene, & Ronningen, 2011), ABIS (Wahlberg, Vaarala, Ludvigsson, & for the ABIS Study Group, 2011), and The Environmental Determinants of Diabetes in the Young (TEDDY; Lönnrot et al., 2017) studies.

Stress is considered a potential trigger of IA and T1D. A review of 11 studies concluded that there was strong evidence for a link between psychological stress or stressful negative life events (NLEs) and increased risk of IA and T1D (Sepa & Ludvigsson, 2006). Stressful experiences may affect physical and psychological health as well as immune function (Faresjo, 2015; Nygren, Carstensen, Koch, Ludvigsson, & Frostell, 2015; Wyman et al., 2007). Stress could directly affect autoimmunity contributing to IA and T1D (Littorin, Sundkvist, Nystrom, Carlson, Landin-Olson, Östman et al., 2001; Sepa, Frodi, & Ludvigsson, 2005; Lundgren, Ellström, Larsson, for the DiPiS study group, 2018) and could also lower resistance to infections, leading to greater susceptibility to illness, which, in turn, may increase the risk of IA and T1D (Guo, Du, & Wang, 2015; Oh et al., 2018; Segerstrom & Miller, 2004; Steptoe, Hamer, & Chida, 2007). Support for this hypothesis comes from experimental studies linking stressful life events and respiratory infections in healthy young adults in The Pittsburgh Common Cold Study (Cohen, 2005; Cohen et al., 2002; Cohen, Janicki-Deverts, & Miller, 2007; Cohen, Tyrrell, & Smith, 1993; Cohen & Williamson, 1991) as well as observational longitudinal studies in children (Oh et al., 2018; Turner-Cobb & Steptoe, 1998). To date, the majority of scientific studies on childhood adversity and biological health outcomes have focused on adults. Furthermore, most paediatric studies have been cross-sectional in nature. A recent systematic review (Oh et al., 2018) examined the link between childhood adversity and paediatric health outcomes—infections and illnesses—in longitudinal studies (Caserta et al., 2008; Flaherty et al., 2009; Flaherty et al., 2013; Wyman et al., 2007) and asthma (Kozyrsky et al., 2008; Lange et al., 2011; Lanier, Janson-Reid, Stahlschmidt, Drake, & Constantino, 2010; Wolf, Miller, & Chen, 2008). However, no prior longitudinal study has examined the possible link between NLEs and respiratory infections in children at risk for IA and T1D.

Significant life events are viewed as a stressor, which requires adaptation; they may be positive or negative (Holmes & Rahe, 1967; Luhmann, Eid, Hofman, & Lucas, 2012). In the framework of IA and T1D, only adverse or NLEs were considered in this study. The role of stressful life events has been investigated retrospectively, from 1 week to 1 year or longer after diagnosis of T1D (Littorin et al., 2001; Lundgren et al., 2018; Nygren et al., 2015; Sepa et al., 2005; Sepa & Ludvigsson, 2006) or the onset of infections and illnesses (Cohen, 2005; Cohen et al., 2002; Cohen et al., 2007; Cosgrove, 2004; Faresjo, 2015; Segerstrom & Miller, 2004; Steptoe et al., 2007; Turner-Cobb & Steptoe, 1998; Wyman et al., 2007). However, retrospective reports of this type raise serious concerns of reporting bias. The TEDDY study is a longitudinal observational study designed to identify environmental triggers of IA and T1D in children genetically at risk for T1D; all the TEDDY children entered the study before 3.5 months of age. Information about life events and infections are collected every 3 months during the first 4 years of the child's life and twice a year thereafter, permitting an unbiased prospective assessment of any possible link between infections, stress, and the development of IA and T1D. In a prospective analysis, the TEDDY investigators have documented a link between recent respiratory infections and an increased risk of IA in the first 4 years of a TEDDY child's life (Lönnrot et al., 2017).

The goal of this paper was to conduct a prospective analysis of the association between stressful NLEs and the development of respiratory infections during the same interval—the first 4 years of a TEDDY child's life. Any link between NLEs and respiratory infections confirmed in a prospective analysis would provide one mechanism by which life stress could increase a child's risk of IA and T1D (Lönnrot et al., 2017).

2 | METHOD

2.1 | The TEDDY study

TEDDY is a prospective multinational (Finland, Sweden, Germany, United States) cohort study investigating the environmental determinants of T1D. Both infants from the general population with no family history of T1D and infants with a first-degree T1D relative were screened at birth for genetic predisposition for T1D by analysing their human leukocyte antigen (HLA-DR and DQ genotypes). Parents of infants who met the study's genetic eligibility requirements were invited to take part in the TEDDY; all families had to join the study before the infant was 3.5 months of age. Characteristics of families who were enrolled or refused to be enrolled are described elsewhere (Baxter et al., 2012; Lernmark et al., 2011). Between September 2004 and March 2010, 8,676 children were enrolled and are being followed up for environmental exposures potentially associated with IA and T1D (The TEDDY Study Group, 2007; The TEDDY Study Group, 2008).

The TEDDY protocol is demanding with diet records, stool samples, toenail clippings, parental questionnaires, and study visits for blood draws, nasal swabs, height and weight measurements, and parental interviews scheduled every 3 months during the first 4 years of the child's life. Parents keep detailed records of the child's illnesses, life stresses, and other environmental exposures in the TEDDY book, a diary given to the parents to keep at home and return to study nurses at each TEDDY clinic visit. Demographic variables as well as maternal lifestyle behaviours and measures of the mother's understanding of and anxiety about the child's T1D risk are collected as part of the TEDDY study; these factors were taken into consideration when examining the relationship between stressful NLEs and respiratory illnesses.

In all countries, the TEDDY study was approved by the respective institutional review board or research ethics committee, and a written consent was obtained from all participating families.

2.2 | Study population

A study population of 6,985 TEDDY children followed up a minimum of 12 months and a maximum of 48 months who had not develop IA or T1D was identified. Children who missed two or more consecutive visits were excluded (N = 1,367) in order to limit the possibility of recall bias and to avoid low count of respiratory infection episodes (RIEs) due to long recall intervals between study visits, leaving a final study sample of 5,618 TEDDY children.

2.3 | Measures of socio-demographic variables, maternal lifestyle behaviours, maternal risk perception, maternal anxiety, day care, and season

Because all child illness records were provided by the child's mother, we considered it important to statistically adjust for factors that might be associated with mother-reported illnesses in the child.

2.3.1 | Socio-demographic measures

These included the TEDDY site (Finland, Germany, Sweden, Colorado, Seattle, Georgia/Florida); child's gender (male, female); child's ethnic minority status (United States: the TEDDY child's mother's first language is not English or the mother was not born in the United States or the child is a member of an ethnic minority group—yes/no; Europe: the child's mother's first language or country of birth is other than that of the TEDDY country in which the child resides—yes/no); child has a first-degree relative (FDR) with T1D (yes/no); child is an only child (yes/no); maternal age at child's birth; mother's education (1, basic primary education includes primary school through some trade school; 2, graduated trade school or some college/university; 3, higher education includes graduated university/college or higher); parent's marital status (married or living together vs. single parent); and crowding (number of rooms in the household).

2.3.2 | Maternal lifestyle behaviours

As smoking in the home can be associated with increased respiratory illness in children (Gergen, Fowler, Maurer, Davis, & Overpeck, 1998; Jarvie & Malone, 2008), we assessed maternal smoking at 9 months and annually thereafter (yes/no). At the same time, we also collected information about whether the mother was working outside the home (yes/no) because that could influence child day care placement, the amount of time mothers had to observe their children and record illness episodes in the TEDDY book, and how attentive mothers might be to potential illness symptoms in the child.

2.3.3 | Maternal risk perception

As part of the TEDDY informed consent process, all parents are informed of the child's increased risk for T1D, which is communicated both orally and in writing (Swartling, Lynch, Smith, Johnson, and the TEDDY Study Group, 2016). Parent risk perception accuracy is assessed by the following item at 3, 6, and 15 months and annually thereafter: "Compared to other children, do you think your child's risk for developing diabetes is (mark only one answer)—much lower, somewhat lower, about the same, somewhat higher, much higher." Mothers answering "much lower," "somewhat lower," or "about the same" were classified as inaccurate because all the TEDDY children are at increased risk for T1D. Mothers answering "somewhat higher" or "much higher" were classified as accurate.

2.3.4 | Maternal anxiety about the child's T1D risk

Maternal anxiety was measured by a six-item scale (State Anxiety Inventory) adapted from the 20-item state component of the State Trait Anxiety Inventory (Spielberger, Edwards, Montuori, & Lushene, 1970). Mothers were asked to respond to each item while thinking specifically about their child's risk for T1D; their six-item score was then converted to a score comparable with that obtained from the full 20-item scale. The scale is highly reliable in the TEDDY population (coefficient α = 0.90; Johnson et al., 2016) and has been used in numerous studies of children or adults at high risk for T1D (Hummel, Ziegler, & Roth, 2004; Johnson, 2011; Johnson, Baughcum, Carmichael, She, & Schatz, 2004; Johnson, Lynch, Roth, Schatz, and the TEDDY Study Group, 2017).

2.3.5 | Day care

Date of the child's entry into a social group and childcare was carefully recorded in the TEDDY and was considered in the analysis as acute upper respiratory and gastrointestinal infections are common in children who attend childcare settings (Roberts et al., 2000) and school (Sandora, Shih, & Goldmann, 2008); children cared for in the home have fewer bacterial and viral infections (Louhiala, Jaakkola, Ruotsalainen, & Jaakkola, 1995).

2.3.6 | Season

Infections are known to increase during the fall and winter months (Carlsson et al., 2015; Lee et al., 2012; Winther, Hayden, & Hendley, 2006), a finding replicated in the TEDDY (Lönnrot et al., 2015). Consequently, season at the time illness events were recorded was included in the analysis.

2.4 | Infections

Mothers are asked to record all symptoms of illness in the child in a diary called the TEDDY book, which is brought in and reviewed at each TEDDY visit. The mother is encouraged to report all illnesses including the common cold, upset stomach, headaches, asthma, allergies, and pinworms. A trained study nurse then translates all reports of child illness into the World Health Organization's *International Classification of* Diseases, 10th Revision (*ICD-10*). For analysis purposes, the *ICD-10* codes were further organized into four categories: (a) respiratory infections, (b) gastrointestinal infections, (c) other infections, and (d) unknown febrile infections (Lönnrot et al., 2015). An infection episode approach was used in order to reduce the possibility of overestimation of infections. *ICD-10* codes within the respiratory category are merged into one single episode if they are reported within 7 days. To be counted as a separate infection episode, a minimum of 6 days without symptoms must occur (Lönnrot et al., 2015). Only episodes of respiratory infections (common cold, laryngitis and tracheitis, influenza, enterovirus, respiratory syncytial virus infection, tonsillitis or streptococcal pharyngitis, sinusitis, infection of the middle ear and mastoid process, bronchitis and lower respiratory infections, conjunctivitis, other bacterial diseases of the respiratory tract not elsewhere classified, with any of the above fever, and gastroenteritis symptoms) were considered in the current study (Lönnrot et al., 2015).

2.5 | Stressful NLEs

At each TEDDY visit, mothers are given a list of life events that might have happened in the 3-month period since their last TEDDY visit (serious illness/injury, hospitalization, family member/close friend died, separation/divorce, marriage, victim of violence, quit/lost job, started new job, serious conflicts, legal conflicts, financial difficulties, moved, and changed family composition) and a list of life events that might have happened to their child (illness/injury, hospitalization, family member/friend/pet died, separation from parent, moved, new sibling, started day care, changed day care, and new step-parent). If the mother indicated she or her child had experienced any of the events, she was asked to rate the event's impact as very bad, bad, good, or no impact. Mothers are also asked to describe any other life events not on the lists and to rate their impact. Only adverse events with very bad or bad impact were considered. The total number of NLEs in each 3-month study window was recorded for mother and child separately.

2.6 | Statistical analyses

To limit the possibility of recall bias and to avoid low count of RIEs due to long intervals between visits, families missing two or more consecutive study visits at any time during the first 4 years of life were excluded (n = 1,367). In order to identify possible differences between participants included and excluded from our subsequent analyses, we compared the two groups using multiple regression.

The number of RIEs and NLEs experienced by the child and the number of NLEs experienced by the mother since the last study visit were recorded at each 3-month study visit. For the purposes of this study, the number of RIEs was presented as a rate per person-year. The resulting history of RIE rate and NLEs in the final study sample consisted of a 3-month time series from enrolment up to 48 months.

NLEs experienced by the child and by the mother were separately examined in relation to the RIE rate calculated at each study visit. We eliminated all child illnesses related NLEs from the analysis to avoid any potentially spurious association between a child's infection episode and the report of a child NLE. At each study time point, NLE rates were bimodally distributed with most participants having no NLEs. Consequently, we treated NLEs as a categorical variable in the analysis (no NLE, $\geq$1 NLE).

Given the longitudinal nature and nonnormal distribution of the count data, generalized estimating equation (GEE) methodology with log link was used to linearly regress NLEs on the number of RIEs. The time period (log years) between visits was included as an offset in the model, allowing for RIE rates to be calculated. All GEE models assumed exchangeable correlation structure. The empirical-based estimates were compared with the model-based estimates to ensure the working correlation was reasonable. Rate of RIEs among participants with an NLE relative to participants without an NLE were presented as rate ratios (95% CI) and were tested for significance using Wald tests.

GEE with logit link was also used to test differences in the percentages (odds) of child NLEs or mother NLEs between the U.S. and European continents. Results were presented as odds ratios (*ORs*; 95% CI).

As there were a number of differences on study variables between the U.S. and European sites, all analyses on RIE rate are adjusted for the variables study site, child age, child gender, child ethnic minority, child FDR status, only child, child started day care, parents married or living together, maternal age at child's birth, maternal education, maternal perception of child's T1D risk, maternal anxiety about child's

T1D risk, household size, mother smoked, mother worked outside home, and season. Because maternal life style, risk perception, and anxiety are time-dependent variables, the value immediately preceding the 3 months between visit window in which an RIE rate was calculated was considered in the analyses. Season is also time dependent. Consequently, season at the time of the RIE recording was used in the analysis.

Four measures of NLEs were created: (a) current NLE (yes/no) defined as an NLE occurring in the same ~3 months between visit window for which RIEs were recorded; (b) previous-year NLE defined as an NLE occurring in the 12-month period prior to, but not including, the 3-month RIE recording window (no NLE, ≥1 NLE); (c) cumulative NLEs defined as the number of NLEs since study inception up to, but not including, the RIE recording window calculated as a rate per year (<1 NLE, ≥1 NLE); and (d) for children > 27 months of age, early-life NLE defined as an NLE occurring in the first 12 months of the TEDDY (no NLE, ≥1 NLE). This allowed examination of long- and short-term temporal effects of NLEs on RIE rate in addition to the effect of any NLE during the period RIEs were recorded. Because the correlation of NLEs between consecutive visits was low, current NLE, previous-year NLEs, and early-life NLEs were included in the same model. We subsequently tested for the effect of cumulative

TABLE 1 Factors associated with exclusion due to missing ≥ 2 consecutive study visits

Factors	Excluded for having more than two consecutive visits missed		Multivariate regression of factors associated with exclusion	
Variables	No *N* (% row)	Yes *N* (% row)	*OR* [95% CI]	*p* value
Study site				
Colorado	909 (82.3%)	196 (17.7%)	1.64 [1.29, 2.09]	
Georgia/Florida	526 (75.0%)	175 (25.0%)	3.16 [2.47, 4.05]	
Washington	741 (72.1%)	287 (27.9%)	3.37 [2.69, 4.23]	
Finland	1,225 (78.7%)	332 (21.3%)	2.56 [2.07, 3.17]	
Germany	305 (65.7%)	159 (34.3%)	5.24 [4.01, 6.84]	<0.001
Sweden	1,912 (89.8%)	218 (10.2%)	1 (reference)	
Maternal education				
Primary school	1,341 (82.3%)	288 (17.7%)	1.26 [1.03, 1.54]	
Secondary/trade school	1,332 (79.0%)	355 (21.0%)	1.23 [1.05, 1.45]	0.001
College	2,724 (84.7%)	493 (15.3%)	1 (reference)	
Child ethnic minority				
No	4,727 (83.5%)	936 (16.5%)	1 (reference)	
Yes	750 (74.5%)	257 (25.5%)	1.23 [1.02, 1.48]	0.008
Smoked				
No	5,108 (83.4%)	1,020 (16.6%)	1 (reference)	
Yes	476 (73.5%)	172 (26.5%)	1.42 [1.15, 1.74]	<0.001
Only child				
No	3,187 (81.0%)	749 (19.0%)	1 (reference)	
Yes	2,388 (84.4%)	443 (15.6%)	0.68 [0.59, 0.79]	<0.001
Maternal age				
Years	Mean (*SD*) 30.99 (5.0)	Mean (*SD*) 29.6 (5.4)	0.96 [0.94, 0.97]	<0.001
Mother NLEs by 12 months				
No	3,448 (81.6%)	777 (18.4%)	1 (reference)	
Yes	2,170 (78.6%)	590 (21.4%)	1.34 [1.17, 1.54]	<0.001
Child NLEs by 12 months				
No	4,811 (80.7%)	1,150 (19.3%)	1 (reference)	
Yes	807 (78.8%)	217 (21.2%)	1.10 [092, 1.31]	0.31
RIEs by 12 months				
Count	Mean (*SD*) 3.4 (2.1)	Mean (*SD*) 2.7 (2.1)	0.90 [0.87, 0.93]	<0.001

TABLE 2A Mothers' negative life events

Life category	Negative life events experienced by the mothers with negative impact: Description	Count during follow-up: Total count N	Cumulative rate/100 person-years
Significant loss	Family member or close friend died, pet died, pet removed from home, other significant loss	2,887	14.7
Separation	Mother separated from their spouse or significant other or got a divorce	389	2.0
Violence	Mother or her family member experienced violence	230	1.2
Job related	Mother or her spouse/significant other quit or lost your job, or returned to work, or started school or new job, or had job stresses	3,337	17.0
Financial difficulties	Mother or her spouse/significant other had financial difficulties or money problems	2,820	14.4
Serious conflict	Mother got married (negative experience) or mother had serious arguments with spouse, other relatives, or friends	2,509	12.8
Legal conflict	Mother or family member, close friend, or relative got in trouble with police/law	45	0.2
Change	Mother moved, household member moved into or out of home, changes in family composition, close friend or relative moved away	823	4.2
Other		2,607	13.3

Total person-years of follow-up = 19,593 person-years by 5,618 mothers.

NLEs with current NLE of the parent and child in the same model. All GEE models were adjusted for demographic, day care, season of infection, and psychosocial factors associated with RIE rates. Statistical analysis was performed using SAS 9.4. p values less than 0.05 were considered statistically significant unless otherwise stated.

3 | RESULTS

3.1 | Comparison of excluded and included subjects

Table 1 depicts the results of the multiple regression identifying significant differences between those excluded and included in the analysis. The 1,367 subjects excluded from the study because they missed two or more consecutive study visits were more likely to come from the United States and Germany ($p < 0.001$). Compared with the study sample, the excluded sample was characterized by lower maternal education ($p < 0.001$), child coming from an ethnic minority ($p = 0.008$), maternal smoking in the first year of the child's life ($p < 0.001$), multiple children in the family ($p < 0.001$), and younger maternal age ($p < 0.001$). Child NLEs during the first year of the child's life had no association with exclusion ($p = 0.31$). However, children who were excluded had fewer RIEs in the first year of life ($p < 0.001$), and their mothers reported more maternal NLEs ($p < 0.001$).

3.2 | Types of mother and child NLEs

Tables 2a and 2b display the nature and types of NLEs most commonly reported by mothers for themselves and for their children, respectively. The correlation between the number of mother and child NLEs reported at each study visit for the preceding 3-month period was low, ranging from 0.14 to 0.18. The correlation between mother and child cumulative NLEs was somewhat higher, ranging from 0.20 to 0.30. These very modest associations suggested that mother and child NLEs should be considered separately.

3.3 | U.S. and European differences in NLEs and RIE rate

The age-specific RIE rate among children and the age-specific percentage of children and their mothers having an NLE since the last visit are shown in Figure 1 for Europe and the United States. As we have previously noted (Lönnrot et al., 2015), the reported RIE rate among children was higher in Europe than in the United States (1.26, 95% CI [1.23, 1.30], $p < 0.001$). In contrast, the percentage (odds) of mothers reporting an NLE ($OR = 1.83$, 95% CI [1.71, 1.96], $p < 0.0001$) or their child having an NLE ($OR = 1.18$, 95% CI [1.09, 1.28], $p < 0.0001$) was lower in Europe compared with the United States, although the difference in child NLE between continents was less pronounced (see Figure 1).

3.4 | Factors associated with the number of mother-reported child RIEs

Table 3 shows the factors associated with the number of mother-reported child RIEs. In addition to large site differences—with higher RIE rates reported among children living in Europe than in the United States—season ($p < 0.001$) was significantly associated with the RIE rate among children, with higher rates reported in the fall/winter months. Male gender ($p < 0.001$), placement in day care ($p < 0.001$), parents married or living together ($p = 0.03$), higher maternal education ($p < 0.001$), and accurate maternal perception of the child's T1D risk ($p < 0.001$) were all associated with an increase in mother-reported RIE rate among the children. In contrast, older child age

TABLE 2B Children's negative life events

Life category	Negative life events experienced by the child with negative impact: Description	Count during follow-up: Total count N	Cumulative rate/100 person-years
Significant loss	Child's close friend or relative died, pet died, pet removed from the home, or other significant loss	29	0.2
Separation	Child was separated from mother or father	2,601	13.3[a]
Violence	Experience violence (include physical or sexual abuse) or witness violence	30	0.2
Legal conflict	Child got in trouble with police	0	0
Change	Child moved, got a new brother or sister, child got a new step-parent, household member moved into or out of home, change in family composition, close friend or relative moved away	617	3.2
Childcare	Child started day care or school, child changed schools or day care, new babysitter or childcare worker, regular babysitter left, other changes in childcare not specified	1,628	8.3
School	Failed an important exam, not promoted to the next grade, significant damage to child's school, suspended from school	6	0.0
Other		1,120	5.7

Total person-years of follow-up = 19,593 person-years by 5,618 children.

($p < 0.001$), female gender ($p < 0.001$), ethnic minority status ($p < 0.001$), only child status ($p < 0.001$), mother working outside the home ($p = 0.02$), and maternal smoking ($p < 0.001$) were all associated with a lower rate of mother-reported RIE in their children (see Table 1). FDR status, maternal age and anxiety about T1D risk, and crowding were not associated with RIE rate (p values > 0.10).

3.5 | The association between NLE and child RIEs

All GEE models examining the association between mother and child NLEs and child RIEs adjusted for all factors in Table 3. Table 4 depicts the association between current, previous-year, and early-life (in those ≥27 months) NLEs and child RIEs. The presence of a child concurrent NLE (RIE rate ratio = 1.07, $p < 0.001$), compared with the absence of a concurrent NLE, but not a mother concurrent NLE (RIE rate ratio = 1.01, $p = 0.26$), during the same period of recorded RIEs was significantly associated with an increase in the RIE rate among children. The associations were consistent in younger (≤27 months) and older (>27 months) children. In contrast, the presence of a mother or child previous-year NLE was associated with an increase in child RIE rate in both younger and older children. Child—but not mother—early-life NLEs occurring in the child's first year of life were also associated with an increase in the child's rate of RIEs.

Because both mother and child previous-year NLEs and child early-life NLEs were all associated with the rate of the child's RIE over and above the effect of current NLEs, we next examined the independent association of mother and child cumulative NLE on the RIE rate among children, controlling for presence of a mother or child current NLE (see Table 5). Current child NLEs were significantly associated with RIE rate overall and in Europe but not in the United States, whereas mother current NLEs were not associated with the RIE rate among children in either continent. Children with child cumulative NLEs ≥ 1 per year had a significantly higher rate of respiratory infections than had children having <1 NLE per year (rate ratio = 1.10, 95% CI [1.06, 1.14], $p < 0.001$). This difference was consistent across continents: United States (rate ratio = 1.07, 95% CI [1.01, 1.14], $p = 0.026$) and Europe (RIE rate ratio = 1.12, 95% CI [1.07, 1.17], $p < 0.001$). Mother cumulative NLEs ≥ 1 per year compared with <1 per year were also significantly associated with the RIE rate among children from either continent, but its effect was small and not significant for Europe when the sample was divided by continent (see Table 5). Figure 2 illustrates the age and continent-specific rate of RIEs for children with and without high rates of cumulative NLEs (≥1 per year). The impact of high cumulative NLEs on the RIE rate among children was markedly greater for child cumulative NLEs compared with mother cumulative NLEs (Figure 2a compared with Figure 2b). When European children experienced a high rate (≥1 per year) of cumulative NLEs beforehand, the age-specific RIE rate was close to six per year until 2 years of age. After 2 years of age, these children had more than one additional respiratory infection per year over children who had low child cumulative NLEs. In the United States, the differences in RIE rates between those children with high and low cumulative NLEs were substantial but somewhat lower than those of European children (Figure 2b).

4 | DISCUSSION

Respiratory infections are a leading cause of illness, outpatient physician visits, and hospitalizations among children (Jensen-Fangel, Mohey, Johnsen, Andersen, Sorensen, & Ostergaard; Nair et al., 2013). In the TEDDY, child RIEs were more commonly reported in Europe than in the United States, a finding consistent with global comparisons conducted by the World Health Organization (2015). The

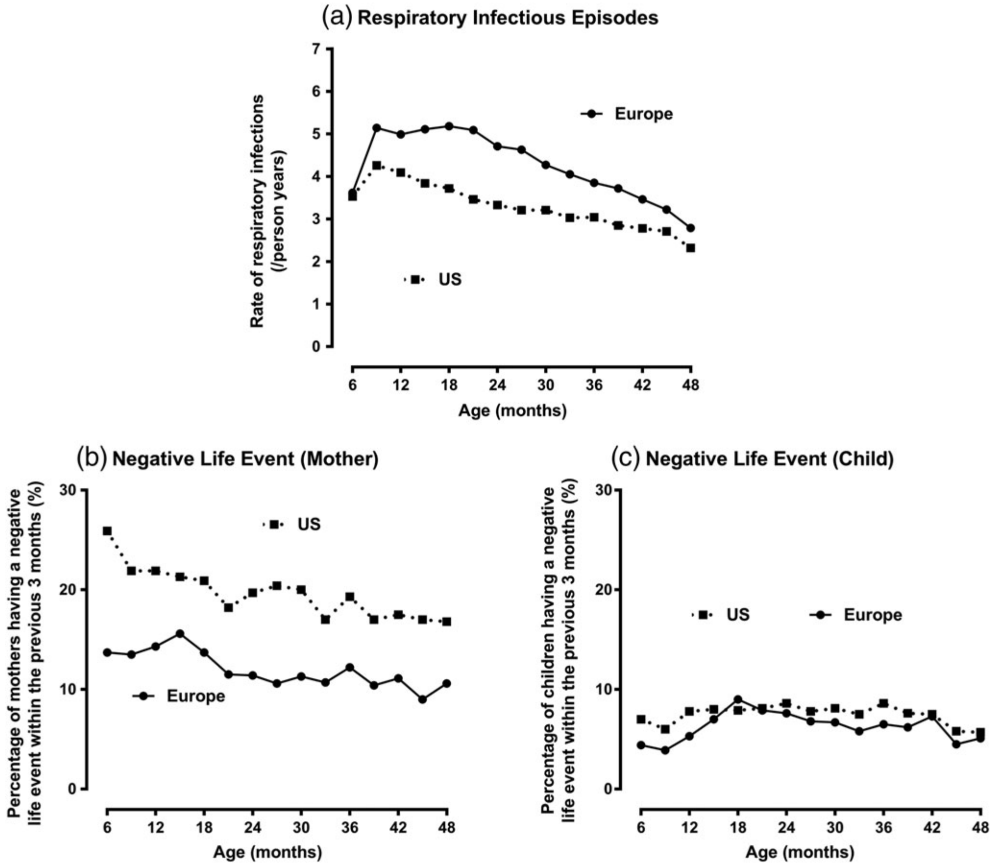

FIGURE 1 Rate of respiratory infection episodes and negative life events by age of child and continent of residence

current study also replicated the seasonal distribution of RIEs previously reported (Carlsson et al., 2015; Lee et al., 2012; Lönnrot et al., 2015; Winther et al., 2006) and the association between day care and an increased frequency of RIEs (Jackson et al., 2013; Roberts et al., 2000).

In the present study, a number of socio-demographic and maternal psychosocial lifestyle factors were associated with the frequency of mother-reported child RIEs. Boys were reported to have more RIEs than girls did, and children with siblings were reported to have more infections than children without siblings, findings that are consistent with the prior literature (Jensen-Fangel et al., 2004; Nair et al., 2013; Jackson et al., 2013; Grüber et al., 2008; Simoes, 2003; Shi et al., 2015). We also found that more educated mothers and those with more accurate perceptions about their child's T1D risk reported more RIEs. In contrast, the TEDDY moms who worked and smoked and whose child was an ethnic minority reported fewer RIEs. Several previous studies have suggested that more educated mothers at higher socio-economic status may be more compliant or attentive to requests to document RIEs in their child leading to higher reports (Bergmann et al., 2002; Grüber et al., 2008; Shi et al., 2015; Simoes, 2003; Zoch et al., 2015). Previous studies have also documented that more concerned parents tend to report more RIEs in the child (Andre et al., 2007; Van Der Gaag & Van Droffelaar, 2012). Mothers who work may be more absent from home and have less time to observe and document illness symptoms of their children. Although some studies report parental smoking is associated with increased reports of RIEs in the child (Jackson et al., 2013), we did not find this to be the case. Grüber et al. (2008) also found no association between parental smoking and child respiratory infections using a diary method to report respiratory infections. The authors suggest that tobacco smoke may contribute to the severity of respiratory infections but might not enhance susceptibility to respiratory infections per se. Smokers may also be less health conscious and less likely to note mild respiratory symptoms in a child.

Because of the numerous factors associated with RIE reporting, all were adjusted for in the analysis of the association between NLEs and RIEs. A clear positive relationship between NLEs and RIEs was observed. This was particularly true when the NLE occurred in the same time frame as the RIE recording. However, previous-year NLE, early-life NLE, and cumulative NLEs all showed significant associations with RIEs in addition to and independent of the effect of current NLE. Child NLEs appeared to be more strongly linked to child RIEs than to mother NLEs despite the fact that child NLEs occurred less frequently. This pattern of results appeared to be consistent across continents.

The observed association between NLEs, particularly child NLEs, and child RIEs is important because it replicates prior cross-sectional studies linking stress to infectious episodes (Caserta et al., 2008; Cohen, 2005; Cohen et al., 2002; Cohen & Williamson, 1991; Drummond & Hewson-Bower, 1997; Turner-Cobb & Steptoe, 1998; Wyman et al., 2007) using a longitudinal prospective design with a

TABLE 3 Factors associated with the rate of respiratory infection episodes (RIEs)

Factors associated with rate of respiratory infection episodes		Sample *N* (%) or mean (*SD*) at 1 year of age	Association with RIE rate		
			RIE rate ratio[a]	95% CI	*p* value
Socio-demographic measures					
Study site	Colorado	909 (16.2)	1.00	Reference	
	Georgia/Florida	526 (9.4)	1.14	[1.08, 1.20]	<0.001
	Washington	741 (13.2)	1.04	[0.99, 1.09]	0.12
	Finland	1,225 (21.8)	1.43	[1.37, 1.50]	<0.001
	Germany	305 (5.4)	1.21	[1.13, 1.30]	<0.001
	Sweden	1,912 (34.0)	1.27	[1.22, 1.32]	<0.001
Child age	Years	1	0.86	[0.85, 0.87]	<0.001
Child gender	Boy	2,844 (50.6)	1.00	Reference	
	Girl	2,774 (49.4)	0.95	[0.93, 0.97]	<0.001
Child ethnic minority	No	4,727 (86.3)	1.00	Reference	
	Yes	750 (13.7)	0.89	[0.86, 0.93]	<0.001
Only child	No	3,187 (57.2)	1.00	Reference	
	Yes	2,388 (42.8)	0.96	[0.94, 0.98]	<0.001
Parents married or living together	No	210 (3.8)	1.00	Reference	
	Yes	5,367 (96.2)	1.07	[1.01, 1.13]	0.03
Maternal education	Primary school	1,035 (18.5)	1.00	Reference	
	Secondary/trade school	1,303 (23.3)	1.05	[1.01, 1.10]	0.01
	College	3,249 (58.2)	1.14	[1.10, 1.18]	<0.001
Started day care	No	1,150 (20.5)	1.00	Reference	
	Yes	4,468 (79.5)	1.26	[1.23, 1.31]	<0.001
Season	Spring/summer	2,852 (50.8)	1.00	Reference	
	Fall/winter	2,766 (49.2)	1.30	[1.28, 1.31]	<0.001
Maternal lifestyle behaviours					
Smoked	No	5,108 (91.5)	1.00	Reference	
	Yes	476 (8.5)	0.91	[0.87, 0.95]	<0.001
Worked outside home	No	3,596 (64.7)	1.00	Reference	
	Yes	1,963 (35.3)	0.97	[0.95, 1.00]	0.02
Maternal perception of child's T1D risk					
Accurate	No	2,102 (37.5)	1.00	Reference	
	Yes	3,500 (62.5)	1.06	[1.04, 1.09]	<0.001

Note. First-degree relative status, mother's age at child's birth, maternal anxiety about child's type 1 diabetes (T1D) risk, and household size were not associated with rate of mother-reported child RIEs (*p* values > 0.10).

[a]Rate ratio (*RR*) = RIE rate relative to RIE rate in reference group; *RR* > 1 indicates higher rate relative to reference group; *RR* < 1 indicates lower rate.

very large sample of young children. The fact that this association was found not only when NLEs and RIEs were recorded in the same time frame (current NLE) but more so when NLEs were measured in time periods prior to the report of RIEs adds further weight to the finding. Documenting this association in the TEDDY population supports the hypothesis that cumulative stress may influence the development of IA and T1D by increasing the child's risk for respiratory infection, which in turn increases the child's risk of IA and T1D (Lönnrot et al., 2017).

Most previous studies examining the association between life stress and IA or T1D have not differentiated between parent and child life events (Littorin et al., 2001; Sepa et al., 2005; Sepa & Ludvigsson, 2006). Our findings suggest that such a distinction may be important. We found that mother and child NLEs in this sample of very young children were not highly correlated and that child NLEs showed a stronger association with child RIEs than did mother NLEs.

A study limitation is its dependence on self-report of both NLEs and RIEs. The usage of a diary and the regular collection of these data every 3 months about a narrow (3-month) time frame was designed to minimize recall bias. Mothers were also prompted by the study nurses with a list of possible life events, and they were asked about illnesses. However, it is certainly possible that reporting bias existed, with some mothers having a tendency to report more events regardless of content. We attempted to adjust for these biases by eliminating all reports

TABLE 4 Rate of respiratory infection episodes (RIE) between visits (average 3 months) reported by those with ≥1 negative life events (NLEs) relative to those with no NLE

Age of child in months	Recording period of NLEs relative to the 3-month period of recorded child RIEs	Mother negative life events			Child negative life events		
		RIE rate ratio	95% CI	*p* value	RIE rate ratio	95% CI	*p* value
3–27	Current NLEs[a]						
	No NLE	1.00	Ref		1.00	Ref	
	With NLEs	1.02	[1.00, 1.05]	0.07	1.08	[1.04, 1.12]	<0.001
	Previous-year NLEs[b]						
	No NLE	1.00	Ref		1.00	Ref	
	With NLEs	1.03	[1.01, 1.06]	0.01	1.12	[1.09, 1.15]	<0.001
27–48	Current NLEs[a]						
	No NLE	1.00	Ref		1.00	Ref	
	With NLE	1.01	[0.98, 1.05]	0.57	1.06	[1.01, 1.11]	0.01
	Previous-year NLEs[b]						
	No NLE	1.00	Ref		1.00	Ref	
	With NLEs	1.05	[1.02, 1.08]	0.001	1.06	[1.03, 1.10]	<0.001
	Early-life NLEs[c]						
	No NLE	1.00	Ref		1.00	Ref	
	With NLEs	1.04	[1.00, 1.07]	0.08	1.09	[1.04, 1.14]	<0.001

Note. NLEs adjusted for all factors in Table 1.

[a]Current NLEs: NLEs occurring in the same 3-month window for which RIEs were recorded.

[b]Previous-year NLEs: NLEs occurring in the 12-month period prior to, but not including, the 3-month RIEs recording window (no NLE; ≥1 NLE).

[c]Early-life NLEs: for children > 27 months of age, NLEs occurring in the first 12 months of life.

of child illness from our measures of NLEs and by controlling for numerous factors (study site, child's age, gender, ethnic minority, siblings, day care attendance, mother's family status, education and lifestyle behaviours as smoking and working outside, and maternal perception of child's T1D risk) associated with RIE reporting in our statistical models. The fact that previous-year, early-life, and cumulative

TABLE 5 Rate of child respiratory infection episodes (RIEs) by child and mother current negative life events and cumulative negative life events (NLEs) for the whole study cohort and for Europe and the United States separately

Recording period of mother or child NLEs relative to the 3-month period of recorded child RIEs	Overall			United States			Europe		
	RIE rate ratio	95% CI	*p* value	RIE rate ratio	95% CI	*p* value	RIE rate ratio	95% CI	*p* value
Mother current NLEs[a]									
No NLE	1.00	Ref		1.00	Ref		1.00	Ref	
With NLEs	1.01	[0.99, 1.03]	0.33	1.02	[0.98, 1.05]	0.36	1.01	[0.98, 1.04]	0.56
Mother cumulative NLEs[b]									
<1 NLE per year	1.00	Ref		1.00	Ref		1.00	Ref	
≥1 NLE per year	1.03	[1.01, 1.06]	0.007	1.05	[1.01, 1.09]	0.007	1.02	[0.99, 1.06]	0.19
Child current NLEs[a]									
No NLE	1.00	Ref		1.00	Ref		1.00	Ref	
With NLEs	1.06	[1.03, 1.09]	<0.001	1.02	[0.97, 1.08]	0.35	1.08	[1.05, 1.12]	<0.001
Child cumulative NLE[b]									
<1 NLE per year	1.00	Ref		1.00	Ref		1.00	Ref	
≥1 NLE per year	1.10	[1.06, 1.14]	<0.001	1.07	[1.01, 1.14]	0.02	1.12	[1.07, 1.17]	<0.001

Note. Mother and child current and cumulative NLEs included in same multivariate generalized estimating equation model and adjusted for all factors in Table 1.

[a]Current NLEs: NLEs occurring in the same 3-month window for which RIEs were recorded.

[b]Cumulative NLEs: number of NLEs since study inception up to, but not including, the RIE recording window calculated as a rate per year (<1 NLE, ≥1 NLE).

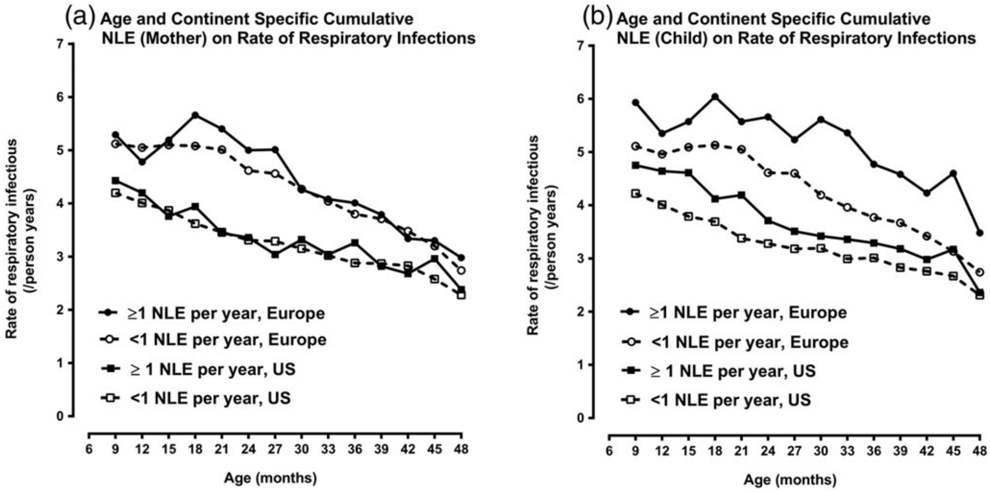

FIGURE 2 Rate of respiratory infection episodes by age of child, continent of residence, and mother and child cumulative negative life events (NLEs)

NLEs occurring in time frames prior to the RIE recording period were all associated with an increase in RIE also suggests that the findings are not spurious products of self-report bias.

The TEDDY population is a highly motivated sample of educated mothers who have volunteered to participate in a longitudinal study with a demanding protocol. We do not get income data from the TEDDY, but we do measure the socio-economic background according to maternal education, marital status, crowding, and ethnic minority status. All of these factors (except crowding, which was not associated with maternal reports of child RIE) were included as control variables in the analysis. Further, those mothers included in the current study were particularly conscientious about coming to study visits where they regularly provided information on mother and child NLEs and child RIEs. Because we were concerned with reporting bias and underestimation of RIEs due to exceeding long periods between study visits, we excluded participants who missed two or more consecutive study visits. We have previously shown that NLEs are not associated with dropout in the TEDDY (Johnson et al., 2016). However, in this study, we found that study participants who were less compliant with study visits and therefore were excluded from the analysis differed from those included in several important ways. These less compliant mothers were younger and less educated, were more likely to have an ethnic minority child and have multiple children in the family, and were more likely to report smoking in the first year of the child's life. Excluded mothers did not differ from included mothers in their reports of child NLEs in the first year of the child's life, but they did report more mother NLEs and fewer child RIEs in that time frame. Because the excluded and included samples did not differ on child NLEs in the first year of the child's life, we believe that our findings of an association between child NLE and child RIEs can be generalized to the full TEDDY cohort. However, the fact that mothers who report more mother NLEs in the first year of the child's life were less compliant and therefore more likely to be excluded from the analysis suggests that we may have underestimated any association between maternal NLEs and child RIEs.

Another limitation of our findings is that the investigation was carried out in a population who is genetically at risk for T1D. That limits the generalizability of the finding, which required replication in unselected cohorts.

5 | CONCLUSION

Previous-year, early-life, and cumulative NLEs occurring in time frames prior to the RIE recording period were all associated with an increase in RIEs and showed a stronger association between child NLEs and RIEs compared with mother NLEs and RIEs. Biomarkers of both NLE and RIE would provide an additional test of the association. Fortunately, some biomarkers of RIE are available in the TEDDY, which can be used to further elucidate this association in subsequent studies. However, the current study's findings suggest one mechanism by which averse negative life stress may lead to the development of IA and T1D in children.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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