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Original Article

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

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Objective: The Environmental Determinants of Diabetes in the Young (TEDDY) study seeks to identify environmental triggers of autoimmunity and type 1 diabetes mellitus (T1DM) in children at increased human-leukocyte-antigen conferred genetic risk for this disease. The objective of this study was to identify predictors of early withdrawal from TEDDY among families with no immediate family history of T1DM.
Method: Logistic multiple regression was used to discriminate 2994 (83%) families currently active in the TEDDY study for ≥1 yr from 763 (17%) families who withdrew in the first year. Data collected on the screening form at the time of the child's birth and from interview and questionnaire data obtained at the baby's first study visit (at ≤4.5 months of age) were used.
Results: Significant and independent predictors of early withdrawal included country of residence, young maternal age, no father participation, and female gender of the study participant. 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 underestimate their child's risk for T1DM and fail to respond to multiple items on the enrollment questionnaires or interview. Among mothers with accurate risk perceptions, those experiencing high anxiety about their child's risk were more likely to be early withdrawals.
Conclusions: Identifying families at high risk for study withdrawal at the time of enrollment allows for targeting these families with individually tailored plans to help maintain their participation in the study.

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The Environmental Determinants of Diabetes in the Young (TEDDY) is a multicenter, multinational epidemiological natural history study initiated by the National Institutes of Health to identify environmental exposures associated with autoimmunity and type 1 diabetes mellitus (T1DM) onset in children at increased human leukocyte antigen (HLA)-conferred genetic risk for this disease (1). The specific HLA genotypes required for study inclusion have been described previously (1). Newborn screening began in September of 2004 and at the time of this data analysis (31 May 2009), over 340 000 newborns had been screened to identify 16 435 HLA eligible infants; 6734 (41%) of these infants had joined the study. Most of these infants (89%) came from the general population, with no first degree T1DM relative.

Study demands on TEDDY families are considerable and include blood draws, stool sample collections, diet records, interviews, and questionnaires. The participating infants are examined every 3 months until 4 yr of age and every 6 months thereafter. As TEDDY participation is both time-consuming and expensive for the families, the investigators, and the funders, any loss of these valuable participants diminishes the power of the study to meet its objectives.

In this report, we describe family characteristics identified at study inception that predicted study withdrawal among general population families during the first year of the TEDDY study. This information may guide future efforts to retain families in studies like TEDDY and should prove useful in the design of future natural history epidemiological studies with pediatric populations.

Methods

The TEDDY study

TEDDY is a natural history study that seeks to identify the environmental triggers of autoimmunity and T1DM onset in genetically at-risk children identified at three centers in the USA (Colorado, Washington, and Georgia/Florida) and three centers in Europe (Finland, Germany, and Sweden). Infants from the general population, as well as infants who have first degree relatives (FDRs) with T1DM, are screened for genetic risk at birth using HLA genotyping. Parents with infants at increased genetic risk for T1DM are invited to participate in TEDDY. Parents are fully informed of the child's increased genetic risk and the protocol requirements of the TEDDY study, including the requirement that eligible infants must join TEDDY before the infant is 4.5 months of age. The TEDDY protocol is demanding with study visits for blood draws and other data and sample collection scheduled every 3 months during the first 4 yr of the child's life. Parents are also asked to keep detailed records of the child's diet, illnesses, life stresses, and other environmental exposures.

Study sample

This analysis focused on two groups of families from the general population: those active in TEDDY for $\geq$1 yr, with the participant's most recent study visit occurring within the last 6 months (actives, n = 2994) and those who enrolled in TEDDY $\geq$1 yr ago but who withdrew from TEDDY during the first year (withdrawals, n = 763). Infants with a T1DM FDR were excluded from this analysis because study withdrawal among this population is rare. To date, only 47 (9%) of enrolled infants with a TIDM FDR have withdrawn during the first year and 94% of all first year withdrawals have come from the general population.

Predictors of early withdrawal

Possible predictors of early withdrawal among general population families were selected from data collected on the screening form at the time of the child's birth and from interview and questionnaire data collected at the baby's first TEDDY visit, which occurred when the child was $\leq$4.5 months of age. The predictor variables included: demographic characteristics – TEDDY country (Finland, Germany, Sweden, USA); mother's age (in years); child's gender; maternal health during pregnancy – number of illnesses, gestational diabetes or type 2 diabetes (yes/no); mother's lifestyle behaviors during pregnancy – smoked at any time during pregnancy (yes/no), alcohol consumption (no alcohol, 1–2 times per month, $\geq$3 times per month during each trimester), employment status (worked during all three trimesters/did not work at all or reduced work hours); baby's health status – birth complications (yes/no), health problems since birth (yes/no), hospitalizations after birth (yes/no); number of stressful life events during and after pregnancy; mother's emotional status including worry and sadness during pregnancy (rated on 5 point scales), anxiety about the child's risk of developing diabetes measured by a six-item scale adapted from the state component of the State-Trait Anxiety Inventory (2–4); the accuracy of the mother's perception of the child's risk for developing diabetes (accurate: indicating the child's T1DM risk was higher or much higher than other children's T1DM risk; inaccurate: indicating the child's T1DM risk was the same, somewhat lower or much lower than other children's T1DM risk); and whether the child's father completed the initial study questionnaire (yes/no).

Data analysis

Hierarchical multiple logistic regression was used to identify significant predictors of early withdrawal from TEDDY. Variables were entered in blocks in the following order: demographic variables (country of residence, child's gender, mother's age); pregnancy/birth variables (maternal diabetes, illness in mother or child, birth complications, maternal smoking; maternal drinking; maternal employment outside the home, maternal worry or sadness during pregnancy, number of stressful life events occurring during pregnancy or after the child's birth); father's participation in TEDDY defined by father's completion of a brief questionnaire; and mother's reactions to the baby's increased T1DM risk (anxiety and accuracy of mother's perception of the child's T1DM risk). Nine percentage of the study sample ($N = 326$) had missing data on one or more variables. The withdrawal rate for participants with complete data (19%) was substantially lower than the withdrawal rate among those with some missing data (35%). Consequently, the analysis was first completed for those with no missing data and then rerun for the full sample using multiple imputation to generate appropriate parameter estimates for missing data using the Proc MI and Proc MIANALYZE procedures available from SAS 9.1 (5).

Results

Table 1 provides the results of the final logistic regression model for the sample of 3431 TEDDY participants with no missing data. The model was highly significant ($\chi^2 = 264.87$, $df = 12$, $p < 0.0001$) and accurately placed 81.6% of the sample into their respective group (actives vs. withdrawals). The data in Table 1 also provide the final logistic regression model for the total sample, with multiple imputation methods used to replace missing data. Because the early withdrawal rate was higher among participants with missing data, we added a variable to the imputed model, more than one missing data point (yes/no). The presence of more than one missing data points predicted early dropout over and above all other variables in the model. The descriptive information for each of the significant predictors is provided in Table 2.

Demographic predictors of early withdrawal included country of residence and maternal age. Both Finland (16%) and Sweden (18%) had lower early withdrawal rates than the US and Germany (25%). On average, mothers who withdrew early were more than 2 yr younger than those who remained active in TEDDY. Child's gender approached statistical significance in the model with no missing data and was significant in the imputed model. Families with at-risk female infants (22%) were more likely to withdraw compared to families with at-risk male infants (19%).

Maternal lifestyle behaviors during pregnancy – smoking, drinking, and working outside the home – also predicted early withdrawal. Only 13% of the mothers stated they smoked during pregnancy but these women were more likely to withdraw from TEDDY in the first year (37% of the smokers withdrew compared to 16% of non-smokers). Most of the mothers stated they did not drink alcohol at all during pregnancy and the number of mothers reporting total abstinence increased from the first trimester (73%) to the second (83%) and third trimesters (82%); however, never drinking was actually associated with higher withdrawal rates. For the purposes of statistical modeling, we chose maternal alcohol consumption during the third trimester because some mothers may not have known they were pregnant in the first trimester. Mothers who reported never drinking during their third trimester were more likely to withdraw during the first year of TEDDY (21%) than those who reported having an occasional drink (13%). Approximately, half of the mothers reported reducing their work hours, quitting work, or never working outside home during their pregnancy. Reducing work hours, quitting or not working at all during pregnancy was associated with higher withdrawal rates (23% compared to 15% for mothers who worked throughout their pregnancy).

Dad participation in TEDDY was high, with the majority (92%) of the fathers completing a study questionnaire at the time the family joined the study. However, 43% of the families with no dad participation withdrew from the study in the first year compared to 18% of the families with dads completing the study questionnaire.

Maternal reaction to the news of her infant's increased T1DM risk was also a predictor of early withdrawal. More than 40% of the mothers underestimated their infants' T1DM risk; these mothers were more likely to withdraw (23%) compared to mothers with accurate perceptions of their child's T1DM risk (16%). Among mothers with accurate T1DM risk perceptions, those who were more anxious about the child's risk for developing T1DM, were more likely to withdraw.

Although 91% of the participants had complete data for analysis, 58% of those with more than one missing data points at study inception withdrew from the study in the first year, whereas only 19% of those with one or no missing data points withdrew from the study in the first year.

Table 1. Logistic regression results for the sample with no missing data and the total sample with missing data imputed

Predictor variable		Sample with no missing data (N = 3431) β	SE	p-Value	OR	95% confidence interval		Sample with missing data imputed (N = 3757) β	SE	p-Value
Intercept		1.126	0.424	0.008				0.982	0.400	0.014
Country	USA			Ref					Ref	
	Finland	−0.420	0.130	0.001	0.657	0.509	0.848	−0.431	0.123	0.0004
	Germany	0.278	0.222	0.211	1.321	0.854	2.042	0.154	0.218	0.481
	Sweden	−0.342	0.110	0.002	0.711	0.572	0.882	−0.346	0.104	0.002
Child sex female	No	Ref								
	Yes	0.160	0.092	0.081	2.316	1.840	2.915	0.217	0.086	0.012
Maternal age (yr)		−0.058	0.009	<0.0001	0.944	0.927	0.961	−0.053	0.009	<0.0001
Maternal lifestyle behaviors during pregnancy										
Smoked	No			Ref					Ref	
	Yes	0.841	0.117	<0.0001	2.318	1.841	2.918	0.803	0.117	<0.0001
Alcohol consumption in last trimester	None			Ref						
	1–2 times per month	−0.343	0.148	0.020	0.709	0.531	0.948	−0.280	0.140	0.045
	>2 times per month	−0.424	0.319	0.183	0.654	0.350	1.222	−0.401	0.299	0.180
Worked all trimesters	No			Ref					Ref	
	Yes	−0.396	0.095	<0.0001	0.673	0.559	0.811	−0.364	0.090	<0.0001
Dad participation	No			Ref					Ref	
	Yes	−0.569	0.162	0.0005	0.566	0.412	0.778	−0.608	0.146	<0.0001
Risk perception	Underestimate			Ref					Ref	
	Accurate	−1.257	0.375	0.0008	0.284	0.137	0.593	−1.032	0.354	0.004
State Anxiety Inventory score		0.001	0.006	0.835	1.001	0.989	1.014	0.001	0.006	0.825
State Anxiety Inventory score × risk perception		0.023	0.009	0.011	1.023	1.005	1.041	0.018	0.009	0.039
>1 missing data points								1.321	0.464	0.007

Significant predictors of study withdrawal in the first year after enrollment in the TEDDY general population.

Discussion

We found that demographic, behavioral, and psychological characteristics of general population families, assessed at the time the family joined TEDDY, predicted study withdrawal within 1 yr. Families from Finland and Sweden were significantly less likely to withdraw than families from the USA and Germany. As, Finland and Sweden have the highest incidence of T1DM in the world (6), perhaps general population families in these countries are more aware of the disorder and as a consequence, more likely to continue participation. Or, there may be other cultural differences that better promote participation in research in these two countries.

Our finding that younger maternal age was associated with greater likelihood of withdrawal, is consistent with reports by a number of other investigators (7–9), suggesting this is a stable finding in longitudinal studies with pediatric populations. The mechanism underlying this effect remains unknown. Younger mothers may be less financial stable and therefore more prone to moving or may be less psychologically mature, making the demands of the study more difficult for them.

Table 2. Characteristics of TEDDY general population families associated with study withdrawal in the first year after enrollment

Characteristic	Actives (n = 2994)	Withdrawals (n = 763)	Total sample (n = 3757)
Country	N (%)	N (%)	N
Finland	747 (84)	140 (16)	887
Germany	106 (75)	36 (25)	142
Sweden	1052 (82)	231 (18)	1283
USA	1089 (75)	356 (25)	1445
Child sex	N (%)	N (%)	N
Male	1538 (81)	352 (19)	1890
Female	1456 (78)	411 (22)	1867
Maternal age (yr)	M (SD)	M (SD)	M (SD)
	30.8 (5.0)	28.5 (5.7)	30.4 (5.2)
Maternal lifestyle behaviors during pregnancy			
Smoking	N (%)	N (%)	N
Smoked	296 (63)	171 (37)	467
Did not smoke	2602 (84)	510 (16)	3112
Data missing	96 (54)	82 (46)	178
Alcohol consumption at third trimester	N (%)	N (%)	N
Alcohol 1–2 times per month	474 (87)	72 (13)	546
Alcohol ≥3 times per month	105 (89)	13 (11)	118
No alcohol	2359 (79)	609 (21)	2968
Data missing	56 (45)	69 (55)	125
Employment status	N (%)	N (%)	N
Worked all three trimesters	1418 (85)	251 (15)	1669
Reduced work, quit, or did not work at all	1426 (77)	417 (23)	1843
Data missing	150 (61)	95 (39)	245
Dad participation in TEDDY	N (%)	N (%)	N
Participated	2813 (82)	624 (18)	3437
Did not participate	181 (57)	139 (43)	320
Maternal reactions to child's increased TIDM risk			
Risk perception	N (%)	N (%)	N
Accurate	1809 (84)	355 (16)	2164
Underestimate	1132 (77)	343 (23)	1475
Data missing	53 (45)	65 (55)	118
State Anxiety Inventory score	M (SD)	M (SD)	M (SD)
Total sample	38.7 (9.7)	40.8 (10.6)	39.1 (9.9)
Risk perception: accurate	38.8 (10.2)	41.7 (10.4)	39.3 (9.6)
Risk perception: underestimate	38.4 (10.2)	39.9 (10.8)	38.8 (10.4)
	N (%)	N (%)	N
Data missing	46 (42)	63 (58)	109
Missing data	N (%)	N (%)	N
≤1 missing data points	2944 (81)	695 (19)	3639
>1 missing data points	50 (42)	68 (58)	118

Maternal lifestyle behaviors during pregnancy predictive of study withdrawal during the first year of TEDDY included smoking, no alcohol consumption, and reducing work hours or not working at all outside of the home. Although only 13% of the mothers reported smoking at all during pregnancy, these mothers were more likely to withdraw. Smoking has been previously associated with study withdrawal (9) and may reflect less health-conscious attitudes that translate into lower commitment to a health monitoring study like TEDDY. As we expected mothers who drank no alcohol during their pregnancy to be more health-conscious, we were surprised that reported total abstinence during the third trimester was associated with increased study withdrawal. It is important to note that frequent drinking during pregnancy was extremely rare in the population who joined the study. Only 3% of all mothers acknowledged drinking ≥3 times per month during their third trimester and 82% stated they did not drink at all. Nevertheless, mothers who acknowledged having an occasional drink were more likely to remain in TEDDY. We can only speculate as to why this might be the case. Perhaps some women were not truthful in response to this question, selecting the no alcohol response in an effort to look good to the study investigators. If this occurred, these women may have found it difficult to be truthful about some of the more difficult aspects of TEDDY and withdrew from the study instead of admitting their difficulties and discussing them with study personnel. On the contrary, mothers who were comfortable having an occasional

drink and admitting it, may cope with the study demands more easily. The reliability of this finding remains to be seen.

About half of our study mothers reduced their work hours, quit work, or did not work outside the home at all during pregnancy and these mothers were more likely to withdraw from TEDDY. A recent longitudinal study of families with a young T1DM child reported similar results (10). However, we did not collect data as to whether mothers' work status during pregnancy was a matter of choice. Some of these mothers may have been unemployed and facing financial distress. Others may have elected not to work during pregnancy and then felt overwhelmed by the demands of a new baby, impeding their ability to take on the extra tasks of the study as well.

We know of no study that has examined father participation as a predictor of study withdrawal in a longitudinal study with a pediatric population. We had a very high rate of father involvement, with 93% of the fathers completing a brief study questionnaire at the time the family joined TEDDY. Study withdrawal was particularly high among families with no father study participation. Completing a brief questionnaire may be a good indicator of father involvement in the family; mothers managing without the support of the child's father may find the study tasks too demanding and withdraw early.

The TEDDY protocol requires professional communication of the child's increased risk for T1DM to the child's parent(s). This is done both orally and in writing. Despite this effort, over 40% of the mothers underestimated their child's T1DM risk when they first joined the study, reporting their child's risk to be 'about the same' or ' somewhat lower' or 'much lower' than other children's risk. Risk underestimation has been reported previously in parents of children at increased genetic risk for T1DM and appears to increase over time (3, 11). In this study, we found it to be predictive of early study withdrawal. Approximately, 23% of the mothers who underestimated their child's T1DM risk withdrew from the study within the first year compared to 16% of the mothers with accurate risk perceptions. Maternal anxiety about the child's T1DM risk was also predictive of study withdrawal but only among mothers with accurate T1DM risk perceptions. Although as a group, mothers with accurate T1DM risk perceptions were more likely to stay in TEDDY, those with very high anxiety scores were more likely to withdraw. For these mothers, study visits may have elicited considerable anxiety as they awaited the outcome of each blood test conducted every 3 months. For these highly anxious mothers who were very much aware of the child's increased T1DM risk, the emotional discomfort associated with the visits may have led to early study withdrawal.

Although only 9% of the participants had missing data on any of the study variables at the study's inception, this group had a higher early withdrawal rate. Among participants with more than one missing data points, 58% withdrew during the first year. The first TEDDY visit includes both a questionnaire for the mother to complete and an interview. Failure to complete these tasks appears to be one behavioral indicator that the family will have difficulty complying with other study tasks in the year to come.

Child's gender was weakly related to study withdrawal, with female infants (22%) more likely to withdraw than male infants (19%). It is possible that parents are less willing to expose their female children to the frequent blood draws demanded in TEDDY.

Several study variables did not predict early withdrawal: maternal physical and mental health during pregnancy, stressful life events during pregnancy and after the birth of the child, and the baby's health status at birth and during the first few months of life. We suspect that these factors may be a better predictor of enrollment in TEDDY rather than dropout during the first year. We expect that mothers facing significant health problems in themselves or their child or other major life stresses would probably not enroll in TEDDY. Consequently, those who did enroll are likely to have few health problems or major life stresses at the beginning of the TEDDY study. Of course, these variables may prove to be predictors of withdrawal later in TEDDY, rather than at its inception.

In order to minimize demands on study participants, we did not collect parent education, family composition, or family medical history data (other than the presence of a FDR with T1DM) at the consent to screen or the first TEDDY visit. Consequently, we were unable to model these variables as potential predictors of early study withdrawal. This is a study limitation as participant education and ethnic-minority status have been associated with study attrition in prior reports (9, 12). Maternal education in particular could have influenced response rates to the study questionnaires, resulting in more missing data. However, both maternal education and ethnic-minority status are collected at the 9-month TEDDY visit and can be used to predict attrition at later points in the study.

In conclusion, this study's findings have important implications for the TEDDY study and for similar pediatric natural history or intervention investigations initiated shortly after birth. Based on these findings, we have modified the study protocol in an effort to better support those at high risk for early study withdrawal. At study inception, a risk score is calculated for each family by the Data Coordinating Center based on data collected at the first TEDDY visit. Each study site is then informed of any participant with an elevated risk score. Each site develops a plan tailored to the needs of

the high risk family in an effort to prevent early withdrawal. For example, a specific study nurse may be assigned to a family who is at high risk for study withdrawal to enhance the personal connection between study staff and the family. Additional between visit phone calls may be used to provide reassurance and to address any concerns or questions. If a family has difficulty attending study visits because of a specific reason (e.g., lack of transportation, difficulty finding child care for siblings), the study staff will work to find a solution.

Although study withdrawal rates among families with a FDR who has T1DM are low, most newly diagnosed T1DM children come from the general population. Similarly, most TEDDY families come from the general population. Developing ways to keep these families successfully engaged in the study protocol is essential to its success.

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