

# Retention & Adherence: Lessons Learned from TIDM Natural History and Prevention Studies

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# Presentation Overview

- Predictors of study withdrawal
- Development and application of a cumulative risk score
- Importance of target study population
- Adherence – behaviors inside and outside of a natural history study or clinical trial



# Predictors of Study Withdrawal in First Year of TEDDY

- Data collected at the first study visit (child was  $\leq 4.5$  mo of age) was used to predict study withdrawal in Year 1 of TEDDY among general population families
- 89% of TEDDY families came from the general population and those with a first degree T1DM relative were less likely to withdraw
- Predictors included:
  - Demographic
  - Pregnancy variables
  - Child health variables
  - Life stress
  - Maternal reactions to baby's T1DM risk
  - Father participation
- 2294 participants active in TEDDY at the end of year 1 were compared to 763 participants who withdrew using multiple logistic regression; only significant predictors in the full model are presented

# Demographic Predictors of Study Withdrawal in First Year of TEDDY

Demographic Characteristic	% Withdrawals	P value
<b>Country</b>		
Finland	16	0.004
Germany	25	0.481
Sweden	18	0.002
USA	25	Ref
<b>Child gender</b>		
Male	19	Ref
Female	22	0.012
<b>Maternal age</b> (years at child's birth)	Actives: M=30.8 Withdrawals: M=28.5	0.0001



# Pregnancy Predictors of Study Withdrawal in First Year of TEDDY

Maternal Lifestyle Behavior during Pregnancy	% Withdrawals	P value
<b>Smoking</b>		
Yes (n=467)	37	0.0001
No (n=3112)	16	Ref
<b>Alcohol consumption- 3<sup>rd</sup> trimester</b>		
1-2 times per month (n=546)	13	0.045
≥ 3 times per month (n=118)	11	0.180
No alcohol (n=2968)	21	Ref
<b>Employment status</b>		
Worked all 3 trimesters (n=1669)	15	0.0001
Reduced work or did not work at all (n=1843)	23	Ref



# Maternal Reactions to Child's T1DM Risk as Predictors of Withdrawal in First Year of TEDDY

Maternal Reaction	Actives	Withdrawals	P value
<b>Risk Perception</b>	%	%	<b>0.004</b>
Accurate (n=2164)	84	16	
Underestimate (n=1475)	77	23	
<b>State Anxiety Score</b>	<b>M (SD)</b>	<b>M (SD)</b>	<b>0.039</b>
Risk Perception: Accurate	38.8(10.2)	41.7(10.4)	
Risk Perception: Underestimate	38.4(10.2)	39.9 (10.8)	



# Father Participation and Missing Data as Predictors of Study Withdrawal in the First Year of TEDDY

Predictor	% Withdrawal	P value
<b>Father Participation – Completed study survey</b>		
Yes (n=3437)	18	0.0001
No (n=320)	43	Ref
<b>Missing data at study inception</b>		
≤ 1 missing data point (n=3639)	19	Ref
> 1 missing data point (n=118)	58	0.007



# Variables that Did Not Predict Study Withdrawal

- Maternal physical and mental health during pregnancy
- Life stress during pregnancy and after the birth of the child
- Baby's health status at birth and in the first few months of life






# Unmeasured - Potential Predictors of Study Withdrawal

- Maternal education
- Ethnic/minority status
  - In the US, ethnic minority status was a predictor with the following withdrawal rates: 17% white, 33% Hispanic, 33% African American, 29% Other Minority
- Family composition:
  - Marital status
  - Only child status
  - Crowding



# Development and Application of a Cumulative Risk Score

- Cumulative Risk Model assumes the total number of risks is more important than the particular risk factors
- The 7 predictors of early withdrawal (8 in US sites because we included ethnic minority status as a predictor) were used to calculate a High Risk for Early Withdrawal (HREW) score
- Based on available data, we selected a HREW cut-off of  $\geq 4$  to identify those at greatest risk for withdrawal

 HREW Score	Total Sample N = 3449	Number of Withdrawals N = 739	% of Withdrawals 21.4	% Withdrawals for HREW <4 and ≥4
US Sites	N = 1367	N = 346	25.3	
0	61	8	13.1	HREW <4 15.2
1	211	20	9.5	
2	294	41	14.0	
3	301	63	20.9	
4	222	75	33.8	HREW ≥ 4 42.8
5	156	69	44.2	
6	63	28	44.4	
7	42	29	69.1	
8	17	13	76.5	
European Sites	N = 2082	N = 393	18.9	
0	70	9	12.9	HREW <4 14.9
1	291	23	7.9	
2	583	74	12.7	
3	640	130	20.3	
4	343	93	27.1	HREW ≥ 4 31.5
5	106	36	34.0	
6	30	16	53.3	
7	19	12	63.2	

# Tailored Intervention for Those with High HREW Scores at Study Inception

- Beginning in June 2009, HREW scores were calculated for all general populations families joining TEDDY
- Families with HREW scores  $\geq 4$  were identified at study inception from data collected at the child's first TEDDY visit
- TEDDY sites were notified of all participants with HREW scores  $\geq 4$
- TEDDY sites developed individually tailored interventions to improve retention for its participants with HREW scores  $\geq 4$

# Common Tailored Interventions for Families at High Risk for Withdrawal

- More phone calls - to check on the visit experience
- Between visit checks - phone, card, email
- Focused reassurance - encouragement and emphasizing successes
- Specific staff assigned to family
- Detailed visit/chart notes to help in personalizing follow-up phone calls



# Percent of TEDDY Participants with HREW scores $\geq 4$ and Percent of Participants Withdrawing from TEDDY in the First Year by Study Cohort

Cohorts (enrollment date)	Involvement in HREW score	Total N	% HREW $\geq 4$	% Withdrawn in first year of TEDDY
1 (Nov 2004 – May 2006)	Used to create HREW score	1421	28.2	12.9
2 (June 2006 – May 2007)	Used to create HREW score	1395	29.5	11.3
3 (June 2007 – May 2008)	Used to create HREW score	1611	30.2	10.0
4 (June 2008 – May 2009)	No involvement	1495	29.4	7.0
5 (June 2009 – July 2010)	HREW notification and intervention	1712	29.3	3.9



# Percent of General Population Withdrawing from TEDDY Before and After HREW Notification with Tailored Intervention

Risk notification implemented	Withdrawal risk	Total N	% Withdrawn in year 1 of TEDDY	OR	95% CI	p-value	Interaction p-value
No	Low (HREW <4)	1053	4.8	1.00	Ref		
	High (HREW ≥4)	426	12.7	2.85	1.91 – 4.26	<0.0001	
Yes	Low (HREW <4)	1204	3.7	1.00	Ref		
	High (HREW ≥4)	524	4.4	1.21	0.72 – 2.03	0.468	0.010



# Percent Withdrawing from TEDDY Before and After HREW Notification with Tailored Intervention: European Sites

Risk notification implemented	Withdrawal risk	Total N	% withdrawn in year 1 of TEDDY	OR	95% CI	p-value	Interaction p-value
No	Low (HREW <4)	568	5.3	1.00	Ref		
	High (HREW ≥4)	178	14.0	2.93	1.67 – 5.13	<0.0001	
Yes	Low (HREW <4)	652	5.1	1.00	Ref		
	High (HREW ≥4)	230	5.2	1.03	0.52 – 2.04	0.926	0.020





# Percent Withdrawing from TEDDY Before and After HREW Notification with Tailored Intervention: US Sites

Risk notification implemented	Withdrawal risk	Total N	% withdrawn in year 1 of TEDDY	OR	95% CI	p-value	Interaction p-value
No	Low (HREW <4)	485	4.3	1.00	Ref		
	High (HREW ≥4)	248	11.7	2.93	1.63 – 5.25	<0.0001	
Yes	Low (HREW <4)	552	2.0	1.00	Ref		
	High (HREW ≥4)	294	3.7	1.91	0.82 – 4.46	0.134	0.418



# Development and Application of a Cumulative Risk Score with Tailored Intervention

- Cumulative Risk Model offers promise for identifying those at greatest risk for study withdrawal
- Delivering a tailored intervention - to those identified at high risk for study withdrawal at study inception - offers promise for a cost-effective means of decreasing withdrawal rates in this high risk group
- Pre-post design, rather than random assignment, limits our confidence in these findings



# Predicting Study Withdrawal in TEDDY Study Years 2-3

- Data collected at the first year of TEDDY was used to predict study withdrawal in Year 2-3 among general population families
- Predictors included:
  - Demographic – added maternal education, family composition, ethnic-minority status, recruitment cohort
  - Maternal lifestyle behaviors: smoking and working during pregnancy and in first year of TEDDY
  - Maternal reactions to baby's T1DM risk – study inception, 6, 15 mo – added depression
  - Serious negative life events during first year of TEDDY
  - Child illness during the first year of TEDDY
  - Father participation – survey completion at study inception, 6, 15 mo
  - Study visit/blood draw compliance during the first year of TEDDY
  - Maternal satisfaction with TEDDY: 6 and 15 mo
- 3042 participants active in TEDDY at the end of year 3 were compared to 432 participants who completed the first year of TEDDY but withdrew during TEDDY years 2-3 using multiple logistic regression; only significant predictors in the full model are presented



# Demographic Predictors of Year 2-3 TEDDY Withdrawal

Factor	N	% Withdrawal	OR	P value
Recruitment Cohort				
Year 1	708	14.8	1.97	
Year 2	1031	13.4	2.03	
Year 3	1204	12.5	1.71	
Year 4	531	8.5	1.00	0.003
Maternal age at child's birth				
<25 years	397	22.7	1.0	
>25 years	3077	11.1	1.35	0.069
Maternal education				
Primary, trade or some college	1483	15.2	1.27	
Graduated college	1911	9.7	1.0	0.065
Household crowding - lowest	479	7.5	1.15	0.011
highest	315	18.1		
Only child				
No	1904	11.3	1.0	
Yes	1494	13.2	1.36	0.012



# Maternal Lifestyle Behaviors, Risk Perception, and Child Illnesses as Predictors of Year 2-3 TEDDY Withdrawal

Factor	N	% Withdrawal	OR	P value
Worked during pregnancy				
Reduced work or did not work at all	1716	14.6	1.34	
Worked all 3 trimesters	1613	9.9	1.0	0.015
Maternal smoking during year 1 of TEDDY				
No	3067	11.3	1.0	
Yes	336	19.6	1.48	0.02
Maternal risk perceptions (15 mo)				
Accurate	1902	8.9	1.0	
Underestimate	1310	14.7	1.42	0.002
Child Illnesses in TEDDY year 1(scored 1-5)			0.89	0.018
1 ( 0 – 2)	361	18.3		
2 (3 – 4)	755	15.6		
3 (5 – 7)	1157	11.4		
4 (8 – 10)	702	11.7		
5 (>10)	484	6.8		



# Father Participation, Study Compliance, Maternal Satisfaction as Predictors of Study Withdrawal in Years 2-3

Factor	N	% Withdrawal	OR	P value
Father participation				
Completed all 3 surveys	2648	10.2	1.0	
Completed 0, 1, 2 surveys	826	19.9	1.57	0.001
Missed visit or blood draw in first year				
No	2859	10.1	1.0	
Missed blood draw but not visit	404	17.8	1.51	
Missed 1 or more visits	211	33.2	2.90	0.0001
Maternal study satisfaction (15 mo)				
Very satisfied	1404	6.5	1.0	
Somewhat satisfied	874	12.6	1.92	
Somewhat dissatisfied	655	15.3	2.58	
Very dissatisfied	273	23.1	4.43	0.001



## Variables that Did Not Predict Study Withdrawal in Years 2-3

- Ethnic minority status & marital status, if maternal education was in the model
- Negative life events in the first year of TEDDY
- Maternal anxiety and depression in the first year of TEDDY



# Predicting Study Withdrawal in TEDDY Study

## Years 2-3: Next Steps

- Use Modified Cumulative Risk Score Approach under Consideration
  - Cumulative risk score with cut off determined
  - Site notification with tailored intervention
  - Sites also informed of high risk cases that include underestimation of T1DM risk and low maternal study satisfaction; interventions designed to address these issues put in place
  - Confidentiality issues need to be addressed



# Predicting Study Withdrawal: Lessons Learned

- Early and late withdrawal can be successfully predicted using multivariate models
- Developing a cumulative risk score with a tailored intervention shows considerable promise as a cost-effective means of reducing study withdrawal in longitudinal studies



# Predicting Study Withdrawal: Lessons Learned

- Some of the most important predictors are rarely measured in clinical trials
  - Maternal age and education, crowding, only child status
  - Maternal lifestyle behaviors (e.g. work during pregnancy and smoking)
  - Maternal reactions (e.g. risk perceptions and anxiety)
  - Mother reports of child illnesses
  - Dad participation
  - Study satisfaction

# Presentation Overview

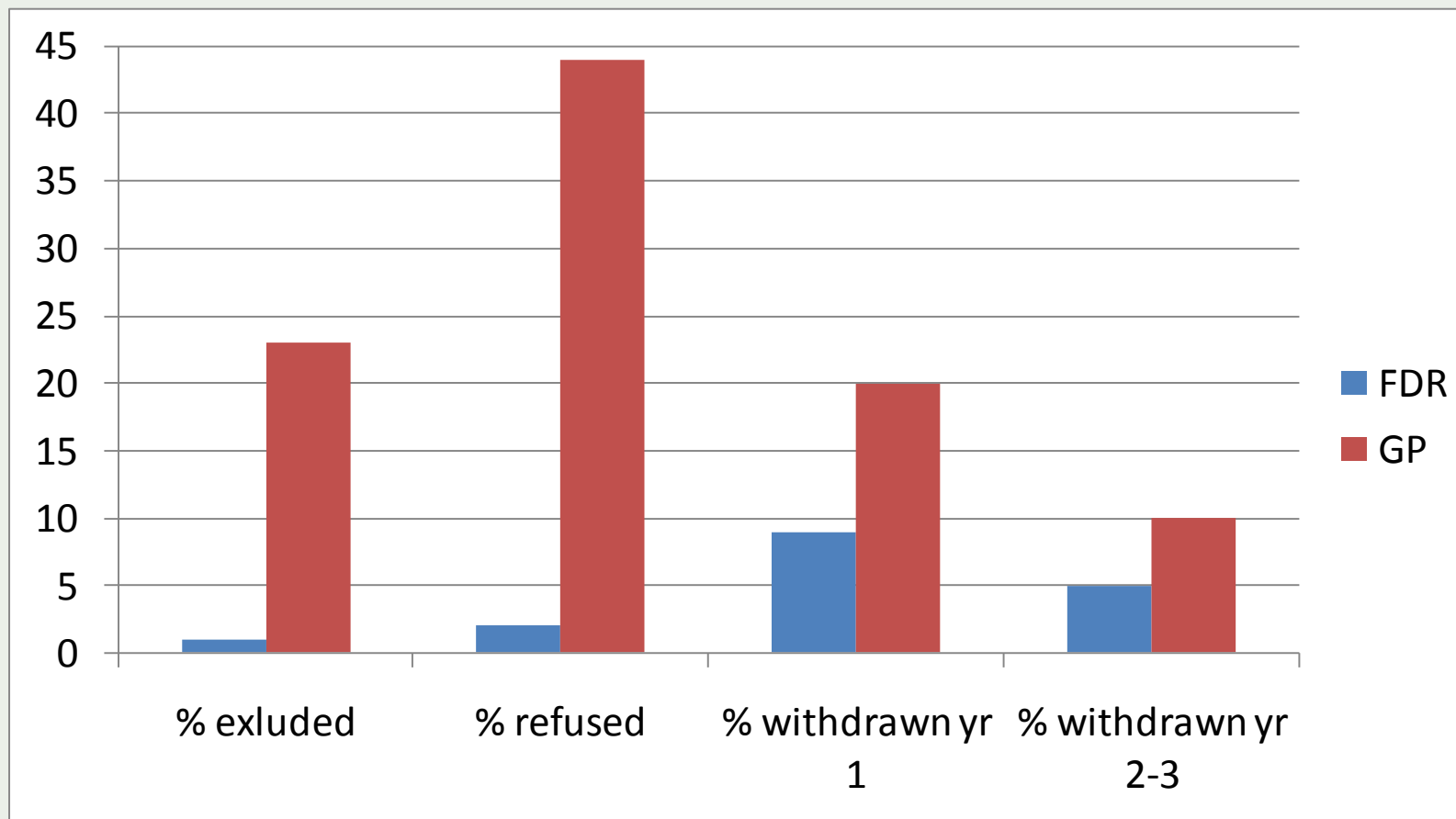
- Predictors of study withdrawal
- Development and application of a cumulative risk score
- Importance of target study population
- Adherence – behaviors inside and outside of a natural history study or clinical trial

## Recruitment, Retention, Adherence, Study Reactions May Differ Depending on Study Population

- Country
- Newly diagnosed versus experienced patient
- Child versus adult
- Parent versus child
- Mother versus father
- General population versus first degree relative

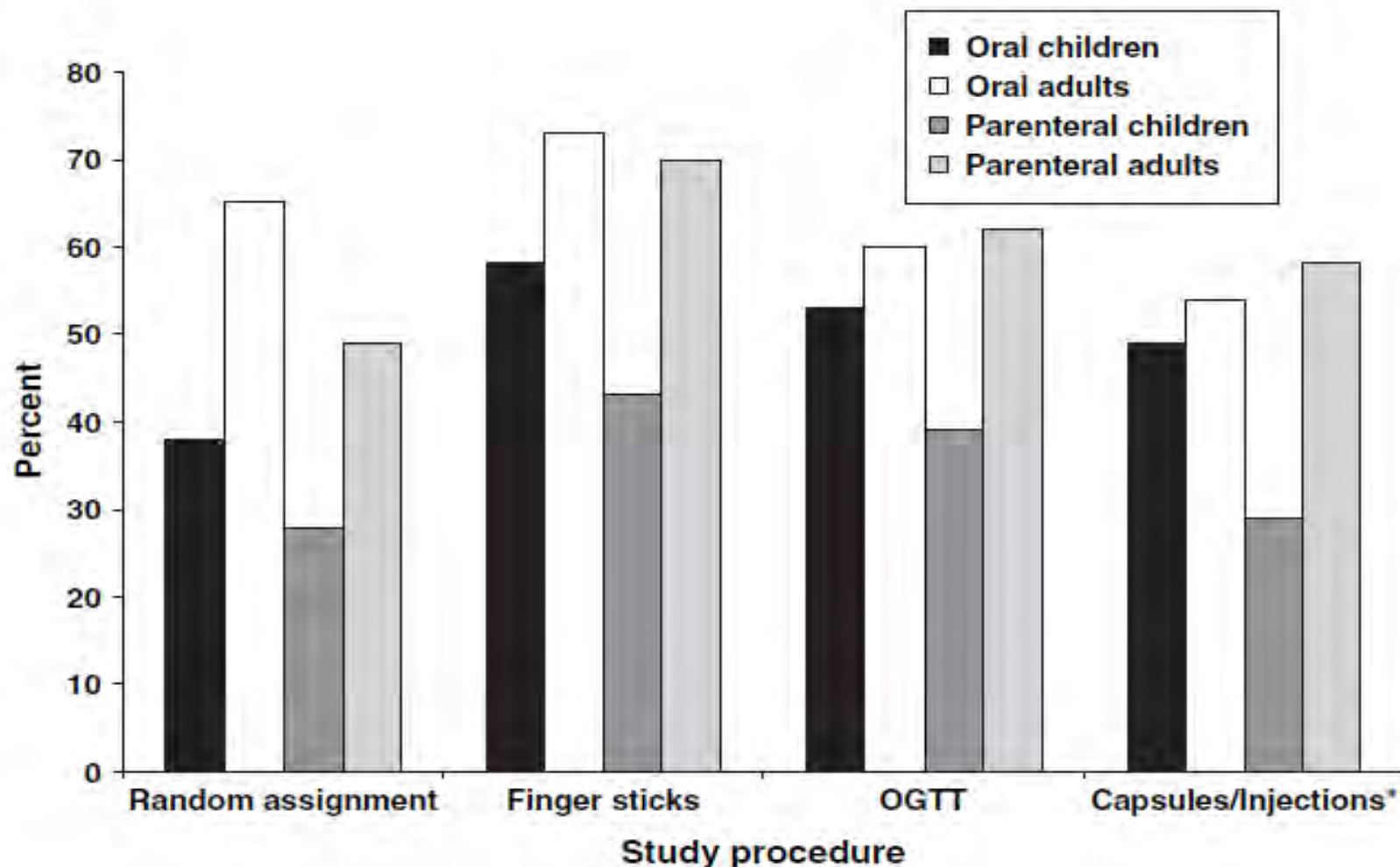


# FDR versus General Population: TEDDY Recruitment and Retention





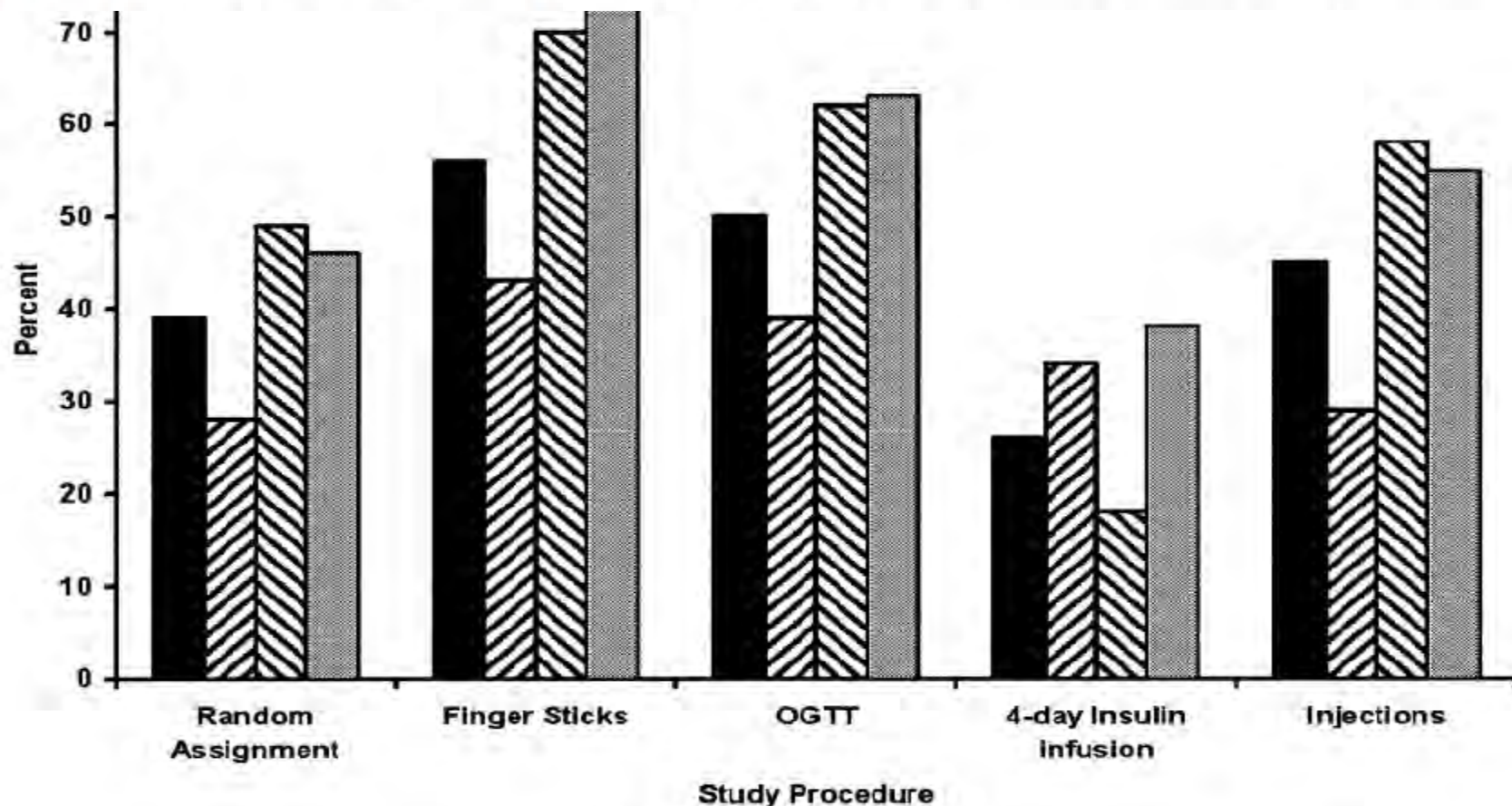
# DPT-1: Percent of Children versus Adults Willing to be in another Study with Similar Procedures





# DPT-1: Percent of Parenteral Child & Adult Participants & Parents Willing to be in another Study with Similar Procedures

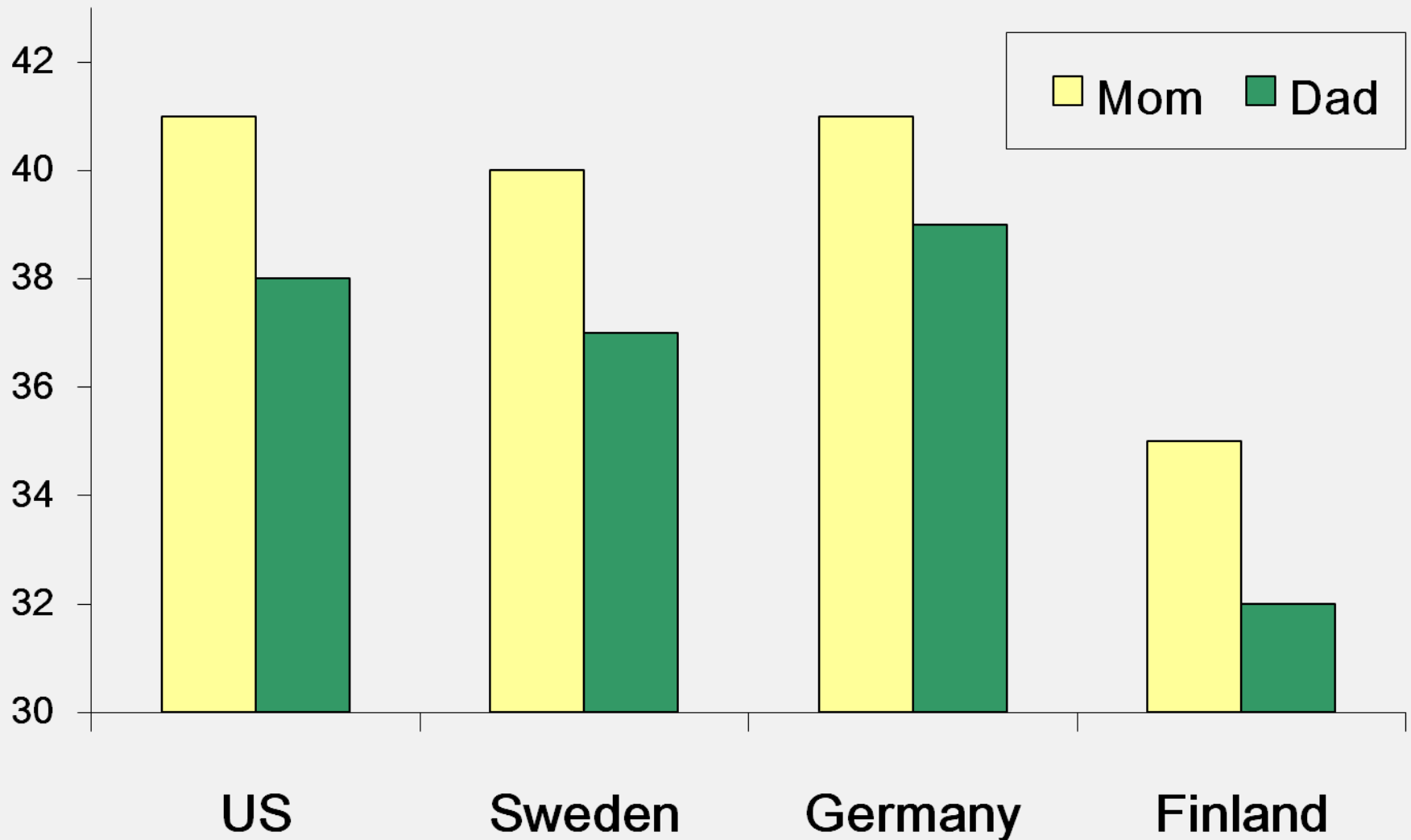
■, all participants; ▨, child participants; ▩, adult participants; ▤, parents.







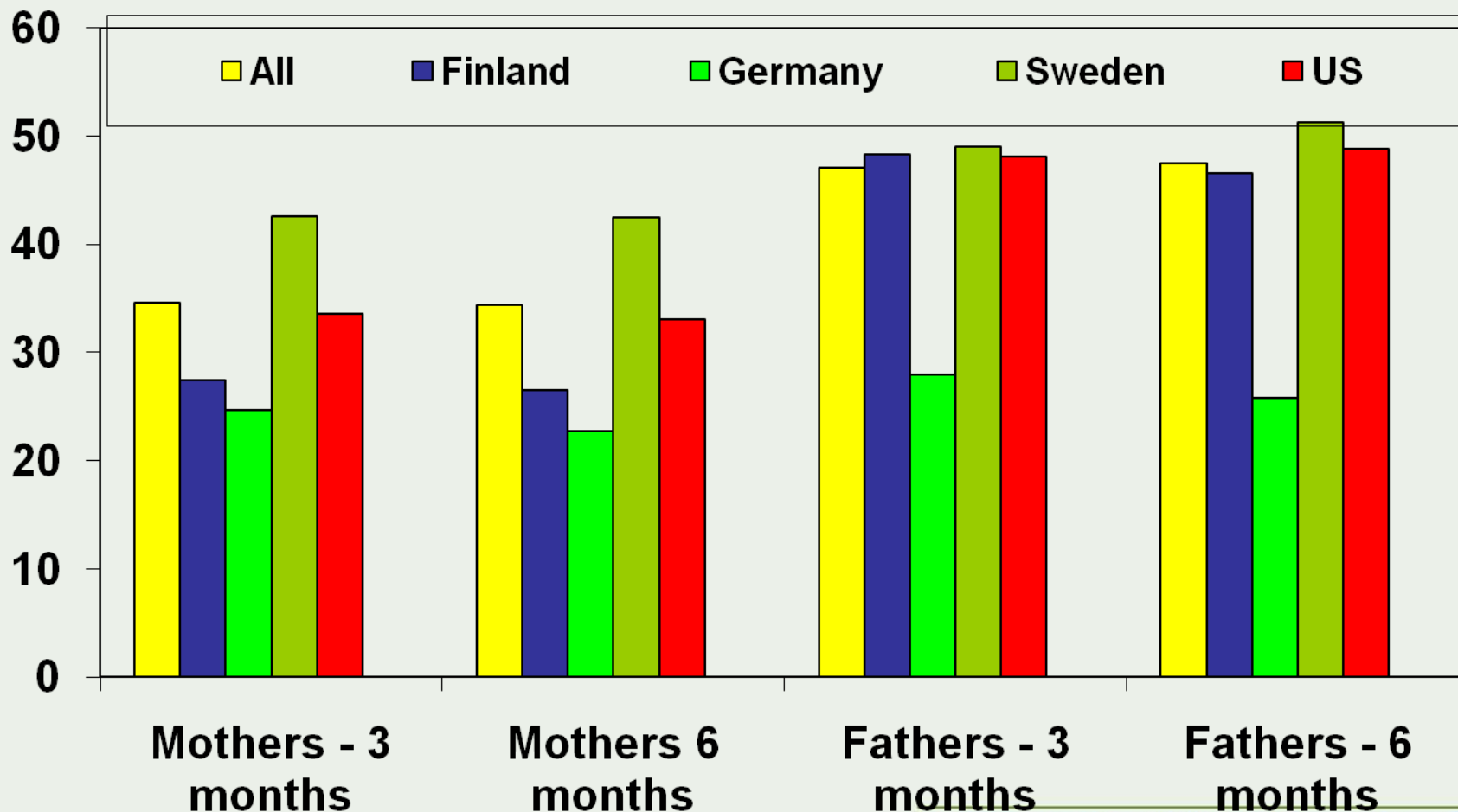
## Initial SAI Anxiety Scores of Parents with Genetically At-Risk Children by TEDDY Country







# TEDDY Parent Percent Underestimation by Time, Parent and Country



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# Study Adherence

- Failure to adhere to study procedures is common and may be influenced by respondent (e.g. parent versus participant), time, and study procedure
- Disease prevention efforts are common even when participants are told that there are no successfully prevention strategies available



# Medication Adherence in the DPT-1

Medication/ Respondent	Doses missed per week		% not taking any med at study end
	Study Beginning	Study End	
Oral Insulin			
Parent	1.24	1.89	3
Participant	1.56	4.34	13
Parenteral Insulin			
Parent	1.04	2.34	7
Participant	1.03	3.52	15

# Participants Efforts to Prevent T1DM

- There is a small but consistent literature that study participants and parents engage in behaviors – outside of the study – to try and prevent the disease
- This occurs despite statements to trial participants that there are no currently available means of preventing T1DM
- Dietary changes are most common, followed by exercise

# Percent Reporting Efforts to Prevent T1DM in DPT-1 and TEDDY

Study/Respondent	Percent Reporting Behavior Change to Prevent T1DM
DPT-1 Oral Insulin Trial	
Parent	38
Participant	48
DPT-1 Parenteral Insulin Trial	
Parent	57
Participant	48
TEDDY year 1	
Parent	40

# Summary and Recommendations

- Study withdrawal can be successfully predicted using multivariate models – however, to be successful, greater attention must be given to measures not typically collected in clinical trials (e.g. participant characteristics, reactions and behaviors, father participation)
- The cumulative risk model - with a tailored intervention - shows considerable promise as a cost-effective means of reducing study withdrawal in longitudinal studies

# Summary and Recommendations

- Characteristics of the target population are critical to all aspects of the study: recruitment, retention, study compliance, and reactions to study participation
- Study adherence may be one important predictor of study withdrawal
- Study adherence is determined by a variety of factors (e.g., time, respondent, procedure); unless measured – study noncompliance threatens the study's validity
- Participants commonly engage in behaviors outside of the trial; unless measured - these also threaten the validity of the study