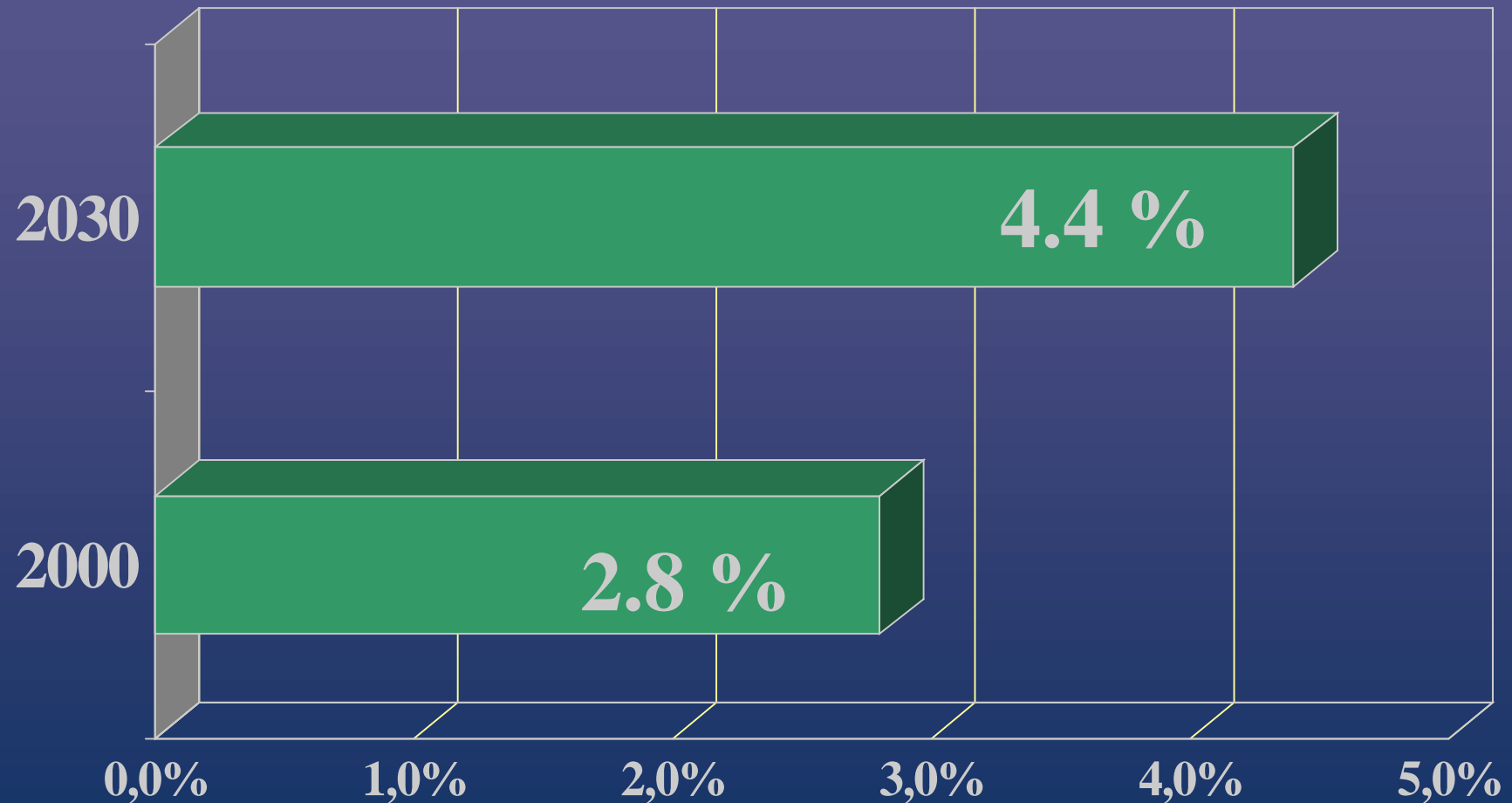


# Diabetes as a risk factor for Alzheimer's dementia

Gaetano Crepaldi  
CNR Center on Aging University of Padua

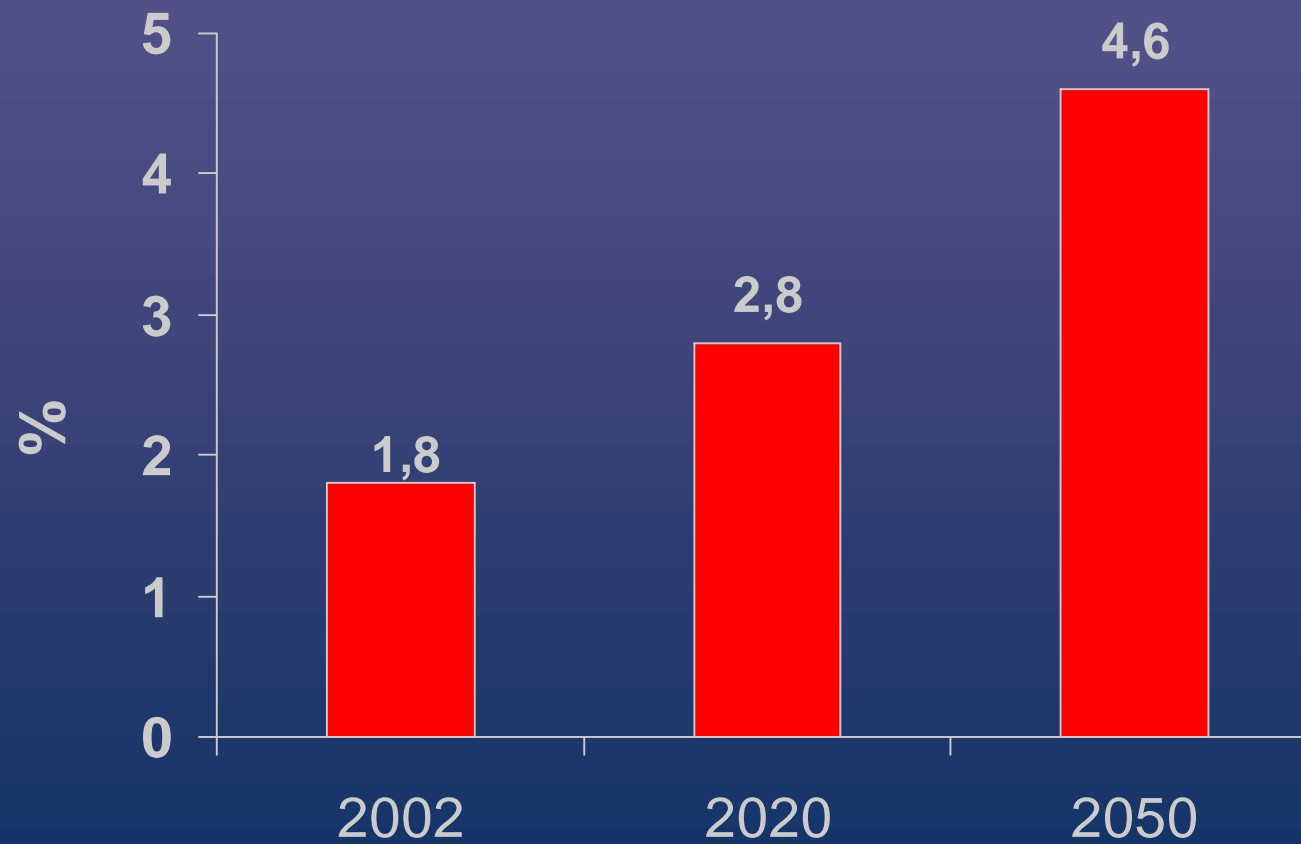
ESC Congress  
3-7 September, 2005  
Stockholm

# Global Prevalence Estimates, 2000 and 2030



Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes. *Diabetes Care*. 2004; 27(5): 1047-1053.

## Global Prevalence Estimates of dementia, 2002 and 2050

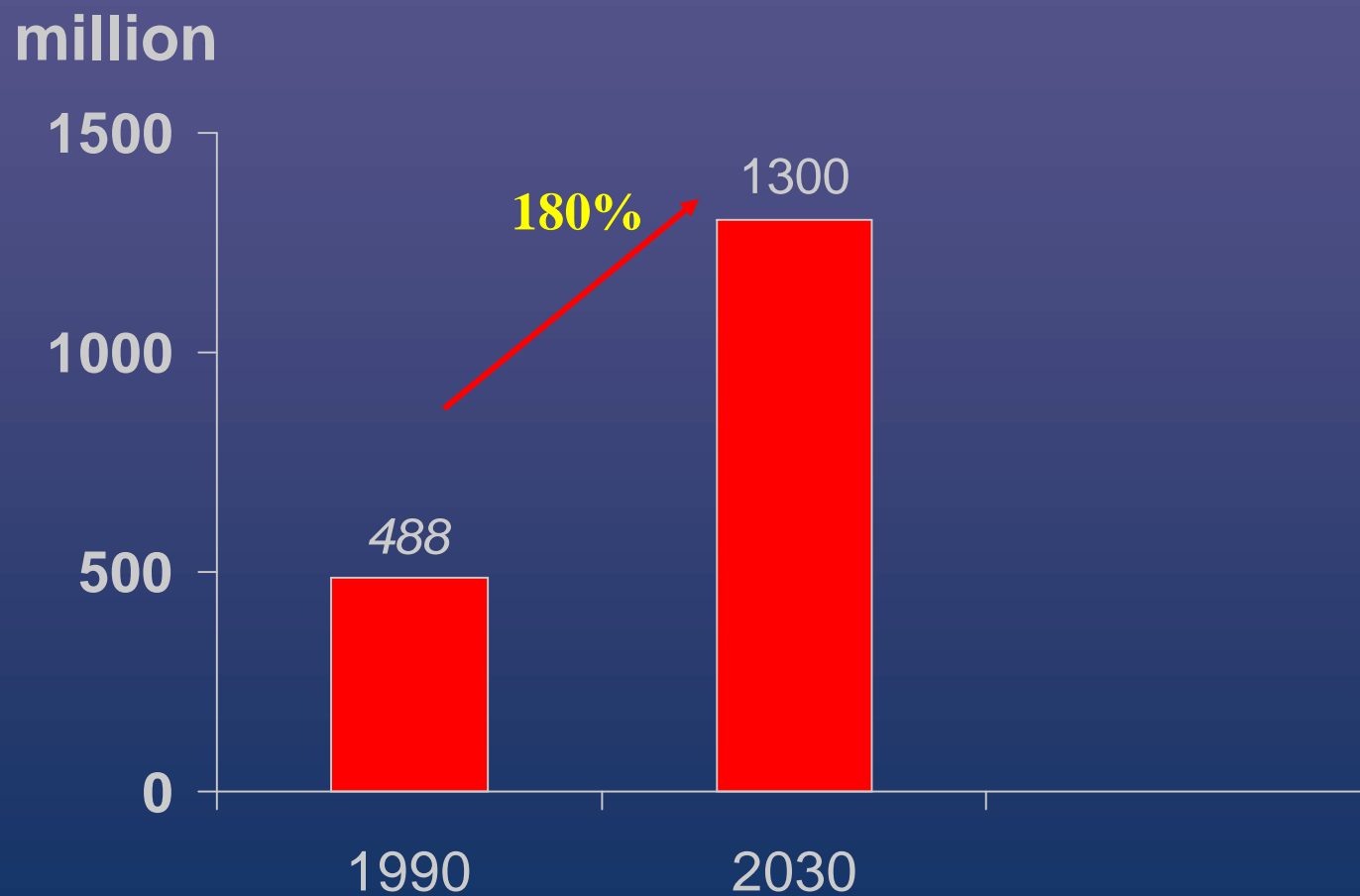


# Incidence rates of dementia in Europe



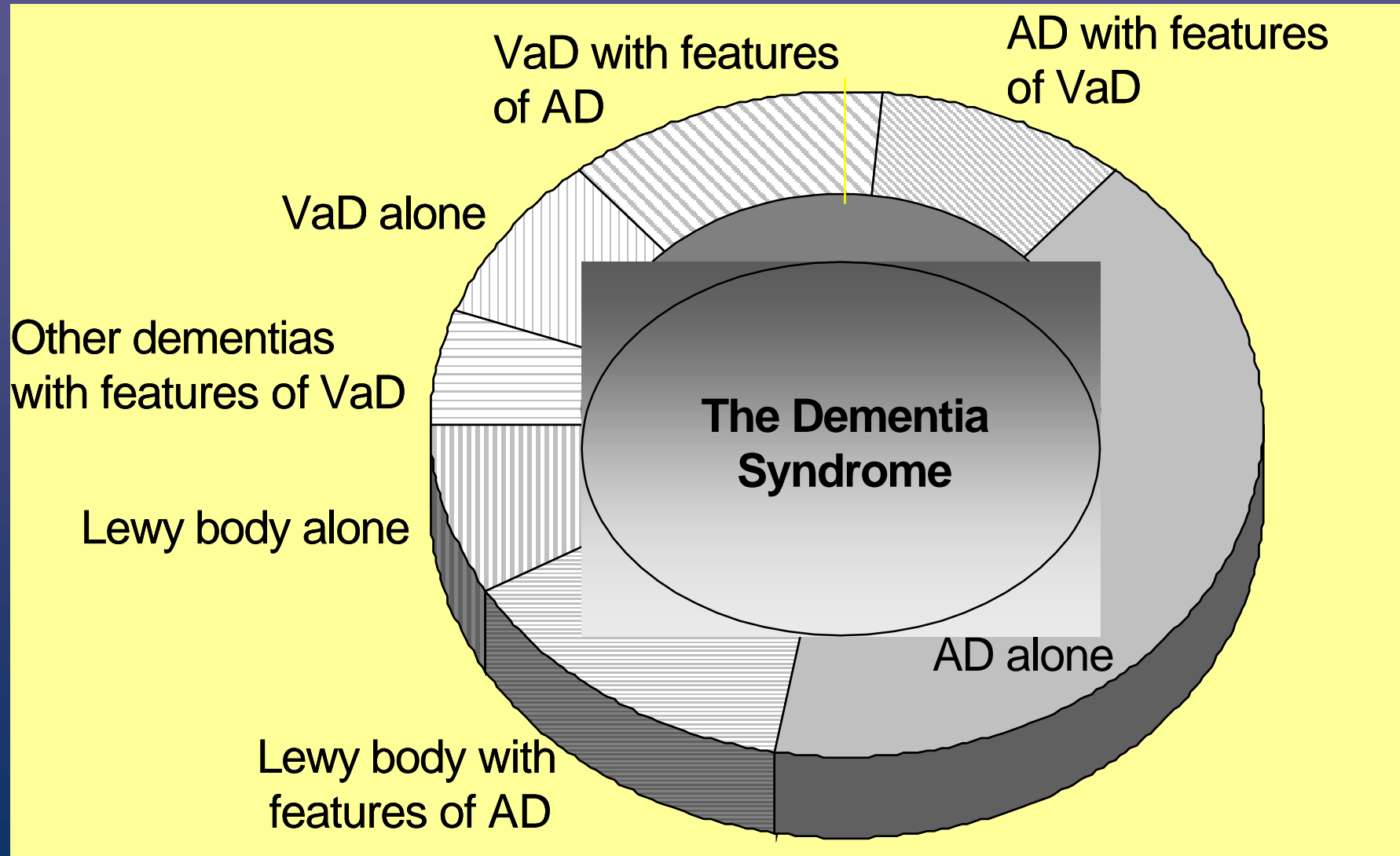
*Fratiglioni L et al. Neurology 54 (suppl 5), 2000*

# World population 60 + years

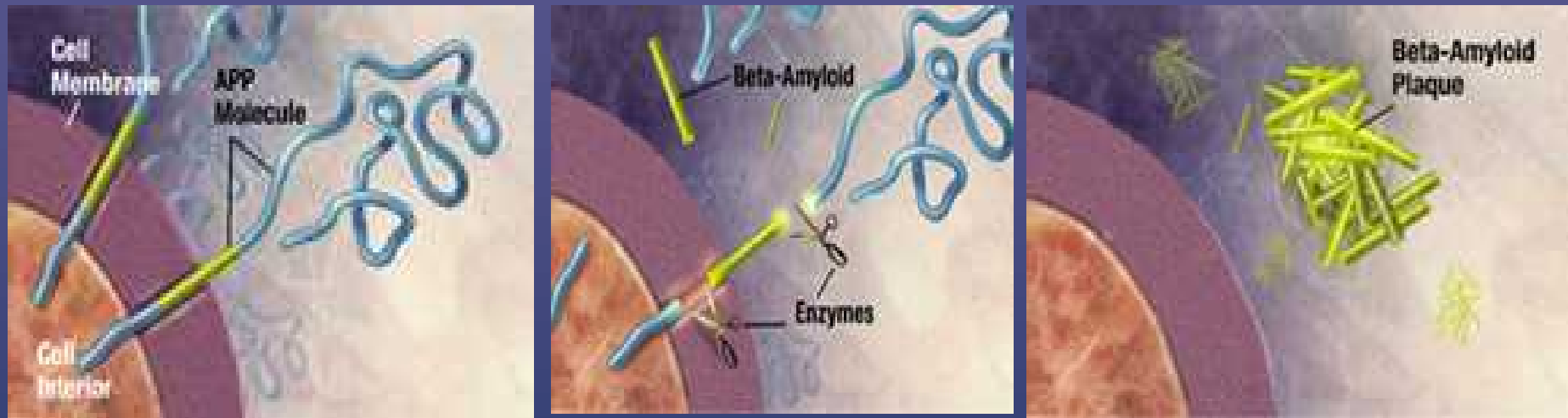


*Kinsella e VelKoff, 2001*

# Dementia syndromes

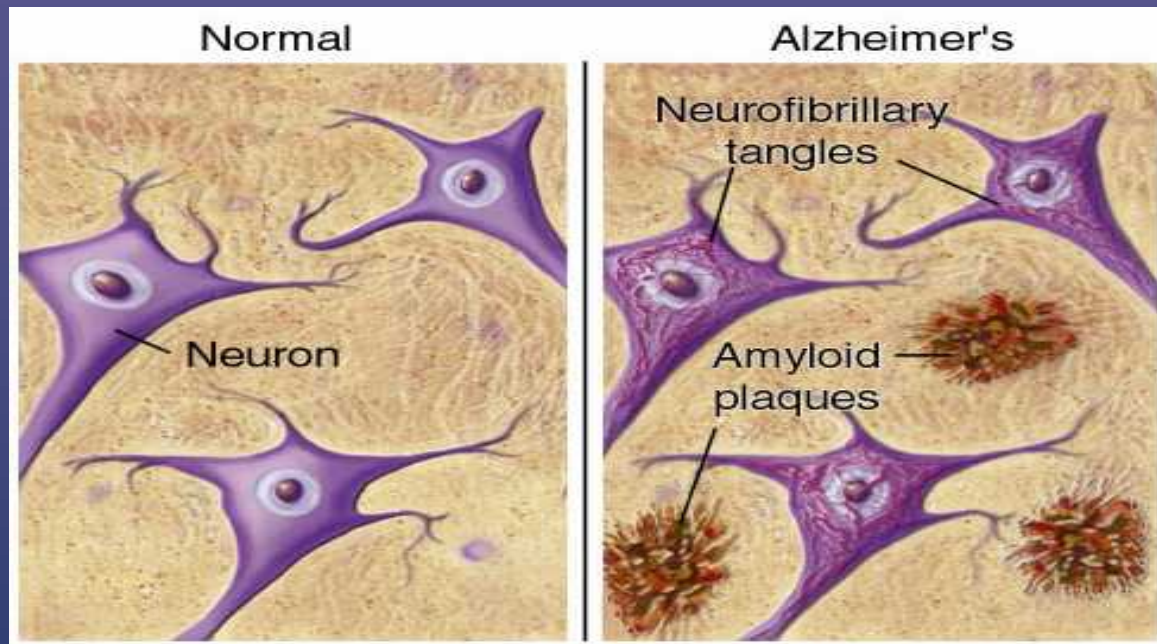


# From APP to beta-amyloid



**One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques between nerve cells (neurons) in the brain. Amyloid is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP). In a healthy brain, these protein fragments would be broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.**

# Neurofibrillary tangles



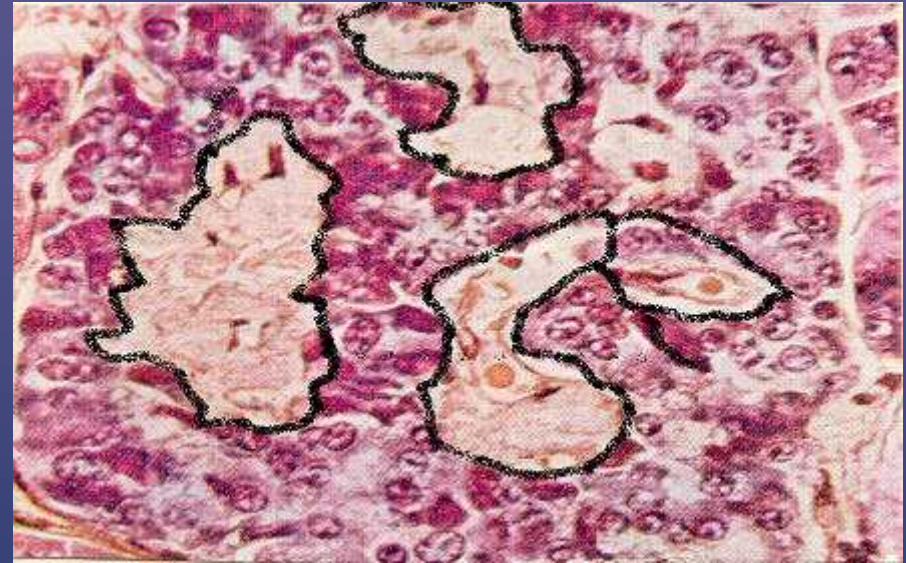
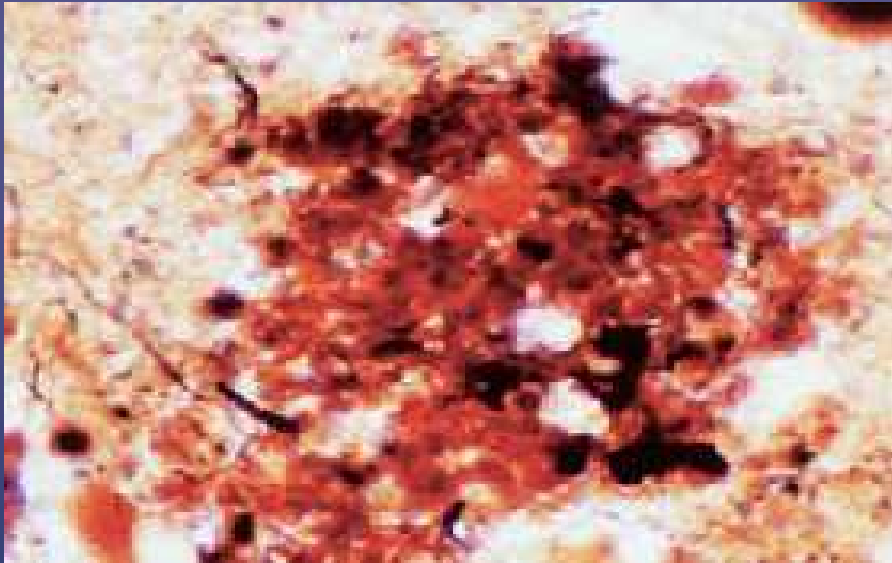
■ **Neurofibrillary tangles consist of insoluble twisted fibers that are found inside of the brain's cells. They primarily consist of a protein called *tau*, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another. In Alzheimer's disease, however, the tau protein is abnormal and the microtubule structures collapse.**

# Diabetes as a risk factor for AD

The evolving concept that diabetes is a risk factor for developing Alzheimer disease is supported by scientific evidence and by the common features of the two conditions, such as:

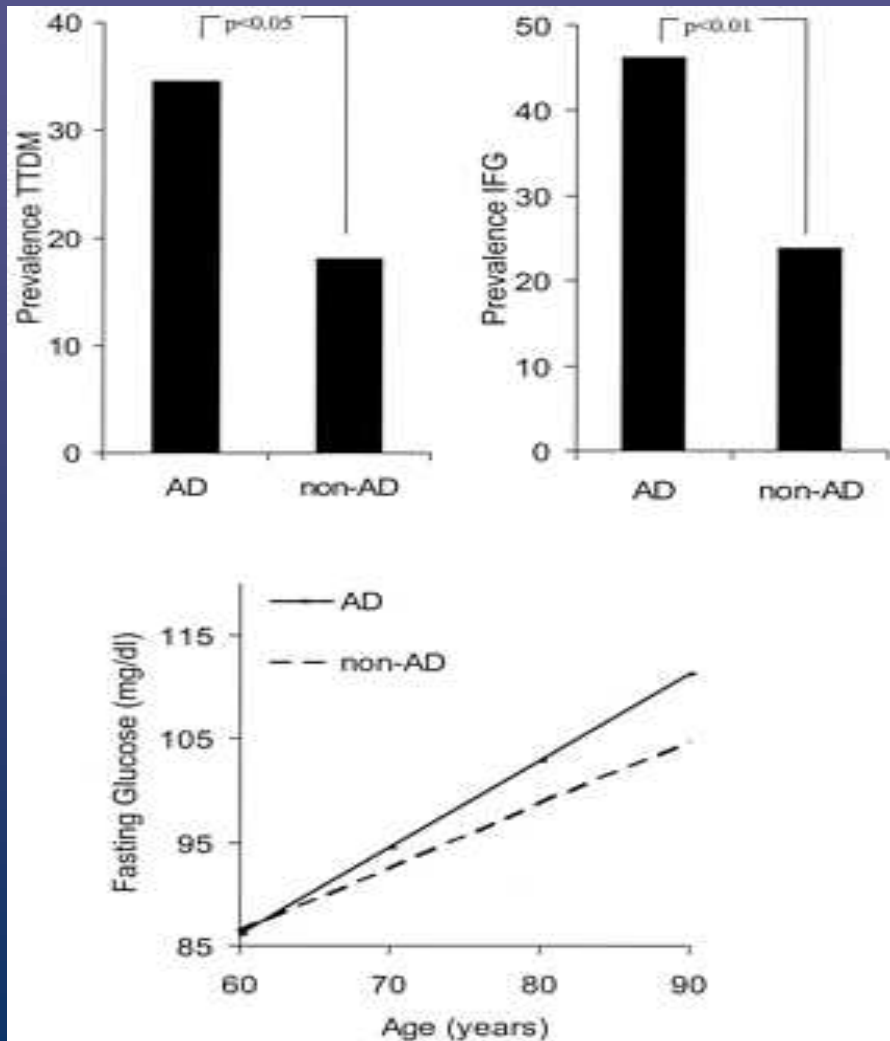
1. increased prevalence with aging
2. a genetic predisposition, and
3. comparable pathological features in the islet and brain (amyloid derived from amyloid beta protein in the brain in Alzheimer disease and islet amyloid derived from islet amyloid polypeptide in the pancreas in type 2 diabetes).

# Diabetes and AD



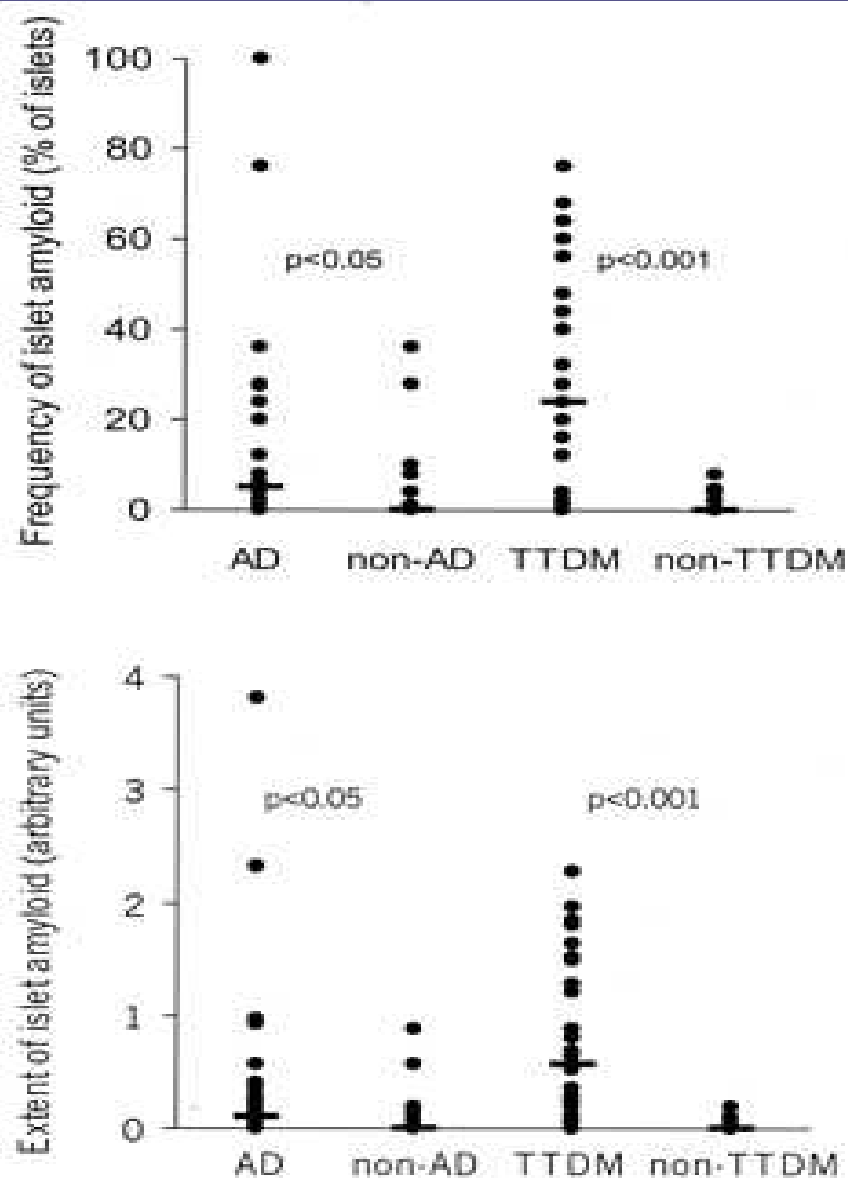
**Evidence is growing to link precursors of amyloid deposition in the brain and pancreas with the pathogenesis of Alzheimer disease and type 2 diabetes, respectively.**

# The Olmsted County Clinical Study.



- The prevalence of Diabetes and IFG is significantly greater in the AD patients (n=100) compared to the controls (n=138)
- The AD group has a greater increase of FPG with aging compared to controls (diabetic subjects excluded)

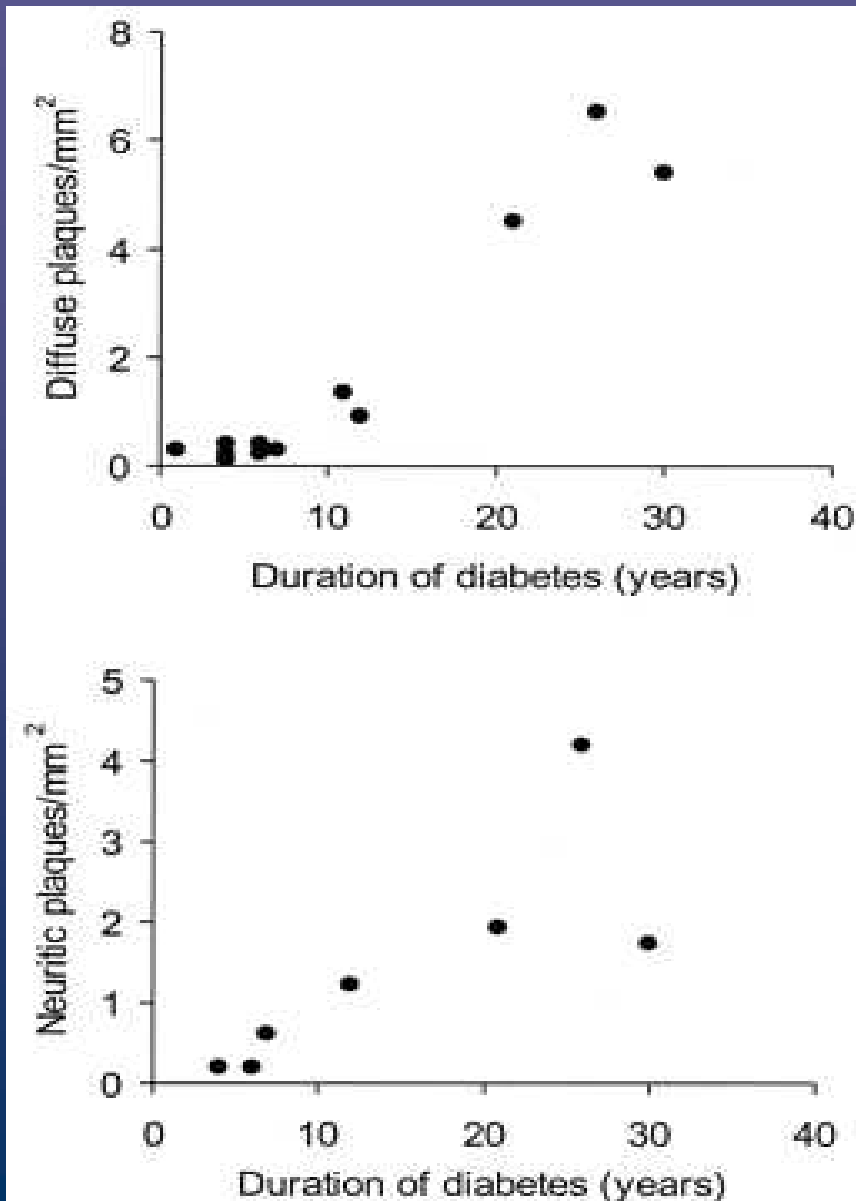
# The Olmsted County Pathological Study.



The **frequency** of islet amyloid (*top*) and **extent** of islet amyloid (*bottom*) are higher in patients with AD (n=28) and in patients with type 2 diabetes (n= 35) compared to their control groups

Janson et al, Diabetes, 2004

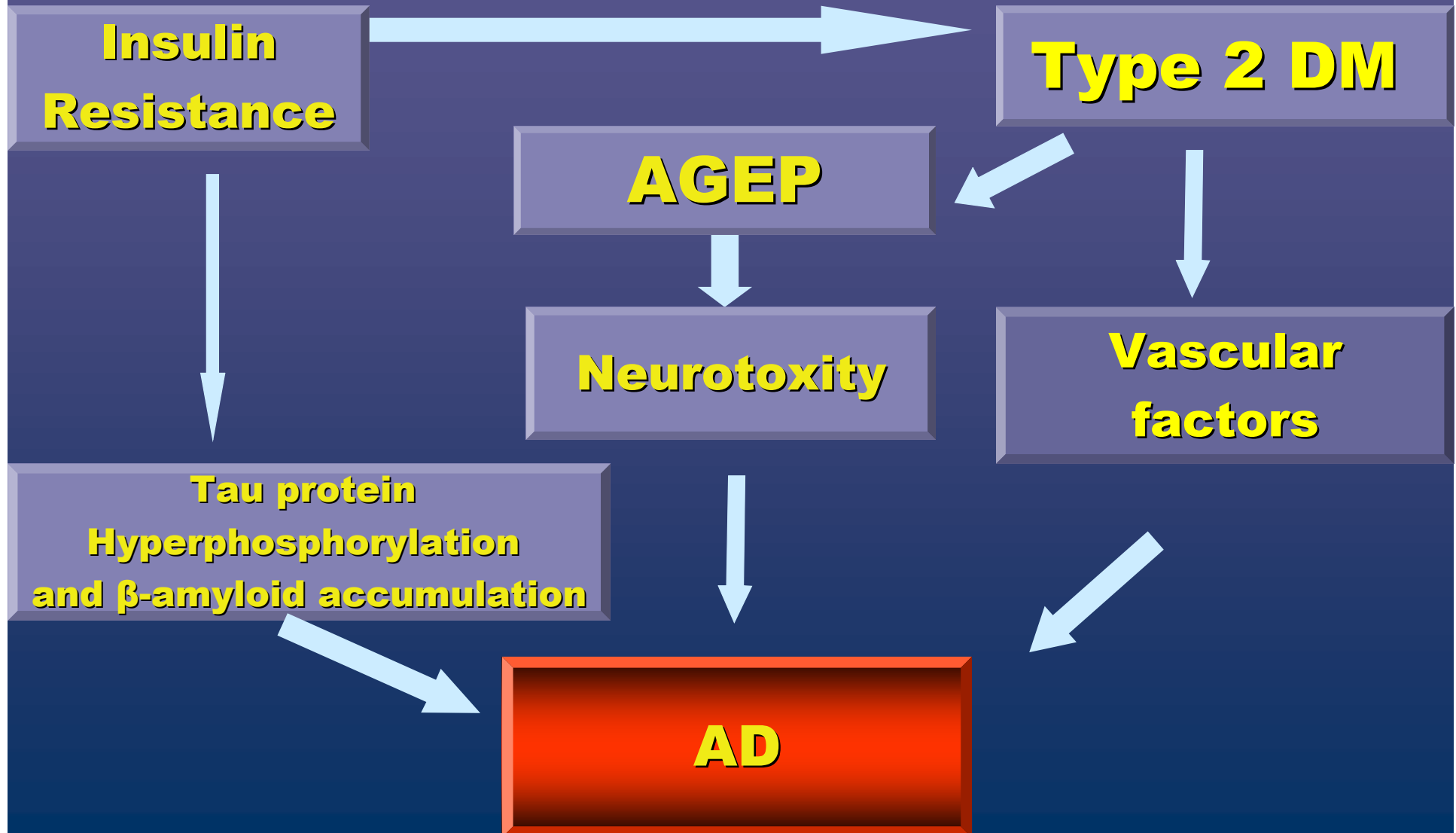
# The Olmsted County Pathological Study.



The assessment of the relationship between the density of **diffuse plaques** or the density of **neuritic plaques** versus the duration of diabetes in patients with type 2 diabetes shows that **brain plaque formation correlates in extent with duration of diabetes**

Janson, Diabetes, 2004

# A model of the interaction between Type 2 DM and AD



## **Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease**

Diet-induced insulin resistance promotes amyloidogenic beta-amyloid (A $\beta$ ) Abeta1-40 and Abeta1-42 peptide generation in the brain of Tg2576 mice, which model AD-like neuropathology.

This corresponds with increased  $\gamma$ -secretase activities and decreased insulin-degrading enzyme activities.

Increased Abeta production also coincides with increased AD-type amyloid plaque burden in the brain and impaired performance in a spatial water maze task.

***Ho et al, The FASEB Journal, 2004***

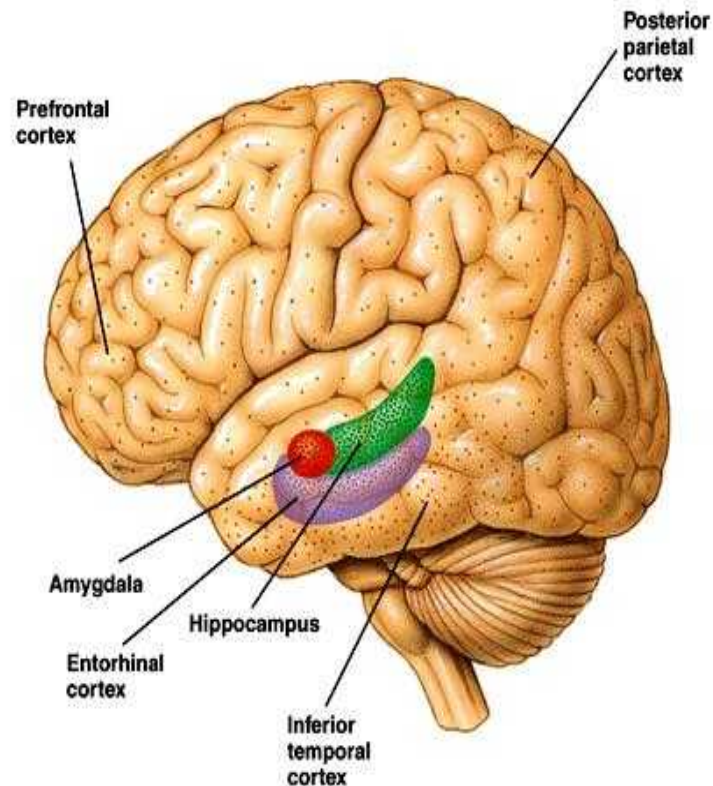
## Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease- is this type 3 diabetes?

- By looking at rodents and post-mortem brain tissue from people with Alzheimer's disease, Steen et al. have found that insulin and its related proteins are actually produced in the brain, and that reduced levels of both are linked to Alzheimer's disease.
- This insulin and its related growth factors and receptors in the brain are vital for the survival of brain cells.
- If they are not produced at normal levels, the cells die.

**E. Steen, J AD, 2005**

# Is this “type 3 diabetes” ?

## ► Neurofibrillary Tangles and Amyloid Plaques



Source: Based on Selkoe, *Scientific American*, 1991, 265, 68-78, and Goedert, *Trends in Neurosciences*, 1993, 16, 460-465.

Insulin and IGF I are significantly reduced in the frontal cortex, hippocampus and hypothalamus – all areas that are affected by the progression of AD. Lower than normal levels of brain insulin, therefore, define ‘Type 3 diabetes’, which appears to be associated with Alzheimer's disease

E. Steen, J AD, 2005

# Epidemiological evidence

## *Methodological problems in case-control studies*

- **Uncertain matching of the two groups**
- **Limited generalizability from what are most often selected outpatients samples**
- **Diagnostic bias: known cases may be equalled in number by unrecognized cases of both diabetes and early-stage AD**

# Overview of population studies on AD

	<b>N</b>	<b>Follow up</b>	<b>Association of DM</b>
<b>Religious Order Study, 2005</b>	824	6 years	<i>65% increased risk of AD</i>
<b>Rotterdam, '96</b>	6330	2 years	<i>double risk of AD</i>
<b>Rochester S, '97</b>	1455	15 years	<i>37% increased risk of AD in women and double risk in men</i>

## Type 2 Diabetes Is Negatively Associated With Alzheimer's Disease Neuropathology

Michal Schnaider Beeri,<sup>1</sup> Jeremy M. Silverman,<sup>1</sup> Kenneth L. Davis,<sup>1</sup> Deborah Marin,<sup>1</sup>  
Hillel Z. Grossman,<sup>1</sup> James Schmeidler,<sup>1,2</sup> Dushyant P. Purohit,<sup>3</sup> Daniel P. Perl,<sup>3</sup>  
Michael Davidson,<sup>4</sup> Richard C. Mohs,<sup>6</sup> and Vahram Haroutunian<sup>1,5</sup>

- *Methods.* The study included specimens from 385 consecutive autopsies of residents of a nursing home (15.8% diabetic). Mean age at death: 84 years.
- *Results.* Diabetics had significantly less AD-associated neuropathology
- *Limits.* Survival effect, small sample

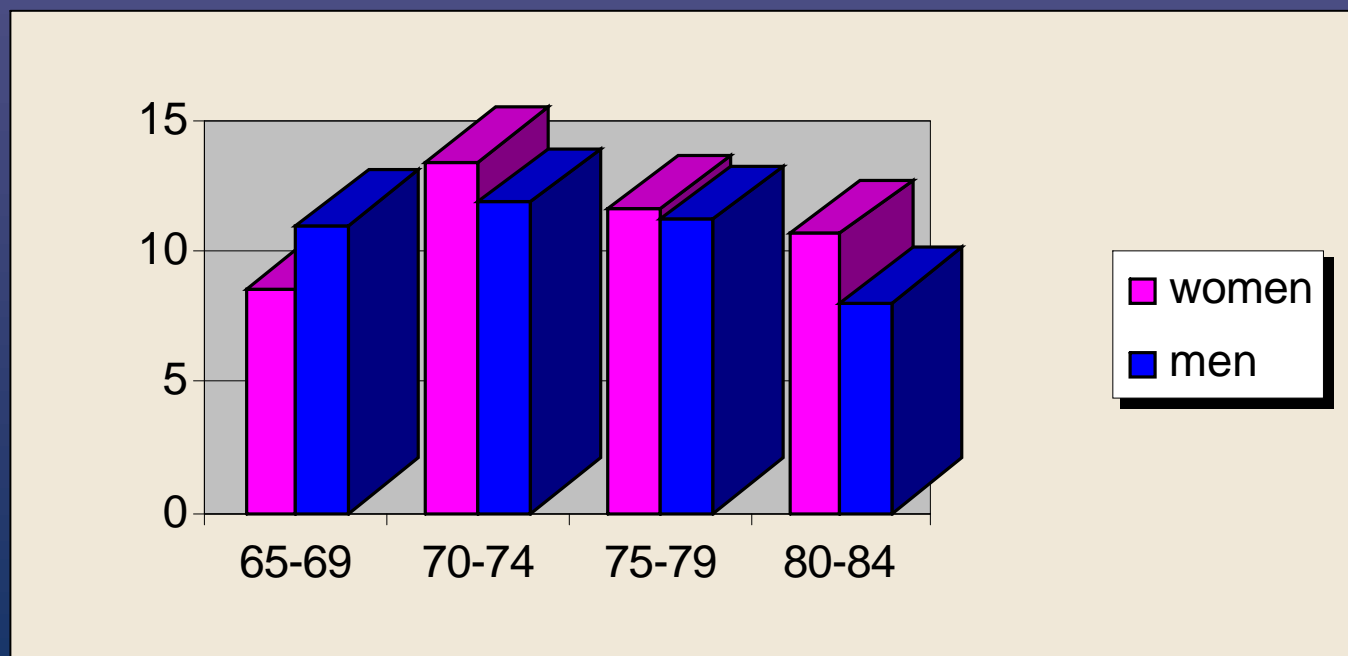
# THE ILSA: STUDY SAMPLE

- 5,632 free-dwelling and institutionalized individuals, aged 65-84, resident in 8 centers (urban, suburban, rural), randomly selected from the local anagraphic lists (equal allocation by sex and 5-year-age groups).

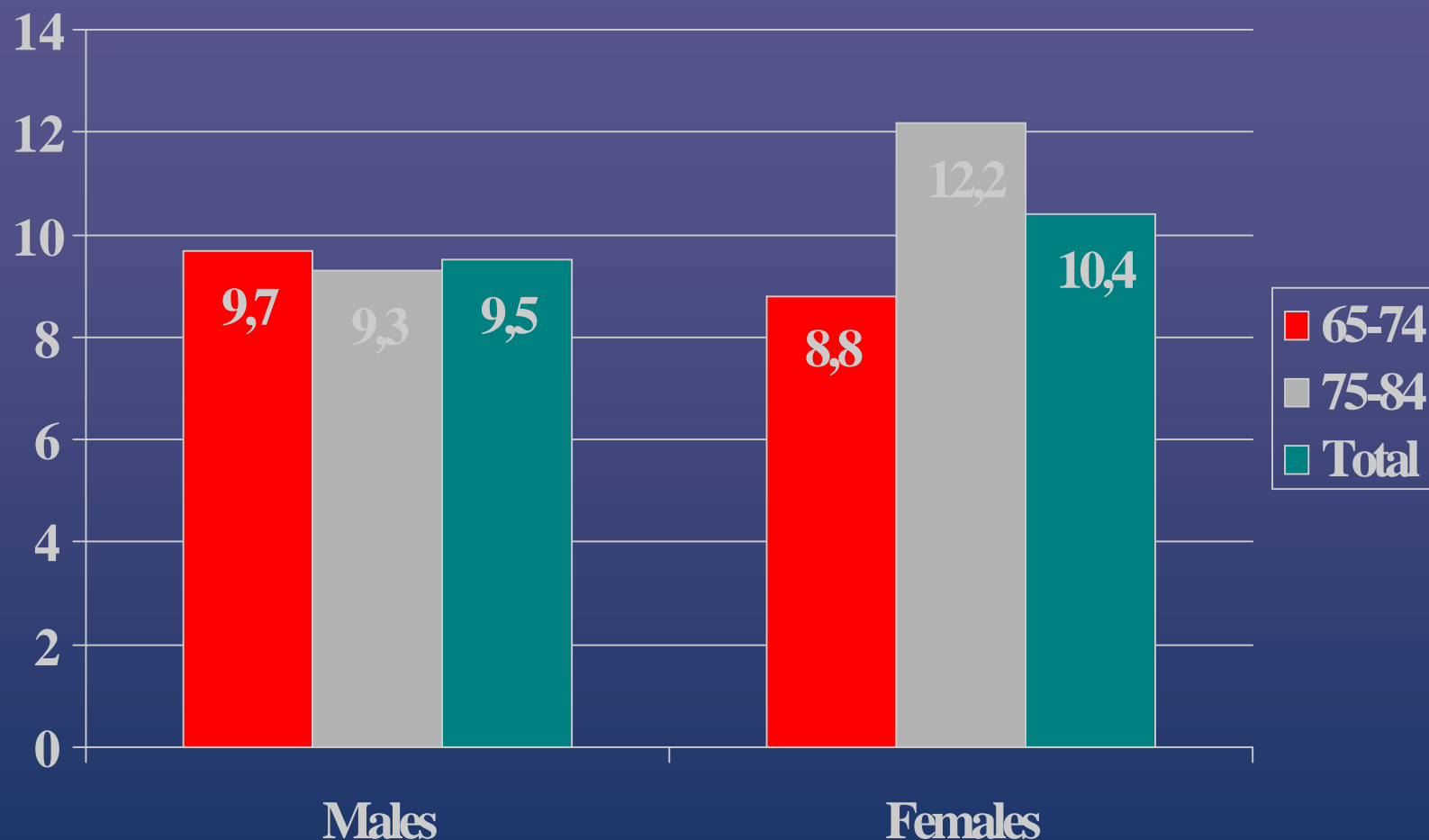


# Diabetes Prevalence rate (%) by sex and age. *ILSA Study*

*N* ≡ 2813 men  
*N* ≡ 2815 women

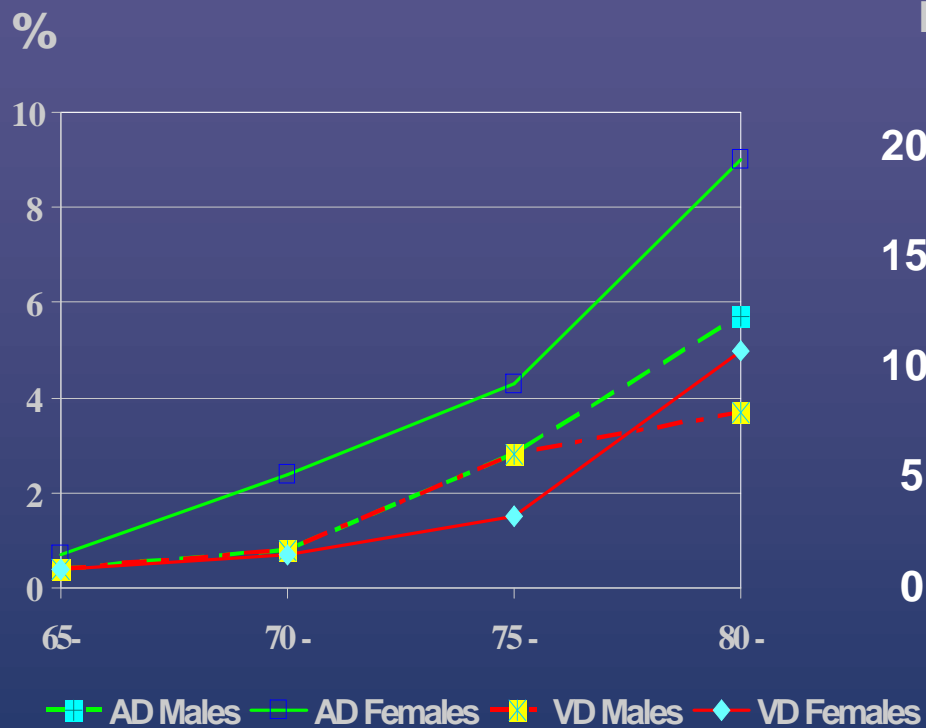


# Diabetes incidence rates (1000/year)

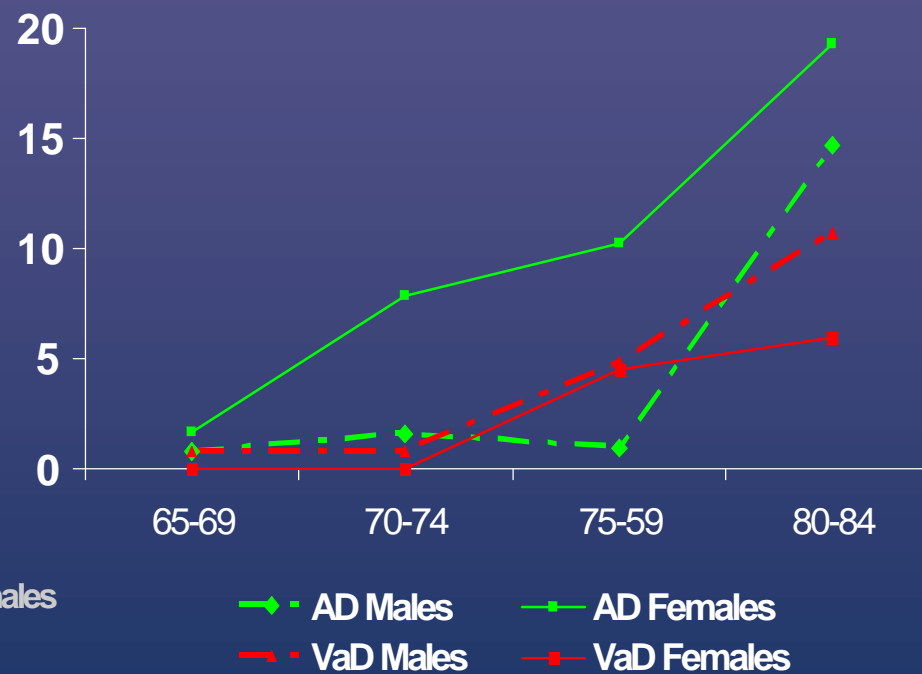


**90,000 new cases of diabetes  
expected in Italy each year in the population over 65**

# Prevalence and incidence rates of dementia ILSA STUDY



Per 1000 persons per year



## Severity of DM and cognitive performance

Cognitive Impairment: MMSE	Model With only HbA1c	Model with HbA1c, Age and education	Model With HbA1c and all confounders <sup>#</sup>
MALES	1.5 (1.1-2.23)	1.5 (1.00-2.33)	1.7 (1.04-2.81)
FEMALES	2.0(1.37-3.05)	1.8 (1.14-2.76)	1.6 (1.02-2.74)

➤ Each model is adjusted for the baseline score

➤ #: age, education, smoking status, alcohol consumption, drugs treatment, BMI, hypertension, heart failure, MI, angina, arrhythmia, stroke, parkinsonisms, peripheral neuropathy, depressive symptomatology and comorbidity

# Is diabetes a risk factor for AD?

## 1. Epidemiological evidence

✓ **yes**

## 2. Biological plausibility

✓ **yes**

# Conclusions

- Diabetes seems to be related to AD
- Poor glycemic control probably leads to greater decline
- Although further research is clearly needed to clarify how insulin resistance in the neurons in the brain interacts with other genetic and biochemical abnormalities in the development of Alzheimer's disease, there are plausible mechanisms explaining a biochemical link between the two conditions.
- Understanding and developing treatments for diabetes may have impact not only in diabetes, but in many other common chronic diseases.