

Is Primary Prevention of T1D A Realistic Expectation?

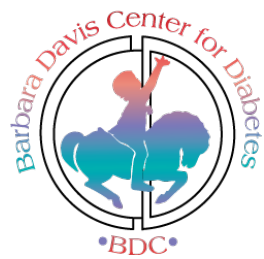
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BDC Keystone Conference

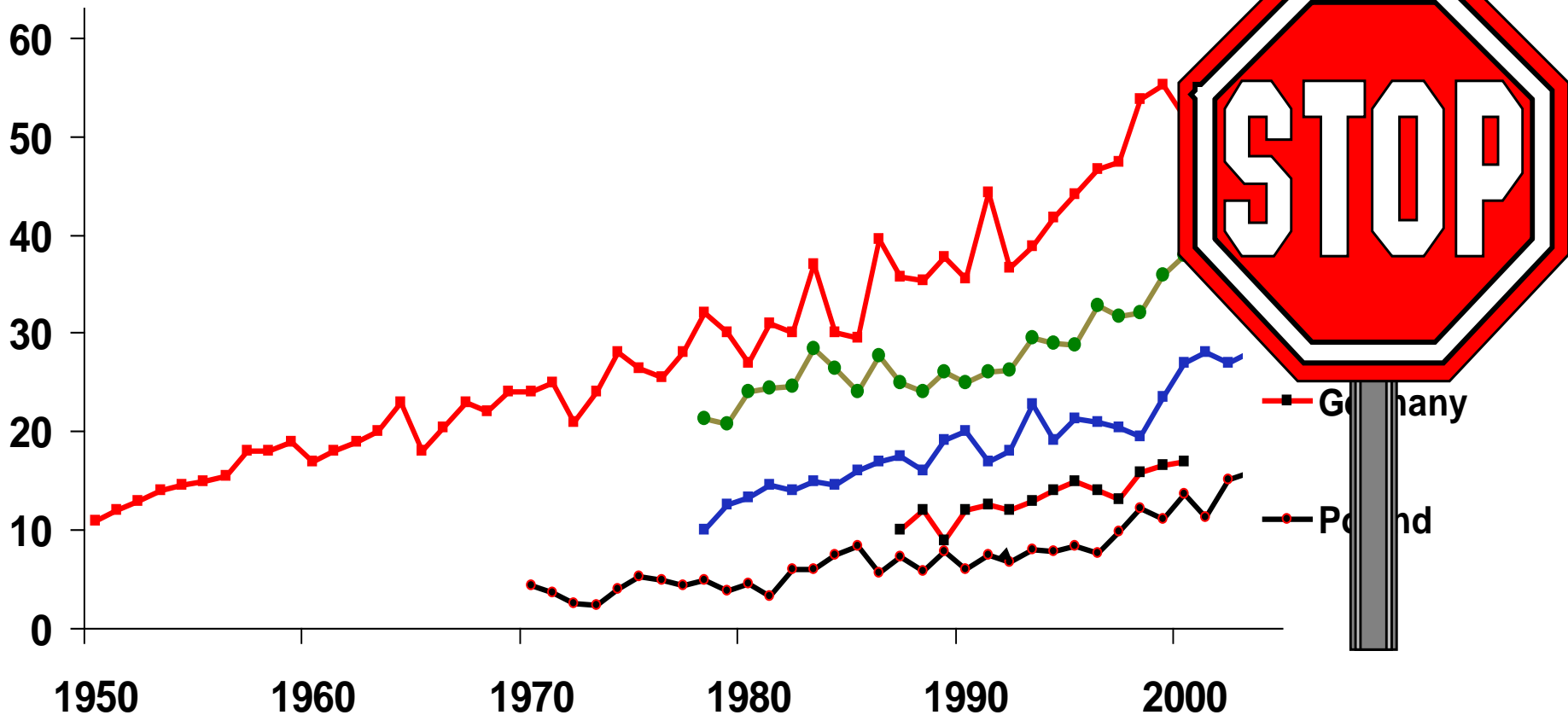
July 18, 2014



T1D incidence is doubling every 20 years

What environmental factors are responsible?

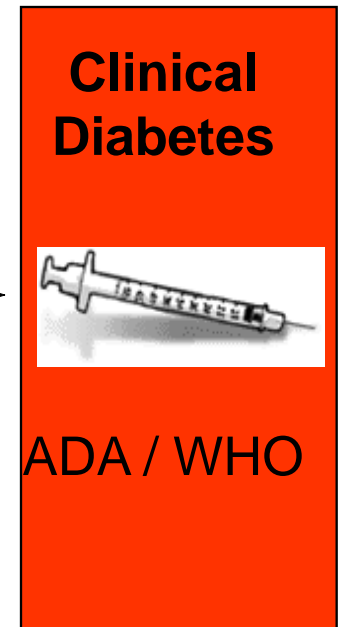
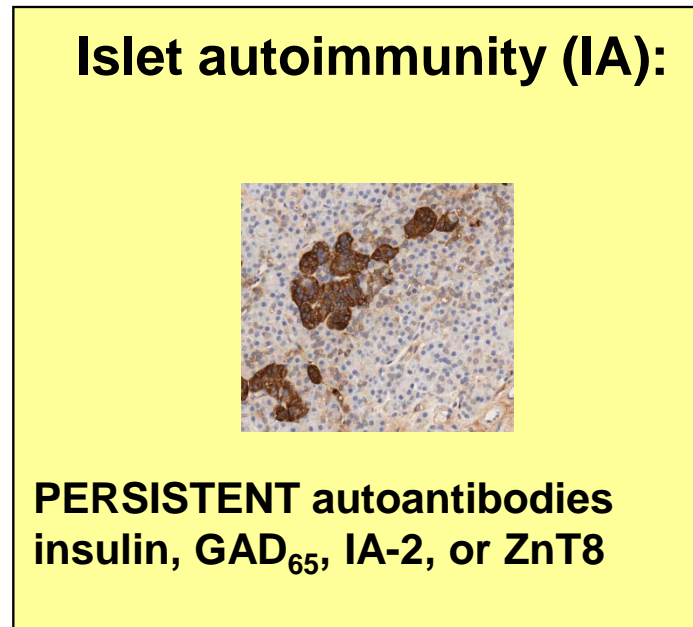
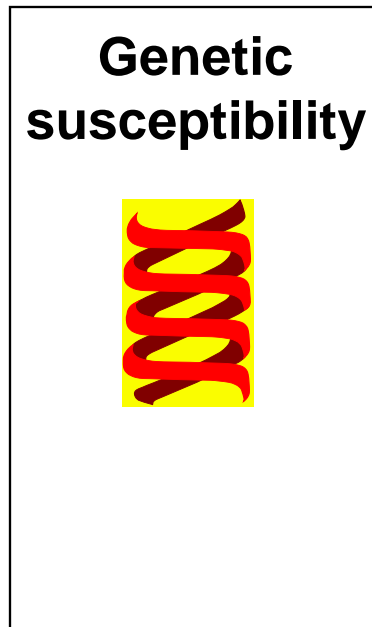
Incidence /100,000/ yr
in children 0-14 yr



Two-step model of pre-T1D

Trigger
virus? diet?

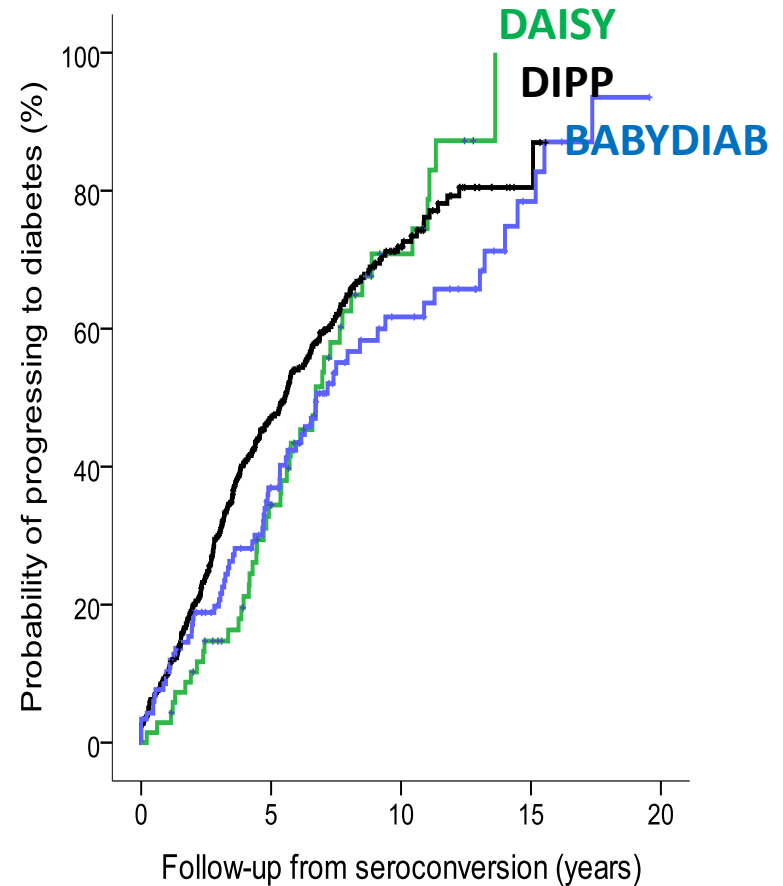
Promoters?



Multiple islet autoantibodies predict progression to diabetes in children

Ziegler A, Rewers M, Simell O et al. JAMA. 2013;2473

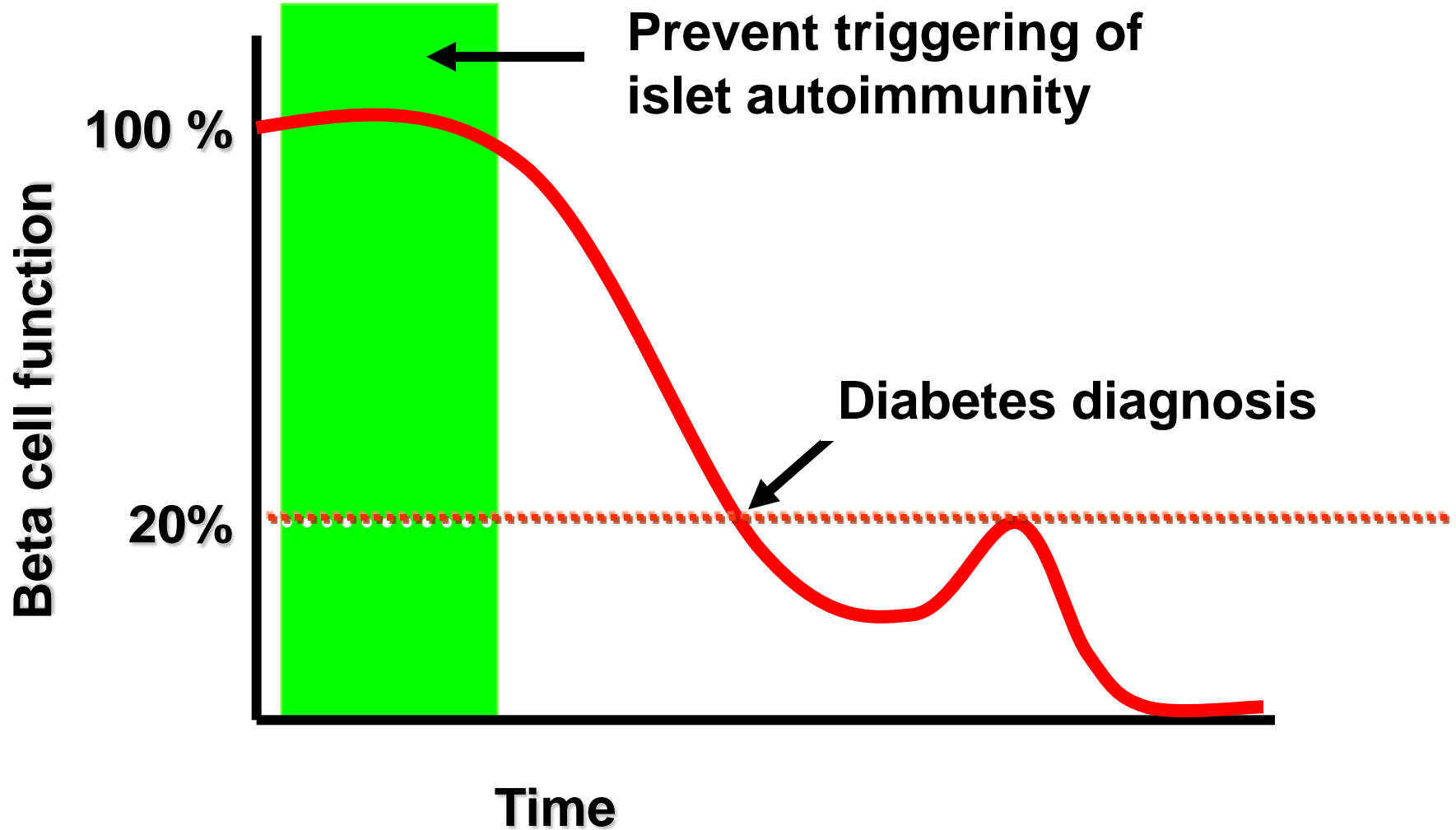
Nearly all children positive for 2+ islet autoantibodies develop diabetes in 15 yrs



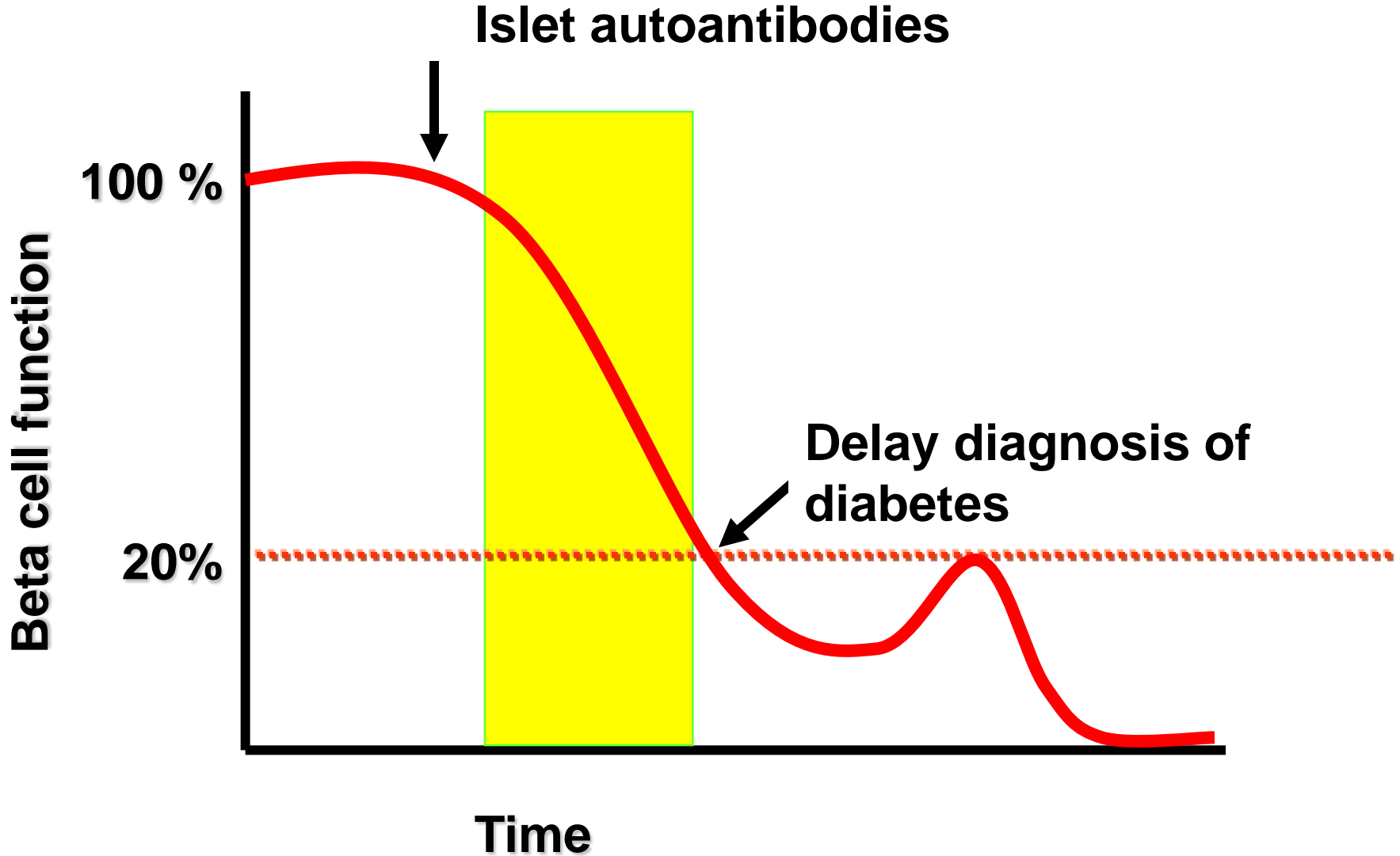
69	38	8	0	0	Colorado
399	158	41	3	0	Finland
117	61	21	5	0	Germany

Primary Prevention

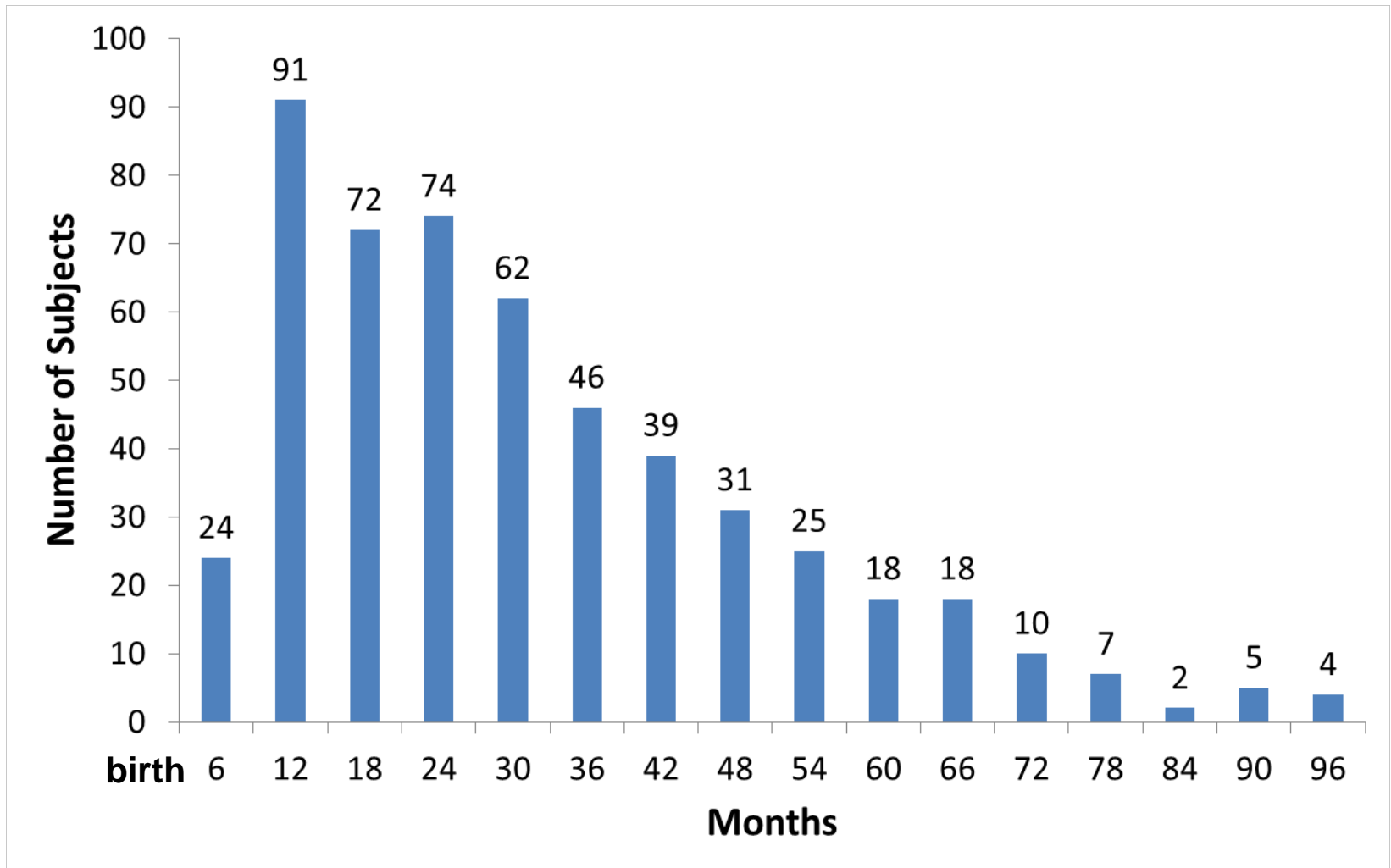
(before islet autoantibodies appear)



Secondary Prevention (in subjects with islet autoantibodies)

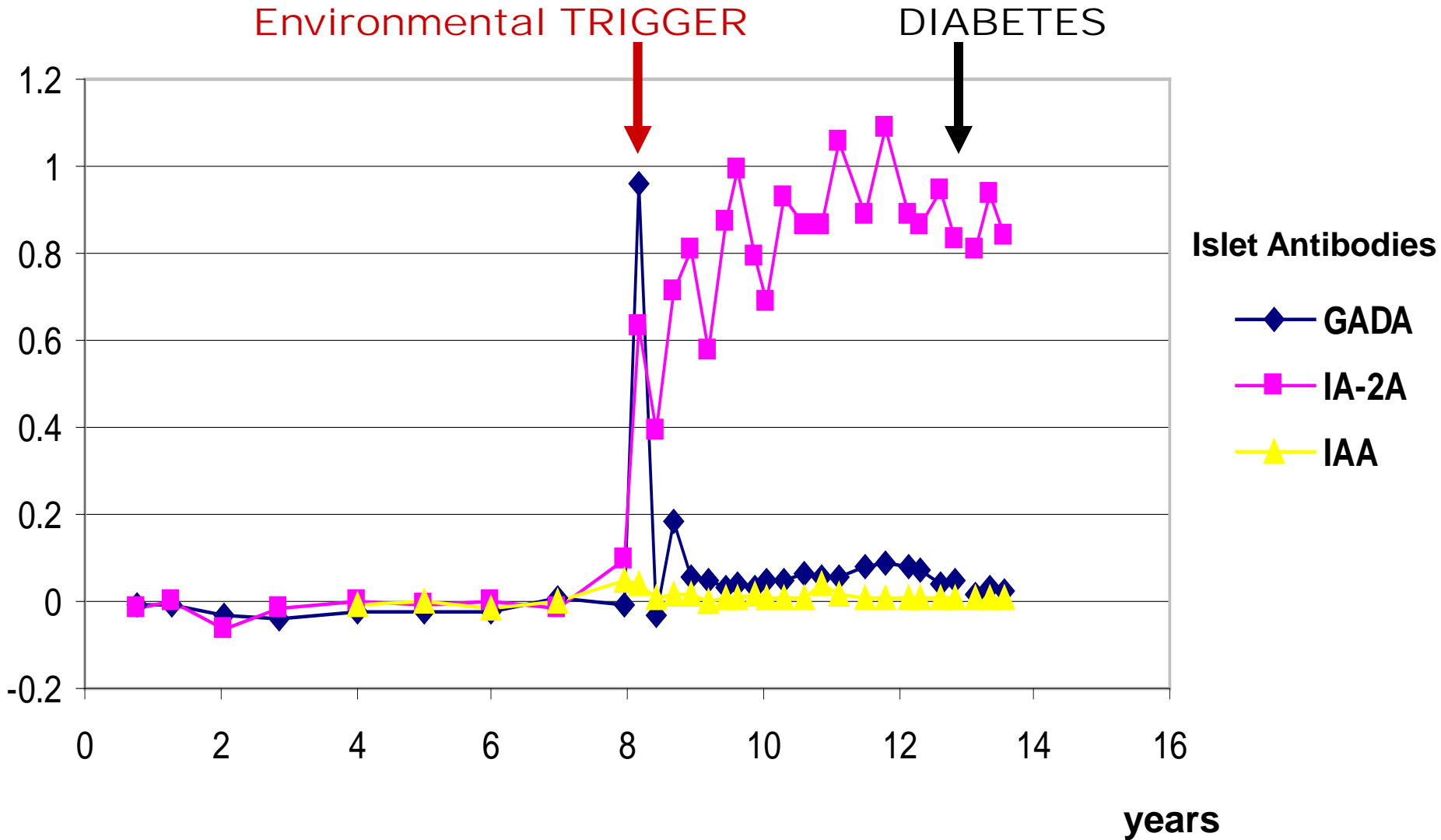


When does islet autoimmunity begin?

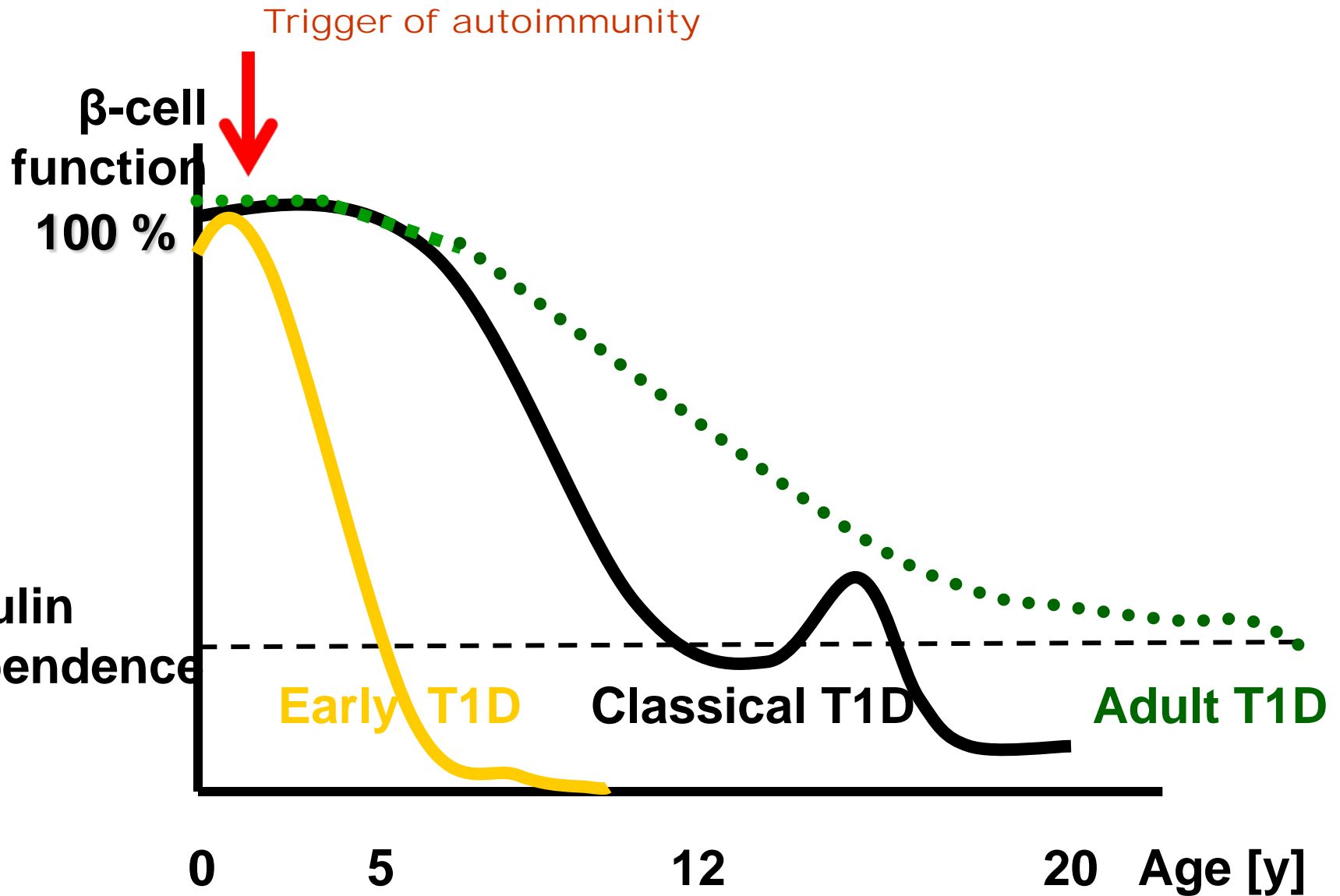


Late onset of islet autoimmunity

DAISY



Phenotypes of Type 1 Diabetes



Candidate environmental causes:

Hot **enteroviruses**

↓ childhood infections = hygiene

↑ food

microbiota

↓ intake of Ω -3 fatty acids

↓ intake of vit. D

mycotoxins

rotavirus

cow's milk

gluten

Not **routine immunizations**



Currently
funded by
the NIH



Find Prevention for T1D !

424,000 newborns screened

**8,677 high-risk children
intensively followed until 15 yrs**



**•Find the environmental trigger
(virus, dietary factor)**



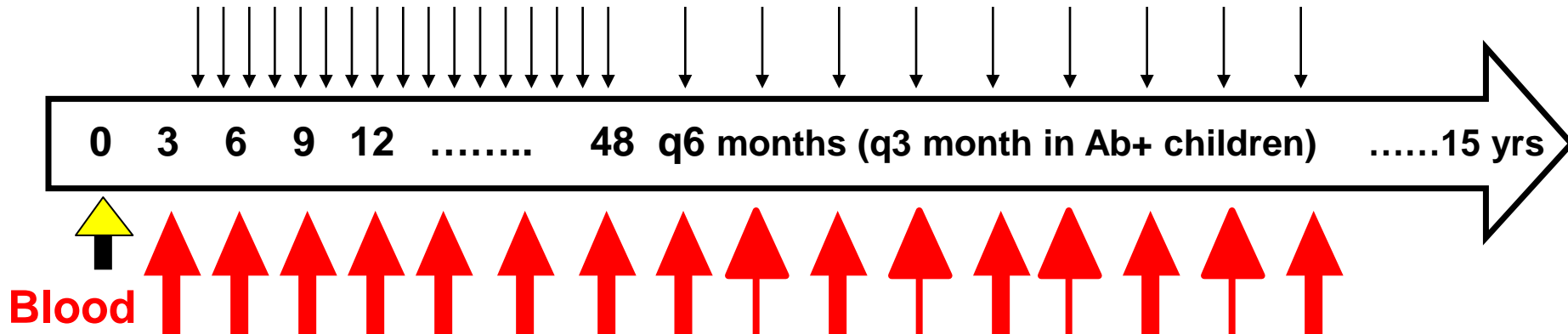
•Develop vaccine/ elimination diet



**•Public health screening and
prevention to eradicate diabetes**

TEDDY protocol

Stool samples collected monthly -> quarterly



Clinic visits every 3 months (including ab+ children older than 4):

Blood for: GADA, IAA, IA-2A, ZnT8; DNA, mRNA, infectious agents, HbA1c, PBMC, erythrocytes, storage plasma/serum;

Nasal swabs, tap water, toenail clippings, and **salivary** cortisol.
urine samples; DNA from FDRs

Interviews: medications, immunizations, infections, family history; maternal pregnancy diet; child's 24 hr recall, 3 day FFQ; negative life events, parental anxiety, depression, physical activity. Accelerometer;

Dietary Factors

- Nitrates, nitrites, nitrosamines
- Coffee/tea
- Cod liver oil
- Vitamin D
- Birth size
- Tubers, root vegetables

- Breast-feeding
- Timing of exposure to:
 - cow's milk
 - cereals/gluten
 - solid foods
 - root vegetables
 - berries
- Vitamin D
- Cod liver oil
- Weight/height gain

- Cow's milk
- Coffee/tea
- Nitrates, nitrites, nitrosamines
- Vitamin C
- Vitamin D
- Vitamin E
- Omega-3 fatty acids
- Nicotinamide
- Zinc
- Weight/height gain



Fetal



Infancy



Childhood



Infant diet and the risk of islet autoimmunity

Cow's milk < 3 month

DAISY

DIPP

BABYDIAB

Cereal < 4 or >6 mo; DAISY

Gluten < 3 months; BABYDIAB

Ω-3 FA intake; DAISY

Ω-3 FA erythrocyte wall; DAISY

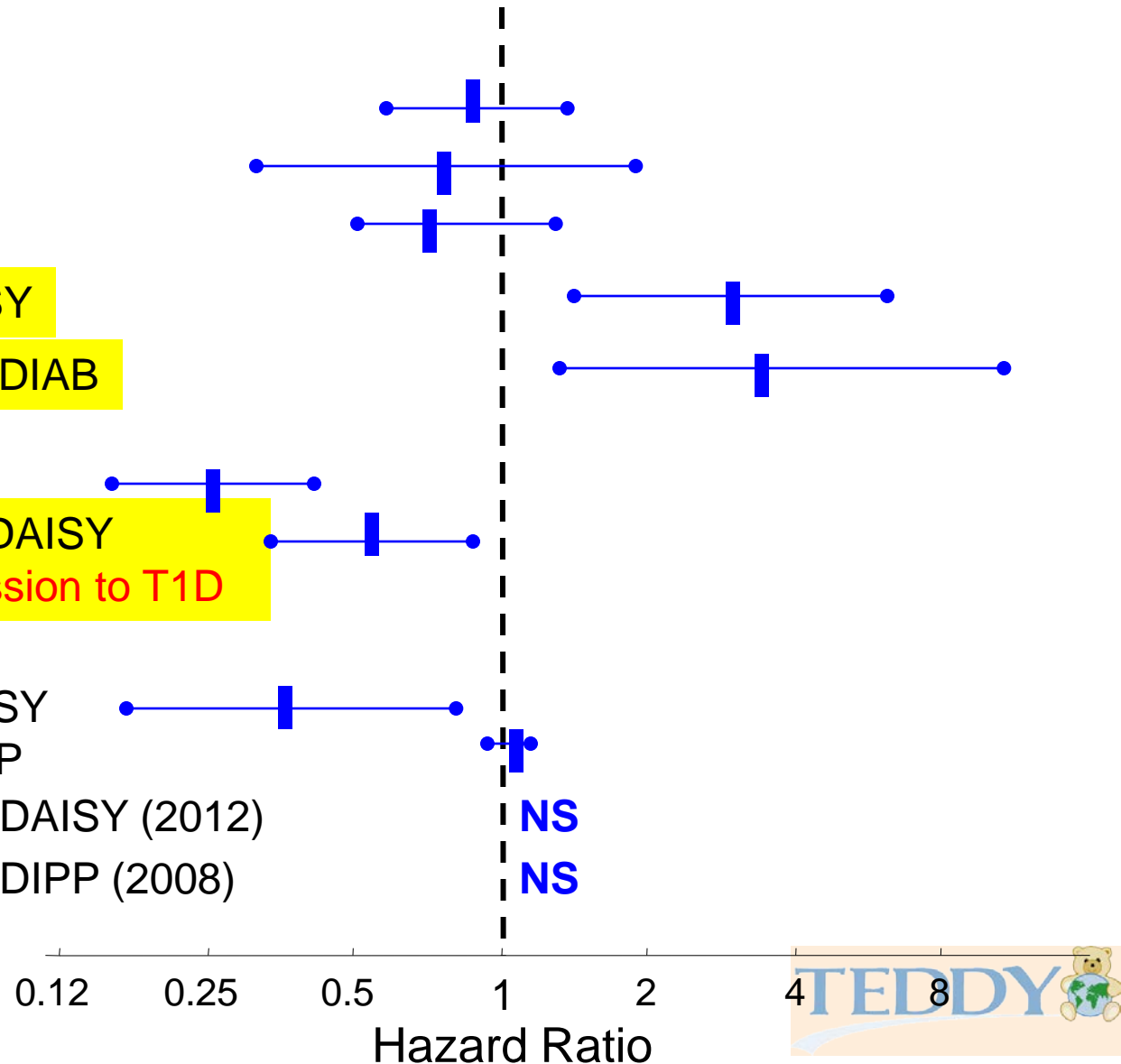
no association with progression to T1D

Maternal Vit D suppl. DAISY

DIPP

Infant Vit D intake DAISY (2012)

Infant Vit D blood levels; DIPP (2008)



Clinical Trials of Infant Diet Modification

None has succeeded, YET !!!

TRIGR (Trial in Genetically at Risk)

Weaning to hydrolyzed vs. intact cow milk formula

BABY-DIET

Delay in gluten exposure 6m -> 12m

NIP (Nutritional Intervention to Prevent T1D) TrialNet

Ω -3 FA docosahexanoic acid (DHA)

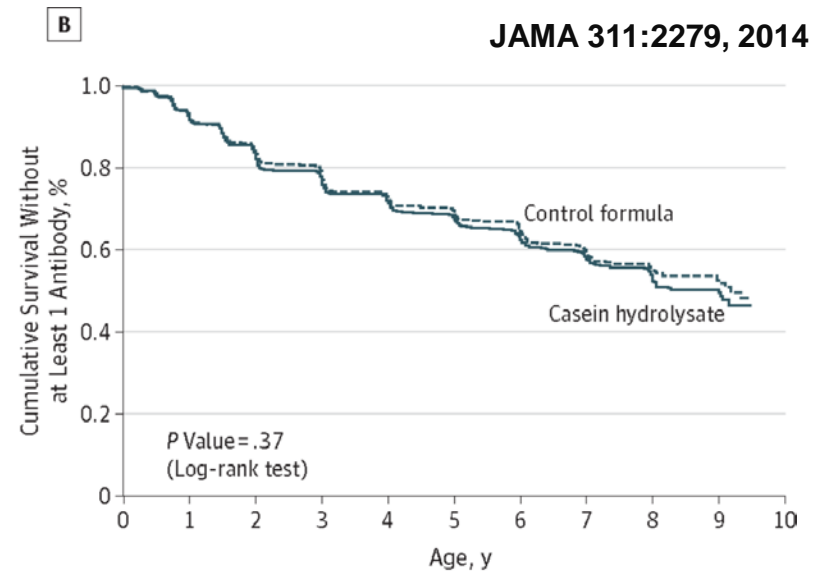
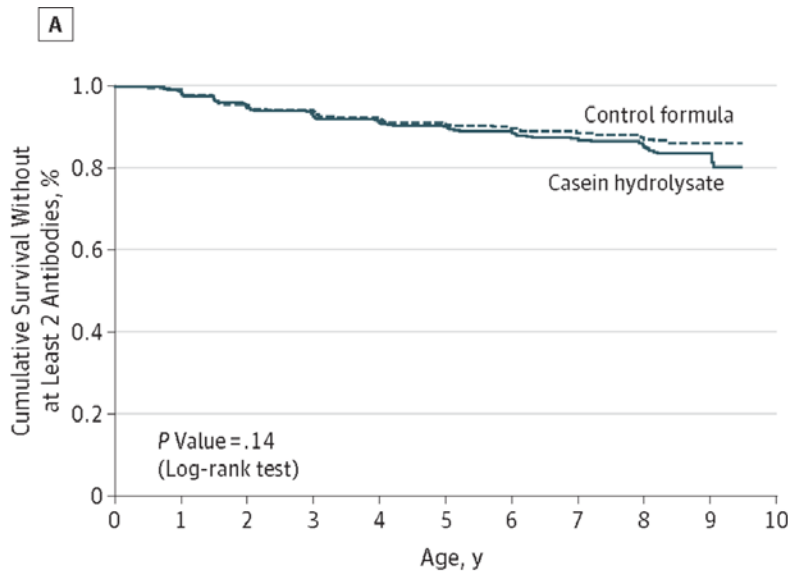
FINDIA - milk formula with low cow's insulin content

Vitamin D supplementation



TRIGR

Larger TRIGR Study - Casein Hydrolysate Does NOT Delay Beta-Cell Autoimmunity



No. at risk

Casein hydrolysate	1078	977	922	891	865	839	747	540	342	149
Control formula	1073	992	928	899	866	842	765	557	357	151

1078	920	809	748	686	637	529	353	207	82
1073	935	824	761	693	655	555	366	216	85

- **2159 high-risk infants newborns in 15 countries**
 - **High-risk HLA haplotypes**
 - **First-degree relative with T1D**
- **Screened regularly for islet autoantibodies**

The BABYDIET study

Diabetes Care 34:1301–1305, 2011

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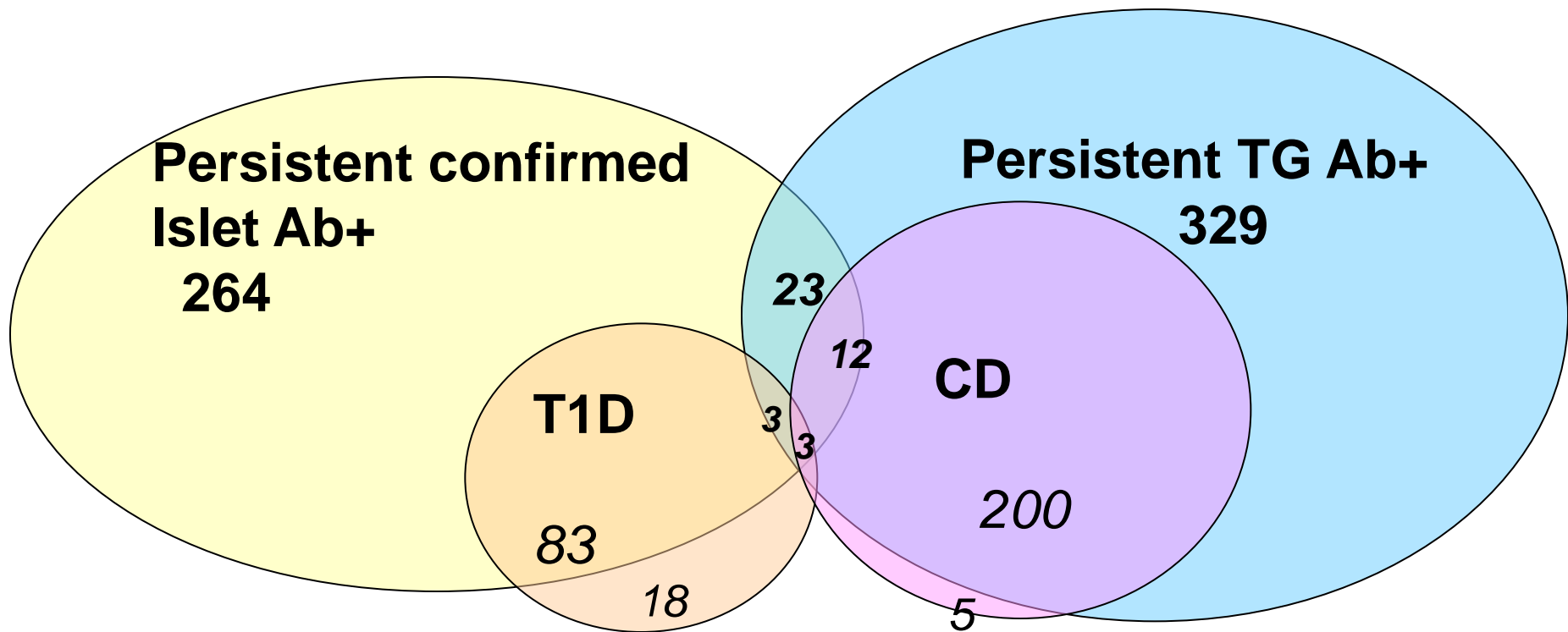
Intervention:

**Gluten introduction
Delayed until age 12 month
vs. standard 6 months**

Eligibility

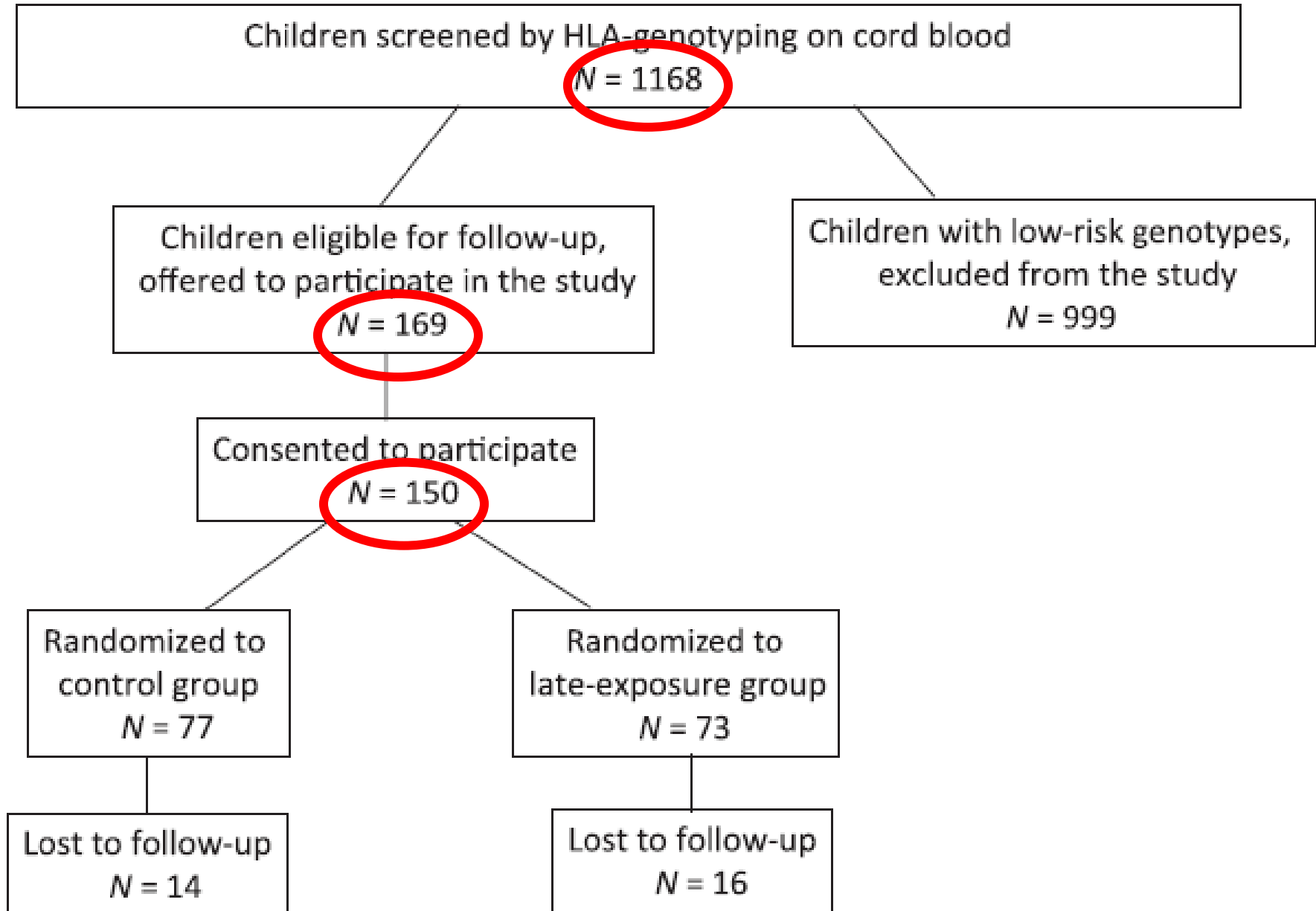
**Age <2 months, no gluten
2 T1D first degree relatives
or
1 relative AND high-risk HLA**

Small Overlap of T1D and Celiac Disease Among TEDDY subjects

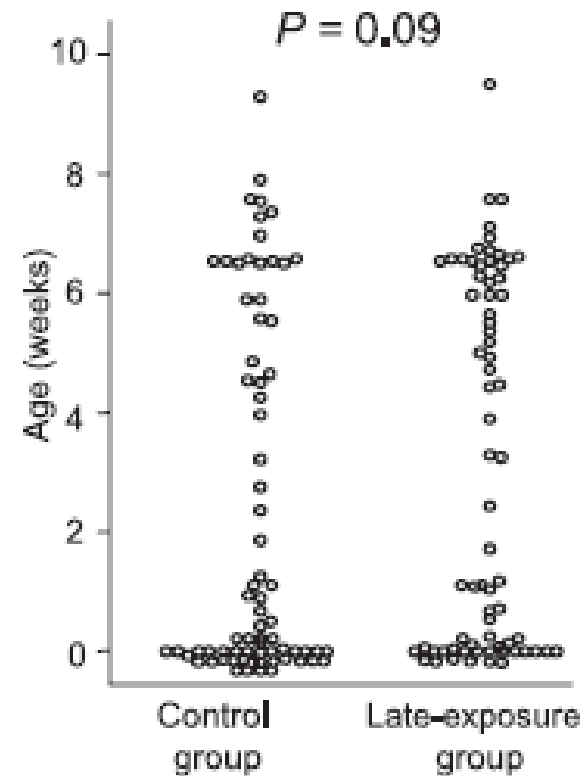
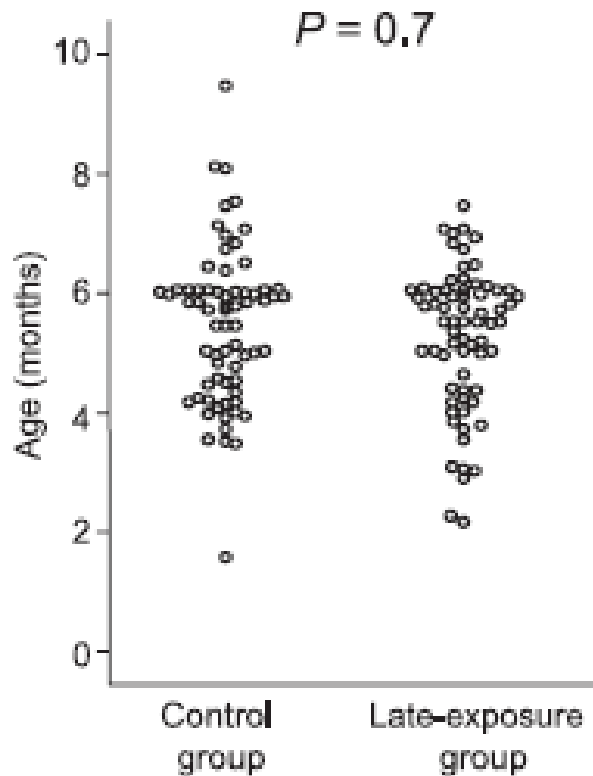
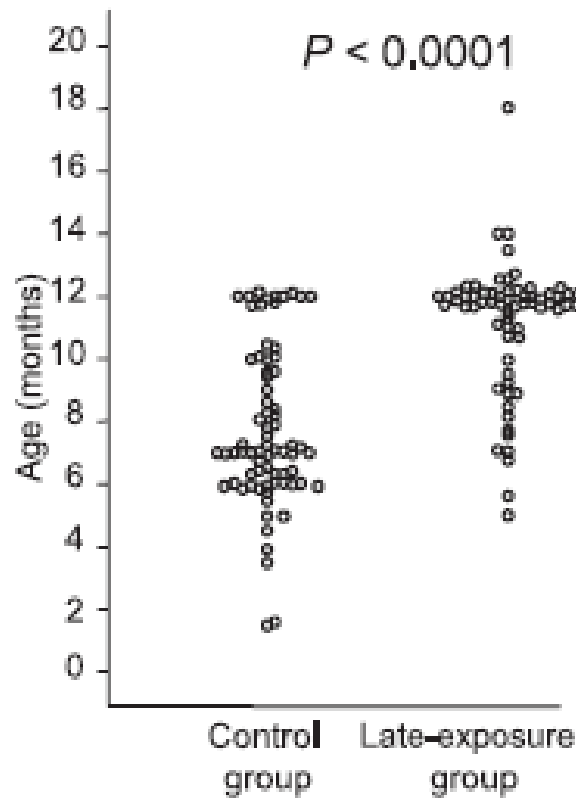


Feb 2012

BABYDIET Study Population



BABYDIET – Reported Exposures



Gluten

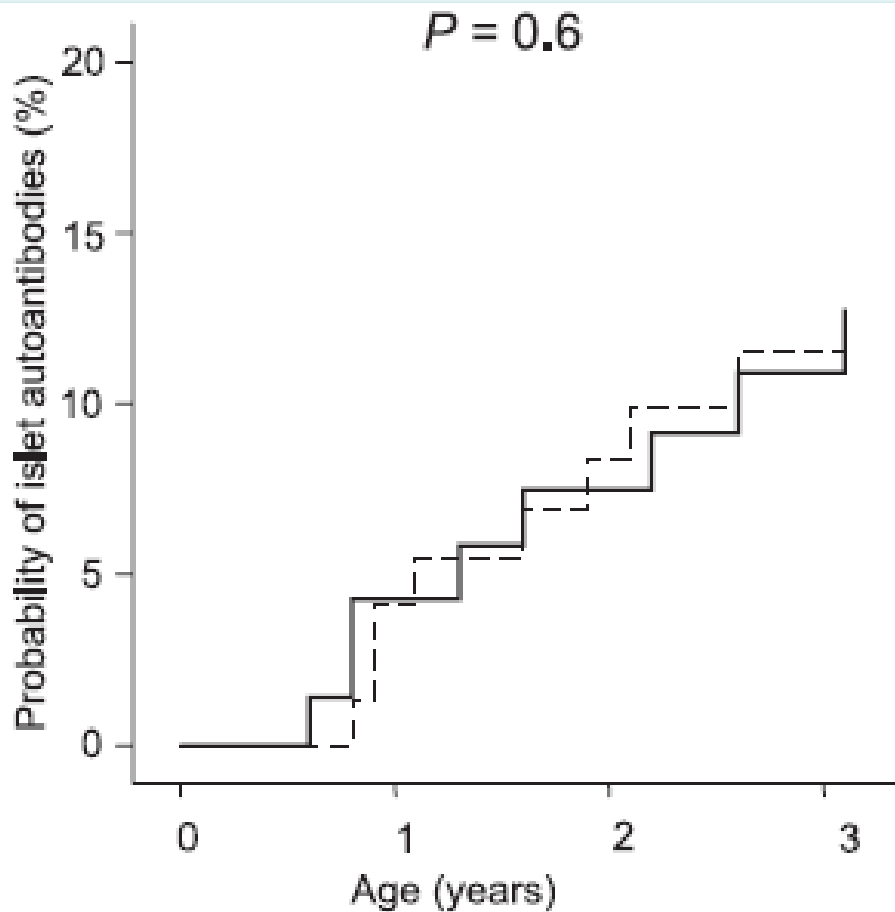
Solid foods

**Duration of exclusive
breastfeeding**

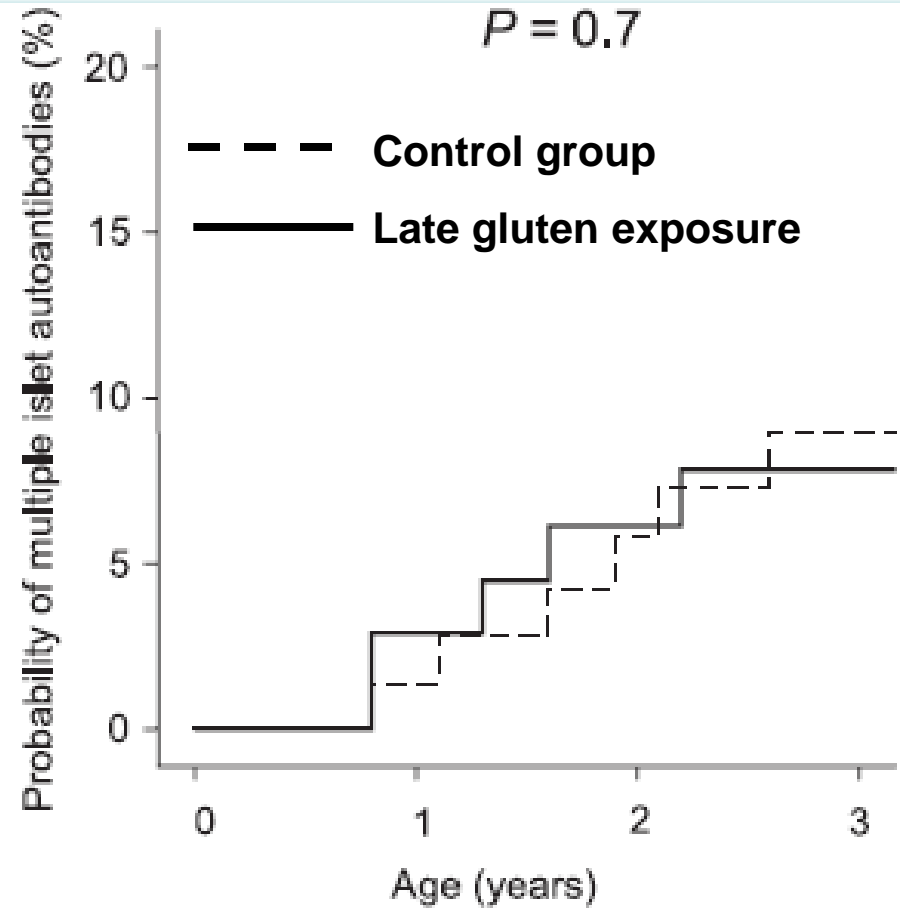
Age at first exposure

BABYDIET – Results

Development of Islet Autoantibodies to insulin, GAD, IA-2



Any autoantibodies



Multiple autoantibodies

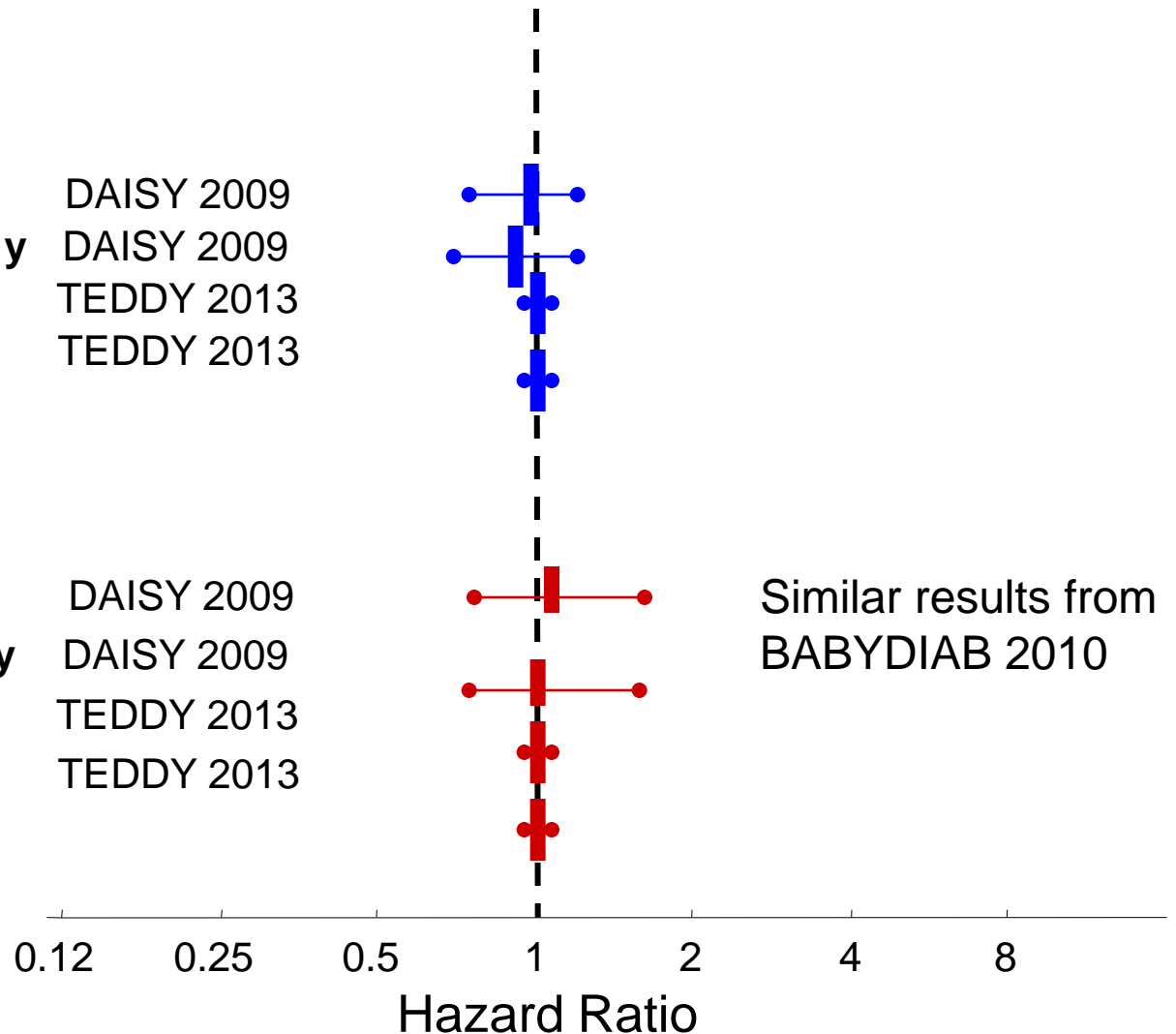
Child's weight gain, BMI and growth are NOT related to islet autoimmunity (IA) or progression to T1D

Islet Autoimmunity

BMI >age 2 y	DAISY 2009
Weight gain velocity >age 2 y	DAISY 2009
Weight <age 2 y	TEDDY 2013
Height <age 2 y	TEDDY 2013

Progression to T1D

BMI >age 2 y	DAISY 2009
Weight gain velocity >age 2 y	DAISY 2009
Weight <age 2 y	TEDDY 2013
Height <age 2 y	TEDDY 2013



Enteroviral infections (EV) and the risk of islet autoimmunity (IA) or progression to T1D

EV and islet autoimmunity

DAISY, Graves 2003 (n=26)

MIDIA, Tapia 2010 (n=27)

DIPP, Salminen 2004 (n=12)

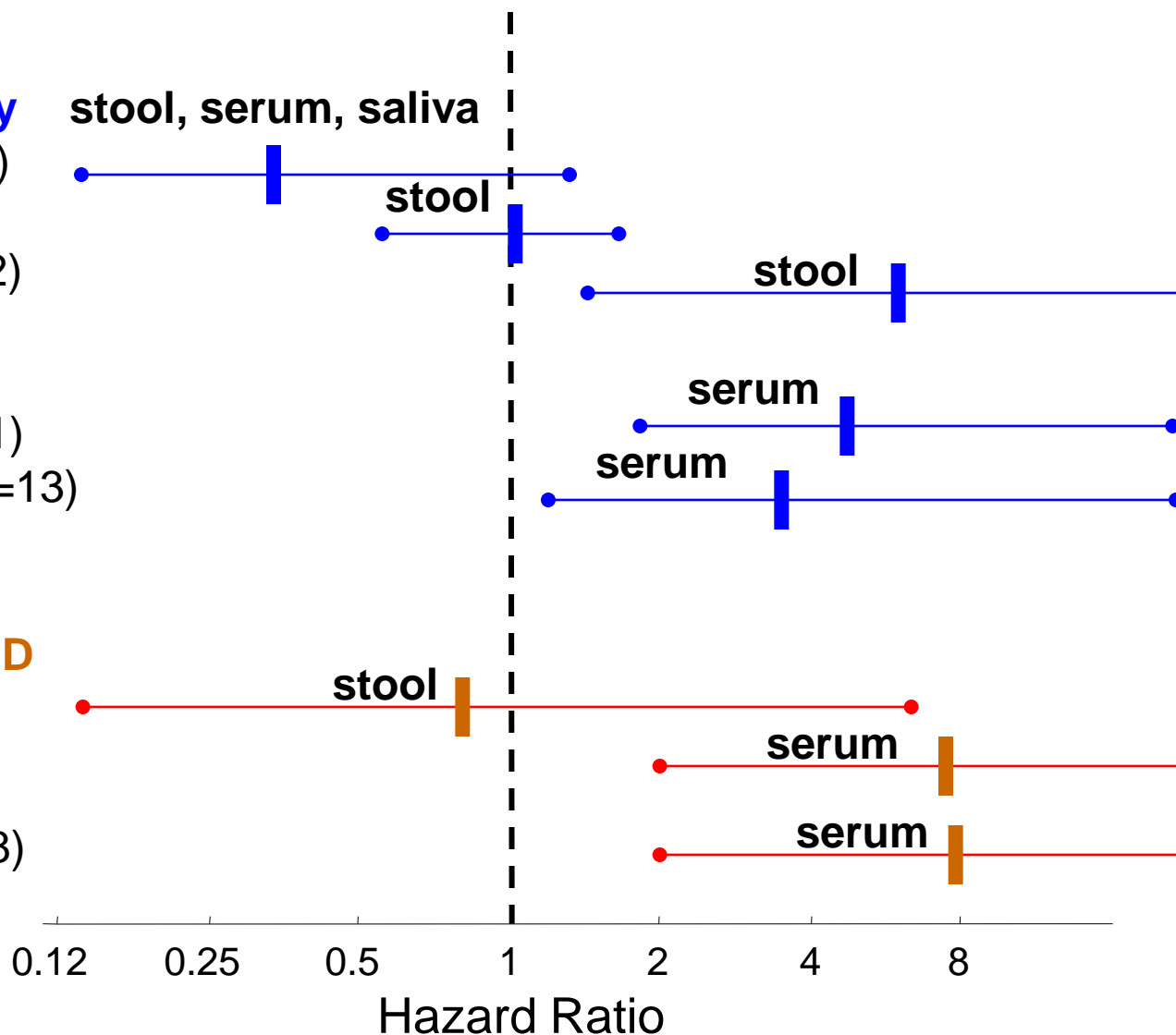
DIPP, Salminen 2003 (n=41)

VIGR, Al-Shaheeb 2010 (n=13)

EV and progression to T1D

DAISY, Stene 2010 (n=50)

DIPP, Oikarinen 2011 (n=38)



Environmental toxins

from food, water processing

- Vacor (rodenticide)
- Mycotoxins (*Streptomyces*)
 - Streptozotocin
 - Bafilomycin



Summary:

- **Unknown environmental factors are doubling the incidence of T1D every 20 years**
- **Triggers and promoters of progression to diabetes are largely unknown**
- **Autoantibody testing may help to pin-point the trigger**
- **Islet autoimmunity usually starts in early childhood, but may develop at any age → different T1D phenotypes**
- **84% of children positive for ≥ 2 islet autoantibodies will develop diabetes in the next 15 years (70% in 10 yrs)**



Summary:

- **Little evidence to support the ‘accelerator hypothesis’ or link between obesity and T1D**
- **Feeding babies with cow’s milk formulas does not cause T1D**
- **Cereals to be added between 4-6 month of life while breast feeding**
- **Omega free fatty acids may be protective from early childhood IA**



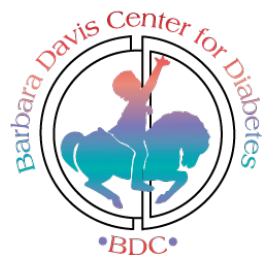
Summary:

- Presence of enterovirus in blood predicts T1D in some cases
- Routine immunizations /timing unrelated to T1D

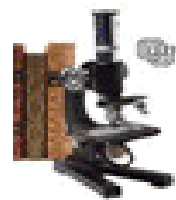
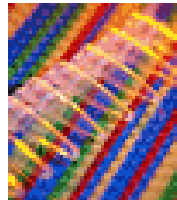
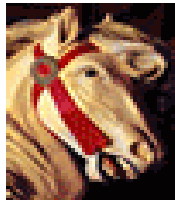
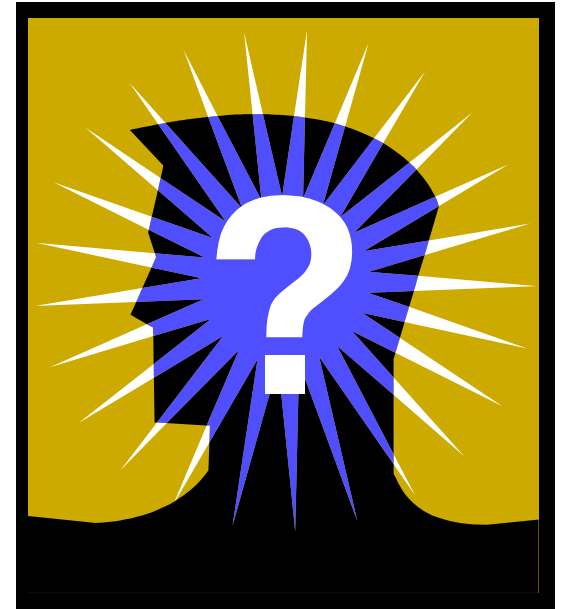


Conclusion:

- **Primary prevention is a realistic expectation**
- **Lot's of work remain to be done**



Questions



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