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**HelmholtzZentrum münchen**

Deutsches Forschungszentrum für Gesundheit und Umwelt  
**Institut für Diabetesforschung**

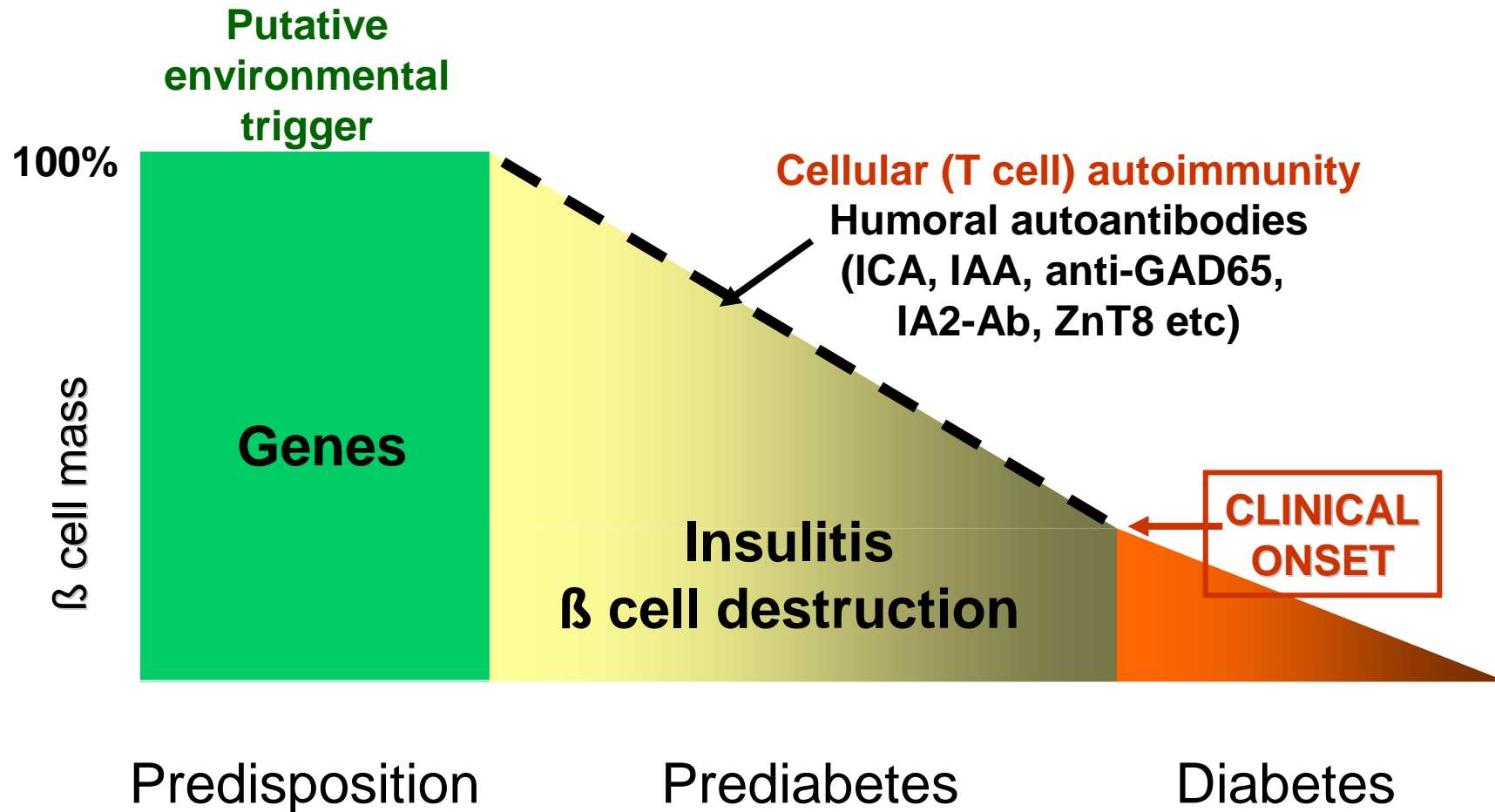


# Randomized clinical trial on infant diet and diabetes risk – experience from the BABYDIET study

Anette-Gabriele Ziegler



# Model of the natural history of type 1 diabetes



*Modifiziert nach GS Eisenbarth*

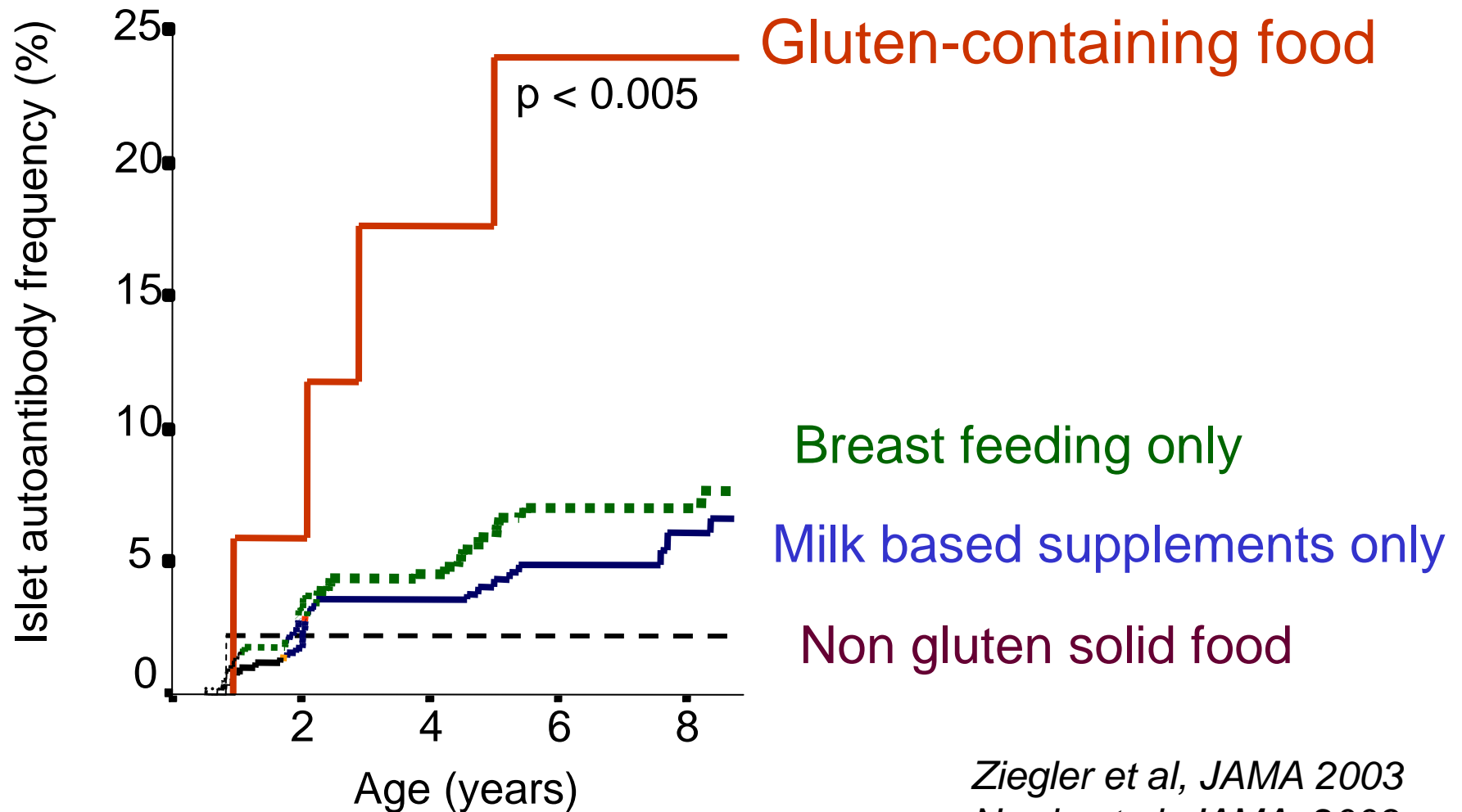
## Questions relevant for the identification of environmental triggers

- When does islet autoimmunity /insulinitis initiate ?
- Is there a time window where initiation of islet autoimmunity is frequent ?
- What environmental exposures are frequent around the that time?

# Natural course of type 1 diabetes development in a child followed from birth

Subject	Age (years)	IAA	GADA	IA-2A	ZnT8A	TPO	tTGA	21-OHA
1032	0.8	++	-	-		-	-	-
	1.9	++	+			-	-	-
	2.4	++	++	++	++	-	-	-
	2.9	++	++	++	++	-	-	-
	3.5	++	++	++	++	-	-	-
	4.0	++	++	+	++	-	-	-
	5.0	++	++	+	++	++	+	-
	6.1	++	++	+	++	+++	++	-
	<b>Diabetes</b> 7.1	++	++	+	++	+++	++	-
	<b>Hypothyroidism</b> 7.3					+++	++	-

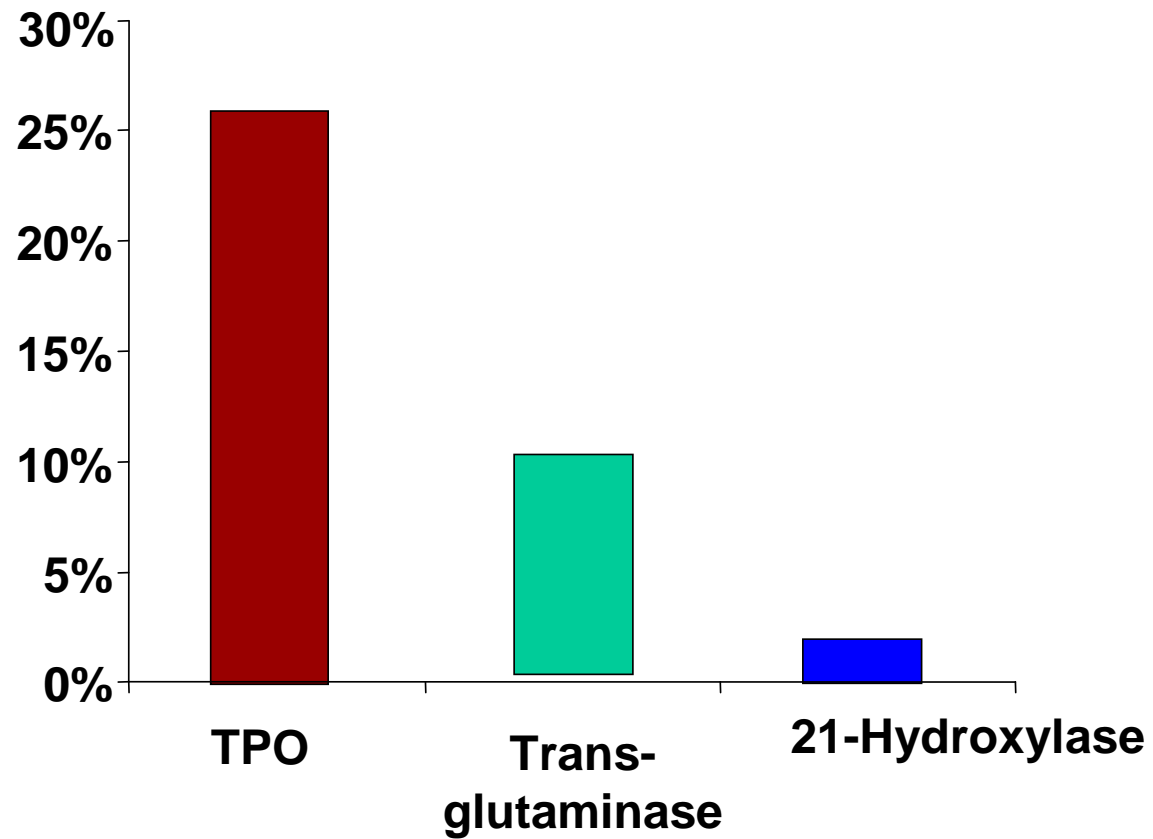
# Food supplementation before age 3 months and islet Abs risk in BABYDIAB offspring



Ziegler et al, JAMA 2003  
Norris et al, JAMA, 2003

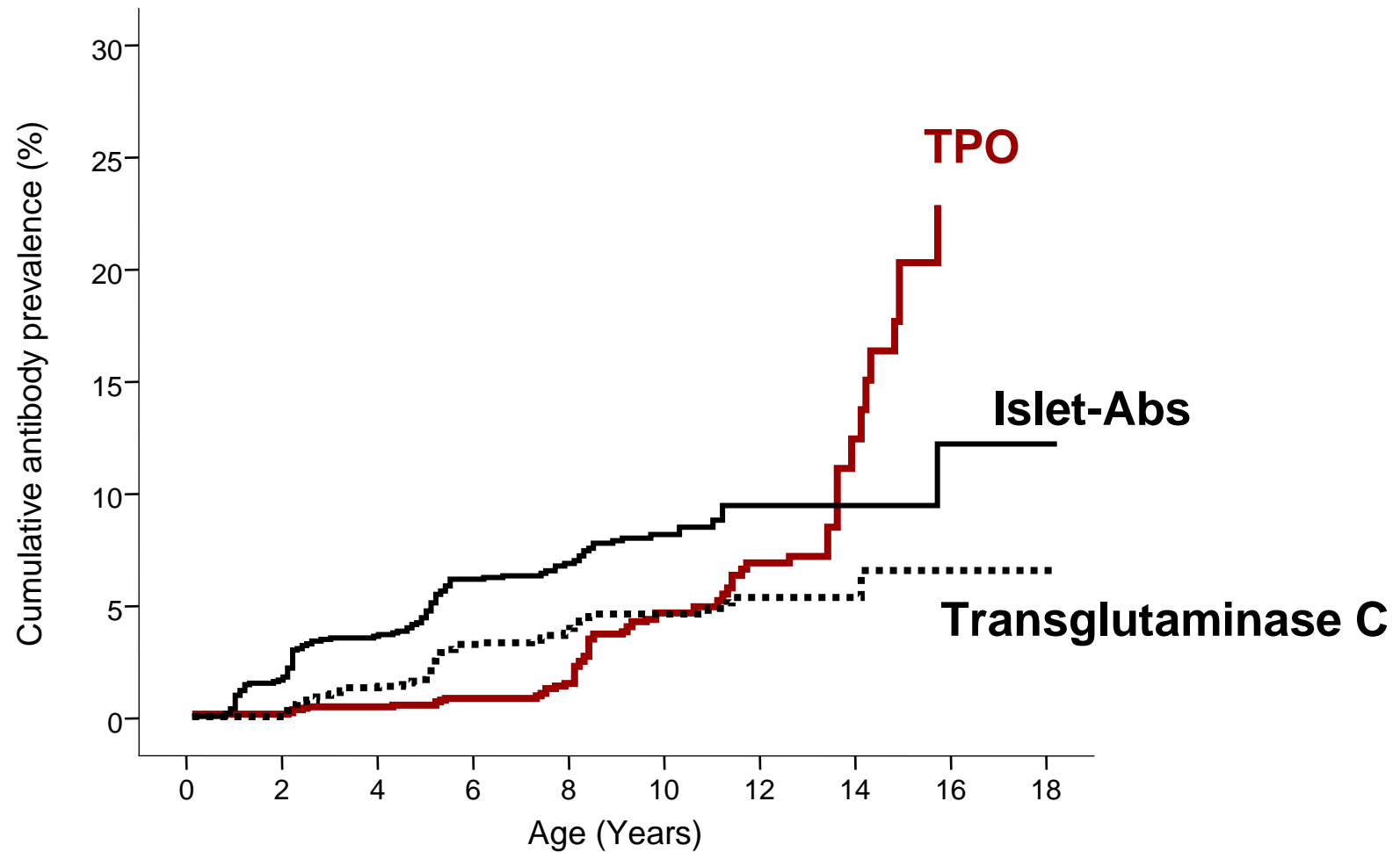
The role of gluten in type 1  
diabetes ?

# Endocrine and gut autoimmunity in patients with T1D

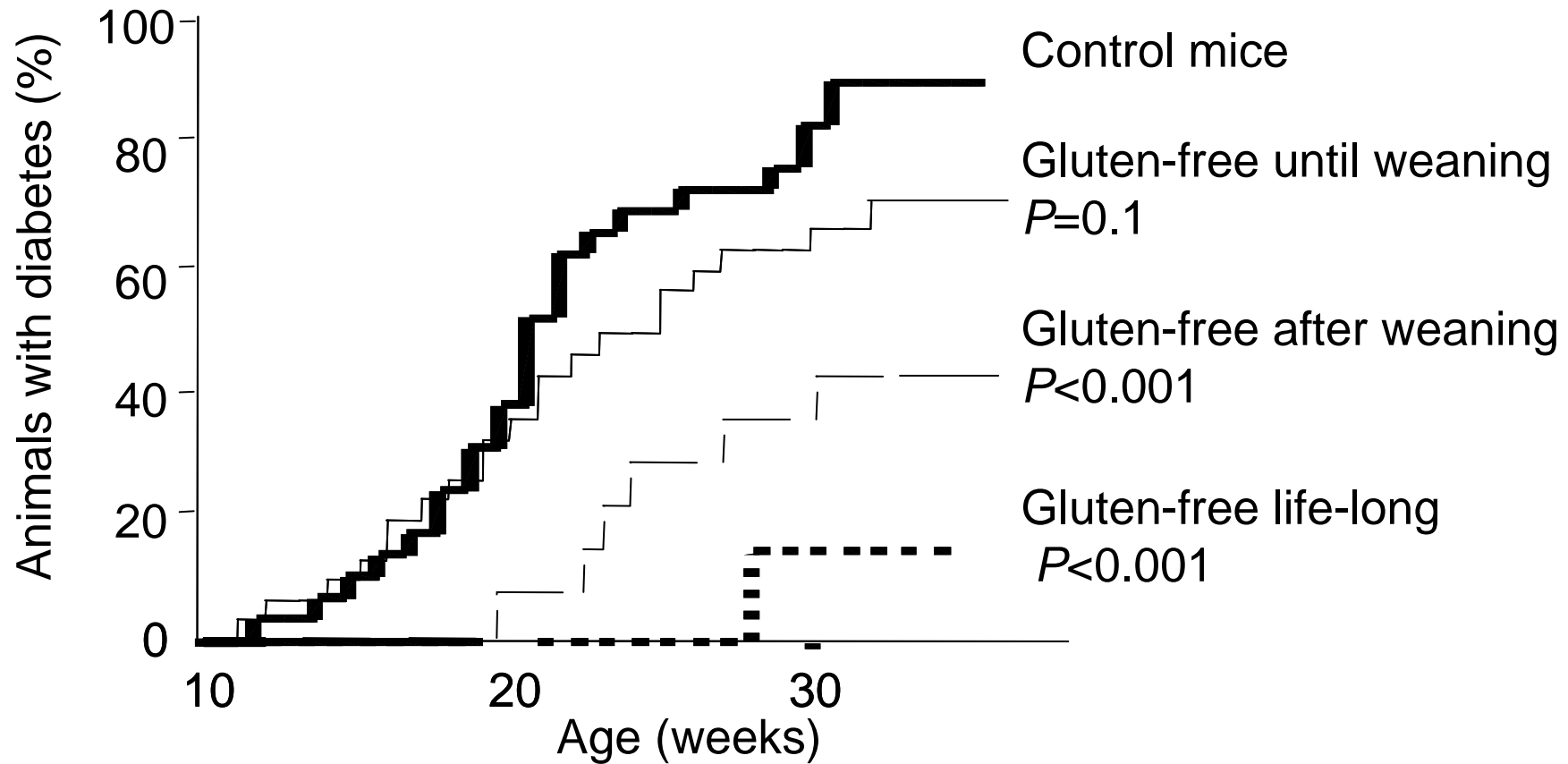


*Barker J et al, Diabetes Care 2005*

# Endocrine and gut autoimmunity in first degree relatives of patients with T1D



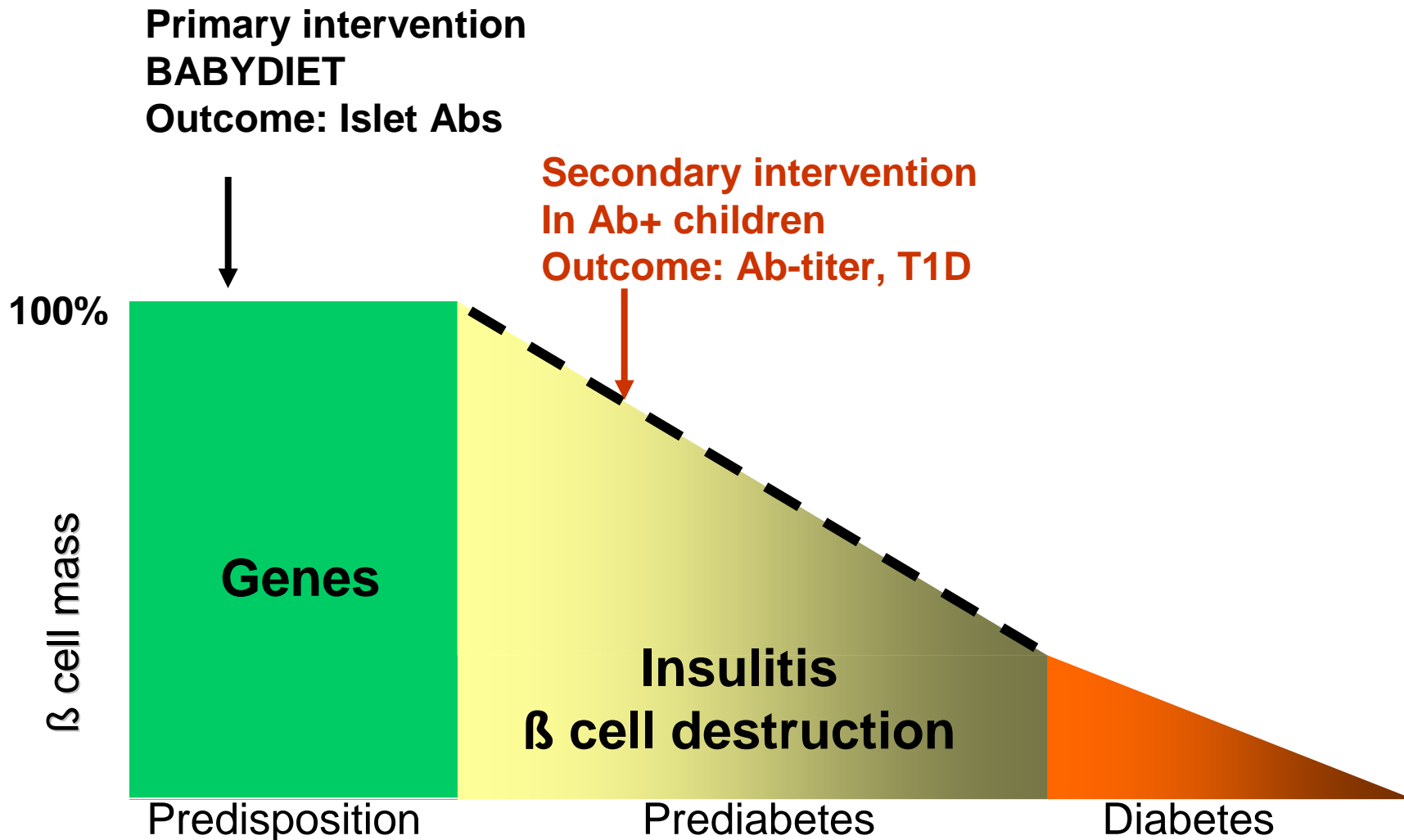
# Eliminating dietary gluten delays diabetes in NOD mice



# Gluten dietary intervention trials in type 1 diabetes

- Secondary prevention
  - In non-diabetic children with positive islet Ab
- Primary prevention
  - in healthy children with high T1D risk

# Gluten dietary intervention trials in type 1 diabetes



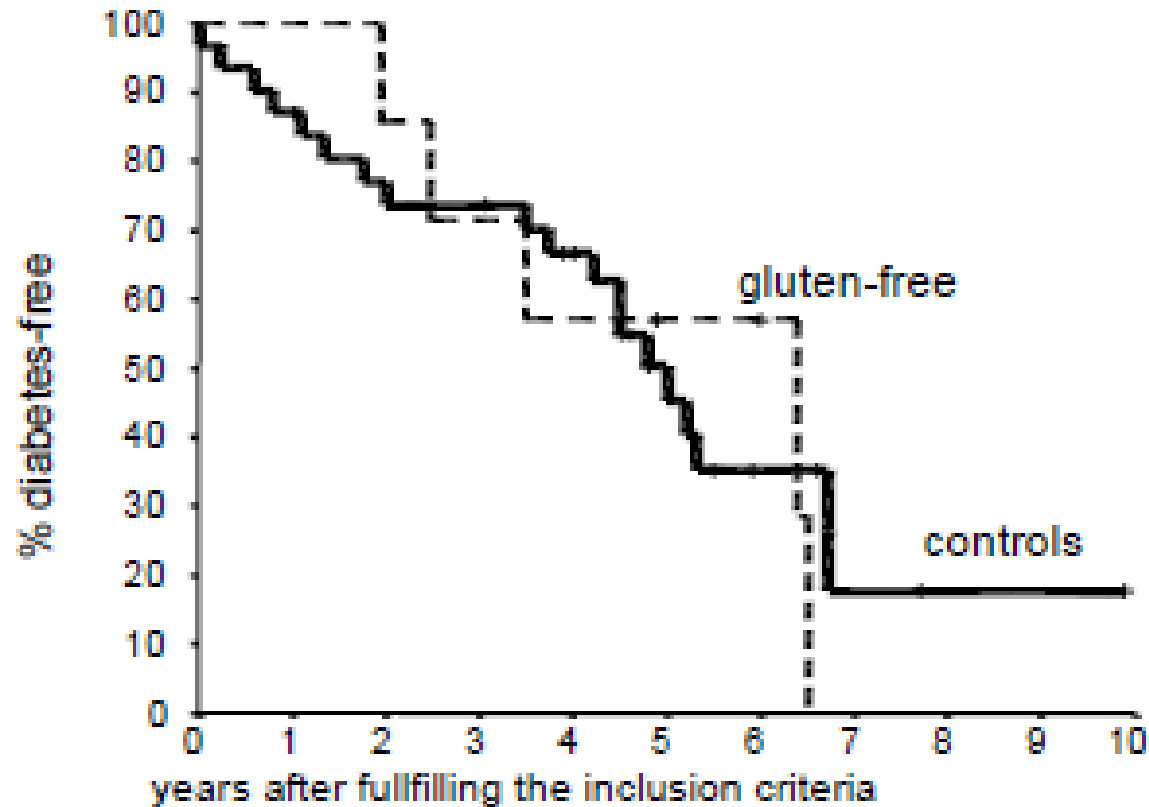
# Elimination of dietary gluten

## secondary prevention

- Open pilot study
- Hypothesis: elimination of gluten will protect from progression to T1D and will lead to a decrease of islet Abs
- Inclusion criteria:
  - sibling or offspring of patient with T1D
  - positive for  $\geq$  two islet Abs, persistent positive
  - $<$  age 6 years
  - normal glucose tolerance
- Intervention:
  - 12 month gluten-free diet, followed by re-exposure to gluten for 12 months
- Endpoint:
  - Titer of islet autoantibodies
  - Type 1 diabetes (compared to historical controls)
- Follow-up after inclusion: median 4.8 years

# Elimination of dietary gluten - secondary prevention

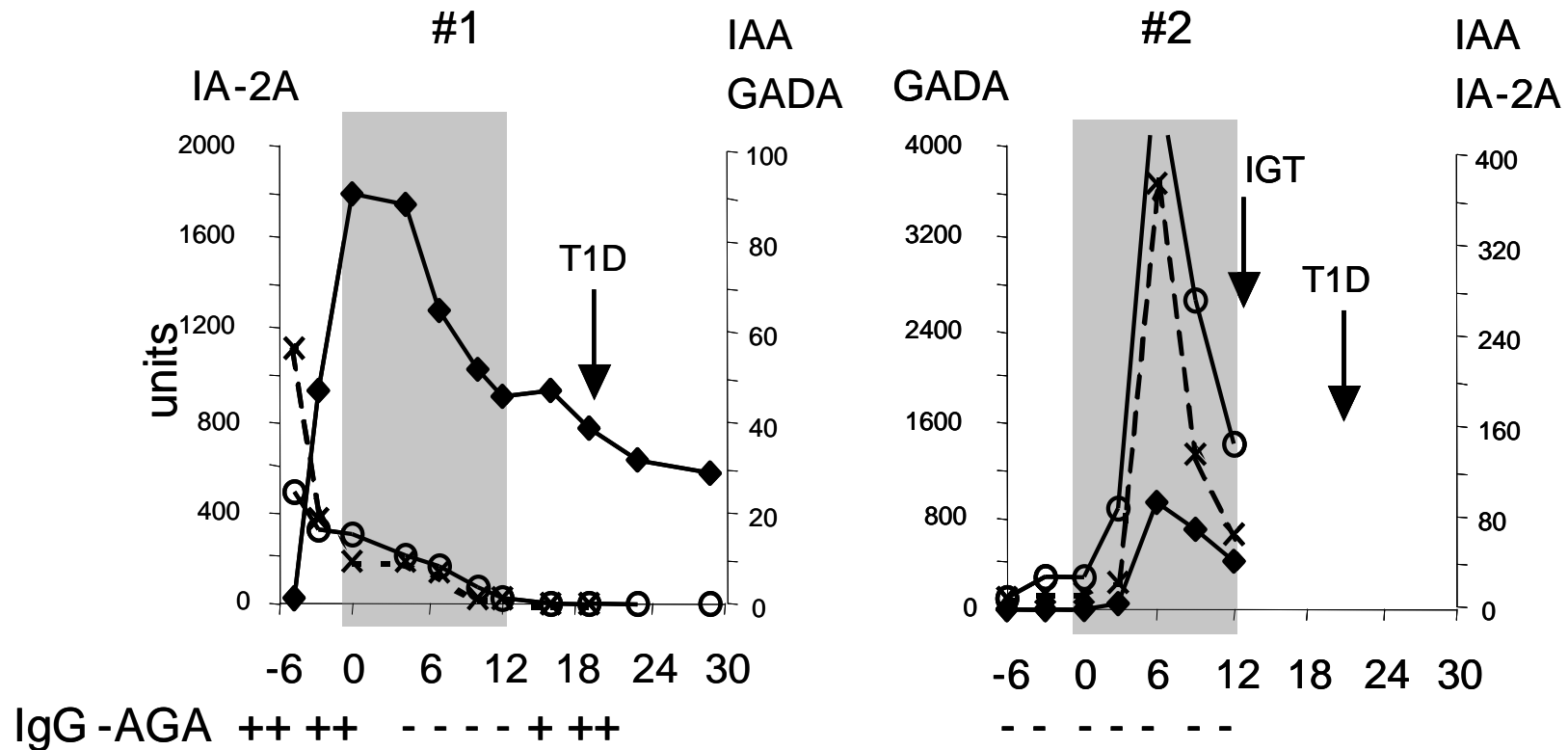
## Risk of progression to diabetes



gluten-free (n=)	7	7	6	5	4	3	3			
controls (n=)	30	27	22	22	18	10	5	2	1	1

# secondary prevention

## Islet autoantibody titers during and after elimination of gluten



# Elimination of dietary gluten

secondary prevention

No effect on islet autoimmunity and type 1 diabetes risk through elimination of gluten in antibody positive children

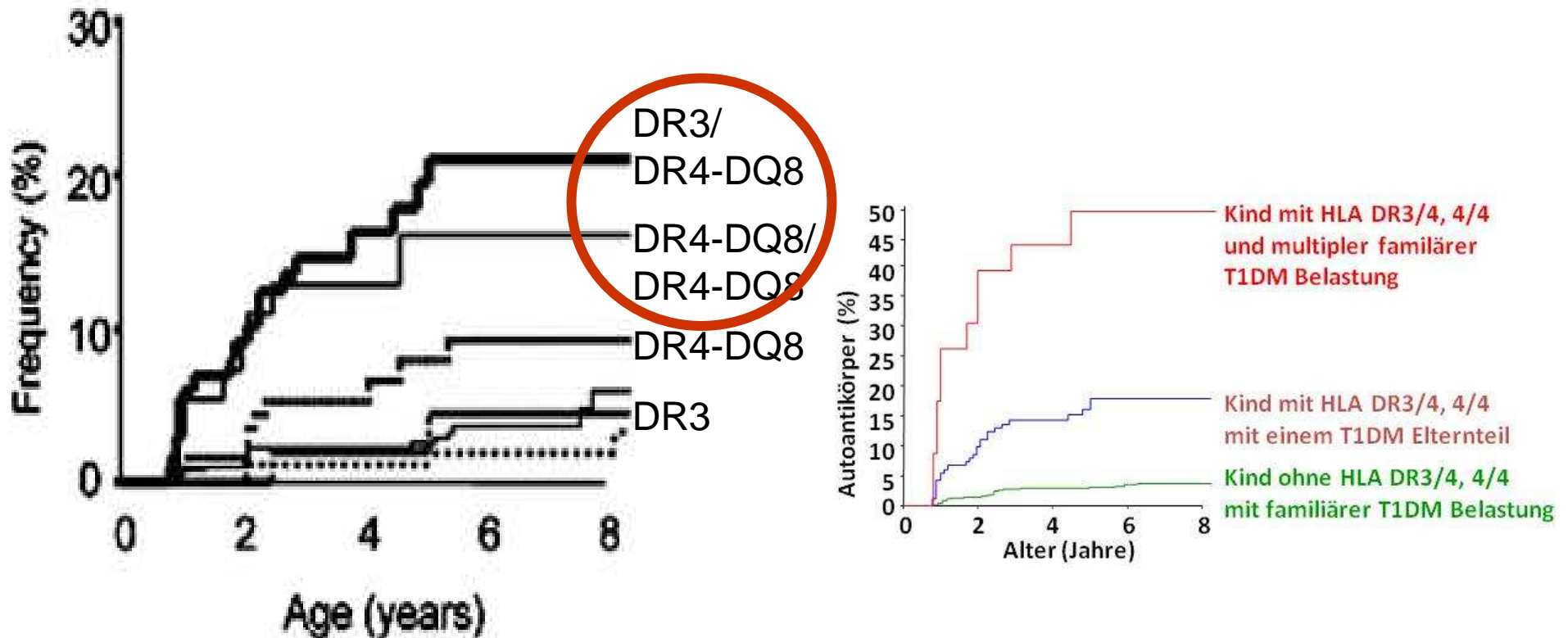
# Delaying gluten exposure in the first year of life -the BABYDIET study primary prevention

- Randomized open study
- Hypothesis:
  - delaying gluten exposure in the first year of life prevents the appearance of islet autoimmunity
- Inclusion criteria:
  - 140 sibling or offspring of patient with T1D
  - recruitment at birth
  - HLA DR3/4 or 4/4 or 3/3 (DQ8)

# Frequency of outcome

-what did we expect for BABYDIET?

## Islet autoantibodies

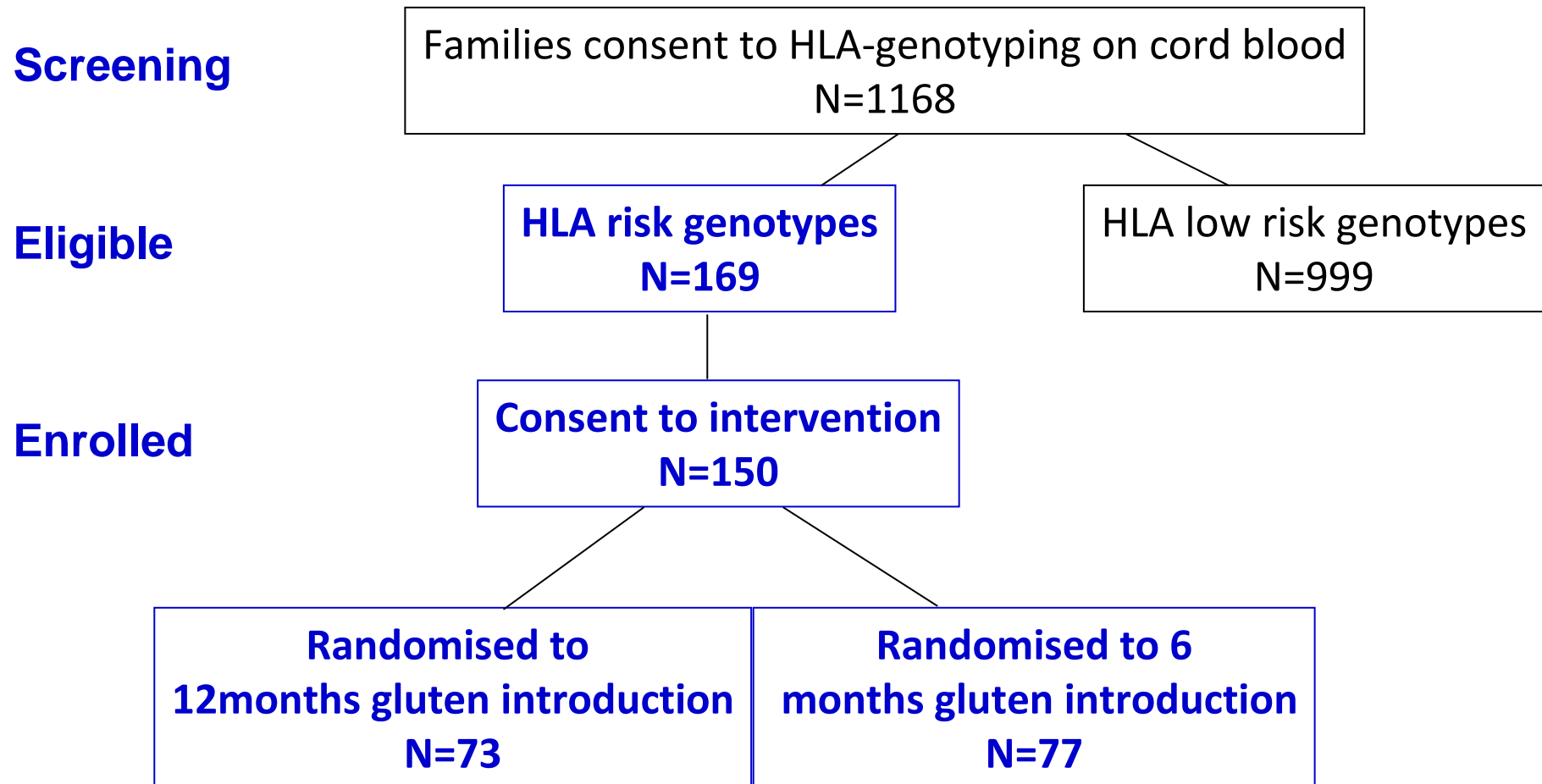


Expected number of islet ab+ subjects in BABYDIET: n~30/150

# Delaying gluten exposure in the first year of life -the BABYDIET study primary prevention

- Dietary Intervention:
  - 70 children randomized to gluten exposure at 6 months
  - 70 children randomized to gluten exposure at 12 months
- Endpoint:
  - Persistent appearance of islet autoantibodies (predicted >25%)
  - Appearance of celiac abs
  - Type 1 diabetes
- Follow-up:
  - 3 months intervals up to at age 3 years
  - blood, stool, urine samples, 3 days dietary records, daily recording of food introduction, infections, medication,
- analysis 2010

# Enrollment in BABYDIET primary prevention



## BABYDIET – subject characteristics

	6 months (n=77)	12 months (n=73)
HLA DR3/4 (n)	34	29
DR4/4 (n)	13	16
DR3/3 (n)	13	15
DR4/1 or 4/8 (n)	11	7
Multiple family history, no risk HLA (n)	6	6
Proband: father (n)	23	25
mother (n)	32	29
sibling (n)	11	8
multiplex (n)	11	11
Birthweight percentile, median (IQR)	64 (35-82)	61 (36-84)
Gestational age, weeks, median (IQR)	39 (38-40)	39 (37-40)
Follow-up, years, median (IQR)	3.8 (2.8-5.0)	3.8 (2.9-5.0)
Sex, female/male (n)	45/32	38/35

# BABYDIET

primary prevention

Results on the effect of delayed gluten exposure on diabetes risk will be available this year – analysis ongoing

# BABYDIET – exposure to gluten

% of children exposed to gluten

