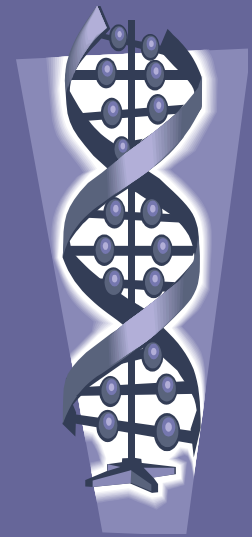


Newborn Genetic Screening for Type 1 Diabetes: Impact on Families

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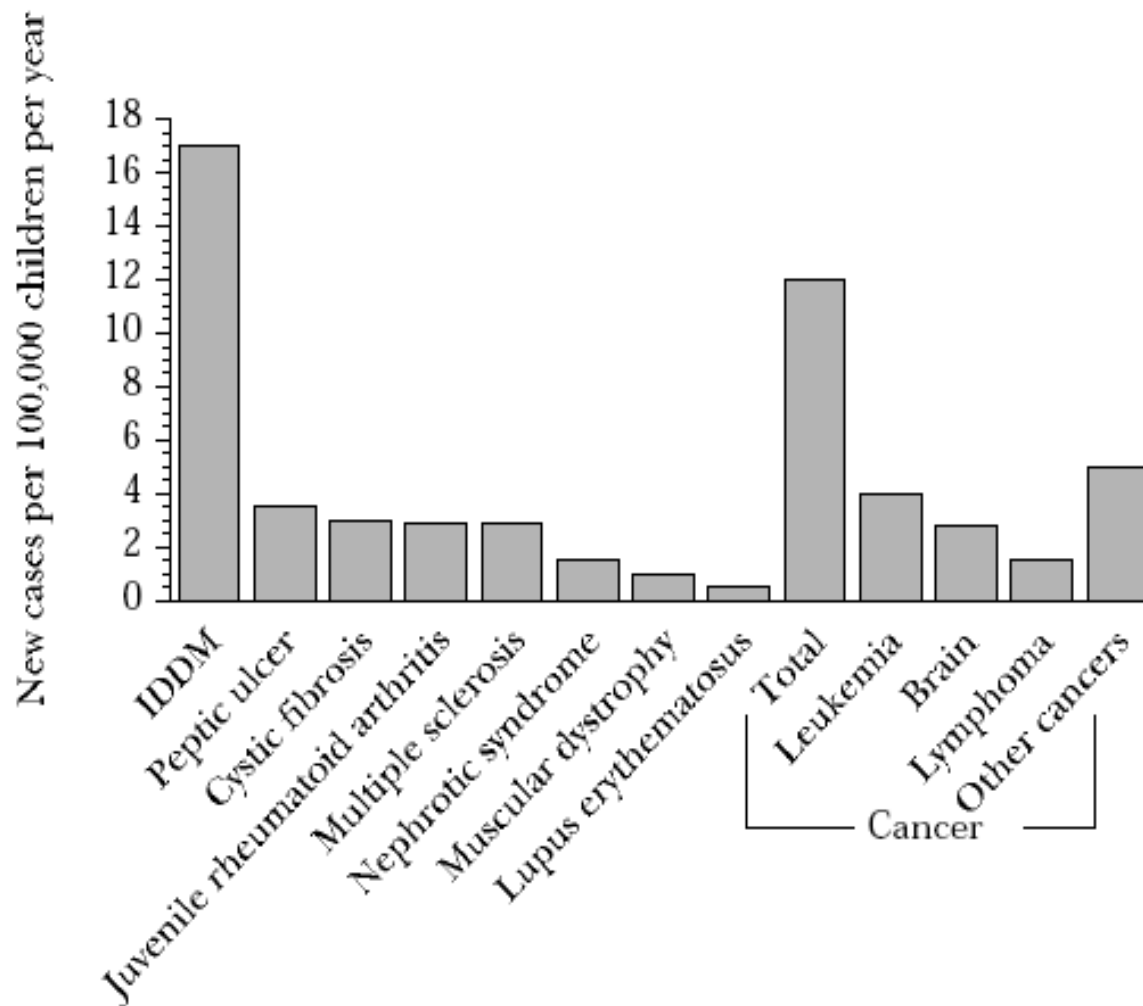
Presentation Overview

- Type 1 Diabetes (T1D)
 - Epidemiology
 - Natural history
- Newborn genetic screening for T1D Risk
- Impact on Families
 - Emotional (anxiety about T1D risk)
 - Cognitive (T1D risk perception)
 - Behavioral (behaviors to prevent T1D; clinical trial participation)
 - Importance of family member role (child, mother, father), culture (country) and family history of T1D on impact
- Future Directions and Reflections
 - Role of psychology and behavioral science

Epidemiology of T1D

- T1D is different from Type 2 Diabetes
 - T1D is typically diagnosed in childhood, not associated with obesity
 - T2D is far more common, usually diagnosed in older adulthood, associated with obesity
- T1D is a common serious disease of childhood
 - 1 in 300 US children; 177,000 US children
 - Varies geographically – highest in Scandinavia, lowest in China
- Increasing world-wide (3-5% annually)
- Peak incidence during puberty; can occur from birth to young adulthood
- Highest increase in incidence is in very young children
- Requires life-long complex treatment regimen, including multiple daily insulin injections for survival

Incidence of IDDM Compared with Other Chronic Diseases of Children Age <16 Years

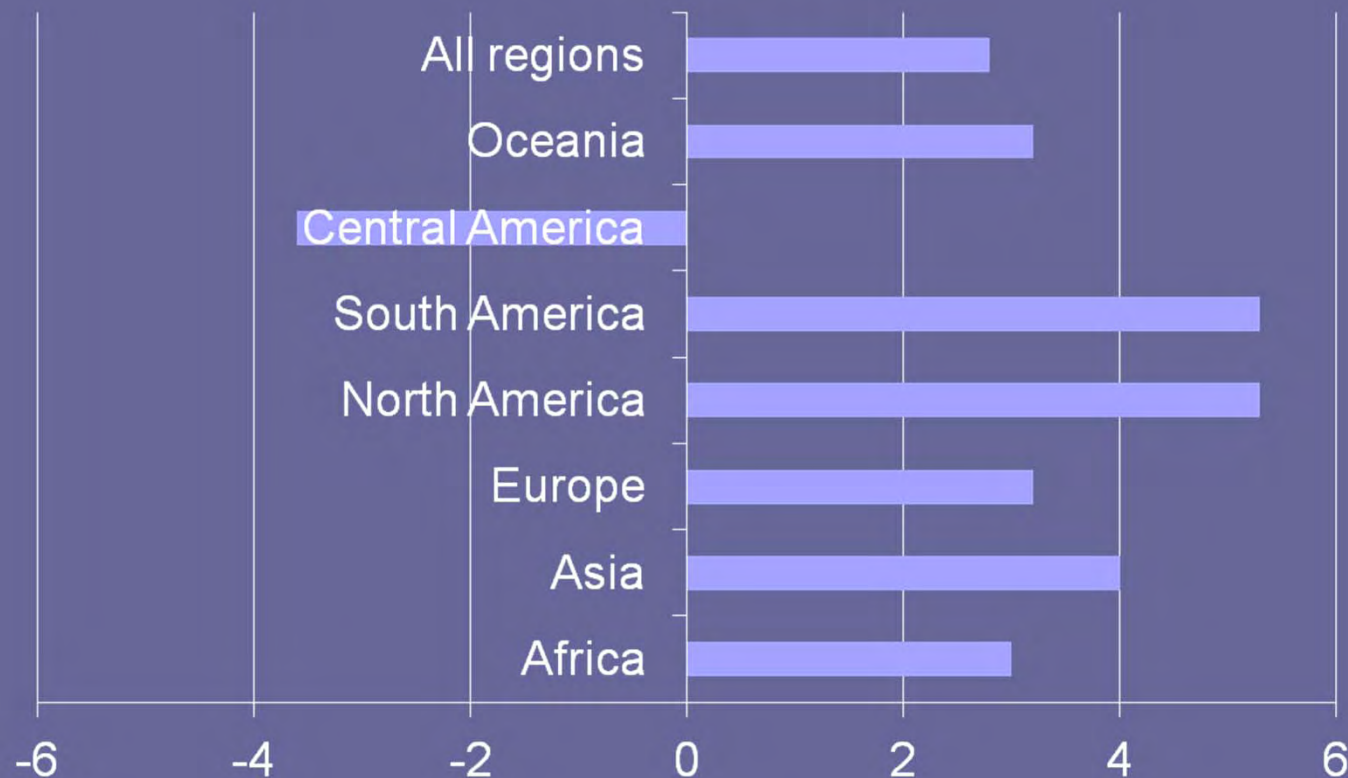


LaPorte et al, Diabetes in America, 2nd Edition



Diabetes in Children is Increasing Worldwide

Annual % Increase in Type 1 Diabetes 1990-1999



The DIAMOND Project Group. Diabetic Medicine 2006

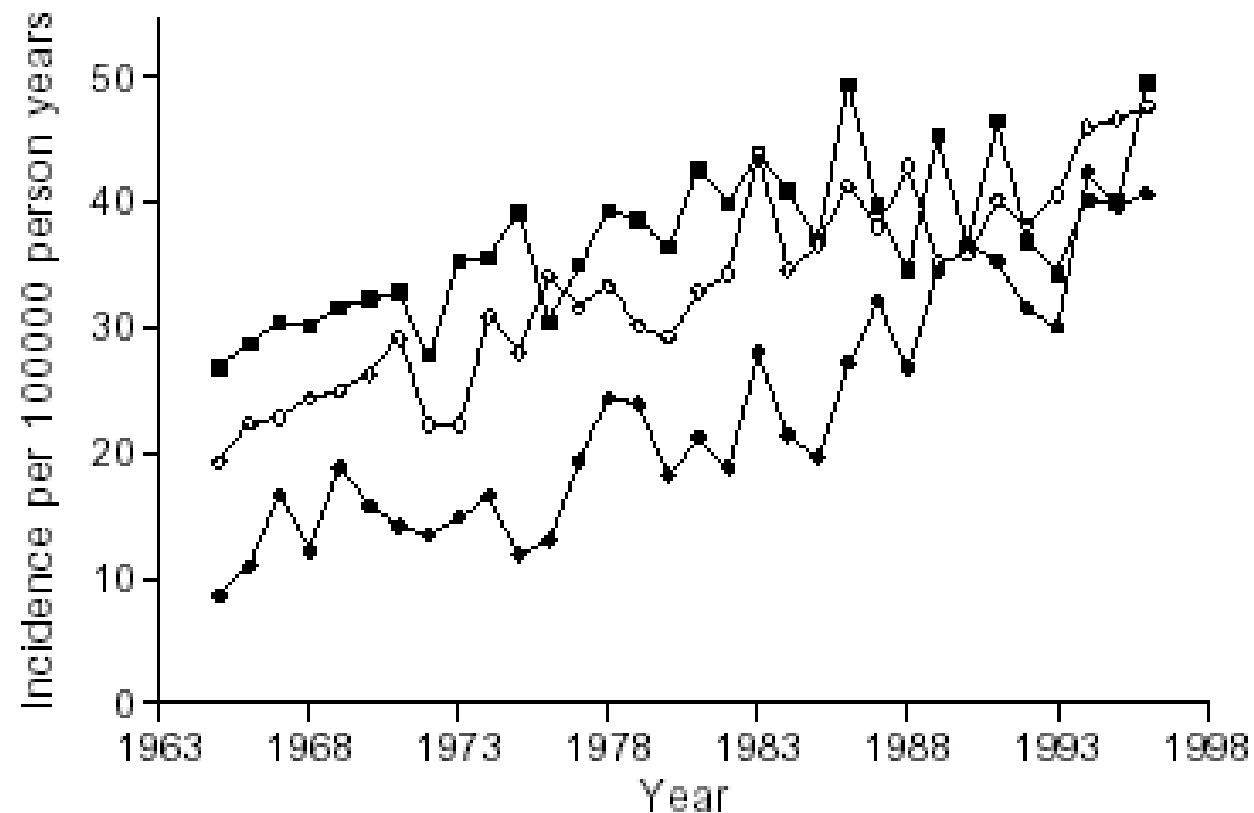
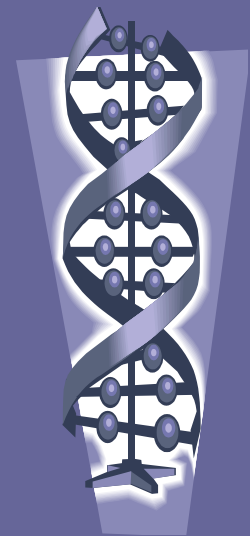
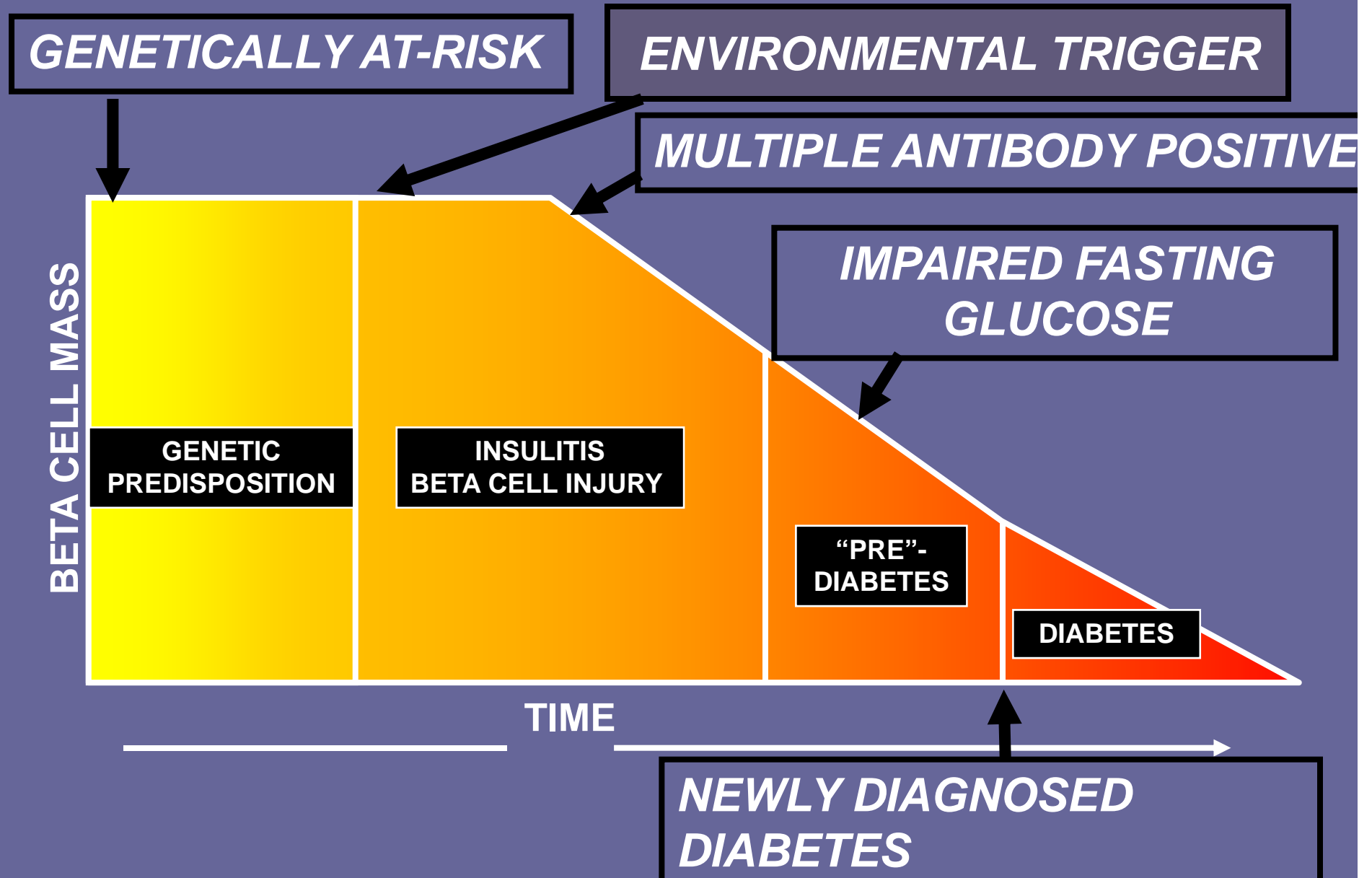


Fig.2. The age-specific annual incidence of Type I diabetes per 100 000 Finnish children aged 1–14 years between 1965 and 1996. ● 1–4 years, ○ 5–9 years, ■ 10–14 years

Tuomilehto et al., Diabetologia, 1999



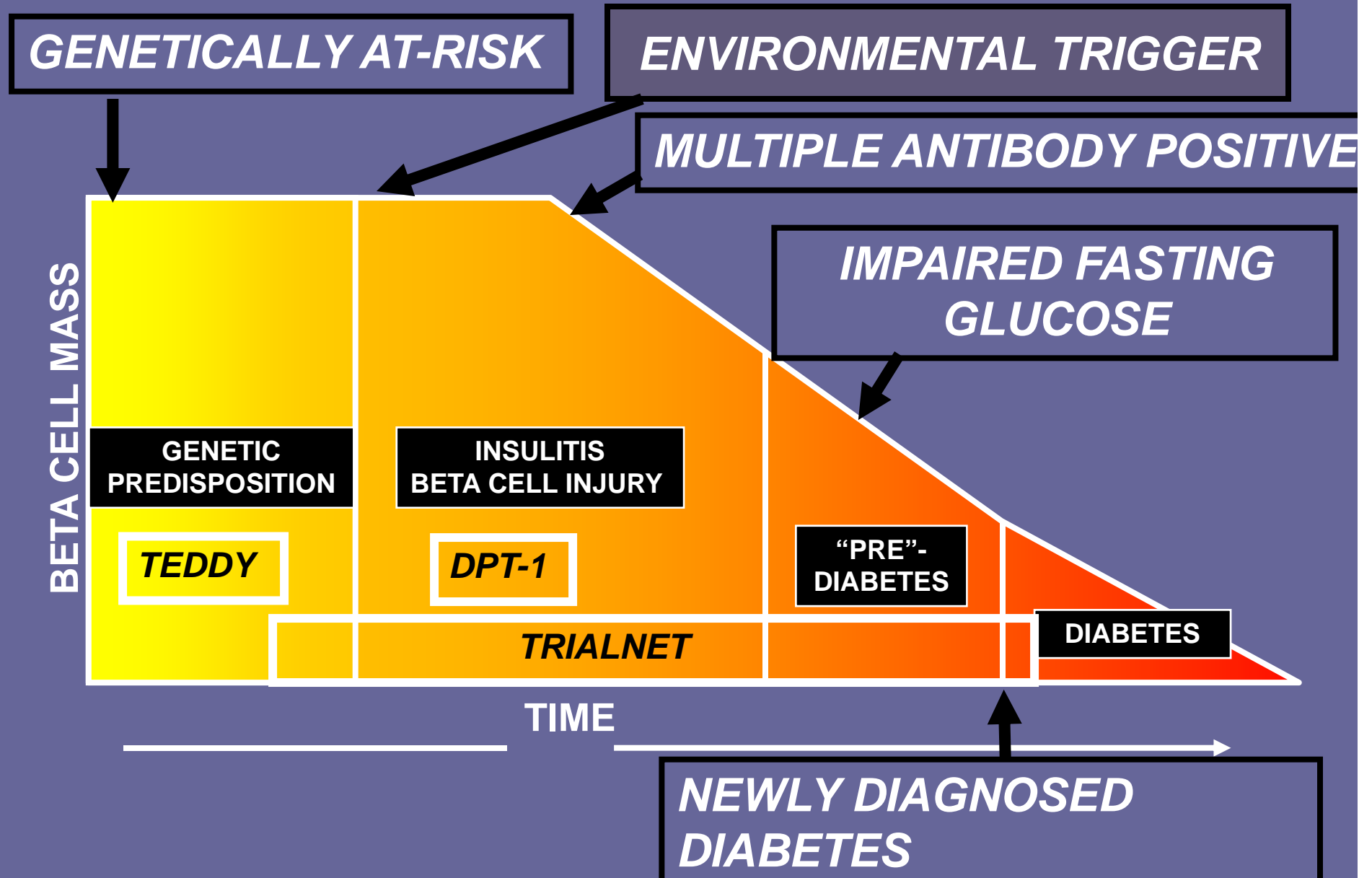
Development of Type 1 Diabetes



Can T1D Be Prevented?

- Understanding the natural history of T1D opens the door for prevention
- NIH Diabetes Prevention Trial – 1 (DPT-1) tested subcutaneous and oral insulin in individuals in the insulinitis phase
 - DPT-1 failed
 - NIH TrialNet is testing potential interventions
<http://www.diabetestrialnet.org/public.html>
- Newborn genetic screening to identify infants at risk may help identify the environmental trigger, leading to possible prevention strategies
 - NIH TEDDY study
<http://teddy.epi.usf.edu/TEDDY/index.htm>

Development of Type 1 Diabetes



Newborn Genetic Screening for T1D Risk is Controversial

- Screening targets children who are unable to provide informed consent
- Positive genetic test results have poor predictive power
- There is no known means of preventing the disease in those at risk
- Testing may increase psychological distress in parents with negative effects on the child
- May interfere with access to health insurance

Newborn Genetic Screening for T1D Risk is Necessary

- To understand the natural history of T1D
- To identify environmental triggers
- To develop prevention strategies
- Newborn genetic screening is ongoing in research studies worldwide:
 - ❖ PANDA (FI/Ga, USA)
 - DAISY (Colorado, USA)
 - DEWIT (Washington, USA)
 - DIPP (Finland)
 - BABYDIAB (Germany)
 - DiPiS (Sweden)
 - ❖ TEDDY – NIH multi-site trial to identify the environmental triggers of T1D



TEDDY: The Environmental Determinants of Diabetes in the Young

- Multi-site NIDDK supported observational study involving 3 sites in the US and sites in Finland, Germany and Sweden
- 420,000 newborns screened for HLA conferred T1D risk
- 21,589 were HLA eligible – most have no family member with T1D
- 8668 joined the TEDDY study
- A host of possible triggers for T1D are monitored (diet, infections, stress)
- Children will be followed up to 15 years

Genetic Screening for T1D: Emotional Impact on Families

- Most studies have been conducted with mothers of children screened for T1D
- Most studies have used the State component of the State Trait Anxiety Inventory



Emotional Impact: Maternal SAI Scores over Time

Genetically at-risk	Country	Pre-test	Post-test	4-6 mos post-test	1 year post-test
Johnson (2004)	US		37	31	28
Carmichael (2003)	US		36	32	30
Johnson (2007)	Finland		36	32	
	Germany		38	39	
	Sweden		40	36	
	US		41	39	
ICA+					
Johnson (1995)	US		55	39	
Hummel (2004)	Germany	43	51		

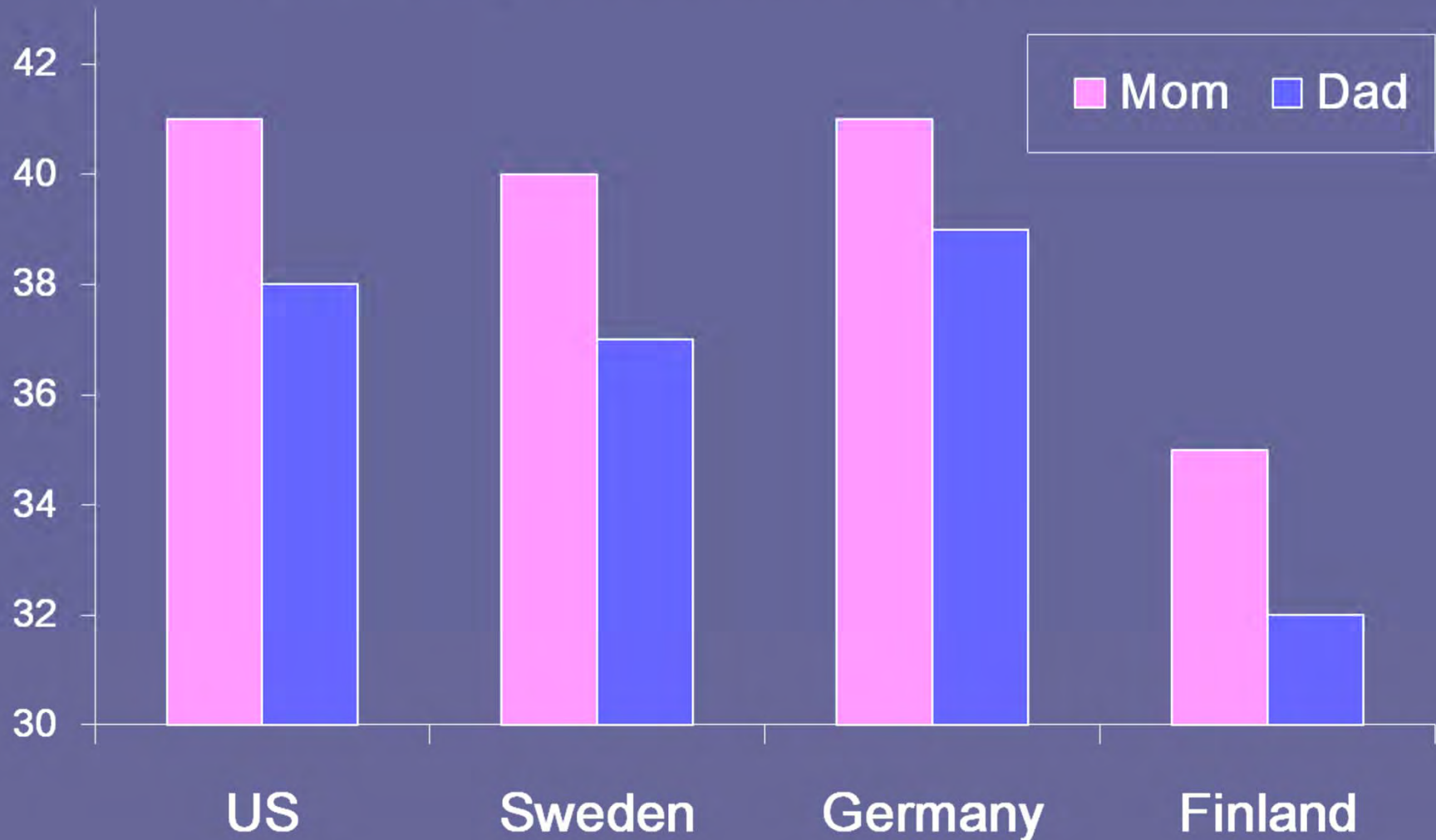
Emotional Impact: SAI scores differ by study population

- Country
- Child versus adult
- Parent versus child
- Mother versus father
- Presence of a T1D family member

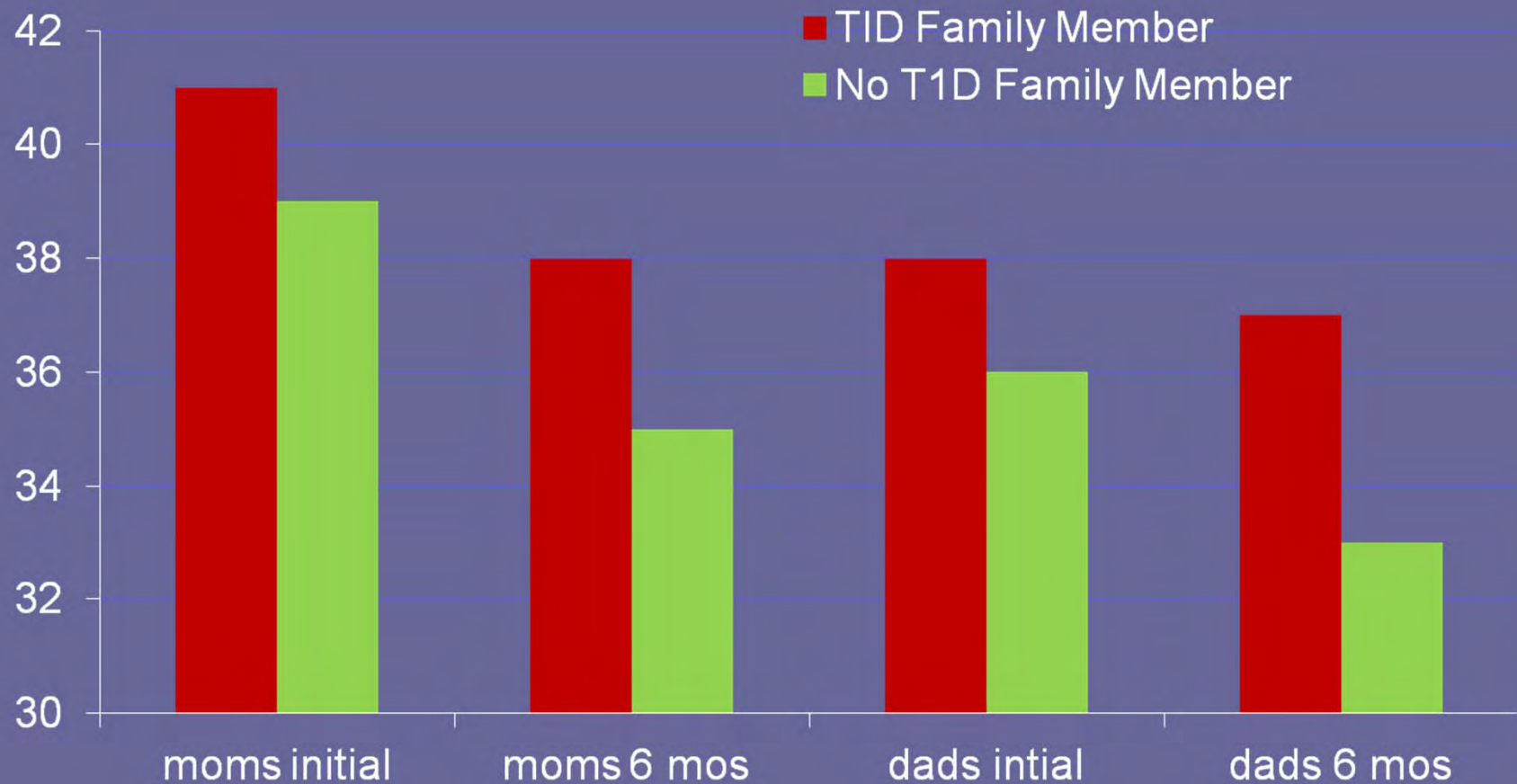
Emotional Impact: SAI scores for Islet Cell Antibody + children and adults and their parents

Islet Cell Antibody + adults	Country	Pre-test	Post-test	4-6 mos post-test
Johnson (1990)	US		52	35
Johnson (1995)	US		45	34
Islet Cell Antibody + children				
Johnson (1990)	US		44	33
Johnson (1995)	US		42	32
Mothers				
Johnson (1995)	US		55	39
Hummel (2004)	Germany	43	51	
Fathers				
Hummel (2004)	Germany	39	44	

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



Emotional Impact: SAI scores for Families With and Without a T1D Family Member



Impact of Genetic Screening for T1D

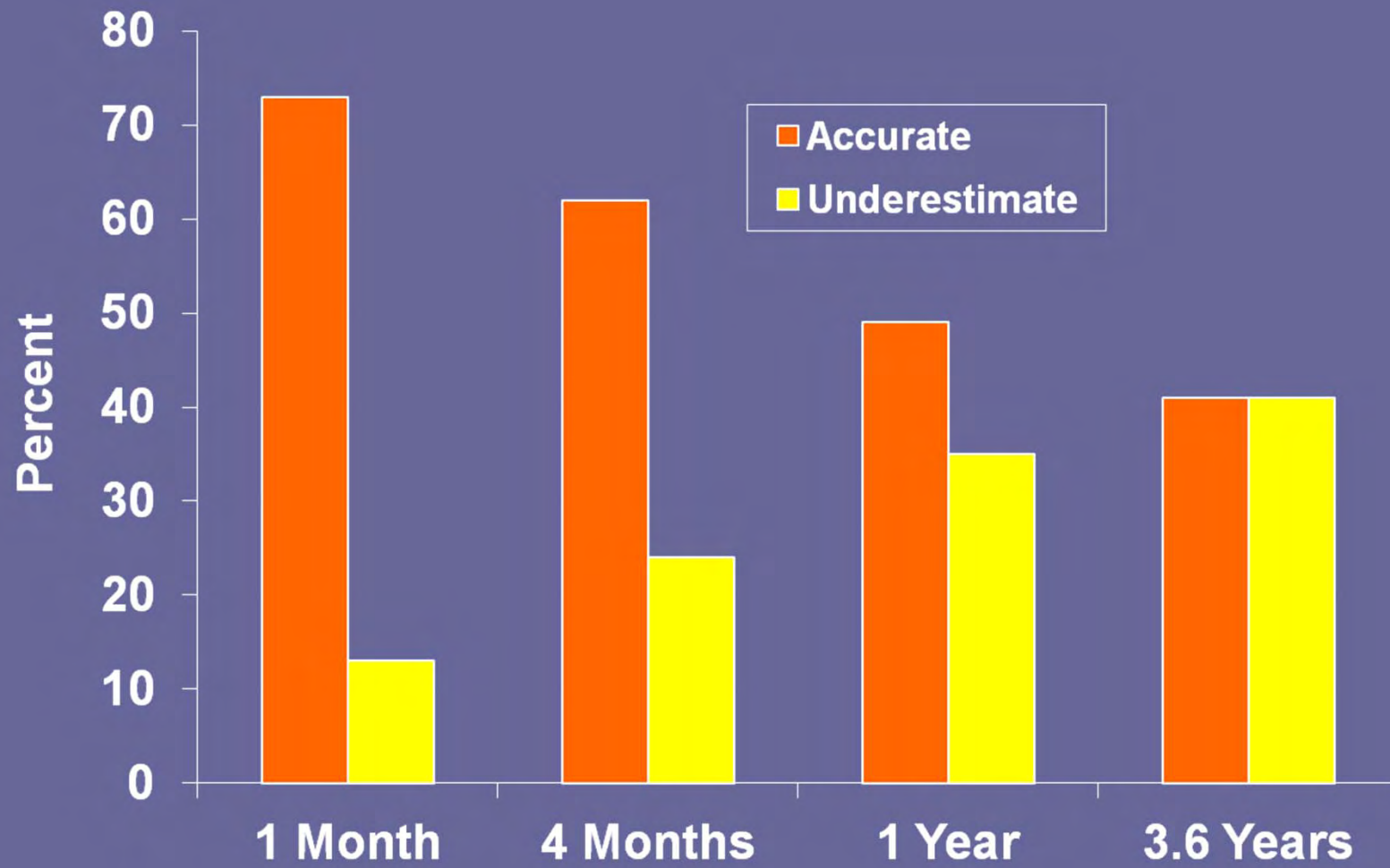
Risk on Families: State Anxiety

- Risk notification is associated with mildly elevated levels of anxiety which declines over time
- Family variables are associated with initial anxiety level and its dissipation over time
 - Adults may be more anxious than children
 - Mothers are more anxious than fathers
 - There are large country differences
 - Having a T1D family member is associated with higher anxiety and a smaller decline in anxiety over time

Genetic Screening for T1D: Cognitive Impact

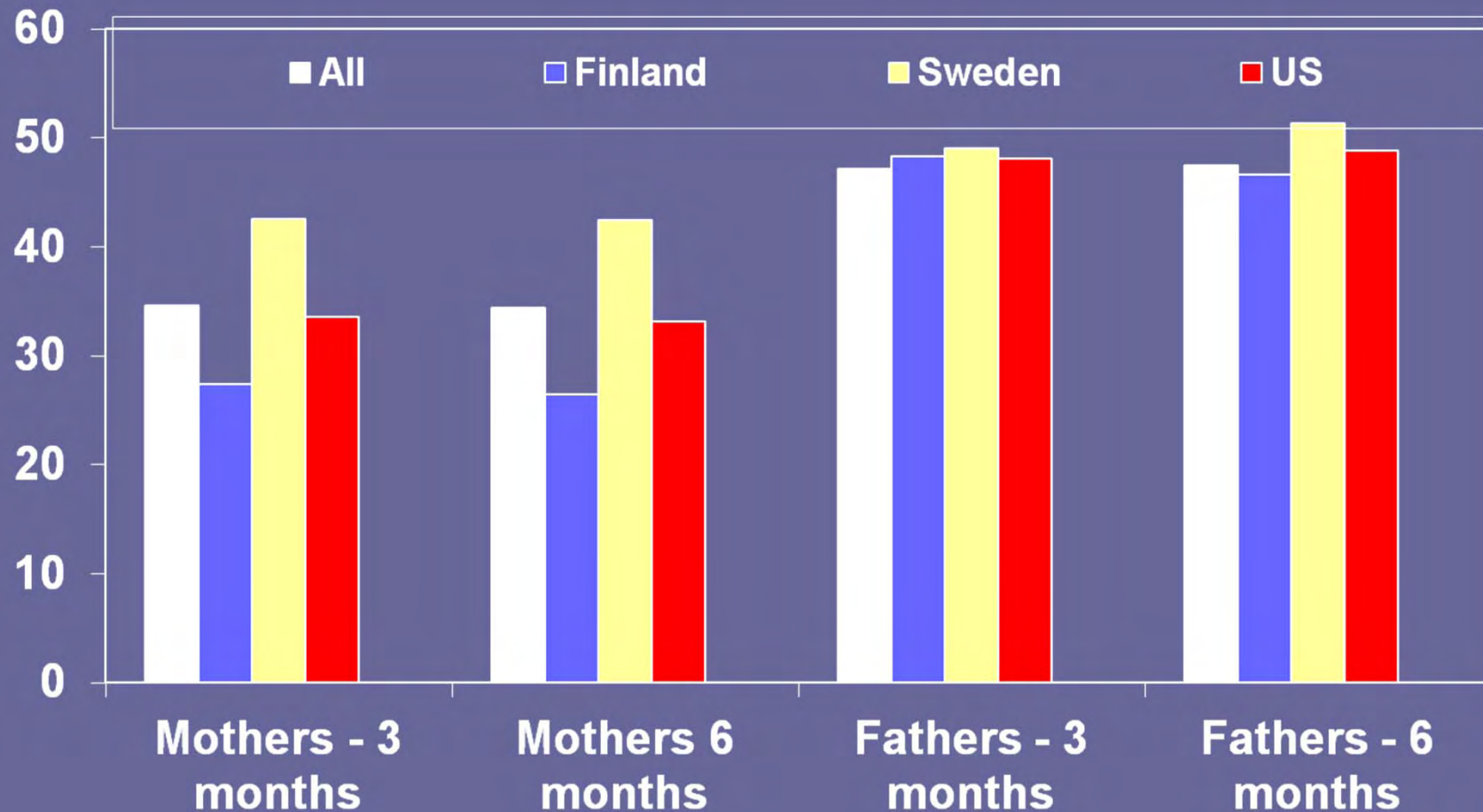
- Some studies have examined whether participants understand the risk information provided
- Most have been conducted with parents, usually mothers

Cognitive Impact of Genetic Screening: Maternal Risk Perception Accuracy Over Time

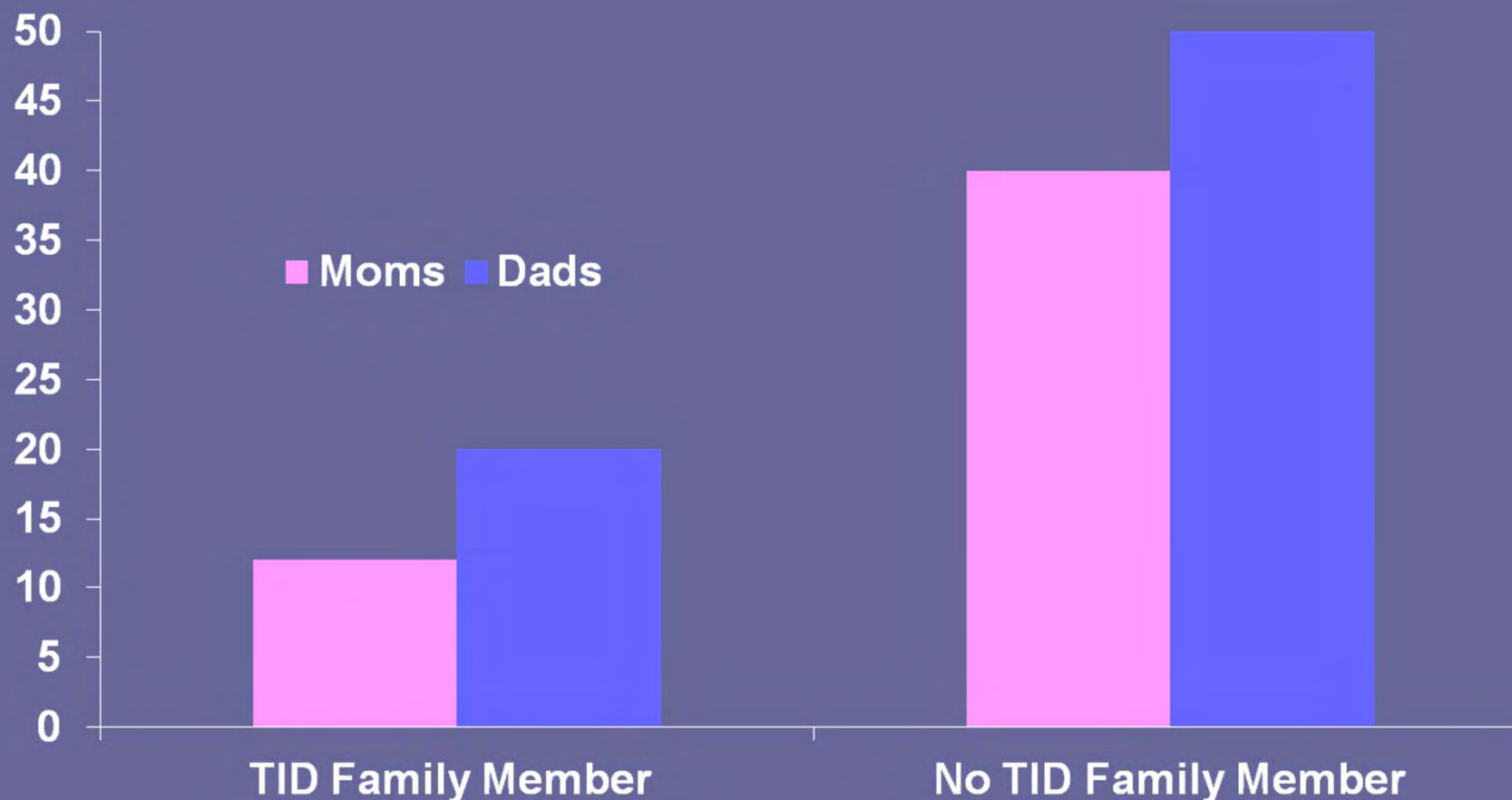


(Johnson, 2006; Baughcum, Johnson et al, 2007)

Cognitive Impact: TEDDY Parent Percent Underestimation by Time and Country



Cognitive Impact: TEDDY Parent Percent T1D Risk Underestimation for Families With and Without a T1D Family Member



Impact of Genetic Screening for T1D Risk on Families: Risk Perception

- Underestimation of risk is common
- Risk underestimation may increase over time unless risk information is repeated
- Family variables influence risk perception:
 - Fathers are more likely to underestimate risk than mothers
 - There are large country differences in risk underestimation
 - Families with no T1D family member are more likely to underestimate risk

Genetic Screening for T1D: Behavioral Impact

- A small literature suggests that many families with positive screening results report behavior changes in an effort to prevent T1D
- T1D monitoring behaviors, changes in diet and exercise are common
- Potentially harmful behaviors (limiting contact with other children, delaying immunizations) are rare

Behavioral Impact: Many Mothers Report Behavior Change in Response to Child's Increased T1D Risk

- 67% mothers reported behavior changes
- Most common behaviors reported:
 - Monitoring behaviors (59%)
 - Dietary changes (34%)
 - Physical activity changes (14%)
- If the at-risk child had a first degree T1D relative, the mother was 19 times more likely to report behavior changes to prevent T1D
- Mothers who were more anxious and who had accurate perceptions about the child's T1D risk were more likely to report behavior changes

(Baughcum, Johnson et al, 2005)

Behavioral Impact: Percent Reporting Efforts to Prevent T1D in DPT-1 and TEDDY

Study/Respondent	Percent Reporting Behavior Change to Prevent T1DM
DPT-1 Oral Insulin Trial (Johnson et al, 2009)	
Parent	38
Participant	48
DPT-1 Parenteral Insulin Trial (Johnson et al, 2007)	
Parent	57
Participant	48
TEDDY year 1	
Mother (No T1D Family Member)	42
Mother (T1D Family Member)	51

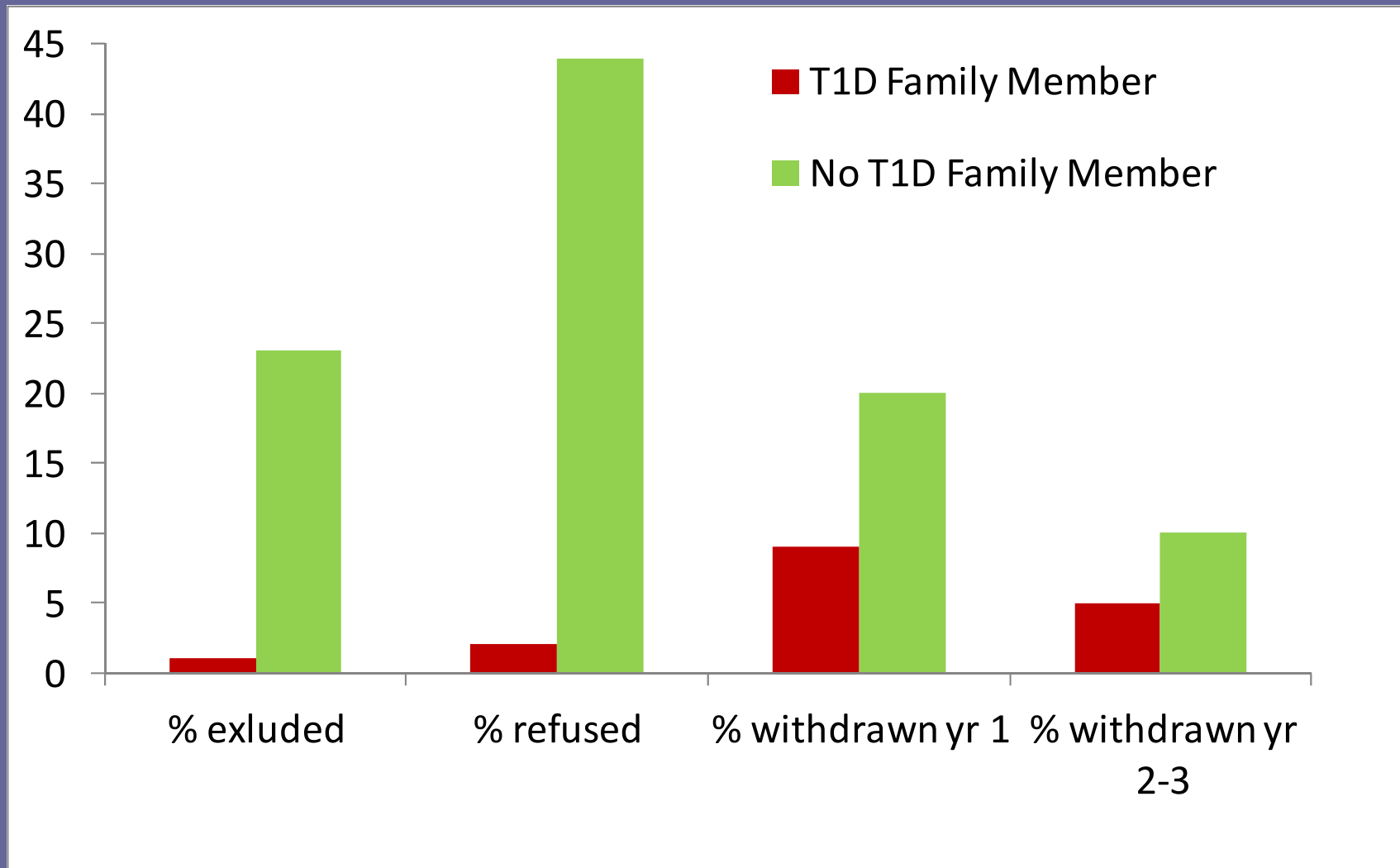
Predictors of Taking Action to Prevent T1D in TEDDY Year 1

Predictor	% taking action
Family member with T1D	Yes: 51% No: 42%
Maternal age	Older mothers more likely to take action
Only child	Yes: 46% No: 40%
Worry about T1D	Never: 29% Rarely: 40% Sometimes to Very Often: 54%
T1D risk perception	Accurate: 46% Underestimate: 37%
Belief that T1D can be prevented	Greater belief, more likely to take action

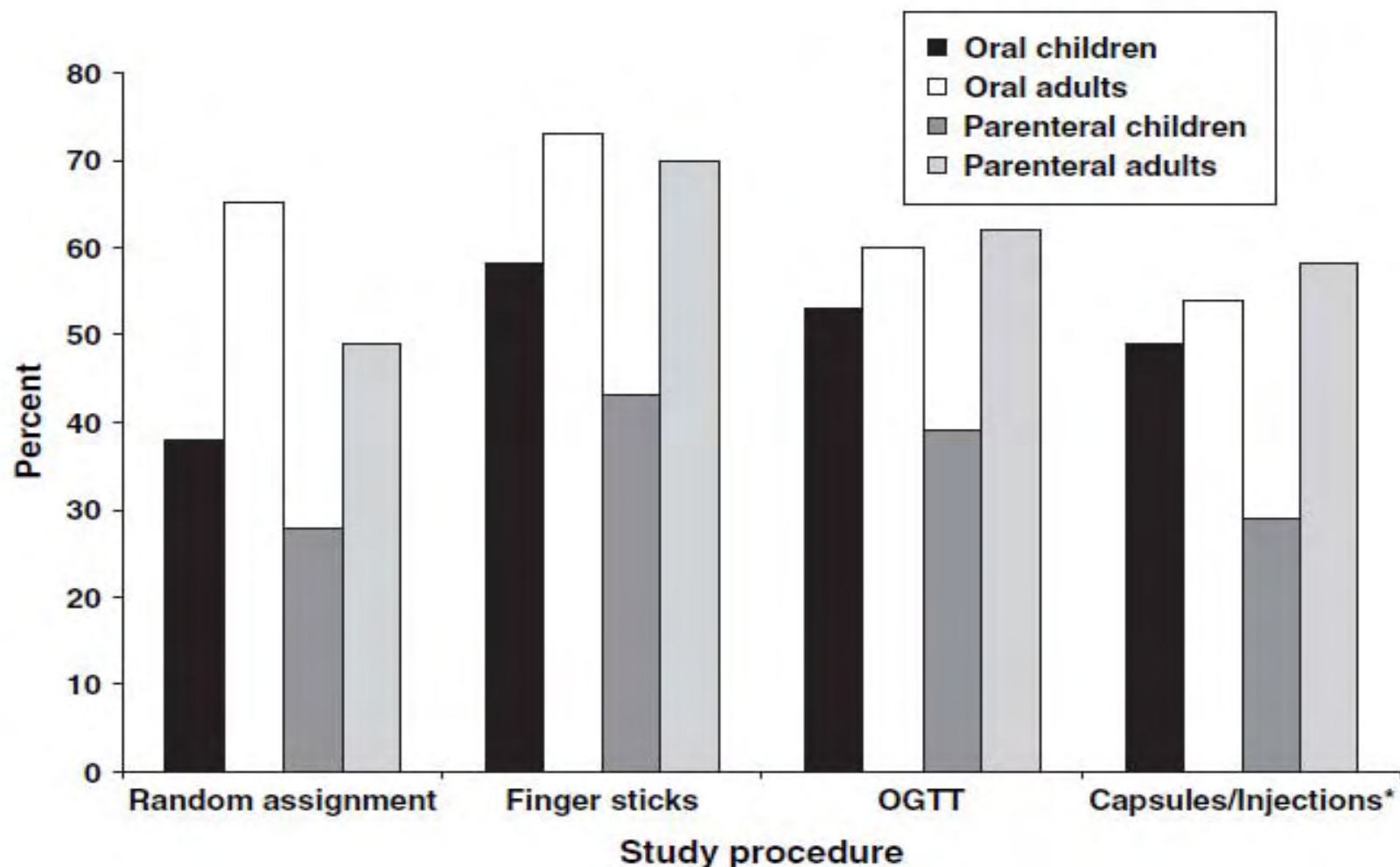
Genetic Screening for T1D: Behavioral Impact

- Genetic screening results may impact trial recruitment and retention
- Recruitment
 - Psychological issues difficult to study
 - Study population clearly important
- Retention
 - Psychological issues understudied but clearly important
 - Study population clearly important

TEDDY Recruitment and Retention Among Families With and Without a T1D Relative

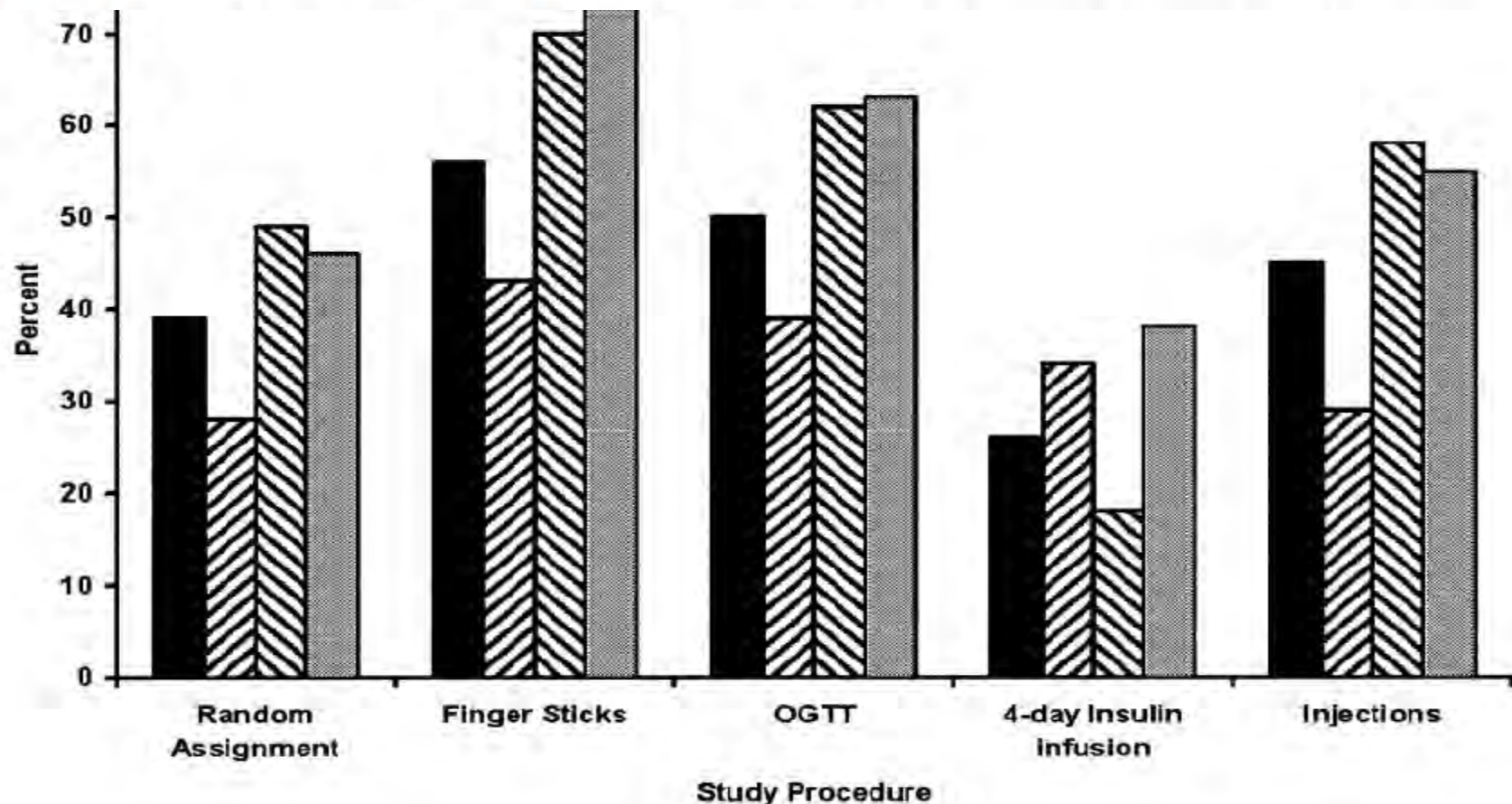


DPT-1: Percent of Children versus Adults Willing to be in another Study with Similar Procedures



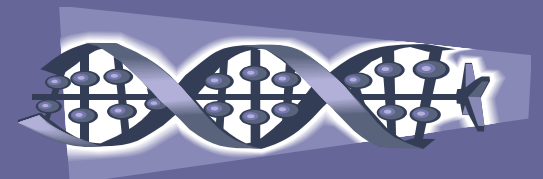
DPT-1: Percent of Parenteral Child & Adult Participants & Parents Willing to be in another Study with Similar Procedures

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



Predictors of Study Retention in TEDDY

- Study retention is critically important in natural history and prevention trials
 - Identification of potential subjects is expensive and labor intensive
 - Retention is critical to study's power
- Predictors of retention/drop out are rarely assessed
- Assessment of psychological variables as possible predictors even rarer.



Demographic Predictors of TEDDY Withdrawal in Families with No T1D Members

Predictor	% withdrawal: year 1	% withdrawal: year 2-3
Country	Finland: 16% Germany: 25% Sweden: 18% USA: 25%	Not significant
Child sex	Male: 19% Female: 22%	Not significant
Only child	Not available	Yes: 13% No: 11%
Child ethnic Minority	Available for US only: White: 17% Hispanic: 33% Black: 33% Other: 29%	Not significant
Maternal age	Withdrawals younger	Withdrawals younger
Maternal education	Not available	Primary: 16% Trade/some college: 15% Graduated college: 10%
Crowding	Not available	Withdrawals more crowded

Emotional/Cognitive Predictors of TEDDY Withdrawal in Families with No T1D Member

Predictor	% withdrawal: year 1	% withdrawal: year 2-3
Maternal Risk Perception	Accurate: 16% Underestimate: 23%	Accurate: 9% Underestimate: 15%
Maternal State Anxiety Score	High anxiety in moms with accurate risk perceptions more likely to withdraw	Not significant
Maternal Study Satisfaction	Not applicable	Extremely satisfied: 7% Very satisfied: 13% Somewhat satisfied: 15% Somewhat dissatisfied: 23%

Behavioral Predictors of TEDDY Withdrawal in Families with No T1D Member

Predictor	% withdrawal: year 1	% withdrawal: year 2-3
Maternal Employment Status During Pregnancy	Worked all trimesters: 15% Reduced work or did not work at all: 23%	Worked all trimesters: 10% Reduced work or did not work at all: 15%
Maternal Smoking	Yes: 37% No: 16%	Yes: 20% No: 11%
Maternal Drinking	Yes: 13% No: 21%	Not assessed
Maternal Reports of Child Illness	Not applicable	More child illnesses, less likely to withdraw 0-2 illnesses: 18% >10: 7%
Dad Participation	Yes:18% No:43%	Yes:10% No: 20%
Study visits missed	Not applicable	Yes: 33% No: 10%

Development and Application of a Cumulative Risk Score to Reduce Study Withdrawal in Year 1 of TEDDY

- 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 Risk for Early Withdrawal (REW) score
- Based on available data, we selected a REW cut-off of ≥ 4 to identify those at greatest risk for withdrawal among TEDDY families with no T1D member

REW Score	Total Sample N = 3449	Number of Withdrawals N = 739	% of Withdrawals 21.4	% Withdrawals for REW <4 and ≥4
US Sites	N = 1367	N = 346	25.3	
0	61	8	13.1	REW <4 15.2
1	211	20	9.5	
2	294	41	14.0	
3	301	63	20.9	
4	222	75	33.8	REW ≥ 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	REW <4 14.9
1	291	23	7.9	
2	583	74	12.7	
3	640	130	20.3	
4	343	93	27.1	REW ≥ 4 31.5
5	106	36	34.0	
6	30	16	53.3	
7	19	12	63.2	

Tailored Intervention for TEDDY Families with No T1D Member with High REW Scores at Study Inception

- Beginning in June 2009, REW scores were calculated for all families with No T1D member at the child's first TEDDY visit
- TEDDY sites were notified of all participants with REW scores ≥ 4
- TEDDY sites developed individually tailored interventions to improve retention for its participants with REW scores ≥ 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 REW scores ≥ 4 and Percent of Participants Withdrawing from TEDDY in the First Year by Study Cohort

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

Percent of Families with No T1D Member Withdrawing from TEDDY Before and After High REW Score Notification with Tailored Intervention

Risk notification implemented	Withdrawal risk	Total N	% Withdrawn in year 1 of TEDDY	Within Group p value	Between Group p value
No	Low (REW <4)	1053	4.8	Low vs High: <0.0001	No/Low vs Yes/ Low: 0.161
	High (REW ≥4)	426	12.7		
Yes	Low (REW <4)	1204	3.7	Low vs High: 0.467	No/High vs Yes/High: <0.0001
	High (REW ≥4)	524	4.4		

Percent of Families with No T1D Member Withdrawing from TEDDY Before and After High REW Score Notification with Tailored Intervention: European Sites

Risk notification implemented	Withdrawal risk	Total N	% Withdrawn in year 1 of TEDDY	Within Group p value	Between Group p value
No	Low (HREW <4)	568	5.3	Low vs High: <0.0001	No/Low vs Yes/ Low: 0.862
	High (HREW ≥4)	178	14.0		
Yes	Low (HREW <4)	652	5.1	Low vs High: 0.926	No/High vs Yes/High: <0.002
	High (HREW ≥4)	230	5.2		

Percent of Families with No T1D Member Withdrawing from TEDDY Before and After High REW Score Notification with Tailored Intervention: US sites

Risk notification implemented	Withdrawal risk	Total N	% Withdrawn in year 1 of TEDDY	Within Group p value	Between Group p value
No	Low (HREW <4)	485	4.3	Low vs High: <0.0001	No/Low vs Yes/ Low: 0.030
	High (HREW ≥4)	248	11.7		
Yes	Low (HREW <4)	552	2.0	Low vs High: 0.128	No/High vs Yes/High: <0.0001
	High (HREW ≥4)	294	3.7		

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

Behavior is Critical to the Success of T1D Genetic Screening and Natural History Studies and Prevention Trials

- Behavior change in response to child's increased T1D risk threatens study internal validity
- Study recruitment and retention determine study power to detect effects
- Family variables are important predictors of both
 - family T1D hx, maternal anxiety, risk perception and beliefs that T1D can be prevented predicted behavior change
 - family T1D hx as well family member role (child, mother, father) is associated with study recruitment and retention
 - maternal education, maternal lifestyle behaviors, work status, risk perception, anxiety, father participation, study satisfaction predicted retention

Summary and Recommendations

- Newborn genetic screening for T1D does impact families in the areas we have examined to date:
 - Risk perception
 - State anxiety
 - Efforts to prevent T1D
 - Study participation
- The nature of that impact is determined by a number of important family characteristics:
 - Role with in the family (child, mother, father)
 - Culture (country)
 - Family history of T1D
- Psychological impact of screening should be monitored in at-risk individuals and families



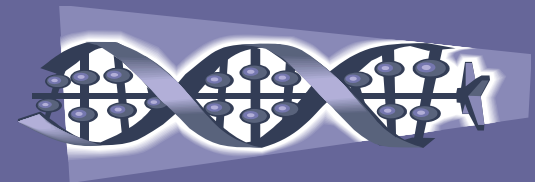
Limitations

- Our work to date is limited by an initial focus on parental reactions very early in the life of the child
- Only a limited number of potential areas of impact have been studied
- Measures used are simple and unable to capture more complex constructs and interactions



Summary and Recommendations

- Our work to date has clear implications for study recruitment and retention as well as the initiation of behaviors outside of the study protocol
- All seriously threaten the success of the scientific enterprise
- Psychological and behavioral science should become an integral component of clinical trial design



Closing Reflections

- Including psychological and behavioral studies as part of newborn genetic screening studies has often been difficult
- Barriers to inclusion
 - Biology bias
 - Psychology and behavioral sciences are seen as “soft” sciences
 - Everyone is a psychologist, everything is “common sense”
 - Money
- Passion, pride, and persistence are essential
 - You will find supporters, advocates, and those who can be educated to be supporters and advocates



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