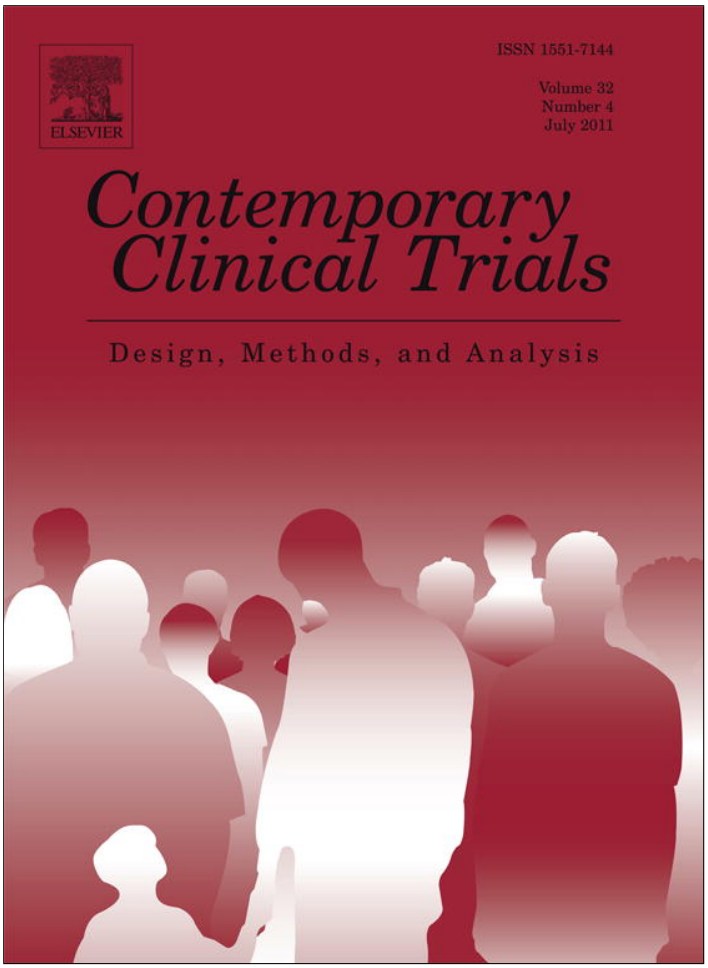

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Enrollment experiences in a pediatric longitudinal observational study: The Environmental Determinants of Diabetes in the Young (TEDDY) study

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ABSTRACT

Objective: Our objective was to identify characteristics of infants and their families who were enrolled, refused to enroll, or were excluded from The Environmental Determinants of Diabetes in the Young (TEDDY) study.
Method: 16,435 infants screened at birth and identified as at increased genetic risk for type 1 diabetes (T1DM) were placed into one of three categories: enrolled, excluded, or refused to enroll. Enrollment, exclusion and refusal rates were compared across countries and between infants from the general population (GP) and infants with a first degree T1DM relative (FDR). A multivariate logistic model was used to identify factors associated with TEDDY enrollment.
Results: TEDDY enrollment, exclusion, and refusal rates differed by country and by GP/FDR status but reasons for refusal to enroll were similar across countries and GP/FDR populations. Sweden had the highest enrollment rate, US had the highest exclusion rate, and Finland had the highest refusal rate. FDR infants were more likely to enroll than GP infants. Inability to re-contact the family was the most common reason for exclusion. Primary reasons for refusal to enroll included protocol factors (e.g. blood draws) or family factors (e.g., too busy). Study enrollment was associated with FDR status, European country of origin, older maternal age, a singleton birth, and having another child in TEDDY.
Conclusions: Findings highlight the importance of country specific estimates for enrollment targets in longitudinal pediatric studies and suggest that enrollment estimates should be lowered when the study involves the general population, painful procedures, or makes multiple demands on families.

Abbreviations: TEDDY, The Environmental Determinants of Diabetes in the Young; NIH, National Institutes of Health; T1DM, Type 1 diabetes; HLA, Human Leukocyte Antigen; FDR, first degree relative; GP, general population; US, United States of America.

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1. Introduction

The enrollment of participants in longitudinal research protocols can be difficult, particularly when children are the target population. However, longitudinal research designs are necessary to understand the natural history of a disease and the role of gene/environment interactions. The extant literature on longitudinal study enrollment is relatively sparse. For behavioral pediatric trials in children with chronic conditions, an overall enrollment rate of 63% has been reported [1]. However, intervention trials may have different enrollment rates than observational trials given risks and/or benefits associated with the intervention. The French longitudinal cohort study tracking the environmental and psychosocial influences on children from birth to adulthood (Elfe), has reported an overall enrollment rate of 55% [2]. These reports, however, have not generally provided a detailed discussion of reasons why participants fail to enroll, or an analysis of factors associated with enrollment. The SEARCH for Diabetes in Youth is being conducted in the US and found participation rates higher for survey completion (68–82%) than for clinic visits which involved blood draws and anthropometric measurements (41–60%); older children, children with type 2 diabetes (compared to type 1 diabetes) and African American children (compared to non-Hispanic white children) were less likely to participate [3]. The All Babies in Southwest Sweden (ABIS) study, a longitudinal epidemiological study targeting children from birth, enrolled 78.6% of eligible participants and noted practical study characteristics such as participant time burden and blood sampling as the most common reasons for enrollment refusal. ABIS data also suggested interactions between participant characteristics (e.g., maternal age, parent education level) and reasons for enrollment refusal [4]. While these studies provide relevant information on enrollment experiences, there may be international differences in these experiences which are not captured by country-specific studies.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is a National Institutes of Health (NIH) supported international, longitudinal, observational investigation that identifies young infants at increased genetic risk for type 1 diabetes (T1DM) [5]. The HLA high-risk genes for T1DM used to recruit TEDDY children are associated with increased risk for T1DM but in fact, most children with high risk HLA genes never get the disease [6]. Consequently, multiple environmental triggers are thought to be involved in the etiology of T1DM. The aim of the TEDDY study is to identify environmental triggers of T1DM in genetically at-risk children through close observation and longitudinal data collection over a 15 year time-frame.

TEDDY sites are located in the USA (Colorado, Georgia/Florida and Washington State), and in Europe (Finland, Germany and Sweden). After parental consent, infants were screened for defined HLA gene alleles associated with increased T1DM risk. The parents of HLA eligible infants less than 4.5 months were invited to participate with their child in the TEDDY study. To meet the objectives of TEDDY, nearly 425,000 newborns were screened for HLA risk alleles to enroll the target sample of over 8600 genetically at-risk children.

The TEDDY protocol is demanding and includes study visits every 3 months for 4 years and biannually thereafter until 15 years of age. Study procedures include blood draws, dietary records, stool samples, questionnaires, and demographic and health histories including illness episodes [5]. The aim of the present study was to identify factors associated with enrollment in TEDDY during the first 4 years of the study. Findings are relevant to other longitudinal observational studies with pediatric populations, especially those across countries.

2. Methods

2.1. Enrollment procedure

2.1.1. Screening

At all centers, mothers were approached at the time of a child's birth for possible participation in the screening. Fathers, if present, were also included in the screening decision. In Sweden, expecting parents were informed about TEDDY by midwives at the Mother Health Care Centers during pregnancy and informed consent obtained in connection with delivery. Finland and the US parents were mainly informed about TEDDY at the time the baby was born and also gave their consent for screening at that time. In Germany, media advertising was used to recruit pregnant women with an immediate family member who has T1DM (i.e., the pregnant woman had T1DM, she had a child with T1DM, or the baby's father had T1DM). At all TEDDY study sites, written informed consent for infant HLA screening was obtained along with contact information for the family. The mother's age, the baby's gender, whether the infant had a first degree T1DM relative (mother, father, or sibling), and whether the child was a singleton, twin or triplet were recorded.

2.1.2. Risk notification

Parents of infants without T1DM HLA high risk gene alleles were sent a standard letter indicating that the child's risk for diabetes was the same as the average child. The letter also noted that this result did not mean that the child would never develop diabetes.

Mothers (or fathers if provided written informed consent) of infants with TEDDY eligible HLA high risk genes were initially contacted by phone when the infant was at least 6 weeks old, but usually closer to 3 months. The parent was told about the child's increased genetic risk and that the infant was eligible to participate in the TEDDY study. If it was not possible to reach a parent or primary caretaker by phone, a letter was sent asking the parent to call the local TEDDY clinic.

During the telephone contact, risk information was provided in a standardized manner which included a numerical estimate of the child's risk for T1DM. The numerical risk varied by country and whether the infant had a first degree relative with T1DM (FDR). For example, the mother of a US or German child from the general population (GP) was told that out of 100 babies with her baby's genetic risk, approximately 3 babies would develop T1DM. Since the overall risk for T1DM is greater in Sweden and Finland, the GP risk estimate provided to the parents in these countries was higher: 7 babies out of 100 were expected to develop T1DM. A mother of a US or German child with a T1DM FDR relative was told that out of 100 babies with her baby's genetic test result,

approximately 14 babies would develop T1DM. For Sweden and Finland there were no distinctions made in risk estimates between infants from GP and FDR families; however, upon request, parents of FDR babies were given more detailed risk estimates depending on whether the family member with T1DM was the child's mother, father or sibling.

After the telephone conversation explaining the child's T1DM risk and eligibility for the TEDDY study, additional information about the study was sent with a follow-up letter re-iterating the child's risk and eligibility for the TEDDY study. Parents were encouraged to contact the TEDDY staff with questions. At some sites, information about the TEDDY study was provided in group meetings with interested parents.

2.1.3. Enrollment

After risk notification and the follow-up materials were sent home, TEDDY staff re-contacted the family to determine their interest in joining the study. To enroll, the informed consent and the first TEDDY study visit was required to be completed before the child was 4.5 months of age. In all countries, there are special TEDDY clinics where enrolled families attend study visits. To meet the families' travel needs, some centers have several clinics within their enrollment area. In Germany, a majority of eligible families live too far from the TEDDY clinic. For these families, only the first TEDDY visit is face to face with TEDDY staff. All subsequent visits are conducted at the child's pediatrician's office where blood draws, weighing and measurement of length and height are performed. Collection of other study data is done through the mail and by interviews over the phone with TEDDY staff.

2.1.4. Exclusion

An HLA eligible baby was excluded from the TEDDY study if (1) the child had an illness or birth defect that precluded long-term follow-up or involved a treatment that might alter the natural history of T1DM (e.g. immunosuppressive medication); (2) the family refused storage of biologic study samples in the NIH Repository; or (3) the first TEDDY visit did not occur before the child was 4.5 months of age. Families who did not respond to calls, messages, or letters from the TEDDY staff were excluded because the first TEDDY visit could not be scheduled prior to the child reaching 4.5 months of age. Families who provided incorrect contact information or who did not show up for a scheduled visit and a new visit could not be scheduled before the child reached 4.5 months of age were also excluded. Occasionally the HLA testing results were not available or the TEDDY site could not schedule the first TEDDY visit before the child was 4.5 months of age; these cases were also excluded from the TEDDY study.

2.1.5. Refused enrollment

Parents who were informed of their child's eligibility for the TEDDY study but refused to join the study were queried about the reasons for their decision. All reasons for refusal were recorded and fell into four categories: (1) the family would be unavailable due to moving out of the area; (2) the parents wanted to “wait and see” and manage diabetes if it occurred; (3) the parents declined participation due to characteristics of the protocol; and/or (4) the parents declined participation for family reasons (e.g., too busy to participate). Parents could provide more than one reason for refusal. If parents did not provide a reason for refusal, this was also recorded.

2.2. Data analysis

All HLA eligible children were placed into one of three categories: enrolled, excluded, or refused to enroll. Univariate analyses were used to describe demographic characteristics according to country and family status (GP or FDR). Categorical differences for all variables were tested using the chi-square test for dichotomous data and independent *t*-test for continuous data. A p-value of 0.05 or less was considered statistically significant. Multivariate logistical regression analyses were conducted to evaluate the independent contribution of demographic characteristics with participation level in the TEDDY study. The multivariate analysis provided odds ratios and 95% confidence intervals to predict those who enrolled versus those who refused to enroll or were excluded. Analyses were conducted using the Statistical Analysis System Software (Version 9.2, SAS Institute, Cary, NC).

3. Results

These data reflect enrollment experiences for the TEDDY study from September 1, 2004 until May 31, 2009. During this period, HLA results from 351,300 screened babies were obtained with 16,435 infants (4.9%) identified as HLA eligible for participation in TEDDY. Out of 345,942 GP children screened, 15,329 (4.4%) were eligible while among 5358 FDR children screened, 1106 (20.6%) babies were eligible for this analyses.

Altogether 6734 children were enrolled in the TEDDY study as of May 31, 2009. There were significant differences between countries. The overall percentages of HLA eligible families that enrolled (n = 6734; 41%), refused to enroll (n = 5864; 36%) or were excluded (n = 3837; 23%) by country and by GP versus FDR status are provided in Fig. 1. Sweden had the highest enrollment rate (68%, $X^2 = 463.09$, $p < 0.0001$). The US had the highest exclusion rate (37%, $X^2 = 2305.50$, $p < 0.0001$) and Finland had the highest refusal rate (48%, $X^2 = 36.95$, $p < 0.0001$) followed by Germany (46%). Enrollment was considerably higher among FDR families (65%) compared to GP families (39%; $X^2 = 276.89$, $p < 0.0001$). GP families were more likely to be excluded (24%) or refuse TEDDY study participation (36%) compared to FDR families (10% excluded, $X^2 = 111.10$, $p < 0.0001$; 25% refused, $X^2 = 60.44$, $p > 0.0001$).

3.1. Exclusion

Table 1 provides the number (%) of HLA eligible children excluded from TEDDY by country and by FDR/GP status as well as the primary reasons for study exclusion. The most common reason for exclusion was that the family did not respond to calls, messages, or letters from the TEDDY staff making it impossible to give any information about the infant's increased risk and to schedule an appointment. These families, who were essentially passively refusing to enroll, constituted >73% of all families excluded from TEDDY and comprised 17% of all HLA eligible children; they more common among GP HLA eligible families (18%) than FDR

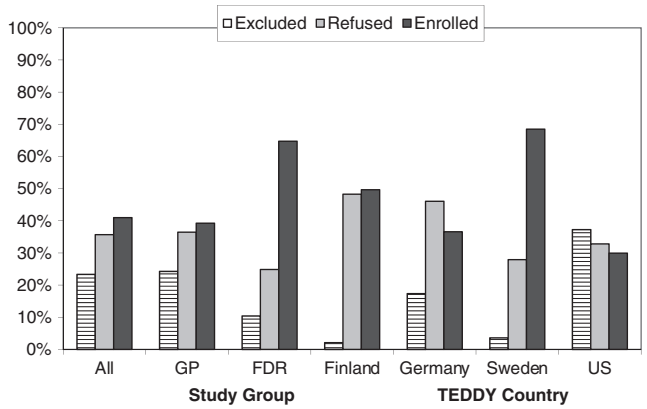

Fig. 1. Percentage of excluded, refused and enrolled shown for all HLA eligible infants and by general population or first degree relative status and by TEDDY country.

HLA eligible families (6%; $X^2 = 102.63$, $p < 0.0001$ — not shown). In all countries, passive refusal of this sort was the most common reason for exclusion although the proportion of children excluded for this reason – among all HLA eligible children – varied between countries. Among US parents of HLA eligible children, 27% exhibited this sort of passive refusal to enroll compared to 16% of German parents, 1% of Finnish parents and 3% of Swedish parents ($X^2 = 1615.19$, $p < 0.0001$ — not shown).

Failure to schedule the first TEDDY appointment before the child was 4.5 months of age, despite verbal agreement to participate by a parent or primary caretaker, was the second most common reason for exclusion — exhibited by 16% of those excluded. Another 8% children excluded from TEDDY had incorrect contact information obtained in connection with the screening, preventing the TEDDY staff from getting in touch with the family; this was particularly a problem in the US. Other reasons for excluding a child from TEDDY were rare: in 81 cases, TEDDY staff were unable to schedule the HLA eligible child's appointment before the child was 4.5 months of age; 24 children were excluded because their HLA test result was not known in time to schedule the child prior to 4.5 months of age; 7 children were excluded due to a disease or birth defect; and 1 child had parents who refused storage of lab specimens in the NIH Repository.

3.2. Refused enrollment

Table 2 provides the primary reasons parents of TEDDY eligible infants refused to enroll in TEDDY by country. Also provided are refusal rates by GP/FDR status. The table shows all TEDDY eligible children remaining after subtraction of children who were excluded from all HLA eligible children. Some aspect of the TEDDY protocol was the most common reason for refusing enrollment; 38% of all families who refused enrollment reported this as the reason and it was the primary reason for refusal among both GP and FDR families (data not shown). For Finland, the most frequent refusal response was “no reason given;” 50% of all Finnish families who refused failed to give a reason for declining participation. Family reasons were also commonly cited across all countries (33% of all families who refused cited this as a reason) and were common among both GP and FDR families (data not shown). Only a few families (4% of all families who refused) said they would be unavailable due to impending moves or other reasons of unavailability. A few parents (4% of families who refused) indicated that the child's risk was not great enough to justify study participation and preferred to wait and see what might happen in the future. Protocol and family reasons were examined in more detail because they were the most common reasons mentioned by parents who refused TEDDY enrollment.

3.2.1. Reasons for refusal — protocol characteristics

Table 3 provides the most common protocol characteristics mentioned by parents as their reason for refusal to enroll in TEDDY. Concerns about the blood draw (18%) were cited most often by both GP (19%) and FDR (14%) parents (not shown). This varied by country ranging from 5% in Finland to 36% in Germany. The demanding nature of the study protocol was also commonly cited (15% across all countries). Swedish families mentioned the frequency of the TEDDY visits as a reason for

Table 1
Number of all HLA eligible [a] children and number of HLA eligible children excluded from the TEDDY study by country and by general population (GP) versus first degree T1DM relative (FDR) status. The primary reasons for exclusion are also shown.

Country	Finland	Germany	Sweden	US	ALL
Number of HLA eligible children [a]	2959	1216	2983	9277	16,435
Number of excluded children (% of HLA eligible children)					
ALL excluded children	62 (2)	211 (18)	107 (4)	3457 (38)	3837 (24)
Excluded GP children	57 (2)	200 (17)	101 (3)	3364 (37)	3722 (23)
Excluded FDR children	5 (0.2)	11 (1)	6 (0.2)	93 (1)	115 (1)
Primary reasons [b] for exclusion: Number excluded by reason (% of children excluded)					
No response to calls/messages [c]	39 (63)	191 (91)	76 (71)	2512 (73)	2818 (73)
Incorrect contact info [d]	1 (2)	7 (3)	6 (6)	295 (9)	309 (8)
Appointment not in window [e]	11 (18)	5 (2)	18 (17)	563 (16)	597 (16)

[a] HLA genotyping is assessed to identify children with increased genetic risk for T1D.
[b] Most common reasons for exclusion are provided; total N across reasons for exclusion listed may not equal total HLA eligible children excluded.
[c] The contact information was correct, but the parents would not respond to calls or messages from the staff to give a reply about participation or not.
[d] The information obtained in connection with the screening was not sufficient for a first family contact.
[e] The TEDDY protocol states that the window for the first TEDDY visit is open until the child is 4.5 months. If the family does not show up at a scheduled visit before the child is 4.5 months the child is excluded if a new visit could not be scheduled within the window.

Table 2
Number of TEDDY eligible [a] children and number (%) of TEDDY eligible families who refused enrolment by country and by general population (GP) versus first degree T1DM relative (FDR) status. Primary reasons for refusal are also shown.

Country	Finland	Germany	Sweden	US	ALL
Number of TEDDY eligible children [a]	2897	1005	2876	5820	12,598
Number of TEDDY eligible families who refused (% of TEDDY eligible children)					
All families who refused	1428 (49)	560 (56)	833 (29)	3043 (52)	5864 (47)
All GP families who refused	1332 (46)	519 (52)	794 (28)	2944 (51)	5589 (44)
All FDR families who refused	96 (3)	41 (4)	39 (1)	99 (2)	275 (2)
Primary Reasons for Refusal: [b] Number refused by reason (% of children who refused)					
Protocol characteristics	389 (27)	300 (54)	320 (38)	1192 (39)	2201 (38)
Family reasons	266 (19)	110 (20)	363 (44)	1187 (39)	1926 (33)
Moving, unavailable	20 (1)	7 (1)	25 (3)	182 (6)	234 (4)
Wants to wait and see	21 (1)	20 (4)	17 (2)	150 (5)	208 (4)
No reason given	719 (50)	126 (23)	105 (13)	332 (11)	1282 (22)

[a] Number of TEDDY eligible children = number of HLA eligible children minus number of children excluded from TEDDY participation.
[b] More than one reason for refusal can have been recorded.

refusal more often than parents from other countries. Travel to the TEDDY clinic was an obstacle for many families (9%) in all countries except Germany and this reason for refusal was particularly prominent in Sweden and Finland.

Some parents reported that they did not want to be reminded of the child's risk. This reason was rare in Finland (1%) and the US (2%) but expressed by 5% and 6% of parents in Germany and Sweden, respectively. The length of the study was quoted as a reason for refusal to enroll by 3% of the parents. All other protocol characteristics (e.g. sending stool samples, filling out forms, doing food diaries, privacy issues, future loss of insurance and no treatment offered) were never or rarely mentioned by parents as a reason for study refusal.

3.2.2. Reasons for refusal — family factors

The most frequently mentioned family-related reasons for refusing to enroll in TEDDY are also listed in Table 3. Being too busy stood out as the most common reason, mentioned by 22% of all parents. However, there were marked differences between the countries, with 34% of the Swedish parents being too busy compared to 5% of the German parents.

3.3. Predicting enrollment

The demographic variables obtained during screening from all participating newborns (FDR/GP status, maternal age, child's gender, if child was born singleton or multiple, having a sibling in TEDDY, and TEDDY country) were entered into a multivariate logistic regression model in order to assess characteristics most associated with TEDDY study enrollment. Since most of the excluded children were passive refusers who failed to respond to TEDDY staff communications, the excluded children were combined with those children whose parents refused participation to comprise the non-enrolled comparison group in this logistic regression. The results are provided in Table 4. Infants born in a European country, with an older mother, and a first degree T1DM relative were more likely to enroll in TEDDY. If another child was already in TEDDY, the child was more likely to be enrolled. However, if the child was a twin or triplet, the family was less likely to enroll. Child's gender was not a significant predictor of TEDDY enrollment. To test whether combining the excluded children with those who refused study participation may have masked important

Table 3
Most frequent protocol and family reasons given for refusing to enroll in TEDDY by country.

Country	Finland	Germany	Sweden	US	ALL
Number of families who refused	1428	560	833	3043	5864
Protocol characteristics: [a] Number (%) of families who refused by protocol characteristic					
Blood draw	71 (5)	202 (36)	125 (15)	669 (22)	1067 (18)
Demanding protocol	171 (12)	106 (19)	108 (13)	517 (17)	902 (15)
Frequency of visits	86 (6)	22 (4)	125 (15)	91 (3)	324 (6)
Travel	157 (11)	0 (0)	158 (19)	213 (7)	528 (9)
Reminded of T1D risk	14 (1)	28 (5)	50 (6)	61 (2)	153 (3)
Study too long	14 (1)	6 (1)	50 (6)	91 (3)	161 (3)
Family factors: [a] Number (%) of families who refused by family characteristic					
Too busy	171 (12)	28 (5)	283 (34)	822 (27)	1304 (22)
Too stressed	43 (3)	17 (3)	50 (6)	91 (3)	201 (3)
Does not want to be in research	0 (0)	11 (2)	17 (2)	152 (5)	180 (3)
Child has medical problems	43 (3)	17 (3)	25 (3)	61 (2)	146 (2)
Family has medical problems	4 (1)	11 (2)	25 (3)	30 (1)	70 (1)
Language barrier	0 (0)	11 (2)	17 (2)	61 (2)	89 (2)

[a] Primary reasons for refusal; parents could give more than one reason.

Table 4
Predictors of enrollment in TEDDY. Enrolled (N = 6734) vs. excluded or refused to enroll (N = 9701).

Possible predictors		OR [a]	95% CI	p-value
Child sex	Male	ref.	–	
	Female	1.00	0.94–1.07	0.9405
Birth type	Singleton	ref.	–	
	Multiple	0.70	0.56–0.87	0.0011
Country	US	ref.	–	
	FIN	2.27	2.09–2.48	<0.0001
	GER	1.14	1.01–1.30	<0.0001
	SWE	5.12	4.68–5.60	<0.0001
Maternal age	Years	1.03	1.02–1.03	<0.0001
Any family member with T1D	No	ref.	–	
	Yes	2.99	2.61–3.42	<0.0001
Other child enrolled in TEDDY	No	ref.	–	
	Yes	2.16	1.78–2.62	<0.0001

[a] Adjusted for all characteristics shown.

differences between children who were excluded versus children who refuse, this analysis was repeated, comparing the enrolled group to the excluded group, and the enrolled group to the refused group; the findings remained the same.

4. Discussion

The most important predictors of TEDDY enrollment were the infant's country of birth and FDR/GP status. FDR infants and infants from European countries were more likely to enroll than GP newborns from the US. FDR families are already well versed in T1DM and may have been less surprised to receive information about the child's increased genetic risk compared to GP families. Motivation to participate was clearly higher in FDR families, probably due to the central role T1DM plays in their lives.

Worldwide, the incidence of T1DM is highest in Finland followed by Sweden [7]. Consequently, the probability that a GP family will know someone with T1DM is more likely in these countries than in the other TEDDY countries, possibly increasing the enrollment rate. Willingness to participate in TEDDY could also differ depending on the level of risk that was communicated to the family. Because the T1DM incidence is higher in Finland and Sweden, the risk of T1DM communicated to HLA eligible GP families (7 out of 100 babies) was higher than the risk communicated to US and German HLA eligible GP families (3 out of 100); this may have further motivated GP families in Finland and Sweden to participate. The particularly high enrollment rate by Swedish parents might be explained by the early information about TEDDY given to all expecting parents at the maternity clinics during the prenatal care. Providing information about TEDDY well in advance of the delivery, gave parents more time to learn about the study and to consider taking part in the screening as well as possible participation in the follow up if the child was eligible. This early preparation might engender a positive attitude towards the TEDDY study. In Sweden and Finland, the TEDDY nurse who called the parents and gave the notification about their newborn's increased genetic risk, remained with the family in the future; each family knew that if they enrolled in TEDDY, they would see the same person in the clinic who gave them information over the phone, answered their questions, and dealt with the parents' initial worries. This approach seemed to be appreciated by many families and may have enhanced enrollment. In fact, the ABIS study reported that trust in the study researcher was a strong reason why families stayed in the study [4]. Perhaps knowing who you are going to meet in the clinic creates initial trust and confidence and increases willingness to enroll.

Older maternal age and a singleton birth were additional predictors of TEDDY enrollment. Older mothers may be better able to manage the demands of TEDDY. Similarly, having one child, versus twins or triplets, may make TEDDY participation more feasible. Not surprisingly, families who were already participating in TEDDY were more likely to have a second child join the protocol compared to families who were new to the TEDDY study.

The likelihood of being excluded from the TEDDY study also differed between countries. Exclusion rates were particularly high in the US where 27% of HLA eligible families did not respond to calls, messages or letters. These families essentially passively refused TEDDY enrollment. The US has a very diverse population that may be less familiar with T1DM compared to smaller and more homogenous countries like Finland and Sweden where the incidence of T1DM is high and the disease may be better known among the general population. Passive refusals were also common in Germany, comprising 16% of their HLA eligible families. Germany recruits TEDDY participants in a very different manner than the other TEDDY sites, focusing primarily on the FDR's. Participants do not meet with TEDDY staff on a regular basis, except by phone. Data collection occurs primarily at the child's pediatrician's office. These procedural differences may have influenced families' willingness to respond to TEDDY staff efforts to contact them for possible participation in TEDDY.

Although enrollment and exclusion rates differed by country, the reasons HLA eligible families refused enrollment were very similar across countries and between GP and FDR populations. Most fell into two categories: aspects of the TEDDY protocol or family reasons. The blood draws were a major concern; a finding also reported in the ABIS study [4]. Parents across all countries also frequently cited the demanding nature of the TEDDY protocol as a reason for refusal. This is not surprising because the TEDDY study requires significant time and effort of families and has a long duration. Many parents also stated they were too busy to participate, a finding consistent with that found in the ABIS study [4]. Families with children have a life that can be very demanding with little time for activities outside the regular day to day schedule.

The third most common circumstance for declining enrollment was “no reason given”. This was particularly common in Finland and among GP families in Germany. In Finland, it is not allowed to explicitly ask for a reason why a person declines participation in a research study, which likely influenced this result. In Germany, unlike the other countries where screening is done at certain hospitals or in certain areas, TEDDY screenings are conducted throughout the country. This might contribute to less willingness to provide a reason for refusal because there is less personal interaction with the TEDDY staff, who are often located far from the family's home town.

Travel to the TEDDY clinic was an obstacle mentioned by many Finnish and Swedish families. Having more than one car in the family in these countries is less common than in the US. Using public transportation with small children might not be a viable alternative for some families and may not be available at all in more rural areas. German families primarily complete their visits at their local pediatrician's clinic and thus do not face this obstacle. In the US, where driving is such an integral part of life and where most families have more than one car, travel was less likely to be cited as a reason for refusing TEDDY enrollment.

Of note, some components of the TEDDY protocol were rarely or never mentioned as an obstacle for joining the study (e.g., sending the child's stool samples to TEDDY every month, recording the child's food intake for 3 days, completing questionnaires). Similarly, refusal to store study samples in the NIH repository was exceedingly uncommon. Although the stool sample collections and dietary recordings may present compliance issues once a family enrolled in TEDDY, these aspects of the study did not impede enrollment.

In conclusion, this study highlights important differences across countries and between GP and FDR populations in enrollment and passive refusal rates. However, reasons for refusal to join TEDDY were strikingly similar across countries and between GP and FDR populations. These reasons consisted of concerns about blood draws, the demanding nature of the TEDDY protocol, and difficulty fitting the demands of TEDDY into the busy lives of families. Other aspects of the TEDDY protocol that appears burdensome, such as stool sample collection or keeping food intake records, were not common reasons for study refusal. Similarly, the requirement that study specimens be stored in the NIH Repository did not impede study enrollment.

As part of TEDDY screening, country, child sex, mother's age, whether the child had a first degree relative with TIDM, and whether the child was a singleton or multiple were the only demographic variables collected. Over 400,000 children will be screened to identify the HLA eligible TEDDY cohort. Such a large number of screenings precluded the collection of other demographic data — such single parent status or ethnic minority status that might be related to study recruitment.

The TEDDY study is an observational longitudinal study that aims to identify the environmental triggers of T1DM in a genetically at-risk pediatric population. TEDDY's enrollment experiences are highly relevant to other investigators planning longitudinal studies with infants and their families. Our findings highlight the importance of country specific estimates for enrollment targets in longitudinal pediatric studies. Although country specific estimates are not always readily available, our findings suggest that enrollment rates are very likely to differ by country based on a variety of factors including prevalence or risk of the disease within a country. Other country-specific factors that might be important include population attitudes toward research, particularly in less educated or ethnic-minority populations. Our findings also suggest that enrollment estimates should be lowered when the study protocol involves enrollment from the general population, painful procedures (e.g. blood draws) or makes multiple protocol demands on families, especially on families who are already leading very busy lives.

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