

Can Diabetes be Prevented with Vitamin D?

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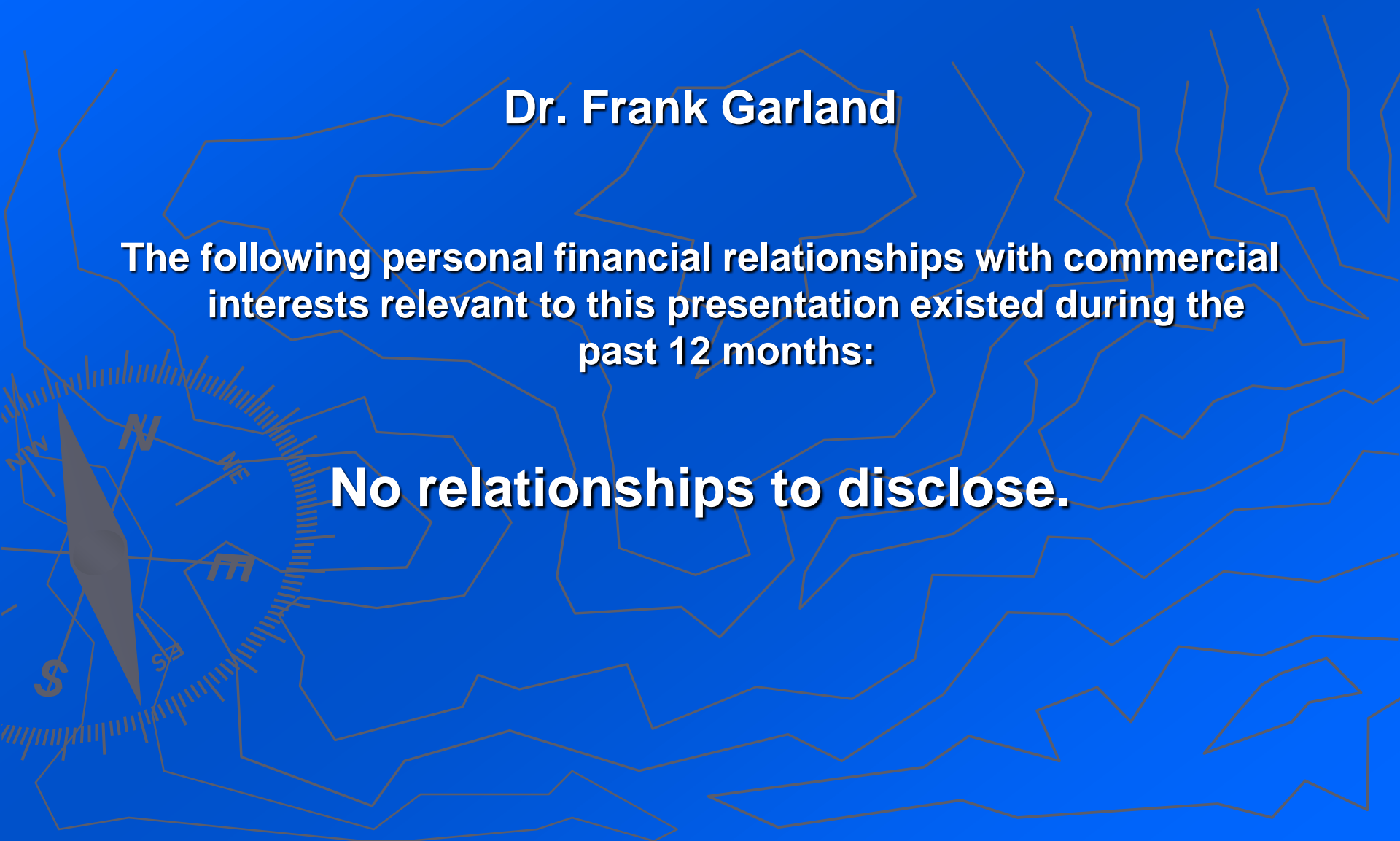
**Naval Health Research Center, San Diego
December 2, 2008**

Presenter Disclosure

Dr. Frank Garland

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose.

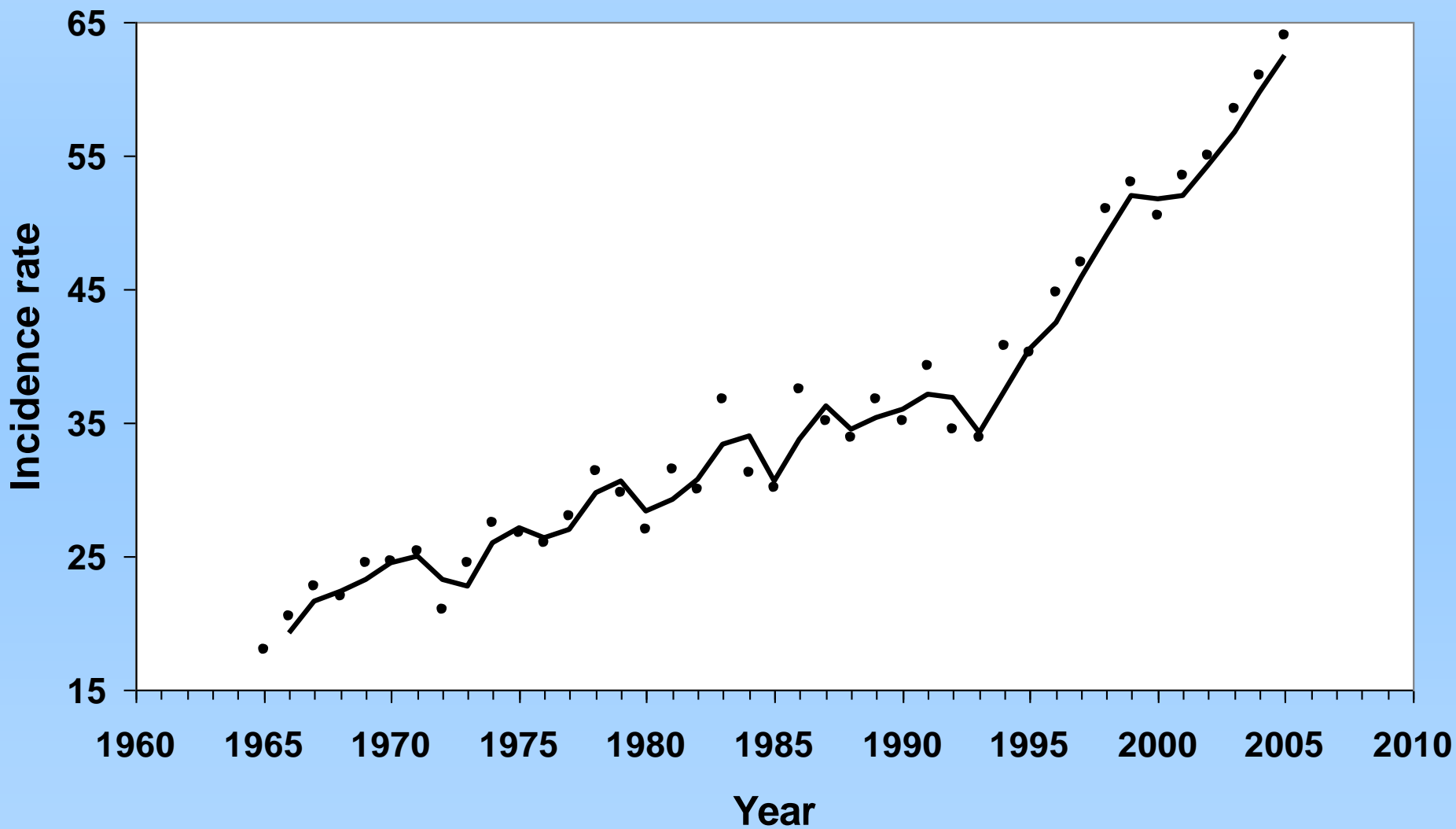


Can Diabetes be Prevented by Vitamin D

Learning Objectives

- 1. Add a disease to the list of ten vitamin D sensitive diseases**
- 2. Quantify potential benefits of solving the vitamin D deficiency**
- 3. Identify and quantify any risk categories for vitamin D treatment**

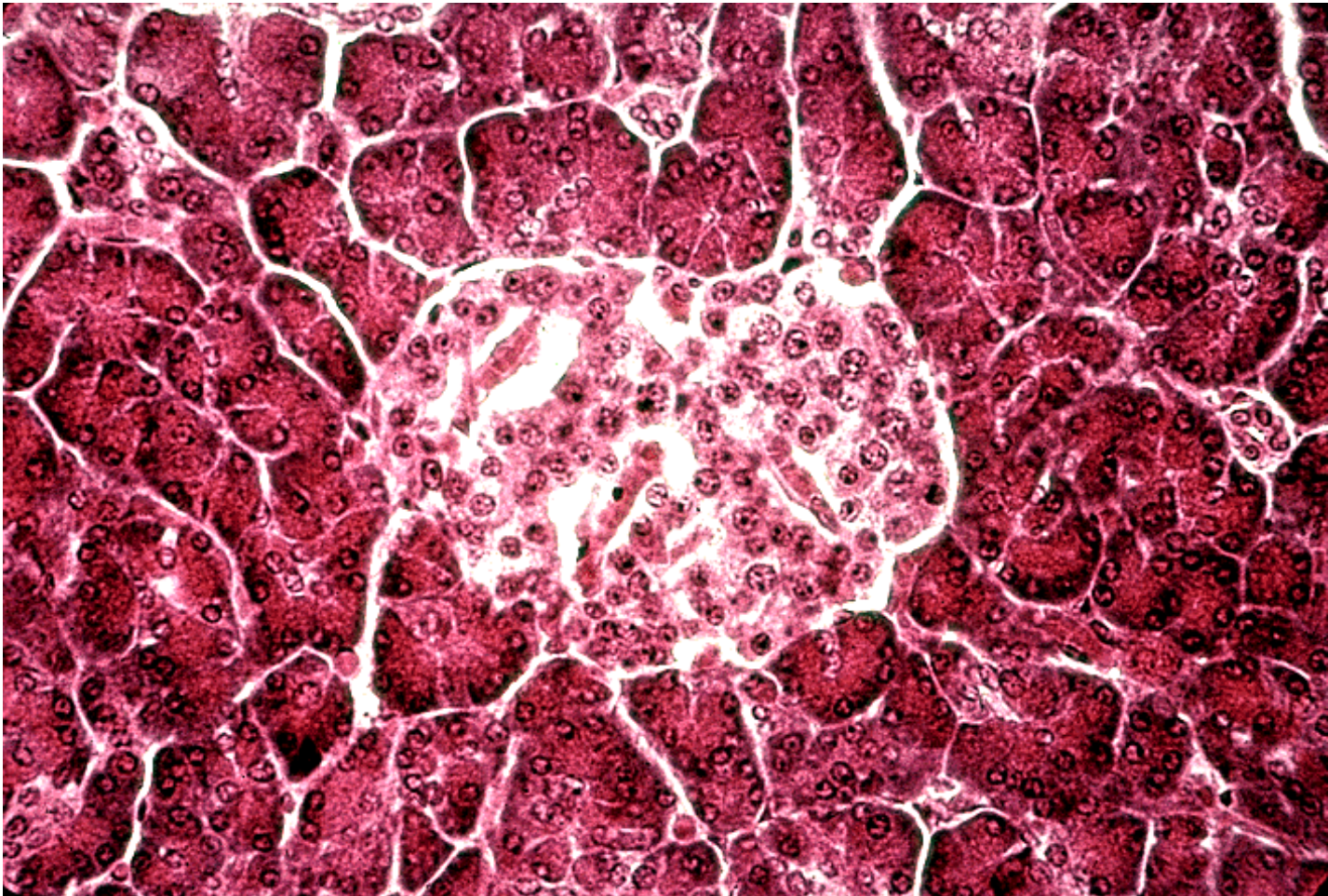
Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, Finland, 1965-2005





The Scene of the Crime

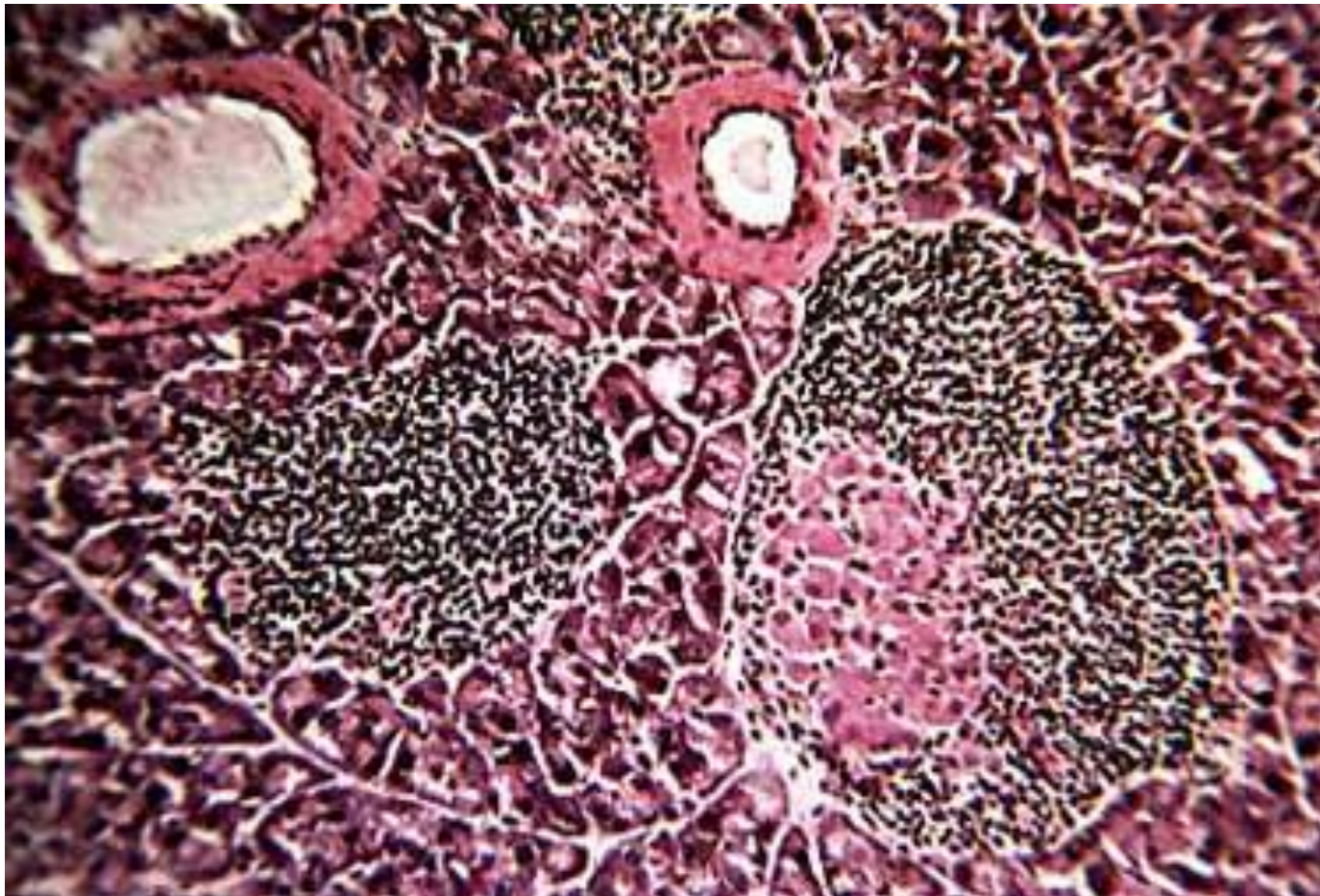
The Islet Cells of the Pancreas





The Scene of the Crime

The Islet Cells of the Pancreas

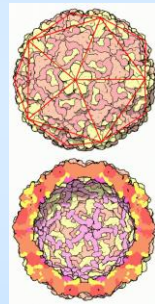




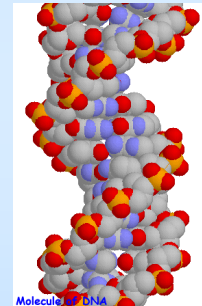
Round up the usual suspects



Environment



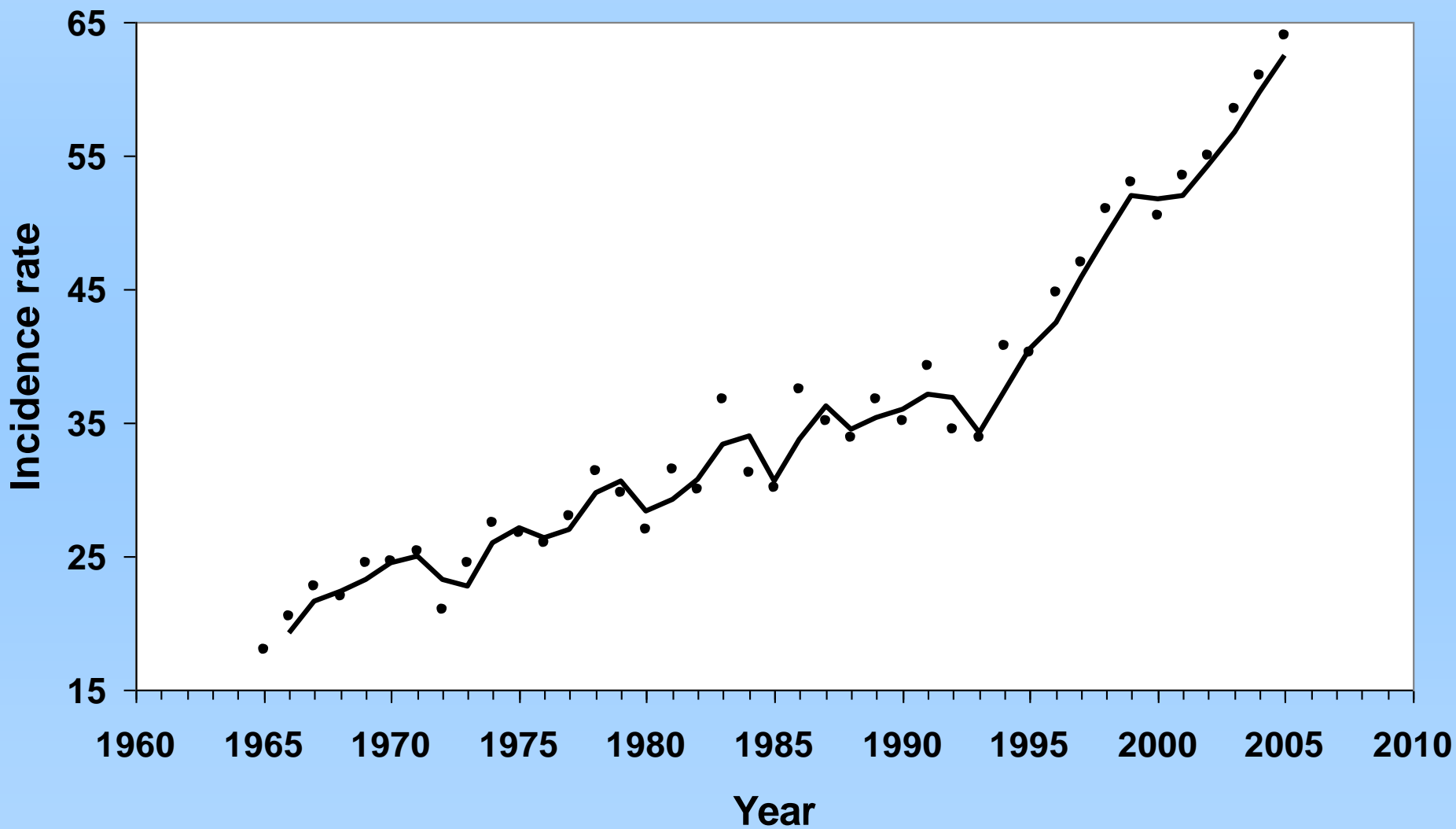
Agent



Host

Disease Causation Triad

Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, Finland, 1965-2005

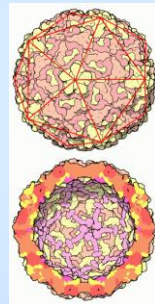




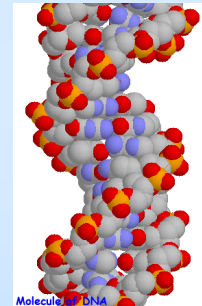
Round up the usual suspects



Environment



Agent



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Disease Causation Triad



Virus theory

Increase in incidence rate of type I diabetes during picornavirus outbreak

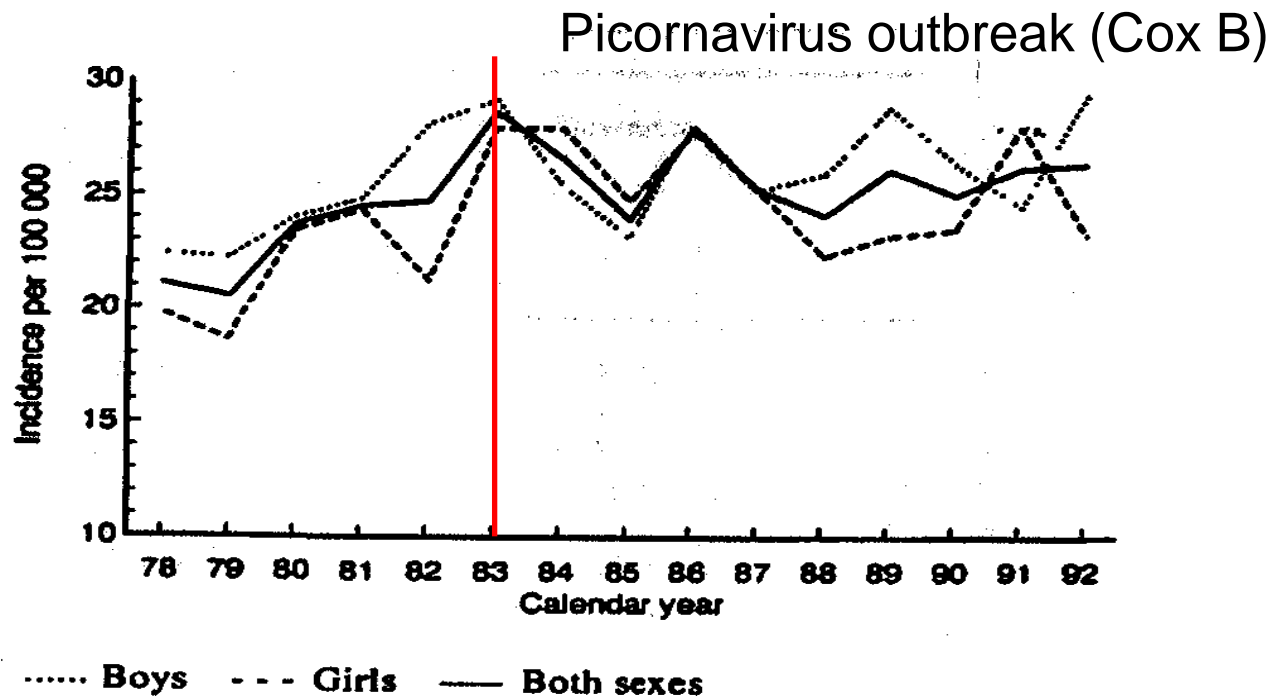


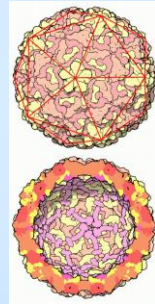
FIGURE 1 Mean annual incidence rate of type 1 (insulin-depend-ent) diabetes mellitus in Swedish children 0–14 years



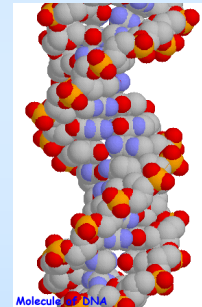
Round up the usual suspects



Environment



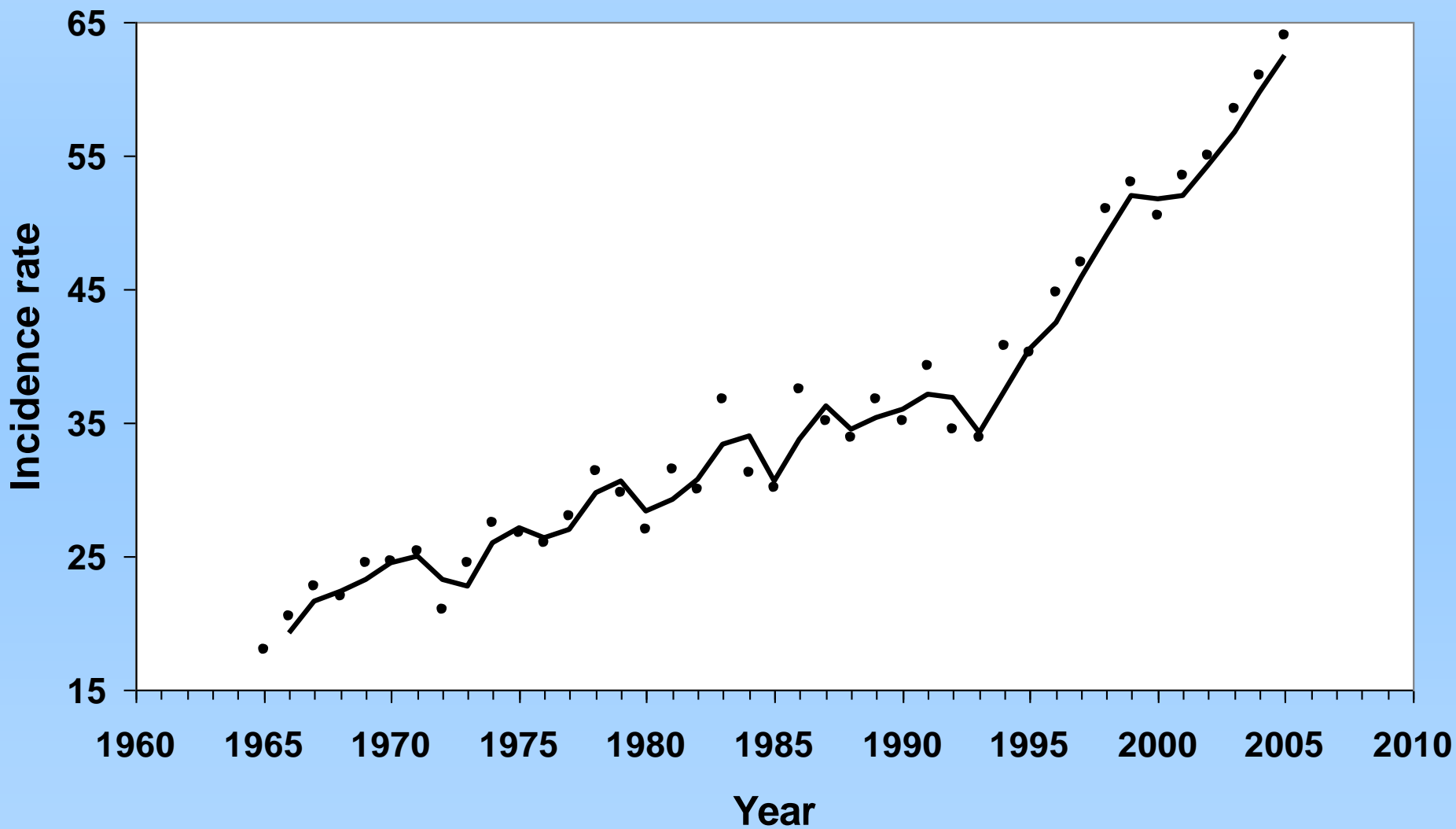
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Disease Causation Triad

Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, Finland, 1965-2005

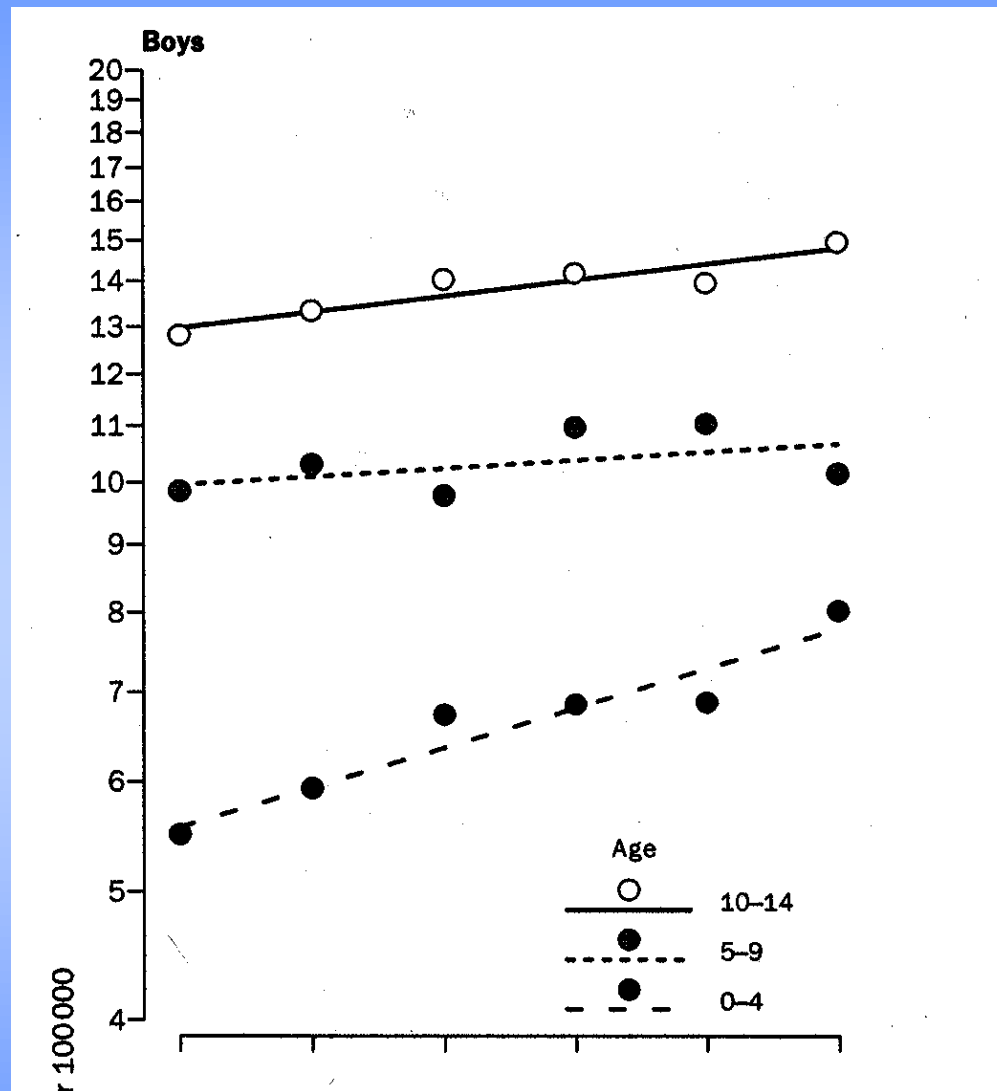




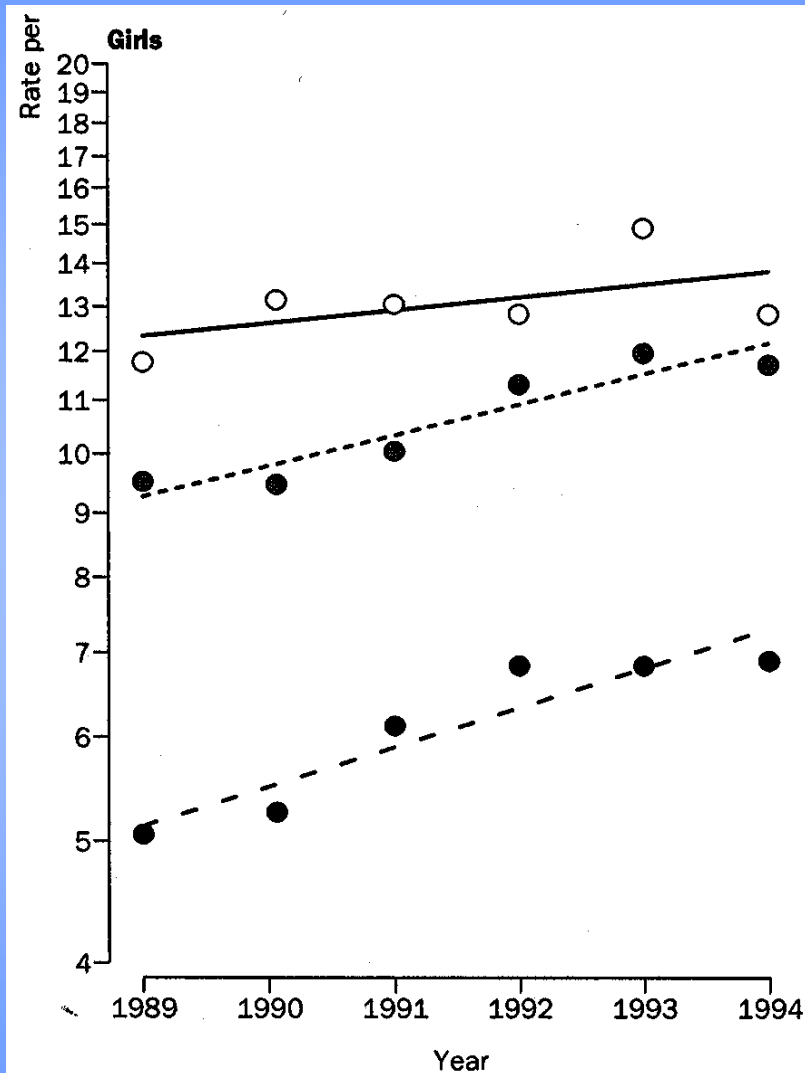
The EURODIAB Study

- **Goal was to study the epidemiology of type 1 diabetes in Europe (43 registries in most countries and Israel)**
- **Started in 1988**
- **Prospective establishment of registries**
- **16,330 cases in children under 15 years of age**
- **Rates of increase per year: 6.2% children 0-4; 3.1% children 4-9; and 2.4% children 10-14 years**
- **Important sub-studies in Norway and Finland**

Trends in Type 1 diabetes, Europe, boys, 1989-1994, Lancet 2000



Trends in Type 1 diabetes, Europe, girls, 1989-1994



Age 10-14

Age 5-9

Age 0-4

Trends in childhood diabetes incidence in Europe during 1989-94 by age group and sex

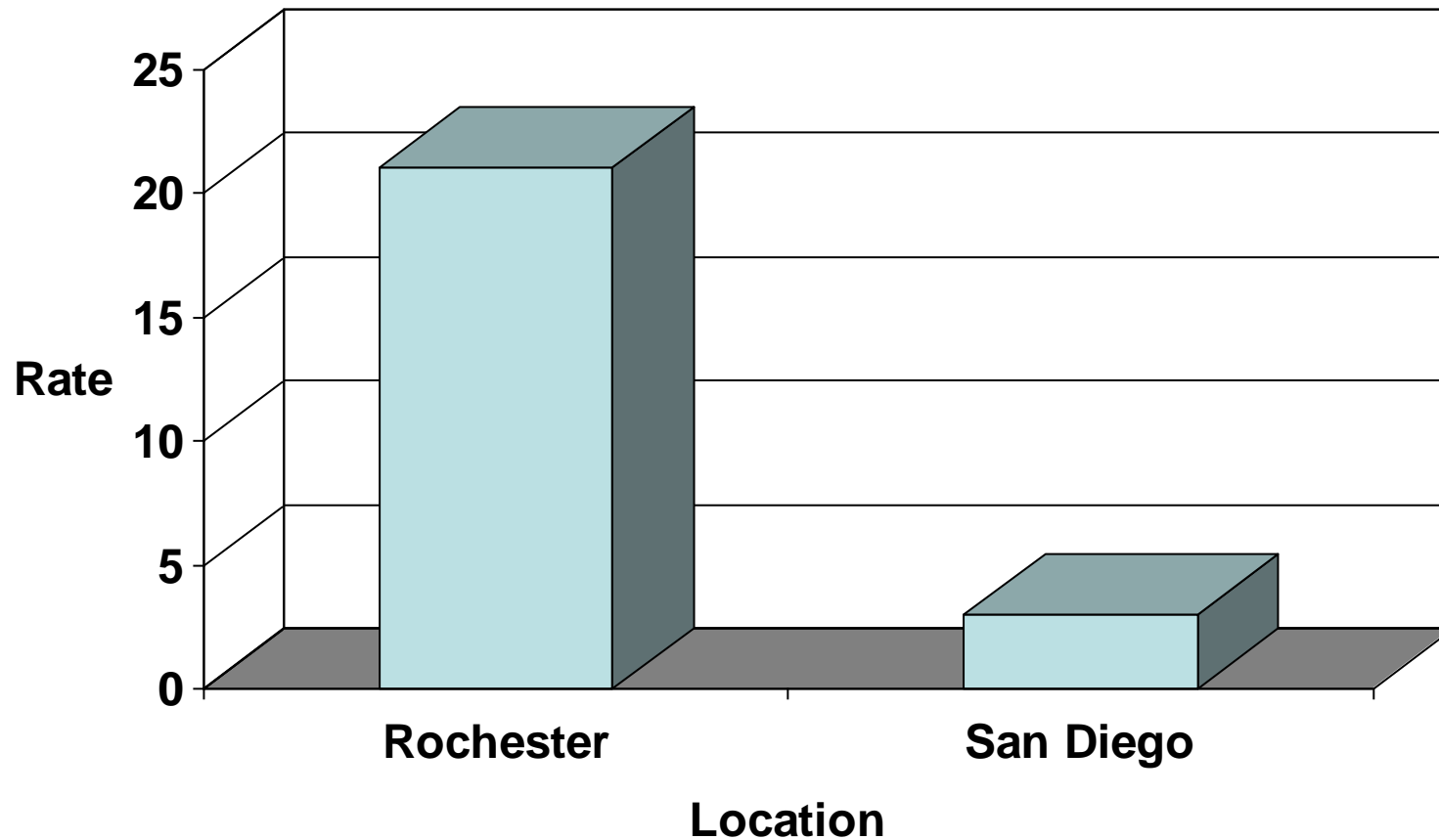
ascertainment. Among the 40 centres validating

**When you should consider that
you may be dealing with a
Vitamin D-Sensitive Disease.**

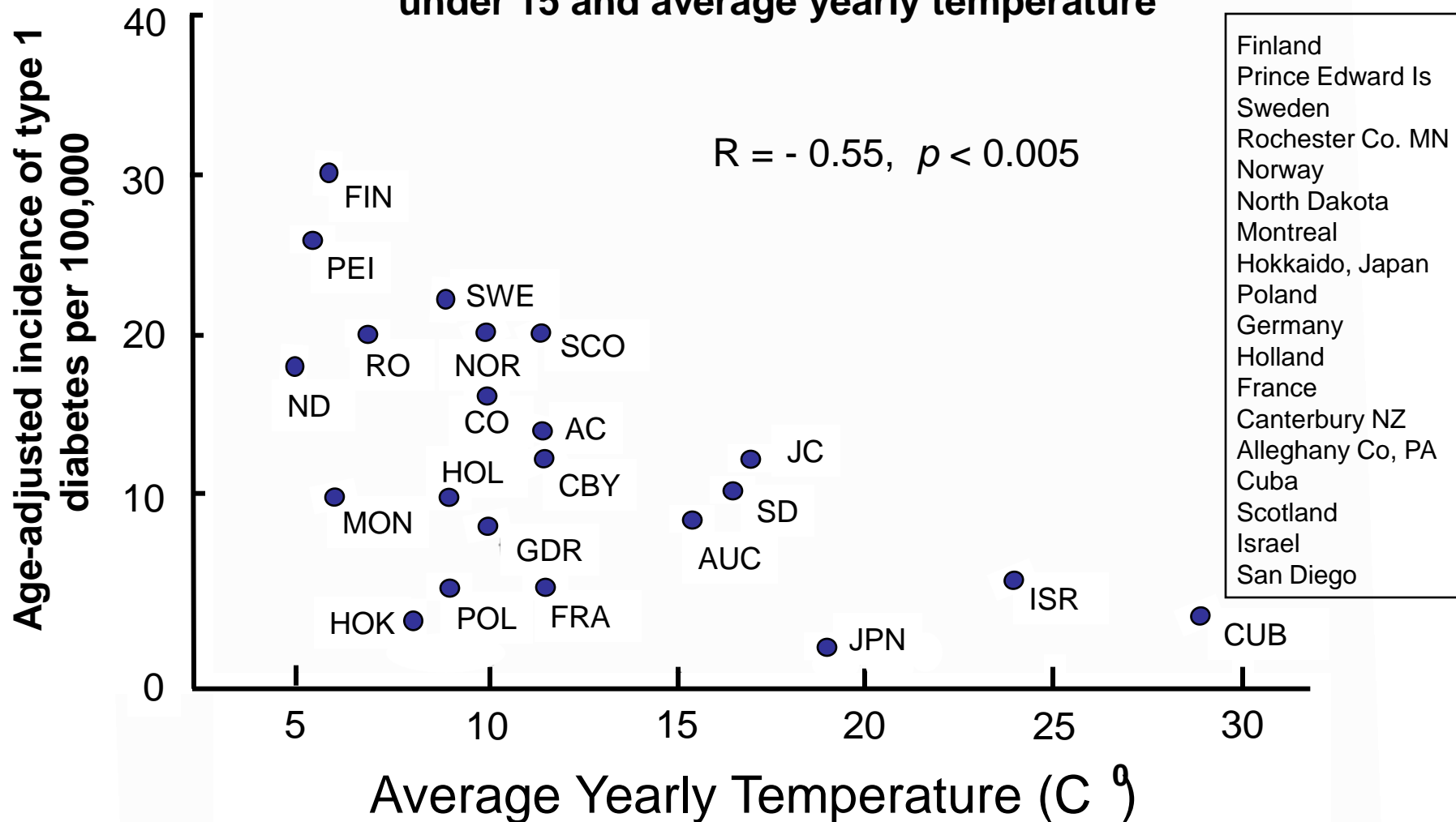
- **Varies by latitude**
- **Varies more by ultraviolet irradiance**
- **Varies by season**
- **Varies by race, BMI, physical activity**



Type I diabetes, San Diego and Rochester MN, annual incidence rates per 100,000 children



Correlation between age-adjusted IDDM incidence in children under 15 and average yearly temperature



EURODIAB. Diabetes. 1988 Aug;37(8):1113-9.

Incidence Rates of Type I Diabetes in 51 Regions

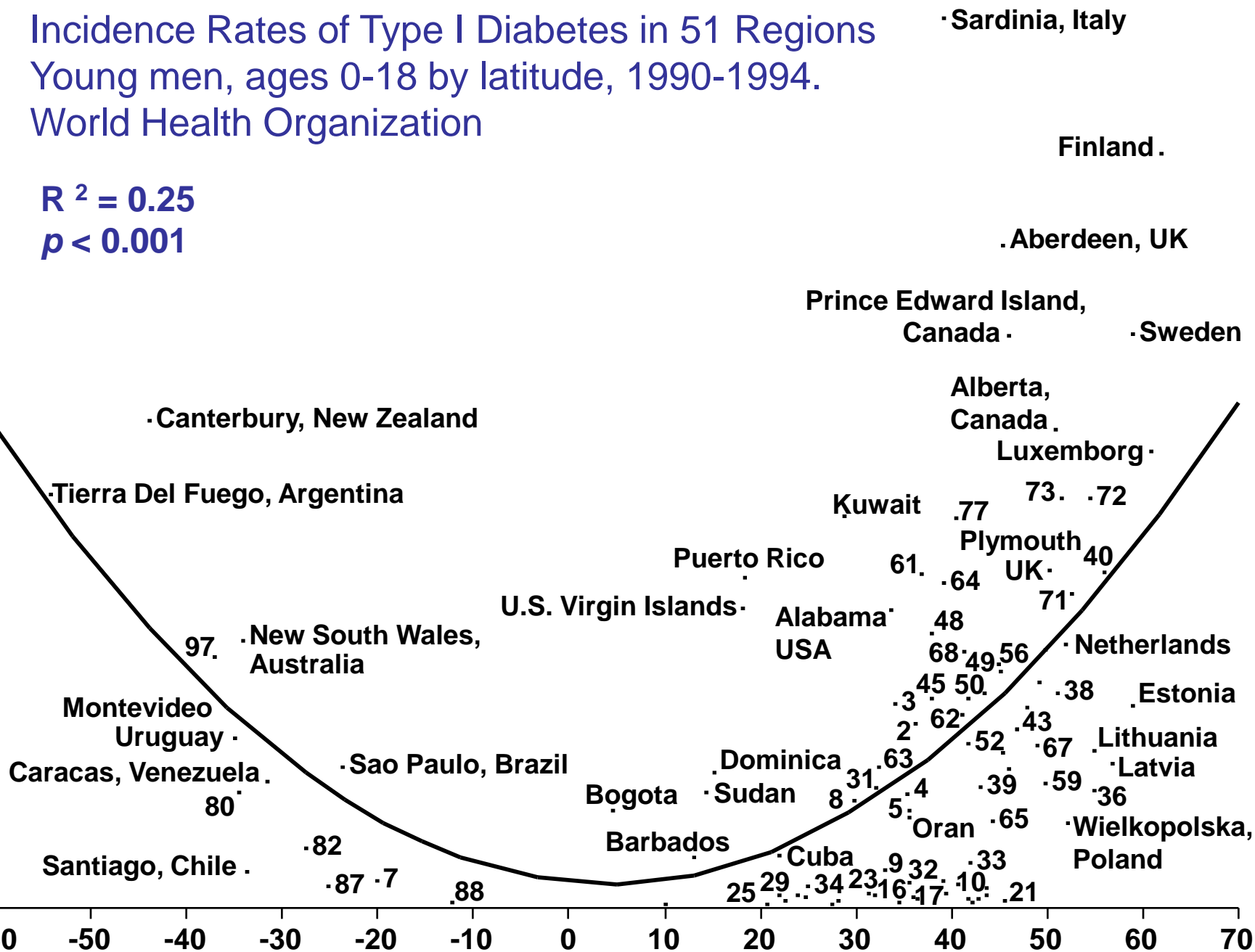
Young men, ages 0-18 by latitude, 1990-1994.
World Health Organization

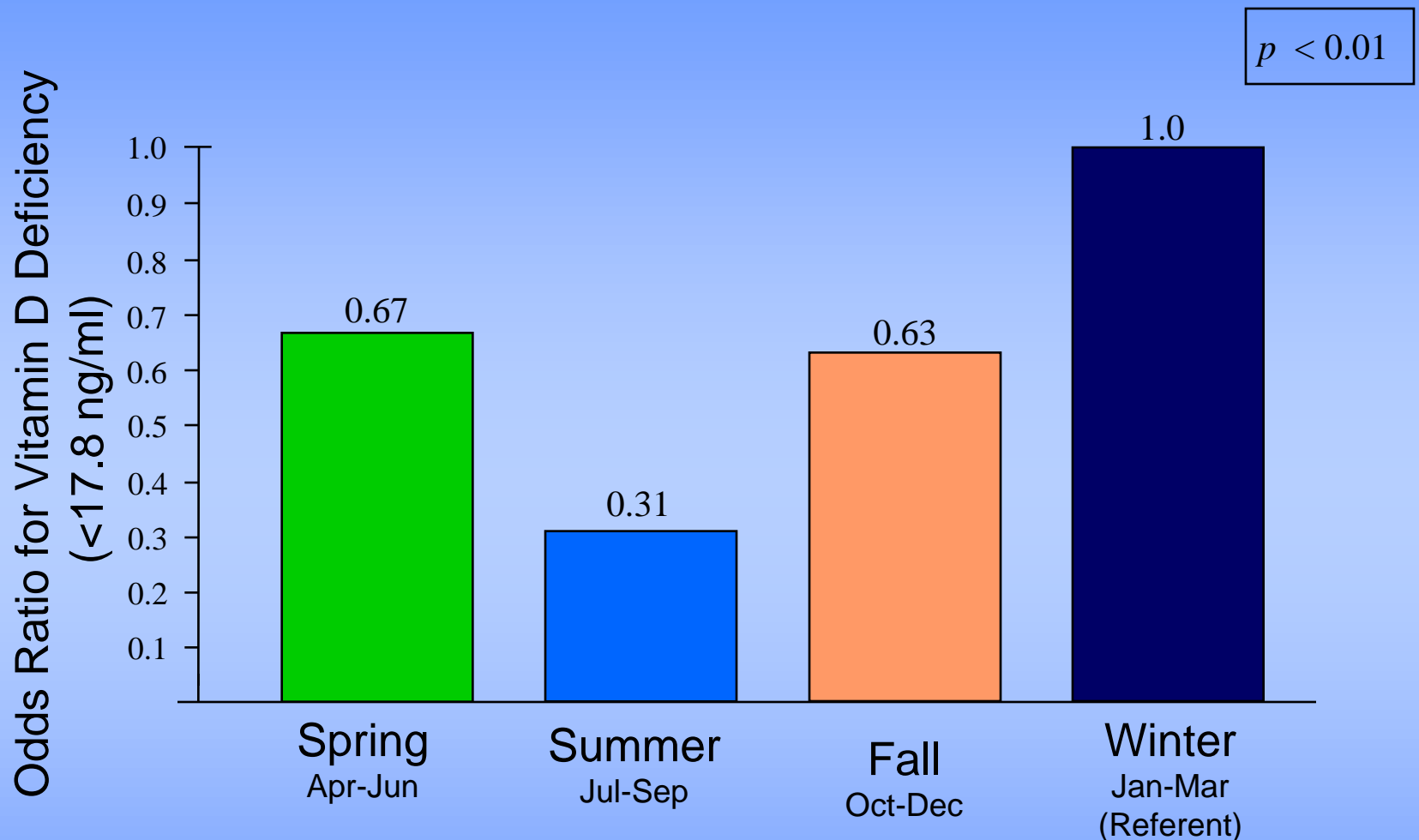
$R^2 = 0.25$

$p < 0.001$

Diabetes incidence rate per 100,000

Latitude

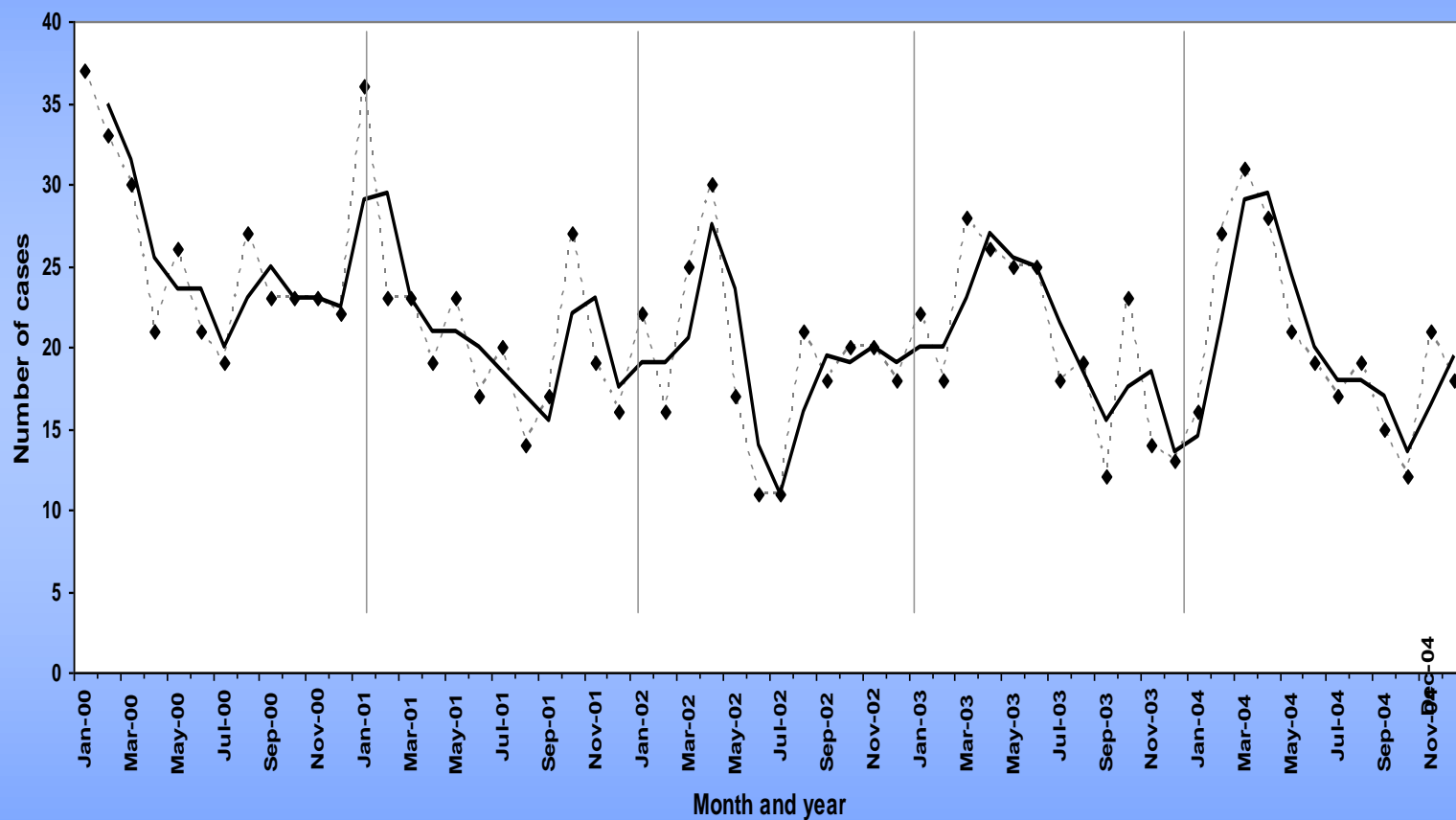




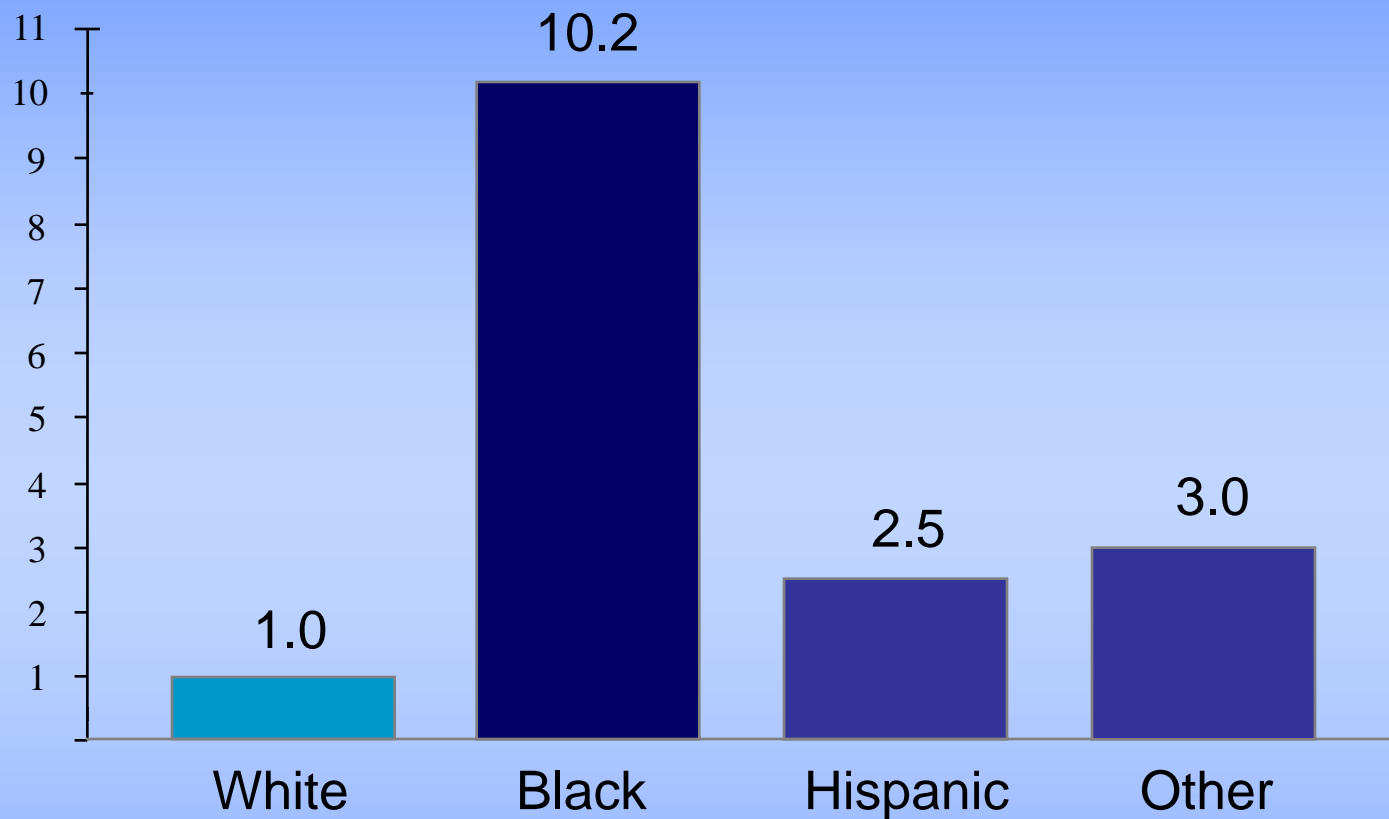
Odds Ratios of 25-hydroxyvitamin D deficiency below 17.8 ng/ml (lowest quartile) by Season of blood draw, National Health and Nutrition Examination Survey III, N=13,331 Participants

Diabetes in the DoD, Seasonality

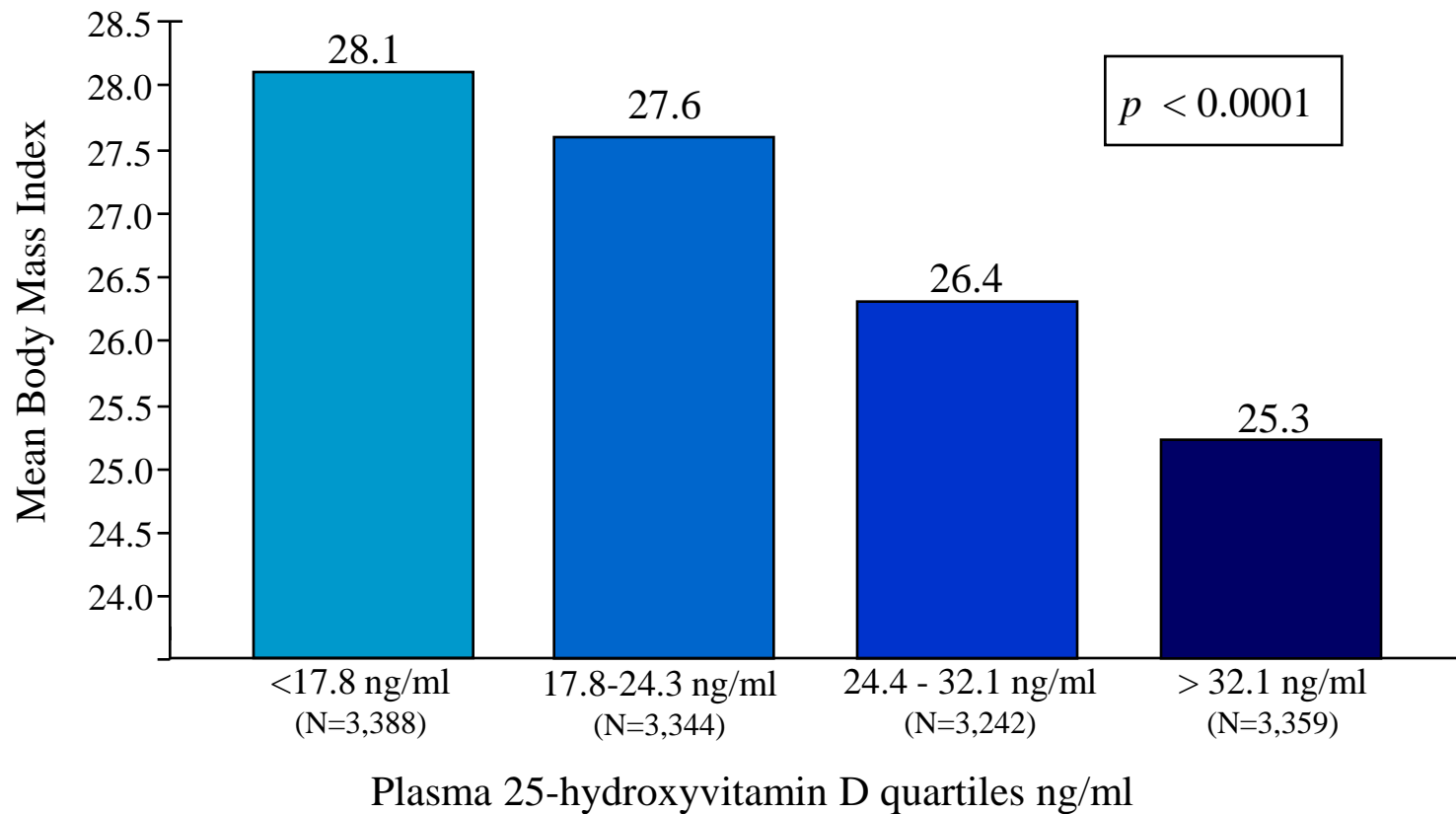
Figure 2. Number of incident cases of Type 1 diabetes by month and year, active duty service members, Department of Defense, 2000-2004



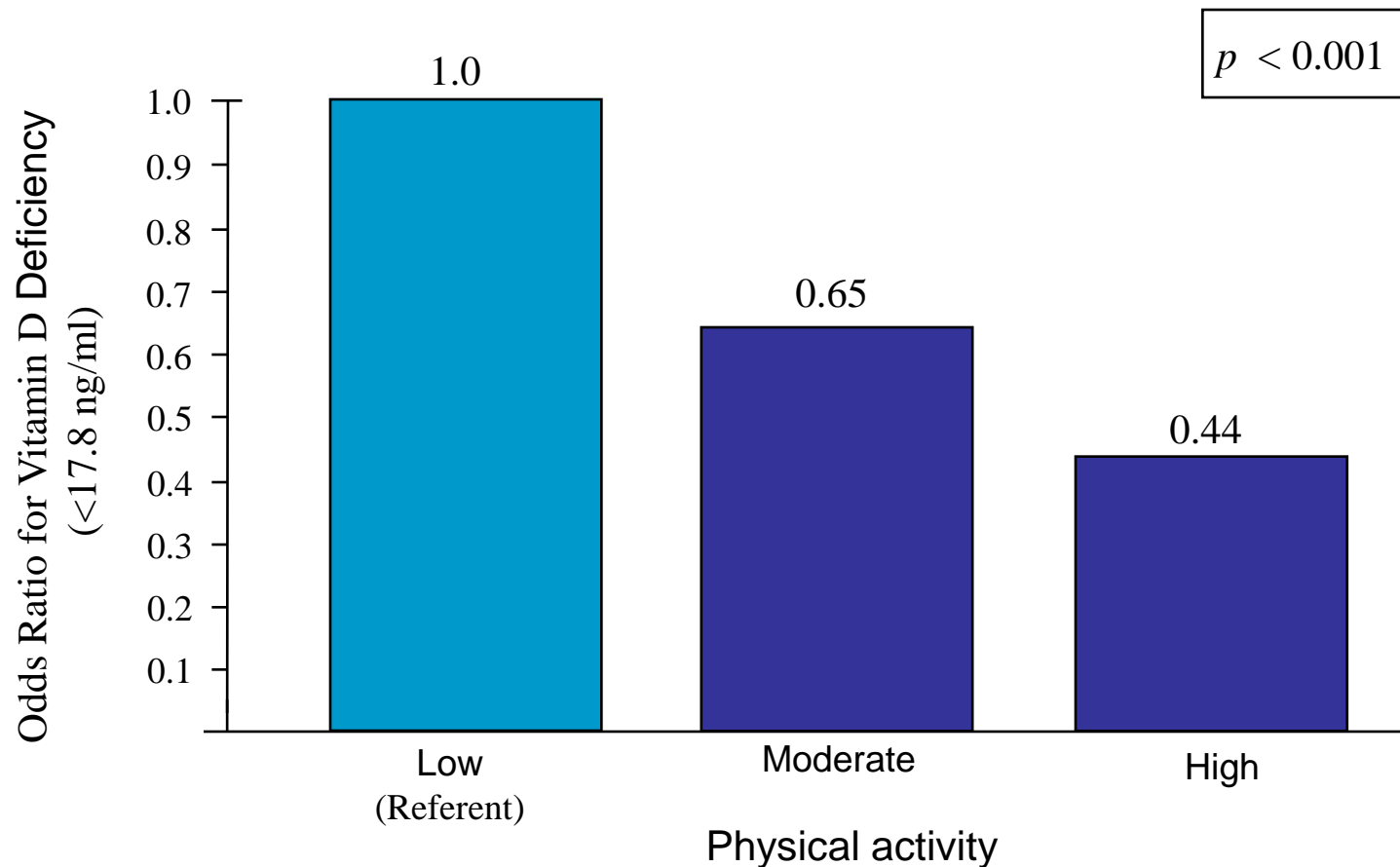
Odds Ratio for Vitamin D Deficiency
(<17.8 ng/ml)



Odds Ratios of 25-hydroxyvitamin D deficiency below 17.8 ng/ml
(lowest quartile) by Race, NHANES III, N=13,331



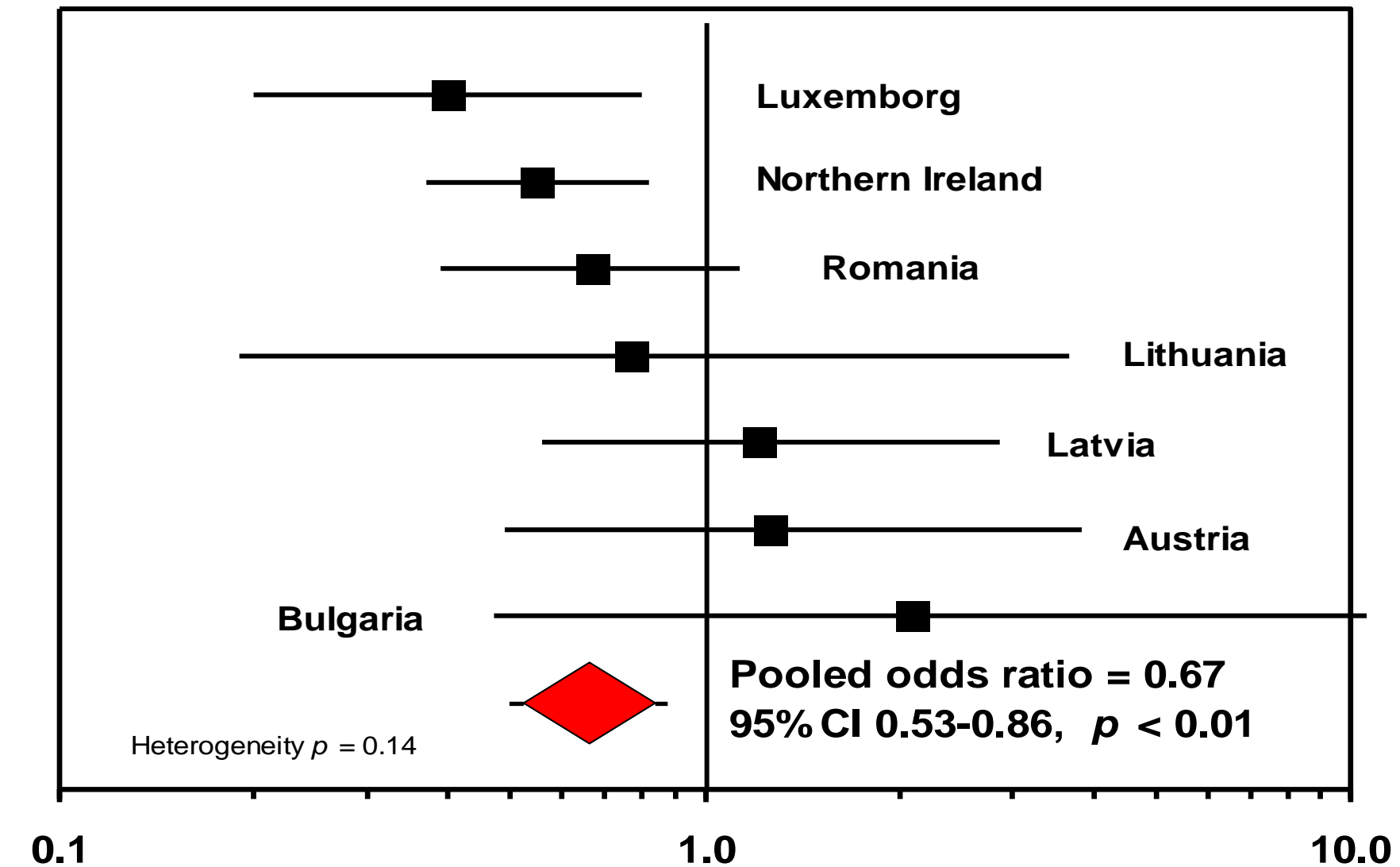
Mean Body Mass Index by Plasma 25-hydroxyvitamin D Concentration Quartiles,
National Health and Nutrition Examination Survey III, N=13,331 Participants



Odds Ratios of 25-hydroxyvitamin D deficiency below 17.8 ng/ml (lowest quartile) by Physical Activity, National Health and Nutrition Examination Survey III, N=13,331 Participants



Person



Odds ratio and 95% confidence limits for developing diabetes before the age of 15 when exposed to vitamin D supplements in early infancy relative to children who were not

Graphic by S. B. Mohr, MPH

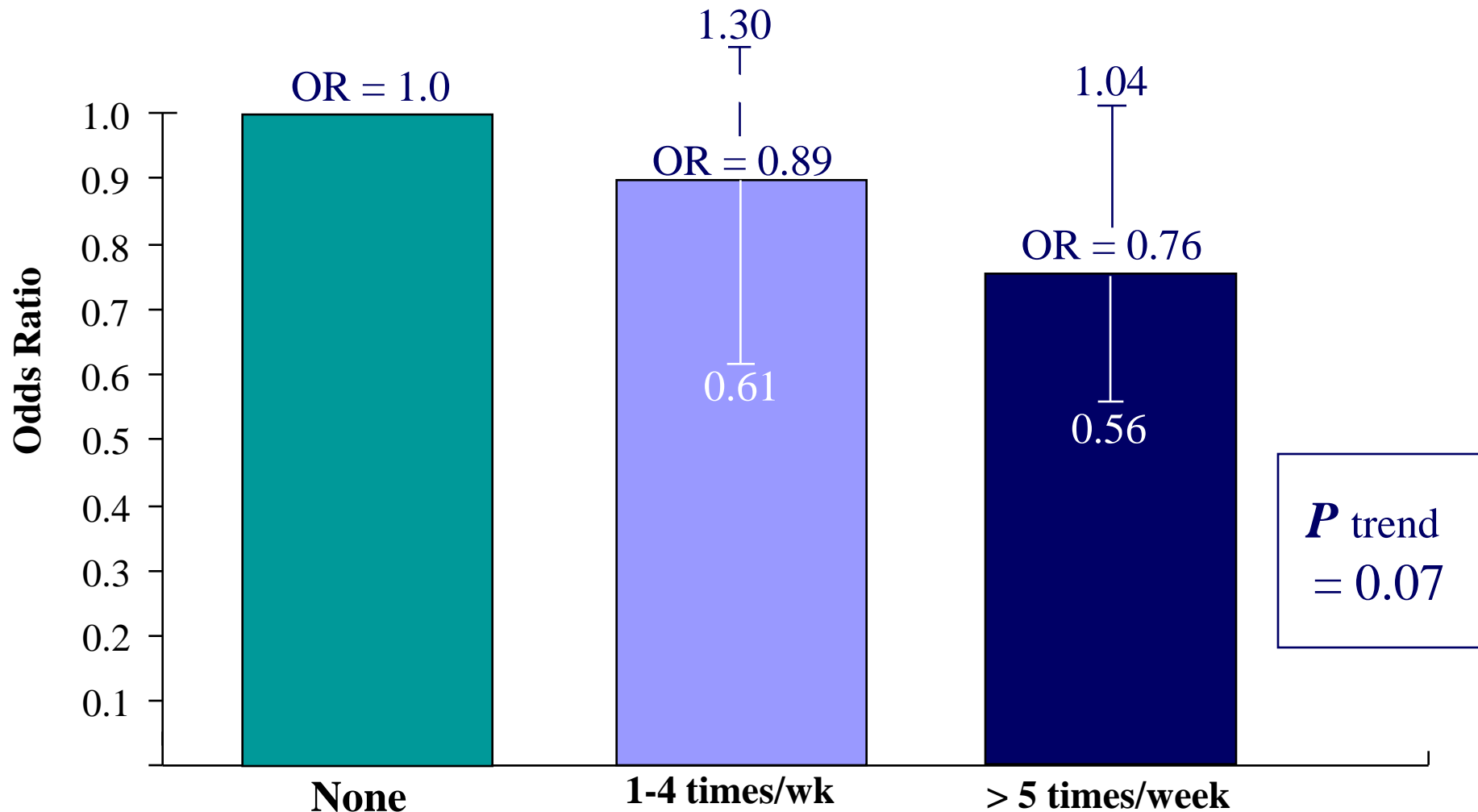


Table 2 Clinical characteristics and plasma 25OHD at diagnosis in young adults with type 1 diabetes vs control subjects (mean±SEM)

| Characteristic | Patients (n=459) | Control subjects (n=208) | Test of difference between patients and controls (<i>p</i> value) |
|----------------|-----------------------|-----------------------------|--|
| Males/females | 1.6 | 1.1 | 0.016 |
| Age (years) | 24.4±0.3 | 25.6±0.5 | 0.027 |
| 25OHD (nmol/l) | | | |
| All | 82.5±1.3 | 96.7±2.0 | <0.0001 |
| Males | 77.9±1.4 ^a | 93.9±2.7 ^b | <0.0001 |
| Females | 90.1±2.4 | 99.7±2.9 | 0.014 |

Test of difference by sex: ^a*p*<0.0001; ^b*p*=0.15

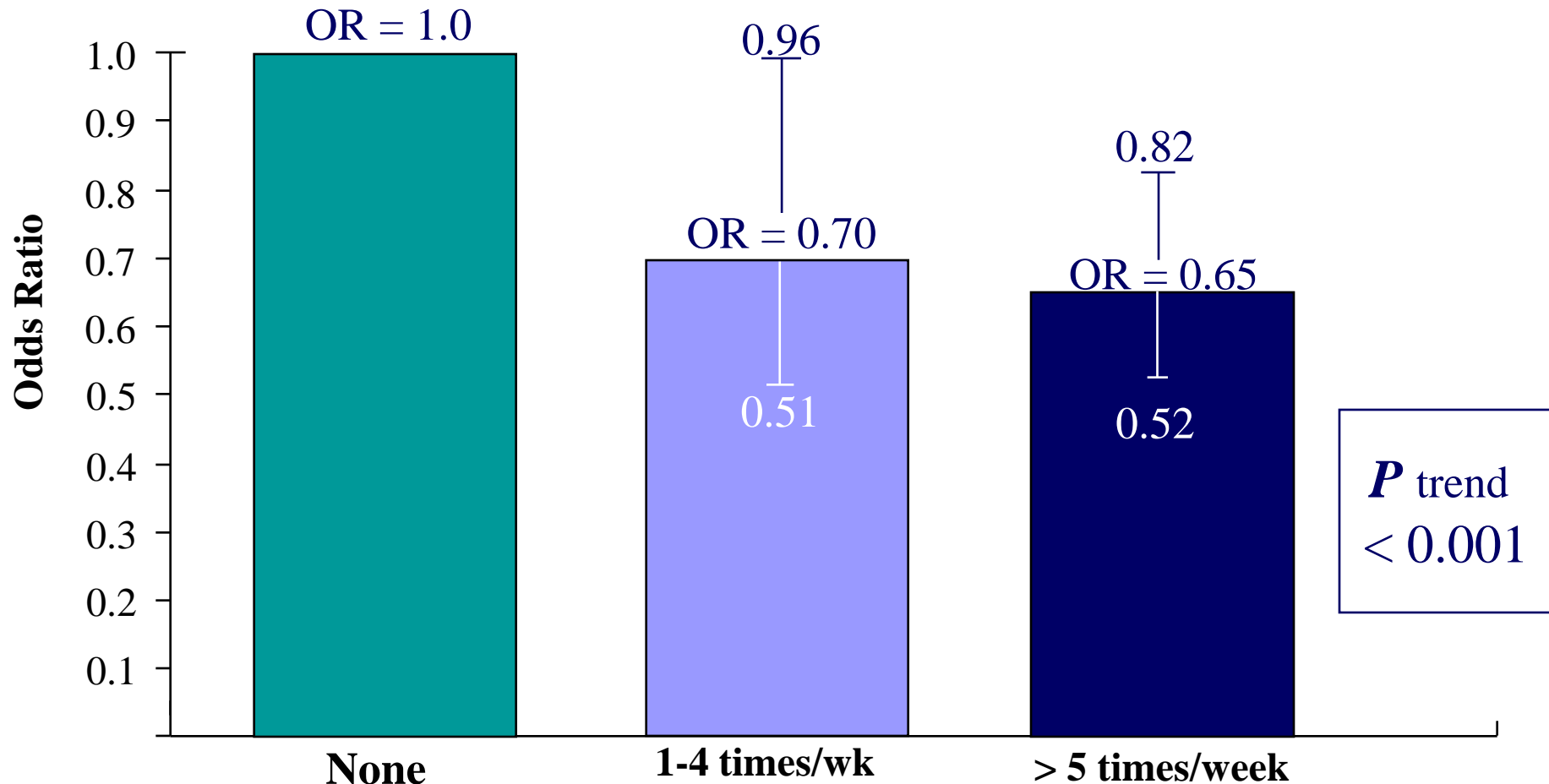
Mother's Use of Cod Liver Oil during Pregnancy and Type I Diabetes in Children in Norway



Odds Ratio and 95% confidence intervals for diabetes by mothers use of cod liver oil, Norway, N=545 cases and 1,668 controls, 1997-2000

Source: Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr. 2003;78:1128-34.

Infants' Supplementation with Cod Liver Oil during First Year and Type I Diabetes in Children in Norway



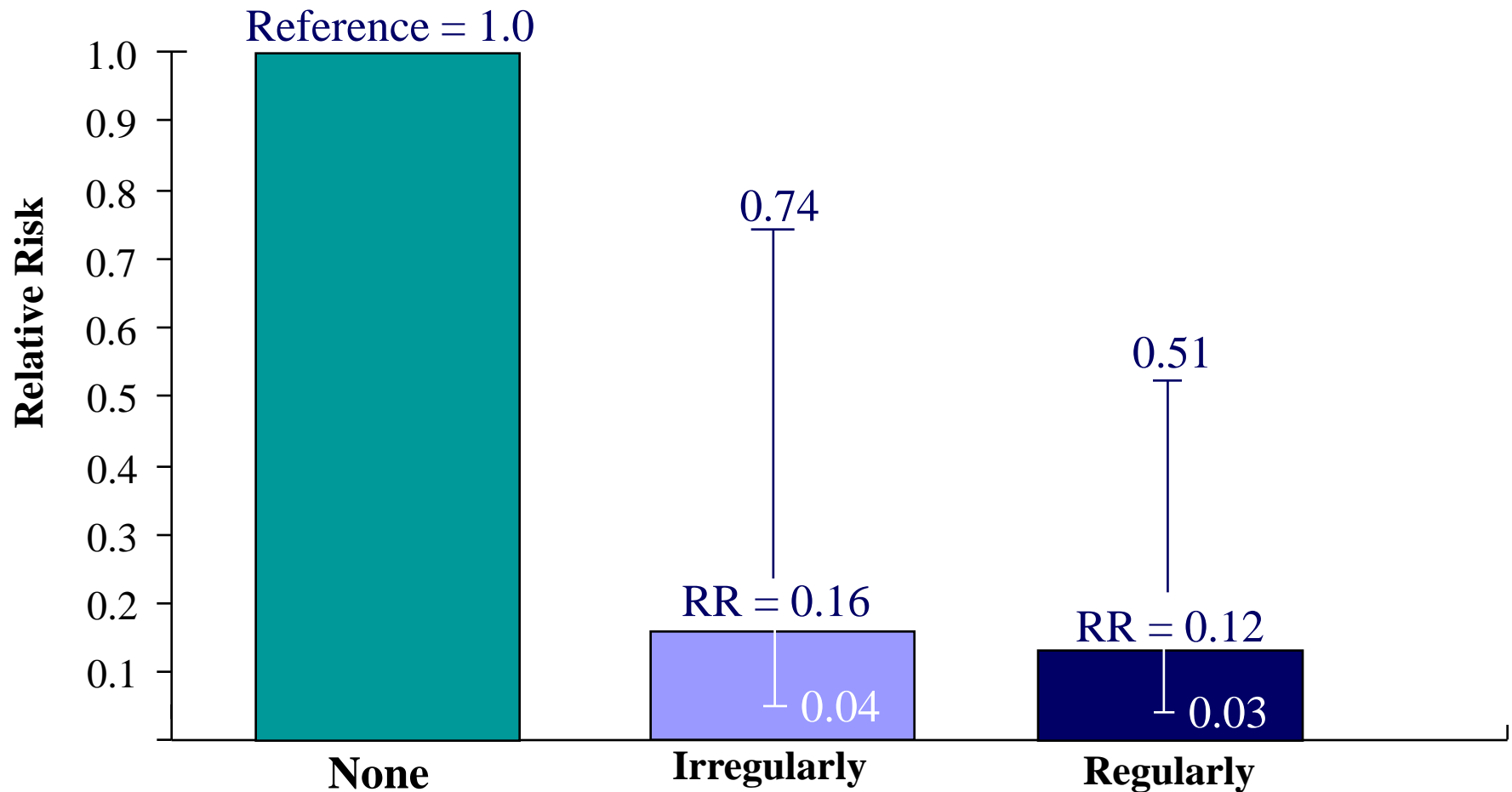
Odds Ratio and 95% confidence intervals for diabetes by supplementation with cod liver oil, Norway, N=545 cases and 1,668 controls, 1997-2000

Source: Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr. 2003;78:1128-34.

Finland study

- Hypponen and colleagues
- Intake of vitamin D and risk of type 1 diabetes: a birth cohort Study (Lancet 2001)
- 12,055 pregnant women who were to give birth in 1966 were followed for outcome until 1997.

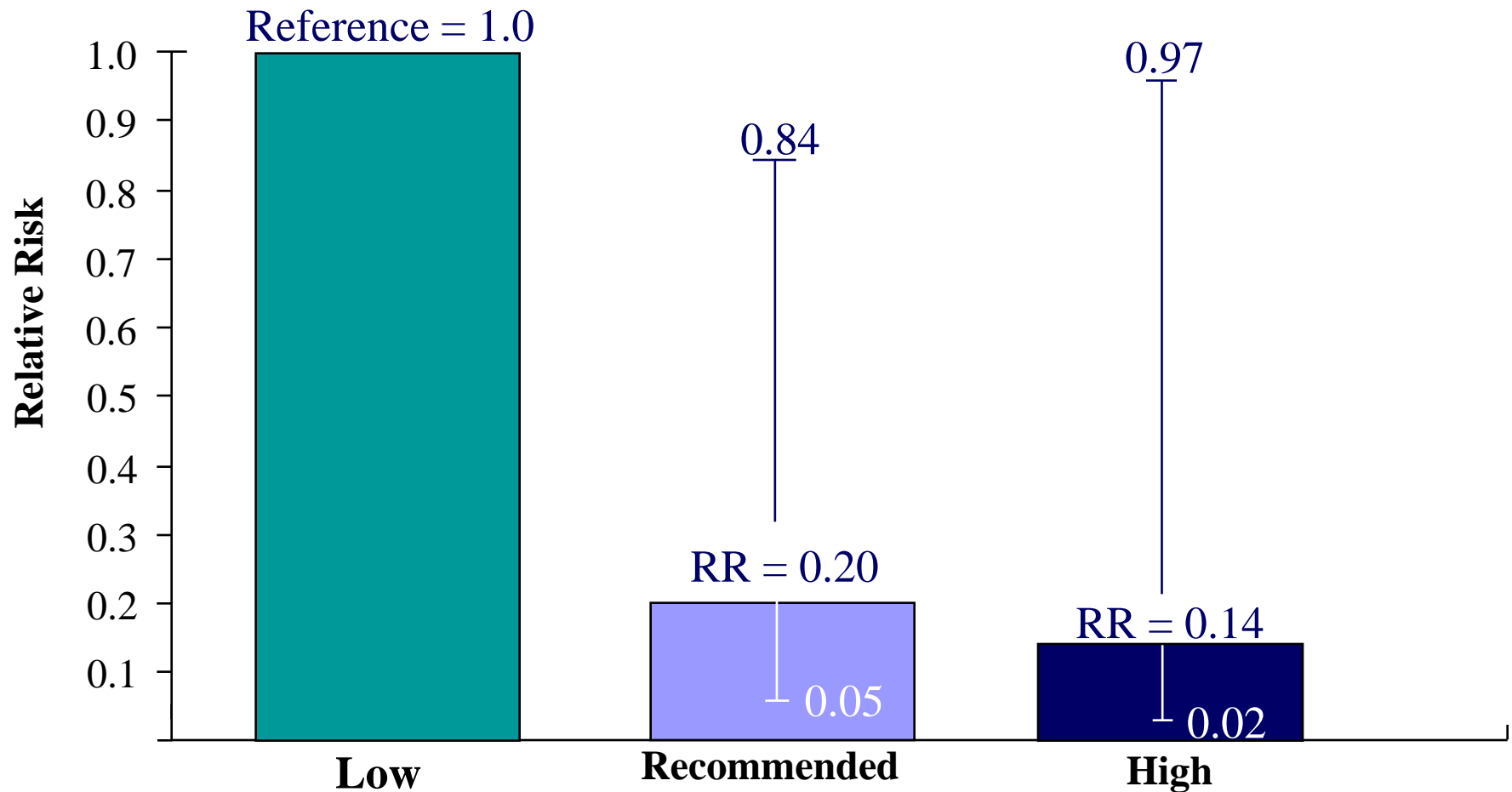
Infants' Supplementation with Vitamin D and Incidence of Type I Diabetes in Children in Northern Finland



Relative Risk* and 95% confidence intervals for diabetes by vitamin D supplementation, Birth Cohort study, N=12,055 pregnant women

*adjusted for gender, gestational age, birth weight, growth rate; maternal parity, age, education, ses
Source: Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: birth-cohort study. Lancet. 2001;358:1500-3.

Infants' Vitamin D Supplementation Dose and Incidence of Type I Diabetes in Children in Northern Finland

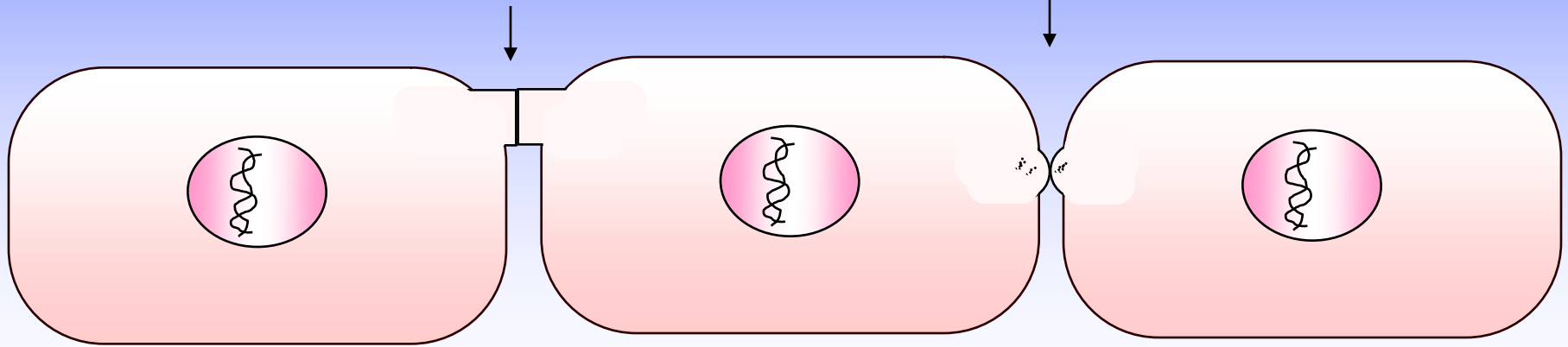


Relative Risk and 95% confidence intervals for diabetes by vitamin D supplementation dose, Birth Cohort study, N=12,055 pregnant women

Proposed Mechanism

**E-cadherin, calcium- and pH-dependent,
labile, depends on vit D and calcium**

**Requires contact or very
close proximity**

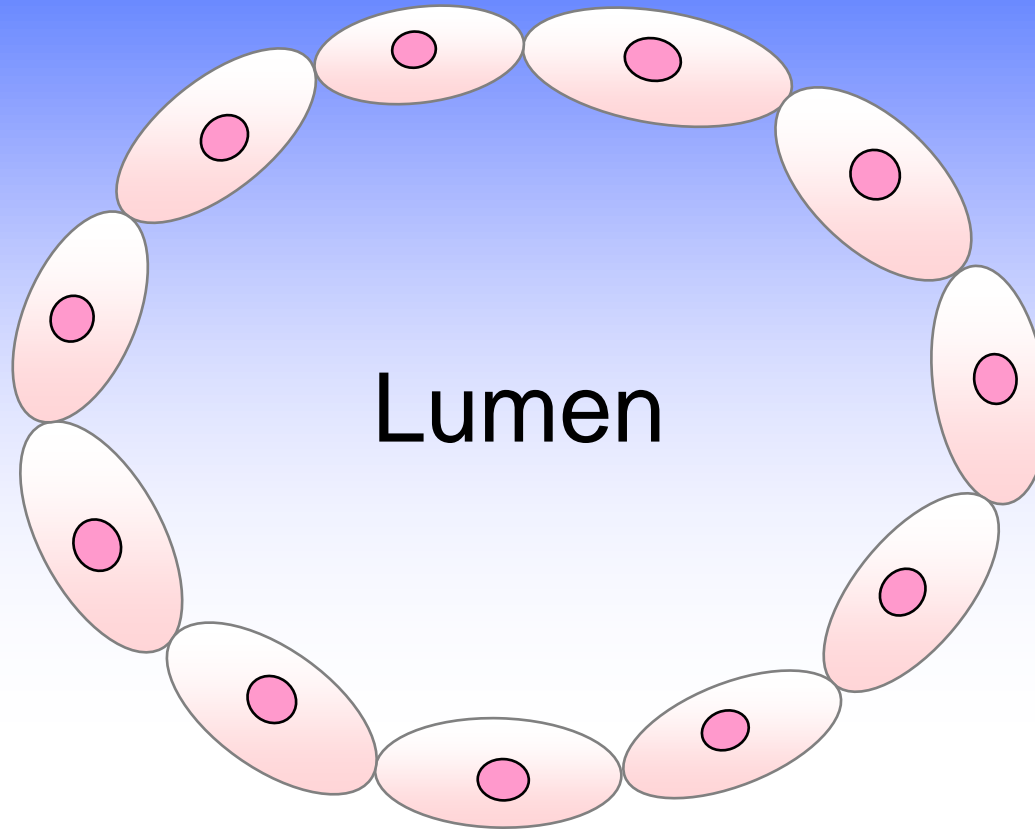


**Tight
junction**

Desmosome

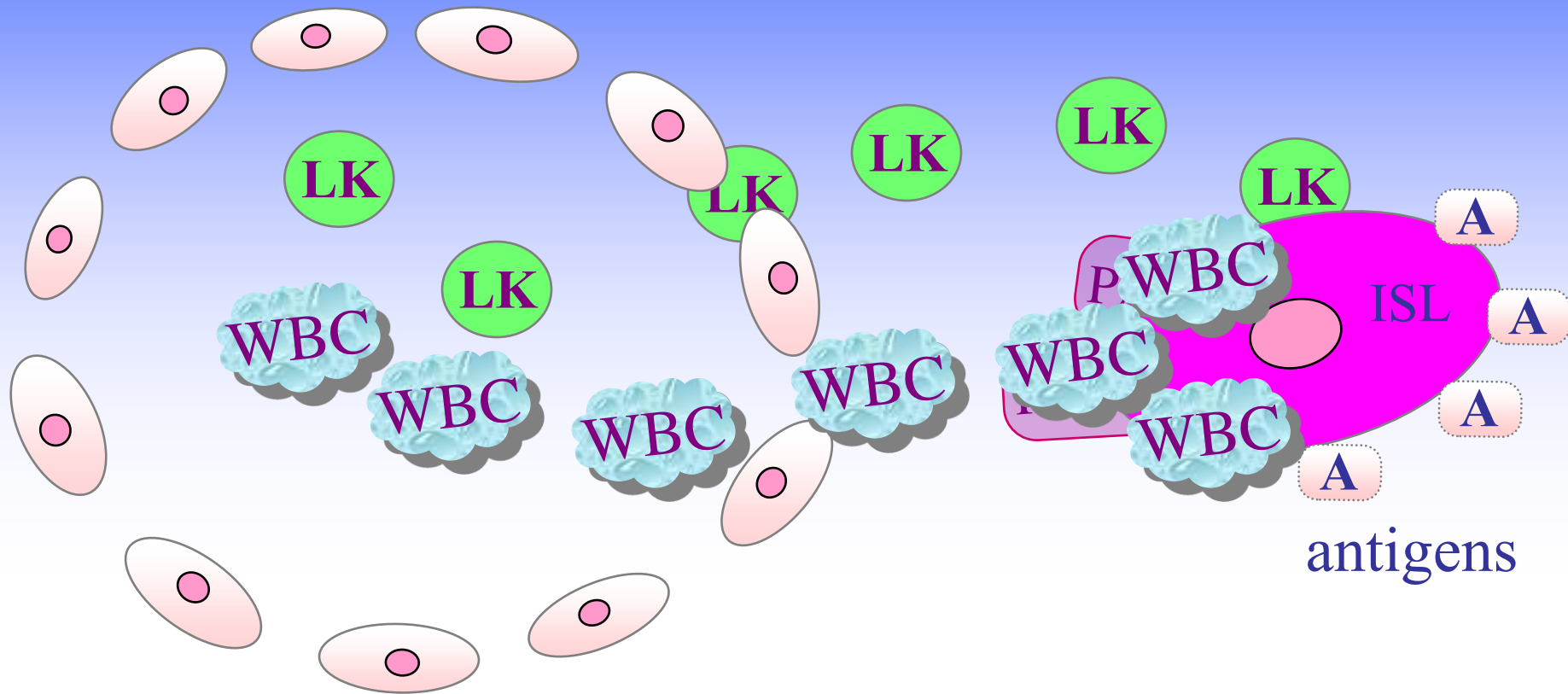
Types of Intercellular Junctions I

Capillary Endothelium



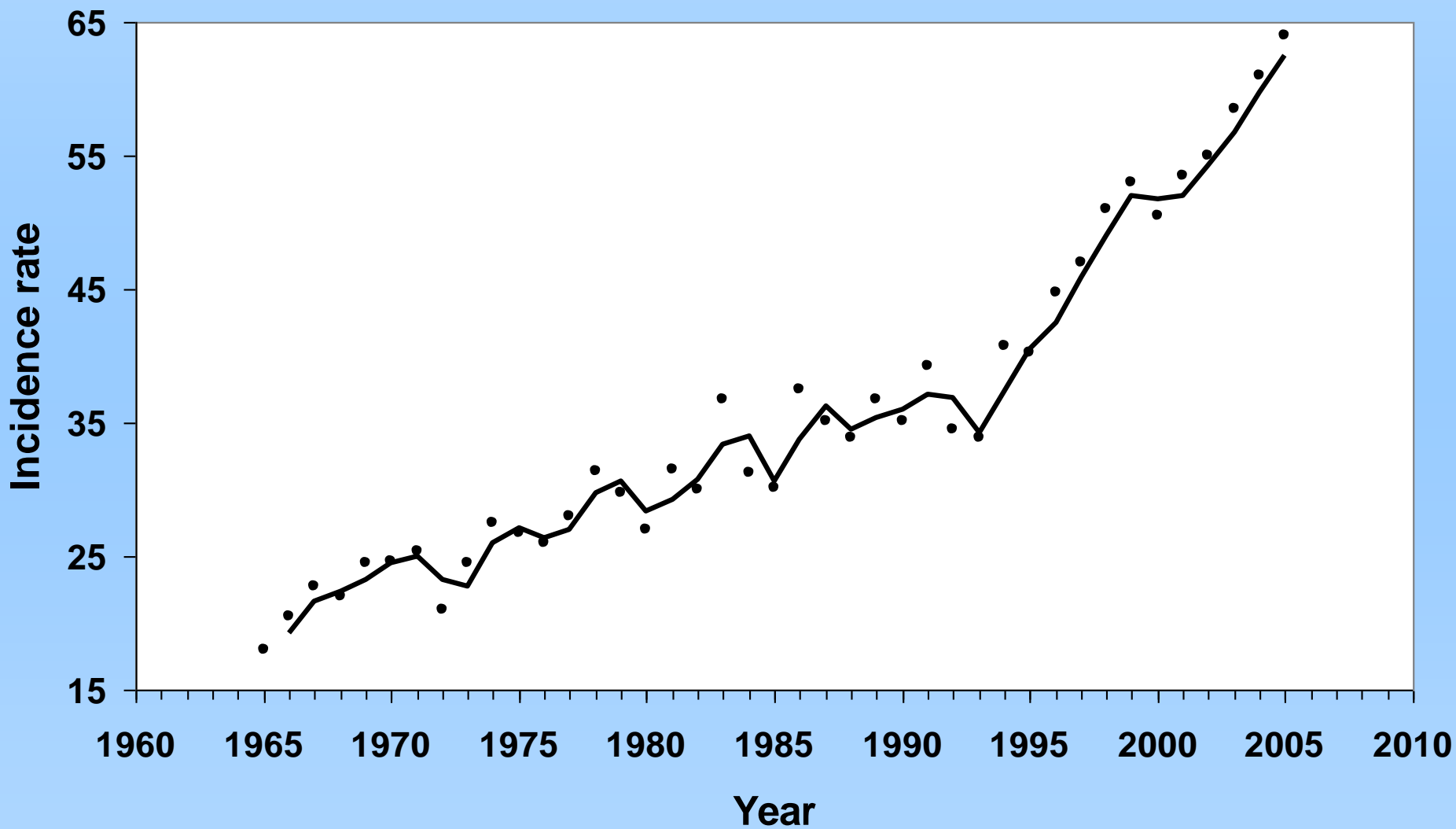
Normal situation with all types of junctions intact

Capillary permeability

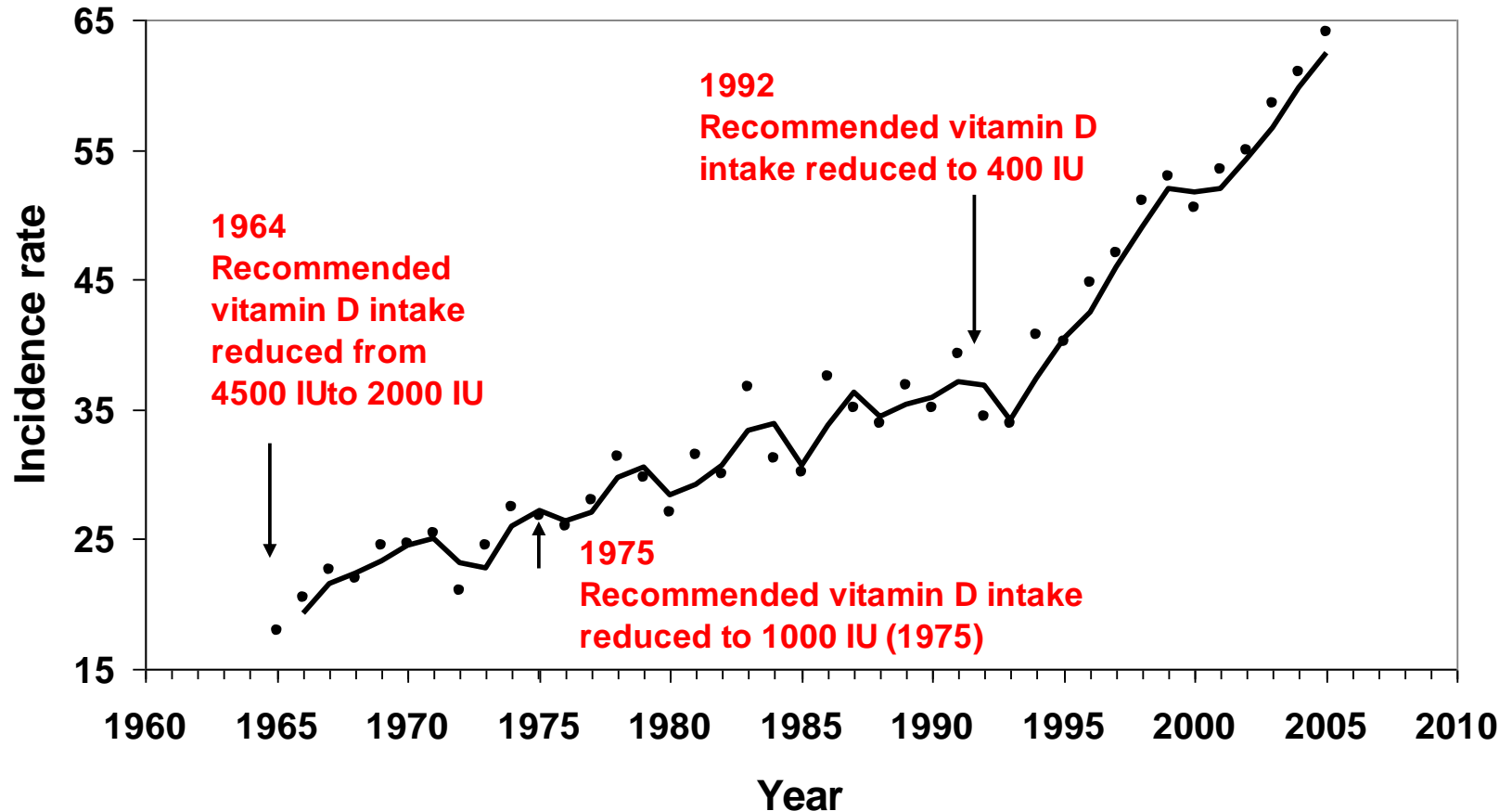


Breakdown of junctions and breakdown of barrier function
due to inadequate vitamin D
immune system attacks Islet Cells

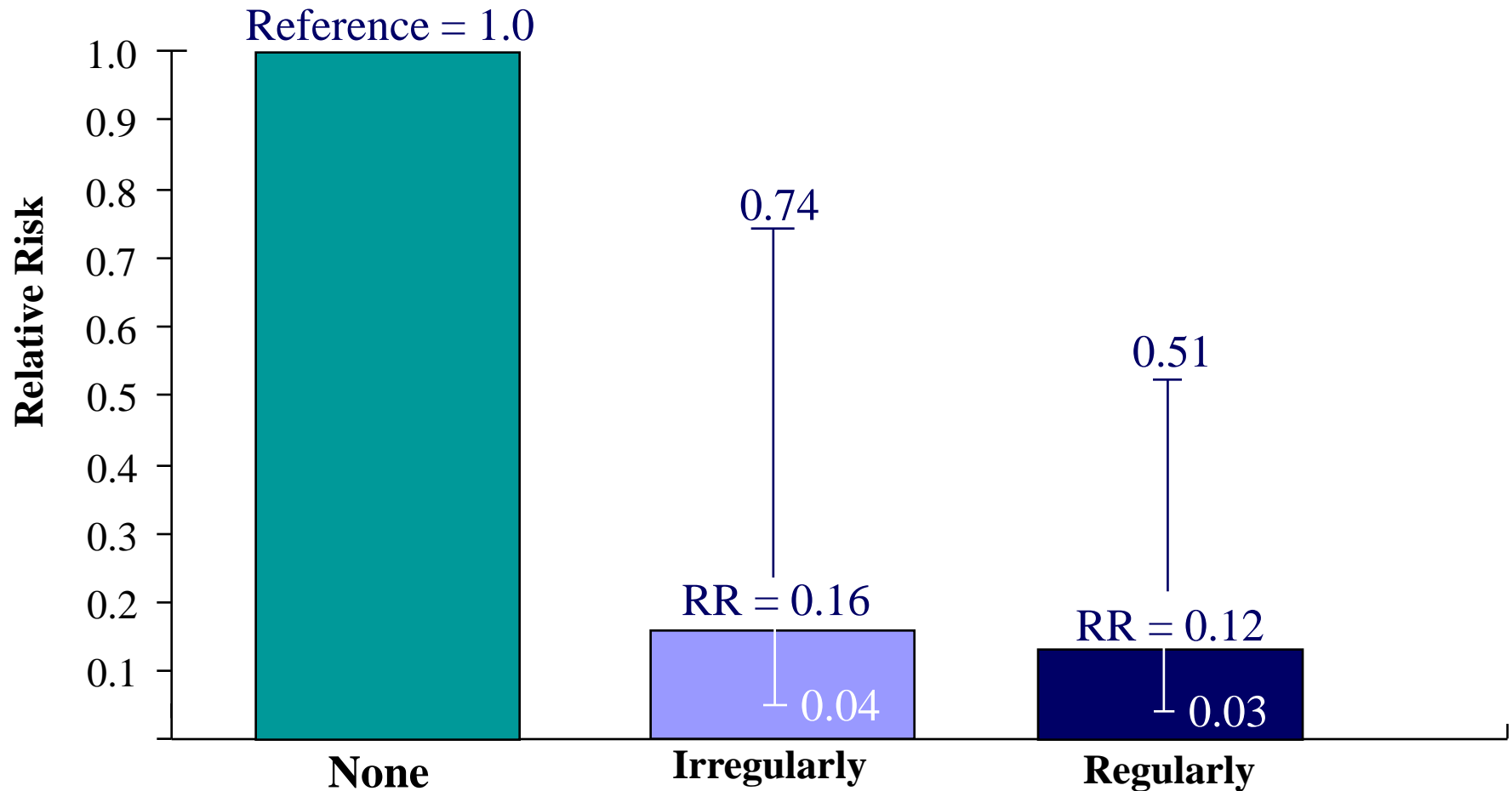
Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, Finland, 1965-2005



Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, and dates of changes in recommended daily intake of vitamin D in infants, Finland, 1965-2005



Infants' Supplementation with Vitamin D and Incidence of Type I Diabetes in Children in Northern Finland



Relative Risk* and 95% confidence intervals for diabetes by vitamin D supplementation, Birth Cohort study, N=12,055 pregnant women

*adjusted for infant's gender, gestational age, birth weight, growth rate; maternal parity, age, education, social status

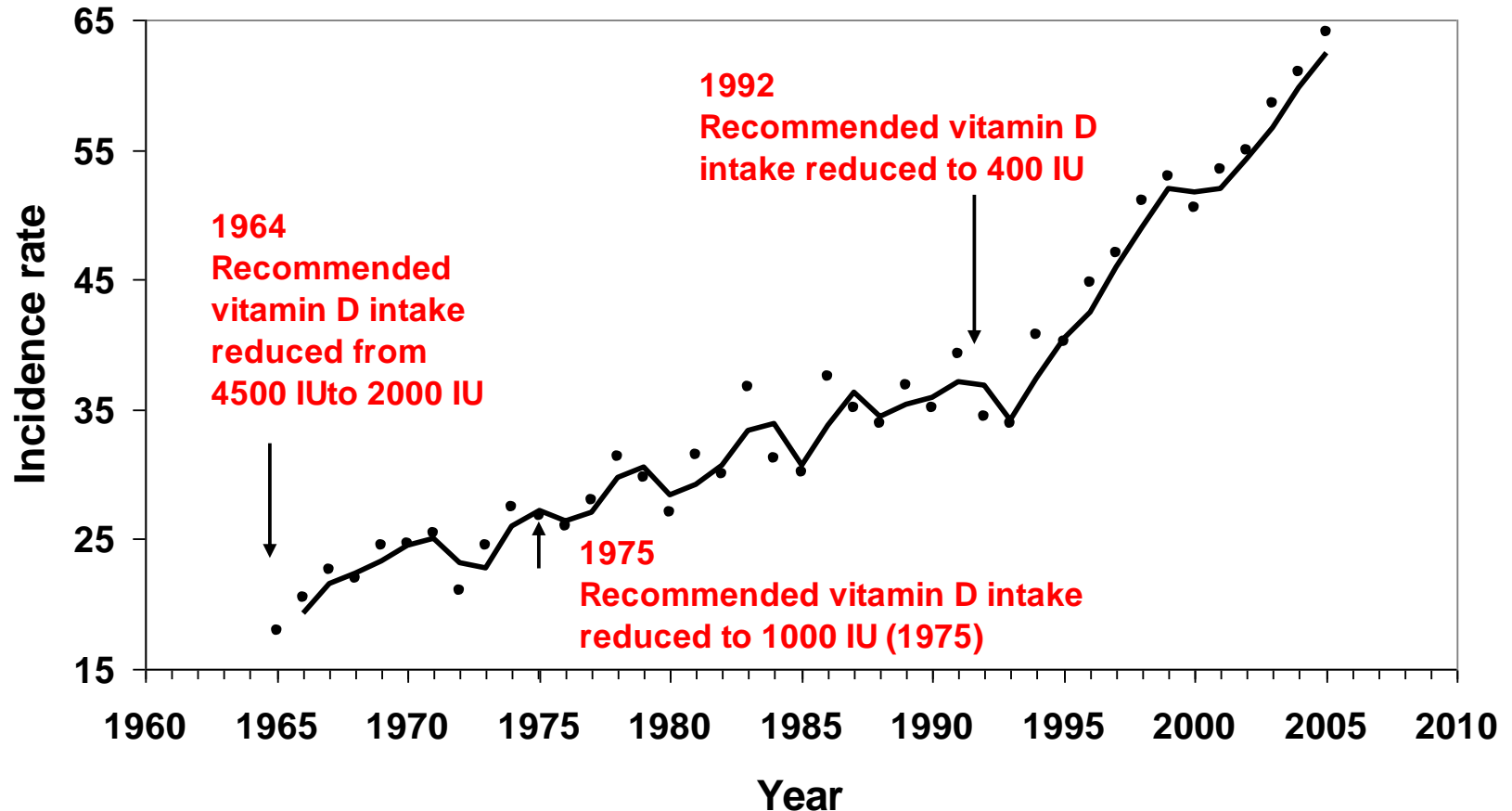
Source: Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001;358:1500-3.

Finland study Conclusion

- Hypponen et al 2001 Lancet
- The authors concluded:

We suggest that, before any changes are made, health workers ensure that all infants are receiving at least the amount of vitamin D indicated in the current recommendation.” The current recommendation is 400 IU per day.

Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, and dates of changes in recommended daily intake of vitamin D in infants, Finland, 1965-2005



What to do to reduce burden of Type I Diabetes in the World

Minimum oral intake of vitamin D3 at 30 degrees or higher, in general:

Infants: NAS UL 1,000 IU-1,800 IU (NAS NOAEL)

Adults: 2,000 (NAS UL)- 2,400 IU (NAS NOAEL)

Children 1-12 years: 2,000 IU

Serum target, all ages: 40-60 ng/ml

Risk/Benefit ratio is infinite since these are within these are within established no adverse affects levels

