VII JORNADES GEDAPS de la CAMFiC

Actualització en diabetis 2015

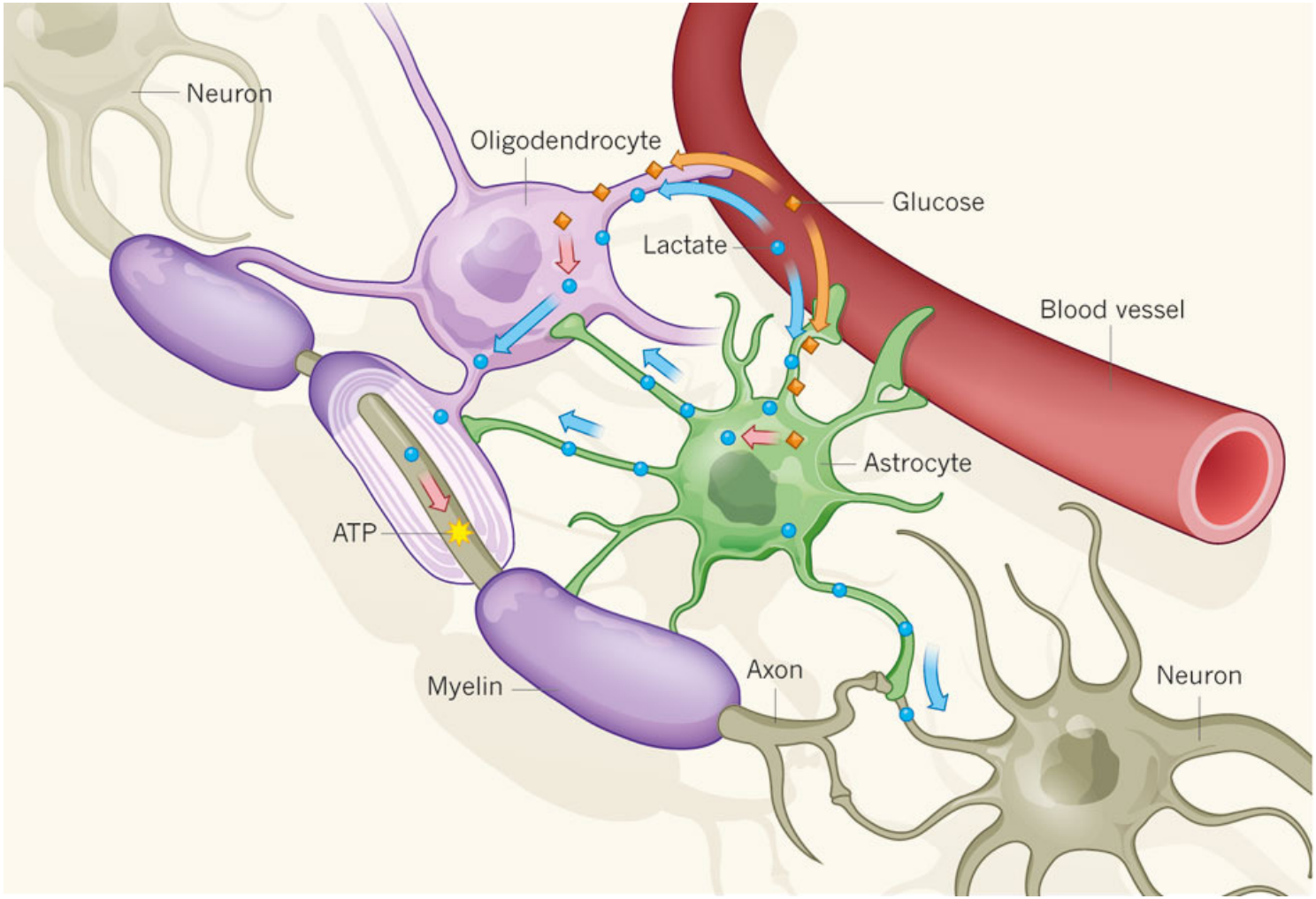
Diabetis i demència

Antonio Rodríguez

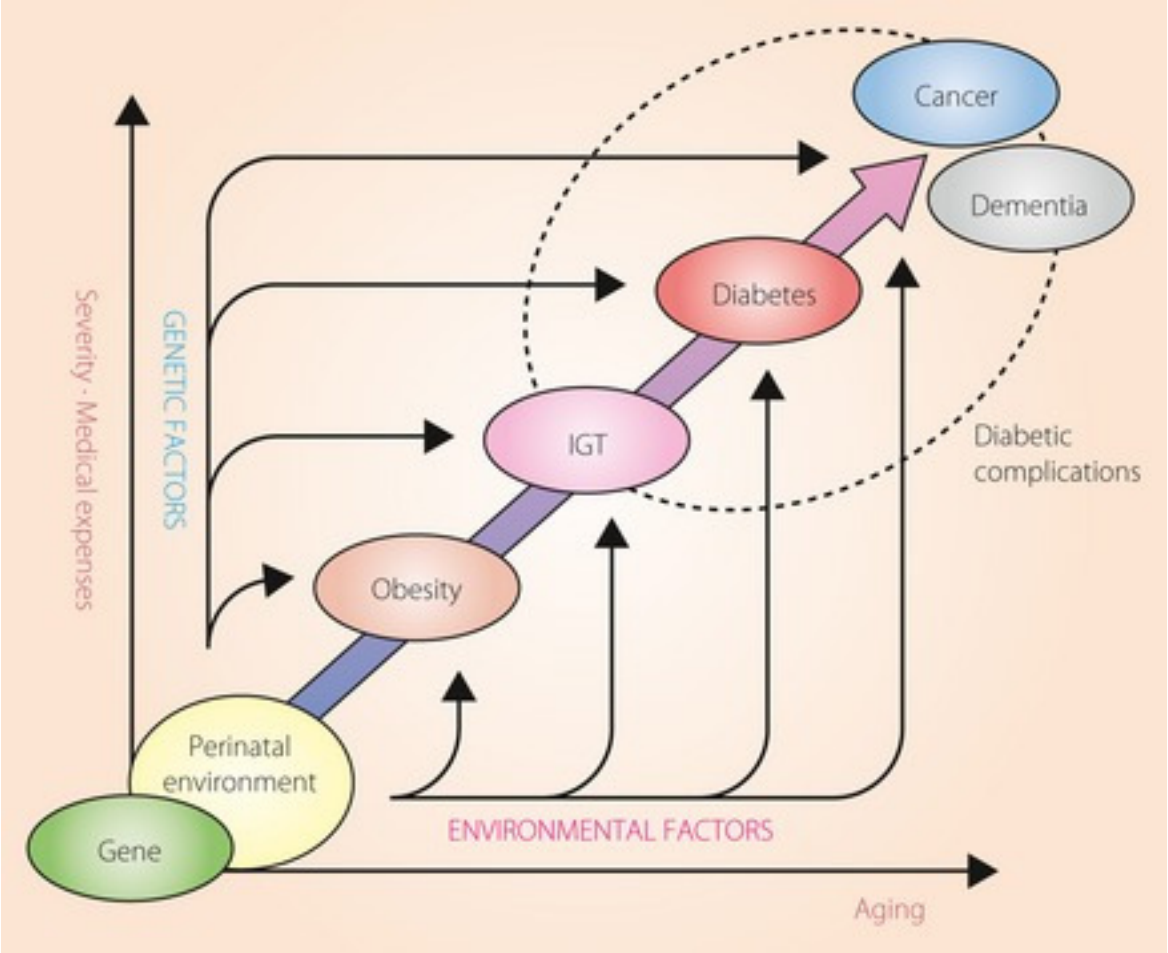
CAP Anglès/Girona

De què parlarem?

- Possible relació entre la diabetis mellitus i la demència (malaltia d'Alzheimer)
- Què diuen els estudis?
- Missatges per recordar

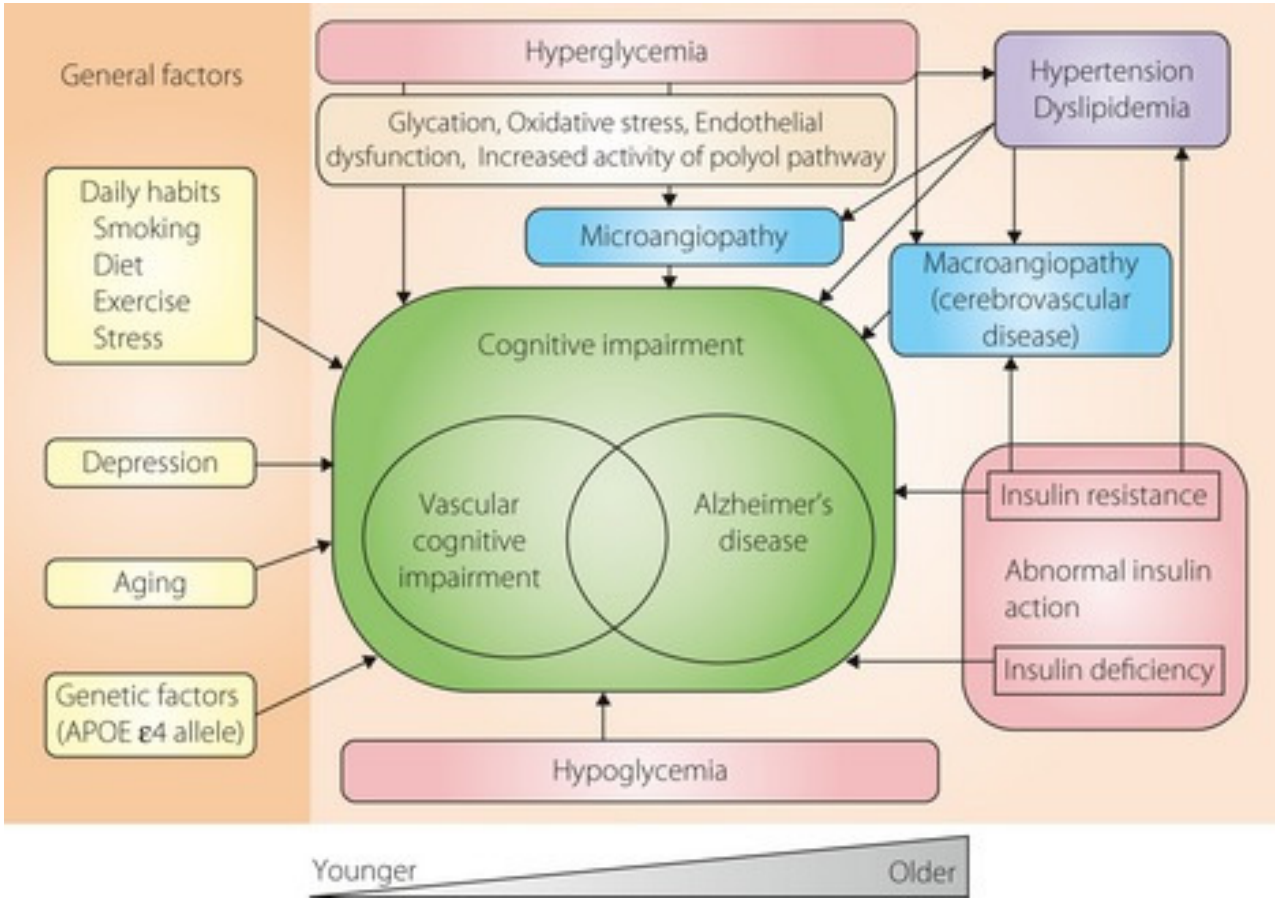

Neuron
Oligodendrocyte
Glucose
Lactate
Blood vessel
Astrocyte
ATP
Myelin
Axon
Neuron

Natural history of patients with diabetes mellitus



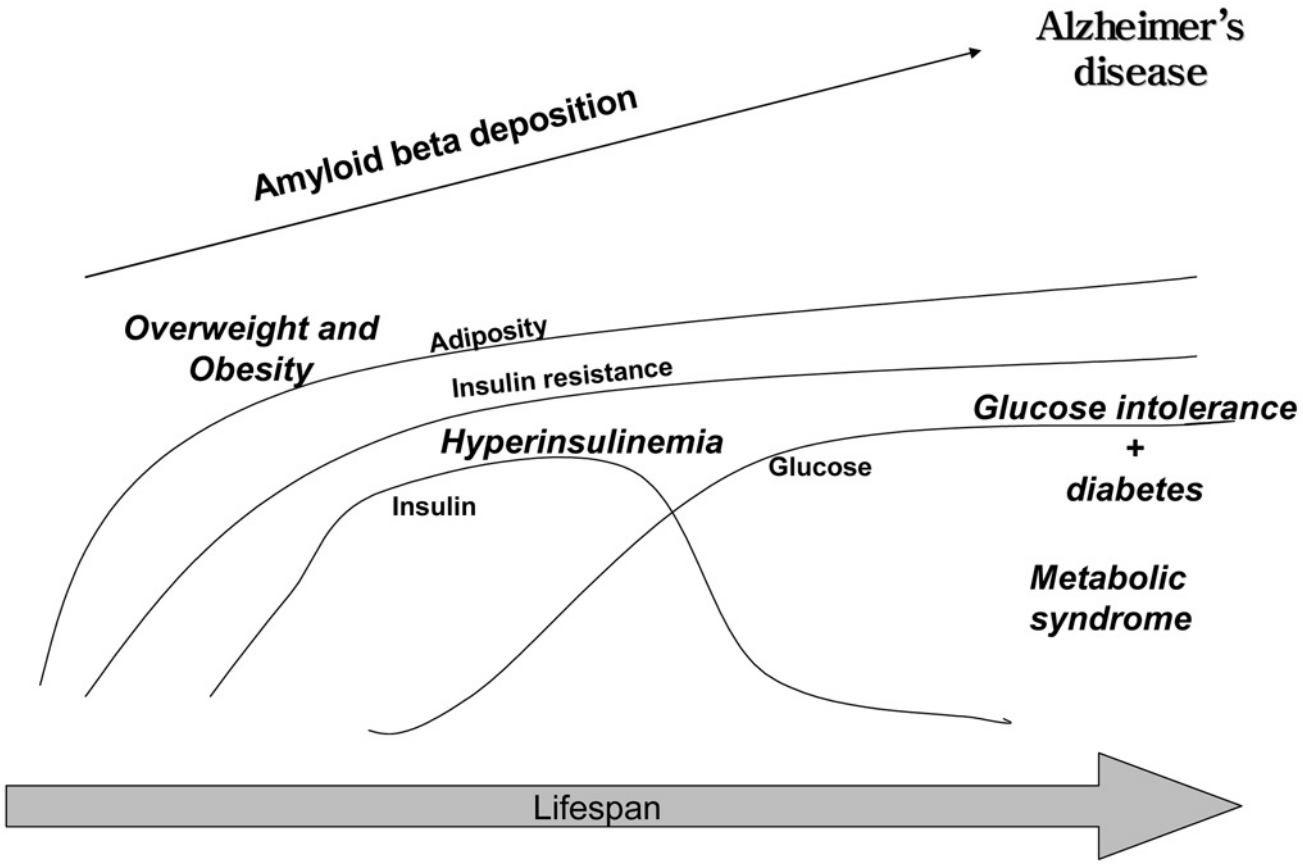
J Diabetes Investig. 2012 18;3:413-23

Posible mechanistic contribution to cognitive impairment seen in diabetes mellitus



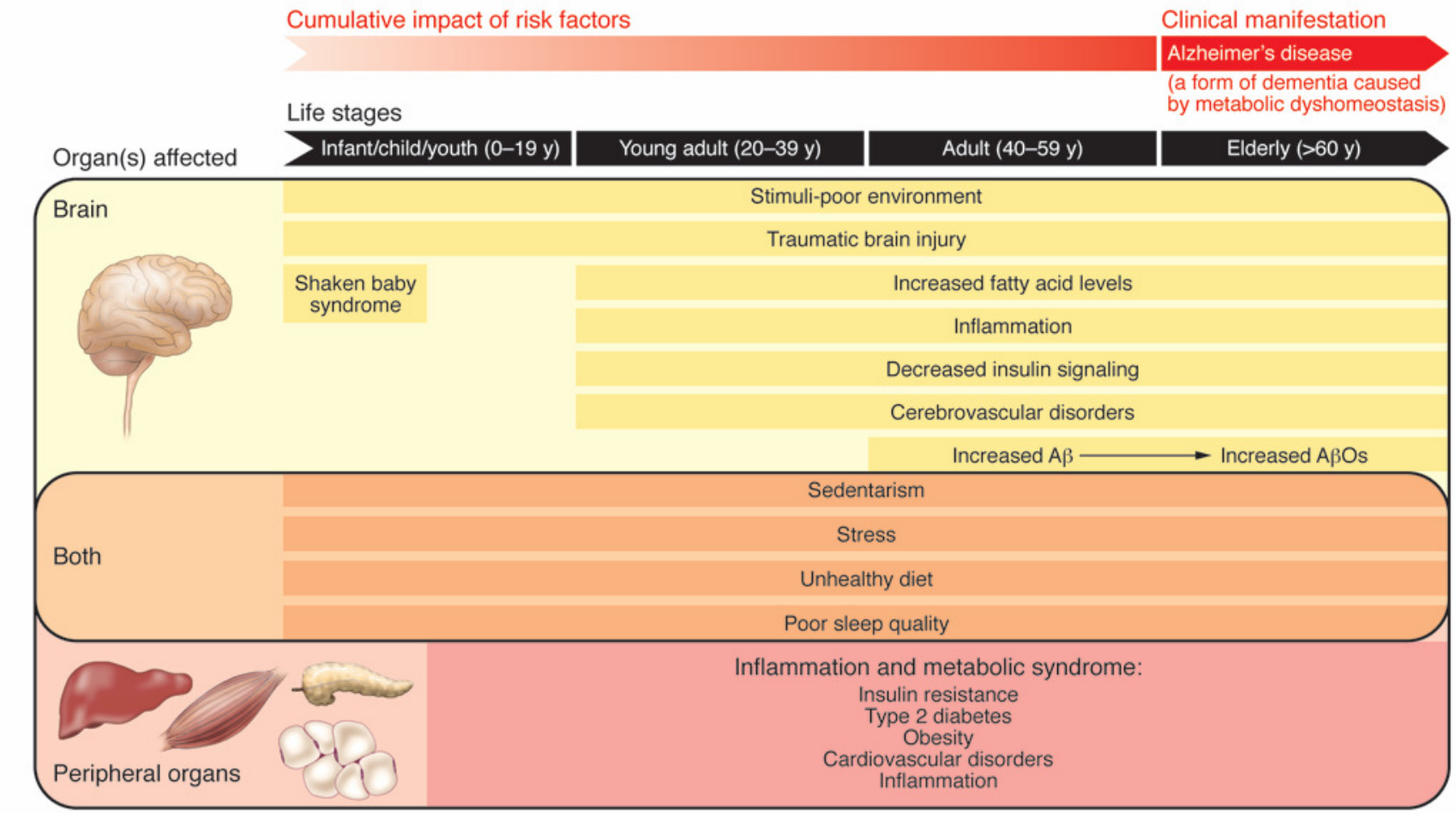
J Diabetes Investig. 2012 18;3:413-23

Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease



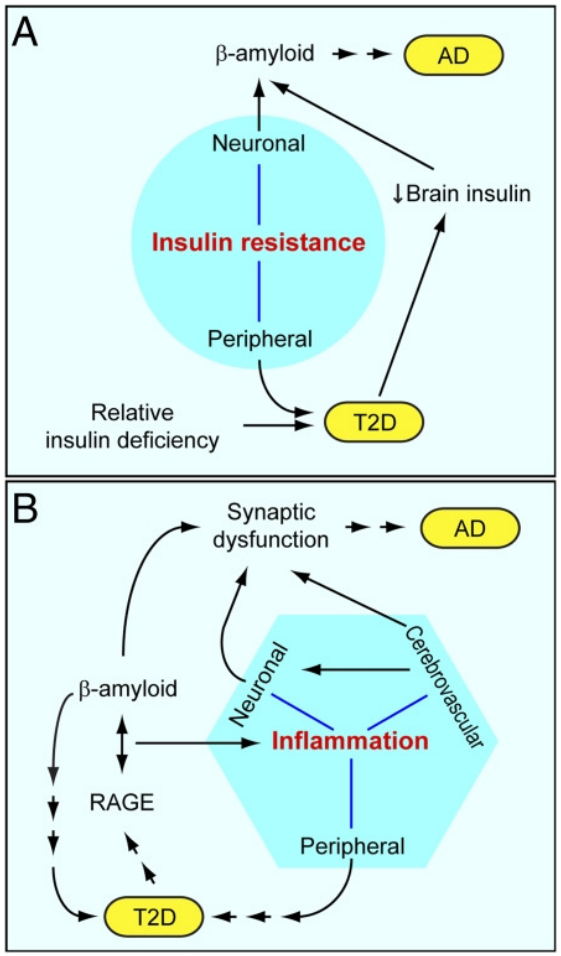
Luchsinger JA. Eur J Pharmacol. 2008;585:119-29.

A cumulative hypothesis for AD



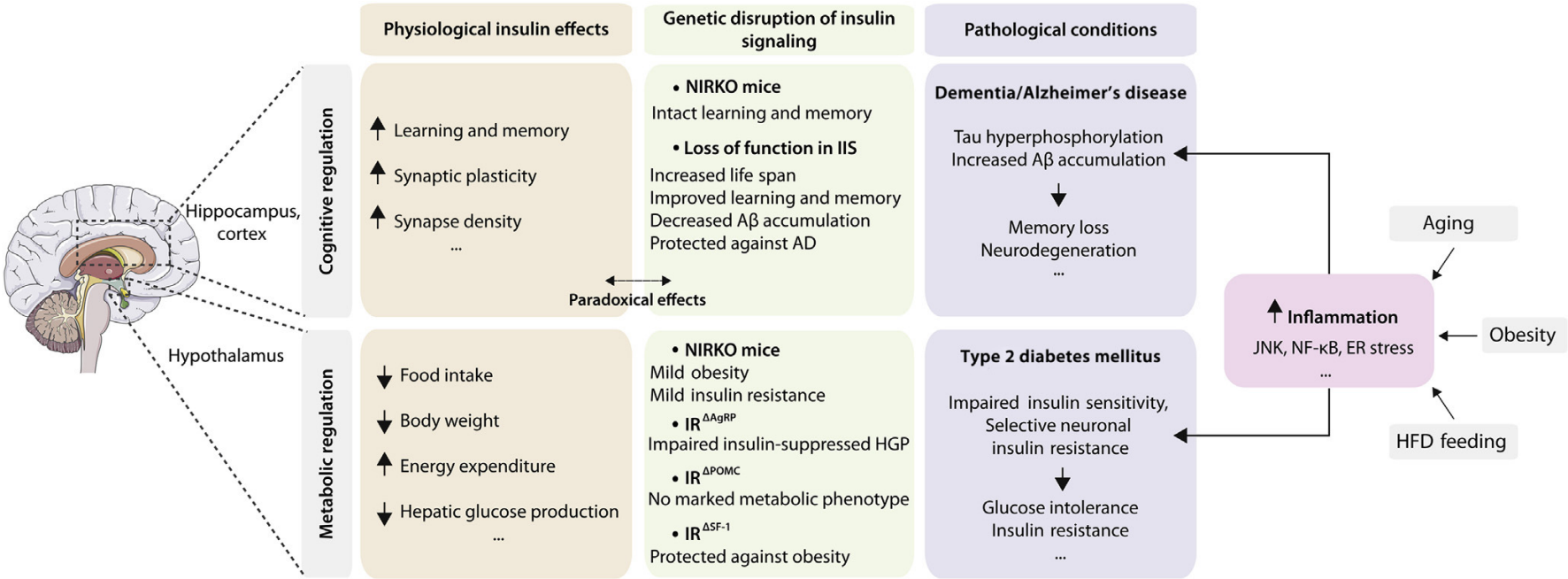
The Journal of Clinical Investigation. doi:10.1172/JCI64595.

Linking type 2 diabetes and Alzheimer's disease



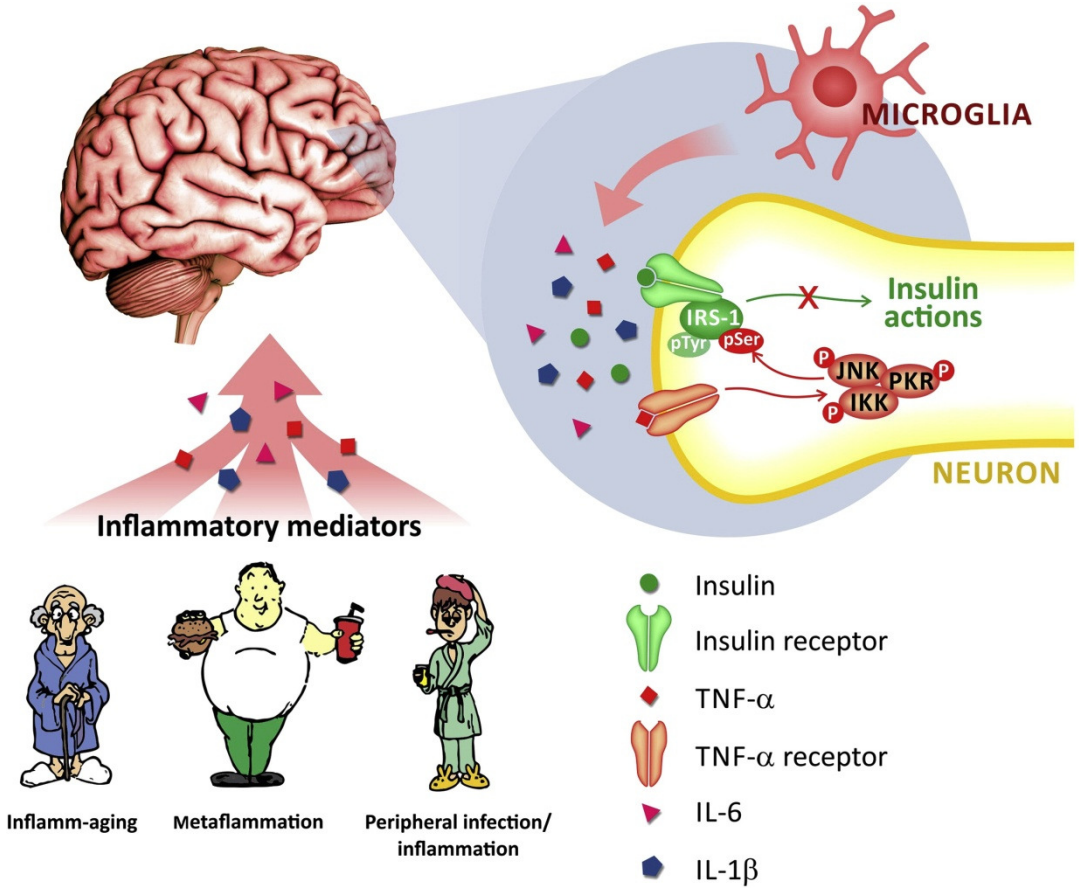
Proc Natl Acad Sci U S A. 2010;107:6557-8

Pathophysiological effects of insulin in metabolic regulation and its paradoxical action in cognition and associated diseases



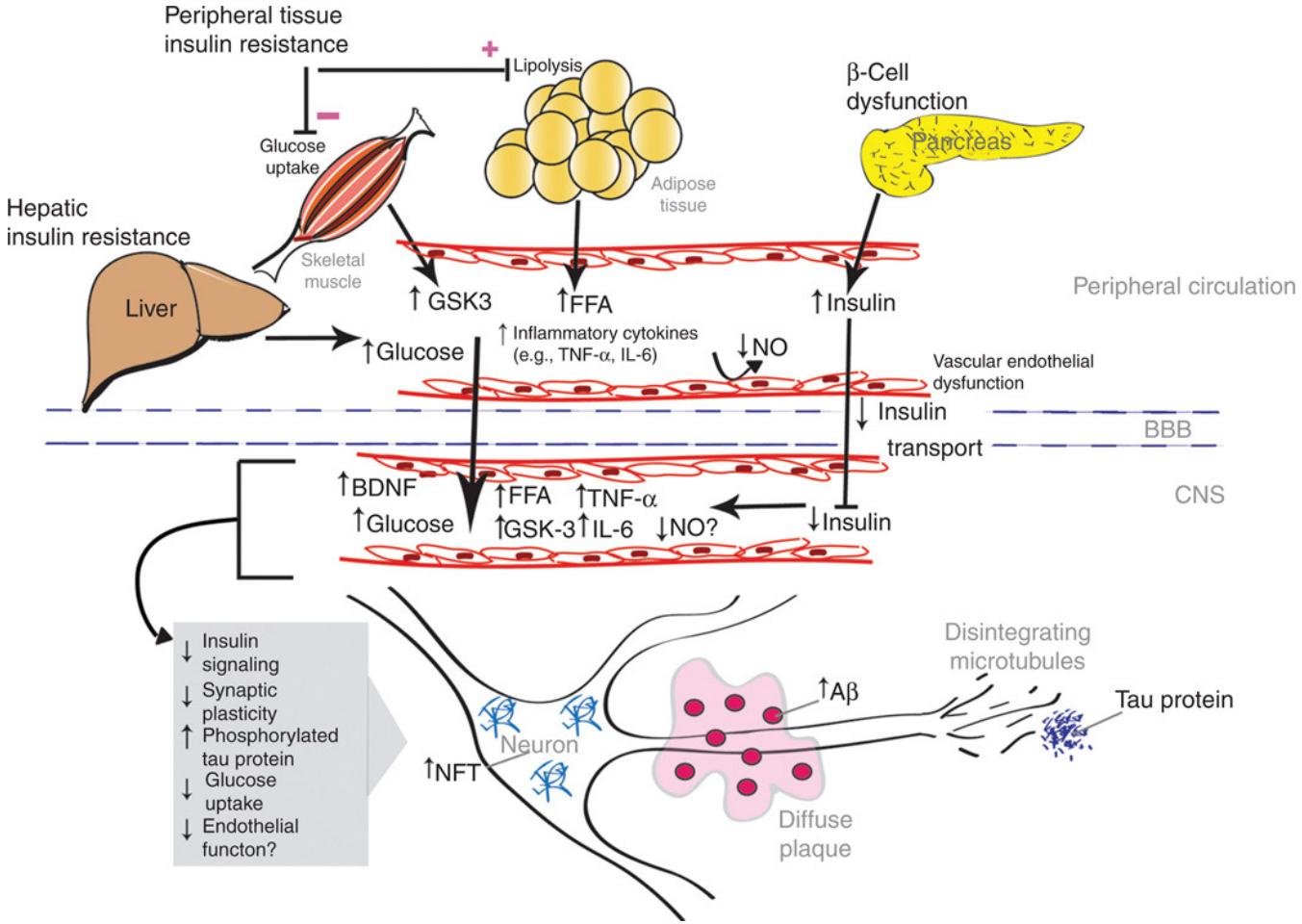
Alzheimer's & Dementia 10 (2014) S3–S11

Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease



Ferreira ST. Alzheimers Dement. 2014;10:S76-83

Obesity, insulin resistance, and Alzheimer's disease.



Obesity (Silver Spring). 2012;20:1549-57.

Epidemiologic Reviews
Vol. 35, 2013
DOI: 10.1093/epirev/mxs012
Advance Access publication:
January 11, 2013

Type 2 Diabetes as a Risk Factor for Alzheimer's Disease: The Confounders, Interactions, and Neuropathology Associated With This Relationship

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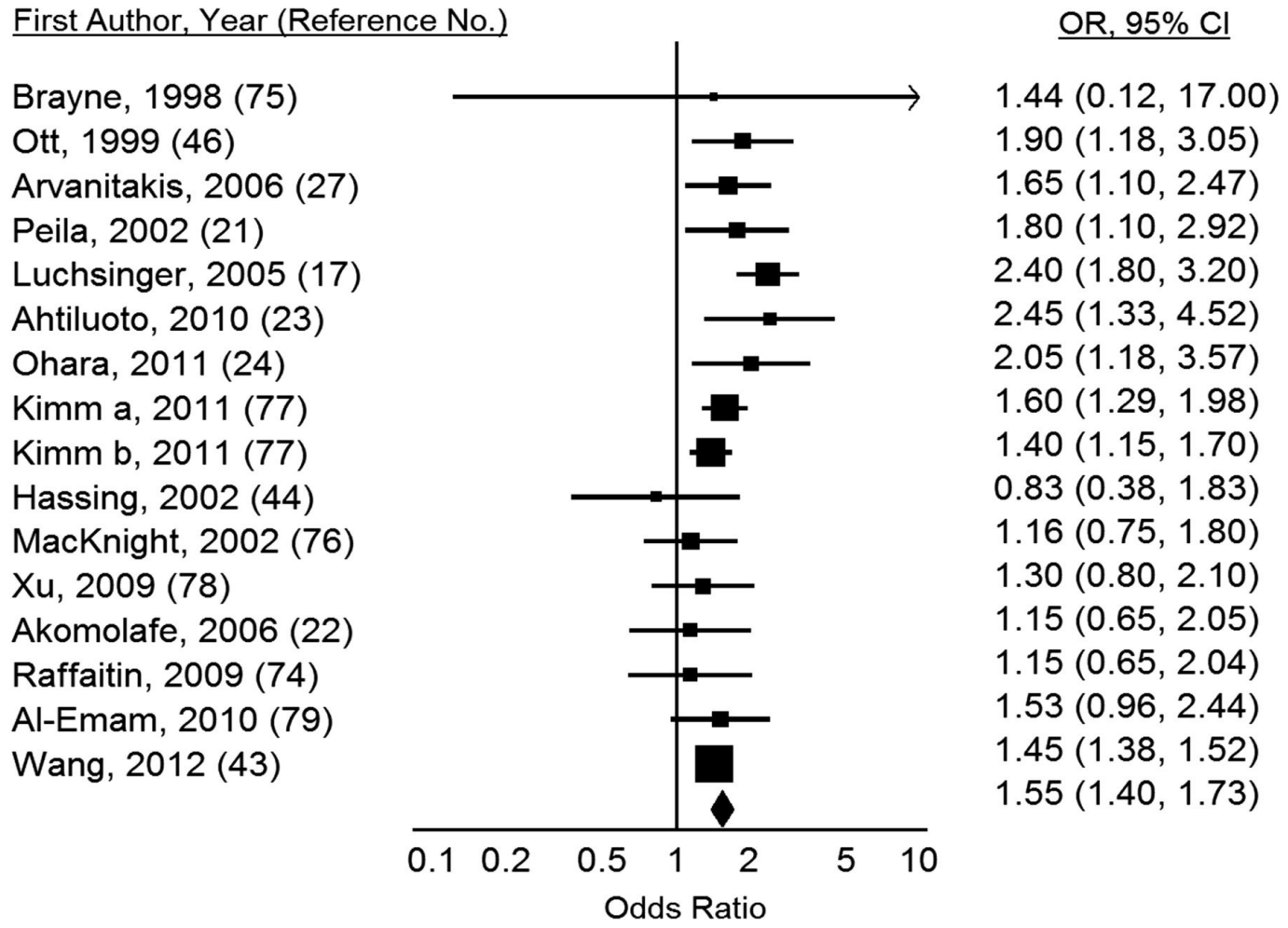
Accepted for publication November 21, 2013.

We performed a systematic review and meta-analysis to explore whether type 2 diabetes mellitus (T2DM) increases the risk of Alzheimer's disease (AD). We also reviewed interactions with smoking, hypertension, and apolipoprotein E ε4. Using a series of databases (MEDLINE, EMBASE, PubMed, Current Contents Connect, and Google Scholar), we identified a total of 15 epidemiologic studies. Fourteen studies reported positive associations, of which 9 were statistically significant. Risk estimates ranged from 0.83 to 2.45. The pooled adjusted risk ratio was 1.57 (95% confidence interval: 1.41, 1.75), with a population-attributable risk of 8%. Smoking and hypertension, when comorbid with T2DM, had odds of 14 and 3, respectively. Of the 5 studies that investigated the interaction between T2DM and apolipoprotein E ε4, 4 showed positive associations, of which 3 were significant, with odds ranging from 2.4 to 4.99. The pooled adjusted risk ratio was 2.91 (95% confidence interval: 1.51, 5.61). Risk estimates were presented in the context of a key confounder—cerebral infarcts—which are more common in those with T2DM and might contribute to the manifestation of clinical AD. We provide evidence from clinico-neuropathologic studies that demonstrates the following: First, cerebral infarcts are more common than AD-type pathology in those with T2DM and dementia. Second, those with dementia at postmortem are more likely to have both AD-type and cerebrovascular pathologies. Finally, cerebral infarcts reduce the number of AD lesions required for the manifestation of clinical dementia, but they do not appear to interact synergistically with AD-type pathology. Therefore, the increased risk of clinically diagnosed AD seems to be mediated through cerebrovascular pathology.

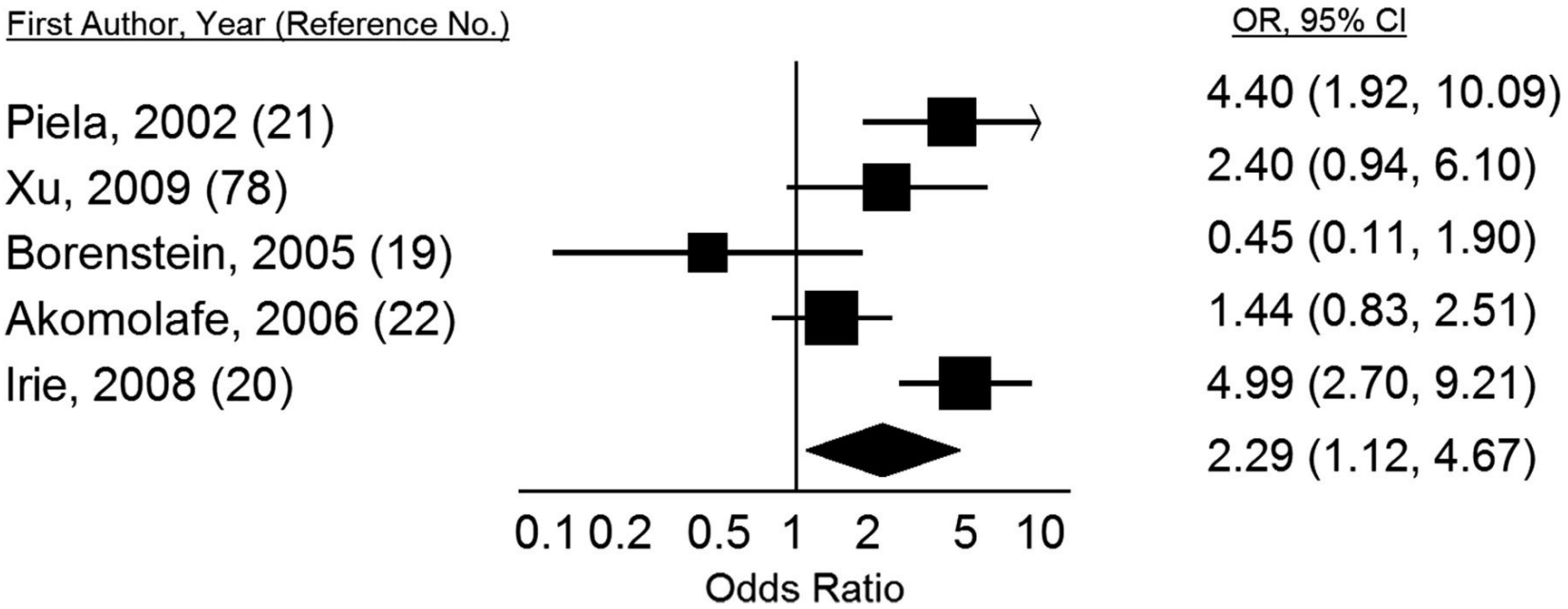
Alzheimer disease; apolipoprotein E; dementia; risk factors; type 2 diabetes mellitus

Effect of type 2 diabetes mellitus on the risk of Alzheimer's disease.



Vagelatos N and Eslick G. Epidemiol Rev 2013;35:152-160

Effect of interaction between type 2 diabetes mellitus and apolipoprotein ε4 on the risk of Alzheimer's disease.



Vagelatos N and Eslick G. Epidemiol Rev 2013;35:152-160

Arch Neurol. 2004 May;61(5):661-6.

Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function.

Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA.

BACKGROUND:

Few prospective studies have assessed diabetes mellitus as a risk factor for incident Alzheimer disease (AD) and decline in cognitive function.

OBJECTIVE:

To evaluate the association of diabetes mellitus with risk of AD and change in different cognitive systems.

DESIGN:

Longitudinal cohort study.

PARTICIPANTS:

For up to 9 years, 824 older (those >55 years) Catholic nuns, priests, and brothers underwent detailed annual clinical evaluations.

MAIN OUTCOME MEASURES:

Clinically diagnosed AD and change in global and specific measures of cognitive function.

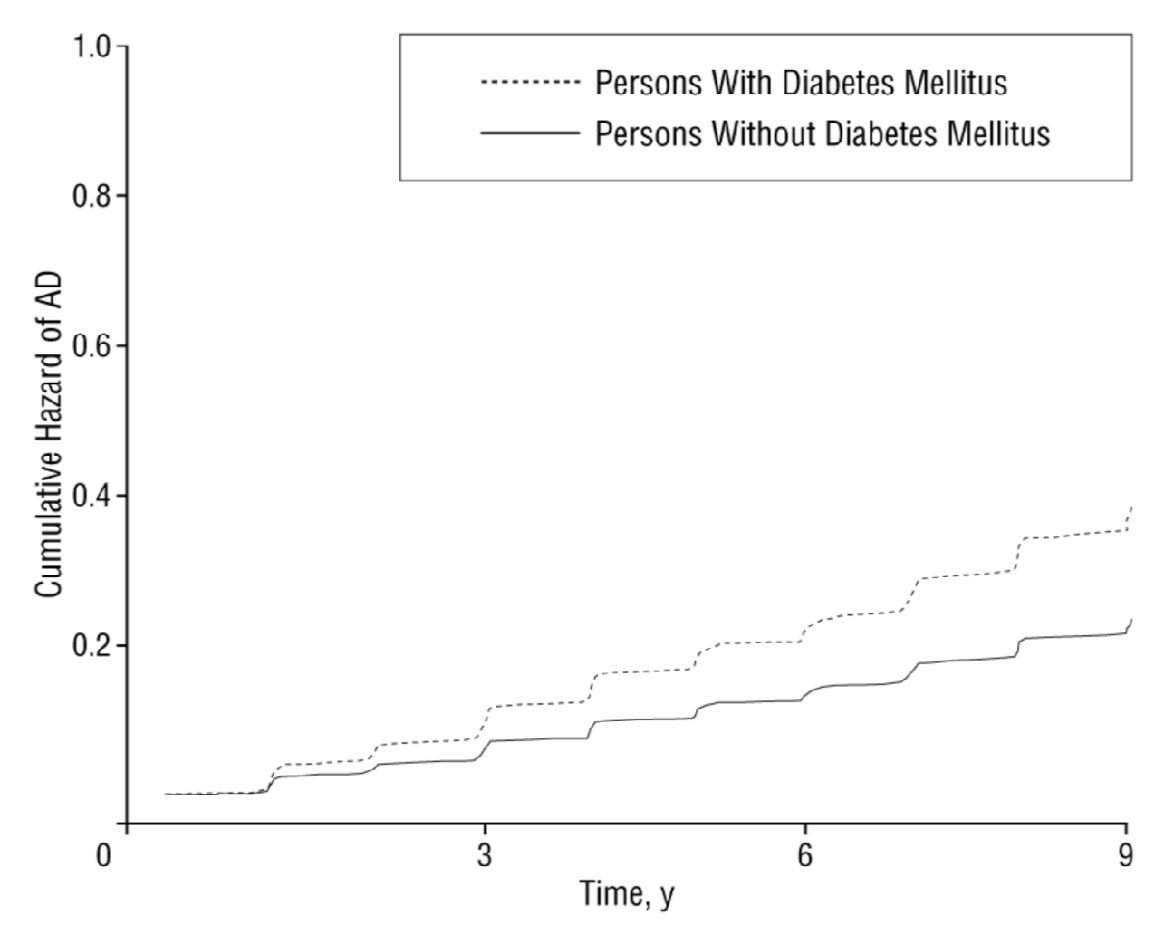
RESULTS:

Diabetes mellitus was present in 127 (15.4%) of the participants. During a mean of 5.5 years of observation, 151 persons developed AD. In a proportional hazards model adjusted for age, sex, and educational level, those with diabetes mellitus had a 65% increase in the risk of developing AD compared with those without diabetes mellitus (hazard ratio, 1.65; 95% confidence interval, 1.10-2.47). In random effects models, diabetes mellitus was associated with lower levels of global cognition, episodic memory, semantic memory, working memory, and visuospatial ability at baseline. Diabetes mellitus was associated with a 44% greater rate of decline in perceptual speed (P =.02), but not in other cognitive systems.

CONCLUSIONS:

Diabetes mellitus may be associated with an increased risk of developing AD and may affect cognitive systems differentially.

Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function



Arch Neurol. 2004;61:661-666.

History of Medically Treated Diabetes and Risk of Alzheimer Disease in a Nationwide Case-Control Study

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ALINA SOLOMON, MD, PHD[1,3]
MIIA KIVIPELTO, MD, PHD[1,3]
MATTI UUSITUPA, MD, PHD[4,5]
HILKKA SOININEN, MD, PHD[1,6]
SIRPA HARTIKAINEN, MD, PHD[2,7]

OBJECTIVE—Type 2 diabetes in midlife or late life increases the risk of Alzheimer disease (AD), and type 1 diabetes has been associated with a higher risk of detrimental cognitive outcomes, although studies from older adults are lacking. We investigated whether individuals with AD were more likely to have a history of diabetes than matched controls from the general aged population.

RESEARCH DESIGN AND METHODS—Information on reimbursed diabetes medication (including both type 1 and 2 diabetes) of all Finnish individuals with reimbursed AD medication in 2005 (n = 28,093) and their AD-free control subjects during 1972–2005 was obtained from a special reimbursement register maintained by the Social Insurance Institute of Finland.

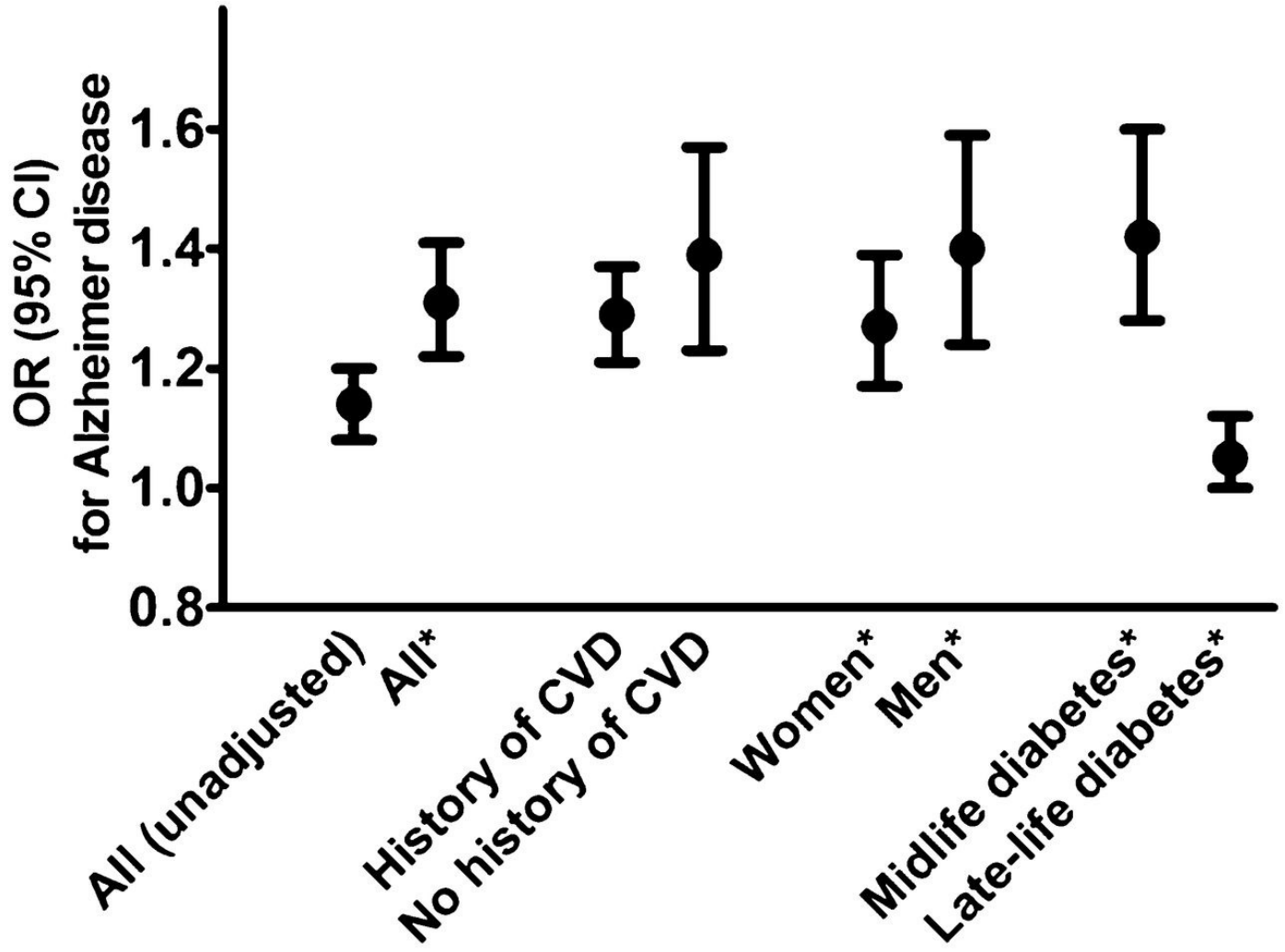
RESULTS—The prevalence of diabetes was 11.4% in the whole study population, 10.7% (n = 3,012) among control subjects, and 12.0% (n = 3,372) among AD case subjects. People with AD were more likely to have diabetes than matched control subjects (unadjusted OR 1.14 [95% CI 1.08–1.20]), even after adjusting for cardiovascular diseases (OR 1.31 [1.22–1.41]). The associations were stronger with diabetes diagnosed at midlife (adjusted OR 1.60 [1.34–1.84] and 1.25 [1.16–1.36] for midlife and late-life diabetes, respectively).

CONCLUSIONS—Individuals with clinically verified AD are more likely to have a history of clinically verified and medically treated diabetes than the general aged population, although the difference is small.

Diabetes Care 36:2015–2019, 2013

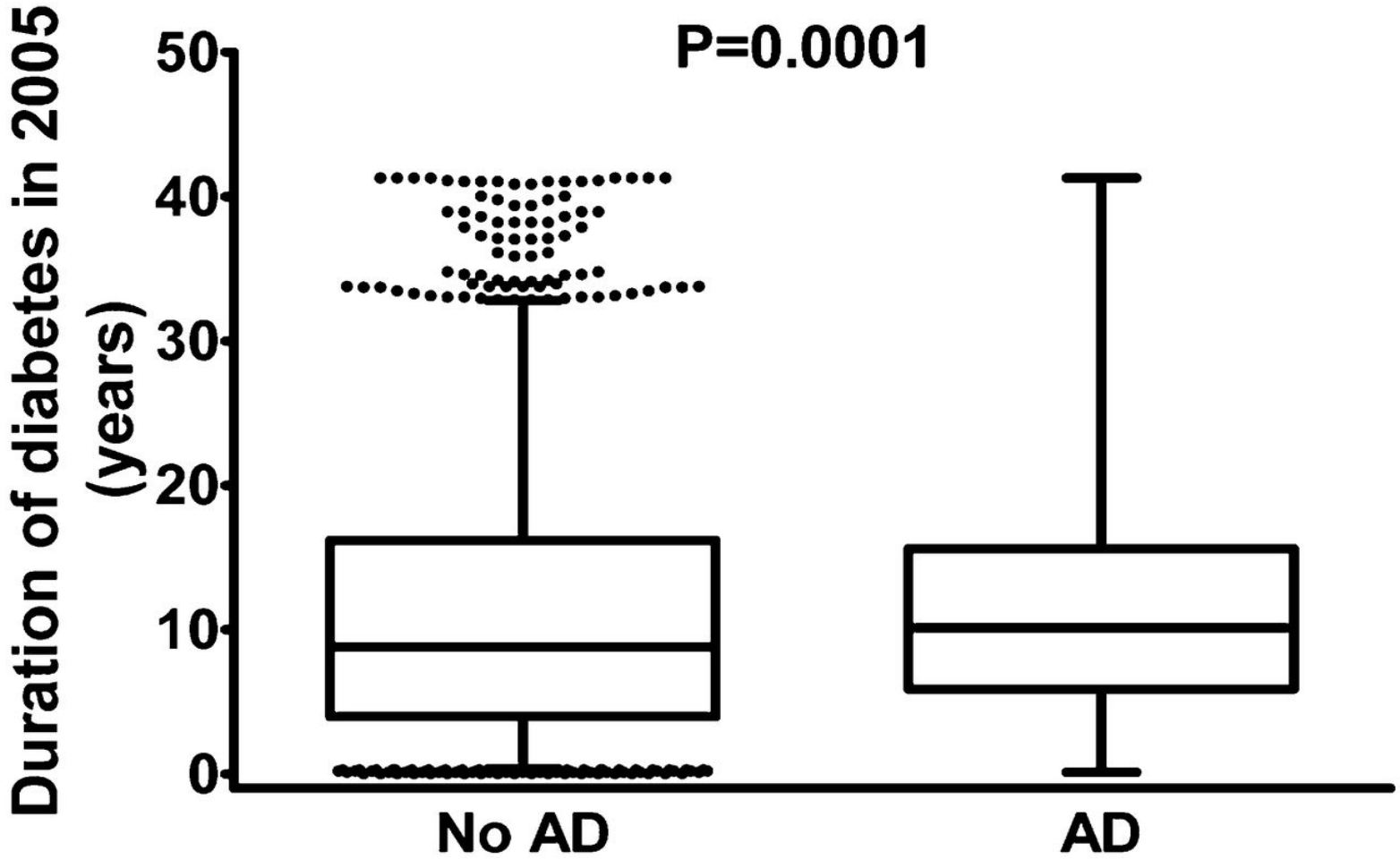
problem solving and mental flexibility have been found to be more common in individuals with type 1 diabetes than in the general population (8,9), to our knowledge, no data on older individuals or in a longitudinal life-course perspective have been reported. Possible explanations include the involvement of insulin in AD pathogenesis (10). Although memory functions are improved immediately after an intravenous insulin dose, chronic hyperinsulinemia and insulin resistance may have negative effects on cognition (11,12). The severity of dementia and cognitive decline seem to be more related to decreased insulin secretion than changes in glucose concentrations in patients with early-stage AD (13). Other suggested mechanisms linking type 2 diabetes and AD include inflammatory cytokines, oxidative stress, amyloid-β deposits, and microvascular disease resulting from T2D (14,15). The association between diabetes and cognitive decline among people who already have AD seems to be more complex, as indicated by inconsistent findings showing a faster

Association between diabetes and incident AD



Tolppanen A et al. Diabetes Care 2013;36:2015-2019

Duration of diabetes and AD



Tolppanen A et al. Diabetes Care 2013;36:2015-2019

JAMA Intern Med. 2013 July 22; 173(14): 1300–1306. doi:10.1001/jamainternmed.2013.6176.

Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus

Kristine Yaffe, MD, **Cherie M. Falvey, MPH**, **Nathan Hamilton, MA**, **Tamara B. Harris, MD**, **Eleanor M. Simonsick, PhD**, **Elsa S. Strotmeyer, PhD, MPH**, **Ronald I. Shorr, MD, MS**, **Andrea Metti, MPH**, and **Ann V. Schwartz, PhD, MPH for the Health ABC Study**
Department of Psychiatry, University of California, San Francisco (Yaffe, Falvey); Department of Neurology, University of California, San Francisco (Yaffe); Department of Epidemiology and Biostatistics, University of California, San Francisco (Yaffe, Schwartz); San Francisco Veterans Affairs Medical Center, San Francisco, California (Yaffe, Falvey, Hamilton); Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, Baltimore, Maryland (Harris); Clinical Research Branch, National Institute on Aging, Baltimore, Maryland (Simonsick); Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania (Strotmeyer, Metti); Department of Aging and Geriatric Research, University of Florida, Gainesville (Shorr)

Abstract

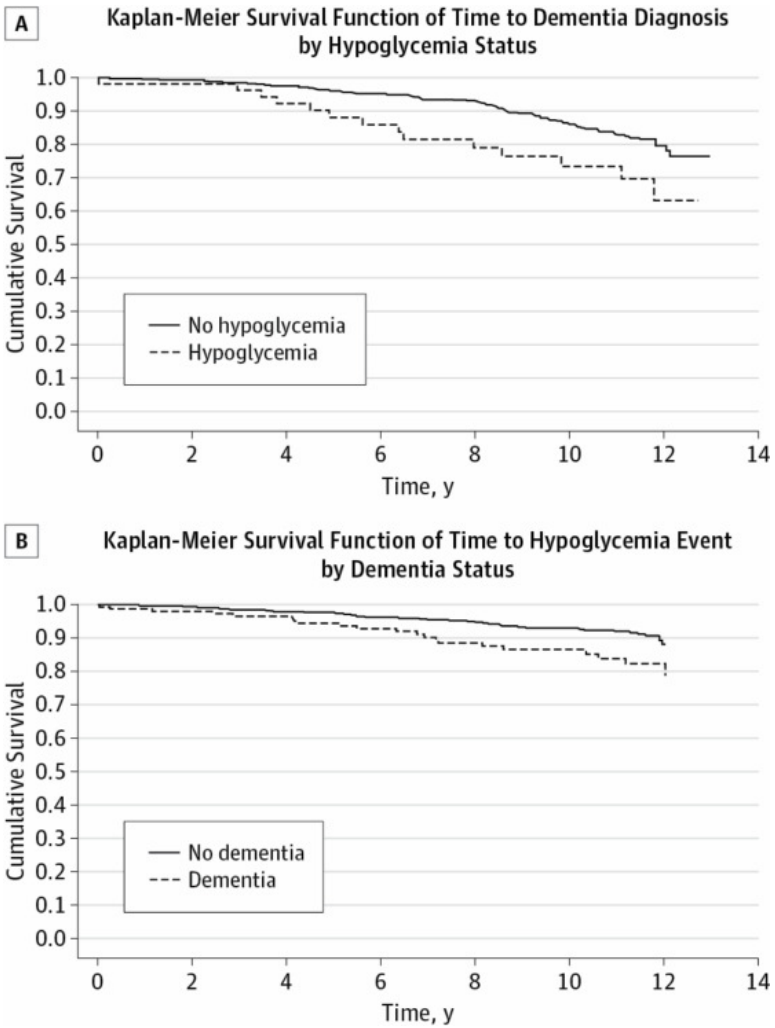
IMPORTANCE—Hypoglycemia commonly occurs in patients with diabetes mellitus (DM) and may negatively influence cognitive performance. Cognitive impairment in turn can compromise DM management and lead to hypoglycemia.

OBJECTIVE—To prospectively evaluate the association between hypoglycemia and dementia in a biracial cohort of older adults with DM.

DESIGN AND SETTING—Prospective population-based study.

PARTICIPANTS—We studied 783 older adults with DM (mean age, 74.0 years; 47.0% of black race/ethnicity; and 47.6% female) who were participating in the prospective population-based

Association Between Hypoglycemia and Dementia



JAMA Intern Med. 2013;173:1300-1306

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PLOS | ONE

Diabetes Mellitus and the Risk of Alzheimer's Disease: A Nationwide Population-Based Study

Chin-Chou Huang[1,2,6,8☯], Chia-Min Chung[12,13☯], Hsin-Bang Leu[2,3,6,9], Liang-Yu Lin[4,7,8], Chun-Chih Chiu[2,6,7], Chien-Yi Hsu[2,6,7], Chia-Hung Chiang[6,7,9,11], Po-Hsun Huang[2,6,7,9], Tzeng-Ji Chen[5,10], Shing-Jong Lin[1,2,6,9], Jaw-Wen Chen[1,2,6,8*¶], Wan-Leong Chan[2,3,7*¶]

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Abstract

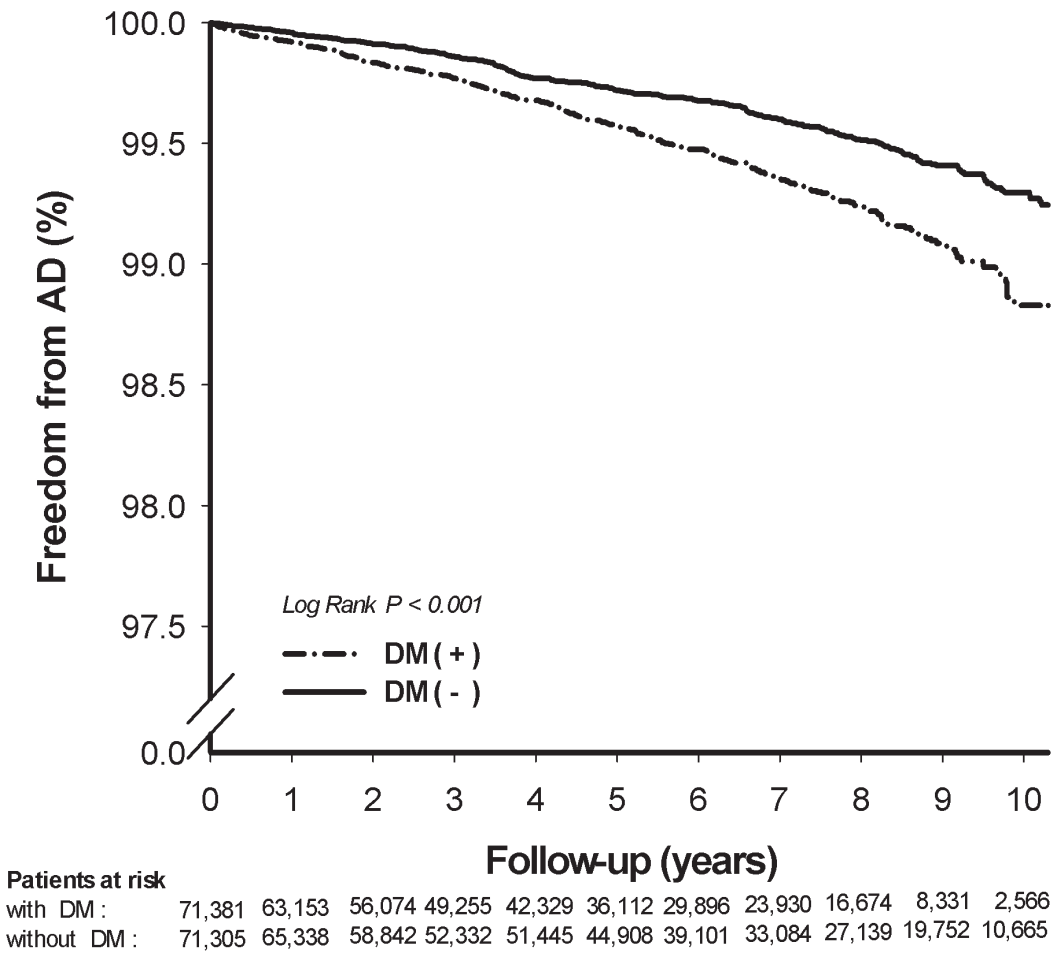
Objectives: Possible association between diabetes mellitus (DM) and Alzheimer's disease (AD) has been controversial. This study used a nationwide population-based dataset to investigate the relationship between DM and subsequent AD incidence.

Methods: Data were collected from Taiwan's National Health Insurance Research Database, which released a cohort dataset of 1,000,000 randomly sampled people and confirmed it to be representative of the Taiwanese population. We identified 71,433 patients newly diagnosed with diabetes (age 58.74±14.02 years) since January 1997. Using propensity score, we matched them with 71,311 non-diabetic subjects by time of enrollment, age, gender, hypertension, hyperlipidemia, and previous stroke history. All the patients were followed up to December 31, 2007. The endpoint of the study was occurrence of AD.

Results: Over a maximum 11 years of follow-up, diabetic patients experienced a higher incidence of AD than non-diabetic subjects (0.48% vs. 0.37%, $p<0.001$). After Cox proportional hazard regression model analysis, DM (hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.50–2.07, $p<0.001$), age (HR, 1.11; 95% CI, 1.10–1.12, $p<0.001$), female gender (HR, 1.24; 95% CI, 1.06–1.46, $p=0.008$), hypertension (HR, 1.30; 95% CI, 1.07–1.59, $p=0.01$), previous stroke history (HR, 1.79; 95% CI, 1.28–2.50, $p<0.001$), and urbanization status (metropolis, HR, 1.32; 95% CI, 1.07–1.63, $p=0.009$) were independently associated with the increased risk of AD. Neither monotherapy nor combination therapy with oral antidiabetic medications were associated with the risk of AD after adjusting for underlying risk factors and the duration of DM since diagnosis. However, combination therapy with insulin was found to be associated with greater risk of AD (HR, 2.17; 95% CI, 1.04–4.52, $p=0.039$).

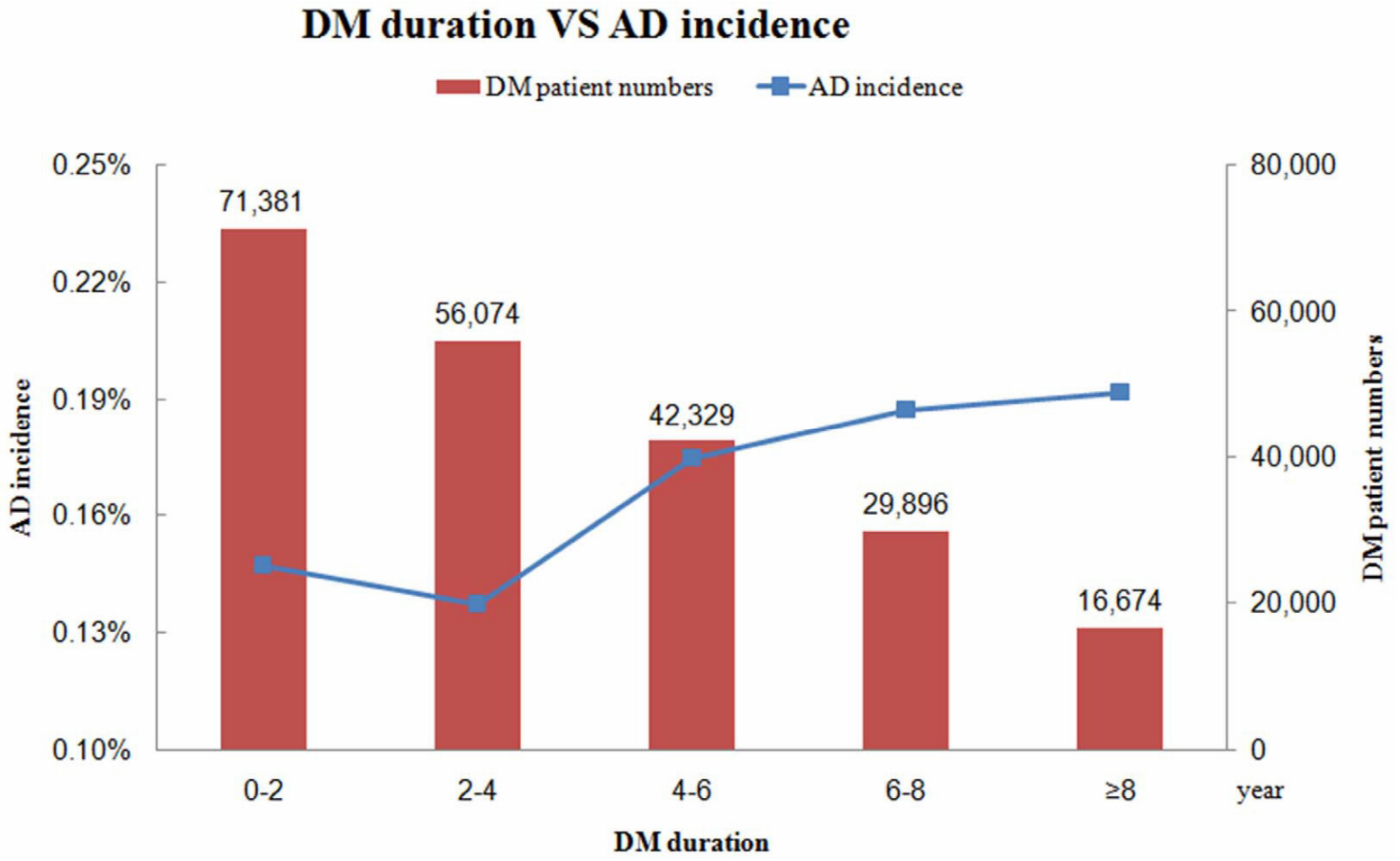
Conclusion: Newly diagnosed DM was associated with increased risk of AD. Use of hypoglycemic agents did not ameliorate the risk.

Kaplan-Meier estimates of survival free of Alzheimer's disease (AD) events in subjects categorized by diabetes mellitus (DM)



PLoS ONE 2014;9(1): e87095. doi:10.1371

Incidence of Alzheimer's disease (AD) according to the duration of diabetes mellitus (DM)



PLoS ONE 2014;9(1): e87095. doi:10.1371

Independent predictors of Alzheimer's disease

Variables	HR	(95% CI)	p-value
Diabetes mellitus	1.76	(1.50–2.07)	**<0.001**
Age, years	1.11	(1.10–1.12)	**<0.001**
Female	1.24	(1.06–1.46)	**0.008**
Hypertension	1.30	(1.07–1.59)	**0.010**
Hyperlipidemia	1.06	(0.75–1.51)	0.742
Stroke	1.79	(1.28–2.50)	**<0.001**
Coronary artery disease	0.94	(0.69–1.27)	0.688
Arrhythmia	1.15	(0.78–1.71)	0.475
Heart failure	0.74	(0.40–1.37)	0.342
Depression	1.44	(0.36–5.80)	0.607
Geographic area			
East	1.00		
South	1.42	(0.82–2.45)	0.205
Central	1.18	(0.67–2.09)	0.569
North	1.28	(0.73–2.24)	0.395
Urbanization status			
Rural area	1.00		
Satellite city/town	1.04	(0.83–1.31)	0.703
Metropolis	1.32	(1.07–1.63)	**0.009**

CI = confidence interval, HR = hazard ratio.
doi:10.1371/journal.pone.0087095.t002

PLoS ONE 9(1): e87095. doi:10.1371

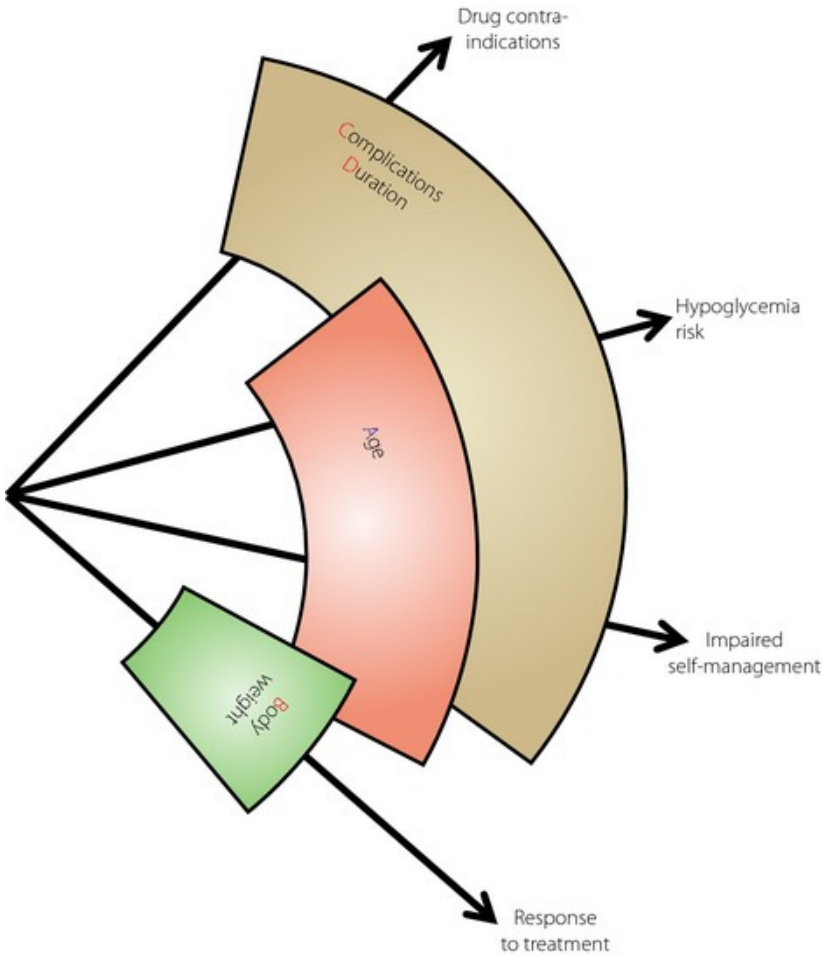
Medication for diabetes mellitus and risk of Alzheimer's disease in diabetic patients.

Medication	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Metformin: monotherapy	0.88 (0.36–2.16)	0.69 (0.28–1.71)
Metformin: combination therapy	0.60 (0.28–1.30)	0.57 (0.26–1.26)
Sulfonylureas: monotherapy	**0.50 (0.34–0.75)***	0.75 (0.50–1.13)
Sulfonylureas: combination therapy	0.53 (0.23–1.23)	0.59 (0.25–1.37)
Thiazolidinediones: monotherapy	0.83 (0.12–5.93)	0.92 (0.13–6.60)
Thiazolidinediones: combination therapy	0.51 (0.22–1.17)	0.86 (0.36–2.02)
α-glucosidase blockers: monotherapy	0.88 (0.22–3.58)	0.71 (0.18–2.89)
α-glucosidase blockers: combination therapy	1.11 (0.53–2.34)	1.37 (0.64–2.93)
Non-sulfonylurea insulin secretagouge: monotherapy	1.67 (0.81–3.44)	1.33 (0.64–2.75)
Non-sulfonylurea insulin secretagouge: combination therapy	**2.58 (1.16–5.75)‡**	2.11 (0.93–4.77)
Insulin: monotherapy	**2.27 (1.47–3.51)***	1.53 (0.98–2.39)
Insulin: combination therapy	**3.79 (1.89–7.58)***	**2.17 (1.04–4.52)‡**

CI = confidence interval, HR = hazard ratio.
*$p<0.001$,
†$p<0.01$,
‡$p<0.05$.
Adjusted for age, sex, comorbidities (including hypertension, hyperlipidemia, stroke, coronary artery disease, arrhythmia, heart failure, and depression), geographic area, and urbanization status.
doi:10.1371/journal.pone.0087095.t003

PLoS ONE 9(1): e87095. doi:10.1371

The ABCD of type 2 diabetes



J Diabetes Investig. 2014;5:134-41

Glucose indices are associated with cognitive and structural brain measures in young adults

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ABSTRACT

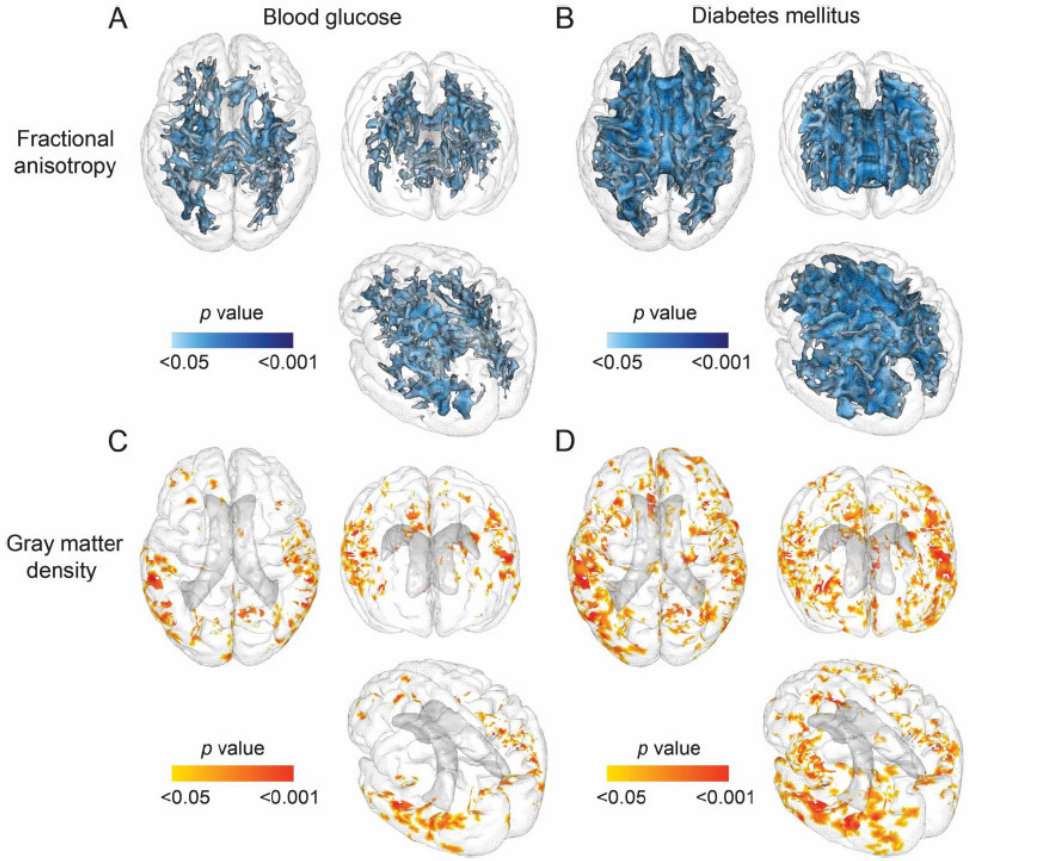
Objective: To evaluate the possible early consequences of impaired glucose metabolism on the brain by assessing the relationship of diabetes, fasting blood glucose (FBG) levels, and insulin resistance with cognitive performance and brain integrity in healthy young and middle-aged adults.

Methods: The sample included dementia-free participants (mean age 40 ± 9 years; 53% women) of the Framingham Heart Study third-generation cohort with cognitive testing of memory, abstract reasoning, visual perception, attention, and executive function (n = 2,126). In addition, brain MRI examination (n = 1,597) was used to determine white matter, gray matter, and white matter hyperintensity (WMH) volumes and fractional anisotropy measures. We used linear regression models to assess relationships between diabetes, FBG, and insulin resistance with cognition, lobar gray matter, and WMH volumes as well as voxel-based microstructural white matter integrity and gray matter density, adjusting for potential confounders. Mediating effect of brain lesions on the association of diabetes with cognitive performance was also tested.

Results: Diabetes was associated with worse memory, visual perception, and attention performance; increased WMH; and decreased total cerebral brain and occipital lobar gray matter volumes. The link of diabetes with attention and memory was mediated through occipital and frontal atrophy, and the latter also through hippocampal atrophy. Both diabetes and increased FBG were associated with large areas of reductions in gray matter density and fractional anisotropy on voxel-based analyses.

Conclusions: We found that hyperglycemia is associated with subtle brain injury and impaired attention and memory even in young adults, indicating that brain injury is an early manifestation of impaired glucose metabolism. ***Neurology*® 2015;84:2329–2337**

3D view of cerebral regions in which increased fasting blood glucose and diabetes are associated with decreased fractional anisotropy and gray matter density



(A–D) The voxel-based regression included fractional anisotropy or gray matter density as the dependent variable and blood glucose or diabetes as independent variables. Age, sex, time between examination 1 and MRI, hypertension, and body mass index were covariates.

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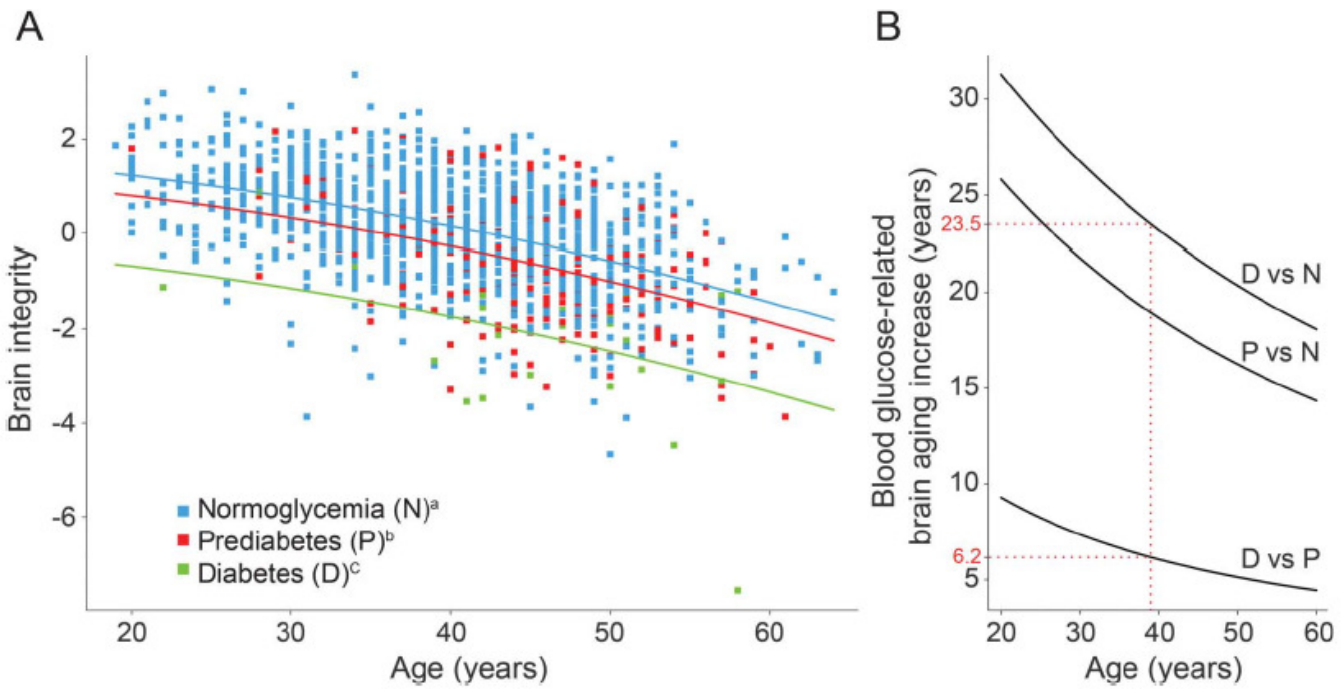
Figure 2 Regression curves



Regression curves relating brain integrity as expressed by the first principal component as a function of fasting blood glucose category and age of the individual (A) and the difference in brain aging increase between glucose categories according to age (B). Red dotted lines indicate brain integrity of a 40-year-old patient by glucose level category. Brain integrity of a 40-year-old prediabetic individual corresponds to that of a normoglycemic individual 6.1 years older, and this difference is 23.2 years when comparing the brain integrity of 40-year-old diabetic and normoglycemic individuals. Brain integrity is calculated from brain regions in which fractional anisotropy and gray matter density are significantly associated with fasting blood glucose. [a]Normoglycemia (fasting blood glucose <100 mg/dL). [b]Prediabetes (fasting blood glucose between 100 and 126 mg/dL). [c]Diabetes (fasting blood glucose >126 mg/dL).

Missatges per recordar

- Els pacients amb diabetis tipus 2 tenen major risc de presentar malaltia d'Alzheimer
- La hipoglucèmia pot augmentar el risc de demència i la demència augmenta el risc de presentar hipoglucèmies
- La malaltia d'Alzheimer podria ser una malaltia neuroendocrina complexa en la qual les cèl·lules del cervell tenen problemes per utilitzar la insulina. Diabetis tipus 3?

Missatges per recordar

- Tant en la diabetis com en la malaltia d'Alzheimer coexisteixen processos inflamatoris crònics
- Donada la probable relació entre ambdues malalties, la prevenció de la diabetis amb un estil de vida saludable, que inclogui activitat física regular i una dieta cardiosaludable, disminuiria la incidència de la malaltia d'Alzheimer
- Aquesta prevenció ha de començar en la infància i intensificar-se en l'edat mitjana de la vida, per a això són necessàries mesures de salut pública