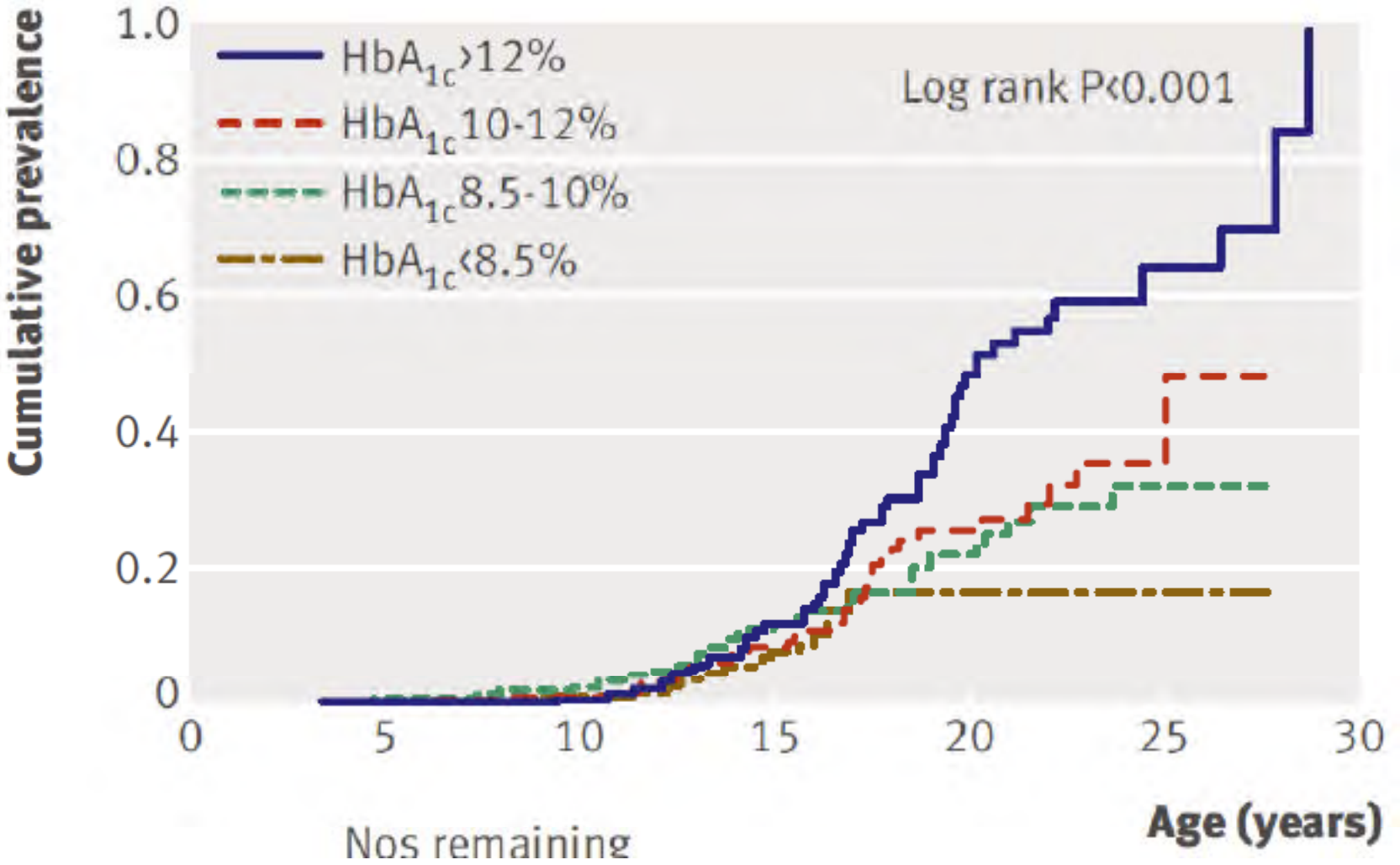
Centre de Référence
des Maladies Endocriniennes
Rares de la Croissance

université PARIS DIDEROT FACULTE DE MEDECINE PARIS 7

# Prevention of type 1 diabetes

Jean-Claude Carel, Hôpital Robert Debré, Paris, France

# Prevalence of microalbuminuria – UK population based study




*Amin, BMJ 2007*

Diabetes incidence in Europe

# Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study

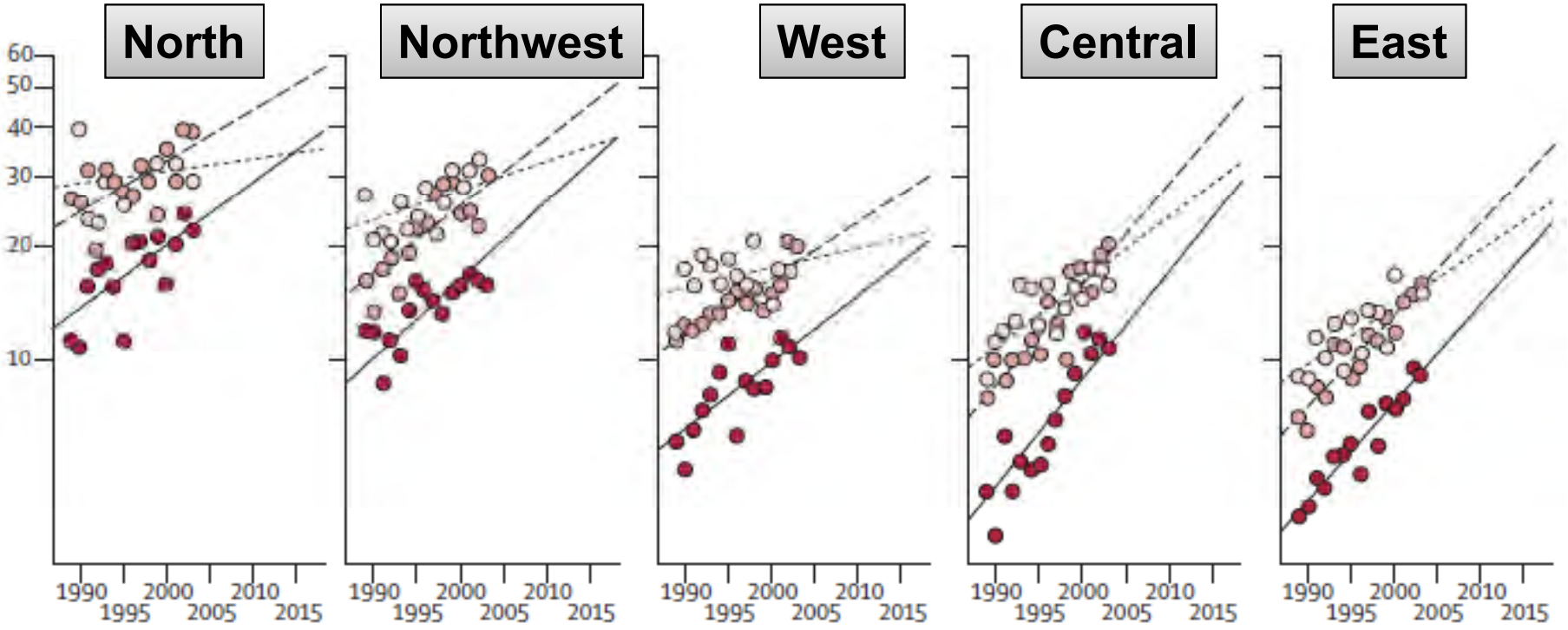
*Christopher C Patterson, Gisela G Dahlquist, Eva Gyürüs, Anders Green, Gyula Soltész, and the EURODIAB Study Group*

www.thelancet.com **Vol 373 June 13, 2009**

THE LANCET

Diabetes incidence in Europe

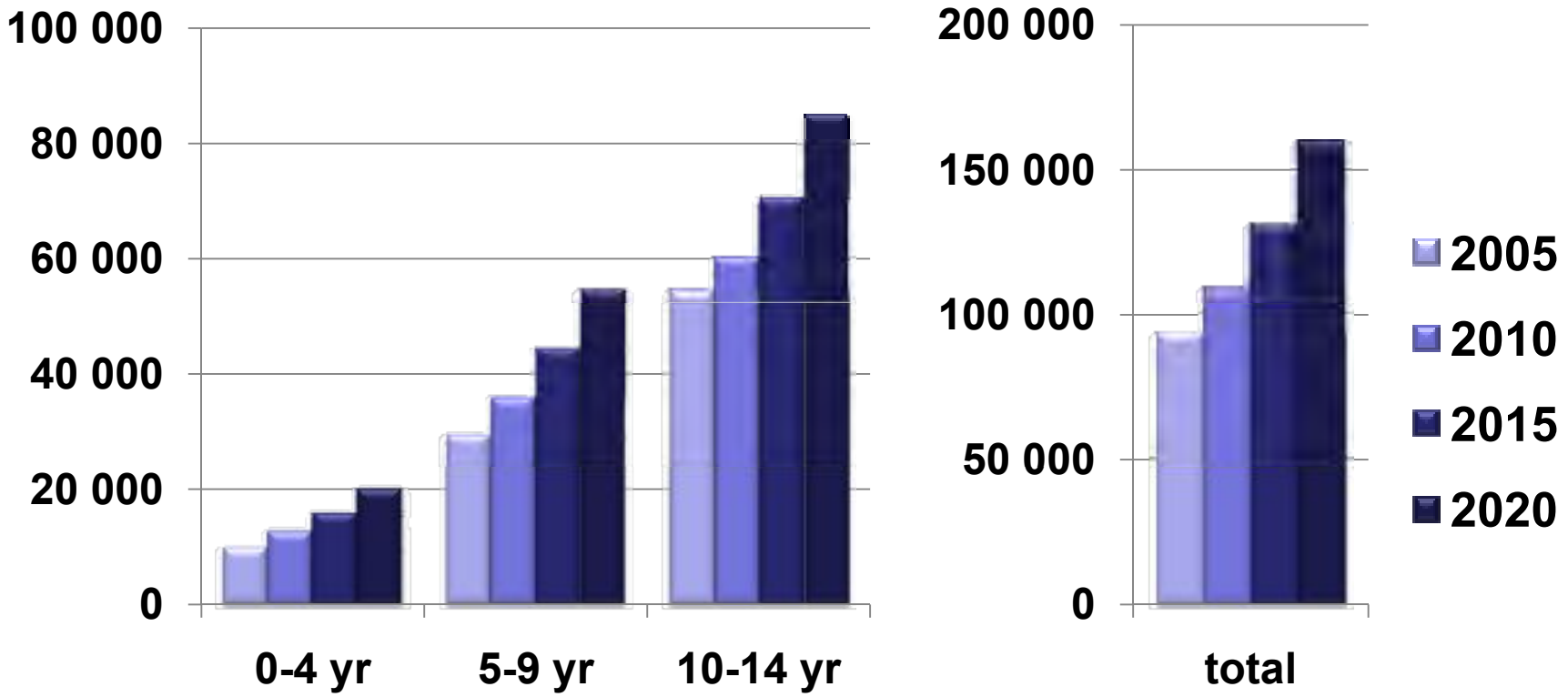
## Incidence rate/$10^5$ girls




**Annual increase:**

- ranges from 2.2 to 6.8%
- higher in younger age group
- higher in low incidence areas
- higher in girls 5 to 9

# Number of prevalent cases in the EU: 2020 trend



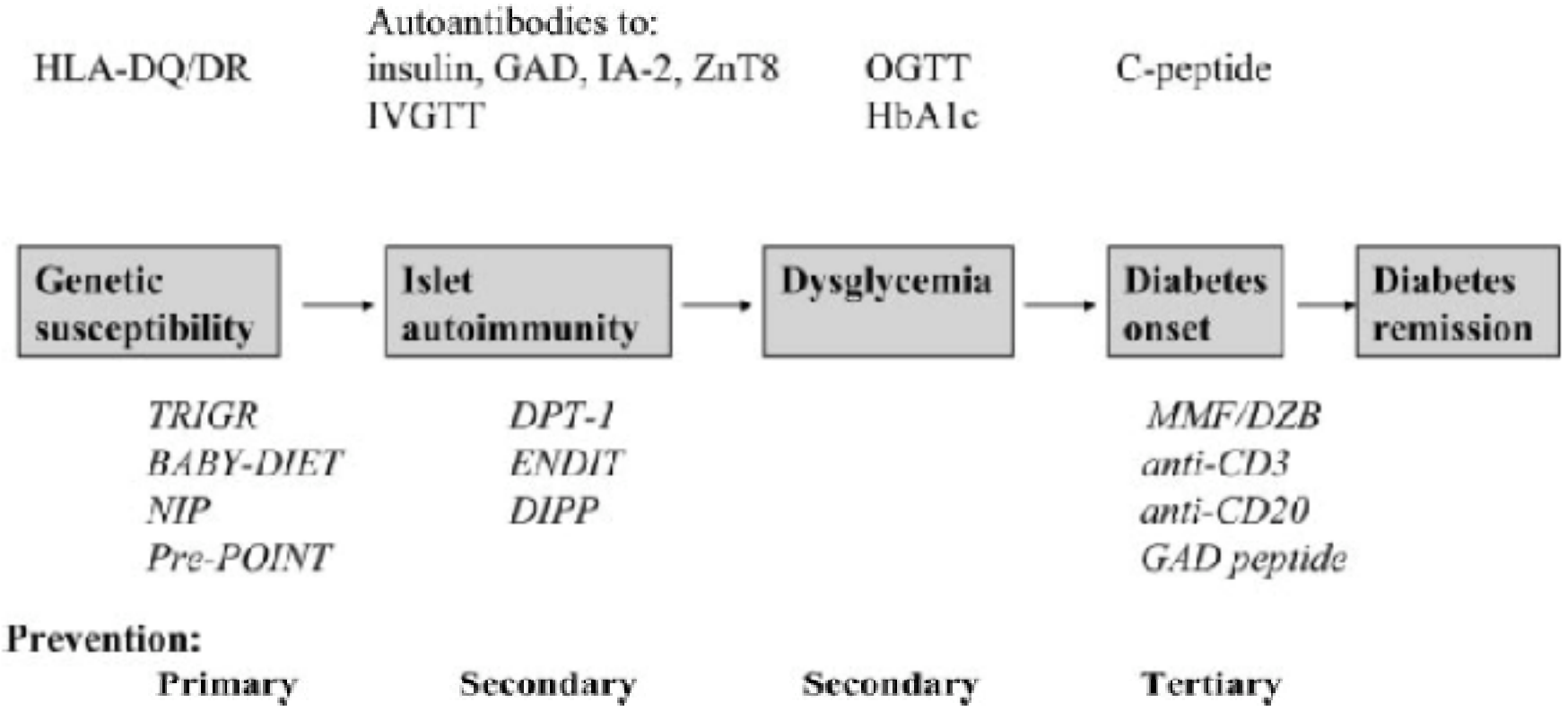
# Prevention of diabetes

- What population?
- At what stage of the disease process?
- How?

# What population?

- Relatives of type 1 diabetic patients
  - motivation for type 1 diabetes screening / prevention
  - most of the experience so far
  - ≈10 to 15% of new onset cases
- General population defined by genetic risk
  - no motivation for diabetes screening
  - variable sensitivity / specificity resulting from selection criteria
- General population
  - final goal of diabetes prevention

# At what stage of the disease process?

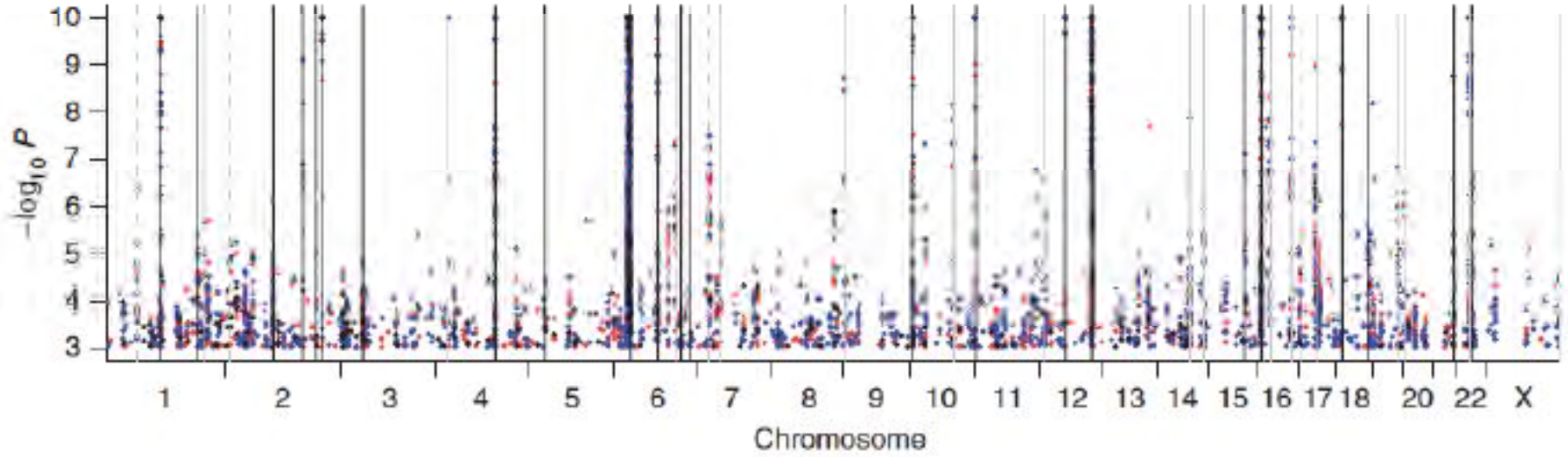


# Type 1 diabetes: epidemiology

| | |
|---|---|
| overall incidence | 10-60/$10^5$/year |
| geographic differences | north / south gradient |
| sex ratio | ~ 1:1 <15 years<br>3:2 male bias 15-40 yrs |
| sibling incidence | 6% |
| $\lambda_s$ | ~ 15 |
| children of diabetic mother | 2-3% |
| children of diabetic father | 6% |
| dizygotic twin concordance | 0-13% |
| monozygotic twin concordance | 25-70% |

# Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes

Jeffrey C Barrett[1], David G Clayton[1], Patrick Concannon[2,3], Beena Akolkar[4], Jason D Cooper[1], Henry A Erlich[5], Cécile Julier[6], Grant Morahan[7], Jørn Nerup[8], Concepcion Nierras[9], Vincent Plagnol[1], Flemming Pociot[8], Helen Schuilenburg[1], Deborah J Smyth[1], Helen Stevens[1], John A Todd[1], Neil M Walker[1], Stephen S Rich[3,10] & The Type 1 Diabetes Genetics Consortium[11]

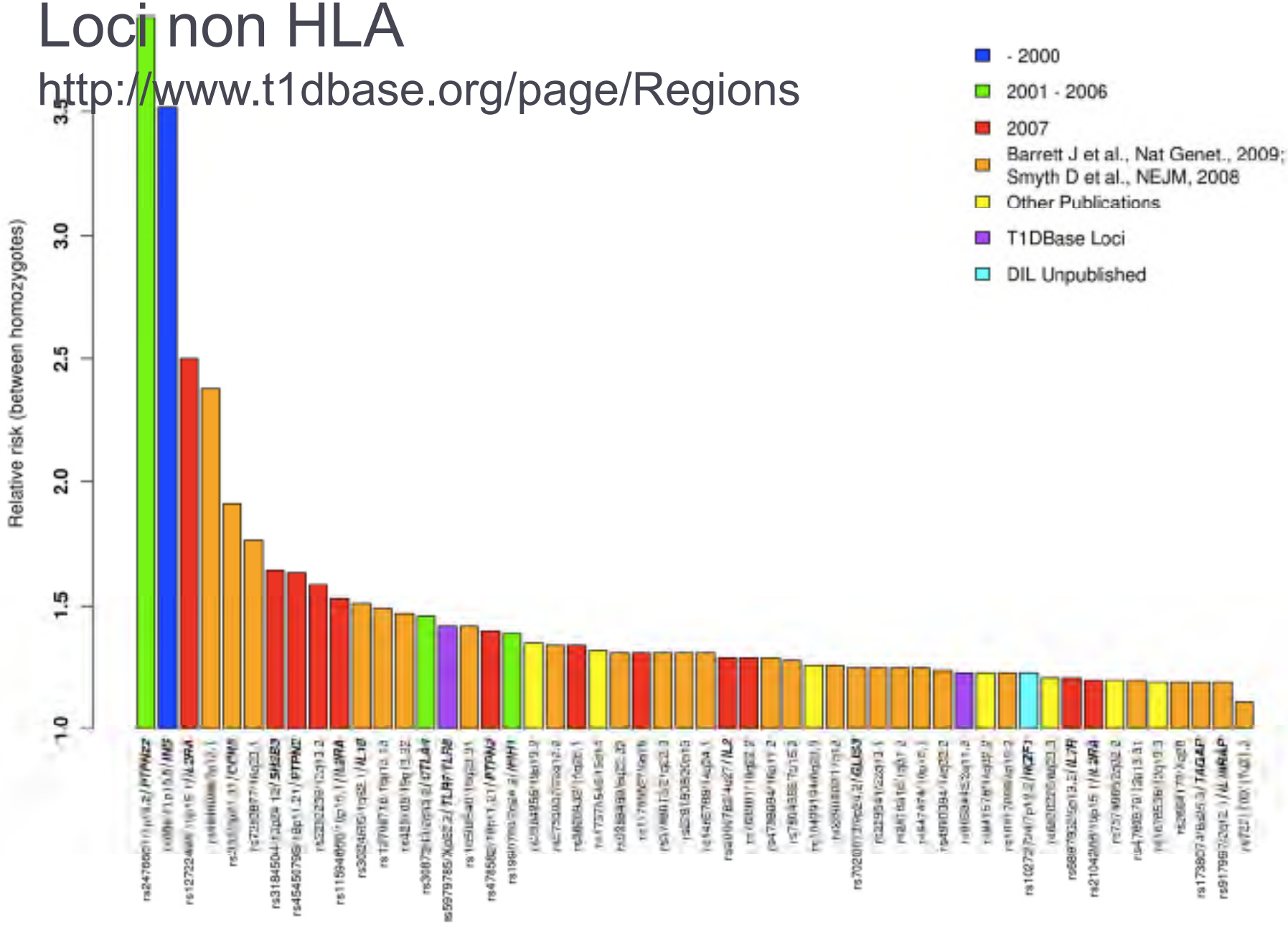



**≈19 000 cases, 21 000 controls**

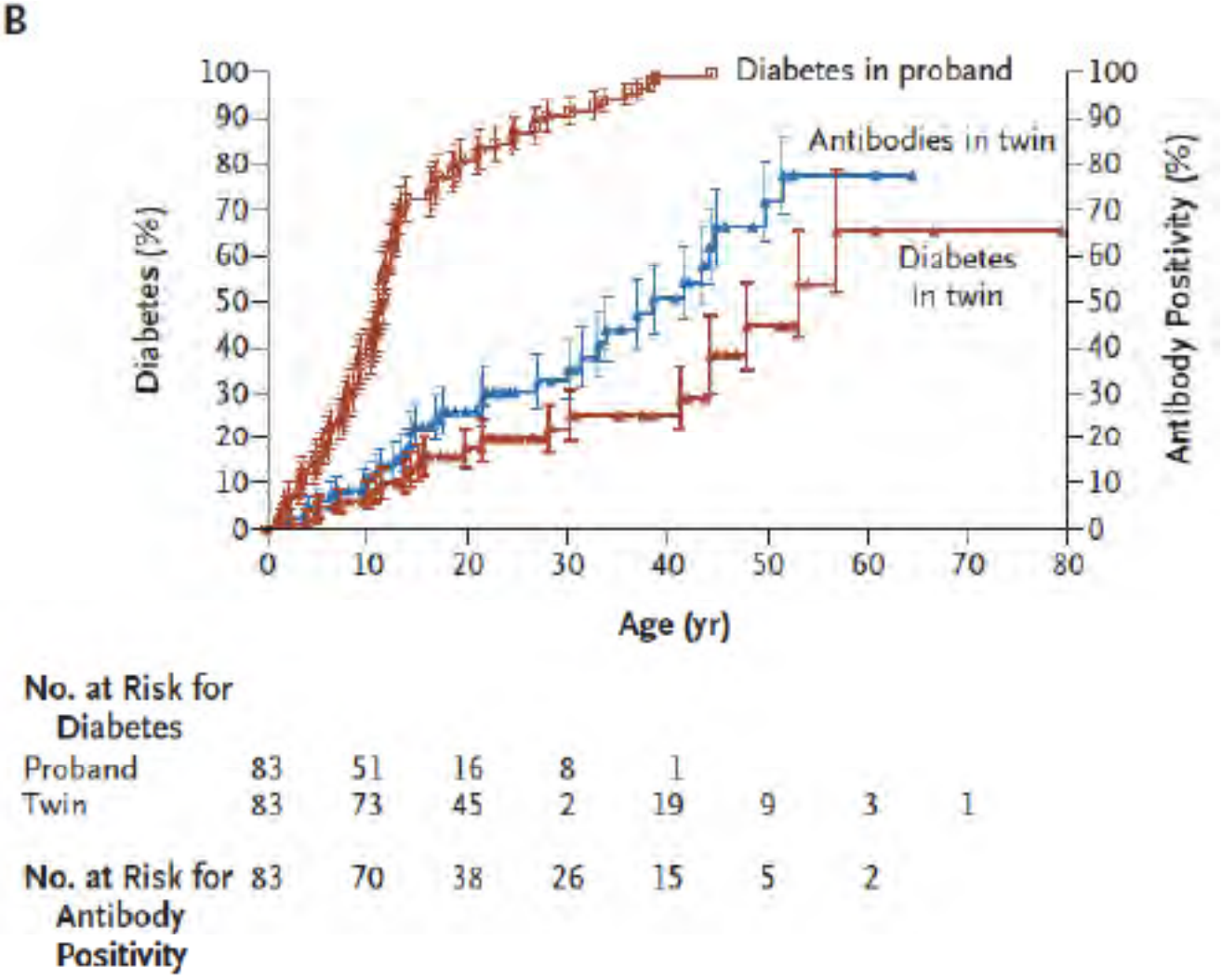
*Nature Genetics, May 2009*

# Loci non HLA

http://www.t1dbase.org/page/Regions

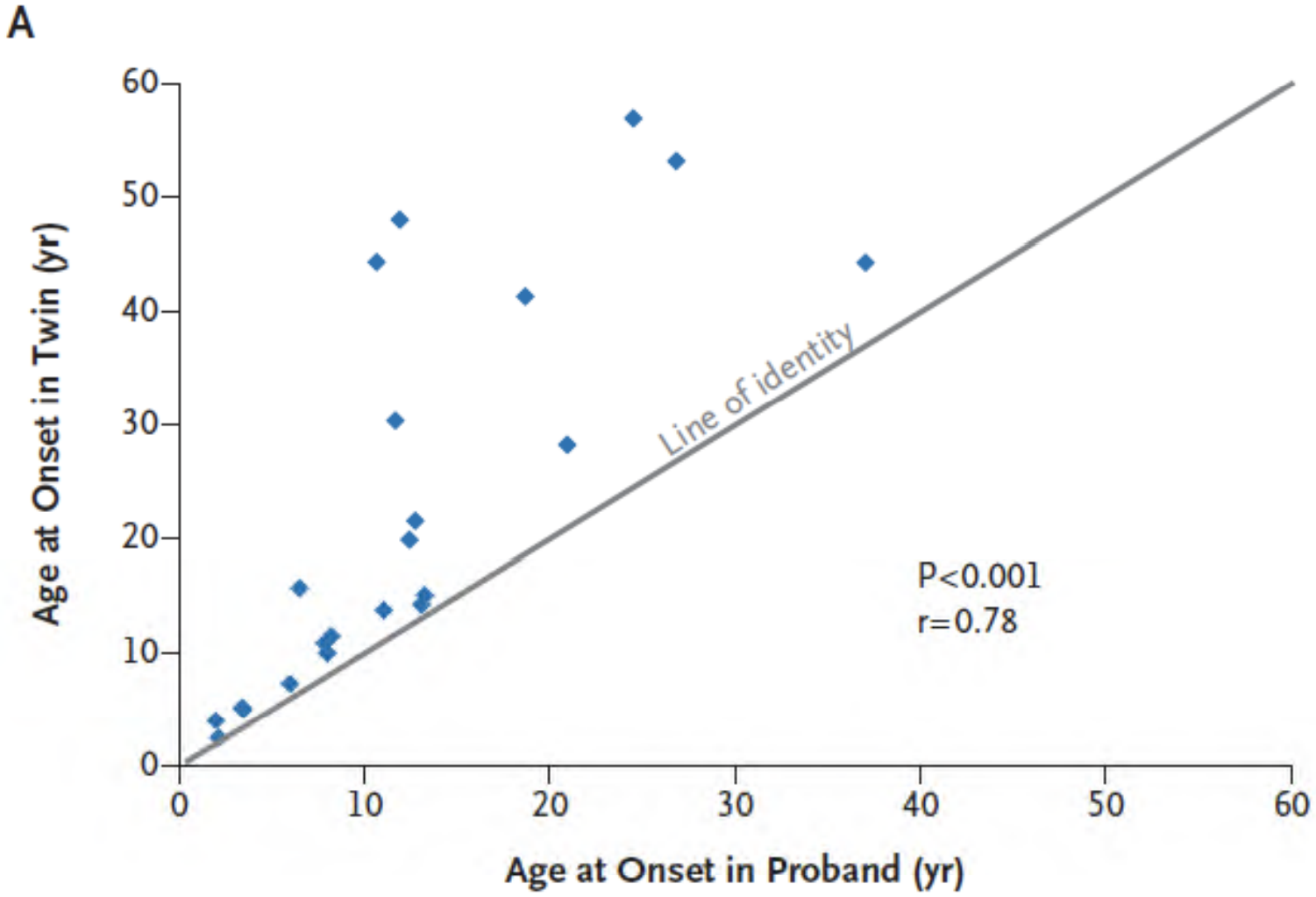


# Twin studies




*Redondo, NEJM 2009*

# Twin studies




***Redondo, NEJM 2009***

# Sensitivity and specificity of HLA typing

| HLA-DR,DQB1 | Type 1 diabetic individuals (n = 1322) n (%) | Population frequency (n = 3339) n (%) | Odds ratio (95% CI) | p-value $\alpha = 0.0025$ |
|---|---|---|---|---|
| 3/4,*0302 | 400 (30.26) | 78 (2.34) | 18.14 (14.08–23.37) | < 0.0001 |
| 4/4,*0302 | 146 (11.04) | 100 (2.99) | 4.02 (3.09–5.23) | < 0.0001 |
| 1/4,*0302 | 96 (7.26) | 75 (2.25) | 3.41 (2.50–4.64) | < 0.0001 |
| 8/4,*0302 | 36 (2.72) | 50 (1.50) | 1.84 (1.19–2.84) | 0.0051 |
| 9/4,*0302 | 13 (0.98) | 11 (0.33) | 3.01 (1.34–6.72) | 0.0049 |
| 7/4*0302 | 39 (2.95) | 82 (2.46) | 1.21 (0.82–1.78) | 0.34 |
| Y/4,*0302† | 116 (8.78) | 242 (7.25) | 1.29 (1.03–1.63) | 0.0281 |
| 2,*0602/4,*0302 | 6 (0.45) | 79 (2.37) | 0.19 (0.08–0.43) | < 0.0001 |
| 2/4,*0302 | 9 (0.68) | 33 (0.99) | 0.69 (0.33–1.42) | 0.3166 |
| 3/3 | 103 (7.79) | 44 (1.32) | 6.33 (4.42–9.06) | < 0.0001 |
| 3/1 | 45 (3.40) | 73 (2.19) | 1.58 (1.08–2.30) | 0.0171 |
| 3/8 | 15 (1.13) | 30 (0.90) | 1.27 (0.68–2.36) | 0.4573 |
| 3/9 | 11 (0.83) | 6 (0.18) | 4.66 (1.72–12.63) | 0.0009 |
| 3/7 | 33 (2.50) | 86 (2.58) | 0.97 (0.65–1.45) | 0.8769 |
| 3/Y† | 45 (3.40) | 182 (5.45) | 0.61 (0.44–0.85) | 0.0034 |
| 3/2,*0602 | 7 (0.53) | 81 (2.43) | 0.21 (0.099–0.46) | < 0.0001 |
| 3/2 | 22 (1.66) | 27 (0.81) | 2.08 (1.18–3.66) | 0.0098 |
| 3/4,*0301 | 30 (2.27) | 33 (0.99) | 2.33 (1.41–3.83) | 0.0006 |
| 4/X,4/4,*0301† | 58 (4.39) | 277 (8.30) | 0.51 (0.38–0.68) | < 0.0001 |
| All others (X/X)‡ | 92 (6.96) | 1750 (52.41) | 0.068 (0.054–0.085) | < 0.0001 |

***Emery, Pediatric Diabetes 2005***

# HLA genotypes in children with diabetes - trend with time

| | All | |
|---|---|---|
| | *n* (%) | OR (95% CI)* |
| DRB1*03-DQB1*02/DRB1*04-DQB1*03 | | |
| 1978–1988 | 39 (39) | |
| 2002–2004 | 75 (28) | **0.6 (0.4–0.99)** |
| DRB1*04-DQB1*03/DRB1*04-DQB1*03, DRB1*04-DQB1*03/X†, DRB1*04-DQB1*03/unknown | | |
| 1978–1988 | 30 (30) | |
| 2002–2004 | 111 (42) | **1.7 (1.1–2.8)** |
| DRB1*03-DQB1*02/DRB1*03-DQB1*02, DRB1*03-DQB1*02/X†, DRB1*03-DQB1*02/unknown | | |
| 1978–1988 | 20 (20) | |
| 2002–2004 | 55 (21) | 1.1 (0.6–1.9) |
| X/X, X/unknown | | |
| 1978–1988 | 11 (11) | |
| 2002–2004 | 23 (8.7) | 0.8 (0.4–1.6) |

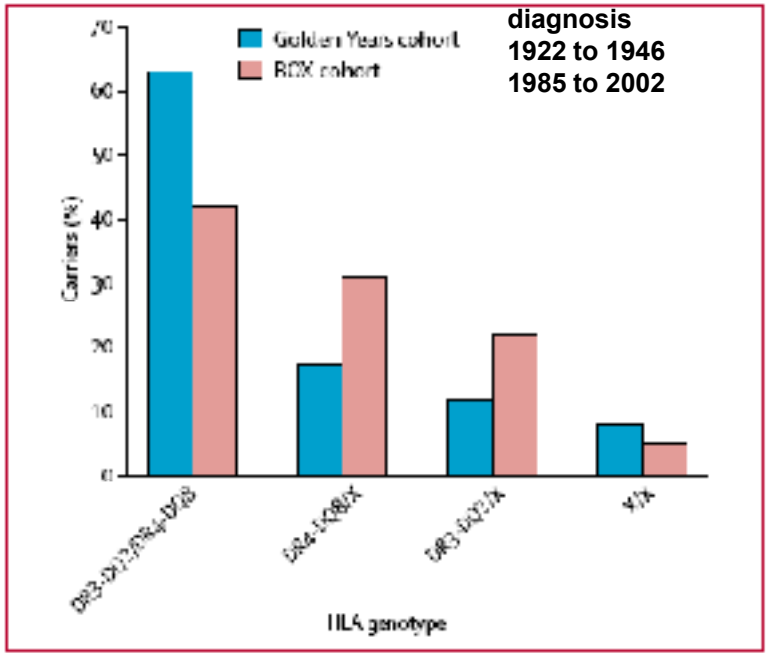
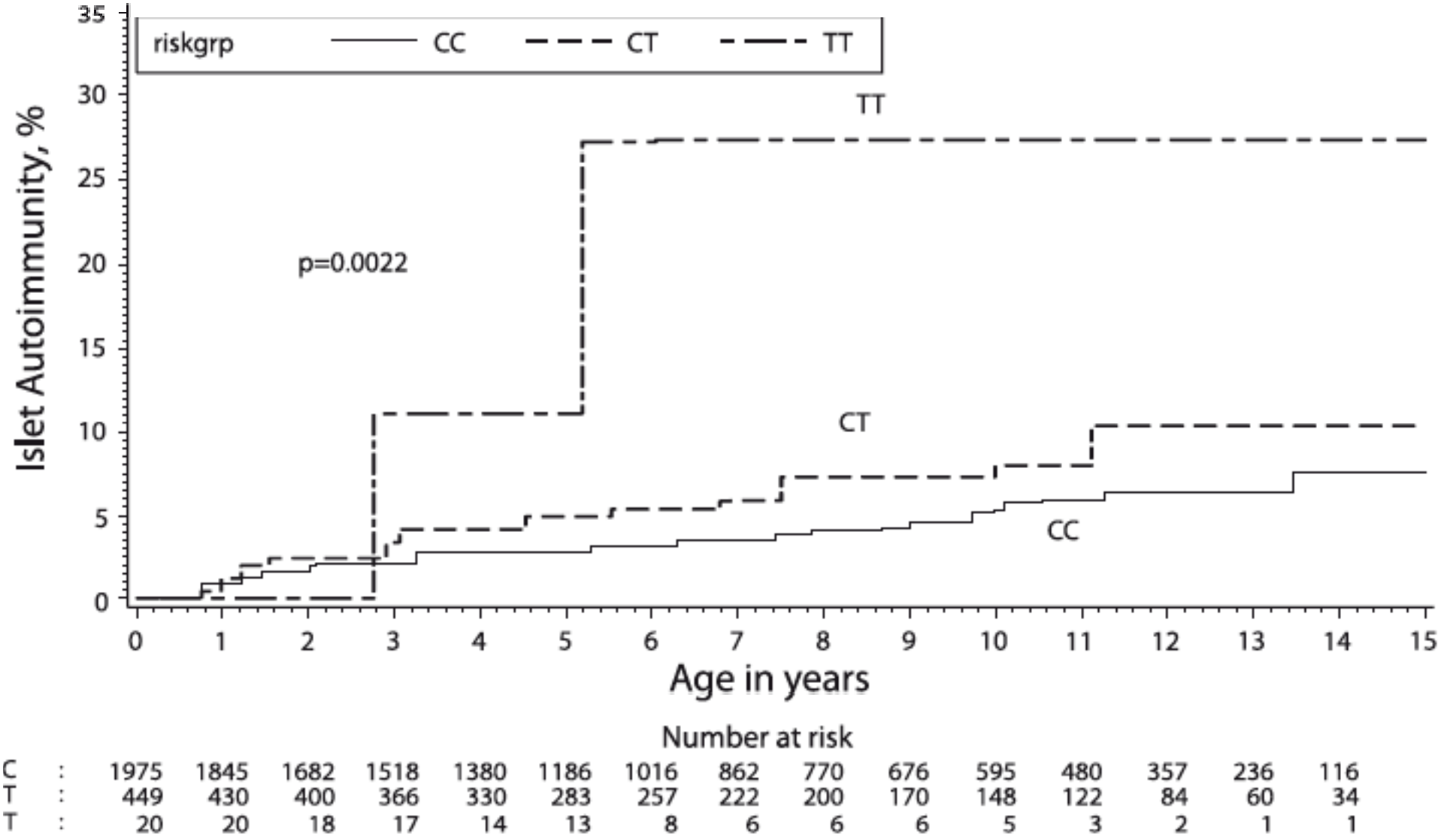
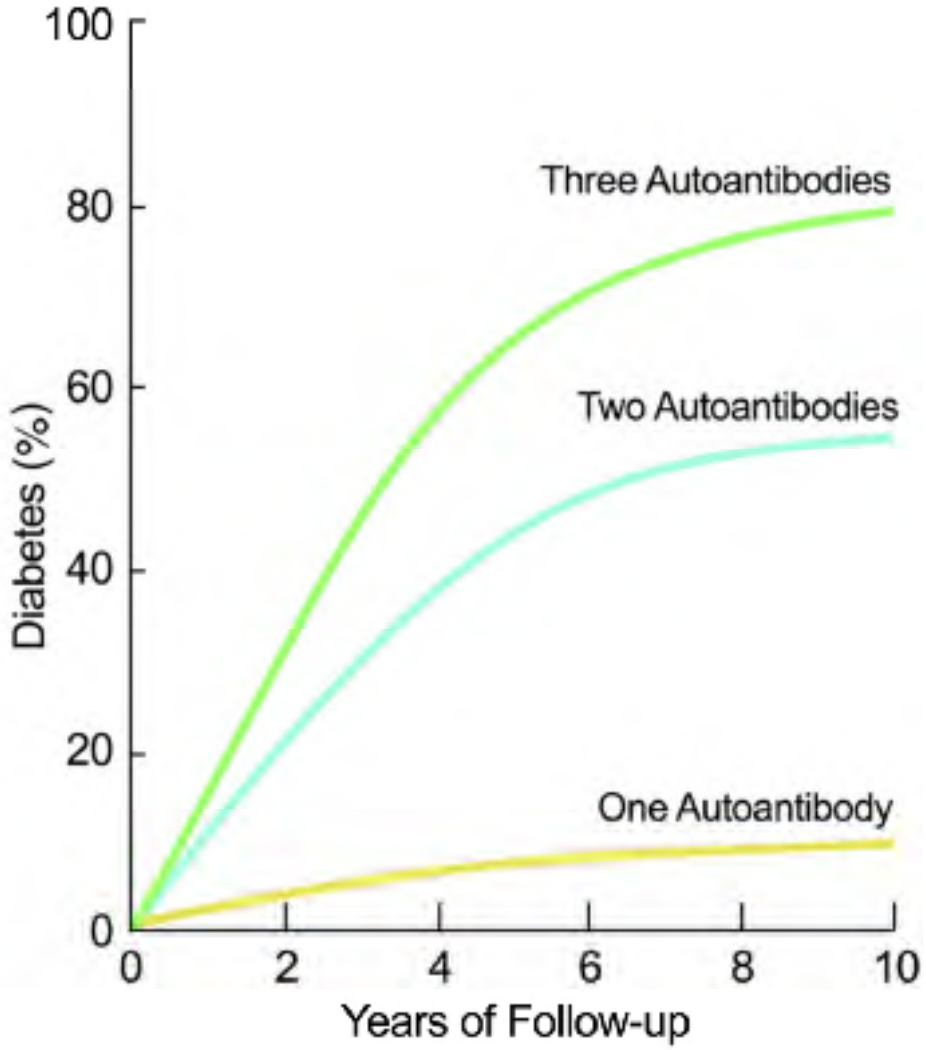



Figure: Distribution of HLA class II haplotypes in Golden Years and BOX cohorts

*Gillespie, Lancet 2004*
***Vehik, Diabetes Care 2010***


riskgrp
CC
CT
TT
Islet Autoimmunity, %
35
30
25
20
15
10
5
0
p=0.0022
TT
CT
CC
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Age in years
Number at risk
C : 1975 1845 1682 1518 1380 1186 1016 862 770 676 595 480 357 236 116
T : 449 430 400 366 330 283 257 222 200 170 148 122 84 60 34
T : 20 20 18 17 14 13 8 6 6 6 5 3 2 1 1

# Disease prediction in relatives




**Disease risk and autoantibodies:**

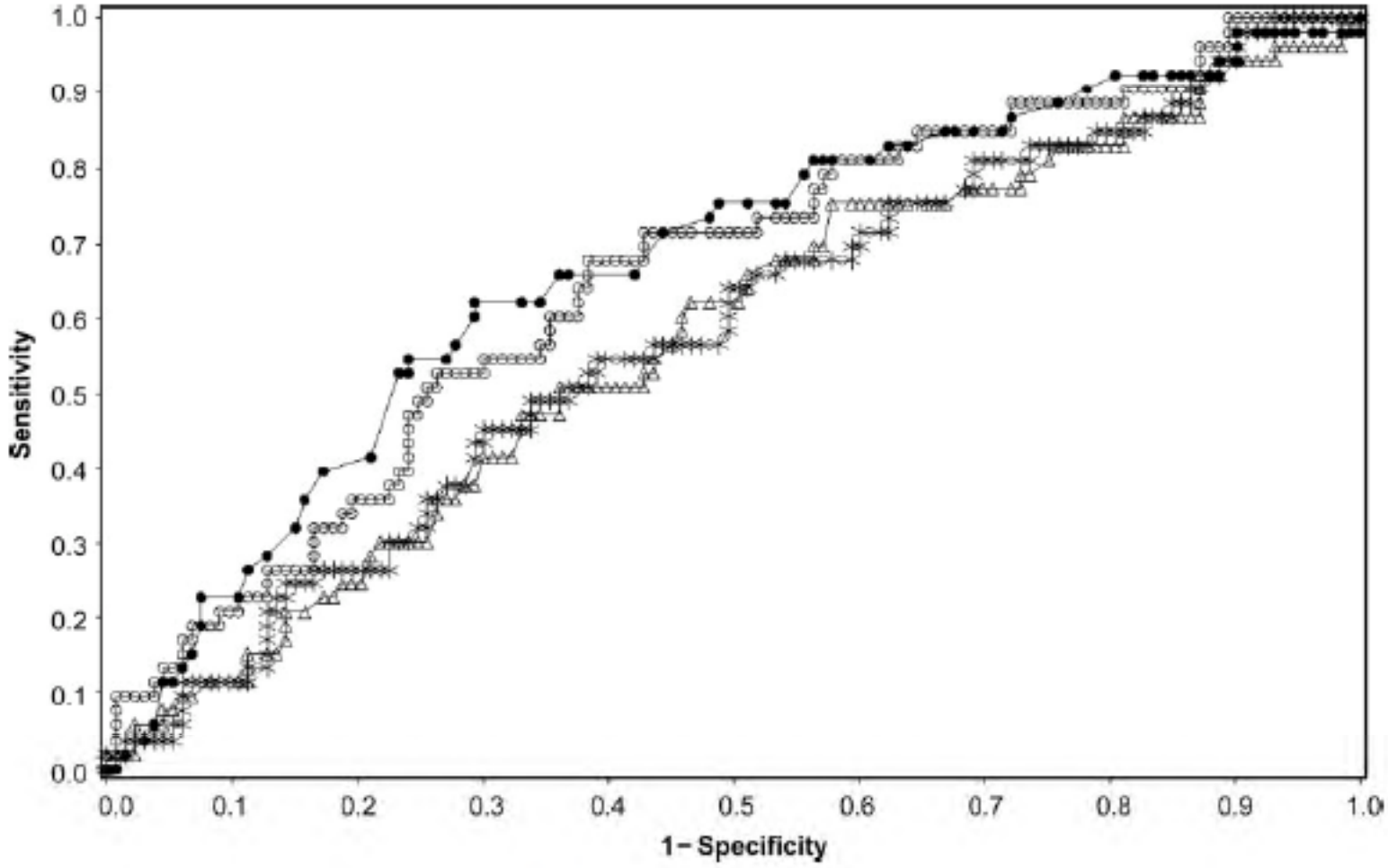
- •GAD
- •insulin
- •IA-2

**Other factors:**

- •age
- •HLA class I and class II
- •insulin secretion

***Lernmark, JCI 2002***

# Predictive value of metabolic indexes in antibody-positive relatives




–*ROC AUC for various metabolic indexes.* ●, *2-h glucose–OGTT;* ○, *FPIR;* △, *FPIR-to–HOMA-IR ratio;* □, *HOMA-IR.*

***Xu, Diabetes Care 2010***

# Environmental factors – modifiable factors?

- Viruses
  - congenital rubella, Coxsackie B, mumps, echovirus, cytomegalovirus, Epstein-Barr virus, retrovirus, rotavirus, parvovirus B19
- Bacteria
  - gut microbiota
- Dietary factors
  - mother or child
  - cow milk, decreased vitamins C, D, and E, early introduction of cereals, potatoes/carrots, fruit/berries, cow's milk, N-nitroso compounds
  - increased calories
- Psychosocial environment
- Non specific triggers
  - hygiene hypothesis
- …

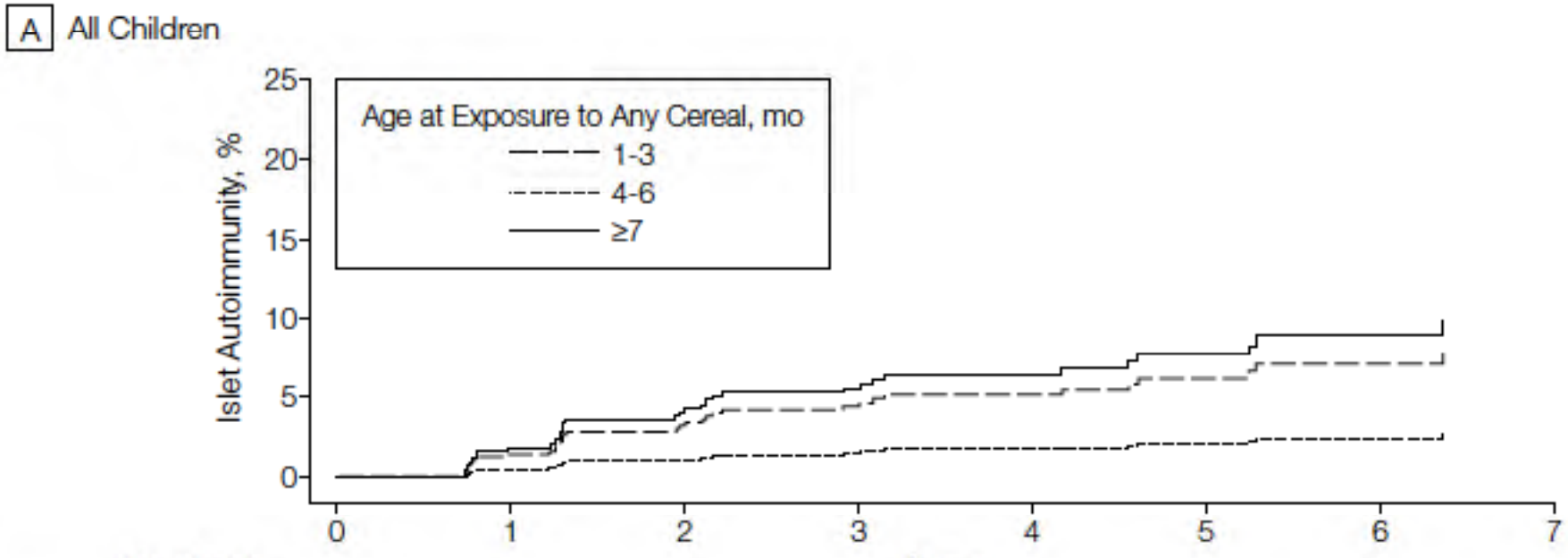
# Cereals in infancy and islet autoimmunity

**Table 3.** Age at Exposure to Cereals in Infancy and Risk of Islet Autoimmunity in Diabetes Autoimmunity Study in the Young Cohort*

| Model 2. Combining Rice and Gluten-Containing Exposures Into an Any Cereal Variable | | |
|---|---|---|
| Age exposed to any cereals, mo | 1-3 | 4.32 (2.00-9.35) |
| | 4-6 | 1.00 |
| | ≥7 | 5.36 (2.08-13.77) |
| Breastfed when first exposed to cereal | Yes vs no | 0.50 (0.25-0.99) |
| HLA genotype | HLA-DRB1*03/04,DQB8 vs other genotypes | 8.69 (4.15-18.16) |
| First-degree relative with type 1 diabetes mellitus | Yes vs no | 7.64 (3.55-16.46) |
| Race/ethnicity | Non-Hispanic white vs other | 2.83 (0.83-9.70) |
| Maternal age | 1-Year increase | 1.05 (0.98-1.12) |

*Norris, JAMA 2003*

# Cereals in infancy and islet autoimmunity




| No. at Risk<br>Age at Exposure to Any Cereal, mo | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1-3 | 259 | 226 | 181 | 149 | 128 | 96 | 59 |
| 4-6 | 818 | 748 | 633 | 526 | 409 | 286 | 181 |
| ≥7 | 106 | 95 | 82 | 67 | 56 | 44 | 25 |

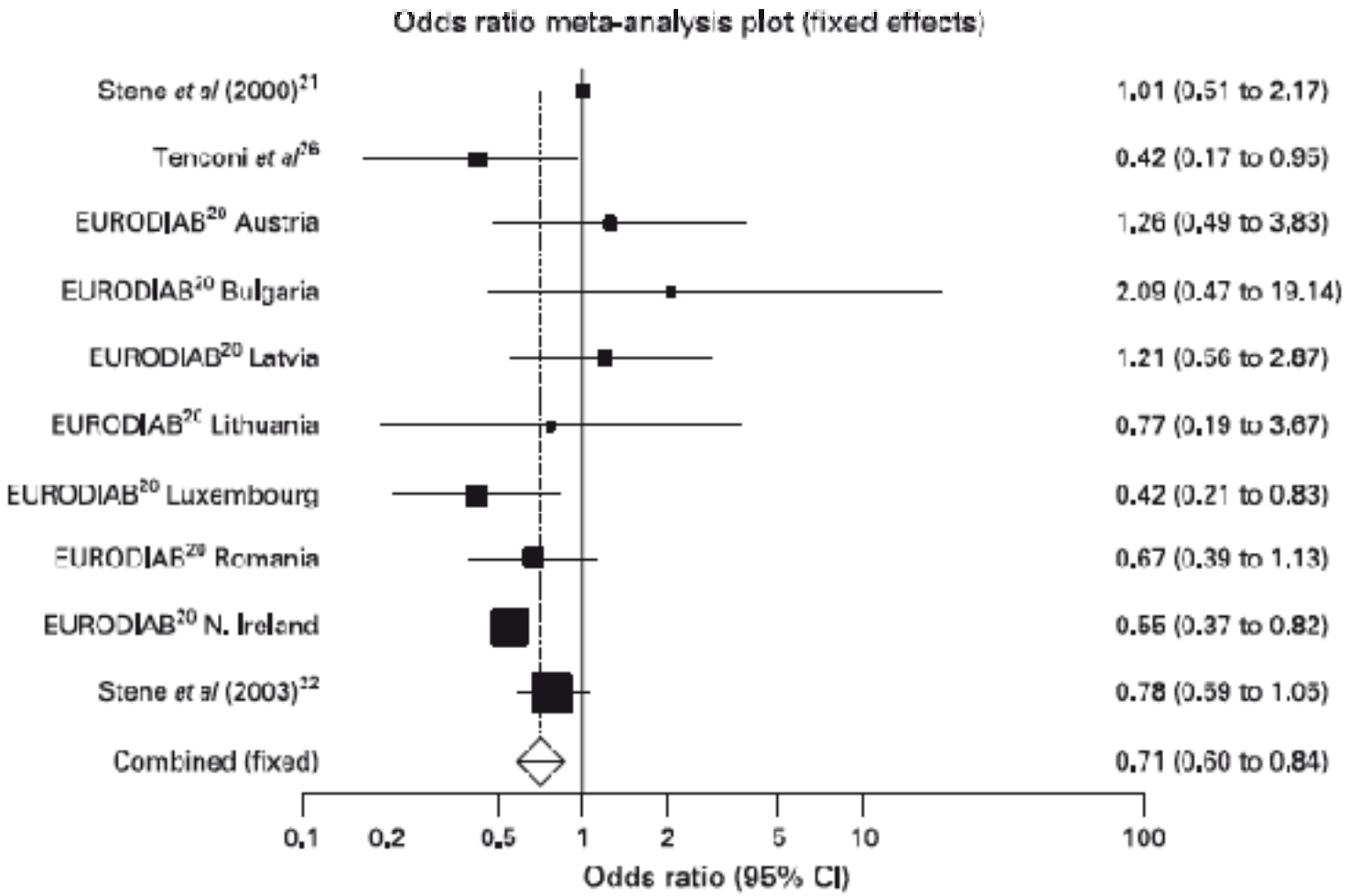
***Norris, JAMA 2003***

# Vitamin D intake in infancy and risk of diabetes

| | Type 1 diabetes | Time at risk (years) | Incidence per 100 000 years at risk | RR (95% CI) | Adjusted RR (95% CI)* |
|---|---|---|---|---|---|
| **Use of vitamin D supplements** | | | | | |
| None | 2 | 981 | 204 | 1 (reference) | 1 (reference) |
| Irregularly | 12 | 36 143 | 33 | 0·16 (0·04–0·72) | 0·16 (0·04–0·74) |
| Regularly | 67 | 276 235 | 24 | 0·12 (0·03–0·47) | 0·12 (0·03–0·51) |
| **Dose of vitamin D†** | | | | | |
| Low | 2 | 2 093 | 96 | 1 (reference) | 1 (reference) |
| Recommended | 63 | 259 779 | 24 | 0·20 (0·05–0·84) | 0·22 (0·05–0·89) |
| High | 2 | 13 245 | 15 | 0·14 (0·02–0·97) | 0·14 (0·02–1·01) |
| **Suspected rickets‡** | | | | | |
| No | 77 | 306 945 | 25 | 1 (reference) | 1 (reference) |
| Yes | 4 | 6 414 | 62 | 2·6 (1·0–7·2) | 3·0 (1·0–9·0) |

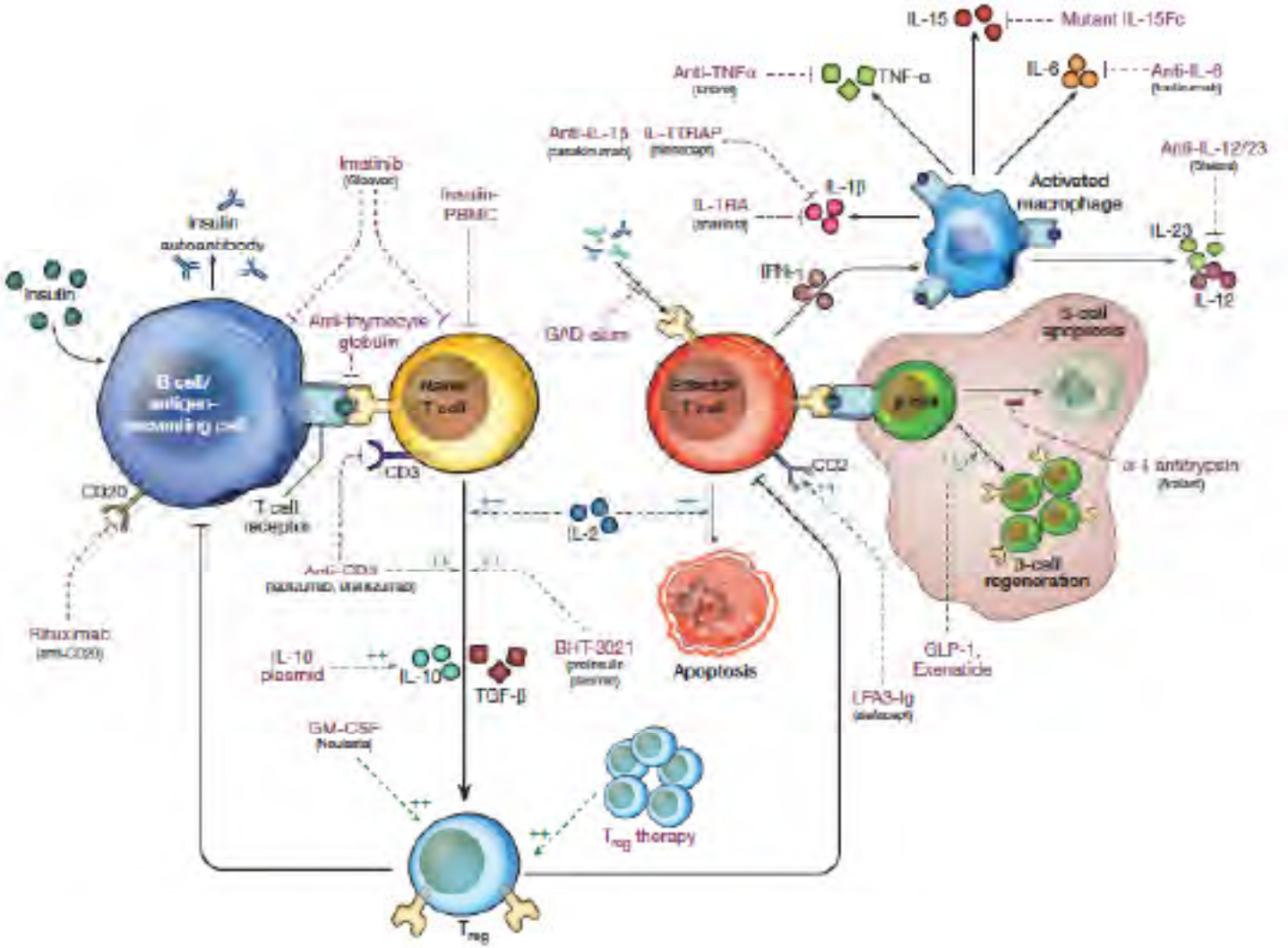
***Hyppönen, Lancet 2001***

# Vitamin D intake in infancy and risk of diabetes: meta-analysis




*Zipitis, ADC 2010*

# Targets of immune intervention in type 1 diabetes




***Bluestone, Nature 2010***

Recruiting — Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus
Condition: Diabetes Mellitus, Type 1
Intervention: Drug: Oral Insulin

Active, not recruiting — TRIGR - Primary Prevention Study for Type 1 Diabetes in Children at Risk
Condition: Diabetes Mellitus, Type 1
Intervention: Dietary Supplement: hydrolysed vs nonhydrolysed infant formula vs breast feeding

Not yet recruiting — Teplizumab for Prevention of Type 1 Diabetes in Relatives "At-Risk"
Conditions: Autoantibody Positive; Non-diabetic Relatives at Risk for Type 1 Diabetes; High Risk; In
Intervention: Drug: Teplizumab

Completed — Prevention of Clinical Onset of Type 1 Diabetes in High Risk First Degree Relatives
Condition: Diabetes, Type 1
Intervention: Drug: Actrapid HM

Active, not recruiting — BABYDIET Study - Primary Prevention of Type 1 Diabetes in Relatives at Increased Genetic Risk
Condition: Type 1 Diabetes
Intervention: Other: Gluten-free diet during the first year of life

Recruiting — Intranasal Insulin for Prevention of Type 1 Diabetes
Condition: Type 1 Diabetes
Intervention: Drug: daily intranasal administration of insulin

Completed — Insulin-free Cow Milk Formula in Prevention of Type 1 Diabetes Associated Autoimmunity - FINDIA Pilot Study
Condition: Beta-cell Autoimmunity
Intervention: Dietary Supplement: Cow's milk formula

Recruiting — Feasibility Study of 2000 IU Per Day of Vitamin D for the Primary Prevention of Type 1 Diabetes
Condition: Type 1 Diabetes
Intervention: Drug: vitamin D3 (cholecalciferol) 2000 IU per day

Completed — The Diabetes Prevention Trial of Type 1 Diabetes (DPT-1)
Condition: Diabetes Mellitus, Type 1
Intervention: Drug: Crystallized human recombinant insulin

Recruiting — Natural History Study of the Development of Type 1 Diabetes
Condition: Diabetes Mellitus, Type 1
Intervention:

Active, not recruiting — Nutritional Intervention to Prevent Diabetes
Condition: Type 1 Diabetes Mellitus
Interventions: Drug: 1. DHA Treatment Group Experimental; Drug: 2. Control Group

Completed — Severe Hypoglycemia in Pregnant Women With Type 1 Diabetes
Conditions: Pregnancy; Diabetes
Intervention:

Active, not recruiting — Nutritional Prevention Pilot Trial for Type 1 Diabetes
Condition: Type 1 Diabetes Mellitus
Interventions: Dietary Supplement: A highly hydrolyzed formula; Dietary Supplement: A regular cow

Terminated — PREVENTID (Prevent Risks by Early Intervention at Nighttime in Type 1 Diabetes for Kidney Disease)
Condition: Type 1 Diabetes
Interventions: Drug: Ramipril; Drug: Placebo

Recruiting — Prevention of Self-care Deterioration in Early Adolescents With Diabetes
Condition: Type 1 Diabetes
Interventions: Behavioral: TeamWork CS Sessions; Behavioral: Diabetes Education

Recruiting — Diabetes Prevention - Immune Tolerance
Condition: Prediabetes
Intervention: Drug: Diamyd®

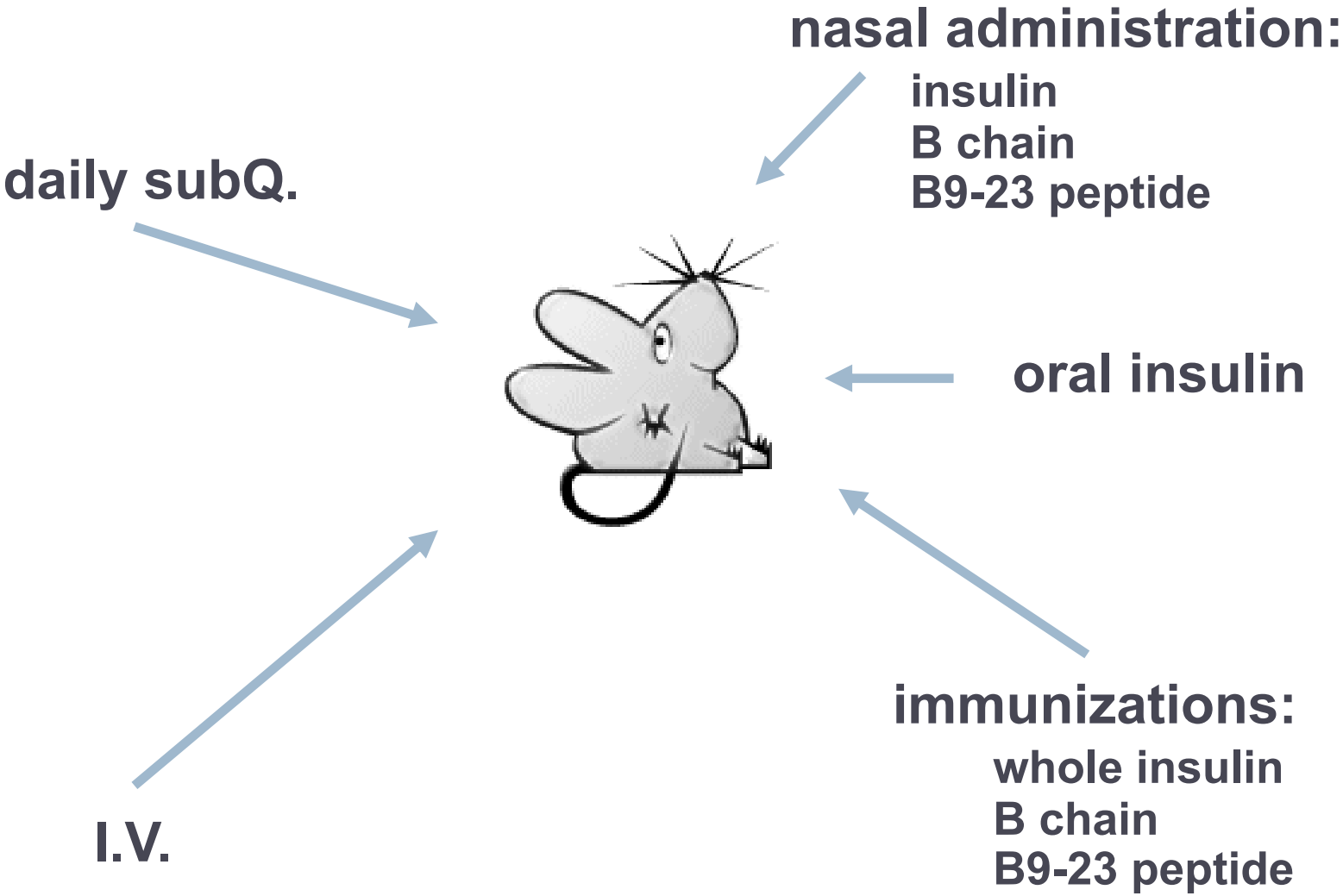
Enrolling by invitation — Regadenoson Blood Flow in Type 1 Diabetes (RABIT1D)
Conditions: Coronary Artery Disease; Type 1 Diabetes Mellitus
Interventions: Procedure: Regadenoson myocardial perfusion imaging; Procedure: Cardiac MRI co measurement

Recruiting — Statins in Children With Type 1 Diabetes and Hypercholesterolemia
Conditions: Type 1 DM; Hypercholesterolemia
Interventions: Drug: Atorvastatin; Drug: Atorvastatin Placebo

Recruiting — Trial of Intranasal Insulin in Children and Young Adults at Risk of Type 1 Diabetes
Condition: Type 1 Diabetes
Intervention: Biological: Intranasal Insulin

| Study (ref.) | Drug/phase |
|---|---|
| TRIGR (23) | Cow's milk hydrolyzate/ phase III |
| BABY DIET (24) | Gluten-free diet/phase II pilot |
| TrialNet NIP (27) | DHA/phase II pilot |
| Vitamin D (31,82) | Vitamin D3/ phase I pilot |
| TrialNet Oral Insulin (33) | Human insulin/ phase III |
| INIT II (34) | Human insulin/ phase II |
| Pre-POINT (26) | Human insulin/ phase I/II |
| FINDIA | Insulin-free whey-based formula/ phase I/II |

# Insulin and prevention of diabetes in NOD mice



# DPT-1 study

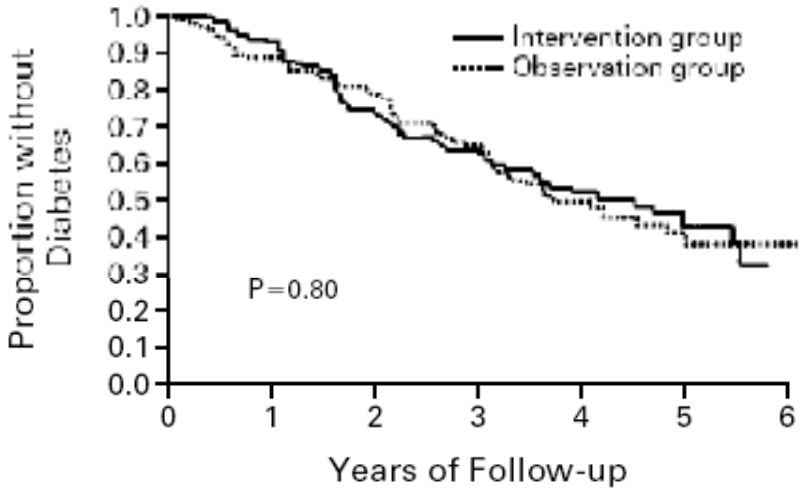
- screening of 89 827 relatives
- inclusion:
  - ICA + (3152, 3.7%)
  - IVGTT: low FPIR
- first inclusion: 31/12/94, end of accrual: 31/10/2000
- randomized: 339 (3-45 years, median 12 years)
- median follow up: 1345 days, loss of follow up: 1.3%/year
- Protocol:
  - i.v. insulin for 4 days once a year + s.c. insulin
  - or observation

# European Pediatric Prediabetes - Subcutaneous Insulin Trial : EPP-SCIT

- Aim: evaluate the effects of small doses of insulin on ß-cell destruction
- Method: double blind controlled trial
- Inclusion criteria:
  - age : 3 - 17 years
  - first degree relatives of type 1 diabetic patients
  - HLA DQB1 ≠ 0602
  - positive antibodies:
    - ICA ≥ 40 JDFU or
    - ICA ≥ 10 JDFU and presence of insulin antibodies or low insulin secretion
    - normal glucose tolerance

# Sub-Q Insulin therapy to prevent type 1 diabetes

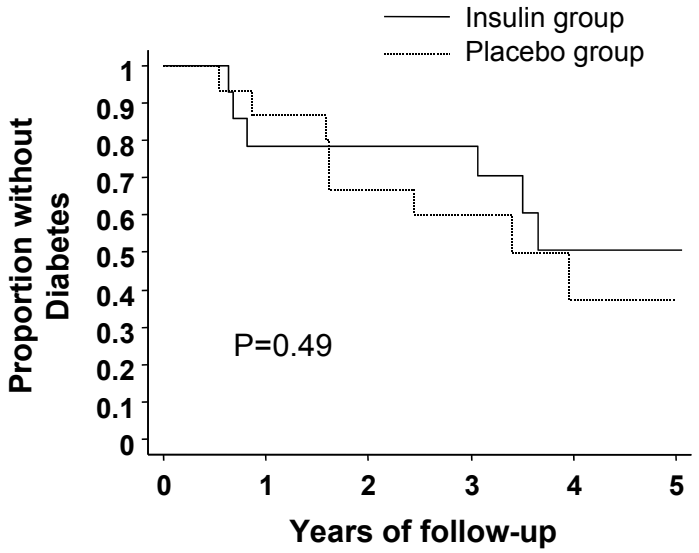
**Diabetes Prevention Trial - 1**
**90 000 siblings screened**
**339 included**




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Intervention | 169 | 144 | 96 | 69 | 39 | 13 | 0 |
| Observation | 170 | 131 | 101 | 69 | 40 | 14 | 1 |

***DPT1, NEJM 2002***

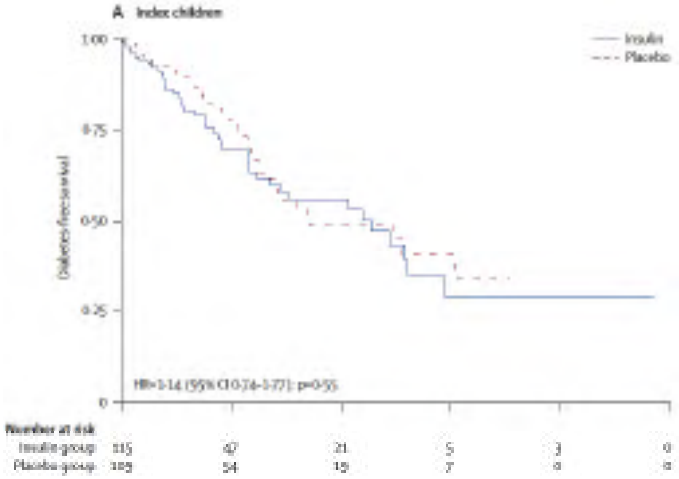
**EPP-SCIT**
**3500 siblings screened**
**29 included**

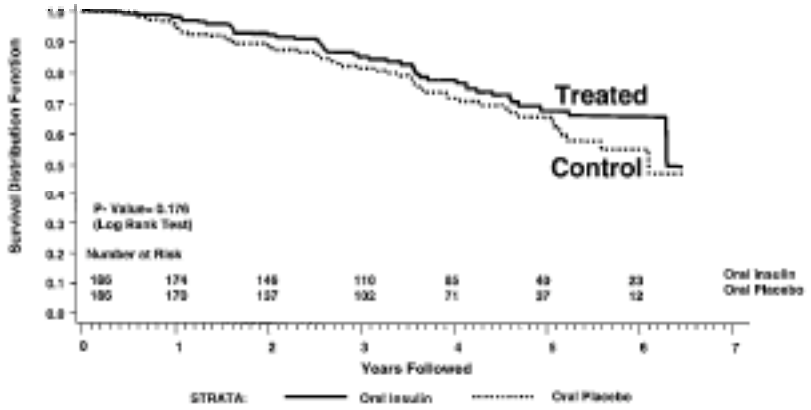


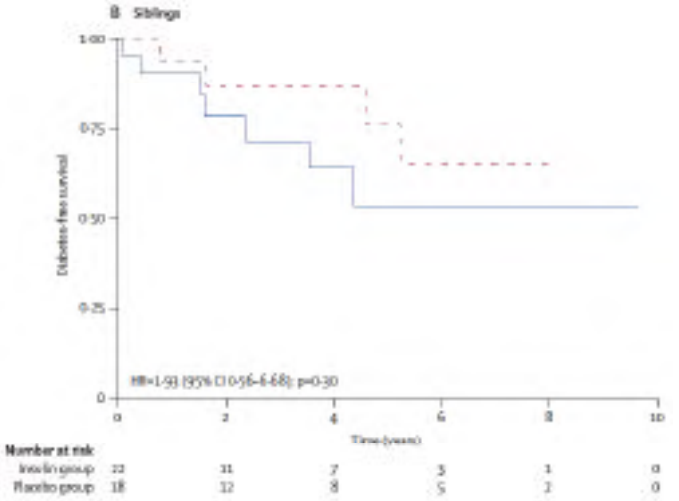

| No at risk | | | | | | |
|---|---|---|---|---|---|---|
| Insulin | 14 | 11 | 11 | 10 | 5 | 1 |
| Placebo | 15 | 13 | 10 | 7 | 3 | 1 |

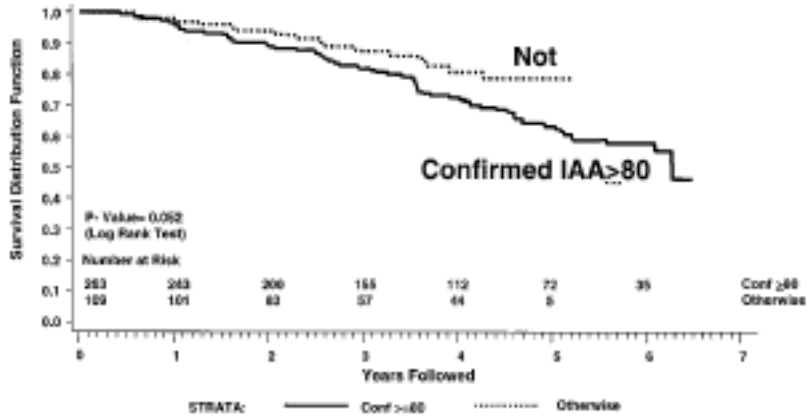
***Carel et al, NEJM 2002***

# Nasal and oral insulin



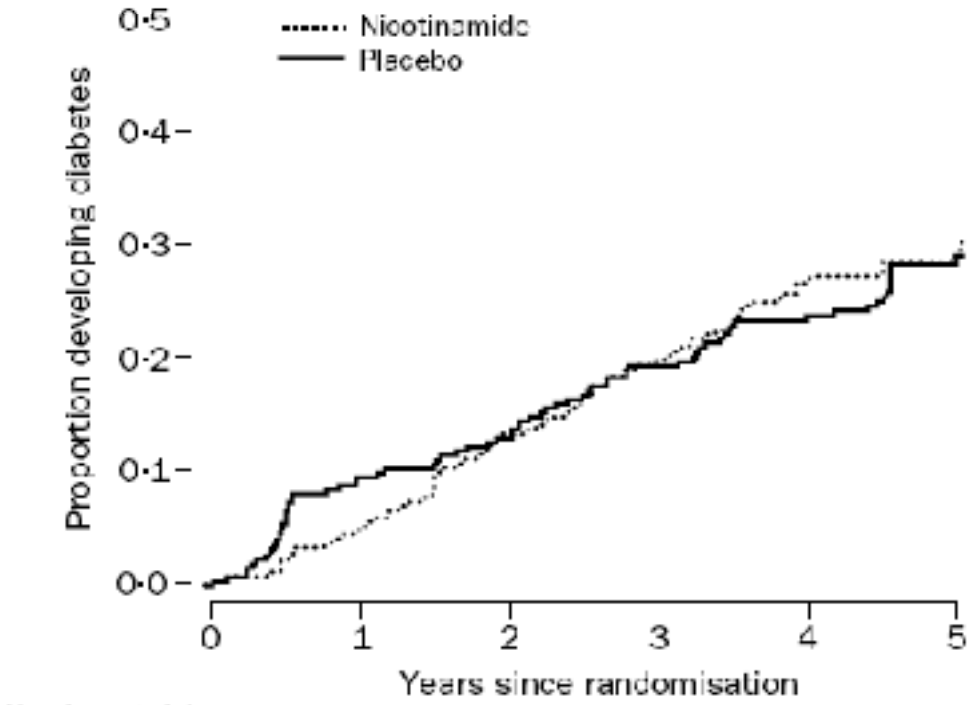




***Näntö-Salonen, Lancet 2008***
***DPT-1, Diabetes Care 2005***

# Nicotinamide in individuals at risk for type 1 diabetes




**Number at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 275 | 245 | 232 | 209 | 184 | 112 |
| Nicotinamide | 274 | 260 | 232 | 208 | 171 | 97 |

Figure 2: **Kaplan-Meier failure curve**

***European Nicotinamide Diabetes Intervention Trial (ENDIT) Group, Lancet 2004***

ORIGINAL ARTICLE

# Dietary Intervention in Infancy and Later

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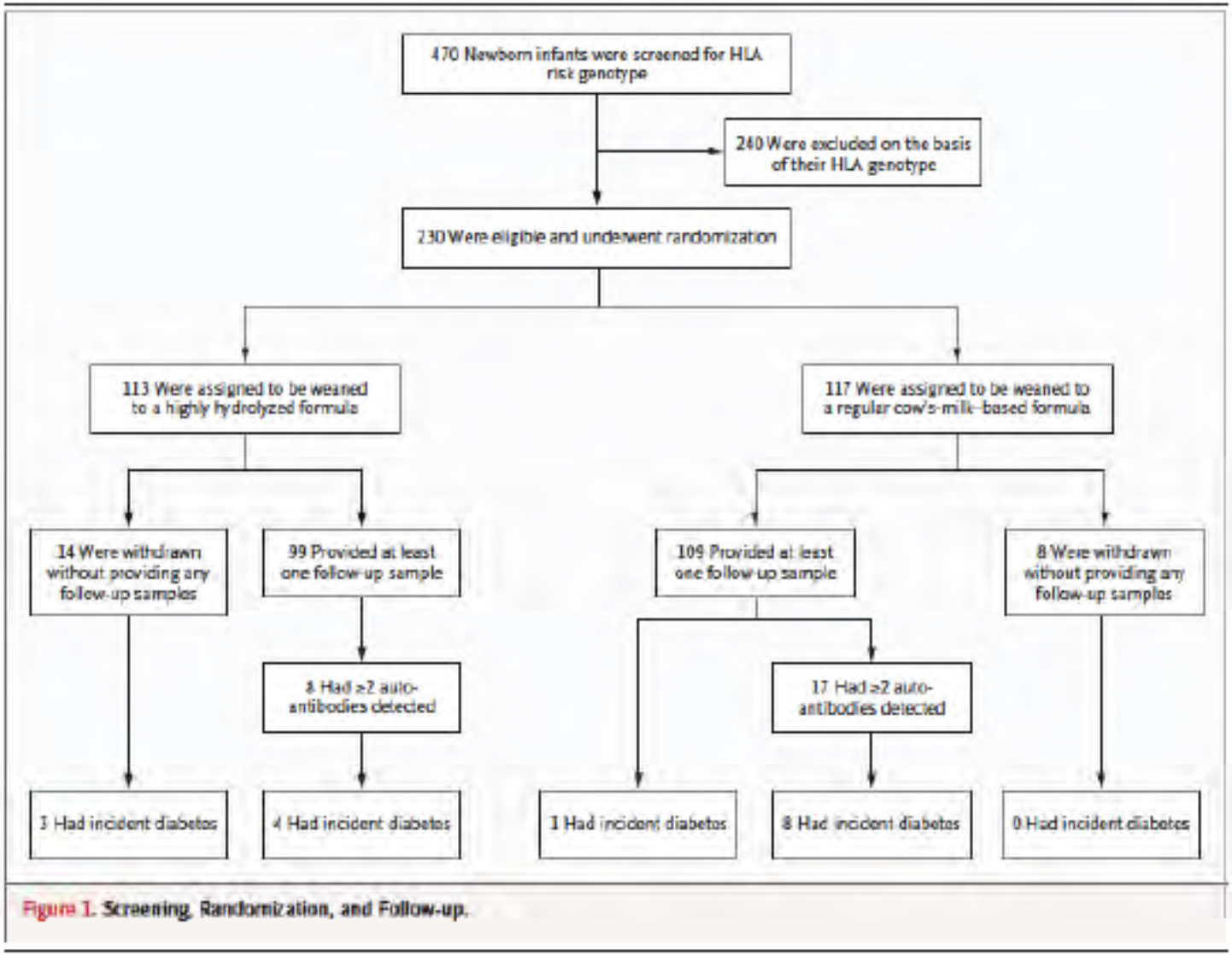
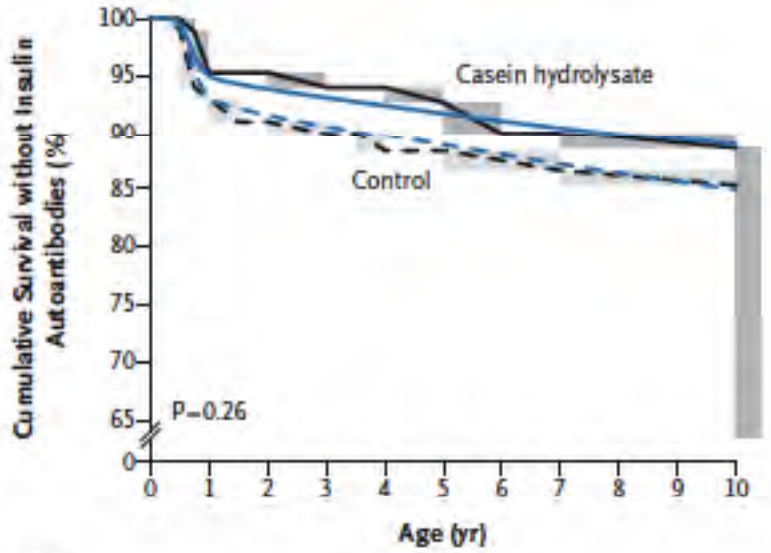



Figure 1. Screening, Randomization, and Follow-up.

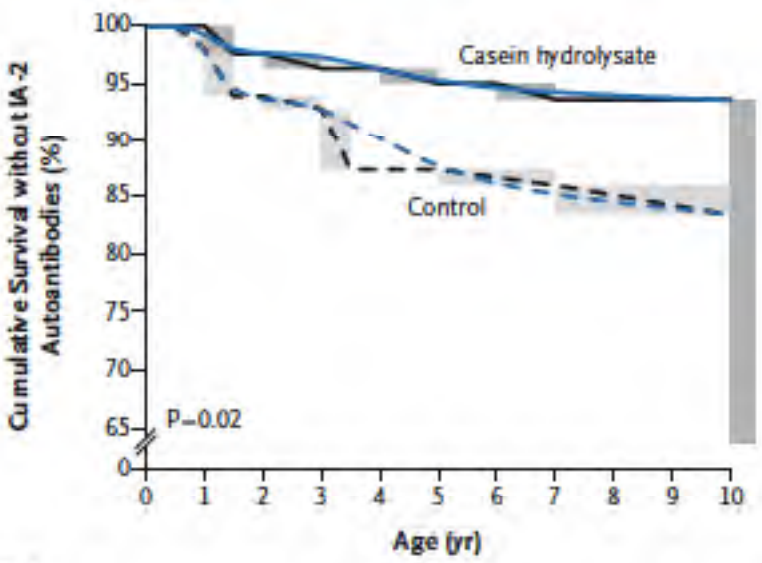
***Knip NEJM 2010***

B




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Casein hydrolysate | 90 | 85 | 81 | 78 | 72 | 66 | 62 |
| Control | 107 | 98 | 95 | 88 | 75 | 76 | 69 |

C

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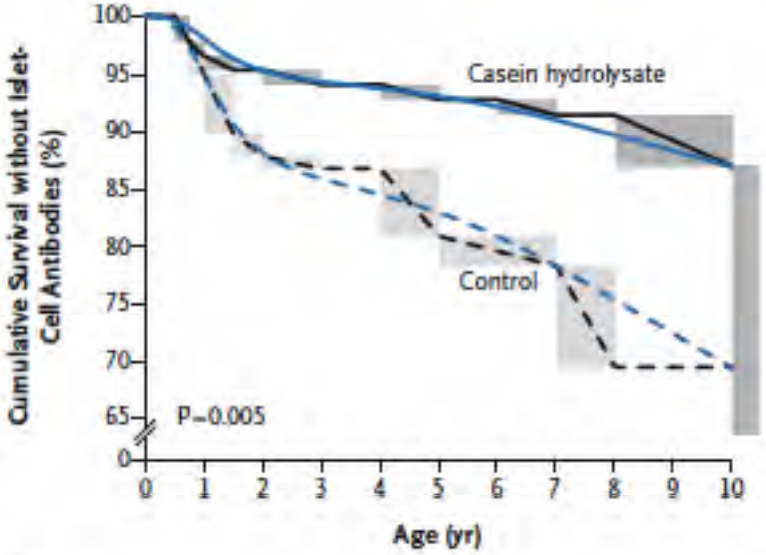


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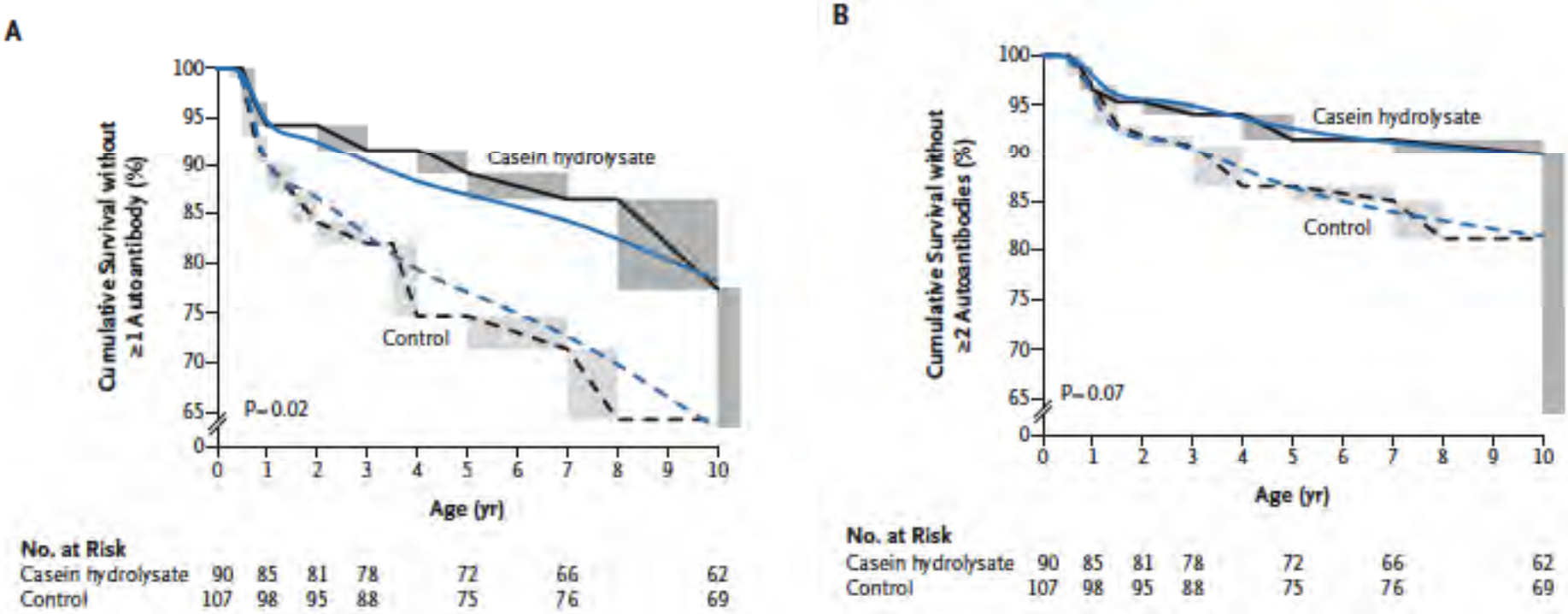


**Table 1. Hazard Ratios with Highly Hydrolyzed Infant Formula, as Compared with Conventional Cow's-Milk–Based Formula, for Seroconversion to Positivity for Autoantibodies Predictive of Type 1 Diabetes.***

| Autoantibodies | No. Who Underwent Seroconversion | Hazard Ratio with Highly Hydrolyzed Formula (95% CI) | P Value | Adjusted Hazard Ratio with Highly Hydrolyzed Formula (95% CI)† | P Value |
|---|---|---|---|---|---|
| Islet-cell antibodies | 37 | 0.38 (0.18–0.77) | 0.006 | 0.37 (0.17–0.75) | 0.005 |
| Insulin autoantibodies | 23 | 0.72 (0.30–1.64) | 0.45 | 0.61 (0.25–1.42) | 0.26 |
| GAD autoantibodies | 23 | 0.87 (0.37–1.97) | 0.74 | 0.80 (0.34–1.85) | 0.61 |
| IA-2 autoantibodies | 20 | 0.36 (0.12–0.94) | 0.04 | 0.32 (0.10–0.83) | 0.02 |
| ZnT8 autoantibodies | 14 | 0.61 (0.19–1.77) | 0.37 | 0.61 (0.19–1.79) | 0.37 |
| ≥1 Antibody | 50 | 0.54 (0.29–0.95) | 0.03 | 0.51 (0.28–0.91) | 0.02 |
| ≥2 Antibodies | 25 | 0.52 (0.21–1.17) | 0.12 | 0.47 (0.19–1.07) | 0.07 |

# Conclusions

- Screening for diabetes associated antibodies in patient's relatives efficiently identifies at risk individuals
- All preventive approaches based on insulin have been inefficient to alter the course of disease
- Other preventive approaches evaluated so far have been similarly disappointing (nicotinamide)
- Dietary intervention is currently being evaluated
- Controlled trial are the only way to evaluate therapeutic approaches
- Given the complexity of such trials, solid data in recent onset diabetes are necessary to embark in diabetes prevention