Pediatric Diabetes

ISPAD International Society for Pediatric and Adolescent Diabetes

Pediatric Diabetes 2014
doi: 10.1111/pedi.12168

Pediatric Diabetes

Original Article

Maternal anxiety about a child's diabetes risk in the TEDDY study: the potential role of life stress, postpartum depression, and risk perception

Roth R, Lynch K, Lernmark B, Baxter J, Simell T, Smith L, Swartling U, Ziegler A-G, Johnson SB, The TEDDY Study Group. Maternal anxiety about a child's diabetes risk in TEDDY study: the potential role of life stress, postpartum depression, and risk perception.
Pediatric Diabetes 2014.

Objective: To understand the association between life stress, postpartum depression (PD), maternal perception of her child's risk for type 1 diabetes (T1D) and a mother's anxiety about her child's T1D risk in mothers of genetically at risk children in The Environmental Determinants of Diabetes in the Young (TEDDY) study.
Methods: A short form of the state component (SAI) of the State-Trait Anxiety Inventory, negative life events (LE), the Edinburgh Postnatal Depression Scale (EPDS), and one question about the child's risk of developing T1D risk perceptions (RP) were given to mothers at the 6-month TEDDY clinic visit. The relationship between the four measures was modeled using multiple regressions.
Results: Controlling for sociodemographic factors, significant country differences in SAI, LE, EPDS, and RP emerged. LE – particularly interpersonal LE – had a strong association to maternal anxiety about the baby's risk of diabetes. Both evidence of PD and accurate risk perceptions (RPs) about the child's T1D risk were associated with increased maternal anxiety about the child's T1D risk.
Conclusion: Heightened maternal anxiety in response to the news that a child is at increased risk for T1D is common. Mothers who have experienced recent negative LE, who experience PD and who accurately understand their child's risk may be particularly vulnerable to high levels of anxiety. The findings reported here need to be confirmed in future prospective studies.

Roswith Roth[a,b], Kristian Lynch[c], Barbro Lernmark[d], Judy Baxter[e,f], Tuula Simell[g], Laura Smith[h], Ulrica Swartling[d], Anette-G Ziegler[a], Suzanne B Johnson[i] and The TEDDY Study Group[†]

[a]Institut für Diabetesforschung, Helmholtz Zentrum München, Ingolstädter Landstraße 1, Neuherberg 85764, Germany; [b]Institute of Psychology, University of Graz, Universitaetsplatz 2/III, Graz 8010, Austria; [c]Pediatrics Epidemiology Centre, University of South Florida, Tampa FL 33612, USA; [d]Department of Clinical Sciences, University Hospital MAS, Lund University, Malmö 20502, Sweden; [e]Barbara Davis Center for Childhood Diabetes, School of Medicine, University of Colorado Denver-AMC, Aurora CO 80045, USA; [f]Department of Community and Behavioral Health, Colorado School of Public Health, University of Colorado Denver-AMC, Aurora CO 80045, USA; [g]Department of Pediatrics, University of Turku, Turku University Hospital, Klinamyllynkatu 4-8, Turku 20520, Finland; [h]Department of Pediatrics, University of South Florida, Tampa, FL 33612, USA; and [i]Department of Medical Humanities and Social Sciences, Florida State University College of Medicine, Talahassee, FL 32306-4300, USA

[†]Members of the TEDDY Study Group are listed in Appendix.

Key words: anxiety about baby's diabetes risk – negative life events – postpartum depression – risk perception – type 1 diabetes

Corresponding author: Roswith Roth
Institut für Diabetesforschung
Helmholtz Zentrum München
Ingolstädter Landstraße 1
85764 Neuherberg
Germany.
Tel: +43 316 380-5119;
fax: +43 316 380-9808;
e-mail: roswith.roth@uni-graz.at

Submitted 29 January 2014.
Accepted for publication 21 May 2014

Type 1 diabetes (T1D) is one of the most common endocrine and metabolic conditions in childhood and the number of children developing this form of diabetes every year is increasing rapidly worldwide, especially among young children (1–4). Genetic screening for T1D risk at birth is now possible but raises concerns about the burden of risk awareness in asymptomatic individuals, most of whom will never develop the disease (5–8). A number of studies used the State-Trait Anxiety Inventory (STAI) (9) to investigate the emotional impact of learning that an individual or their child is at risk for T1D. These studies suggest that anxiety tends to be high in response to the news of increased risk but declines over time (5, 10–15).

Prior studies identified a number of factors associated with heightened anxiety in response to risk notification: lower education, ethnic minority status, and *a priori* history of depression (10, 15, 19). The same factors were associated with increased depressive symptoms in response to risk notification as well (10, 19). Risk underestimation has been reported in TEDDY (13) and previously in parents of children at increased genetic risk for T1D and appears to increase over time (5, 19). Although anxiety and depression symptoms are frequently correlated, differential effects of maternal anxiety and depression symptoms in response to infant T1D risk were reported. Mothers who were more accurate in risk perception (RP) experienced more anxiety and fewer depressive symptoms (19). Likewise, underestimation of risk was associated with fewer anxiety and more depressive symptoms. Individuals with a history of depression may be particularly vulnerable to depressive symptoms (5, 19). Coping strategies like self-blame and avoidance in response to the news that their child is at risk for T1D can prevent accurate RP (5, 19).

Life stress has long been considered a potential trigger for T1D (20) and autoimmunity (21–23). Life events (LE) are often used as an indicator of stress and have been previously associated with both depression (24–28) and anxiety (29, 30). The available literature indicates that there are differences in the report of LE depending on sociodemographic factors such as ethnicity (31, 32), income, and education (32). A few studies have included different countries when measuring LE (33, 34). Furthermore, LE in T1D are typically assessed in a single country (12, 20–22) and measured retrospectively for the past one or more years, introducing recall bias. Experiences of negative LE at a similar time as learning of the baby's risk for T1D may increase stress with impact on anxiety, postpartum depression (PD), and RP.

About 10–15% of women experience PD (35, 36) although prevalence rates differ by race/ethnicity (37), social status (37–39), and country (39, 40). Studies have documented the link between life stress and PD; young mothers with a history of major LE are at a greater risk for PD (38).

However, none of these studies examined the impact of LE, PD, and RP on maternal anxiety about the child's risk for T1D in an international study. Greater consideration of these factors may help us better to support families who are asked to participate in longitudinal natural history studies or diabetes prevention trials.

The TEDDY study offers the opportunity to examine factors associated with maternal anxiety about a child's T1D risk in an international cohort. We are in particular interested in how measures of recent LE (during the last 3 months), PD, and RP are related to maternal anxiety about the child's risk for T1D. This study focuses on the 6-month TEDDY visit. Families enter TEDDY when the child is approximately 3 months of age; so, at the 6-month TEDDY visit, mothers have been aware of their child's increased T1D risk for ≥ 3 months but are still relatively new

to the TEDDY study and their children are still quite young (6 months). Consequently, we hypothesized that all three, LE, PD, and RP, after delivery might be important determinants of the mother's anxiety about the child's T1D risk. We also expected that mothers of children with a first degree relative (FDR) with T1D would be more anxious than mothers from the general population (GP) who are unfamiliar with T1D. Furthermore, we expected that mothers with accurate RP of their child's T1D risk would exhibit more anxiety than mothers who underestimated their child's T1D risk.

Methods

The TEDDY study

The Environmental Determinants of Diabetes in the Young (TEDDY) is a prospective multinational (Finland, Sweden, Germany, USA) cohort study investigating the environmental determinants of T1D. GP and FDR children were screened for genetic predisposition for T1D human leukocyte antigen (HLA-DR and -DQ genotypes) before 3 months of age and if eligible, invited to take part in the study. Characteristics of families who were enrolled or refused to be enrolled are described elsewhere (14, 18). Over 8000 (8668) children were initially enrolled in the study between September 2004 and March 2010 and followed-up for environmental exposures potentially associated with autoimmunity and T1D. Data collected at each study visit including biological data (e.g., blood and nasal swabs); dietary records; demographic and health histories for the child, as well as psychological measurements, including reports of LE, PD, RP; and anxiety about the baby's risk from the parents (41).

In all TEDDY countries, the study was approved by the respective Institutional Review Board or Research Ethics Committee. Demographic variables as well as maternal lifestyle behaviors during pregnancy are collected as part of the TEDDY study; these factors were taken into consideration when examining the relationship between LE, PD, RP, and maternal anxiety about the baby's T1D risk.

Study population

The study population consisted of all families who completed a TEDDY study visit when the baby was 6 months of age (window 4.5–7.5 months of age) as of 30 June 2011 (n = 8133); a small sample of mothers failed to complete the 6-month study questionnaires (n = 521) and were excluded, leaving 7612 families for analysis. Of these, most came from the GP (n = 6786) with no history of T1D but 826 of participating babies had an FDR with T1D.

Sociodemographic and maternal life style measures

The sociodemographic measures included in the analyses were TEDDY country of residence (USA, Finland, Germany, Sweden); child's gender (male, female); child's ethnic minority status (USA: the TEDDY child's mother's first language is not English or the mother was not born in the USA 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 an 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 persons in the household divided by the number of rooms in the household). Because the crowding variable was skewed, it was rescored to normalize the distribution (0–0.49 = 1; 0.50–0.59 = 2; 0.60–0.75 = 3; 0.76–1.00 = 4; >1.00 = 5).

We also included maternal lifestyle behaviors during pregnancy as control variables in our analysis: smoking (yes/no); working all three trimesters vs. reducing work hours or not working at all; and complete abstinence from alcohol during the last trimester of the mother's pregnancy (yes/no).

Maternal anxiety about the child's T1D risk

Maternal anxiety about the child's T1D risk was measured at 6 months by a 6-item scale [State Anxiety Inventory (SAI)] (5, 10, 12–14) adapted from the state component of the STAI (9). Mothers were asked to respond to the SAI while thinking specifically about their baby's risk for T1D and their 6-item scores were converted into total scores comparable to the 20-item scores obtained using the STAI. The alpha coefficient for the SAI at 6 months in the TEDDY sample is 0.901. Because of skewed SAI scores, they were rescored to normalize the distribution ($<23 = 0$, $23–29 = 1$, $30–37 = 2$, $38–45 = 3$, $\geq 46 = 4$).

Life stress

At each TEDDY visit, mothers were given a list of LE that might have happened to them and a list of LE that might have happened to their child. The mother indicated whether she or her child had experienced any of the events and if so, she was asked to rate the event's impact as very bad, bad, good, or no impact. Mothers were asked if another event had occurred

not on the lists and if so, they were asked to describe the event and rate its impact. Events on the parent list included 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. Events on the child list included serious illness/injury, hospitalization, separation from parent, moved, new sibling, started daycare, changed daycare, and new step-parent. Only events with very bad or bad impact were considered. Negative LE were further separated into two categories such as loss/loss threatening LE (disease/injury, hospitalization, death in family, and separation/divorce) and interpersonal LE (job-related, financial difficulties, violence, serious conflicts, legal conflicts, moved, and changed family composition). The total number of negative LE, the total number of loss/loss threatening LE, and the total number of interpersonal negative LE reported in the first 6 months of TEDDY visit was calculated. Because 67% of the sample reported no negative LE, this variable was considered as a categorical variable in all data analyses.

Postpartum depression

Maternal PD was assessed at the 6-month visit by the Edinburgh Postnatal Depression Scale (EPDS) (42, 43). The alpha coefficient for the EPDS in the TEDDY sample was 0.844. Because the EPDS scores were skewed, they were rescored to normalize the distribution ($0=0$, $1–2=1$, $3–5=2$, $6–8=3$, $9–12=3$, $13–27=4$). We considered both the EPDS normalized total score, and whether the score was equal or above the clinical cut-off ($\geq$13) (38, 42, 43).

Risk perception

RP was measured by the question: 'Compared to other children, do you think your child's risk for developing diabetes is much lower, somewhat lower, about the same, somewhat higher, much higher'. The mother's perception of the child's risk for developing diabetes was scored as accurate when she indicated the child's T1D risk was higher or much higher than other children's T1D risk, and was scored as inaccurate if she indicated the child's T1D risk was the same or somewhat lower or much lower than other children's.

Statistical analyses

Chi-square was used to test for differences in proportions between categories and Wald tests using simple linear regression models were used to test for differences in means across countries. Multiple linear regressions were used to develop a model of the association between negative LE, EPDS, RP, and maternal SAI about the child's T1D risk, controlling for country and other sociodemographic and lifestyle variables. Data were available on at least 94.3% of all relevant variables and all multiple regression models retained at least 88.3% of the total cohort (n = 7612). Analyses were conducted using the Statistical Analysis System Software (Version 9.2, SAS Institute, Cary, NC, USA).

Results

Sociodemographic and maternal life style measures by country

The composition by demographic and lifestyle factors differed significantly between the countries (Table 1); only gender of children was distributed proportionally. In the USA, mothers were more likely to be unmarried or not living with the father, have multiple children and to work during pregnancy. The percentage of minority children is also highest. In Europe, mothers were likely to be living in more crowded households than in the USA. In Germany, the percentage of FDR children were highest, maternal age at birth was higher and more mothers reported smoking and drinking alcohol during pregnancy than in the other TEDDY countries. In USA, fewest mothers smoked and alcohol consumption was least likely in Swedish moms. In USA and Finland, about two third of mothers got a higher education, in Sweden and Germany the percentage was lower. In Germany, a graduated trade school education and some college/university was more frequent (50%), basic primary education was more likely in Swedish moms in comparison to other TEDDY sites.

Anxiety about the child's T1D risk, negative life events, postpartum depression, and risk perception

Significant country differences emerged for all four variables (Table 2). SAI scores were highest in German and US mothers and lowest in Finland.

Overall, 19.6% of mothers reported a loss/loss threatening LE, 19.4% reported an interpersonal negative LE, and in total 33% of mothers reported negative LE in either category. Overall, more US mothers reported one or more negative LE compared to mothers in the European TEDDY countries. Types of negative LE reported by country also differed. The USA had the highest rates of both, loss/loss threatening events as well as interpersonal events; Germany had the lowest. The variation in the number of mothers reporting interpersonal negative LE is much greater than that for loss/loss threatening events. Job-related and financial LE, moving and changed family

Table 1. Sociodemographic and maternal lifestyle factors by country

Sociodemographic variables	USA n (%) or M (SD)	Finland n (%) or M (SD)	Germany n (%) or M (SD)	Sweden n (%) or M (SD)	All n (%) or M (SD)
Gender of child					
Boy	1583 (50.9)	829 (51.0)	265 (50.8)	1194 (50.8)	3871 (50.9)
Girl	1527 (49.1)	798 (49.0)	257 (49.2)	1159 (49.2)	3741 (49.1)
Child ethnic minority					
No	2034 (69.9)	1502 (97.0)	429 (87.6)	2105 (92.9)	6070 (84.2)
Yes	874 (30.1)	47 (3.0)	61 (12.4)	160 (7.1)	1142 (15.8)
Child has FDR with T1D					
No	2782 (89.5)	1479 (90.9)	323 (61.9)	2202 (93.6)	6786 (89.1)
Yes	328 (10.5)	148 (9.1)	199 (38.1)	151 (6.4)	826 (10.9)
Child is an only child					
No	1810 (62.7)	875 (55.7)	257 (52.4)	1243 (54.8)	4185 (58.0)
Yes	1075 (37.3)	696 (44.3)	233 (47.6)	1024 (45.2)	3028 (42.0)
Maternal age at child's birth (yr)	30.5 (5.7)	30.0 (5.0)	31.6 (4.9)	30.8 (4.7)	30.6 (5.2)
Maternal education					
Basic primary	441 (15.3)	154 (9.8)	65 (13.3)	767 (33.8)	1427 (19.9)
Graduated trade school education/college	720 (25.0)	447 (28.6)	246 (50.3)	389 (17.2)	1802 (25.0)
Higher education	1723 (59.7)	964 (61.6)	178 (36.4)	1111 (49.0)	3976 (55.2)
Married or living status					
Married or living together	2711 (93.8)	1518 (96.7)	473 (96.5)	2213 (97.7)	6914 (95.8)
Single parent	178 (6.2)	52 (3.3)	17 (3.5)	53 (2.3)	300 (4.2)
Maternal lifestlye variables during pregancy					
Working status					
Did not work or reduced work hours	1368 (46.1)	883 (56.7)	302 (58.3)	1245 (54.7)	3798 (51.9)
Worked all three trimesters	1599 (53.9)	673 (43.3)	216 (41.7)	1030 (45.3)	3518 (48.1)
Smoking during pregnancy					
No	2748 (90.5)	1393 (87.2)	425 (82.7)	2038 (87.7)	6604 (88.4)
Yes	287 (9.5)	204 (12.8)	89 (17.3)	287 (12.3)	867 (11.6)
Alcohol during pregnancy					
No	2345 (76.6)	1331 (82.5)	381 (73.1)	2131 (90.8)	6188 (82.0)
Yes	715 (23.4)	283 (17.5)	140 (26.9)	217 (9.2)	1355 (18.0)
Household crowding*	1.6 (1.3)	2.5 (0.9)	2.4 (1.1)	2.1 (1.1)	2.0 (1.2)

FDR, first degree relative; T1D, type 1 diabetes.
Except for child's gender ($p = 0.99$), all variables significantly differed across countries ($p < 0.0001$).
*Normalized scores.

composition was more frequently reported in the USA than in the European TEDDY countries.

Overall, the prevalence of PD (EPDS scores ≥ 13) was 9% for the total sample. However, significant country differences arose. Germany showed the highest prevalence of PD (11.3%) and Sweden the lowest (7.3%). Considering the normalized scores, mothers from Finland had the highest EPDS means and Swedish mothers the lowest.

Although communication of the child's increased T1D risk was given to the child's parents orally and in writing, risk underestimation was high. In Finland and Germany, about a third of mothers underestimated their child's risk in USA and in Sweden the percentages were even higher (40.1% and 46.3%, respectively).

Predictors of maternal anxiety about the child's T1D risk

We used a multiple regression approach to predict mother's anxiety. In order to control for mediating or confounding variables (44, 45), we built several models. The first model includes country and the sociodemographic factors; only significant predictors were retained. The second model added negative loss/loss threatening and interpersonal LE as predictor variables (Table 3). The third model added the EPDS clinical cut-off score and the fourth and final model added RP as a predictor variable (Table 3).

Country was a significant predictor in all four models; US and German moms had higher SAI scores than Finnish and Swedish mothers. Sociodemographic variables that were predictors of SAI scores in all four models included child ethnic minority and FDR status, maternal age, education, and maternal alcohol consumption and smoking during pregnancy. Mothers of ethnic minority children, of FDR children, who were younger and less educated and who never drank alcohol but smoked during pregnancy, had higher SAI scores. Child's gender, only child status, household crowding, and mothers' work status during pregnancy were not associated with SAI scores. Marital status

Table 2. Maternal SAI scores, number of negative LE and types of LE reported at 6 months by country, EPDS scores and risk perception

	TEDDY country				
	USA M (SD) or n (%)	Finland M (SD) or n (%)	Germany M (SD) or n (%)	Sweden M (SD) or n (%)	All M (SD) or n (%)
Maternal anxiety (SAI)	n = *3072*	n = *1626*	n = *519*	n = *2338*	n = *7555*
Mean (SD) SAI score	37.6 (10.6)	32.0 (8.3)	39.4 (10.9)	35.6 (9.0)	35.9 (10.0)
Mean (SD) normalized SAI score	2.16 (1.3)	1.52 (1.0)	2.39 (1.2)	1.96 (1.1)	1.98 (1.2)
Life events (LE)	n= *3006*	n = *1610*	n = *494*	n= *2325*	n = *7434*
≥1 LE with negative impact: N (%)	1268 (42.2)	394 (24.5)	90 (18.2)	702 (30.2)	2454 (33.0)
	LE yes n (%)	*LE yes* n (%)	*LE yes* n (%)	*LE yes* n (%)	*LE yes* n (%)
Loss or loss threatening events					
Disease, injury, hospitalization (A)	453 (15.1)	144 (8.9)	36 (7.3)	321 (13.8)	954 (12.8)
Death and significant loss (B)	150 (5.0)	46 (2.9)	12 (2.4)	106 (4.6)	314 (4.2)
Separation and divorce (C)	148 (4.9)	95 (5.9)	16 (3.2)	78 (3.4)	337 (4.5)
Overall (categories A, B, or C)	690 (23.0)	260 (16.1)	59 (11.9)	448 (19.3)	1457 (19.6)
Interpersonal events					
Job related (D)	256 (8.5)	29 (1.8)	6 (1.2)	76 (3.3)	367 (4.9)
Financial difficulties (E)	322 (10.7)	51 (3.2)	0 (0.0)	48 (2.0)	421 (5.7)
Violence, serious conflict, legal conflict (F)	229 (7.6)	66 (4.1)	11 (2.2)	145 (6.2)	451 (6.1)
Moved, changed family composition (G)	375 (12.5)	68 (4.2)	24 (4.9)	127 (5.5)	594 (8.0)
Overall (categories D, E, F, or G)	885 (29.4)	188 (11.7)	39 (7.9)	341 (14.7)	1453 (19.5)
Postpartum depression (EDPS)	n = *3105*	n = *1627*	n = *522*	n = *2352*	n = *7606*
Mean (SD) EPDS score	6.33 (4.4)	6.53 (4.4)	6.11 (4.7)	5.72 (4.2)	6.17 (4.4)
Mean (SD) normalized EPDS score	2.62 (1.4)	2.70 (1.3)	2.52 (1.4)	2.43 (1.3)	2.57 (1.4)
Clinical cut-off score ≥13: n (%)	296 (9.5)	151 (9.3)	62 (11.9)	172 (7.3)	681 (9.0)
Risk perception (RP)	n= *3095*	n = *1625*	n = *521*	n = *2343*	n = *7584*
Underestimation	1242 (40.1)	461 (28.4)	153 (29.4)	1084 (46.3)	2940 (38.8)
Accurate	1853 (59.9)	1164 (71.6)	368 (70.6)	1259 (53.7)	4644 (61.2)

SAI, state anxiety inventory; LE, life events; EPDS, Edinburgh Postnatal Depression Scale; RP, risk perception
SAI scores, number (%) of mothers reporting negative LE and EPDS scores differed significantly across the countries ($p < 0.0001$). The frequency of mothers reporting loss or loss threatening events or interpersonal events differed signficantly across the countries ($p < 0.0001$).

lost significance in the final model. Negative LE were significant predictors of SAI scores, but only interpersonal LE stayed significant when EPDS clinical cut-off score was introduced in the analysis (final model). When EPDS normalized score was used instead, smoking during pregnancy and interpersonal LE lost significance in the final model (data not shown). RP had an independent contribution to mother's anxiety.

Discussion

In the framework of T1D research, LE have typically been collected retrospectively from one to several years before diabetes manifestation (20), 1 yr or longer before the appearance of autoantibodies (12, 21–23). In TEDDY, parents are asked about LE at each TEDDY visit, using a recall window of the preceding 3 months in an effort to minimize the impact of recall bias inherent in prior studies (46).

There are a few studies comparing life stress across different countries and those that do exist have focused on cardiovascular disease (33) or posttraumatic stress disorder (PTSD) (34). To our knowledge, TEDDY is the first study to prospectively collect recent LE under comparable conditions in an international cohort of families with small children. In the TEDDY cohort as a whole, 33% of mothers reported one or more negative LE at the baby's 6-month TEDDY visit. However, prevalence rates varied from a high of 42% in the USA to a low of 18% in Germany. Country differences were greatest for interpersonal negative LE; 29% of US moms reported such events compared to only 8% of German mothers. Moving or changing family composition, job-related and financial difficulties were particularly pronounced in the USA.

The prevalence of PD worldwide is currently estimated at 10–15% (36, 38, 40), with considerable differences between countries (39, 40) depending on the clinical cut-off scores (between ≥9 and ≥13) (39) and the time of measurement (39, 40). Consistent with other newborn screening studies (19, 47), EPDS scores in TEDDY were in the normal range, with an overall PD prevalence rate of 9%, varying from 12% in Germany to 7% in Sweden. Affonsoa et al. (40) reported similar

Table 3. Mulitple linear regression results predicting maternal SAI about the child's T1DM risk

Factors	Total or mean N or mean (SD)	Sociodemographic factors as predictors of SAI scores β	95% CI	p-value	Sociodemographic factors and negative LE as predictors of SAI scores β	95% CI	p-value
Country of residence							
USA	2624	0.00	Ref		0.00	Ref	
Finland	1499	−4.67	−5.29 to 4.05		−4.34	−5.97 to −3.72	
Germany	457	1.56	0.59 to 2.53		1.99	1.01 to 2.97	
Sweden	2182	−1.46	−2.02 to 0.89	<0.001	−1.19	−1.77 to −0.62	<0.001
Child ethnic minority							
Yes	989	0.00	Ref		0.00	Ref	
No	5773	−3.79	−4.46 to 3.12	<0.001	−3.76	−4.43 to 3.09	<0.001
Child has FDR with T1DM							
No	6029	0.00	Ref		0.00	Ref	
Yes	733	2.91	2.17 to 3.65	<0.001	2.89	2.15 to 3.63	<0.001
Maternal age at child's birth (yr)	30.7 (5.1)	−0.07	−0.11 to 0.02	0.006	−0.07	−0.11 to −0.02	0.006
Maternal education							
Basic primary	1328	0.00	Ref		0.00	Ref	
Graduated trade school/college	1669	−1.39	−2.10 to 0.69		−1.39	−2.10 to −0.69	
Higher education	3765	−1.79	−2.44 to 1.13	<0.001	−1.73	−2.38 to −1.08	<0.001
Married or living together							
No	268	1.32	0.15 to 2.50		1.10	−0.07 to 2.72	
Yes	6494	0.00	Ref	0.027	0.00	Ref	0.066
Smoking during pregnancy							
No	6022	0.00	Ref		0.00	Ref	
Yes	740	0.64	−0.11 to 1.38	0.092	0.76	0.01 to 1.50	0.048
Alcohol during pregnancy							
No	4438	0.00	Ref		0.00	Ref	
Yes	2324	−0.61	−1.10 to 0.13	0.012	−0.65	−1.13 to −0.17	0.008
Loss or loss theatening negative LE							
No	5472	—	—	—	0.00	Ref	
Yes	1290	—	—	—	0.77	0.20 to 1.34	0.008
Interpersonal negative LE							
No	5486	—	—	—	0.00	Ref	
Yes	1276	—	—	—	1.65	1.06 to 2.23	<0.001
EPDS score ≥ 13							
No	6188	—	—	—	–	—	—
Yes	574	—	—	—	—	—	—
Risk perception							
Underestimation	2572	—	—	—	—	—	—
Accurate	4190	—	—	—	—	—	—

Factors	Total or mean N or mean (SD)	Sociodemographic factors, negative LE and EPDS as predictors of SAI scores β	95% CI	p-value	Sociodemographic factors, negative LE, EPDS, and RP as predictors of SAI scores β	95% CI	p-value
Country of residence							
USA	2624	0.00	Ref		0.00	Ref	
Finland	1499	−4.50	−5.12 to −3.88		−4.77	−5.39 to −4.16	
Germany	457	1.76	0.79 to 2.73		1.59	0.64 to 2.55	
Sweden	2182	−1.20	−1.76 to −0.63	<0.001	−1.09	−1.65 to −0.53	<0.001
Child ethnic minority							
Yes	989	0.00	Ref		0.00	Ref	
No	5773	−3.58	−4.25 to −2.92	<0.001	−3.87	−4.53 to 3.21	<0.001
Child has FDR with T1DM							
No	6029	0.00	Ref		0.00	Ref	
Yes	733	2.83	2.10 to 3.56	<0.001	2.11	1.37 to 2.84	<0.001
Maternal age at child's birth (yr)	30.7 (5.1)	−0.07	−0.11 to −0.02	0.005	−0.07	−0.12 to −0.03	0.002

Table 3. Continued

Factors	Total or mean N or mean (SD)	Sociodemographic factors, negative LE and EPDS as predictors of SAI scores β	95% CI	p-value	Sociodemographic factors, negative LE, EPDS, and RP as predictors of SAI scores β	95% CI	p-value
Maternal education							
Basic primary	1328	0.00	Ref		0.00	Ref	
Graduated trade school/college	1669	−1.27	−1.97 to −0.58		−1.49	−2.18 to −0.80	
Higher education	3765	−1.51	−2.16 to −0.86	<0.001	−2.07	−2.72 to −1.43	<0.001
Married or living together							
No	268	0.79	−0.37 to 1.95		0.81	0.34 to 1.96	
Yes	6494	0.00	Ref	0.183	0.00	Ref	0.168
Smoking during pregnancy							
No	6022	0.00	Ref		0.00	Ref	
Yes	740	0.73	−0.01 to 1.47	0.054	0.78	−0.05 to 1.52	0.036
Alcohol during pregnancy							
No	4438	0.00	Ref		0.00	Ref	
Yes	2324	−0.73	−1.21 to −0.26	0.002	−0.81	−1.28 to −0.34	0.001
Loss or loss theatening neg LE							
No	5472	0.00	Ref		0.00	Ref	
Yes	1290	0.52	−0.05 to 1.08	0.073	0.44	−0.12 to 1.00	0.125
Interpersonal negative LE							
No	5486	0.00	Ref		0.00	Ref	
Yes	1276	1.17	0.59 to 1.76	<0.001	1.09	0.52 to 1.67	<0.001
EPDS score ≥13							
No	6188	0.00	Ref		0.00	Ref	
Yes	574	5.10	4.30 to 5.90	<0.001	5.02	4.23 to 5.82	<0.001
Risk perception							
Underestimation	2572	—	—	—	0.00	Ref	
Accurate	4190	—	—	—	2.80	2.34 to 3.27	<0.001

T1D, type 1 diabetes; SAI, state anxiety inventory; LE, life event(s); EPDS, Edinburgh Postnatal Depression Scale; RP, risk perception; FDR, first degree relative.
Child's gender, only child status, household crowding, and mothers' work status during pregnancy were not associated with SAI scores. When EPDS normalized scores were used smoking during pregnancy and interpersonal LE lost significance.

results, with Sweden having the lowest rate of PD, followed by Finland and the USA (Germany was not included in the Affonsoa study). Halbreich et al. (39) observed slightly higher percentages but nearly the same country order of PD measured by EPDS with lower clinical cut-off scores (from ≥10 to ≥11) from 17.7% in Germany, 16.6% in Finland, 15.4% in the USA, and 12.3% in Sweden.

Mothers' reactions to their child's T1D risk varied significantly by TEDDY country. Mothers in Germany and the USA reported the highest anxiety scores and Finland reported the lowest. Germany had the highest percentage of FDR babies in the study; mothers of FDR babies often exhibit higher levels of anxiety (5, 10, 12, 19, 47). However, the higher anxiety rates seen in the USA and Germany remained, even with FDR status in the model. Anxiety about the baby's risk to get T1D is comparable to anxiety of pregnant women and working women. Parents of islet cell antibodies (ICA) plus children and pregnant women undergoing amniocentesis show higher anxiety (10, 12). Although Finland has the highest incidence of T1D in the world (16) a number of studies documented low rates of anxiety in Finish people (5, 6, 13, 17). Because T1D is so common in Finland, families might view the disease as less anxiety provoking (5, 17). Consistent with prior literature, younger mothers who were less educated and who had an ethnic minority child reported greater anxiety about the child's T1D risk (5, 10, 14). Mothers who reported drinking alcohol during pregnancy reported lower anxiety scores. We suspect that alcohol use may be one way these mothers manage their anxiety; unfortunately, we did not collect information on alcohol use after the birth of the baby. Smoking during pregnancy was related to higher anxiety; smoking is often used as a coping strategy in response to stress and anxiety (48).

In addition to these sociodemographic predictors of maternal anxiety about her child's TID risk, LE, PD, and maternal RP were all strongly related to mothers SAI scores at the 6-month TEDDY visit. These findings are important in a number of respects. First, it was possible to collect LE in an international cohort, under very similar conditions, considering a window of 3 months, minimizing recall bias. Second, the opportunity to examine the relationship between

LE, PD, RP, and anxiety about a child's risk for disease in an international cohort is rare and informative. We were able to elucidate important country differences and identify other sociodemographic factors associated with maternal anxiety about the child's risk for T1D. More importantly, we were able to model the relationship between LE, PD, RP, and anxiety, with the effects of country and other sociodemographic and lifestyle factors controlled. As expected, we found that life stress has a strong association with anxiety about the baby's diabetes risk. However, the association between loss/loss threatening LE and maternal anxiety about the child's T1D risk was reduced when PD was introduced in the analysis. The results indicate that the relationship between loss/loss threatening LE, to a lesser extent interpersonal LE and maternal anxiety about the baby's risk is mediated by PD; such as negative LE increase the risk of PD which in turn is associated with higher levels of maternal anxiety about the child's T1D risk. Accurate RP about the child's risk was an independent predictor of maternal anxiety. The differential effects of mother's anxiety and depression symptoms in response to RP as reported earlier (5, 10, 19) could not be observed in TEDDY.

If mothers scored $\geq$13, the clinical EPDS cut-off score, TEDDY nurses recommended seeing a psychological counselor. Family adversities like distress in mothers in infancy predict children's depression and anxiety in adolescence; early interventions are suggested to reduce not only mother's distress but also long-term consequences for children (49). Mothers with accurate RPs experiencing high anxiety about their child's risk were more likely to withdraw from the study. A tailored intervention has been introduced to prevent them from drop out (13).

We acknowledge that the TEDDY population is a highly motivated sample of educated mothers who have volunteered to participate in a longitudinal study with a demanding protocol. Consequently, our study findings may not replicate in other populations.

Another limitation is the cross-sectional nature of the study, with self-report measures collected at the same point in time (the TEDDY 6-month study visit). There is a risk of inflated associations between variables because of shared method variance and the causal direction of significant associations cannot be confirmed. For example, although we suspect that negative LE reported in the 3-month window prior to the study visit led to higher reports of maternal PD and anxiety about the child's T1D risk, one cannot rule out the possibility that mothers who are more anxious or depressed are more likely to recall a negative LE in the prior 3 months, whereas mothers who are not depressed or anxious simply do not remember such events. We believe this is unlikely as all participants were prompted with a list of negative LE – most of which would be difficult to 'forget' when prompted (e.g., serious illness, getting a divorce, losing a job). Nevertheless, prospective studies are needed to confirm the findings reported here. As TEDDY is a longitudinal study in which LE data is collected at each TEDDY visit, it holds great promise for discerning the impact of negative LE on study outcomes – both psychological (e.g., anxiety and depression) and physical (child illness and autoantibody development). The findings reported here strongly suggest that future prospective studies are warranted.

Acknowledgements

This study was funded by DK 63829, 63861, 63821, 63865, 63863, 63836, 63790 and UC4DK095300 and Contract No. HHSN267 200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC).

References

1. D.I.A.M.O.N.D. Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med 2006: 23: 857–866.
2. Patterson CC, Dahlquist GG, Gyürüs E et al. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009: 373: 2027–2033.
3. S.E.A.R.C.H. for Diabetes in Youth Study Group, Liese AD, D'Agostino RB et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics 2006: 118: 1510–1518.
4. Gale EAM. The rise of childhood type 1 diabetes in the 20th Century. Diabetes 2002: 51: 3353–3361.
5. Johnson SB. Psychological impact of screening and prediction in type 1 diabetes. Curr Diab Rep 2011: 11: 454–459.
6. Goldstein E, Hermann R, Renfors TJ et al. From genetic risk awareness to overt type 1 diabetes: parental stress in a placebo-controlled prevention trial. Diabetes Care 2009: 32: 2181–2183.
7. Ross LF. Minimizing risk: the ethics of predictive diabetes mellitus screening research in newborns. Arch Pediatr Adolesc Med 2003: 157: 89–95.
8. Roth R. Psychological and ethical aspects of prevention trials. J Pediatr Endocrinol Metab 2001: 14 (Suppl. 1): 669–674.
9. Spielberger CD, Gorsuch RL, Lushene R. Test Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.
10. Johnson SB, Baughcum AE, Carmichael SK, She J-X, Schatz DA. Maternal anxiety associated with newborn genetic screening for type 1 diabetes. Diabetes Care 2004: 27: 392–397.

11. Ludvigsson J, Gustafsson-Stolt U, Liss PE, Svensson T, and the ABIS Study Group. Mothers of children in ABIS, a population-based screening for prediabetes, experience few ethical conflicts and have a positive attitude. Ann N Y Acad Sci 2002: 958: 376–381.
12. Hummel M, Ziegler AG, Roth R. Psychological impact of childhood islet autoantibody testing in families participating in the BABYDIAB study. Diabetic Med 2004: 21: 324–328.
13. Johnson SB, Lee H-S, Baxter J et al. The Environmental Determinants of Diabetes in the Young (TEDDY) study: predictors of early study withdrawal among participants with no family history of type 1 diabetes. Pediatr Diabetes 2011: 12: 165–171.
14. Baxter J, Vehik K, Johnson SB et al. Differences in recruitment and early retention among ethnic minority participants in a large pediatric cohort: the TEDDY Study. Contemp Clin Trials 2012: 33: 633–640.
15. Simonen P, Korhonen T, Simell T et al. Parental reactions to information about increased genetic risk of type 1 diabetes mellitus in infants. Arch Pediatr Adolesc Med 2006: 160: 1131–1136.
16. Onkamo P, Vaanenen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of type 1 diabetes - the analysis of data on published incidence trends. Diabetologia 1999: 42: 1395–1403.
17. Johnson SB, Lernmark B, Baxter J et al. At-risk for type 1 diabetes (T1D): parent anxiety in response to newborn genetic screening results in The Environmental Determinants of Diabetes in the Young (TEDDY) study. Diabetes 2007: 56 (Suppl. 1): A498.
18. Lernmark B, Johnson SB, Vehik K et al. Enrollment experiences in a pediatric longitudinal observational study: The Environmental Determinants of Diabetes in the Young (TEDDY) study. Contemp Clin Trials 2011: 32: 517–523.
19. Hood K, Johnson SB, Carmichael SK, Laffel LM, She J, Schatz DA. Depressive symptoms in mothers of infants identified as genetically at risk for type 1 diabetes. Diabetes Care 2005: 28: 1898–1903.
20. Robinson N, Fuller JH. Role of life events and difficulties in the onset of diabetes mellitus. J Psychosom Res 1985: 29: 583–591.
21. Sepa A, Ludvigsson J. Psychological stress and the risk of diabetes-related autoimmunity: a review article. Neuroimmunomodulation 2006: 13: 301–308.
22. Sepa A, Frodi A, Ludvigsson J. Mothers' experiences of serious life events increase the risk of diabetes-related autoimmunity in their children. Diabetes Care 2005: 28: 2394–2399.
23. Karlén J, Faresjö T, Ludvigsson J. Could the social environment trigger the induction of diabetes related autoantibodies in young children? Scand J Public Healt 2012: 40: 177–182.
24. Hammen C. Stress and depression. Annu Rev Clin Psychol 2005: 1: 293–319.
25. Risch N, Herrell R, Lehner T et al. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression - a meta-analysis. JAMA 2009: 301: 2462–2471.
26. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry 1999: 156: 837–841.
27. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of intracategory variability. Psychol Bull 2006: 132: 477–495.
28. Kendler KS, Thornton LM, Prescott CM. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry 2001: 158: 587–593.
29. Spinhoven P, Roelofs K, Hovens JG et al. Personality, life events and the course of anxiety and depression. Eur J Pers 2011: 25: 443–452.
30. Matthev S, Barnett B, Howie P, Kavanagh DJ. Diagnosing postpartum depression in mothers and fathers: whatever happened to anxiety? J Affect Disord 2003: 74: 139–147.
31. Vines AI, Myduc T, Esserman D, Baird DD. A comparison of the occurrence and perceived stress of major life events in black and white women. Women Health 2009: 49: 368–380.
32. Hatch SL, Dohrenwend BP. Distribution of traumatic and other stressful life events by race/ethnicity, gender, SES and age: a review of the research. Am J Commun Psychol 2007: 40: 313–332.
33. Rosengren A, Hawken S, Ôunpuu S et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control. Lancet 2004: 364: 953–962.
34. Dobricki M, Komproe IH, de Jong JTVM, Maercker A. Adjustment disorders after severe life-events in four postconflict settings. Soc Psychiatry Psychiatr Epidemiol 2009: 45: 39–46.
35. Gibson J, McKenzie-McHarg K, Shakespeare J, Price J, Gray R. A systematic review of studies validating the Edinburgh Postnatal Depression Scale in antepartum and postpartum women. Acta Psychiatr Scand 2009: 119: 350–364.
36. Gorman LL, O'Hara MW, Figueiredo B et al. Adaptation of the structured clinical interview for DSM IV disorders for assessing depression in women during pregnancy and post-partum across countries and cultures. Br J Psychiatr Suppl 2004: 184 (Suppl. 46): 17–23.
37. Segre LS, O'Hara MW, Arndt S, Stuart S. The prevalence of postpartum depression. The relative significance of three social status indices. Soc Psychiatry Psychiatr Epidemiol 2007: 42: 316–321.
38. Yonkers KA, Ramin M, Rush AJ et al. Onset and persistence of postpartum depression in an inner-city maternal health clinic system. Am J Psychiatry 2001: 158: 1856–1863.
39. Halbreich U, Karkun S. Cross-cultural and social diversity of prevalence of postpartum depression and depressive symptoms. J Affect Disord 2006: 91: 97–111.
40. Affonsoa DD, Deb AK, Horowitzc JA, Mayberryd LJ. An international study exploring levels of post-partum depressive symptomatology. J Psychosom Res 2000: 49: 207–216.
41. The TEDDY Study Group. The environmental determinants of diabetes in the young (TEDDY) study: study design. Pediatr Diabetes 2007: 8: 286–298.
42. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression development of the 10-item

edinburgh postnatal depression scale. Br J Psychiatr 1987: 150: 782–786.
43. Wisner KL, Parr BL, Piontek CM. Postpartum depression. N Engl J Med 2002: 347: 194–199.
44. Baron RM, Kenny DA. The moderator-mediator distinction in social psychological research. Conceptual, strategic and statistical considerations. J Pers Soc Psychol 1986: 51: 1173–1182.
45. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. Prev Sci 2000: 1: 173–181.
46. Hassan E. Recall bias can be a threat to retrospective and prospective research designs. Int J Epidemiol 2006: 3. doi:10.5580/2732.
47. Aas KK, Tambs K, Kise MS, Magnus P, Rønningen KS. Genetic testing of newborns for type 1 susceptibility: a prospective cohort study on effects on maternal mental health. BMC Med Genet 2010: 11: 112–121.
48. Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychol Bull 2003: 129: 270–304.
49. Karevold E, Røysamb E, Ystom E, Mathiesen KS. Predictor and pathway from infancy to symptoms of anxiety and depression in early adolescence. Dev Psychol 2009: 45: 1051–1060.

Appendix

The Teddy Study Group. Colorado Clinical Center: Marian Rewers, MD, PhD, PI[1,4,6,10,11], Katherine Barriga[12], Kimberly Bautista[12], Judith Baxter[9,12,15], George Eisenbarth, MD, PhD, Nicole Frank[2], Patricia Gesualdo[2,6,12,14,15], Michelle Hoffman[12,13,14], Lisa Ide, Rachel Karban[12], Edwin Liu, MD[13], Jill Norris, PhD[2,12], , Kathleen Waugh[7,12,15] Adela Samper-Imaz, Andrea Steck, MD, University of Colorado, Anschutz Medical Campus, Barbara Davis Center for Childhood Diabetes.

Georgia/Florida Clinical Center: Jin-Xiong She, PhD,PI[1,3,4,11], Desmond Schatz, MD*[4,5,7,8], Diane Hopkins[12], Leigh Steed[6,12,13,14,15], Jamie Thomas*[12], Katherine Silvis[2], Michael Haller, MD*[14], Meena Shankar*[2], Kim English, Richard McIndoe, PhD, Haitao Liu, MD†, John Nechtman†, Joshua Williams, Gabriela Foghis, Stephen W. Anderson, MD^, Georgia Health Sciences University, *University of Florida, †Jinfiniti Biosciences LLC, Augusta, GA, ^Pediatric Endocrine Associates, Atlanta, GA.

Germany Clinical Center: Anette G. Ziegler, MD, PI[1,3,4,11], Alexandra Achenbach PhD*[12], Heike Boerschmann[14], Ezio Bonifacio, PhD*[5], Melanie Bunk, Johannes Försch, Lydia Henneberger[2,12], Michael Hummel, MD[13], Sandra Hummel, PhD[2], Gesa Joslowski[¥2], Mathilde Kersting PhD[¥2], Annette Knopff[7], Nadja Kocher, Sibylle Koletzko, MD[¶13], Stephanie Krause, Claudia Matzke, Astrid Mittermeier, Claudia Peplow*[12], Maren Pflüger[6], Claudia Ramminger, Elisabeth Strauss, Sargol Rash-Sur, Roswith Roth, PhD[9], Julia Schenkel, Joanna Stock, Katja Voit, Christiane Winkler PhD[2,12,15], Anja Wosch, Forschergruppe Diabetes e.V. at Helmholtz Zentrum München, *Center for Regenerative Therapies, TU Dresden, ¶Dr. von Hauner Children´s Hospital, Department of Gastroenterology, Ludwig Maximillians University Munich, ¥Research Institute for Child Nutrition, Dortmund.

Finland Clinical Center: Olli G. Simell, MD, PhD, PI[¥^1,4,11,13], Heikki Hyöty, MD, PhD*[±6], Jorma Ilonen, MD, PhD[¥¶3], Mikael Knip, MD, PhD*[±], Maria Lonnrot, MD, PhD*[±6], Elina Mantymaki[¥^], Juha Mykkänen, PhD[^¥], Kirsti Nanto-Salonen, MD, PhD[¥^12], Tiina Niininen[±]*, Mia Nyblom*[±], Anne Riikonen*[±2], Minna Romo[¥^], Barbara Simell[¥^12,15], Tuula Simell, PhD[¥^9,12], Ville Simell[^¥13], Maija Sjöberg[¥^12,14], Aino Stenius[μ¤], Eeva Varjonen[¥^], Riitta Veijola, MD, PhD [μ¤], Suvi M. Virtanen, MD, PhD*[§2±]. ¥University of Turku, *University of Tampere, μUniversity of Oulu, ^Turku University Hospital, ±Tampere University Hospital, ¤Oulu University Hospital, §National Institute for Health and Welfare, Finland, ¶University of Kuopio.

Sweden Clinical Center: Åke Lernmark, PhD, PI[1,3,4,8,10,11,15], Daniel Agardh, MD, PhD[13], Peter Almgren, Eva Andersson, Carin Andrén-Aronsson[2,13], Maria Ask, Ulla-Marie Karlsson, Corrado Cilio, MD[5], PhD, Jenny Bremer, Emilie Ericson-Hallström, Thomas Gard, Joanna Gerardsson, Gertie Hansson[12,14], Monica Hansen, Susanne Hyberg, Rasmus Håkansson, Fredrik Johansen, Linda Jonsson, Helena Larsson MD, PhD[14], Barbro Lernmark, PhD[9,12], Maria Markan, Theodosia Massadakis, Jessica Melin, Maria Månsson-Martinez, Anita Nilsson, Kobra Rahmati, Monica Sedig Järvirova, Sara Sibthorpe, Birgitta Sjöberg, Anna Skogberg, Carina Törn, PhD[3,15], Anne Wallin, Åsa Wimar, Sofie Åberg. Lund University.

Washington Clinical Center: William A. Hagopian, MD, PhD, PI[1,3,4, 5, 6,7,11,13, 14], Xiang Yan, MD, Michael Killian[6,7,12,13], Claire Cowen Crouch[12,14,15], Kristen M. Hay[2], Stephen Ayres, Carissa Adams, Brandi Bratrude, David Coughlin, Greer Fowler, Czarina Franco, Carla Hammar, Diana Heaney, Patrick Marcus, Arlene Meyer, Denise Mulenga, Elizabeth Scott, Jennifer Skidmore, Joshua Stabbert, Viktoria Stepitova, Nancy Williams. Pacific Northwest Diabetes Research Institute.

Pennsylvania Satellite Center: Dorothy Becker, MD, Margaret Franciscus[12], MaryEllen Dalmagro-Elias[2], Ashi Daftary, MD, Children's Hospital of Pittsburgh of UPMC.

Data Coordinating Center: Jeffrey P. Krischer, PhD, PI[1,4,5,10,11], Michael Abbondondolo, Lori Ballard[3,9,14,15], Rasheedah Brown[12,15], Brant

Burkhardt, PhD[5,6], David Cuthbertson, Christopher Eberhard, Steven Fiske, Veena Gowda, David Hadley, PhD[3,13], Hye-Seung Lee, PhD[3,6,13,15], Shu Liu, Kristian Lynch, PhD[9], Jamie Malloy, Cristina McCarthy[12,15], Wendy McLeod[2,5,6,13,15], Laura Smith, PhD[9], Susan Smith[12,15], Ulla Uusitalo, PhD[2,15], Kendra Vehik, PhD[4,5,9,14,15], Earnest Washington, Jimin Yang, PhD, RD[2,15]. University of South Florida.

Project Scientist: Beena Akolkar, PhD[1,3,4,5,7,10,11], National Institutes of Diabetes and Digestive and Kidney Diseases.

Other Contributors: Kasia Bourcier[5], National Institutes of Allergy and Infectious Diseases, PhD Thomas Briese, PhD[6,15], Columbia University, Henry Erlich, PhD[3], Children's Hospital Oakland Research Institute, Suzanne Bennett Johnson, PhD[9,12], Florida State University, Steve Oberste, PhD[6], Centers for Disease Control and Prevention.

Committees: [1]Ancillary Studies, [2]Diet, [3]Genetics [4]Human Subjects/Publicity/Publications, [5]Immune Markers, [6]Infectious Agents, [7]Laboratory Implementation, [8]Maternal Studies, [9]Psychosocial, [10]Quality Assurance, [11]Steering, [12]Study Coordinators, [13]Celiac Disease, [14]Clinical Implementation, [15]Quality Assurance Subcommittee on Data Quality.