My Child Is Islet Autoantibody Positive: Impact on Parental Anxiety

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https://doi.org/10.2337/dc17-0166

OBJECTIVE

To assess parent anxiety in response to genetic and islet autoantibody (IA) testing in children at increased genetic risk for type 1 diabetes followed from birth in The Environmental Determinants of Diabetes in the Young (TEDDY) study.

RESEARCH DESIGN AND METHODS

Parent anxiety about TEDDY children's risk was assessed with the State Anxiety Inventory (SAI). Parents completed the SAI when the child was 3, 6, and 15 months old and annually thereafter. Children were tested for IA every 3 months for 4 years and every 6 months thereafter. Parent SAI scores of 6,799 children followed with IA testing for at least 1 and up to 6 years were examined.

RESULTS

At study inception, parents showed high levels of anxiety in response to their child's increased genetic type 1 diabetes risk; mothers were more anxious than fathers, and parents with diabetes in the family were more anxious than parents with no family history. In response to repeated IA-negative (IA−) test results, parent anxiety declined to normal levels. Anxiety increased in parents faced with an IA-positive (IA+) test result. Parents faced with two or more types of IA+ test results showed particularly high levels of anxiety (all $P < 0.001$).

CONCLUSIONS

Infant genetic screening for type 1 diabetes raises parent anxiety when the child is at increased risk, but anxiety dissipates over time in cases of repeated IA− results. IA+ results heighten parent anxiety, and parents faced with two or more types of IA+ results may experience considerable anxiety for longer periods.

Infants at genetic risk for type 1 diabetes can now be identified at birth and followed for the development of antibodies associated with autoimmune β-cell destruction (1). However, the lack of a current means to prevent the disease raises a number of ethical concerns. Genetic screening for type 1 diabetes risk typically is conducted in young children who do not have the cognitive capacity to make their own decisions. Furthermore, current genetic testing methods provide only a crude estimate of the child's probability of developing type 1 diabetes. Both the uncertainty of a type 1 diabetes diagnosis and the lack of any means to prevent the disease raise concerns about the psychological well-being of parents informed that their child is genetically at risk for type 1 diabetes or is islet autoantibody positive (IA+) (2). Prior studies have used the State Anxiety Inventory (SAI) (3) to document increased parental anxiety in response to such information, suggesting that parent anxiety is initially elevated but dissipates over

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Received 23 January 2017 and accepted 2 June 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0166/-/DC1.

**A complete list of the TEDDY Study Group can be found in the Supplementary Data online.*

time (2,4–7). However, most of these studies monitored anxiety over a relatively short time frame in a small number of parents, usually mothers, drawn primarily from populations with first-degree relatives (FDRs) with this disease. Only one prior study examined parent anxiety before and after a child's IA+ (or IA-negative [IA−]) test result; the number of positive results was small (n = 22), all were FDRs, and no long-term assessment of parent anxiety was done (6).

The Environmental Determinants of Diabetes in the Young (TEDDY) is an international observational cohort study to identify triggers of type 1 diabetes in genetically at-risk children identified at birth. Funded by the National Institutes of Health, TEDDY screened newborns for HLA-conferred type 1 diabetes genetic risk at sites in Finland, Germany, Sweden, and the U.S. Eligible babies were required to join TEDDY before 4.5 months of age and are followed until type 1 diabetes diagnosis or 15 years of age. Primary study outcomes include the development of persistent IA and type 1 diabetes (8).

The TEDDY study is in a unique position to examine the impact of childhood IA test results on parent anxiety because *1*) it measures anxiety on multiple occasions, permitting assessment of parent anxiety before and after IA test results; *2*) anxiety measures are obtained from both mothers and fathers; *3*) large numbers of children have IA+ test results; *4*) children come from the general population (GP) with no family history of type 1 diabetes as well as from FDR families; and *5*) children come from four different countries. Such a robust data set permits us to examine the impact of IA test results across time and whether the impact differs for mothers versus fathers, for GP versus FDR families, and across countries. Furthermore, because TEDDY children's IA status is measured repeatedly, we were able to examine whether repeated IA+ results affects parent anxiety more severely than a single result.

RESEARCH DESIGN AND METHODS

The TEDDY Study

TEDDY was designed to identify triggers of type 1 diabetes in genetically at-risk children. More than 420,000 newborns were screened for type 1 diabetes–related HLA alleles at sites in Finland, Germany, Sweden, and the U.S.; 21,589 were identified as HLA eligible, and 8,676 joined TEDDY before 4.5 months of age. Most participants (89%) had no family history of type 1 diabetes. TEDDY children are seen every 3 months for 4 years and then every 6 months thereafter. At each visit, blood is drawn and dietary, life stressors, and illness records obtained. Questionnaires are used to assess participant psychological functioning. Parents are fully informed of their child's increased type 1 diabetes risk at study onset and of all subsequent IA test results. The TEDDY study was approved by each site's institutional review board.

IA Testing

At each TEDDY visit, blood was drawn and tested for IAs to insulin (IAA), GADA, or insulinoma antigen 2 by radiobinding assay (9,10) at the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver (U.S. sites) or the University of Bristol in the U.K. (European sites). Both laboratories have previously shown high sensitivity and specificity (11) as well as concordance. A TEDDY child must have two consecutive positive test results for the same IA, confirmed in a second laboratory, to be considered as having persistent confirmed IA+ (12). A child with one type of persistent confirmed IA was classified as single persistent IA+. A child with two or more persistent confirmed IAs (e.g., IAA and GADA) was classified as multiple persistent IA+. The remaining children with a positive test result at only one visit or persistent but not confirmed in a second laboratory were classified as nonpersistent IA+.

Reporting of Laboratory Results to Families

TEDDY children are tested for IA at each study visit. Negative results were reported to families by letter with a statement that the child's risk for type 1 diabetes had not changed. This letter also restated the child's increased genetic risk for type 1 diabetes, that IA may appear later, and that TEDDY will continue to test for IA at each study visit.

Any IA+ test result was reported by a telephone conversation with the parents and followed up with a letter. At the time of the first IA+ result, the parents were told that their child's risk of type 1 diabetes may have increased slightly but that positive test results sometimes return to normal levels, and the child's IA status will continue to be monitored at each study visit. In cases where the child's IA+ test result reverted to negative on subsequent testing, parents were told that IA test results often change over time and that a negative test result does not indicate a reduction in the child's risk for type 1 diabetes unless future tests findings are negative.

In cases where the child's test results were IA+ for a second time, the parents were informed that the child's risk for type 1 diabetes had increased and that out of 100 children with their child's IA test results, 15 will develop type 1 diabetes. Parents were told that the child's IA and blood glucose levels will continue to be monitored at each study visit.

In cases where the child had IA+ results for two or more types of IAs (e.g., IAA and GADA), the parents were told that the child's risk for type 1 diabetes had significantly increased and that out of 100 children with their child's test results, 50 will develop type 1 diabetes. The parents were provided with signs and symptoms of type 1 diabetes, encouraged to be in contact with the child's primary care physician, and asked to have the child take an oral glucose tolerance test every 6 months as part of a regularly scheduled TEDDY visit to monitor the child for progression to type 1 diabetes.

Study Population

This study focused on parents of children who had been in the TEDDY study for at least 1 year and were followed with IA testing up to 6 years of age as of 31 October 2015 (N = 7,301). We excluded children who had maternal antibodies or antibodies at enrollment (n = 262). We also excluded children with IA− test results whose mothers did not complete at least one SAI (n = 17) and children with IA+ results whose mothers did not complete at least one SAI before and after the child's IA+ result (n = 223). From the remaining 6,799 children, three cohorts were created. Cohort 1 included parents of 5,985 children with only IA− test results up to 6 years of age (5,985 mothers, 5,788 fathers). Cohort 2 comprised parents of 814 children with IA+ test results who had completed an SAI before and after the IA+ test result (814 mothers, 661 fathers). Cohort 3 included parents of 718 children with IA+ test results who were followed for 1–4 years after the child's initial IA+ test result (718 mothers, 651 fathers).

Measures

Demographic Variables

We included demographic variables previously found to be associated with parent SAI scores (13): country, GP/FDR status, ethnic minority status (U.S.: the TEDDY child's mother's first language is not English or the mother was not born in the U.S. 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]), parent age at the child's birth, parent education (primary education or high school, trade school or some college, graduated from college), marital status (married or living together versus single), and child's age and sex. Most of the study sample resided in the U.S. (41%), Sweden (31%), and Finland (22%), with a smaller number living in Germany (6%). Most were GP participants (91%). Approximately one-half of the sample was male (51%), and 15% were classified as an ethnic minority. Most parents were married (69%) or living together (27%). Mothers averaged 31 years of age at the TEDDY child's birth and were highly educated (25% some college or trade school, 56% graduated from college). Fathers were also highly educated (25% some college or trade school, 49% graduated from college).

Parent Anxiety About Their Child's Type 1 Diabetes Risk

Parent anxiety was assessed with a 6-item measure adapted from the 20-item state component of the SAI (3,5,14). The SAI measures feelings of tension, anxiety, and nervousness at a single point in time and commonly is used to assess change in anxiety in various situations or across time (3,5,14–16). Because the SAI is a measure of anxiety at a single point in time, normative data are not available. However, studies that use the SAI for screening purposes have identified a score of >40 as indicative of high anxiety (15,16). The SAI was given at the first TEDDY visit, at two subsequent visits when the child was 6 and 15 months of age, and annually thereafter. Parents were asked to respond to the SAI while thinking specifically about their child's risk for type 1 diabetes. The 6-item score was then converted to a total score comparable to the 20-item SAI score. The α-coefficients for parent SAI scores in this sample were excellent (maternal and paternal SAI $\alpha \geq 0.89$). Parents with SAI scores >40 were considered to be highly anxious.

Parent Risk Perception Accuracy

Risk perception accuracy was assessed by the following item at the initial, 6-month, and 15-month study visit and annually thereafter: "Compared with other children, do you think of your child's risk for developing diabetes is (mark only one answer) - much lower, somewhat lower, about the same, somewhat higher, much higher." Parents answering much lower, somewhat lower, or about the same were classified as inaccurate, whereas parents answering somewhat higher or much higher were classified as accurate (17).

Data Analytic Approach

Cohort 1 was used to examine the percentage of parents with a high SAI score (>40) at study inception; McNemar and χ^2 tests were used to calculate differences between mothers and fathers and between FDR and GP parents, respectively. Cohort 1 was also used to examine SAI scores over time in parents of children who had repeated IA− test results. Generalized estimating equations (GEEs) were used to test for significant differences in the rate of change in mean parental SAI scores over time. Cohort 2 was used to examine the change in SAI scores after parents first learned that their child was IA+. Because the SAI was administered annually after the child was 15 months of age, a post-IA+ SAI score could have been obtained a number months after the parent first learned of the child's IA+ test result. Dependent *t* tests were used to evaluate change in SAI scores before and after the first IA+ test result. However, to control for the time between the IA+ test result and the post-IA+ test result SAI score, linear regression was used to examine predictors of parent post-IA+ test SAI scores. Cohort 3 was used to examine the long-term impact of an IA+ test result. GEEs were used to examine predictors of mean SAI scores during the period of 1–4 years after learning that the child had an IA+ test result. By controlling for demographic factors, parent risk perception accuracy, the parent's SAI score after the child's first IA+ test result, and time since the first IA+ test result, we compared parent SAI scores of children with a single nonpersistent IA+ test result with parent SAI scores of children with single persistent and multiple persistent IA+ test results. All GEE models assumed an exchangeable correlation structure. The empirical-based estimates were compared with the model-based estimates to ensure that the working correlation was reasonable. Statistical analysis was performed by using SAS 9.4 software. $P < 0.05$ was considered significant unless otherwise stated.

RESULTS

Parent Anxiety at Study Onset

At study onset, 47% of mothers had high anxiety scores (>40), and more FDR mothers had high scores than GP mothers (53% vs. 46%, $\chi^2 = 9.6$; $P = 0.002$). Fewer fathers (34%) than mothers (47%) had high scores ($\chi^2 = 243.3$; $P < 0.0001$), but FDR fathers were more likely to have high scores than GP fathers (45% vs. 33%, $\chi^2 = 28.1$; $P < 0.0001$).

Impact of Repeated IA− Test Results on Parent Anxiety

Figure 1 provides the parent SAI scores across time for children who never had an IA+ test result for GP and FDR parents. For all cohorts, a significant decline was seen in SAI scores over time ($P < 0.001$).

Initial Impact of IA+ Test Results on Parent Anxiety

The pre- and post-SAI scores closest in time to parent notification of IA+ test results were selected for this analysis. A significant increase in SAI scores occurred for both mothers (mean increase 3.2, $t = 11.8$; $P < 0.001$) and fathers (mean increase 2.5, $t = 7.9$; $P < 0.001$). This effect is illustrated in Fig. 2. We used multiple regression to examine predictors of post-IA+ SAI scores by controlling for demographic factors, time between IA+ test result and post-IA+ SAI score, and parent

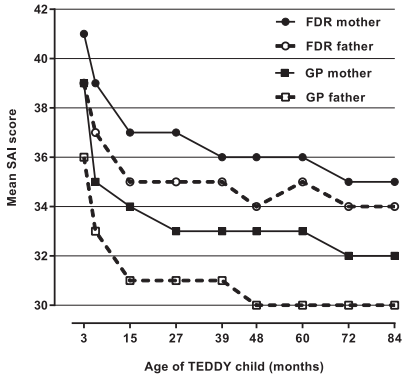

Figure 1—Parent SAI scores across time for GP and FDR children with IA− test results.

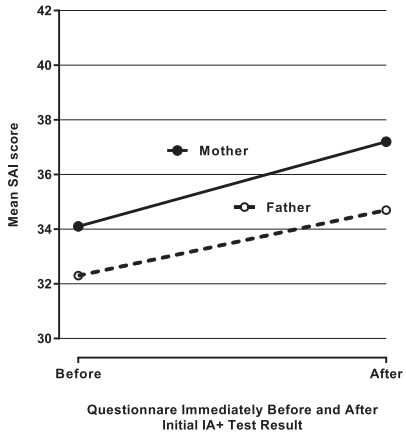

Figure 2—Parent SAI scores before and after a child's first IA+ test result.

SAI scores immediately before the IA+ test result. Parent pre-IA+ SAI score and risk perception accuracy were the only factors predicting post-IA+ SAI scores (all $P < 0.001$) (Table 1). Parents with higher SAI scores before an IA+ test result showed higher SAI scores after an IA+ test result, and parents with more accurate perceptions of their child's type 1 diabetes risk showed higher SAI scores after an IA+ test result. Country and FDR/GP status were not significant predictors; elevations occurred in all countries and in both FDR and GP families.

Long-Term Impact of IA+ Test Results on Parent Anxiety

In this analysis, we were interested in whether parents' SAI scores differed depending on whether their child had a single nonpersistent IA+ test result, a single persistent IA+ test result, or multiple persistent IA+ test results. We controlled for other factors associated with a parent's SAI score (i.e., SAI score after the first IA+ test result, time between the initial IA+ test result and the time the SAI was obtained during the follow-up period, parent risk perception accuracy, demographic factors). The results were similar for both mothers and fathers. Higher SAI scores during the follow-up period were associated with higher SAI scores in response to the first IA+ test result ($P < 0.0001$), the child being an ethnic minority (mothers only, $P = 0.004$), living in the U.S. ($P < 0.05$), and accurate parent perceptions of the child's type 1 diabetes risk ($P < 0.0001$), whereas the longer the follow-up period, the lower the SAI score ($P < 0.05$). With these factors controlled, a strong association existed between both single persistent ($P = 0.008$) and multiple persistent ($P < 0.0001$) IA+ test results and heightened maternal anxiety; paternal anxiety was strongly associated with multiple persistent IA+ results ($P < 0.0001$) (GEE results are provided in the Supplementary Data). Figure 2 illustrates this effect. Parents of children with multiple persistent IA+ test results showed the highest levels of anxiety. More than one-half (57%) of these mothers had SAI scores >40, indicating high levels of anxiety 1 year after their child's first IA+ test result, and 43% were still reporting very high scores 3 years later (Fig. 3*A*). Nearly one-half (44%) of these children's fathers also reported high anxiety 1 year after their child's first IA+ test result, and 34% were still reporting high levels of anxiety 3 years later (Fig. 3*B*).

CONCLUSIONS

To our knowledge, TEDDY is the largest long-term study of the impact of genetic and IA testing in young children on their parents' anxiety about the child's type 1 diabetes risk. Many previous studies have used the SAI to assess parent anxiety in this population, but no study has reported follow-up periods longer than 1 year, and most have been limited to the assessment of an immediate or a short-term (4–6-month) impact (2). Furthermore, previous studies have focused primarily on mothers of FDR children (2), whereas TEDDY has long-term follow-up data from both GP and FDR children and from fathers as well as from mothers.

We found evidence of heightened anxiety in response to the news that the TEDDY child was at increased genetic risk for type 1 diabetes. Mothers were more affected than fathers, and FDR parents were more affected than GP parents. Overall, nearly one-half of TEDDY mothers and one-third of TEDDY fathers had high SAI scores when they first learned of their child's increased genetic risk for type 1 diabetes. However, SAI scores rapidly declined with repeated IA− test results. Although FDR parent SAI scores of children with IA− test results remained higher than those of GP parents of children with IA− results, GP parent SAI scores were comparable to those reported in other parent samples of healthy children (16,18–20).

Because of TEDDY's longitudinal design, we were able to monitor the impact of an IA+ test result on parent anxiety. The availability of SAI scores before and

Table 1—Factors associated with parent SAI scores after parents were informed about their child's first IA+ test result

	Mother				Father			
Factor	*n*	B	95% CI	*P* value	*n*	B	95% CI	*P* value
Country								
U.S.	331	0.00	Ref		264	0.00	Ref	
Finland	160	−0.86	−2.27 to 0.55		155	−0.87	−2.44 to 0.69	
Germany	30	1.60	−1.16 to 4.38		28	0.71	−2.26 to 3.69	
Sweden	292	0.08	−1.09 to 1.24	0.32	276	−0.20	−1.55 to 1.14	0.63
Child has FDR relative with type 1 diabetes								
No	694	0.00	Ref		618	0.00	Ref	
Yes	119	0.62	−0.87 to 2.10	0.42	105	0.71	−1.00 to 2.43	0.41
SAI score before IA+ test result	813	0.76	0.71−0.82	<0.0001	723	0.67	0.60−0.73	<0.001
Risk perception								
Underestimate	299	0.00	Ref		365	0.00	Ref	
Accurate	514	2.39	1.30−3.49	<0.001	358	2.25	1.07−3.43	<0.001

Child age, sex, and ethnic minority status; parent education and marital status; and time between IA+ test result and next available SAI survey were not associated with parent post IA+ test result SAI score. Ref, reference.

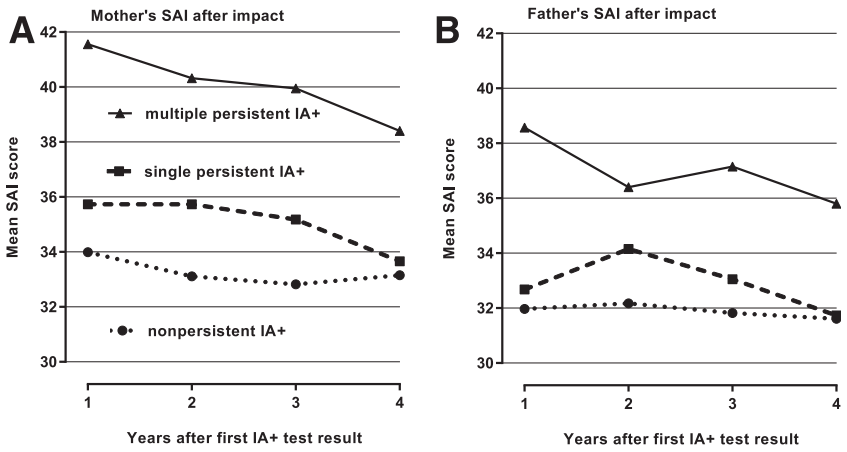

Figure 3—Mother (*A*) and father (*B*) SAI scores 1–4 years after a child's first IA+ test result.

after an IA+ test result is exceedingly rare in the published literature; we were able to find only one study that involved a very small sample of parents of children with IA+ test results (8). In TEDDY, we found that a child's initial IA+ test result significantly increased parent SAI scores. Parents with higher SAI scores before receiving an IA+ test result and parents with accurate perceptions of their child's type 1 diabetes risk showed greater increases in SAI scores. An increase in anxiety in response to an IA+ result is to be expected, and that more anxious parents and those with accurate perceptions of their child's type 1 diabetes risk would be most affected is not surprising. We found no country or GP/FDR differences in response to an IA+ test result, suggesting that all parents were affected in similar ways.

TEDDY is the first study to our knowledge to examine the impact of nonpersistent as well as single persistent and multiple persistent IA+ test results on parent anxiety over the long term (up to 4 years after the child's initial IA+ test result). We found that whether a parent came from a GP or an FDR family had no impact on long-term parent anxiety. Country and time also exhibited a minimal impact. Most important was the parents' level of anxiety in response to an initial IA+ test result, the accuracy of parent perception of the child's type 1 diabetes risk, and whether the child had multiple persistent IA+ test results. Parents with accurate perceptions of the child's type 1 diabetes risk, who were more anxious in response to the child's first IA+ test result, and who were faced with multiple persistent IA+ results showed the highest levels of anxiety. TEDDY protocol requires that parents of children with multiple persistent IA+ test results be informed that their child's risk for type 1 diabetes has significantly increased and be provided signs and symptoms of type 1 diabetes. These parents are also encouraged to contact the child's primary care provider and to have the child begin oral glucose tolerance testing to monitor possible disease progression. Parent knowledge of the child's elevated risk of type 1 diabetes substantially increases parent anxiety. More than one-half of mothers and nearly one-half of fathers of children with multiple persistent IA+ results had elevated SAI scores 1 year after the child's first IA+ test result. Although the number of parents with very high scores declined slightly over time, the average SAI scores among these parents remained high and are comparable with those reported by mothers of young children with type 1 diabetes (21) and parents of children with other chronic health conditions (19,20,22,23).

These parents' anxiety may be particularly acute not only because the child's type 1 diabetes risk is so high but also because the parent can do nothing to prevent the disease and the timing of actual diabetes onset is unknown. Unpredictable and uncontrollable stressors are some of the most difficult for humans to manage (24), and uncertainty often is the single greatest source of stress in parents of medically ill children (25). Parents of children genetically at risk for a disease often face similar levels of uncertainty. Genetic screening studies must be prepared to provide psychological support to parents whose child is at very high risk of developing type 1 diabetes. In response to these findings, TEDDY resources are being directed at improving parent understanding of the child's risk as well as at helping the parent to view monitoring the child for disease progression as a means of reducing unpredictability. Parents are actively encouraged to identify personal resources (e.g., the child's pediatrician, family members) who can help should the child develop type 1 diabetes, providing parents with confidence that they have needed support and resources in place. Finally, parents must be provided with a sense of hope that should their child develop type 1 diabetes, the child and family can manage the disease successfully, and the child can have a long and happy life.

Although a strength of TEDDY is its large multinational sample, parents who agree to join TEDDY may not represent the larger population of children at risk for type 1 diabetes. Many parents of children eligible for TEDDY did not join, and they differ from those who agreed to participate in important ways (26,27). In fact, mothers with accurate perceptions of their child's type 1 diabetes risk who were also highly anxious were more likely to leave TEDDY in the first year. Consequently, the impact of IA testing on TEDDY parents' anxiety as reported here may not accurately reflect the impact on other parents offered similar genetic and IA testing results.

Simply participating in TEDDY could also affect parent response to genetic and IA+ testing. Parents who have their TEDDY child continually monitored may respond differently to IA+ test results than parents who are presented with such results with no prior experience or preparation. TEDDY parents whose child develops type 1 diabetes possibly will respond to the diagnosis with less distress than typically occurs when a child's diagnosis is completely unexpected, but also possible is that a diagnosis of type 1 diabetes may overwhelm some parents already stressed by years of worry about their child. Ongoing studies in TEDDY will address this important issue. However, given the numerous ethical issues associated with genetic screening of children for disease risk where no means to prevent the disease is available, such screening programs should be limited to studies that carefully monitor participants' psychological well-being and provide

necessary resources to address their psychological concerns.

Funding. TEDDY is funded by National Institutes of Health grants U01-DK-63829, U01-DK-63861, U01-DK-63821, and U01-DK-63865 and by U01-DK-63863, U01-DK-63836, U01-DK-63790, UC4-DK-63829, UC4-DK-63861, UC4-DK-63821, UC4-DK-63865, UC4-DK-63863, UC4-DK-63836, UC4-DK-95300, UC4-DK-100238, UC4-DK-106955, and contract No. HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, JDRF, and Centers for Disease Control and Prevention. This work was supported in part by the National Center for Advancing Translational Sciences Clinical and Translational Science Awards to the University of Florida (UL1-TR-000064) and University of Colorado (UL1-TR-001082).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.B.J. contributed to the study and analysis design, conducted the literature searches, and wrote the manuscript. K.F.L. conducted the data analyses and contributed to the interpretation and presentation of study findings. R.R. contributed to the study design and literature searches. D.S. contributed to the interpretation of the study findings. All authors reviewed, edited, and approved the final manuscript. S.B.J. and K.F.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015.

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