Temporal/geographic trends in type 1 diabetes

JAAKKO TUOMILEHTO

University of Helsinki

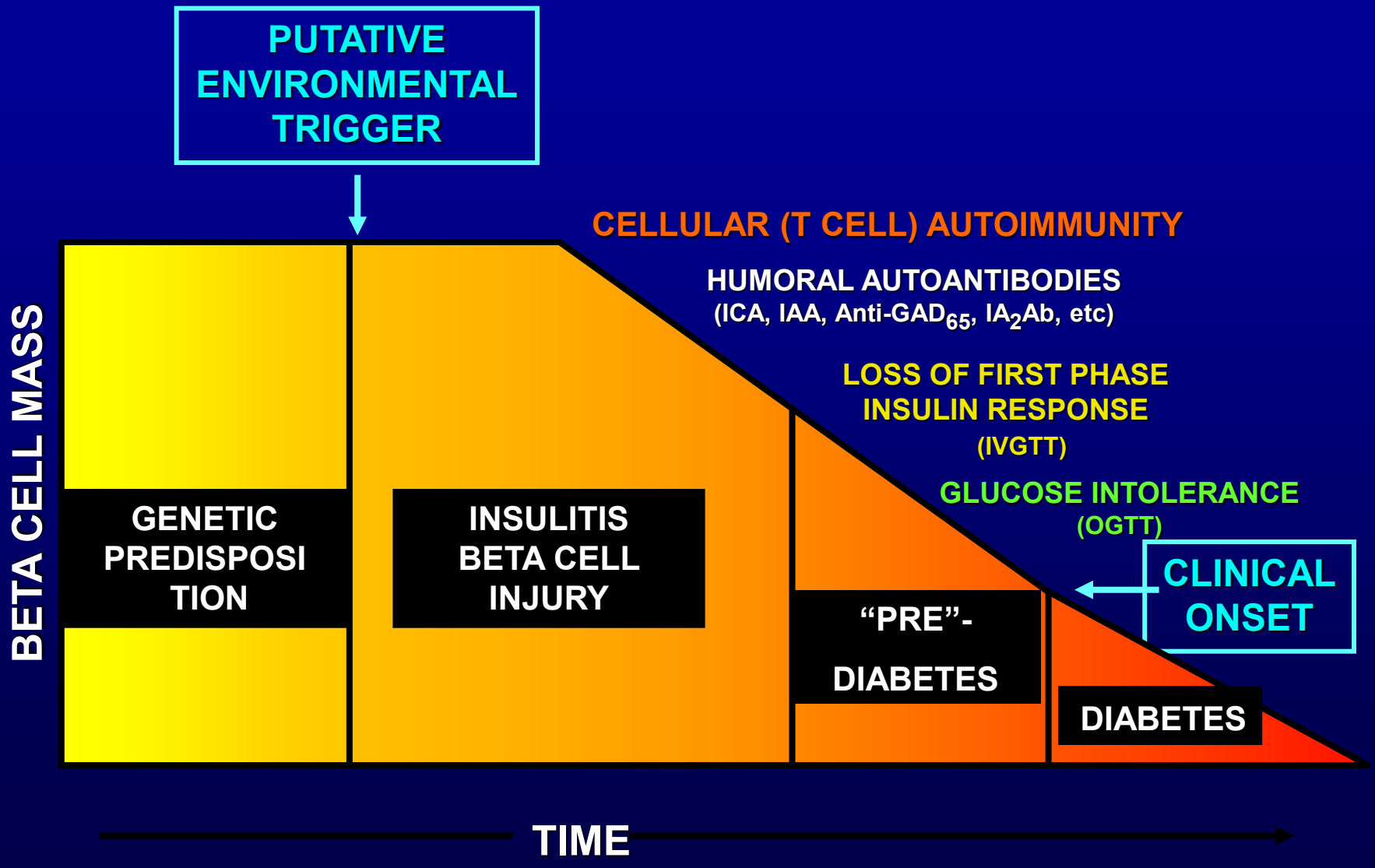
Department of Public Health

Helsinki, Finland

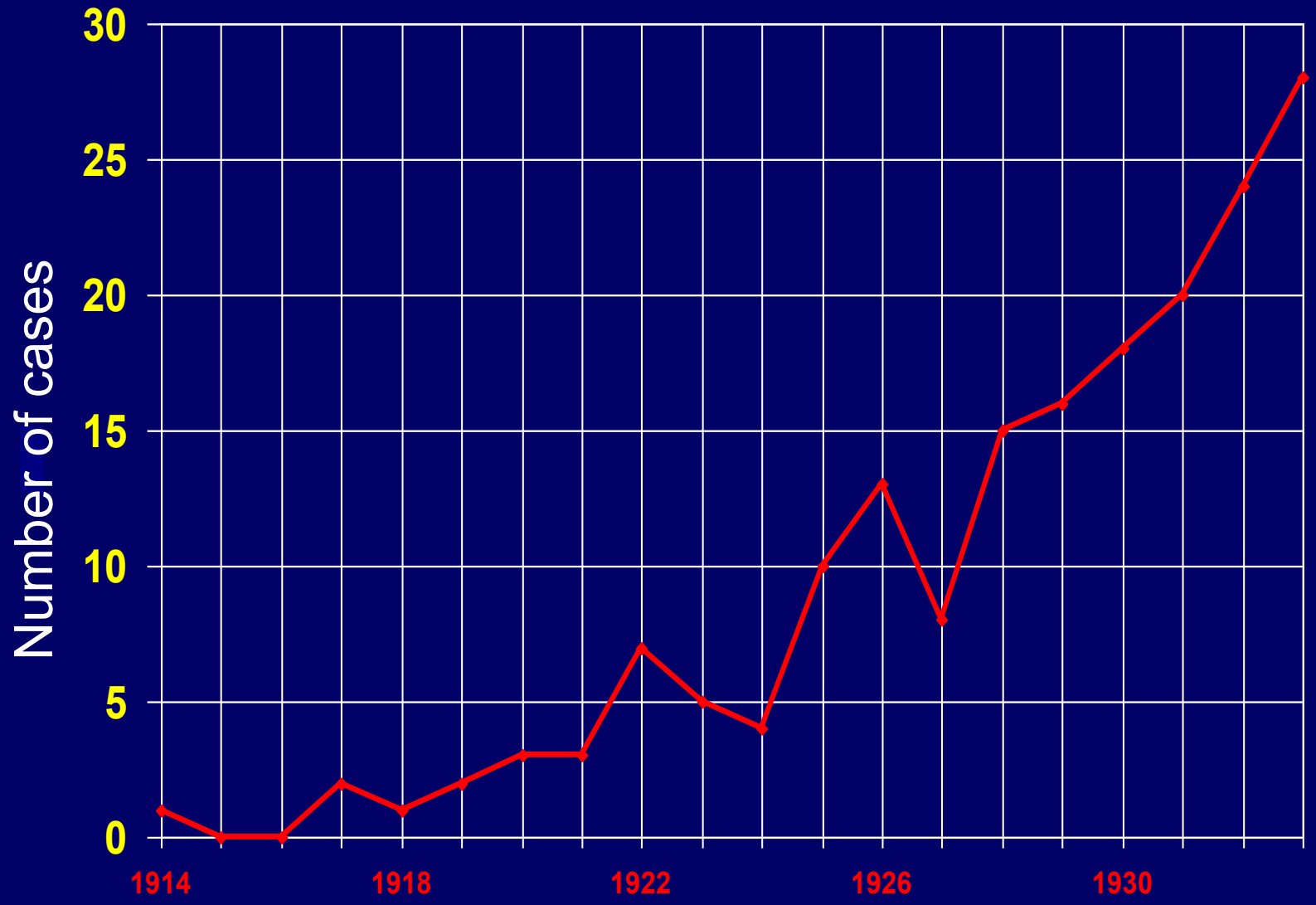
Type 1 diabetes mellitus

- Acute presentation: hyperglycemia, tiredness, weight loss, polyuria, thirst, nausea, vomiting, signal of impending ketoacidosis
- Patients need insulin replacement to live
- Honeymoon period: temporary remission in some patients
- In long-standing patients: micro + macro vascular complications
- Mortality increased 4-7 fold (nephropathy, card/vx disease)
- Some patients survive without major complications

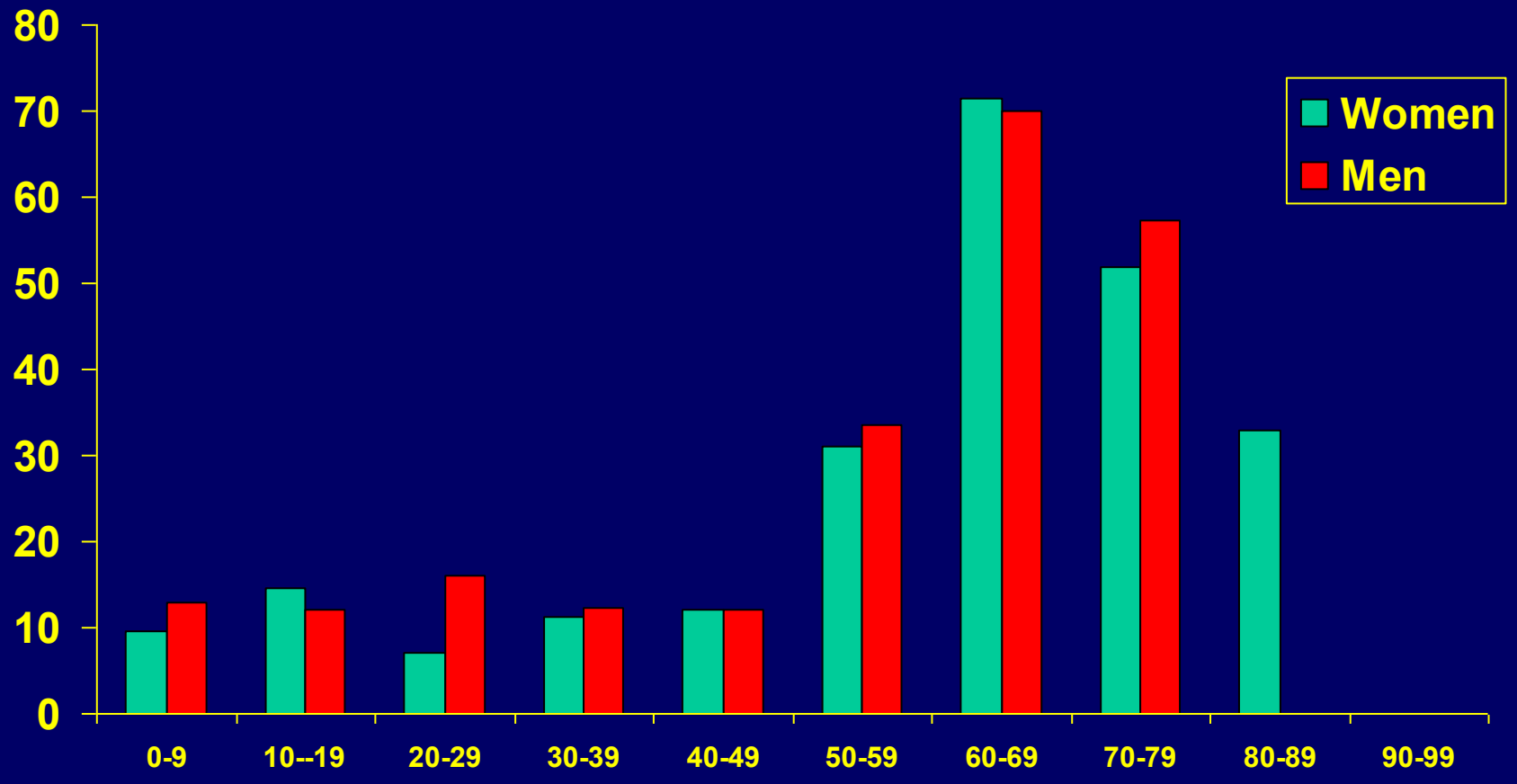
Natural History of Type 1 Diabetes



New cases of childhood diabetes per year admitted to the Helsinki University Hospital, Finland during (1914-1933)

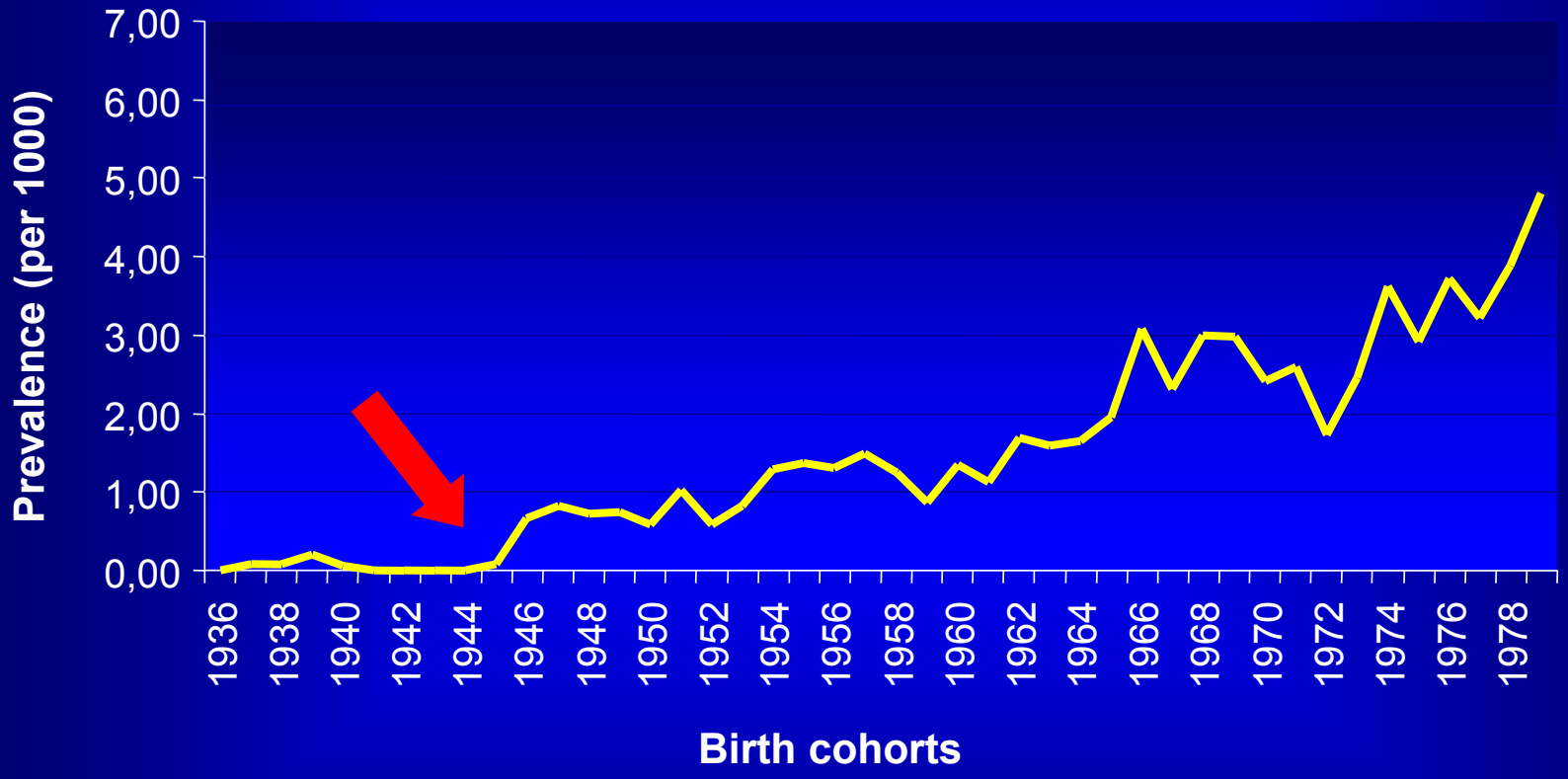


Diabetes mortality in Finland in 1927-1929 per 100 000



Epidemiology of T1D

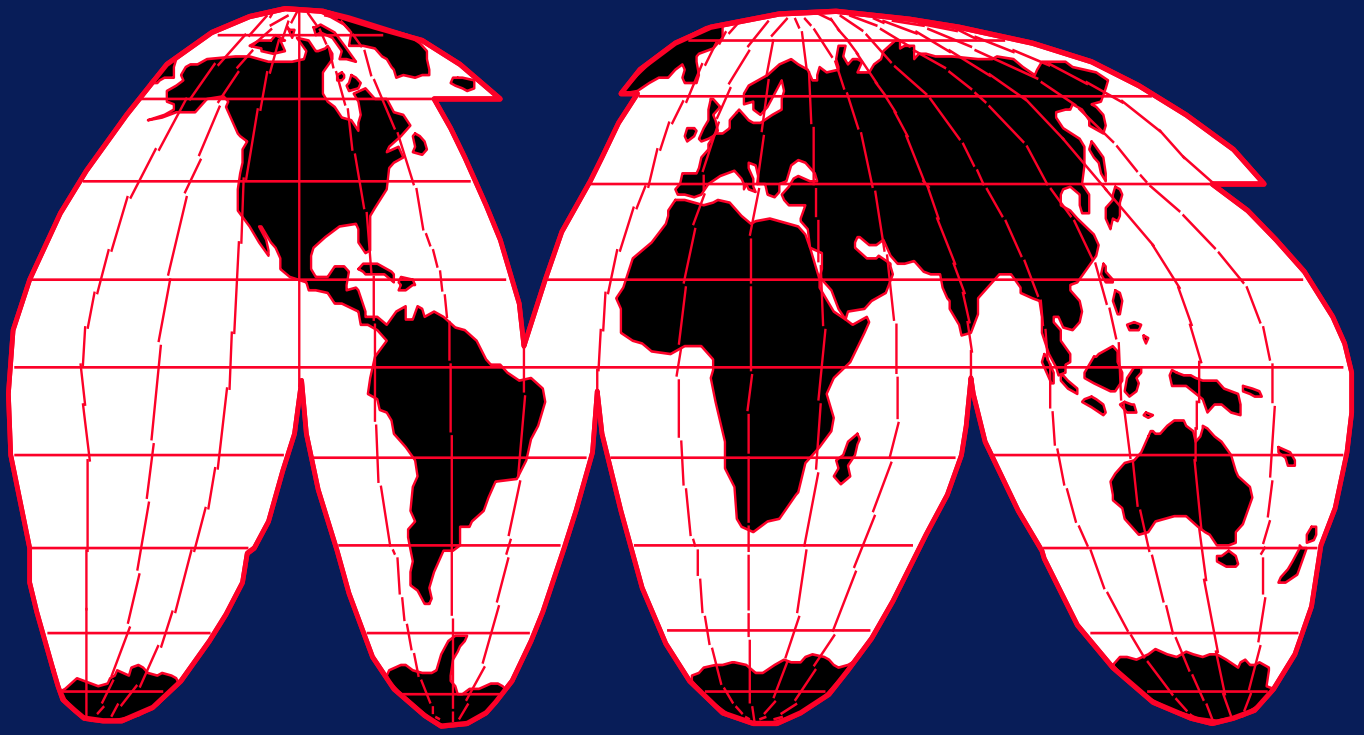
Secular trend of T1D in Sardinia



Male conscript register - 18 years of age

Casu, Bottazzo, Songini et al 2000.

WHO
Diabetes Mondiale



WHO Multinational Project for Childhood Diabetes

DiaMond

Diabetes Mondial - DiaMond

Establishment of Population Based Registries for 1990-99

- **Diagnosed as T1DM**
- **On Insulin at first Hospital discharge**
- **Diagnosed between 1/1/90 and 31/12/99**
- **Age at onset 0-14**
- **Member of a defined community**

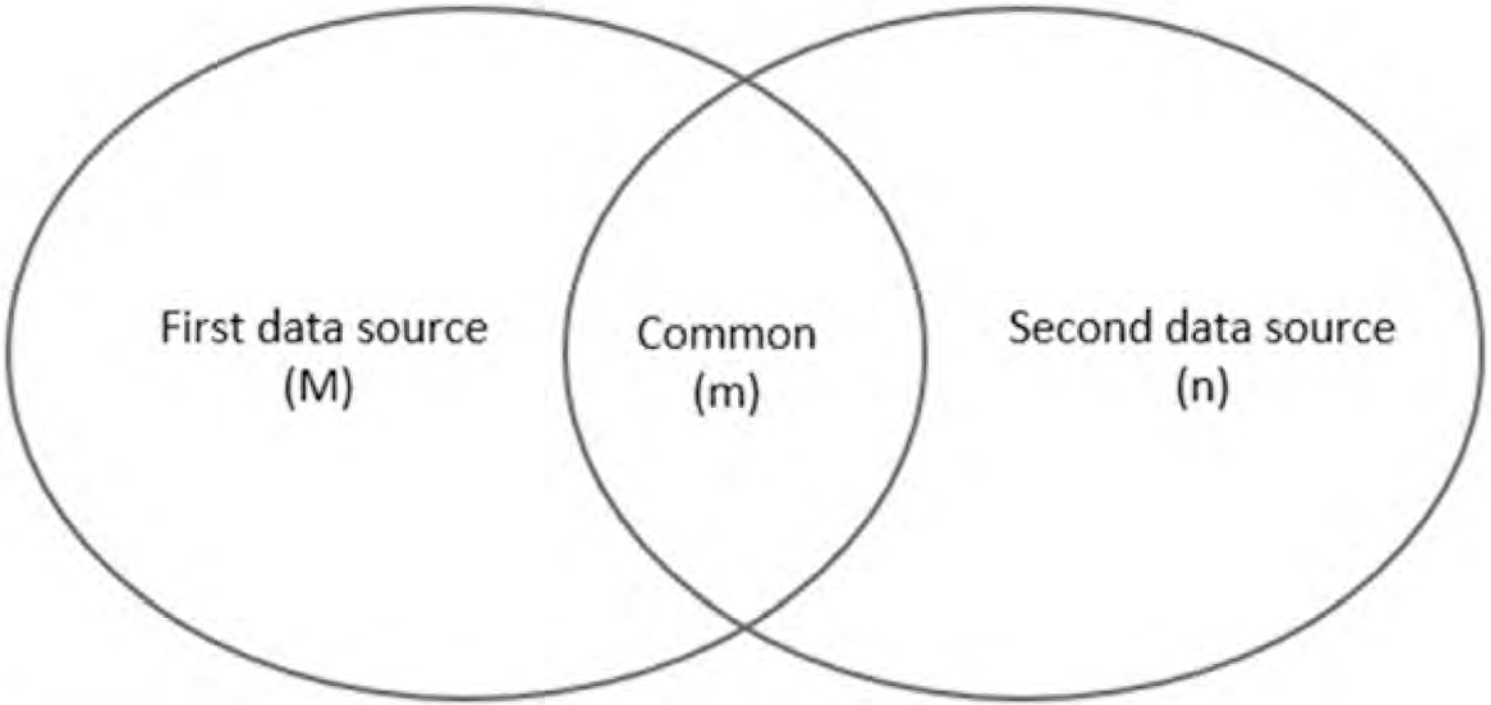


FIGURE 1. Two-sample capture–recapture method diagram and Chapman's formula.

TABLE 1—Numbers of Dog Bites Reported by Different Sources: Pittsburgh, Pa, 1993

Police/Victim	Both Animal Control and Hospital	Animal Control	Hospital	Neither Animal Control nor Hospital
Yes	1	15	7	326
No	27	91	323	. . .

Note. The animal control category includes reports from animal control agencies, the Animal Rescue League, and the Humane Society; the hospital category includes reports from hospitals, doctors, health centers, and health systems; and the police/victim category includes reports from victims, victims' family members and friends, police, and others.

Incidence: 58.9/100,000

Yue-Fang Chang, PhD, Joan E. McMahon, MPH, RN, Deidre L Hennon, Ronald E. LaPorte, PhD, and Jeffrey H. Coben,

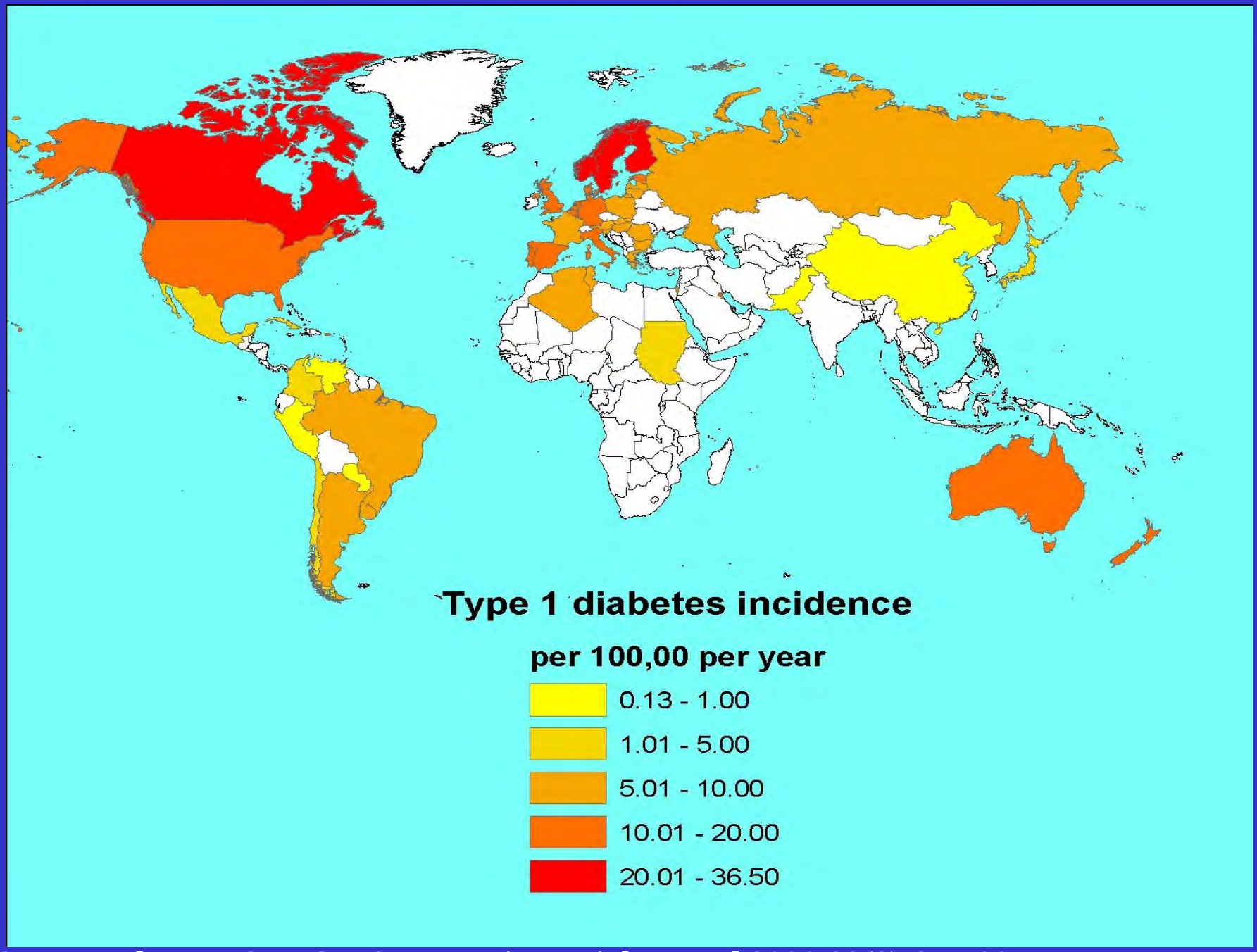
Am J Public Health 1997;87:1703

WHO DiaMond project

- **43,013 cases of T1DM**
- **443 499 882 person years**
- **112 centers have provided data**
- **71 countries**

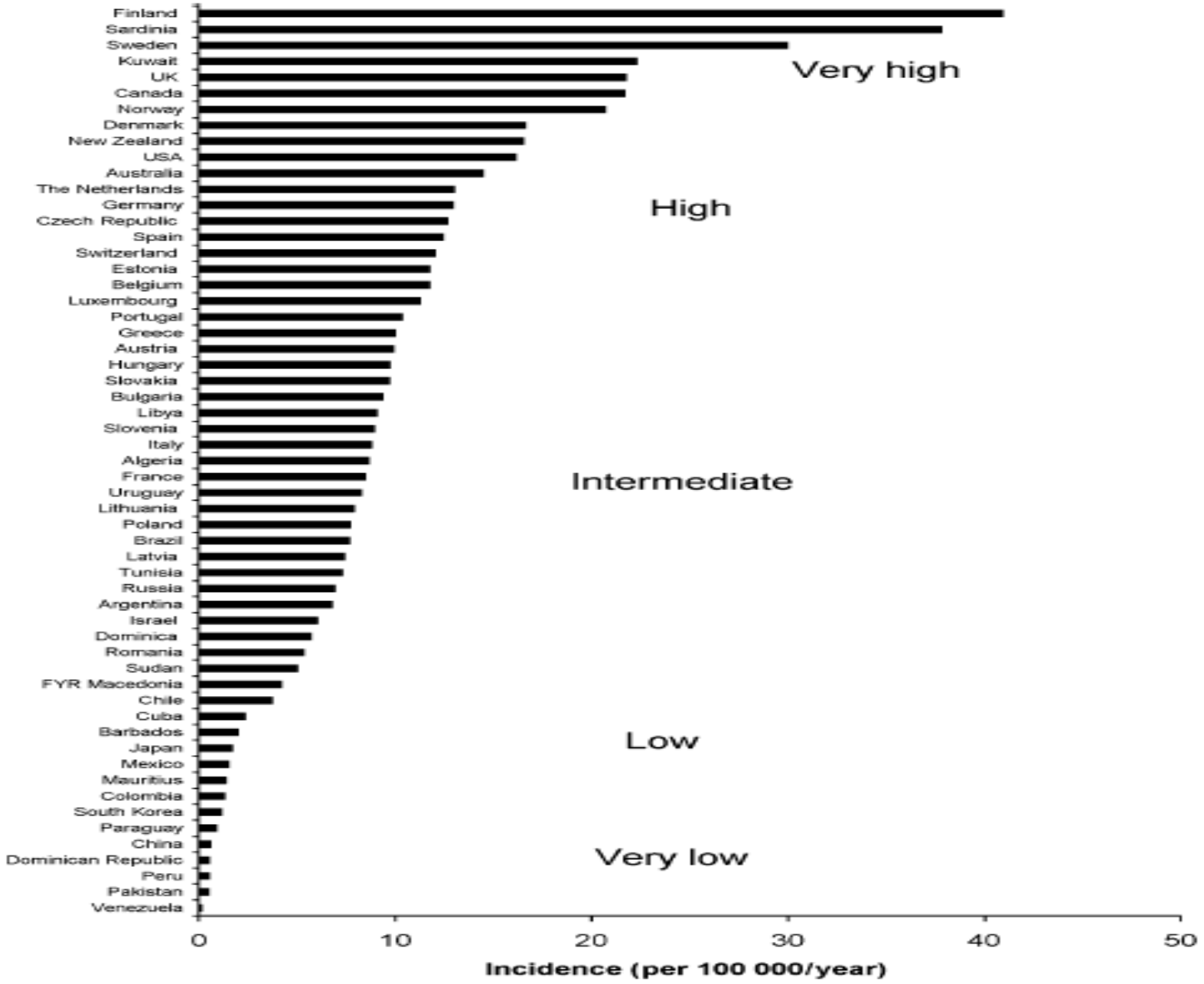
Diabetes Care, 2000; 23: 1516-1526

Diabetic Med. 2006; 23:857-66

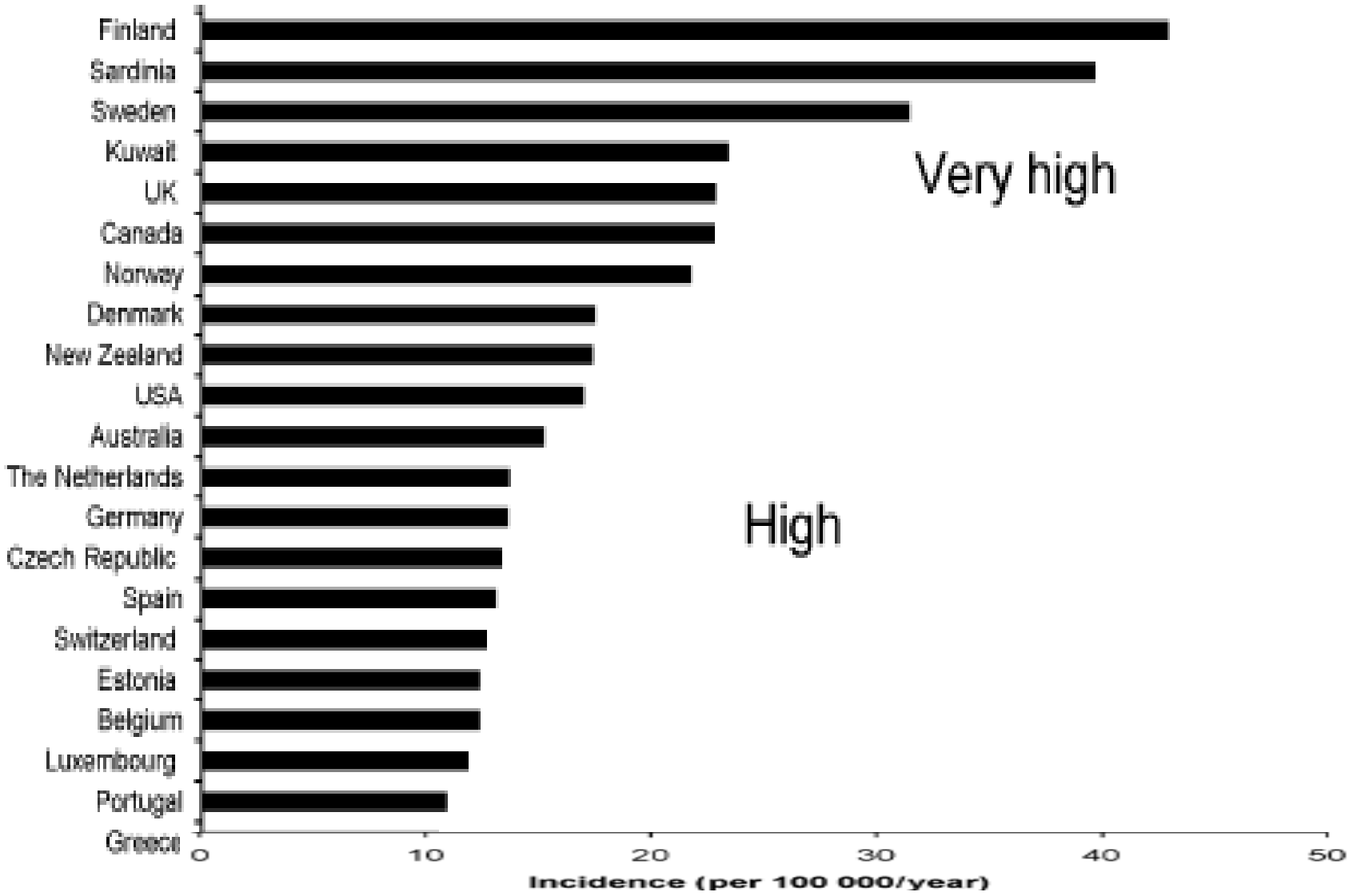


Source: The WHO DIAMOND Project. Diabet Med 2006;23(8):857-66.

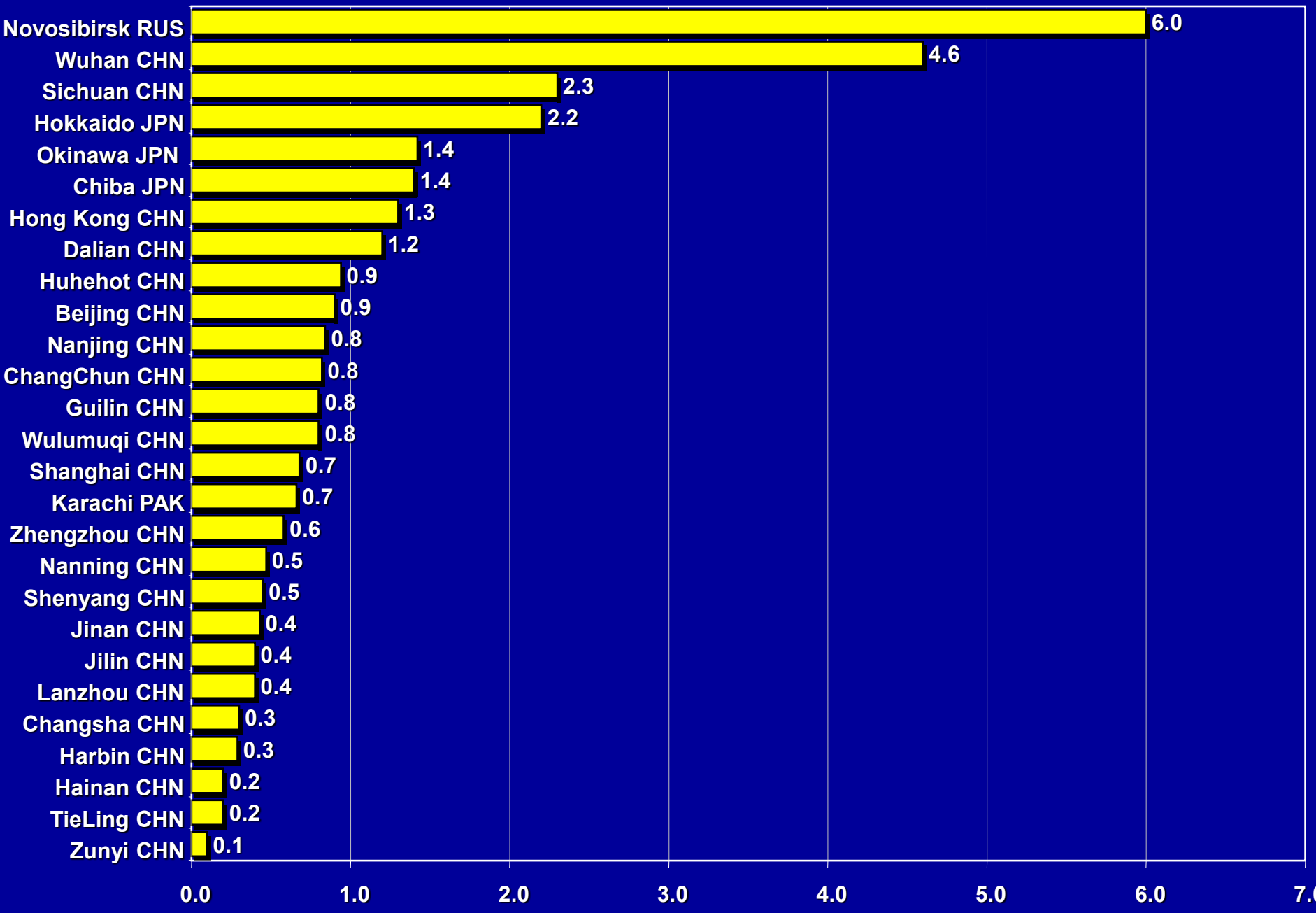
Incidence and trends of childhood Type 1 diabetes worldwide 1990–1999 The DIAMOND Project Group



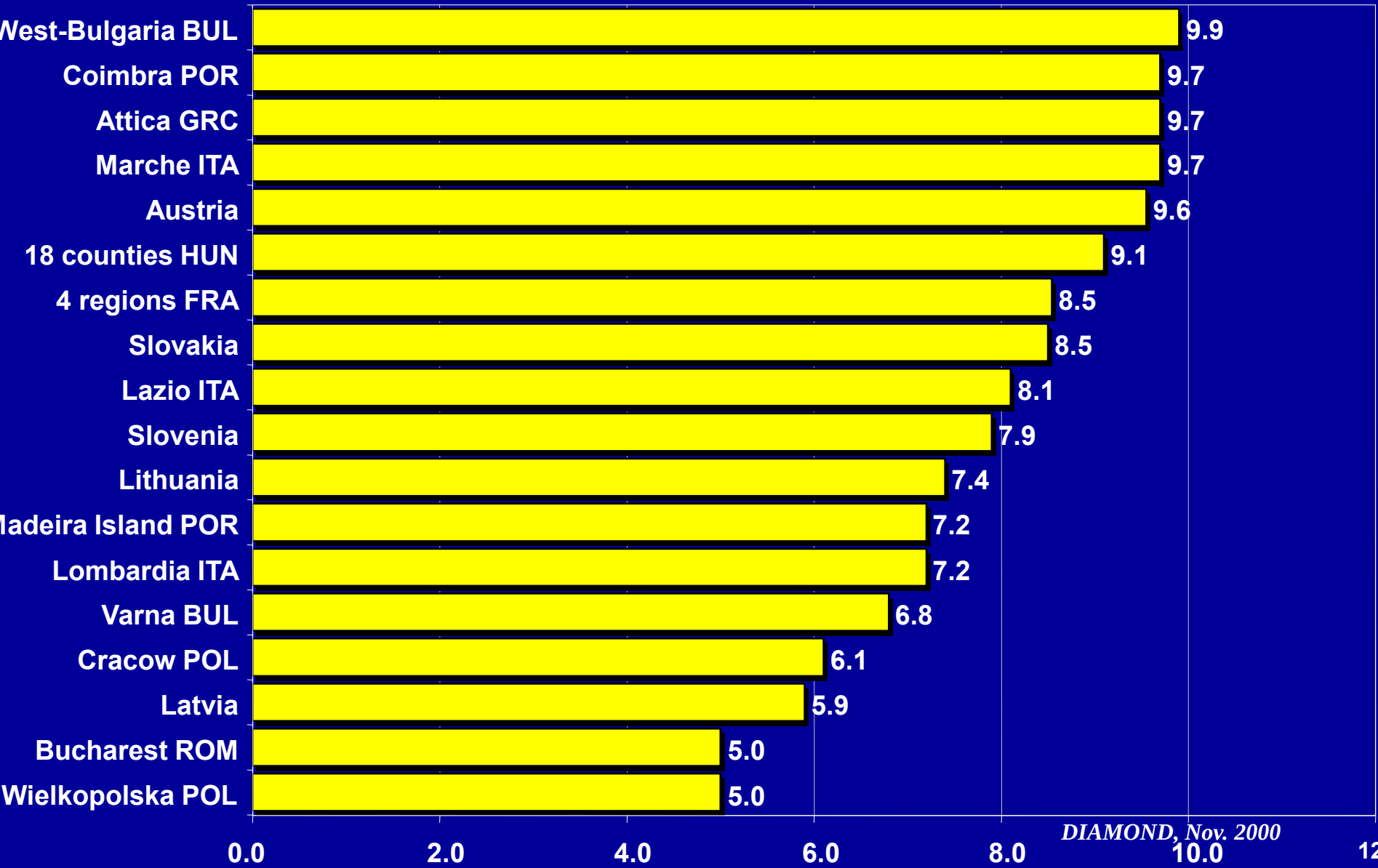
The DIAMOND study: high incidence countries during 1990-1999



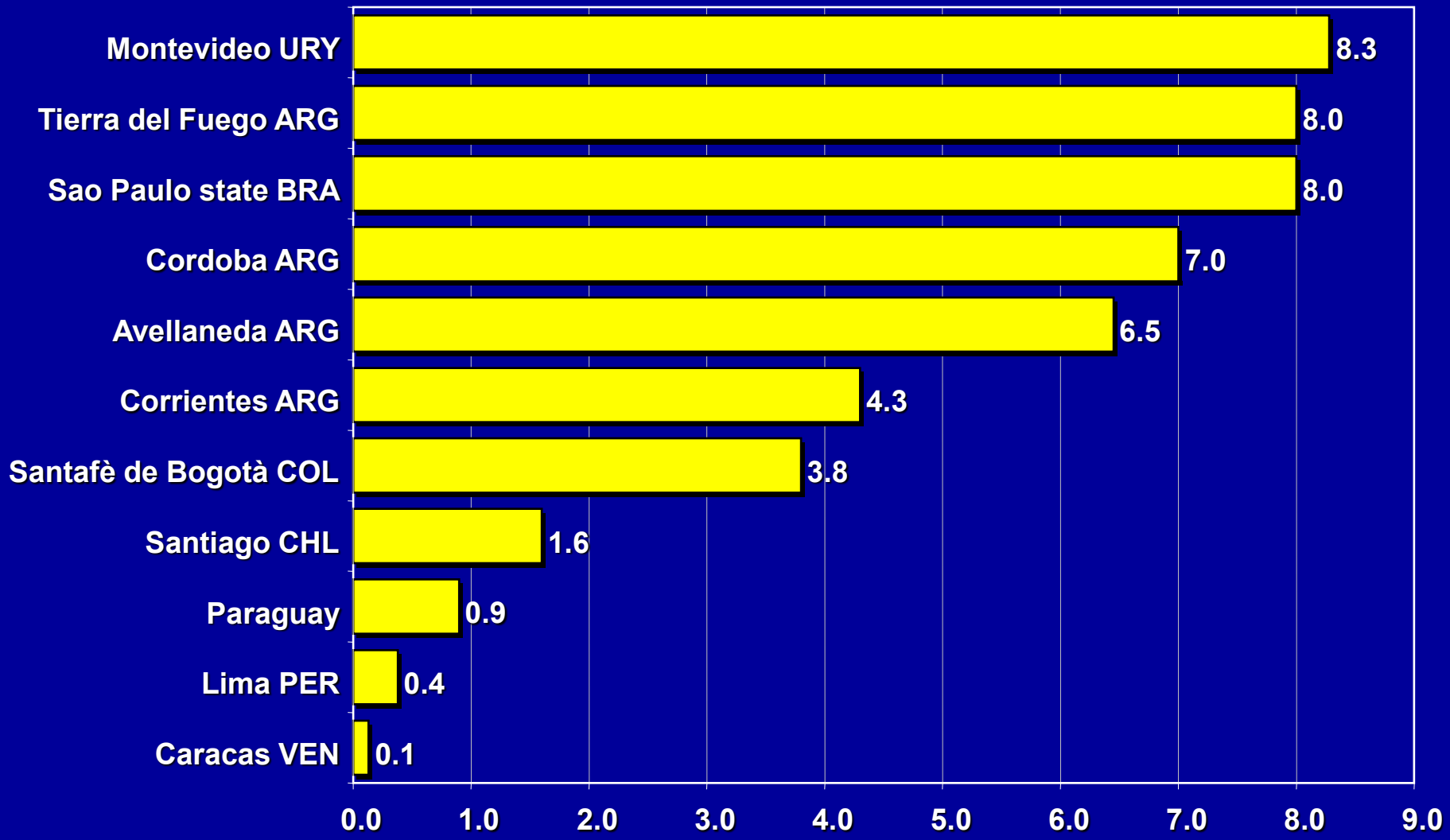
Incidence of Type 1 diabetes mellitus in Asia (per 100,000/year), 1990-4



Incidence of Type 1 diabetes mellitus in Europe (per 100,000/ year), low incidence populations, 1990-1994

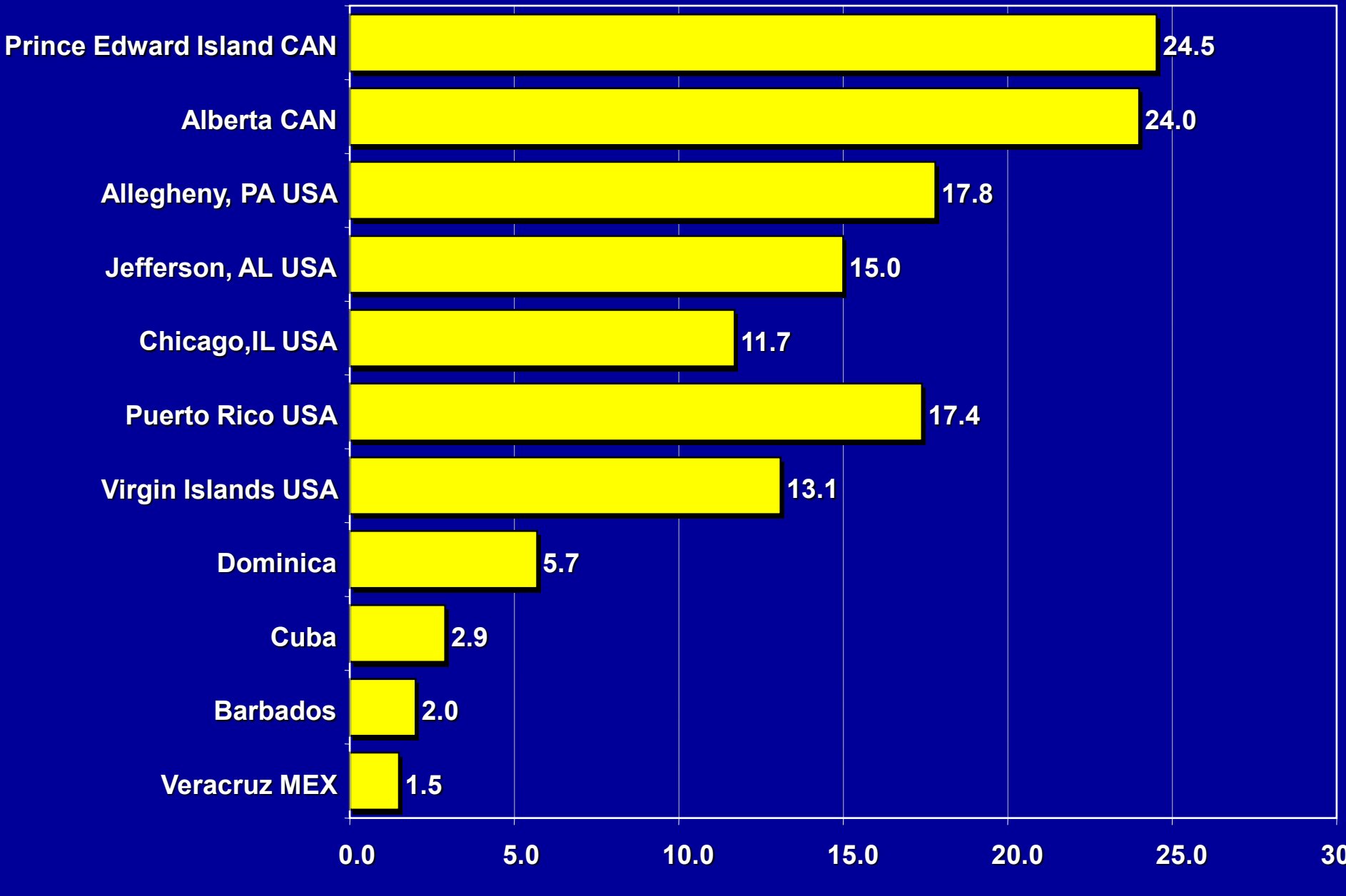


Incidence of Type 1 diabetes mellitus in South America (per 100,000/ year), 1990-1994

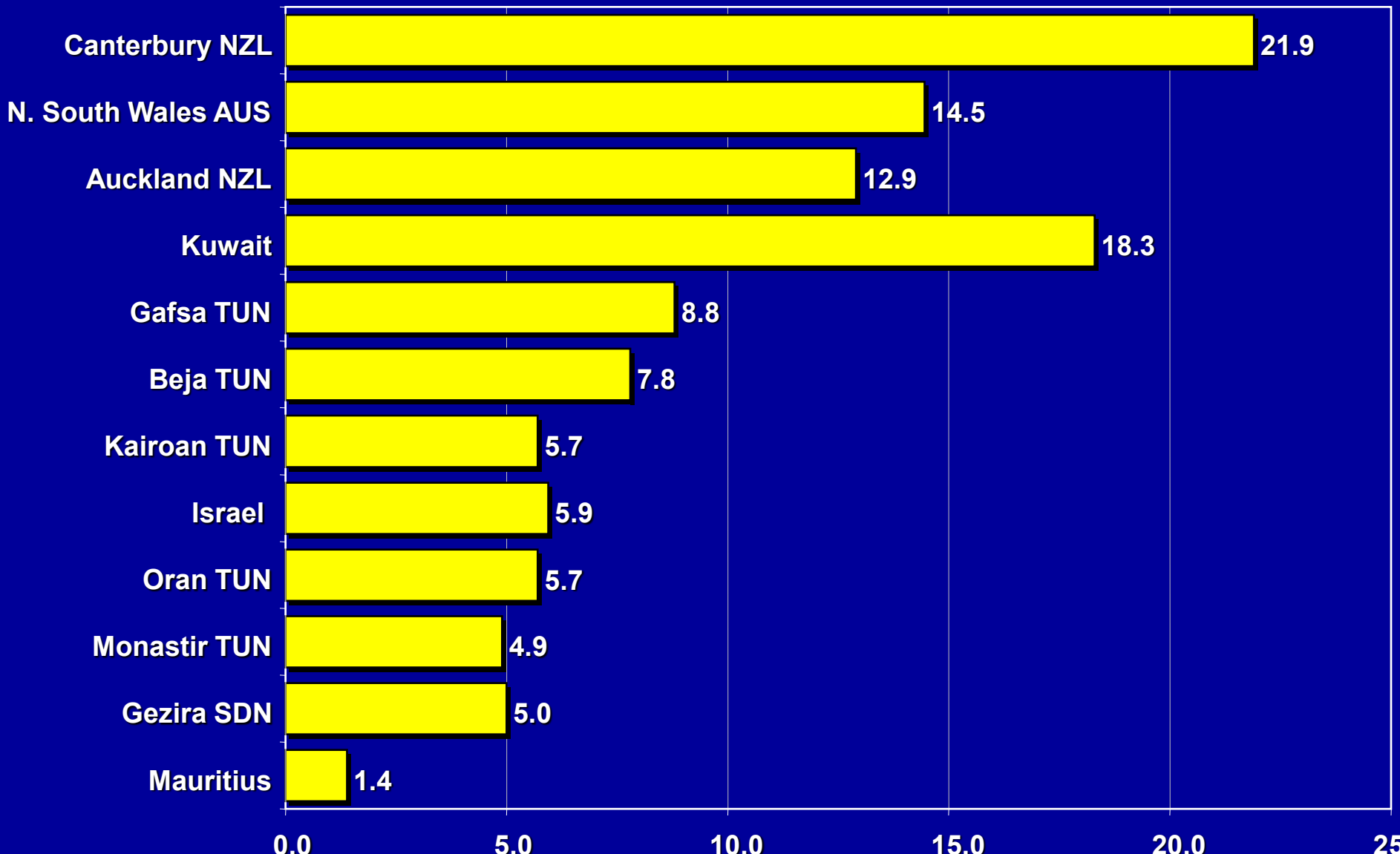


DIAMOND, Nov. 2000

Incidence of Type 1 diabetes mellitus in North America, in Central America and West Indies (per 100,000/year), 1990-4

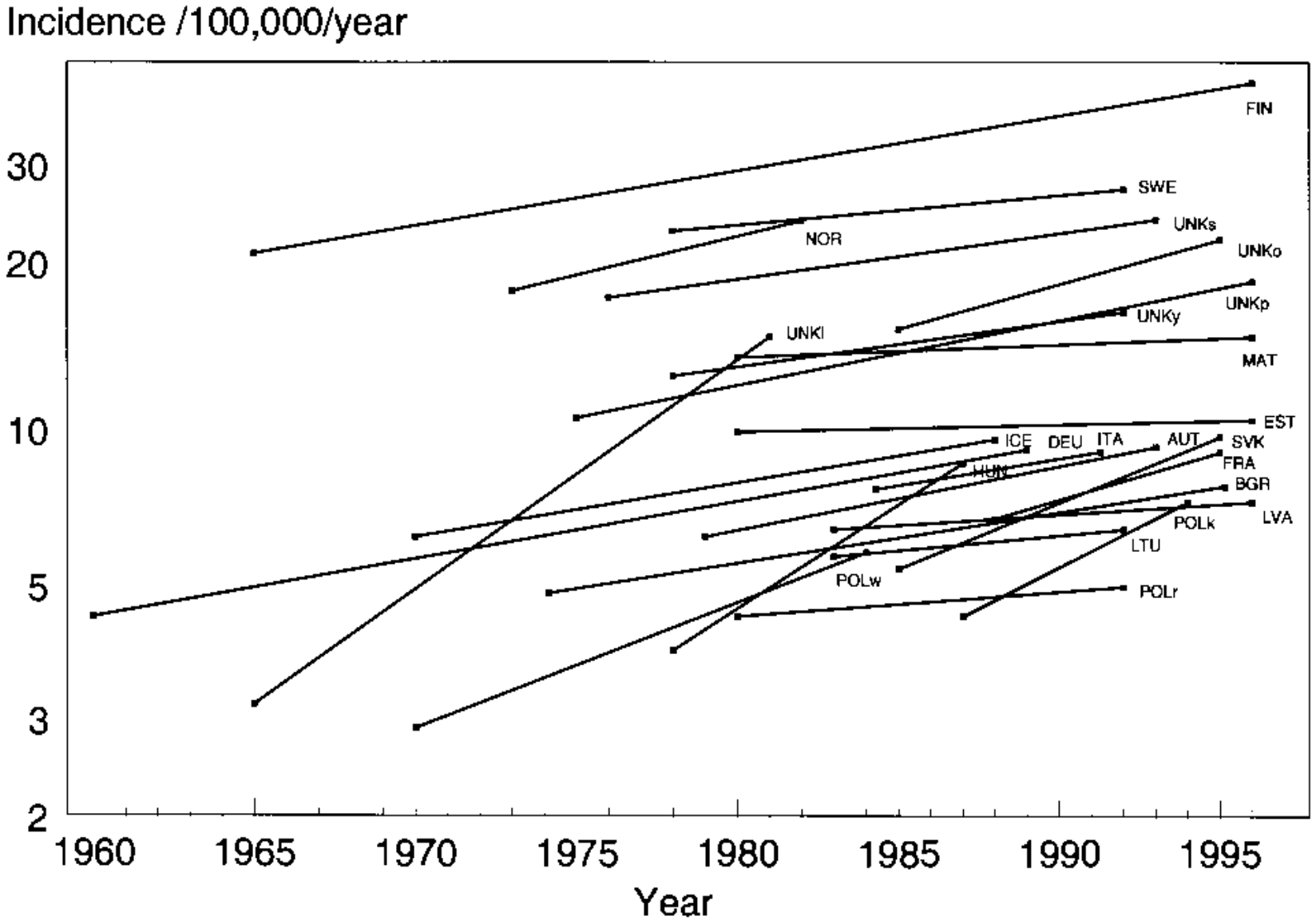


Incidence of Type 1 diabetes mellitus in Oceania, Africa, and Near East (per 100,000/year), 1990-1994.



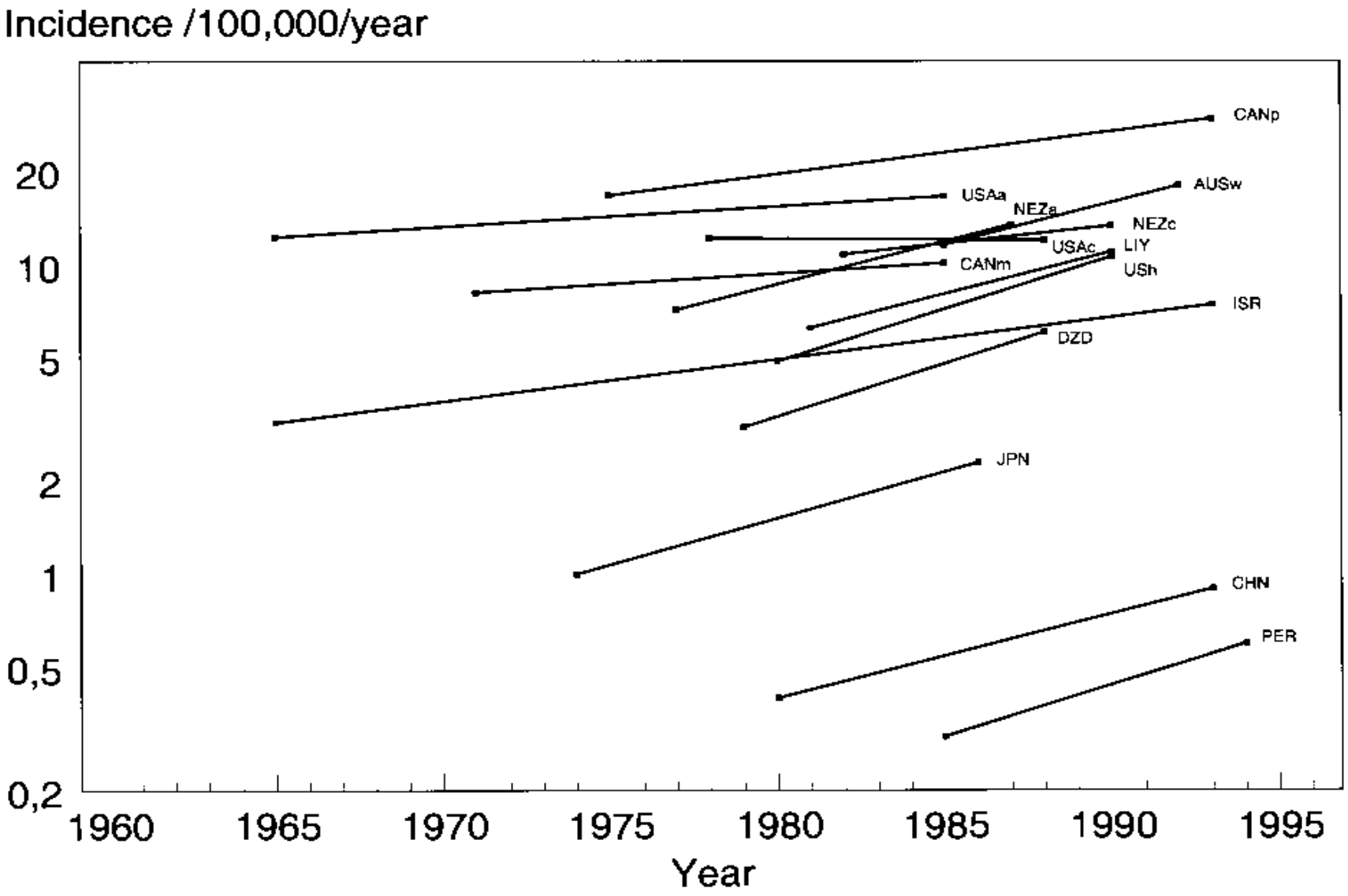
DIAMOND, Nov. 2000

INCIDENCE TRENDS FOR CHILDHOOD-ONSET TYPE 1 DIABETES - EUROPE



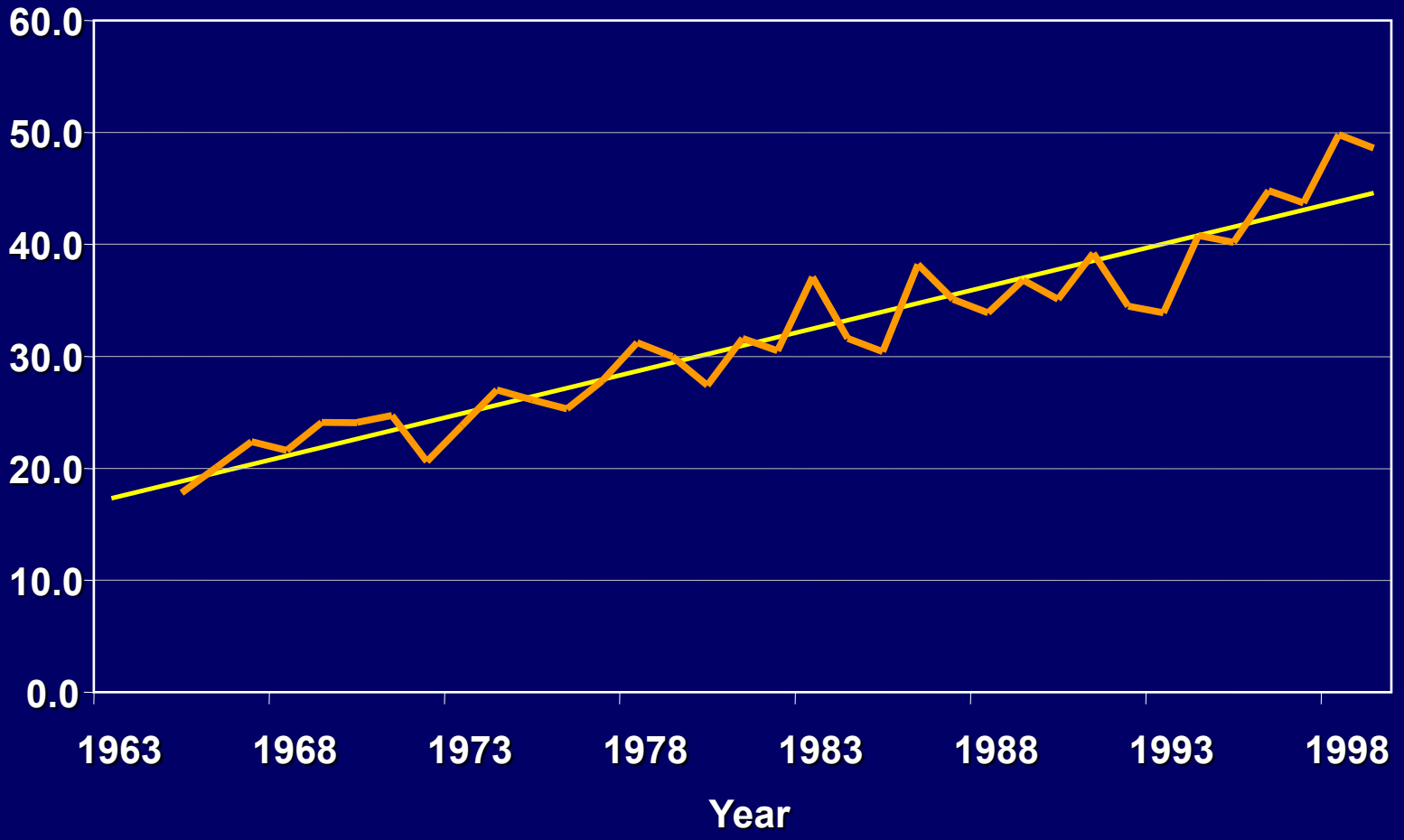
Onkamo et al. Diabetologia 1999

INCIDENCE TRENDS FOR CHILDHOOD-ONSET TYPE 1 DIABETES - OUTSIDE EUROPE



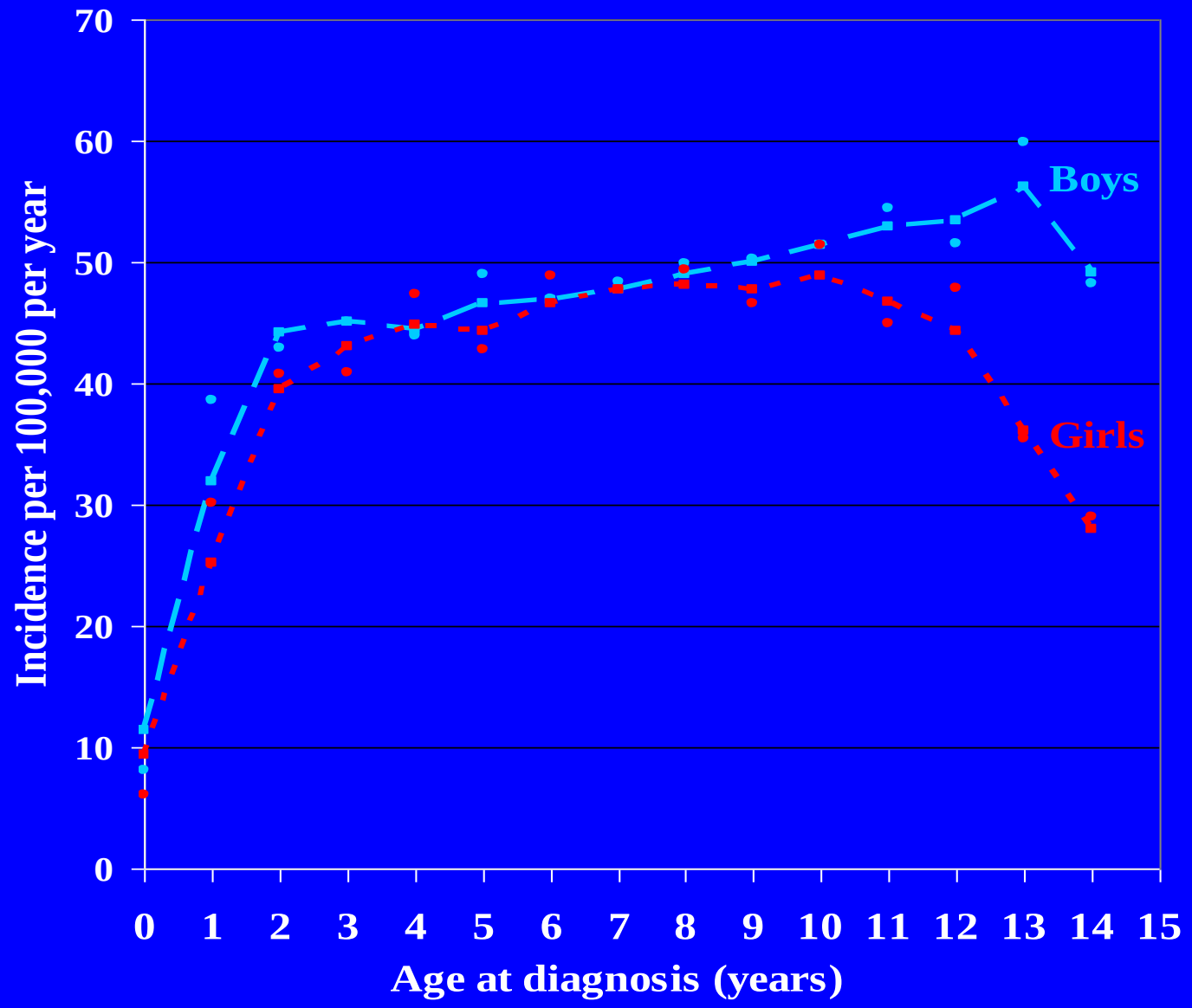
Onkamo et al. Diabetologia 1999; 42: 1395-1403 .

The trend in the incidence of Type 1 diabetes in Finnish children aged 14 or under

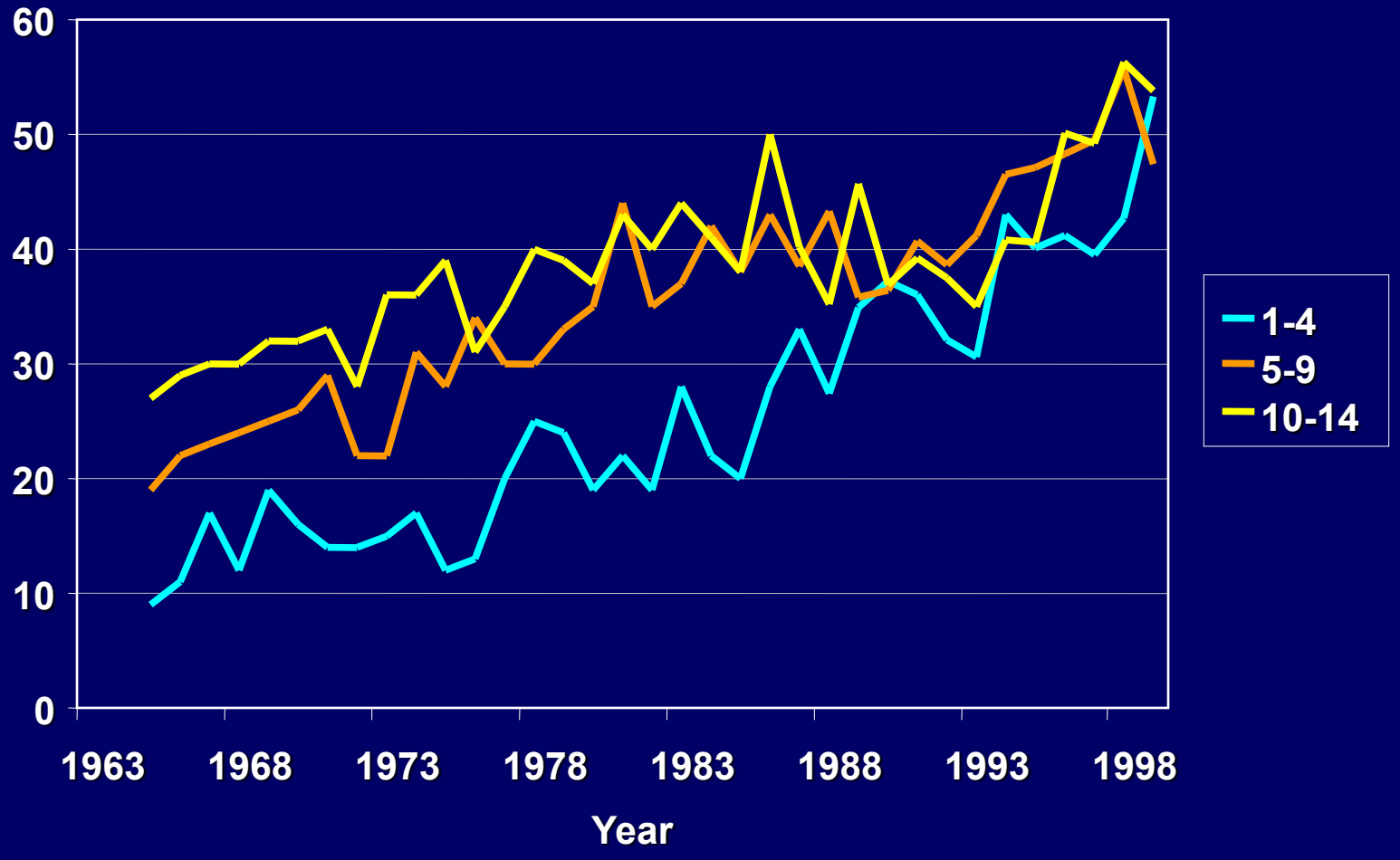


Tuomilehto et al. Diabetologia 1999

Age-specific and sex-specific T1D incidence rates in Finland



Age-specific annual incidence of Type 1 diabetes per 100,00
Finnish children aged 1-14 years between 1965 and 1996.



Karvonen et al. Diabetes Care 1999

Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study

Valma Harjutsalo, Lena Sjöberg, Jaakko Tuomilehto

Summary

Background Finland has the highest incidence of type 1 diabetes worldwide, reaching 40 per 100 000 people per year in the 1990s. Our aim was to assess the temporal trend in type 1 diabetes incidence since 2000 in Finnish children aged younger than 15 years and to predict the number of cases of type 1 diabetes in the future.

Lancet 2008; 371: 1777–82

See Editorial page 1723

See Comment page 1730

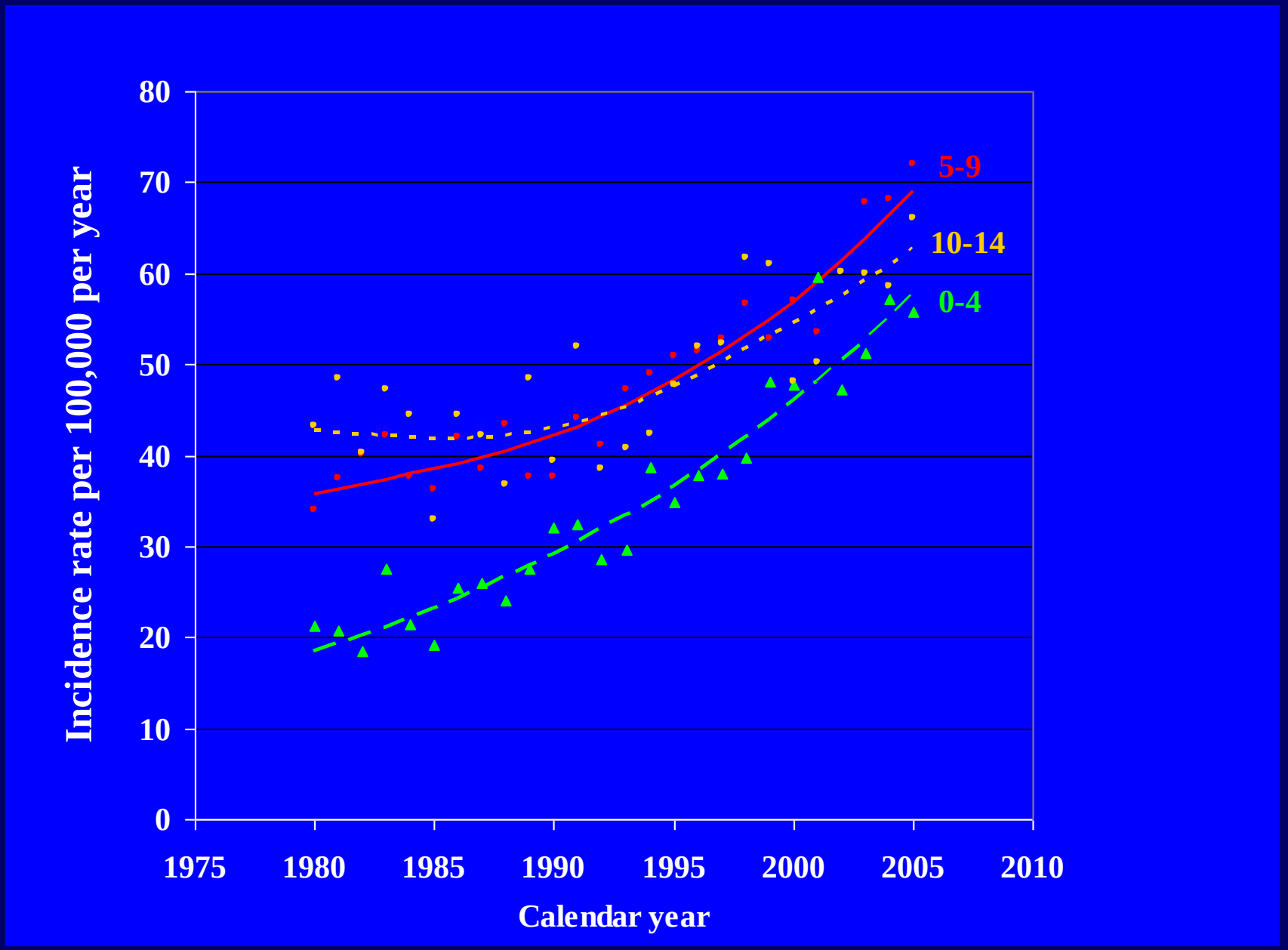
Diabetes Unit, Department of

Age-specific incidence rates (95% CI) of T1D per 100,000/year during 1980-2005

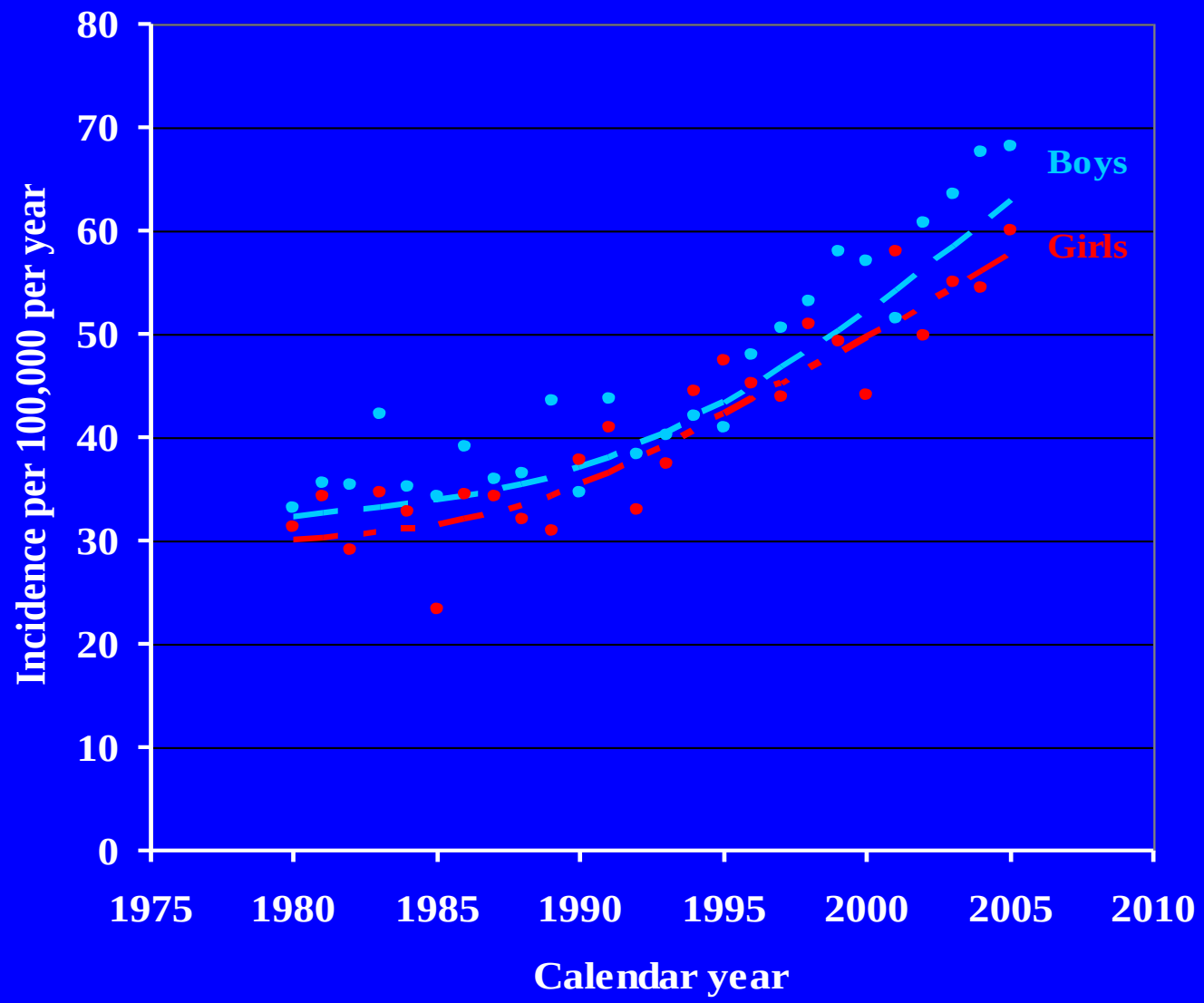
Age	1980-84 incidence	1985-89 incidence	1990-94 incidence	1995-99 incidence	2000-05 incidence	Annual increase % (95% CI)	Trend test (p)
0-4	21.9	24.4	32.3	39.5	53.1	4.7 (3.7-5.6)	<0.0001
5-9	38.3	39.5	43.8	52.9	62.8	2.7 (2.0-3.5)	<0.0001
10-14	42.9	40.2	41.9	54.1	56.4	1.7 (1.1-2-6)	<0.0001
0-14	34.3	34.7	39.3	49.0	57.6	3.0 (2.2-3.8)	<0.0001

The number of new T1D cases 10737; 5816 boys and 4921 girls

Time trends in age-specific incidence of T1D in Finland



Time trends in T1D incidence in Finnish boys and girls



Increase in incidence of childhood T1D globally: The DiaMond study

Table 3 Annual increase (%) of incidence of Type 1 diabetes by age groups and by continents in children aged 14 or under in 1990–1999; the results of the Poisson regression analyses

	Total Age/ year*			0–4 years		5–9 years		10–14 years		
Continent	Trend %	95% CI	*P*	Trend %	95% CI	Trend %	95% CI	Trend %	95% CI	*P*
Africa	3.0	(0.3; 5.8)	0.029	0.9	(−5.6; 7.9)	9.2	(3.8; 14.9)	0.6	(−3.0; 4.3)	0.154
Asia	4.0	(1.8; 6.2)	<0.001	1.3	(−3.5; 6.2)	5.0	(1.4; 8.8)	5.1	(1.8; 8.5)	0.238
Europe	3.2	(2.7; 3.6)	<0.001	4.7	(3.9; 5.6)	3.4	(2.7; 4.0)	2.2	(1.6; 2.8)	<0.001
North America	5.3	(3.3; 7.3)	<0.001	6.9	(2.4; 11.5)	4.7	(1.4; 8.1)	5.1	(2.3; 8.1)	0.674
South America	5.3	(2.8; 7.9)	<0.001	6.5	(1.2; 12.0)	9.2	(4.7; 13.9)	1.7	(−2.0; 5.6)	0.071
Central America and West Indies	−3.6	(−5.0; −2.2)	<0.001	−3.6	(−6.7; 0.3)	−4.2	(−6.5; −1.9)	−3.2	(−5.3; 1.0)	0.881
Oceania	3.2	(−0.4; 6.9)	<0.001	11.1	(3.2; 19.6)	−0.6	(−6.4; 5.5)	2.1	(−3.3; 7.8)	0.042
All regions	2.8	(2.4; 3.2)	<0.001	4.0	(3.1; 4.9)	3.0	(2.4; 3.7)	2.1	(1.5; 2.7)	<0.001

*Interaction between age group and calendar year.

The DIAMOND Project Group. Diabetic Med 2006

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

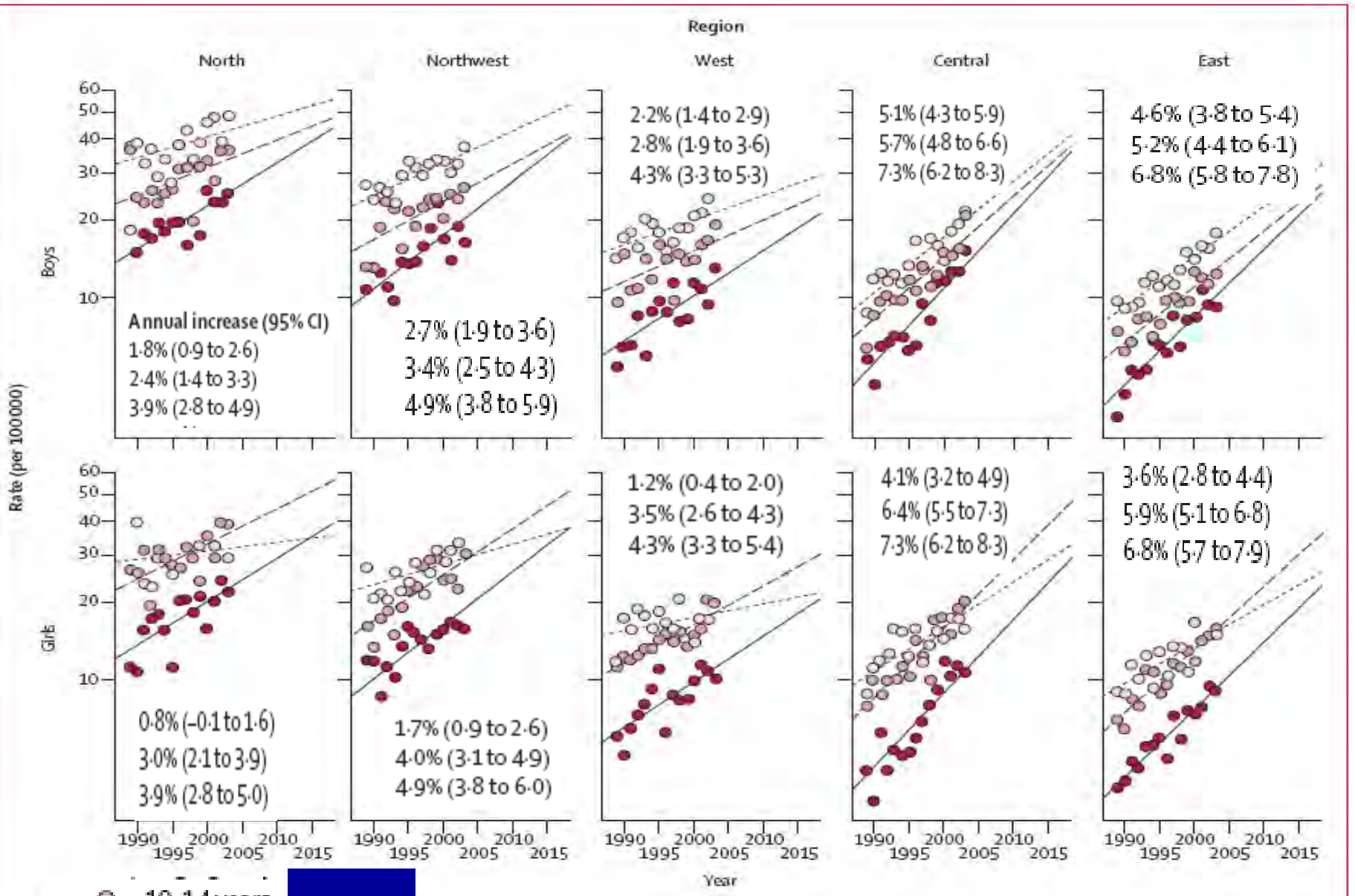
Summary

Background The incidence of type 1 diabetes in children younger than 15 years is increasing. Prediction of future incidence of this disease will enable adequate fund allocation for delivery of care to be planned. We aimed to establish 15-year incidence trends for childhood type 1 diabetes in European centres, and thereby predict the future burden of childhood diabetes in Europe.

Lancet 2009; 373: 2027–33

Published Online May 28, 2009

DOI:10.1016/S0140-6736(09)60568-7



T1D incidence trends by region in Europe

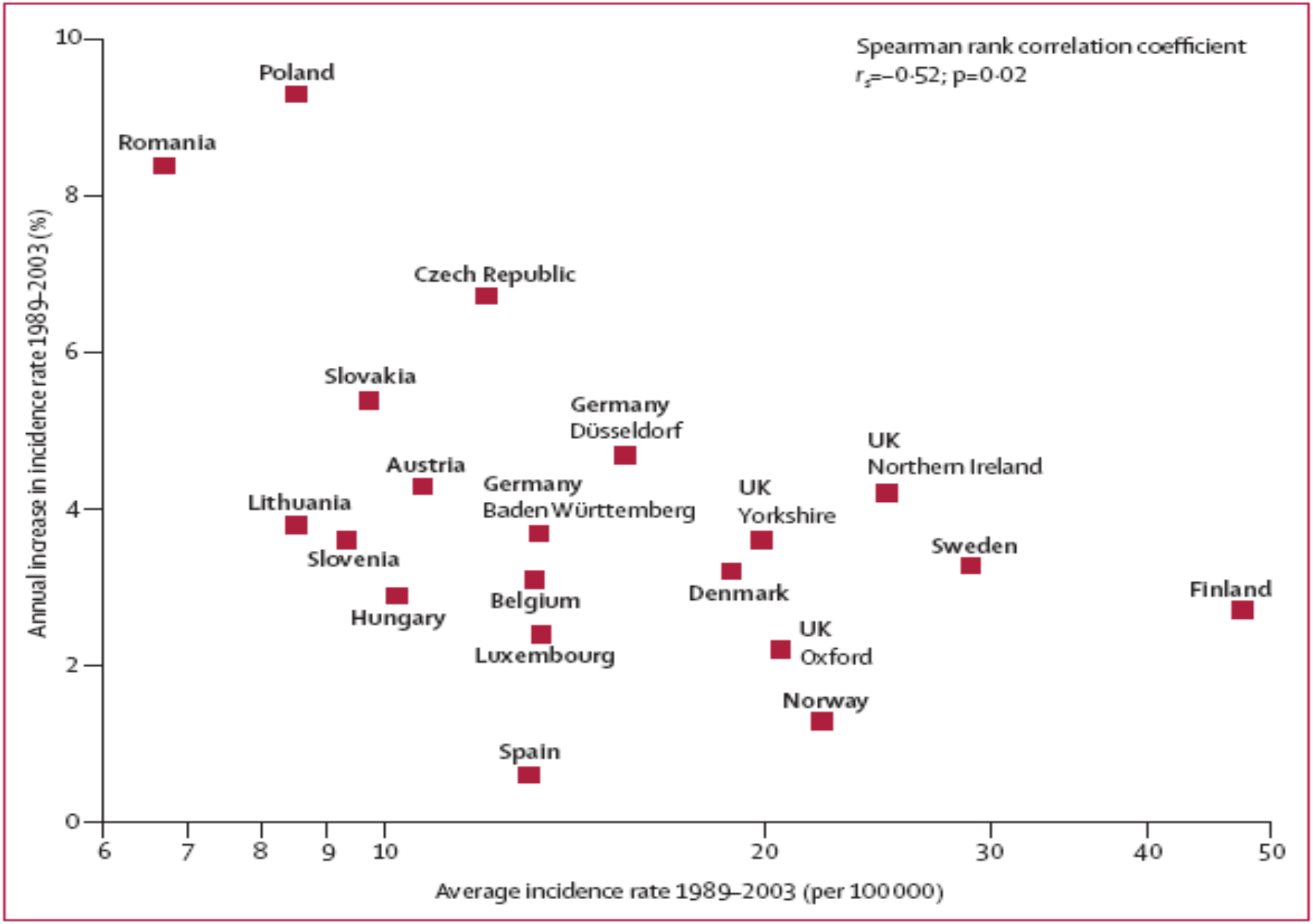
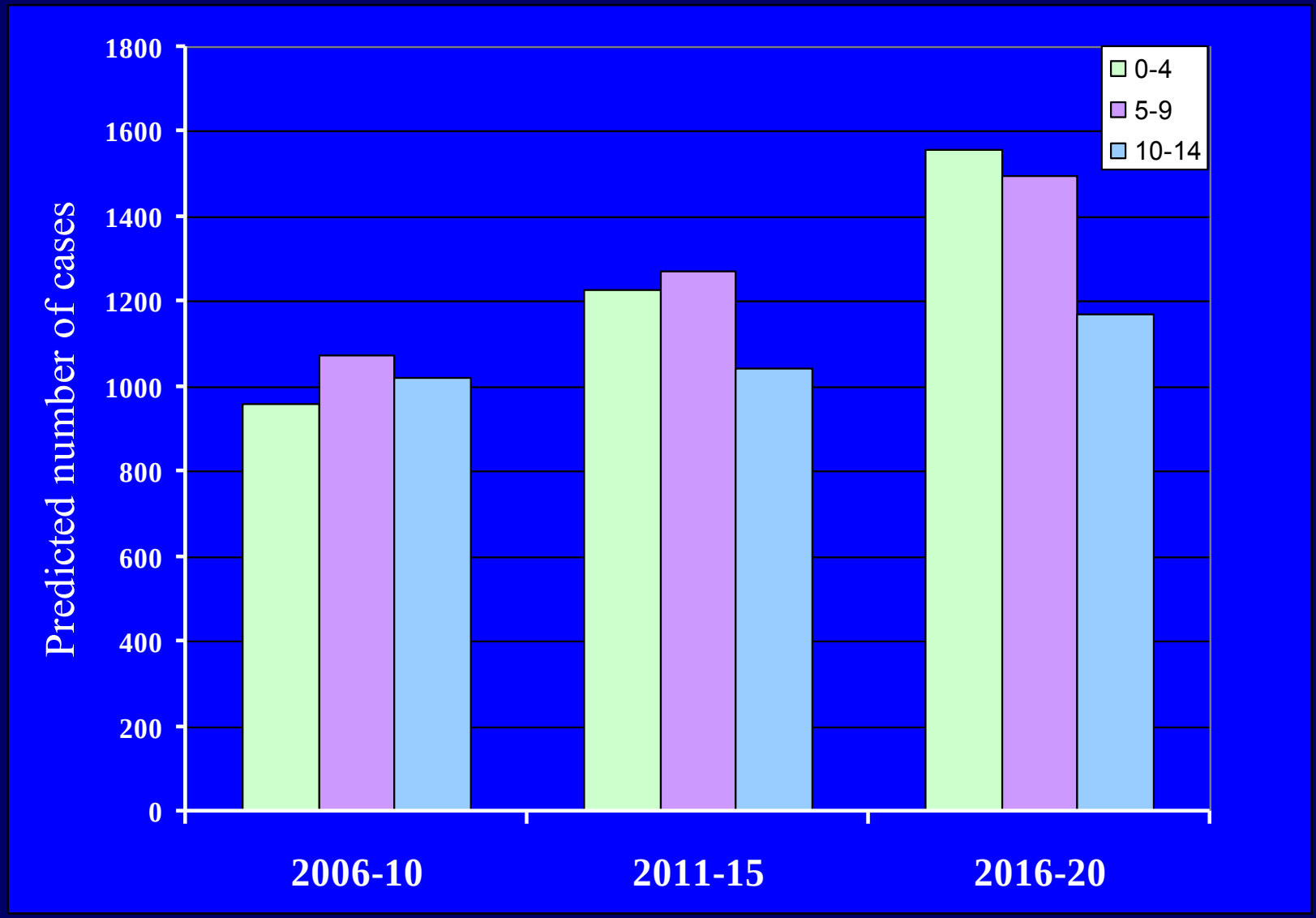


Figure 2: **Inverse association between rate of incidence increase and average incidence**
Incidence rate on horizontal axis, plotted on a logarithmic scale. Spearman rank correlation coefficient r_s=–0·52, p=0·02.

Predicted future numbers of newly diagnosed cases of childhood-onset T1D in Finland by age group



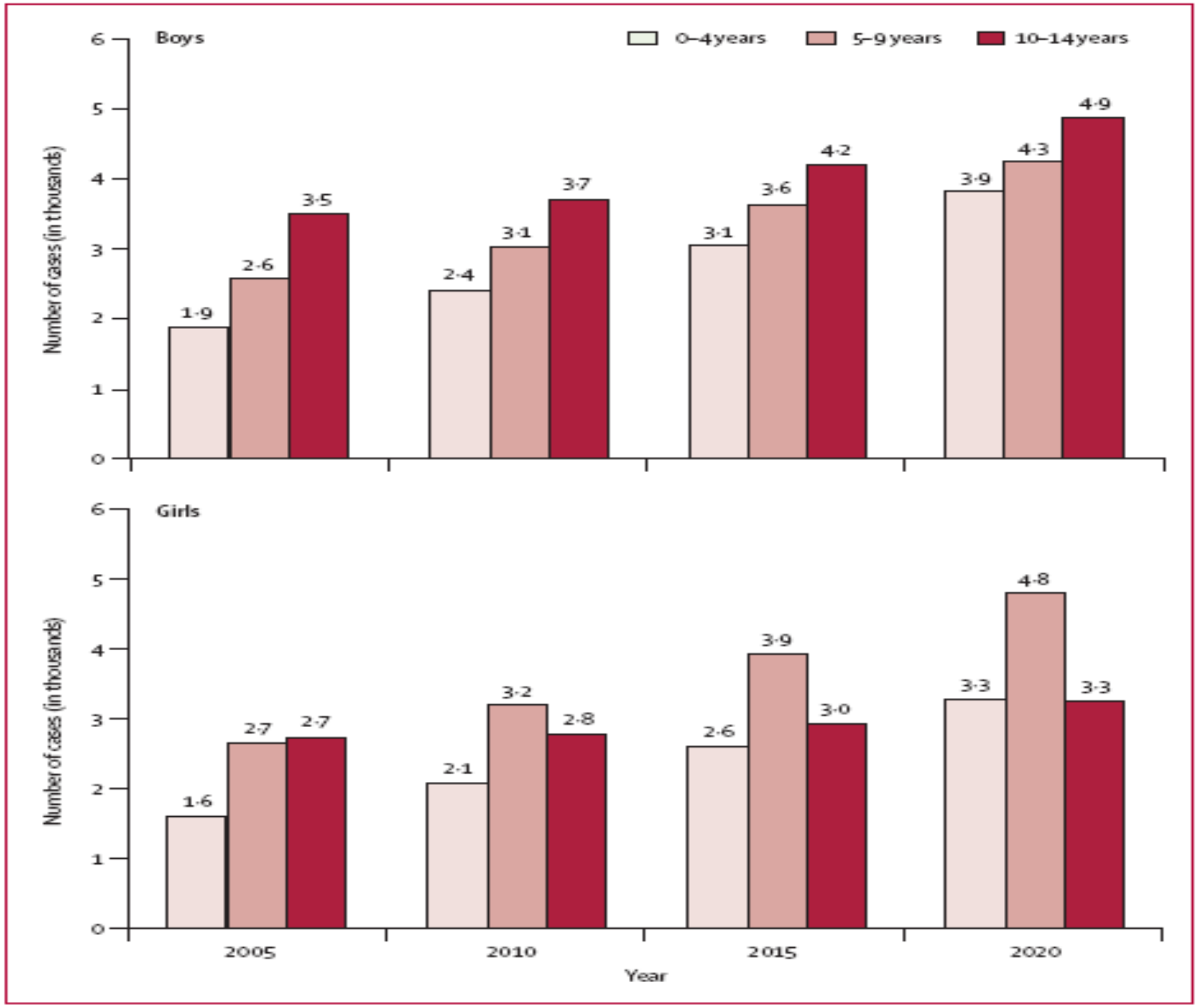
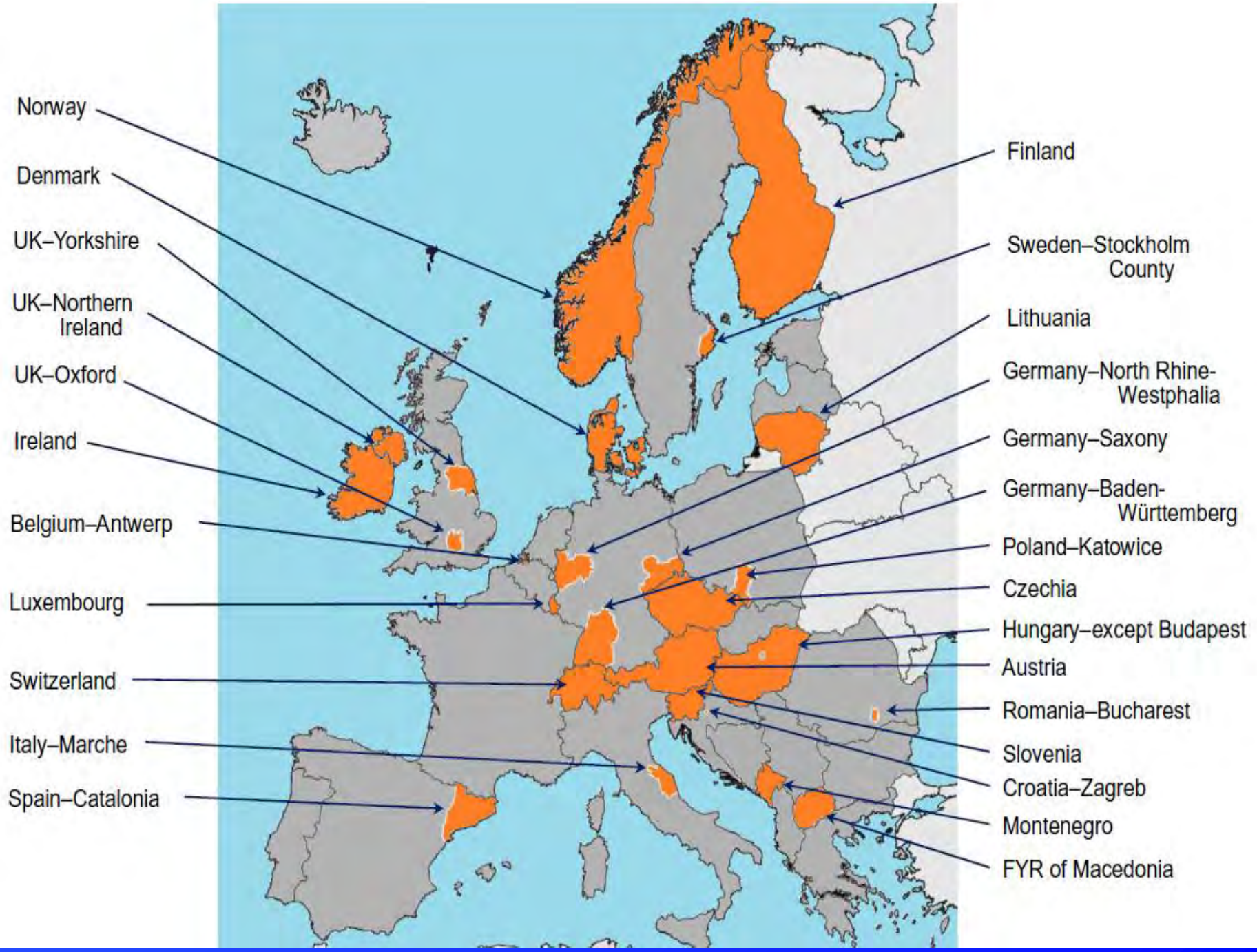


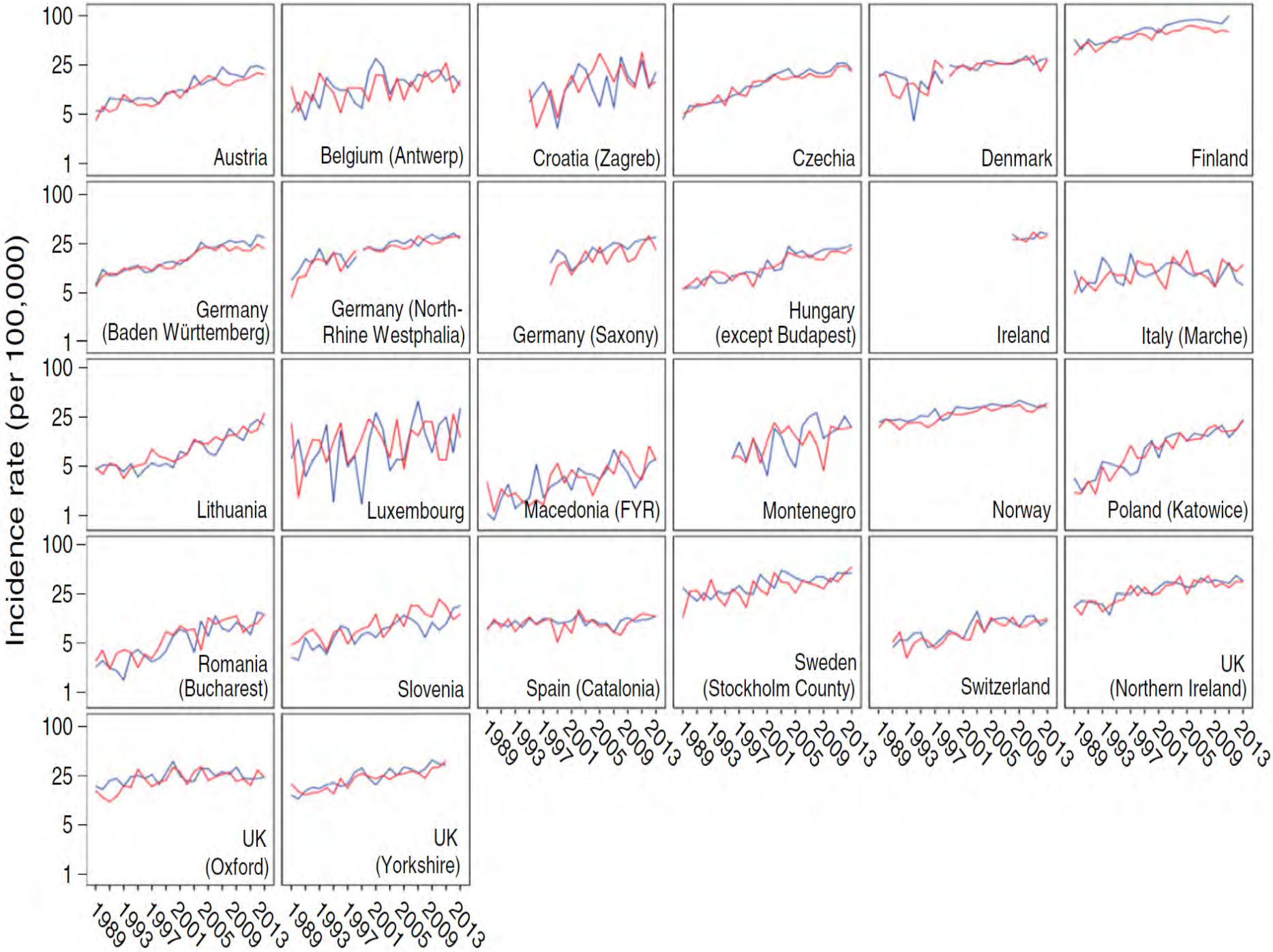
Figure 4: Estimated (2005) and predicted cases of newly diagnosed type 1 diabetes
Predicted new cases for future years in Europe (excluding Belarus, the Russian Federation, Ukraine, Moldova, and Albania) on the basis of the best fitting Poisson regression model.

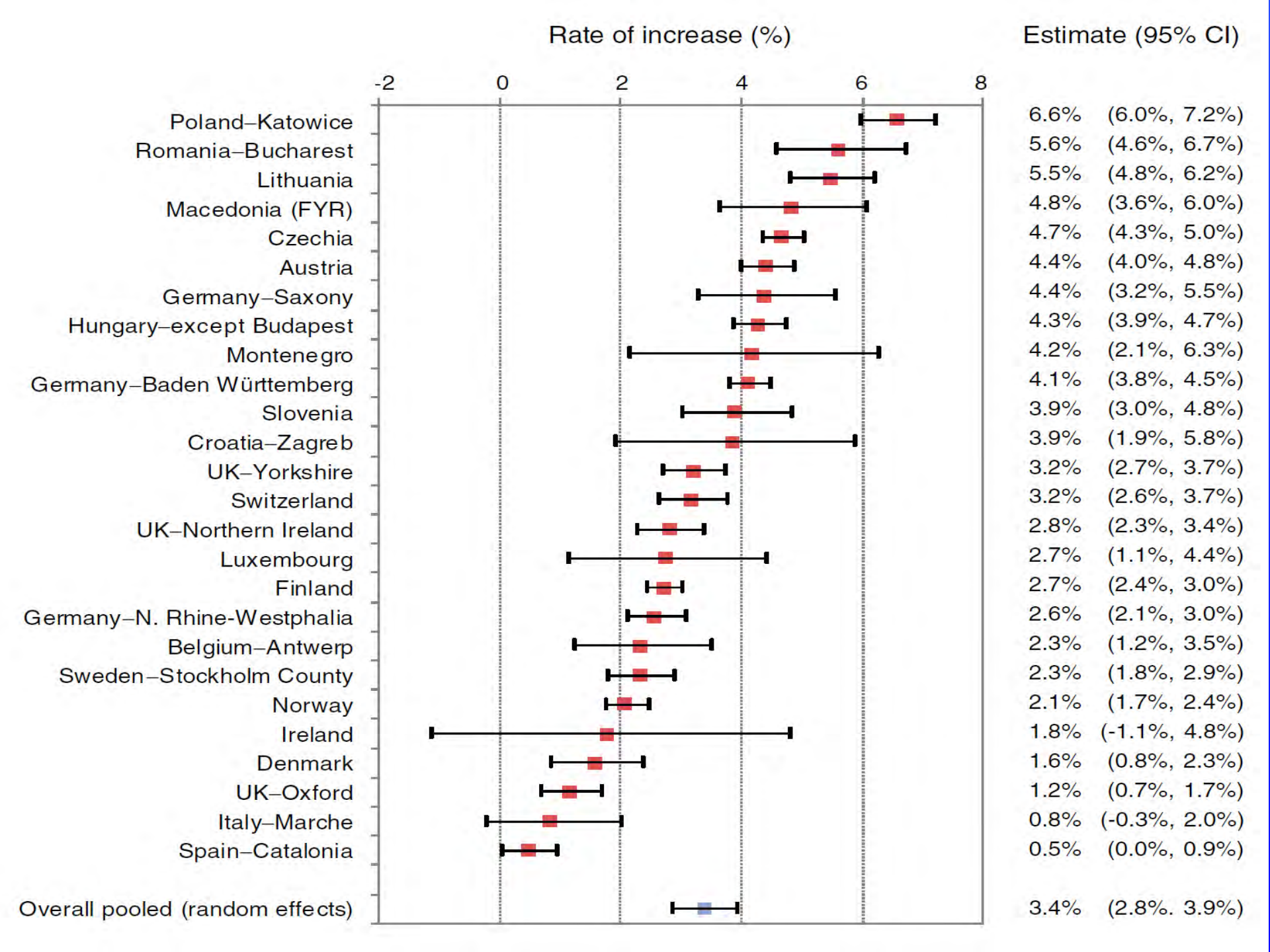
Diabetologia (2019) 62:408–417
https://doi.org/10.1007/s00125-018-4763-3

ARTICLE

Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study

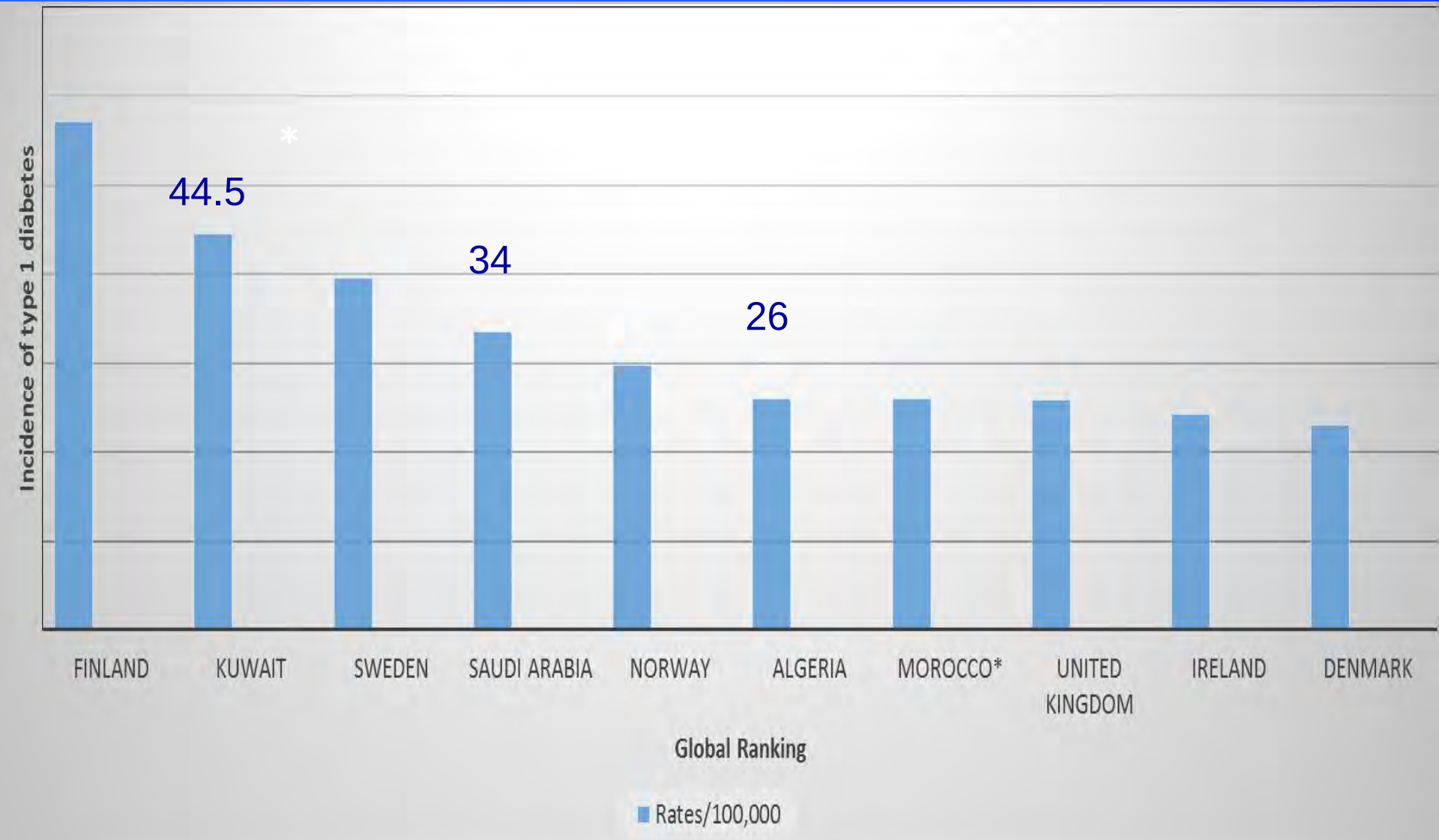

Norway
Denmark
UK–Yorkshire
UK–Northern Ireland
UK–Oxford
Ireland
Belgium–Antwerp
Luxembourg
Switzerland
Italy–Marche
Spain–Catalonia
Finland
Sweden–Stockholm County
Lithuania
Germany–North Rhine-Westphalia
Germany–Saxony
Germany–Baden-Württemberg
Poland–Katowice
Czechia
Hungary–except Budapest
Austria
Romania–Bucharest
Slovenia
Croatia–Zagreb
Montenegro
FYR of Macedonia


Incidence rate (per 100,000)
100
25
5
1
Austria
Belgium (Antwerp)
Croatia (Zagreb)
Czechia
Denmark
Finland
Germany (Baden Württemberg)
Germany (North-Rhine Westphalia)
Germany (Saxony)
Hungary (except Budapest)
Ireland
Italy (Marche)
Lithuania
Luxembourg
Macedonia (FYR)
Montenegro
Norway
Poland (Katowice)
Romania (Bucharest)
Slovenia
Spain (Catalonia)
Sweden (Stockholm County)
Switzerland
UK (Northern Ireland)
UK (Oxford)
UK (Yorkshire)
1989
1993
1997
2001
2005
2009
2013


Rate of increase (%)
Estimate (95% CI)
-2
0
2
4
6
8
Poland–Katowice 6.6% (6.0%, 7.2%)
Romania–Bucharest 5.6% (4.6%, 6.7%)
Lithuania 5.5% (4.8%, 6.2%)
Macedonia (FYR) 4.8% (3.6%, 6.0%)
Czechia 4.7% (4.3%, 5.0%)
Austria 4.4% (4.0%, 4.8%)
Germany–Saxony 4.4% (3.2%, 5.5%)
Hungary–except Budapest 4.3% (3.9%, 4.7%)
Montenegro 4.2% (2.1%, 6.3%)
Germany–Baden Württemberg 4.1% (3.8%, 4.5%)
Slovenia 3.9% (3.0%, 4.8%)
Croatia–Zagreb 3.9% (1.9%, 5.8%)
UK–Yorkshire 3.2% (2.7%, 3.7%)
Switzerland 3.2% (2.6%, 3.7%)
UK–Northern Ireland 2.8% (2.3%, 3.4%)
Luxembourg 2.7% (1.1%, 4.4%)
Finland 2.7% (2.4%, 3.0%)
Germany–N. Rhine-Westphalia 2.6% (2.1%, 3.0%)
Belgium–Antwerp 2.3% (1.2%, 3.5%)
Sweden–Stockholm County 2.3% (1.8%, 2.9%)
Norway 2.1% (1.7%, 2.4%)
Ireland 1.8% (-1.1%, 4.8%)
Denmark 1.6% (0.8%, 2.3%)
UK–Oxford 1.2% (0.7%, 1.7%)
Italy–Marche 0.8% (-0.3%, 2.0%)
Spain–Catalonia 0.5% (0.0%, 0.9%)
Overall pooled (random effects) 3.4% (2.8%. 3.9%)

Top 10 countries/ territories for the incidence rates (100,000 children/ year) with T1D

IDF 2017



The trend of T1D in children in Kuwait

HYPOTHESES FOR THE INCREASE IN T1DM INCIDENCE

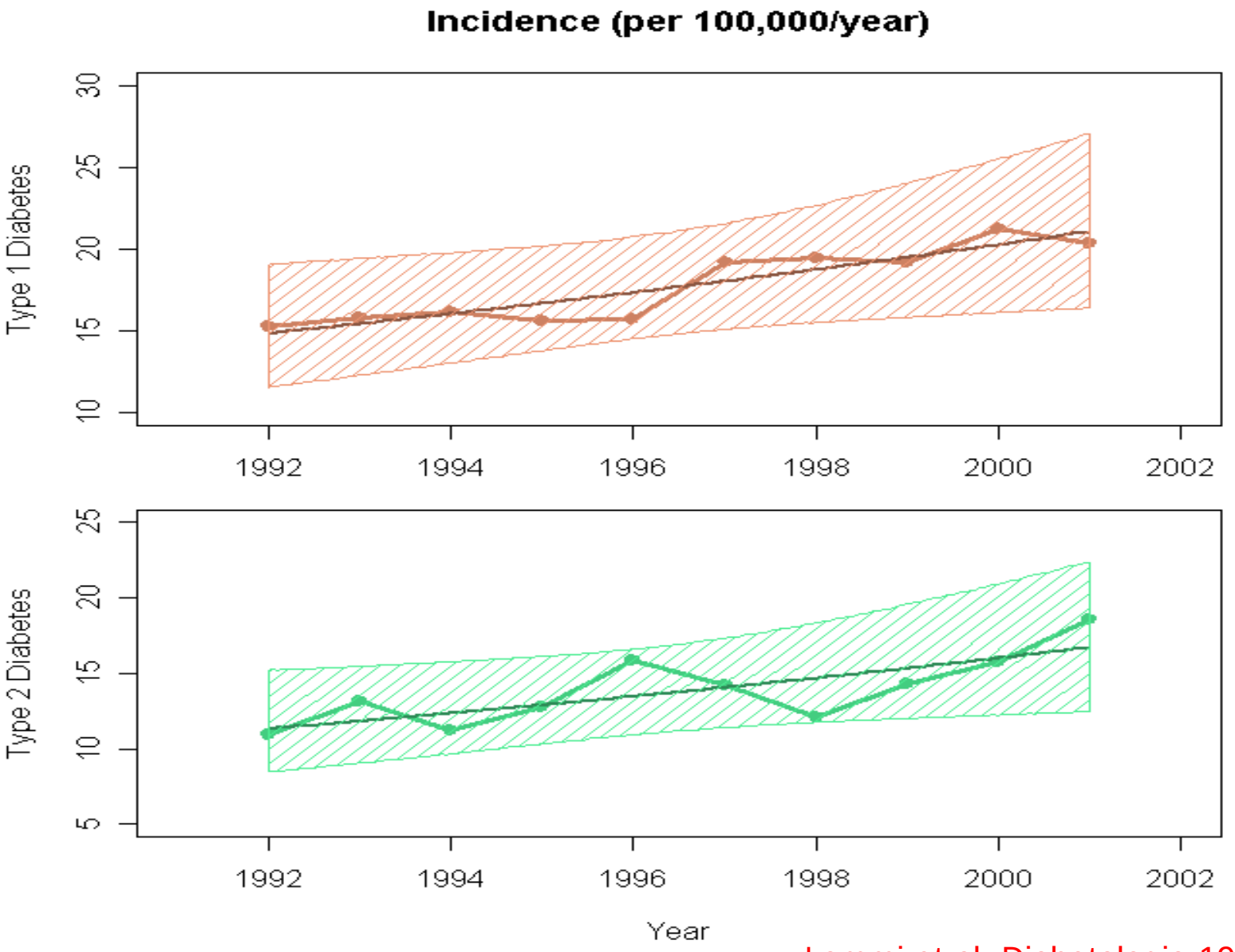
- ***"The acceleration hypothesis":***

  some factor has increased in the populations: obesity

- ***"The spring harvest hypothesis":***

  the disease onset is earlier, but the lifetime cumulative incidence is not changing

Change in incidence of diabetes among Finns aged 15-39 years – a nationwide study



Lammi et al. Diabetologia 1998

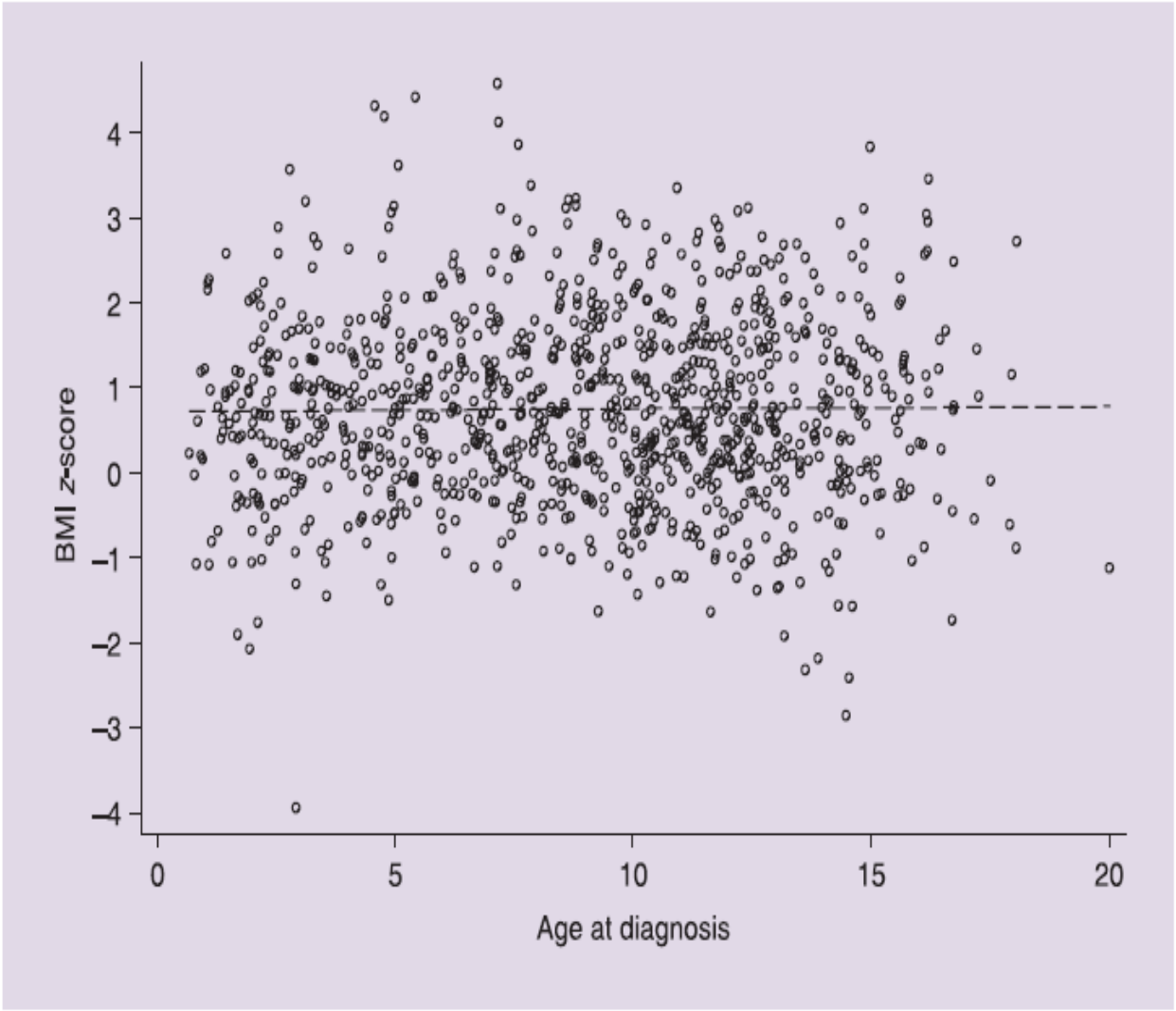
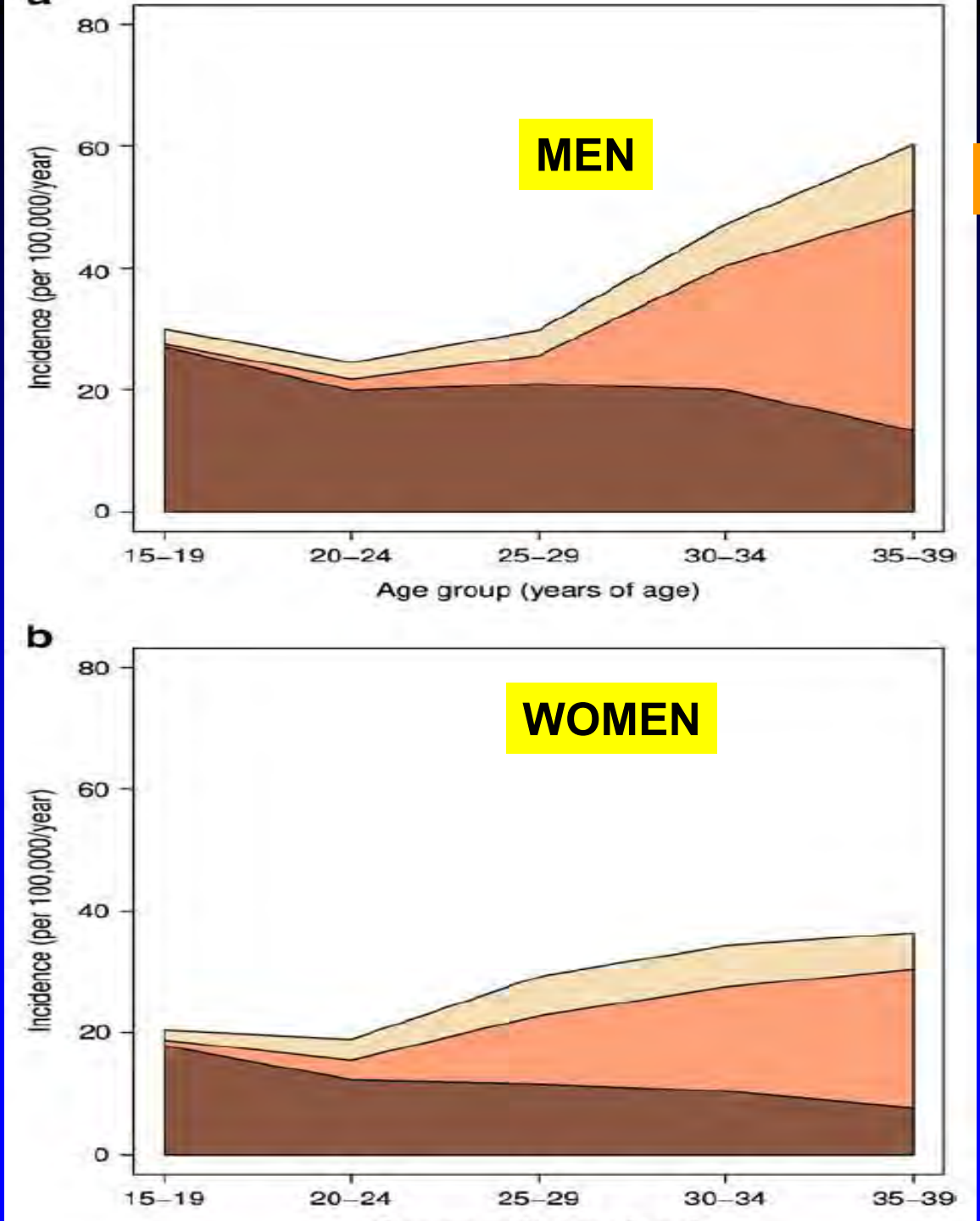


FIGURE 1 Body mass index standard deviation scores (BMI SDS) [6] and age at diagnosis; $r^2 = 0.001$, $P = 0.7$.



Unspecified

T2D

T1D

Incidence of diabetes in Finnish men and women aged 15-39 during 1992-1996 by diabetes type

REASONS FOR THE INCREASE IN INCIDENCE OF CHILDHOOD T1DM

1. Genetic factors
2. Reduced mortality in T1DM
3. Increased reproduction in people with T1DM
4. Changes in environmental risk factors causing T1DM

POSSIBLE RISK: ENVIRONMENTAL FACTORS FOR T1DM

- Viral infections
- Short breast feeding
- Early cow's milk supplementation
- Vitamin D deficiency
- Pancreas toxins and stimulating agents
  - nitrates and nitrites
  - caffeine
  - pesticides

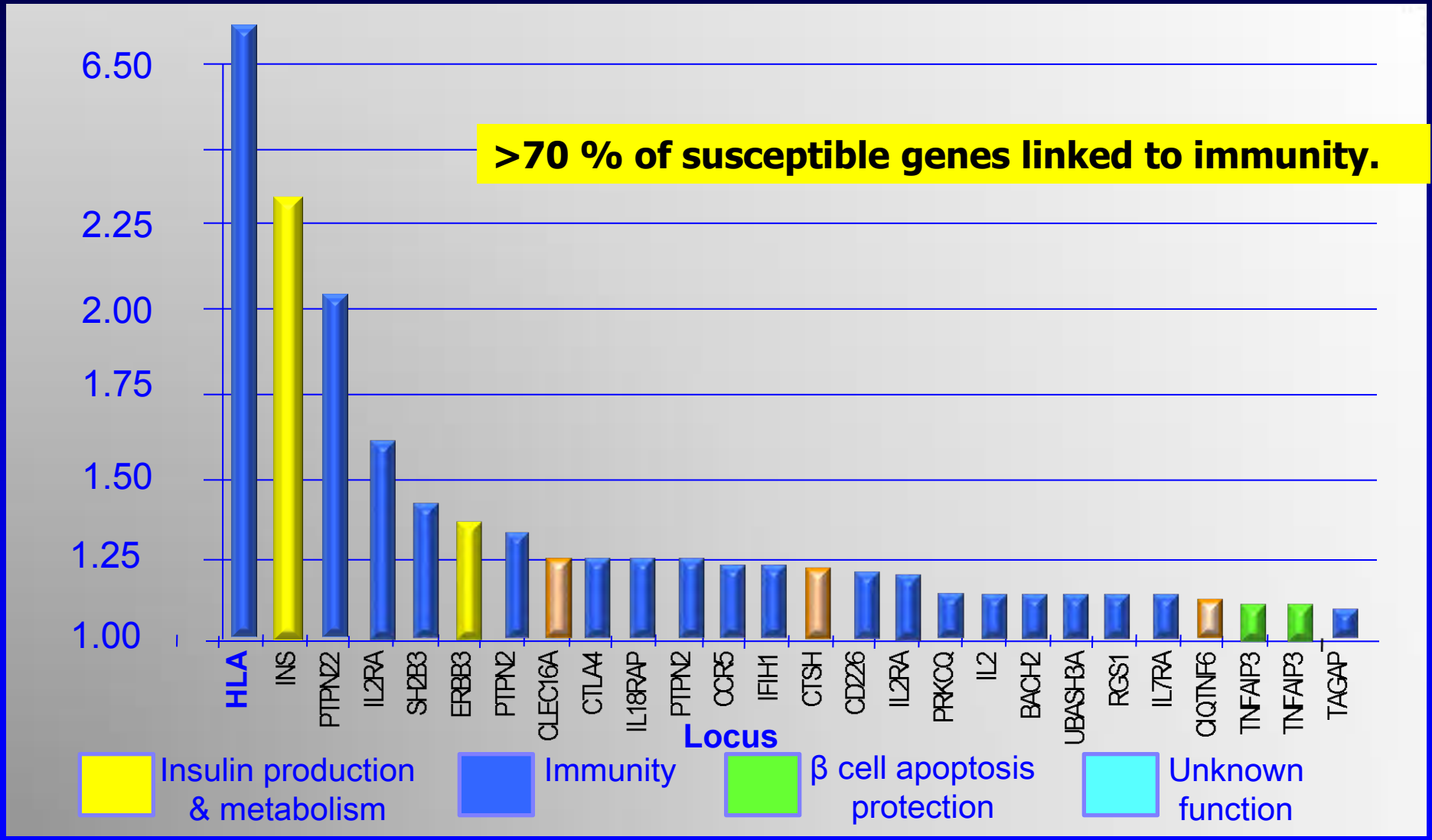
INCREASE IN CHILDHOOD DIABETES INCIDENCE: GENETIC FACTORS

1. Increase in the pool of genetically susceptible individuals
2. Preferential transmission of certain susceptibility genootypes
3. Increased penetrance of the susceptibility genes
4. Increased genetic diversity in high risk HLA haplotypes
5. Anticipation
6. Inbreeding
7. Inprinting - Epigenetics

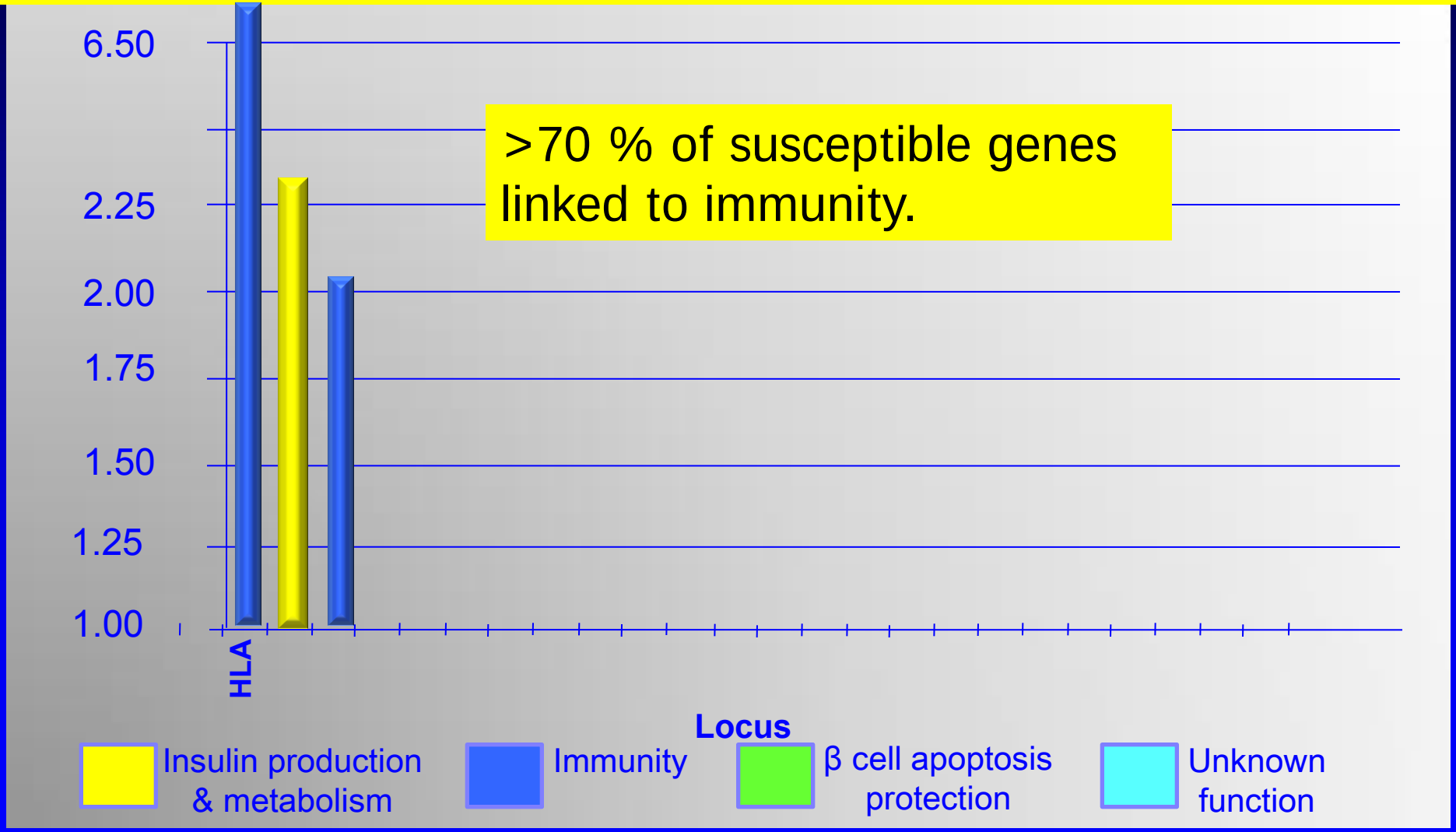
GENETIC HYPOTHESIS FOR T1DM

- **The proportion of people genetically predisposed varies markedly among populations**
- **This proportion has steadily increased over time**
- **The initial number and the rate of its increase varies among populations**
- **Recessive mode of inheritance unlikely, i.e. the contribution from one parent is sufficient.**
- **The penetrance of the susceptibility genes is low, therefore, the majority of the predisposed individuals do not develop T1D, but remain as disease risk carriers.**

Genome-wide association in T1D: >80% of T1D patients carry the high-risk HLA haplotype



Genome-wide association in T1D: >80% of T1D patients carry the high-risk HLA haplotype



HLA

H HUMAN

L LEUKOCYTE

A ANTIGEN

1956 “Mac” = A2 Prof Dausset, Paris
1980 Nobel Prize

HLA REGION

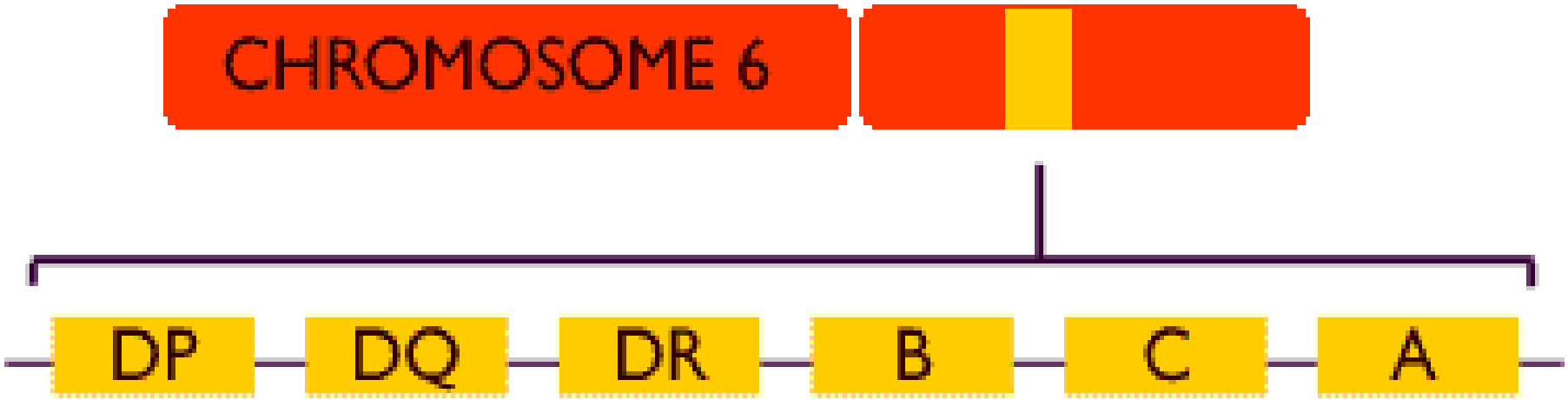
Highly polymorphic region of closely linked loci

Phylogenetically conserved region

Very good anthropologic markers

Function of HLA molecules is to collect peptide fragments inside the cell and transport them to the cell surface

8-9 amino acids for class I (A,B,C)
12-25 amino acids for class II (DR, DQ,DP)



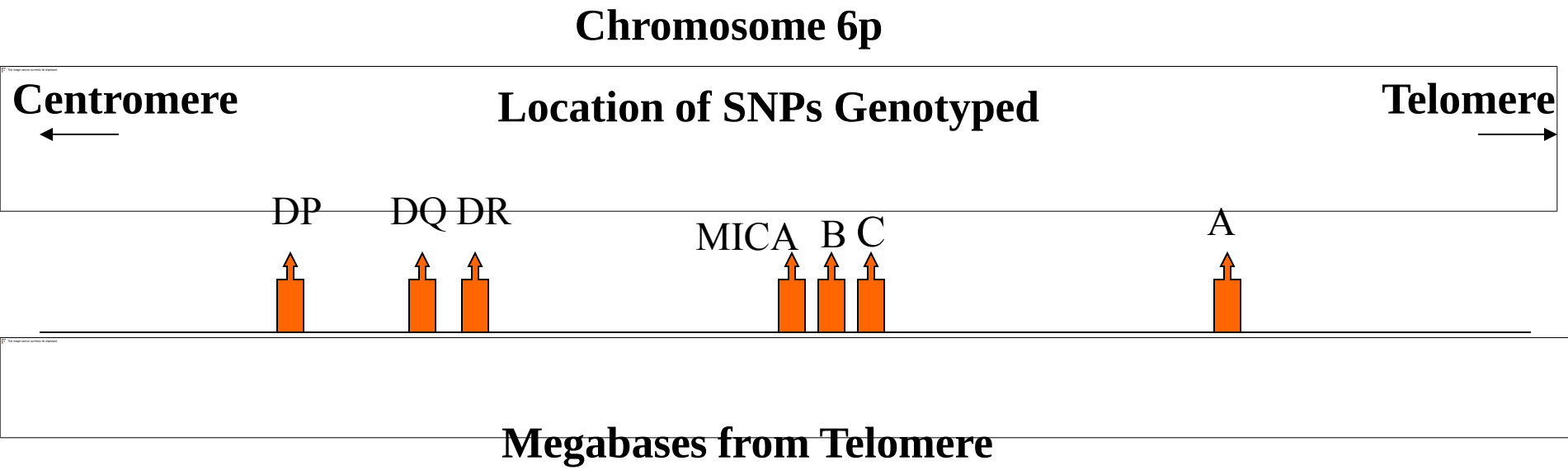
CELL SURFACE PROTEINS:

CLASS I HLA-A, HLA-B, HLA-C

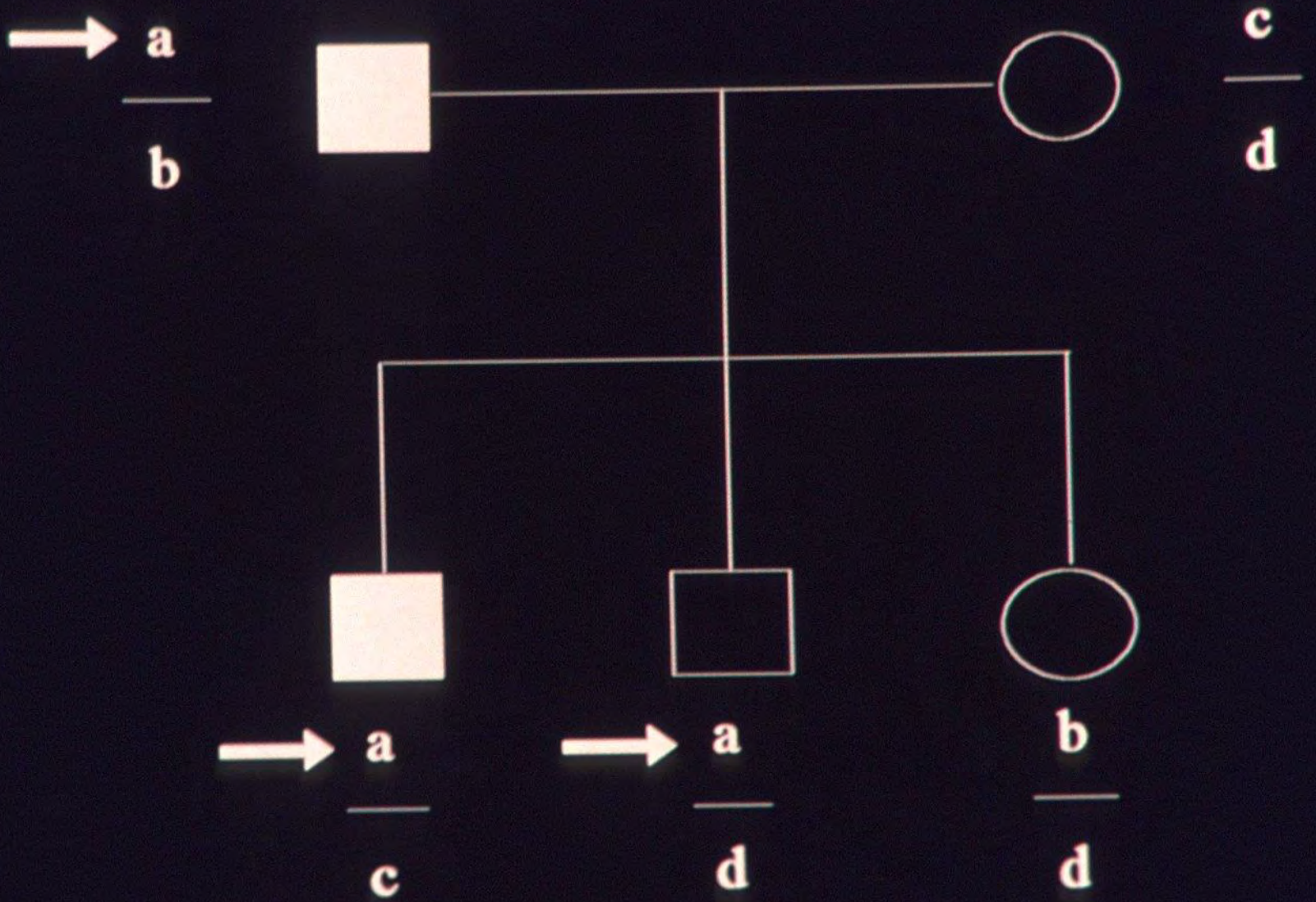
CLASS II HLA-DR, HLA-DQ, HLA-DP

The HLA genes are found on chromosome 6.

HLA Region loci



DIABETIC FATHER

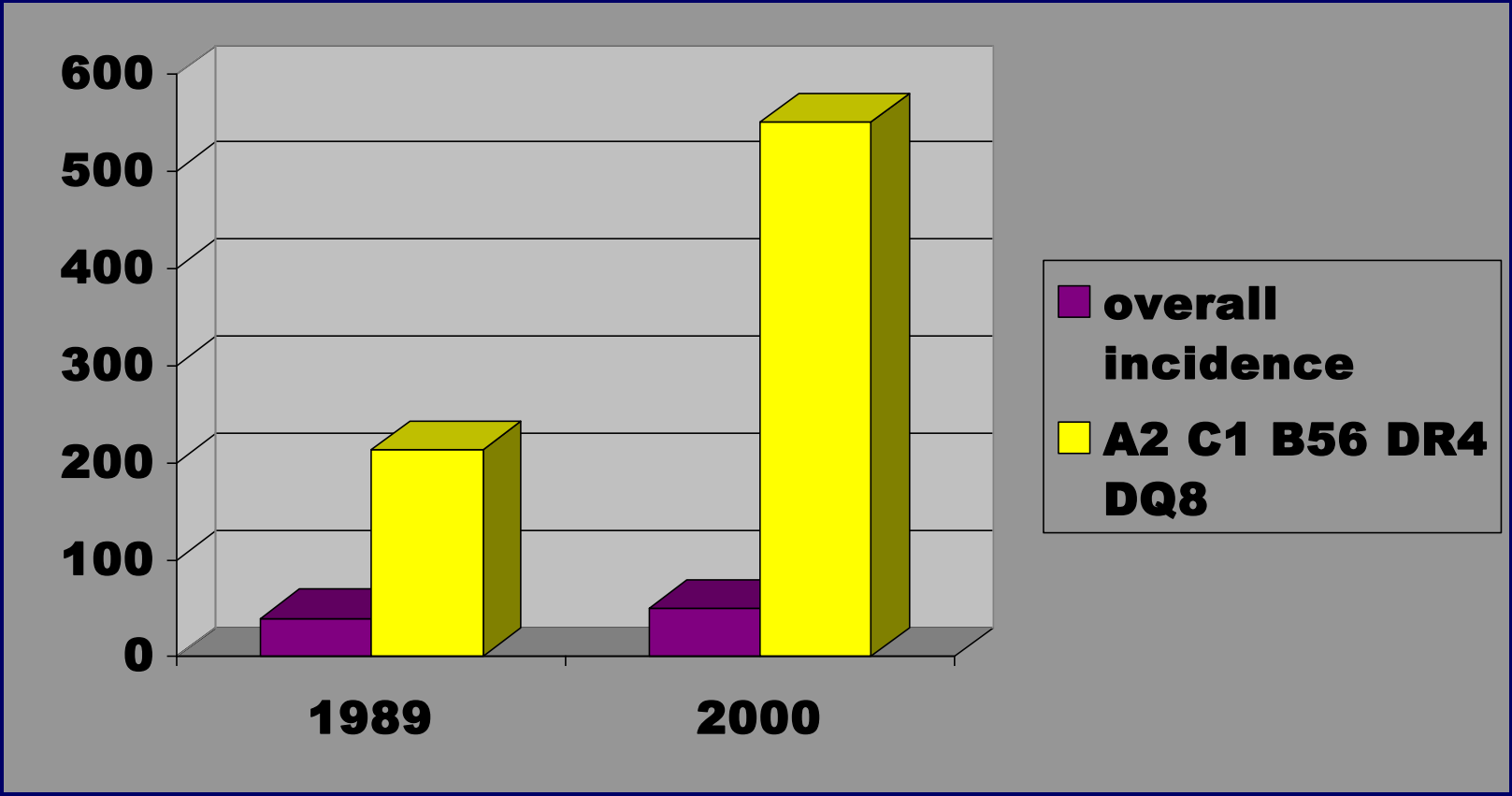


HLA HAPLOTYPES

DIME and CONTROL Studies

					diabetic n=1518		control n=198	
A	C	B	DR	DQ	n	%	n	%
2	1	56	4	8	82	5.4	1	0.5
2	3	62	4	8	142	9.3	3	1.5
3	3	62	4	8	41	2.7	0	0.0
2	7	8	3	2	49	3.2	4	2.0
1	7	8	3	2	139	9.2	13	6.6
24	7	39	4	8	53	3.5	1	0.5
2	3	60	4	8	20	1.3	2	1.0
			TOTAL		526	34.6	24	12.1

FOLLOW-UP FOR FAMILY MEMBERS WITH A2, Cw1, B56, DRB1*0401, DQA1*0301,DQB1*0302

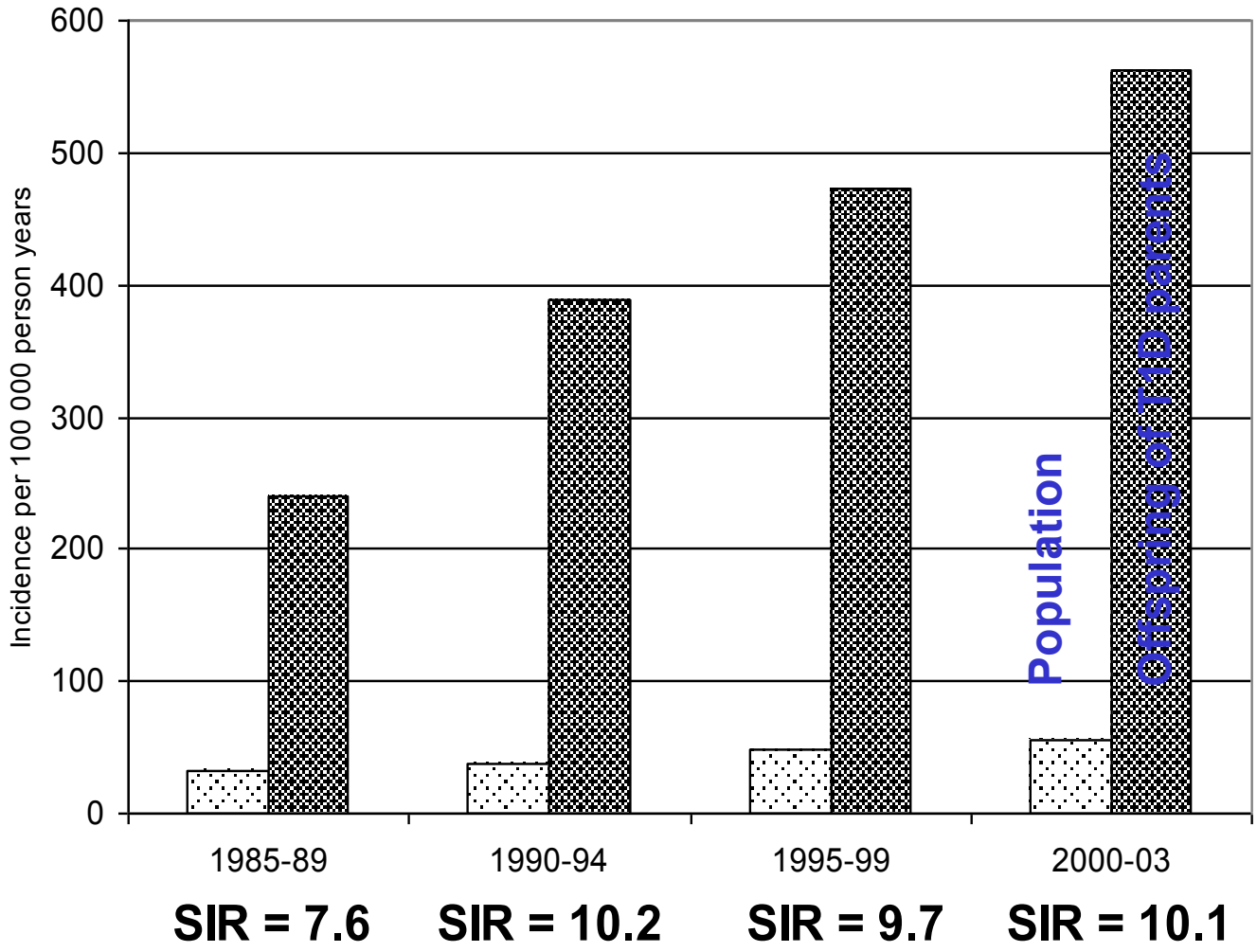


How To Estimate The Penetrance of T1DM Susceptibility Genes?

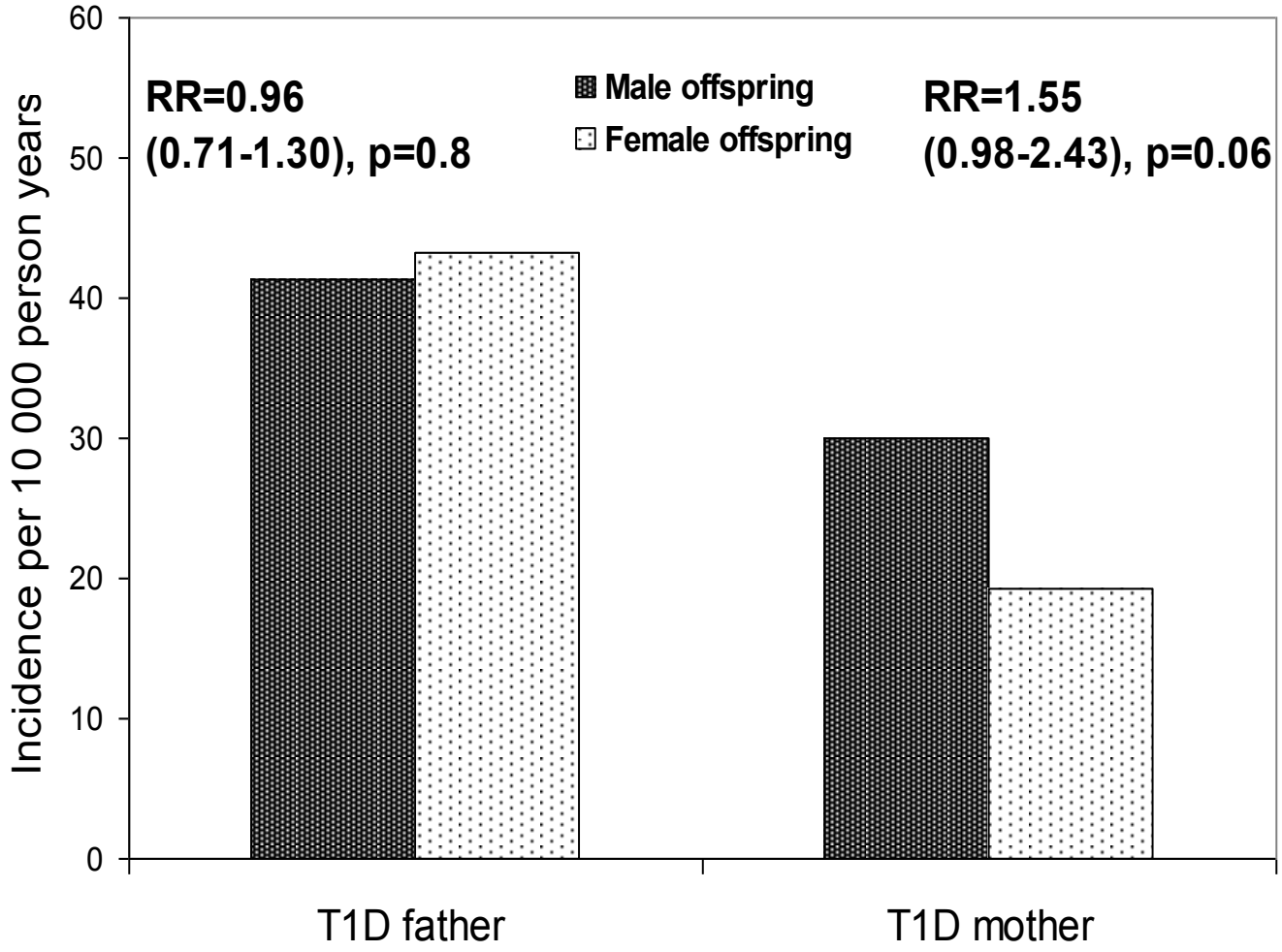
- Parents of IDDM patients
- Siblings of IDDM patients
- Twin pairs with IDDM

Standardized incidence ratios (SIRs) per 100,000 person-years in the offspring of T1D parents.

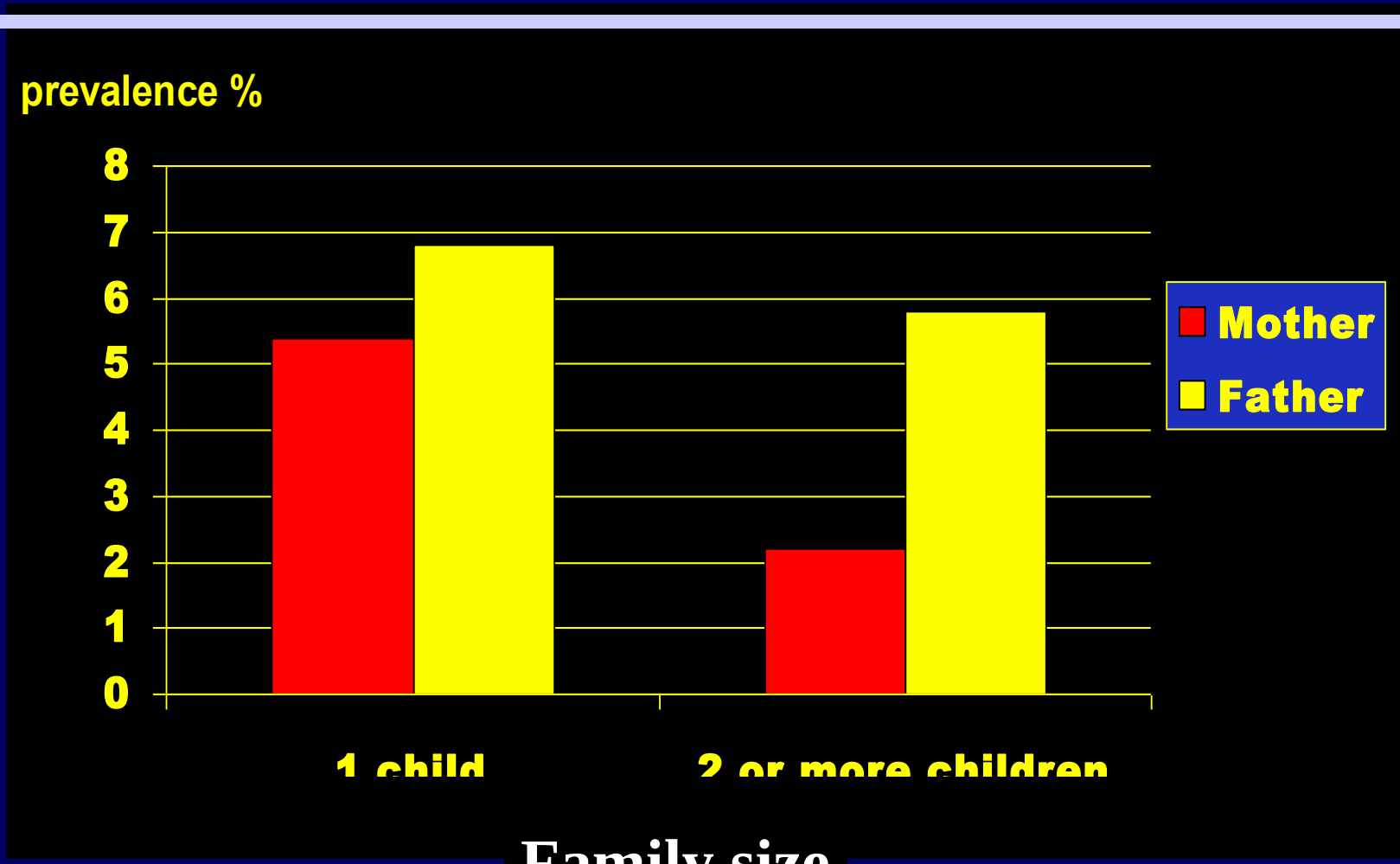
The age of diagnosis of T1D was 14 years or under.



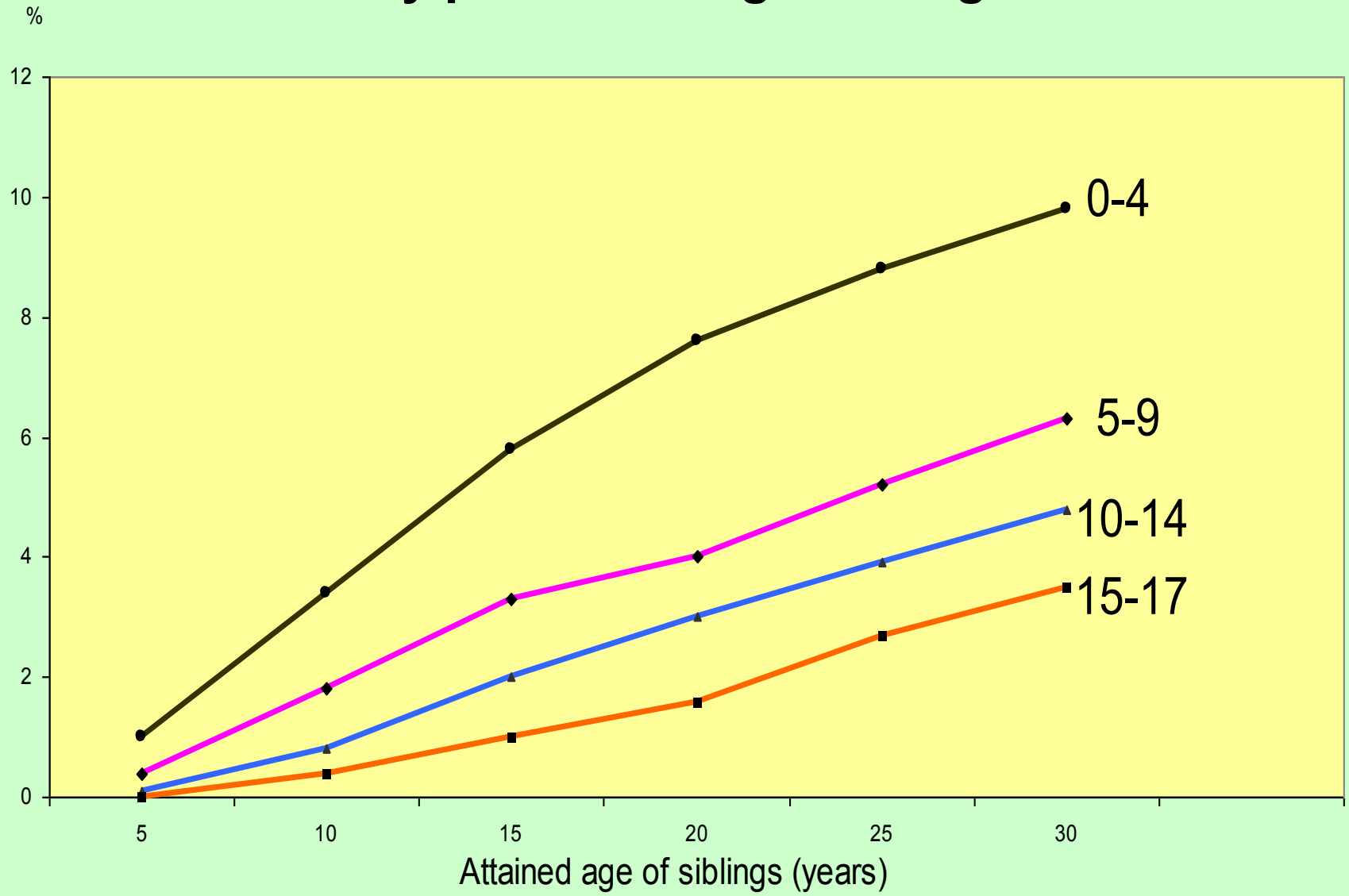
Incidence of T1D in the offspring of T1D parents by sex of the offspring and the parent with T1D. Offspring who had both parents with T1D were excluded.



Prevalence of T1DM in parents of T1DM probands by family size in Finland



Risk of diabetes in siblings of diabetic children by proband's age at diagnosis



INCIDENCE OF T1DM IN SIBLINGS OF FINNISH DIABETIC CHILDREN BY HLA HAPLOTYPE SHARING

HLA sharing of siblings with the proband	Incidence 100 000 / yr	RR versus population
HLA- identical	1124	31.2
HLA- haploidentical	322	8.9
HLA- nonidentical	155	4.3
Background population	36	1.0

PENETRANCE OF T1DM SUSCEPTIBILITY GENES IN FINLAND

- **Prevalence of diabetes in parents**
  - Fathers 7.3%
  - Mothers 2.7%
- **Cumulative risk of T1DM in siblings by 15 years**
  - HLA- identical 22.5%
  - HLA- haploidentical 6.9%
  - HLA- nonidentical 1.9%
- **Pairwise concordance of T1DM in twin pairs**
  - Monozygotic 27.3%
  - Dizygotic 3.8%

DIFFERENCES IN T1DM INCIDENCE BETWEEN POPULATIONS

IF ENVIRONMENTAL :

- The concordance for T1DM among siblings should be much higher in high incidence populations, reflecting the level of environmental exposure
- The prevalence of T1DM in parents should change in the same way as the incidence of T1DM in children is changing over time

DIFFERENCES IN T1DM INCIDENCE BETWEEN POPULATIONS

IF GENETIC :

- **The concordance for T1DM among siblings, should be approximately the same in different populations**
- **The prevalence of T1DM in parents should be higher in high incidence populations, reflecting the risk in the background population**

PREVALENCE OF T1DM IN PARENTS AND SIBLINGS OF NEWLY DIAGNOSED DIABETIC CHILDREN IN AUSTRIA (incidence 10/100,000) AND FINLAND (incidence 40/100,000)