

## Research Article

# Participant Experiences in the Environmental Determinants of Diabetes in the Young Study: Common Reasons for Withdrawing

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Received 23 January 2015; Accepted 2 May 2015

Academic Editor: Nitin Gupta

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**Background.** To characterize participant reasons for withdrawing from a diabetes focused longitudinal clinical observational trial (TEDDY) during the first three study years. **Methods.** 8677 children were recruited into the TEDDY study. At participant withdrawal staff recorded any reason parents provided for withdrawal. Reasons were categorized into (1) family characteristics and (2) protocol reasons. Families who informed staff of their withdrawal were classified as active withdrawals (AW); families without a final contact were considered passive withdrawals (PW). **Results.** Withdrawal was highest during the first study year ( $n = 1220$ ). Most families were AW ( $n = 1549$ ; 73.4%). PW was more common in the United States ( $n = 1001$ ; 37.8%) and among young mothers ( $p = 0.001$ ). The most frequent protocol characteristic was blood draw (55%) and the most common family reason was not having enough time (66%). The blood draw was more common among female participants; being too busy was more common among males. Both reasons were associated with study satisfaction. **Conclusions.** Results suggest that, for families of children genetically at risk for diabetes, procedures that can be painful/frightening should be used with caution. Study procedures must also be considered for the demands placed on participants. Study satisfaction should be regularly assessed as an indicator of risk for withdrawal.

## 1. Introduction

The Environmental Determinants of Diabetes in the Young (TEDDY) study is a multicenter longitudinal clinical observational trial studying the natural history of the development of type 1 diabetes (T1DM) in children. Soon after birth,

children were tested for HLA conferred genetic risk for T1DM. Children with the highest genetic risk were invited to participate in TEDDY. The purpose of the TEDDY study is to identify environmental factors that trigger autoimmunity and T1DM [1].

The success of longitudinal research studies, investigating important factors that contribute to T1DM, like TEDDY, is dependent upon study retention. It is important to investigate what study and psychosocial characteristics prompt families to leave a study in order to (1) implement possible preventive actions to increase retention and (2) design future longitudinal studies for this at-risk T1DM population in ways that enhance study retention. Although this topic is critical for the success of longitudinal trials, the extant literature is somewhat sparse. In fact, only 55% percent of pediatric trials report refusal or withdrawal reasons based on a recent literature review [2]. Previous work within more varied pediatric populations and interventional studies (e.g., T1DM, asthma, and obesity intervention trials) has suggested that a number of sociodemographic factors (e.g., older child age, minority status, and lower income) and psychological factors (e.g., greater depression and lower quality of life) were related to study withdrawal [3–6]. However, these findings from intervention studies in chronic illness populations may not be fully applicable to the TEDDY at-risk for T1DM population. Further, previous studies have tended to focus on existing characteristics of participants who do not complete a study rather than directly ascertaining reasons for withdrawal from the participants themselves.

A longitudinal study similar to the TEDDY study reported that logistical matters like blood sampling and lack of time were the reasons most often mentioned by families who withdrew [7]. In the TEDDY population, we have reported that characteristics of the study protocol, like blood draws, and family factors, like being too busy, were the primary reasons families did not join the study [8]. Study enrollment was associated with sociodemographic factors such as whether the child had a mother, father, and/or sibling with T1DM (first degree relative (FDR)), had an older mother, was a singleton, or had a sibling already enrolled in the study. Enrollment rates differed between the TEDDY countries, with a larger proportion of parents recruited from the European countries [8].

In other prior works, we identified predictors of withdrawal during the first year (up to the 15 months' visit) of TEDDY among families from the general population (GP) who had no immediate family member with T1DM [9]. Study withdrawal was more common if the mother was young, the father did not participate, or the study child was female. Also, mothers of children who withdrew were more likely to report smoking during pregnancy, abstaining from alcohol, and reducing their work hours or not working at all during pregnancy. Mothers who withdrew were also more likely to fail to complete items on study questionnaires and to underestimate their child's T1DM risk. Among mothers with accurate perceptions of their child's T1DM risk, high maternal anxiety was associated with study withdrawal [9]. This information was used to identify families at high risk for leaving the TEDDY study in the first year; these families were then provided with an intervention to promote retention [10]. While factors associated with withdrawal could be used to screen for families at risk of dropout, the effectiveness of interventions aimed at improving the retention of participants can also be influenced by the families' specific reasons for withdrawing.

Thus, in this study we examined data from all families who left TEDDY (both GP and FDR) during the first three study years, including sociodemographic and psychosocial variables, and their reasons for opting out of the study.

## 2. Methods

**2.1. TEDDY Study and Data.** The TEDDY study has centers in four countries (Finland, Germany, Sweden, and the United States) and is supported by the National Institutes of Health (NIH). The study protocol includes study visits every three months from 3–4 months of age until the child is four years old and biannually thereafter. The study protocol includes blood draws, nasal swabs, height and weight measurements, and parental interviews where aspects of the child's health are recorded together with different types of life events. At regular intervals TEDDY parents fill out questionnaires with demographic questions, health histories, life events, and parents' worries and anxiety concerning the child's increased genetic risk for T1DM. Parents are also requested to complete food diaries and collect stool samples. Altogether, the TEDDY study protocol is very demanding in length and in terms of the frequency and nature of its components [1].

The collection of cord blood for screening and possible TEDDY enrollment started in September 1, 2004, and ended February 28, 2010. A total of 424,788 children were screened for increased HLA conferred genetic risk for T1DM and 21,589 were HLA eligible [11]. The enrollment rate of families with children at increased genetic risk was 38.4% from the general population (GP) and 64.8% from FDR families. The number and proportion of eligible children as well as the number of children enrolled differed both between countries and between GP and FDR families [8].

The earlier a family withdrew from the study, the fewer data points were available. For all children, demographic factors like country, gender, month of birth, FDR/GP status, and mother's age were obtained in connection with the collection of cord blood to determine eligibility for TEDDY. Data for all children enrolled in TEDDY were also available from the questionnaires that each parent completed in connection with the first TEDDY visit. These psychosocial measures contained questions on parents' views on the child's risk for developing diabetes, their worries about that possibility, and their thoughts on having the child tested for genetic T1DM risk. The mother also answered questions on lifestyle factors during pregnancy (smoking and alcohol consumption). For families withdrawing after the first study year, there were additional demographic data collected during the first year of TEDDY, including parents' education, child ethnic minority status, only child status, and household crowding. Psychosocial data were collected repeatedly starting at the 3 and 6 months' visits, at 15 months, at 27 months, and yearly. In the current study, the psychosocial data collected immediately before withdrawal were used. These data are worries (e.g., *How often do you worry that your child will get diabetes: never/very often*), anxiety (*short version of the State-Trait Anxiety Inventory (SAI)*) [12], depression (*Bradley's Wellbeing Scale*) [13], study satisfaction (*three correlated questions summed into a satisfaction score: Overall, how do you feel*

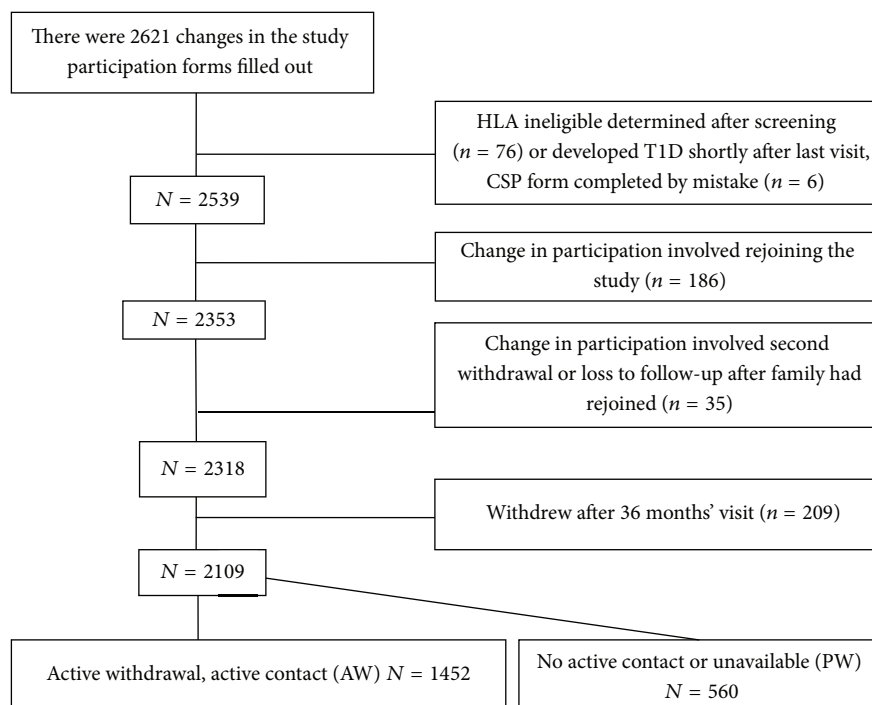


FIGURE 1: Study population.

about having your child participate in the TEDDY study? Do you think your child's participation in the TEDDY study was a good decision? Would you recommend the TEDDY study to a friend?), and risk perception (Compared to other children do you think your child's risk to develop diabetes is much lower/much higher?).

**2.2. Data Collection.** When a family withdrew from TEDDY, a Change in Study Participation Form (CSP Form) was filled out by TEDDY staff and any reason the parent gave for leaving the study was recorded. More than one reason could be recorded. If a family did not give a reason for leaving the study this was also noted. The last visit when any data were collected from the family was taken as the time of withdrawal even though the CSP form could be completed at a much later date. For some families, the decision to withdraw from TEDDY was difficult and could span over a long period of time with several cancelled visits and no collection of data before a final decision to leave the study. If a family did not come to the clinic for more than a year despite scheduled visits and did not contribute any data over the course of one year, the family was considered to be a Passive Withdrawal (PW) and a CSP Form was completed. Families that became unavailable and impossible to reach were also PW and were considered TEDDY withdrawals.

**2.3. Statistical Analysis.** Differences in frequencies between categorical groups were tested by chi-square tests. For continuous variables, differences in means were tested by independent two-sample *t*-tests. Multiple linear regression was used to examine the association of demographic and psychosocial variables with specific common reasons for withdrawing.

Demographic variables available on all subjects were examined first and later psychosocial factors were added. Data from the last questionnaire prior to withdrawal were used to estimate maternal anxiety, risk perception, worry, and study satisfaction. If for any reason there were missing data, information was taken from the last questionnaire available. Univariate and multiple logistic regression models were used to test for significant factors associated with type of withdrawal (PW versus AW). Analyses were performed using SAS 9.2. *p* values less than 0.05 were considered statistically significant.

### 3. Results

A total of 8677 children were recruited into the TEDDY study. From September 1, 2004, until July 31, 2012, there were 2621 CSP forms filled out. CSP forms from all children who left the study on or before the 3-year visit were selected for analysis. Figure 1 gives an overview of how the study cohort was created. In all, 512 forms were excluded from the study for reasons outlined in the figure, resulting in 2109 CSP forms describing the first time withdrawal of the family from the study. Of these, 1549 forms came from families who told the staff they wanted to withdraw from TEDDY (AW); 90% gave at least one reason why they opted out. A total of 560 families (26.6%) did not respond to repeated scheduling attempts for more than a year or became impossible to contact and were withdrawn by the TEDDY staff without any further contact (PW). In Figure 2, the number of AW and PW for the different countries is shown by visit. Overall, study withdrawal was highest during the first year of the study and decreased thereafter and AW was far more common than PW. The United States had the highest frequency of PW ( $n = 378$ ;

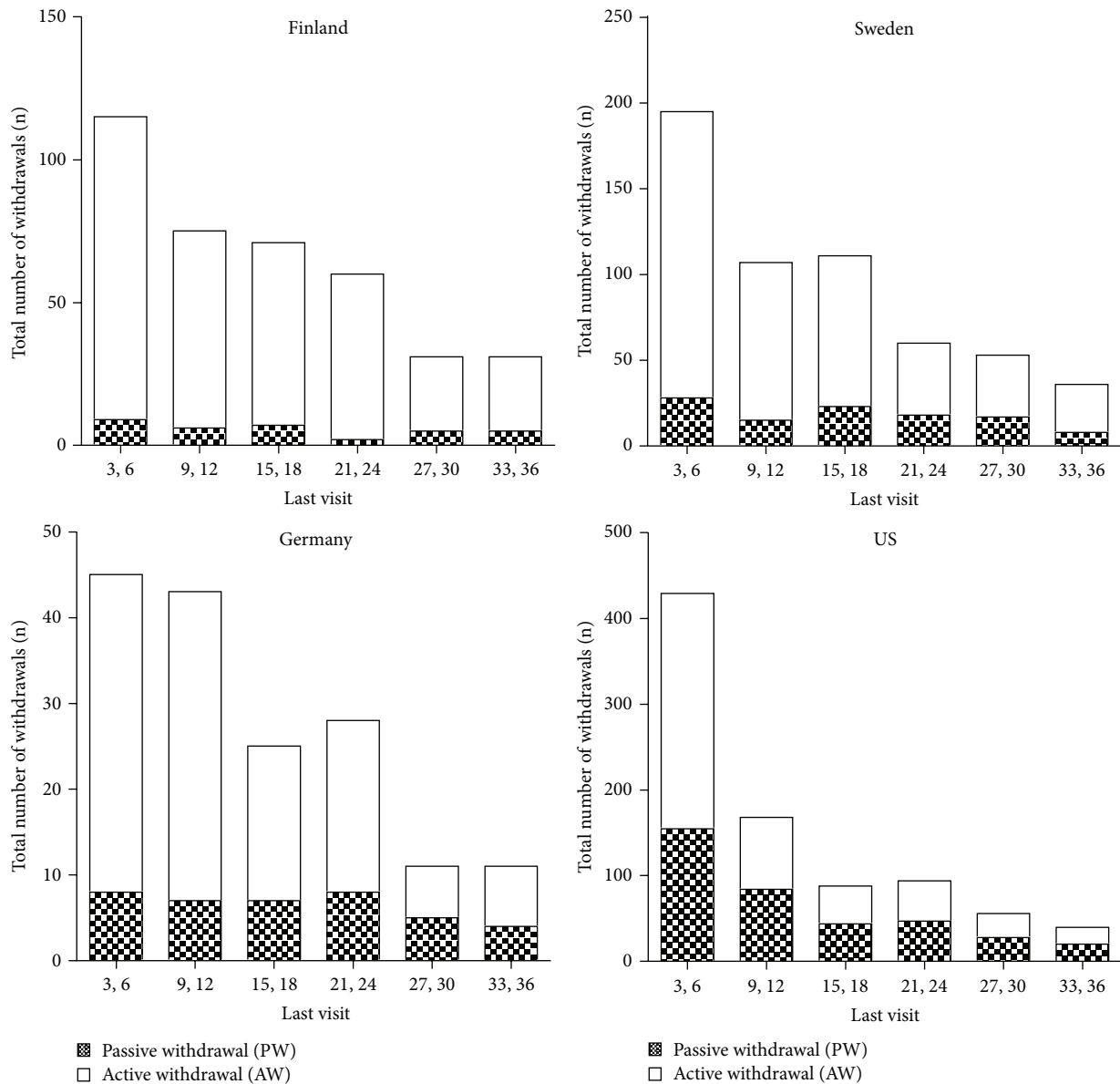


FIGURE 2: Number of withdrawals by age of last visit and by country divided into passive withdrawals (PW) (checked) and active withdrawals (AW) (white).

23.9%) and the relative proportion of PW increased over time. Finland had the lowest PW rate ( $n = 34$ ; 8.9%) and it remained low across all study years. In Germany 39 children (23.9%) and in Sweden 109 children (19.0%) were classified as PW. There was a significantly increasing trend of PW proportion over the study period in Germany ( $p = 0.024$ ) and Sweden during the three years ( $p = 0.001$ ) even though the number of both PW and AW decreased.

Univariate and multiple regressions were used to identify factors that differentiated between AW and PW. PW were significantly more common in other countries compared to Finland, among young moms, and in older children. In the univariate models, high anxiety, maternal smoking during pregnancy, and lack of father participation in TEDDY were

associated with PW. However, these factors did not remain significant in the multivariate model (Table 1).

Table 2 depicts characteristics of the AW by age of the child at the time of withdrawal. In the first half year after enrollment, 24.1% of the AW were young mothers (<25 years) which was significantly different compared to year 3 when 14.8% were young mothers. The early AW were also more anxious mothers (<0.001) and mothers more worried about their child developing diabetes ( $p = 0.003$ ) compared to those remaining in the study. There were no significant associations between the accuracy of the mother's T1DM risk perception or study satisfaction and the child's age at withdrawal.

The frequencies of different reasons reported by the AW distributed over visits during the three study years are shown

TABLE 1: Factors associated with passive withdrawal (PW) versus active withdrawal (AW).

| Factors <sup>a</sup>                  | Number<br>mean (SD) | % of PW | Univariate |           |                | Multivariate |           |                |
|---------------------------------------|---------------------|---------|------------|-----------|----------------|--------------|-----------|----------------|
|                                       |                     |         | OR         | 95% CI    | <i>p</i> value | OR           | 95% CI    | <i>p</i> value |
| Country of residence                  |                     |         |            |           |                |              |           |                |
| Finland                               | 383                 | 8.9     | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Sweden                                | 562                 | 19.4    | 2.47       | 1.64–3.72 |                | 2.86         | 1.85–4.44 |                |
| Germany                               | 163                 | 23.9    | 3.22       | 1.95–5.34 |                | 3.73         | 2.16–6.43 |                |
| US                                    | 1001                | 37.8    | 4.28       | 3.26–9.06 | <0.001         | 6.57         | 4.35–9.93 | <0.0011        |
| Maternal age at child's birth (years) |                     |         |            |           |                |              |           |                |
| Years                                 | 28.9 (5.7)          |         | 0.94       | 0.93–0.96 | <0.001         | 0.95         | 0.93–0.97 | <0.001         |
| <29 years                             | 1016                | 32.0    |            |           |                |              |           |                |
| ≥29 years                             | 1093                | 21.5    |            |           |                |              |           |                |
| Child's age of withdrawal (years)     |                     |         |            |           |                |              |           |                |
| Years                                 | 1.16 (0.80)         |         | 1.12       | 0.99–1.25 | 0.08           | 1.33         | 1.16–1.52 | <0.001         |
| <1.16 years                           | 1231                | 25.8    |            |           |                |              |           |                |
| ≥1.16 years                           | 878                 | 27.6    |            |           |                |              |           |                |
| Gender                                |                     |         |            |           |                |              |           |                |
| Female                                | 1094                | 25.9    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Male                                  | 1015                | 27.3    | 1.08       | 0.88–1.31 | 0.46           | 1.10         | 0.88–1.36 | 0.40           |
| FDR <sup>a</sup>                      |                     |         |            |           |                |              |           |                |
| No                                    | 1957                | 26.8    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Yes                                   | 152                 | 23.7    | 0.85       | 0.57–1.25 | 0.41           | 0.95         | 0.62–1.47 | 0.81           |
| Smoking during pregnancy              |                     |         |            |           |                |              |           |                |
| No                                    | 1556                | 25.2    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Yes                                   | 415                 | 30.4    | 1.30       | 1.02–1.64 | 0.03           | 1.31         | 1.00–1.72 | 0.05           |
| Alcohol 3rd trimester                 |                     |         |            |           |                |              |           |                |
| No                                    | 1713                | 26.1    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Yes                                   | 289                 | 27.3    | 1.07       | 0.81–1.41 | 0.66           | 1.16         | 0.85–1.60 | 0.35           |
| Worked during pregnancy               |                     |         |            |           |                |              |           |                |
| No or reduced hours                   | 1184                | 26.6    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Yes or increased hours                | 819                 | 25.8    | 0.96       | 0.78–1.17 | 0.67           | 0.92         | 0.74–1.15 | 0.45           |
| High anxiety (SAI > 48)               |                     |         |            |           |                |              |           |                |
| Score                                 | 40.9 (10.7)         |         | 1.02       | 1.01–1.03 | <0.001         | 1.00         | 0.99–1.01 | 0.80           |
| <40.9 score                           | 1059                | 22.6    |            |           |                |              |           |                |
| ≥40.9 score                           | 921                 | 29.4    |            |           |                |              |           |                |
| Risk perception                       |                     |         |            |           |                |              |           |                |
| Underestimate                         | 901                 | 27.3    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Accurate                              | 1097                | 25.2    | 0.90       | 0.73–1.09 | 0.28           | 0.99         | 0.80–1.23 | 0.93           |
| Father not active (3 mo) <sup>b</sup> |                     |         |            |           |                |              |           |                |
| No                                    | 1807                | 25.0    | 1.00       | Ref.      |                | 1.00         | Ref.      |                |
| Yes                                   | 302                 | 36.1    | 1.70       | 1.31–2.20 | <0.001         | 1.27         | 0.90–1.78 | 0.17           |

<sup>a</sup>FDR = first degree relative has type 1 diabetes. <sup>b</sup>Father did not answer 3-month questionnaires.

TABLE 2: Active withdrawals by child's age of withdrawal and demographic factors, maternal psychosocial factors, and maternal study satisfaction.

| Factors  | All<br>3–36 m<br>(N) | Year 1<br>3–6 m<br>N (row %) or<br>mean (SD) | Year 1<br>9–12 m<br>N (row %) or<br>mean (SD) | Year 2<br>15–24 m<br>N (row %) or<br>mean (SD) | Year 3<br>27–36 m<br>N (row %) or<br>mean (SD) | <i>p</i> value |
|--|----------------------|--|---|--|--|----------------|
| Number of active withdrawals                         | 1549                 | 584 (37.7)                                   | 324 (20.9)                                    | 431 (27.8)                                     | 210 (13.6)                                     |                |
| Country of residence                                 |                      |  |   |  |  |                |
| Finland  | 349                  | 106 (30.4)                                   | 69 (19.8)                                     | 122 (35.0)                                     | 52 (14.9)                                      |                |
| Sweden   | 453                  | 167 (36.9)                                   | 92 (20.3)                                     | 130 (28.7)                                     | 64 (14.1)                                      |                |
| Germany  | 124                  | 37 (29.8)                                    | 36 (29.0)                                     | 38 (30.6)                                      | 13 (10.5)                                      |                |
| US   | 623                  | 274 (44.0)                                   | 127 (20.4)                                    | 141 (22.6)                                     | 81 (13.0)                                      | <0.001         |
| Gender   |                      |  |   |  |  |                |
| Female   | 811                  | 323 (39.8)                                   | 159 (19.6)                                    | 232 (28.6)                                     | 97 (12.0)                                      |                |
| Male   | 738                  | 261 (35.4)                                   | 165 (22.4)                                    | 199 (27.0)                                     | 113 (15.3)                                     | 0.07           |
| First degree relative with T1D                       |                      |  |   |  |  |                |
| No   | 1433                 | 534 (37.3)                                   | 302 (21.1)                                    | 406 (28.3)                                     | 91 (13.3)                                      |                |
| Yes  | 116                  | 50 (43.1)                                    | 22 (19.0)                                     | 25 (21.6)                                      | 19 (16.4)                                      | 0.30           |
| Maternal age at child's birth<br>years               | 29.4 (5.6)           | 28.9 (5.8)                                   | 29.0 (5.2)                                    | 29.6 (5.5)                                     | 30.9 (5.5)                                     | <0.001         |
| Highly anxious at last visit (SAI > 48) <sup>a</sup> |                      |  |   |  |  |                |
| No   | 1241                 | 413 (33.3)                                   | 259 (20.9)                                    | 375 (30.5)                                     | 191 (15.4)                                     |                |
| Yes  | 229                  | 116 (50.7)                                   | 55 (24.0)                                     | 45 (19.7)                                      | 13 (5.7)                                       | <0.001         |
| Worry about diabetes at last visit <sup>a,b</sup>    |                      |  |   |  |  |                |
| Never or rarely                                      | 706                  | 104 (14.7)                                   | 166 (23.5)                                    | 290 (41.4)                                     | 144 (20.4)                                     |                |
| Sometimes or very often                              | 344                  | 56 (16.3)                                    | 114 (33.1)                                    | 113 (33.4)                                     | 59 (17.2)                                      | 0.004          |
| Risk perception at last visit <sup>a</sup>           |                      |  |   |  |  |                |
| Underestimate  | 692                  | 247 (35.7)                                   | 147 (21.2)                                    | 207 (30.1)                                     | 90 (13.0)                                      |                |
| Accurate   | 783                  | 283 (36.1)                                   | 170 (21.7)                                    | 213 (27.5)                                     | 115 (14.7)                                     | 0.63           |
| Study satisfaction at last visit <sup>a,b</sup>      |                      |  |   |  |  |                |
| Very satisfied                                       | 276                  | 38 (13.8)                                    | 77 (27.9)                                     | 108 (39.1)                                     | 53 (19.2)                                      |                |
| Satisfied  | 289                  | 44 (15.2)                                    | 87 (30.1)                                     | 99 (34.3)                                      | 59 (20.4)                                      |                |
| Somewhat satisfied                                   | 274                  | 39 (14.2)                                    | 71 (25.9)                                     | 115 (42.0)                                     | 49 (17.9)                                      |                |
| Neutral or dissatisfied                              | 208                  | 38 (18.3)                                    | 44 (21.2)                                     | 84 (40.4)                                      | 42 (20.2)                                      | 0.47           |

<sup>a</sup>If no measure last visit, the second to last visit is taken if available.

<sup>b</sup>Study satisfaction and worry about diabetes are not asked in the first questionnaires so there are fewer available answers at 3 and 6 months.

in Table 3. The different reasons are grouped into “protocol characteristics” or “family factors.” The two reasons most frequently given for leaving TEDDY were concerns about the blood draw ( $n = 359$ ; 55% of all protocol characteristics) and being too busy/not having enough time ( $n = 587$ ; 66.6% of all family factors). Other frequently mentioned protocol characteristics included the following: the protocol is too demanding, transportation difficulties, and the frequency of visits. Among the family factors, feeling overwhelmed/being too stressed is the second most common reason given ( $n = 206$ , 23.4%). Having concerns about the blood draw was more often mentioned for older children ( $p = 0.039$ ), not wanting to be reminded of the child's risk was significantly more often reported as a reason for withdrawal during the first visits ( $p = 0.003$ ), and being too busy/not having enough time was more often reported in the later visits ( $p = 0.037$ ). During the study

period, 11% ( $n = 97$ ) of the families cited moving out of the area as a reason for opting out. A total of 165 families (10.7%) did not want to give a reason for leaving or only wanted to wait and see what might happen.

The result of multiple regressions examining demographic factors in all AW subjects for the two most often mentioned reasons for withdrawal (concerns about blood draw and being too busy) is presented in Table 4. German and US mothers were more likely to report the blood draw as the reason for leaving TEDDY compared to Finland and Sweden. Also, the blood draw was mentioned more often as the child got older and if the child was a girl. Being too busy was given as the reason for leaving TEDDY most often among Swedish mothers and least often among German mothers. This reason was more common in families with an older TEDDY child and if the child was a boy.



TABLE 3: Frequency of common reasons for withdrawing from the TEDDY study during the first three study years. Percentages for reasons mentioned more frequently are shown.

| Withdrawals   | Last visit before withdrawal (month) |                   |                   |                   |             | All               |  |
|---|--------------------------------------|-------------------|-------------------|-------------------|-------------|-------------------|--|
|   | Year 1<br>3–6 m                      | Year 1<br>9–12 m  | Year 2<br>15–24 m | Year 3<br>27–36 m | 3–36 m      |                   |  |
|   | N (row %)                            | N (row %)         | N (row %)         | N (row %)         | N           | %                 |  |
| Active withdrawals (AW)   | <b>584 (37.7)</b>                    | <b>324 (20.9)</b> | <b>431 (27.8)</b> | <b>210 (13.6)</b> | <b>1549</b> | <b>73.4</b>       |  |
| Reasons for withdrawal  |                                      |                   |                   |                   |             |                   |  |
| <b>Protocol characteristics</b>   | <b>244 (37.4)</b>                    | <b>128 (19.6)</b> | <b>195 (29.9)</b> | <b>86 (13.2)</b>  | <b>653</b>  | <b>100</b>        |  |
| Concerns about blood draw   | 124 (34.5)                           | 63 (17.5)         | 112 (31.2)        | 60 (16.7)         | 359         | 55.0 <sup>a</sup> |  |
| Protocol too demanding  | 68 (40.0)                            | 41 (24.1)         | 43 (25.3)         | 18 (10.6)         | 170         | 26.0 <sup>a</sup> |  |
| Transportation difficulties   | 44 (41.1)                            | 21 (19.6)         | 35 (32.7)         | 7 (6.5)           | 107         | 16.4              |  |
| Concerns about frequency of visits                                      | 40 (39.2)                            | 20 (19.6)         | 33 (32.4)         | 9 (8.8)           | 102         | 15.6              |  |
| Concerns about stool samples  | 14                                   | 9                 | 13                | 7                 | 43          | 6.6               |  |
| Concerns about questionnaires   | 15                                   | 8                 | 10                | 4                 | 37          | 5.7               |  |
| Food diaries too troublesome  | 12                                   | 1                 | 2                 | 1                 | 34          | 5.2               |  |
| Do not want to be reminded of risk                                      | 19                                   | 6                 | 5                 | 1                 | 31          | 4.7               |  |
| Duration of study is too long   | 1                                    | 3                 | 5                 | 1                 | 10          | 1.5               |  |
| No treatment to prevent offered   | 3                                    | 1                 | 2                 | 1                 | 7           | 1.1               |  |
| Worried about privacy   | 1                                    | 1                 | 0                 | 0                 | 2           | —                 |  |
| Worried about loss of insurance   | 3                                    | 0                 | 0                 | 0                 | 3           | —                 |  |
| Other protocol characteristics  | 2                                    | 3                 | 5                 | 2                 | 12          | 1.8               |  |
| <b>Family factors</b>   | <b>279 (35.6)</b>                    | <b>162 (20.7)</b> | <b>231 (29.5)</b> | <b>112 (14.3)</b> | <b>784</b>  | <b>100</b>        |  |
| Too busy/not enough time  | 187 (31.9)                           | 134 (22.8)        | 185 (31.5)        | 81 (13.8)         | 587         | 66.6 <sup>a</sup> |  |
| Feeling overwhelmed/stressed  | 82 (39.8)                            | 40 (19.4)         | 58 (28.2)         | 26 (12.6)         | 206         | 23.4              |  |
| Moving out of the study area  | 33 (30.4)                            | 23 (23.7)         | 22 (22.7)         | 19 (19.6)         | 97          | 11.0              |  |
| Child medical/behavioral problems                                       | 29 (40.3)                            | 16 (22.2)         | 16 (22.7)         | 11 (19.6)         | 72          | 8.2               |  |
| Family member emotional problems  | 15                                   | 9                 | 18                | 10                | 52          | 5.9               |  |
| Does not want to be in research   | 9                                    | 3                 | 8                 | 5                 | 25          | 2.8               |  |
| Family member does not agree to participate                             | 8                                    | 0                 | 5                 | 4                 | 17          | 1.9               |  |
| Family member in another study  | 1                                    | 0                 | 2                 | 0                 | 3           | —                 |  |
| Subject already in another study  | 0                                    | 1                 | 0                 | 0                 | 1           | —                 |  |
| Fam. health care provider not recommended                               | 1                                    | 0                 | 0                 | 0                 | 1           | —                 |  |
| Language barrier  | 1                                    | 0                 | 0                 | 0                 | 1           | —                 |  |
| Other family factors  | 4                                    | 2                 | 4                 | 3                 | 13          | 1.5               |  |
| <b>Active contact made but no reason given or wants to wait and see</b> | <b>70 (42.4)</b>                     | <b>28 (17.0)</b>  | <b>42 (25.4)</b>  | <b>25 (15.2)</b>  | <b>165</b>  | <b>10.7</b>       |  |

<sup>a</sup>Significant difference between age groups: concerns about blood draw ( $p = 0.039$ ), do not want to be reminded of risk ( $p = 0.003$ ), and too busy/not enough time ( $p = 0.037$ ).

Maternal smoking during pregnancy, mother working during pregnancy, maternal alcohol consumption during pregnancy, father participation in TEDDY, and whether the TEDDY child was a FDR or from the GP were not associated with either reason for leaving TEDDY.

In Table 5, two logistic regressions explore maternal psychosocial factors in relation to the two most frequently

mentioned factors for withdrawing, concerns about blood draw and being too busy. The regressions are adjusted for country of residence, maternal age, age of child at study withdrawal, and gender. The results show that concerns about blood draw were associated with the mother's study satisfaction both at 6 months and at the last visit before withdrawal. At both 6 months and the last visit, mothers

TABLE 4: Multiple logistic regression examining demographic factors in relation to (a) concerns about blood or (b) being too busy as a reason for withdrawing among those who actively withdrew.

| Factors at enrollment               | Demographic measures in relation to concerns about blood draw and being too busy ( <i>n</i> = 1549) |           |                |                    |           |                |
|-------------------------------------|---|-----------|----------------|--------------------|-----------|----------------|
|                                     | (a) Concerns about blood draw   |           |                | (b) Being too busy |           |                |
|                                     | OR  | 95% CI    | <i>p</i> value | OR                 | 95% CI    | <i>p</i> value |
| Country of residence                |   |           |                |                    |           |                |
| Finland                             | 1.00  | Ref.      |                | 1.00               | Ref.      |                |
| Sweden                              | 1.33  | 0.91–1.93 |                | 1.47               | 1.10–1.96 |                |
| US                                  | 1.72  | 1.21–2.43 |                | 0.83               | 0.63–1.09 |                |
| Germany                             | 7.80  | 4.89–12.4 | <0.001         | 0.48               | 0.30–0.77 | <0.001         |
| Maternal age at child's birth (yrs) |   |           |                |                    |           |                |
| Years                               | 1.05  | 1.02–1.07 | <0.001         | 1.00               | 0.98–1.01 | 0.62           |
| Child's age of withdrawal (months)  |   |           |                |                    |           |                |
| Months                              | 1.20  | 1.03–1.40 | 0.02           | 1.15               | 1.01–1.31 | 0.04           |
| Gender                              |   |           |                |                    |           |                |
| Male                                | 1.00  | Ref.      |                | 1.00               | Ref.      |                |
| Female                              | 1.44  | 1.12–1.85 | 0.004          | 0.78               | 0.63–0.96 | 0.02           |

Note: FDR/GP status, smoking during pregnancy, working during pregnancy, alcohol consumption during pregnancy, and dad's participation in TEDDY were not associated with either concerns about blood draw or being too busy.

who reported less satisfaction with TEDDY were more likely to report concerns about the blood draw as the reason for leaving TEDDY. The relationship between study satisfaction and mothers' report of being too busy as the reason to leave TEDDY was less clear. No other psychosocial factors (maternal anxiety or mother's risk perception) showed an association with the two most common reasons for leaving the TEDDY study.

#### 4. Discussion

The TEDDY study, which seeks to identify factors associated with the development of T1DM, has a demanding protocol for both the children and their parents. The study is also longitudinal with four visits to a TEDDY clinic each year until the child is four years of age and biannually thereafter until the child is fifteen years of age. After 8 years, 72.2% of the recruited children are still participating in the study. The majority of families who left gave a reason for leaving. PW was more common among the US participants. Being a large country with a diverse population, it is more difficult to track people compared to the European countries. We previously reported that U.S. families often failed to respond to phone messages or letters inviting them to join TEDDY [8], constituting passive refusal, which is similar to PW.

Finland had the lowest number of PW and similar numbers over the years, while the proportion of PW in Germany and Sweden tended to increase during the three study years even though the total number of withdrawals decreased significantly. Some study sites may keep a TEDDY participant as "active" in TEDDY despite multiple missed visits. After getting to know TEDDY staff over many months some families may have difficulty directly telling staff that they are leaving the study and may instead just "no-show." Differences

between study centers in how families are managed might develop over time and this is a weakness of the current results reported. However, it is difficult for a large study like TEDDY to systematically define how staff uniformly manage study families over many years.

Sociodemographic factors also related to study withdrawal. PW mothers were younger and more likely to smoke during pregnancy than those retained in the study. In the univariate analysis, lack of father participation in TEDDY was associated with PW but this effect was not statistically significant in the multivariate model. In previous work, we found that lack of father participation was an important predictor of study withdrawal in the first year of TEDDY [9]. Father involvement in a study may be a more important determinant of whether a family stays in a study or withdraws; it may not predict whether the withdrawal is active or passive.

Logistical aspects of the study were found to be common reasons for withdrawal. Even though TEDDY staff is very skilled, drawing blood from a small child can be very challenging and cause unpleasant experiences both for the child and the parent. Other studies have reported that blood draws can be an obstacle for study participation and a reason for opting out [7]. Reporting the blood draw as a reason for leaving TEDDY was more common later in the study than in the early phase. All blood draws are done after application of dermal anesthetics so a baby might react less than a slightly older child who might have learned to fear the blood draw. This observation has been verified by Swedish TEDDY nurses who conducted a parent survey of the child's reaction to the blood draw. In fact, parents tended to rate stronger reactions in older children (personal communication).

Being too busy and not having time to do the TEDDY tasks was the most frequently mentioned reason for leaving the study. Being stressed and feeling overwhelmed was



TABLE 5: Logistic regression examining maternal psychosocial factors in relation to (a) concerns about blood draw or (b) being too busy as a reason for withdrawing after adjusting for country of residence, maternal age, child's age at withdrawal, and gender (see Table 4).

| Psychosocial factors             | Psychosocial measures in relation to concerns about blood and being too busy after adjusting for demographic factors ( $n \sim 1031$ ) |           |                |                    |           |                |
|----------------------------------|--|-----------|----------------|--------------------|-----------|----------------|
|                                  | (a) Concerns about blood draw  |           |                | (b) Being too busy |           |                |
|                                  | OR   | 95% CI    | <i>p</i> value | OR                 | 95% CI    | <i>p</i> value |
| Maternal high anxiety (SAI > 48) |  |           |                |                    |           |                |
| Score                            | 1.00   | 0.98–1.01 | 0.42           | 0.99               | 0.98–1.00 | 0.09           |
| Mother's risk perception         |  |           |                |                    |           |                |
| Underestimate                    | 1.00   | Ref.      |                | 1.00               | Ref.      |                |
| Accurate                         | 1.01   | 0.74–1.38 | 0.95           | 0.91               | 0.70–1.18 | 0.49           |
| Study satisfaction (6 mo)        |  |           |                |                    |           |                |
| Very satisfied                   | 1.00   | Ref.      |                | 1.00               | Ref.      |                |
| Satisfied                        | 1.38   | 0.89–2.15 |                | 1.24               | 0.88–1.74 |                |
| Somewhat satisfied               | 1.80   | 1.16–2.78 |                | 1.80               | 1.27–2.59 |                |
| Neutral or dissatisfied          | 2.73   | 1.68–4.42 | <0.001         | 1.11               | 0.73–1.69 | 0.007          |
| Study satisfaction (last visit)  |  |           |                |                    |           |                |
| Very satisfied                   | 1.00   | Ref.      |                | 1.00               | Ref.      |                |
| Satisfied                        | 1.57   | 0.99–2.49 |                | 1.19               | 0.84–1.69 |                |
| Somewhat satisfied               | 2.54   | 1.61–4.03 |                | 1.43               | 1.00–2.05 |                |
| Neutral or dissatisfied          | 2.64   | 1.62–4.31 | <0.001         | 1.33               | 0.89–1.97 | 0.252          |

another important reason for not participating anymore. Being busy was significantly more often mentioned as a reason for withdrawal at the later study visits. It may be that when a baby is born, the mother is often home caring for the baby and may not experience the TEDDY tasks as burdensome, compared to later when she may return to work. Also, some TEDDY tasks are easier to complete when the child is a baby like collecting stool samples or doing a 3-day food diary. Also, being in the beginning of a study may give participants a feeling of curiosity and enthusiasm, something that may disappear as the study seems less novel to families.

Psychological reasons also played a role in withdrawal for some families, particularly early in the study. Mothers in families who withdrew early, after the first or second TEDDY visit, appeared to be more anxious and worried about their child getting diabetes compared to mothers in families leaving the study at 9 months or later. This is underscored by the observation that mothers who reported that they did not want to be reminded of the child's risk of T1DM as a reason for withdrawal often left TEDDY after the first two visits.

The two most important factors mentioned as reasons for withdrawal (blood draw and being too busy) were each analyzed in separate regression models, first in relation to demographic factors and in a second model in relation to maternal psychological factors and study satisfaction. Reporting the blood draw as a reason for withdrawal was more common if the child was a girl while stating that the family was too busy to participate was more common if the child was a boy. A study on infant pain response following immunization injection demonstrated that parental behavior has a key role in influencing how infants respond to painful procedures with differences between female and male infants

[14]. We can only speculate that parents may be more sensitive to the possible discomfort of the blood draw in girls than in boys; boys are often expected to be braver than girls. Another study found that girls' pain threshold is lower than that of boys, at least for slightly older children compared to the TEDDY children in our study [15]. This could indicate that the reaction of girls to the blood draw might be stronger than that of the boys and therefore the parents might be more prone to opt out when the child is a girl even when the child is younger.

Why being too busy was more often mentioned when the child was a boy is harder to explain. Sometimes boys are more physically active and this may create more problems for parents in collecting TEDDY samples and data in preparation for the visit. It may also mean that boys are more likely to openly protest going to the TEDDY clinic. All this taken together might give parents a feeling of not having time and being too busy. In the current study, parents who gave the blood draw as a reason for leaving often expressed lower satisfaction with the study both at 6 months, when this was first assessed in TEDDY, and in the survey completed before opting out. It is likely that difficulties with the blood draw were seen early in the study, sometimes continued, and resulted in lower satisfaction with the TEDDY experience and ultimately withdrawal from the study.

In a prior study exploring reasons of why parents stay in TEDDY, having someone watching the child for development of T1DM was the most often mentioned reason. Among the minority of parents who had considered leaving the study, the blood draw, being too busy/not having enough time, a demanding protocol, and food diaries were the most frequently reported reasons for considering leaving [16].

These results are in line with what was found in the present study.

In this study, reasons for withdrawal were obtained by the TEDDY staff via interview when the parents decided to leave TEDDY, while our prior published work collected this information by questionnaire [16]. Therefore, the method of obtaining this data does not seem to be important as the results were similar. What is lacking is a more in-depth explanation of why parents are too busy and do not have time to remain in TEDDY. Retention and compliance in a longitudinal study like TEDDY are critical for the success of the study so detailed information about why families leave is important for developing strategies for improving study retention.

## 5. Conclusion

Results from this study suggest some significant factors that should be taken into account to counteract opting out in longitudinal studies focusing on a population at genetic risk for T1DM like TEDDY. Psychological factors clearly play a role in early withdrawal and thus early in the study it is important to record and pay attention to parents' anxieties and worries and to implement procedures that may reduce or address these challenges. Also, young mothers, particularly if the father is not fully present, are at early risk for leaving the study and may need extra attention. Procedures that can be experienced as painful and frightening, like a venous blood draw, need to be used with great caution and all ways to facilitate obtaining the specimen need to be considered. It is important for researchers to carefully think through all components in the study that might increase the demands on the participants and it is important to avoid overburdening families, which may increase the risk of withdrawal. Regular investigations of the subjects' satisfaction with the study can give important information on how the study subjects are experiencing their participation and can predict withdrawal.

## Appendix

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## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Acknowledgments

The TEDDY Study Group (see Appendix) is funded by U01 DK63829, U01 DK63861, U01 DK63821, U01 DK63865, U01 DK63863, U01 DK63836, U01 DK63790, UC4 DK63829, UC4 DK63861, UC4 DK63821, UC4 DK63865, UC4 DK63863, UC4 DK63836, UC4 DK95300, and UC4 DK100238 and by Contract no. HHSN267200700014C 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). This work was supported in part by the NIH/NCATS Clinical and Translational Science Awards to the University of Florida (UL1 TR000064) and the University of Colorado (UL1 TR001082).

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