Consiglio Nazionale delle Ricerche

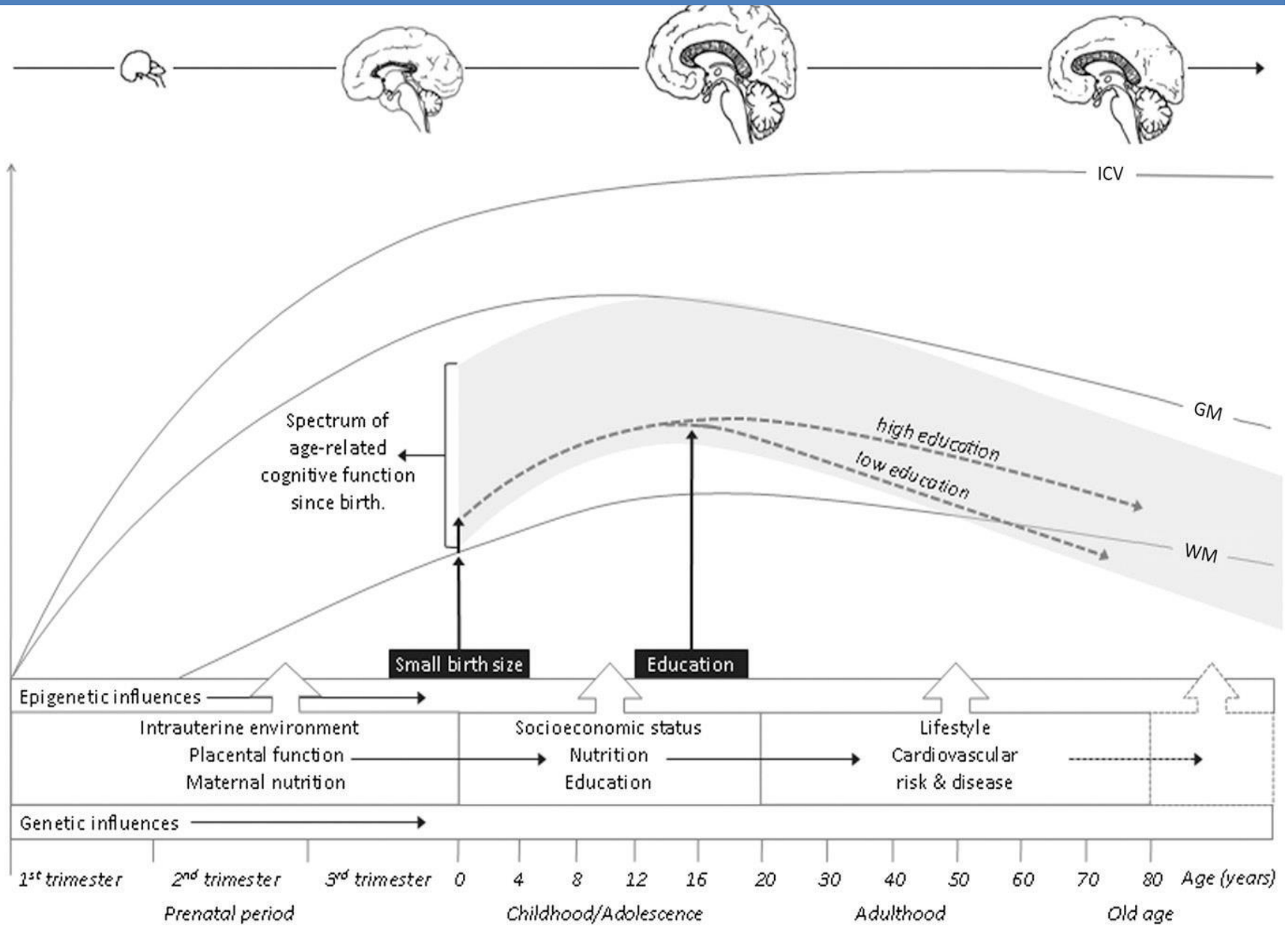
Quale approccio al paziente con disturbo cognitivo

Stefania Maggi

CNR Istituto di Neuroscienze

Padova

Modello che ipotizza le origini e l'andamento nell'arco della vita dell'invecchiamento cerebrale



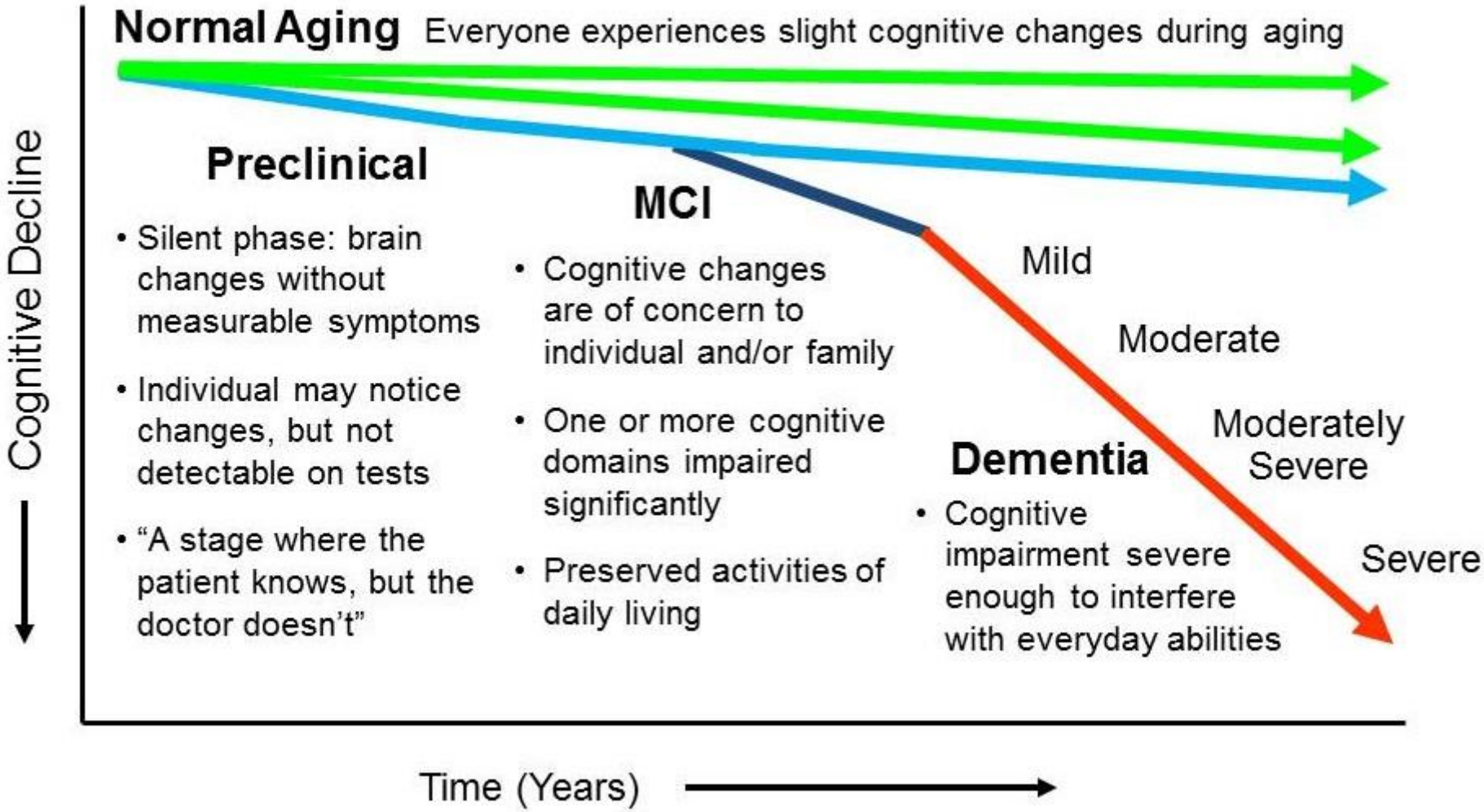
Muller et al, Pediatrics 2014

Mild Neurocognitive Disorder (MCI)

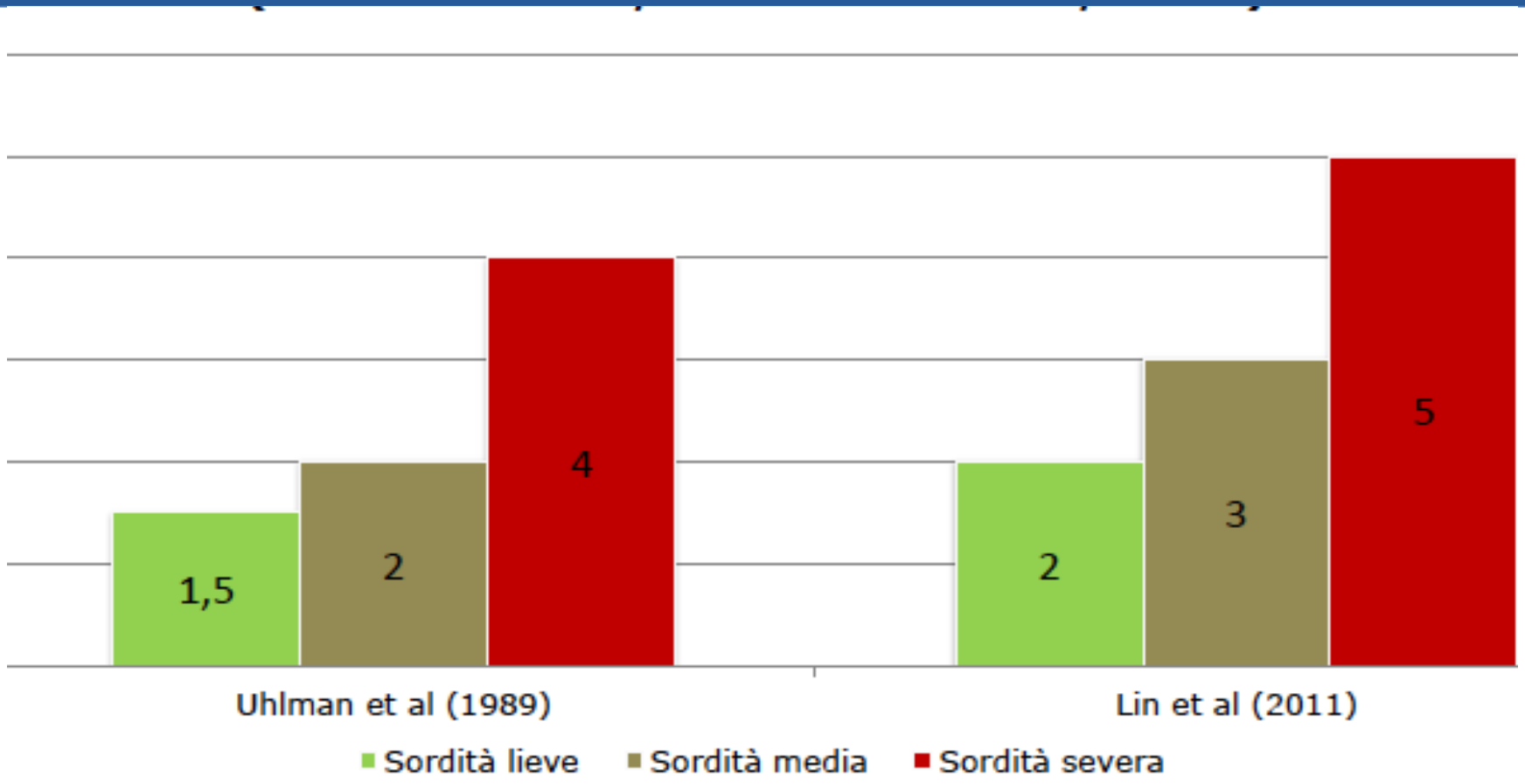
1. Cognitive decline
2. Single cognitive domain impaired (usually)
3. Preservation of independence

Major Neurocognitive Disorder (Dementia)

1. Cognitive decline
2. Significant cognitive impairment in one or more often multiple cognitive domains
3. Loss of independence

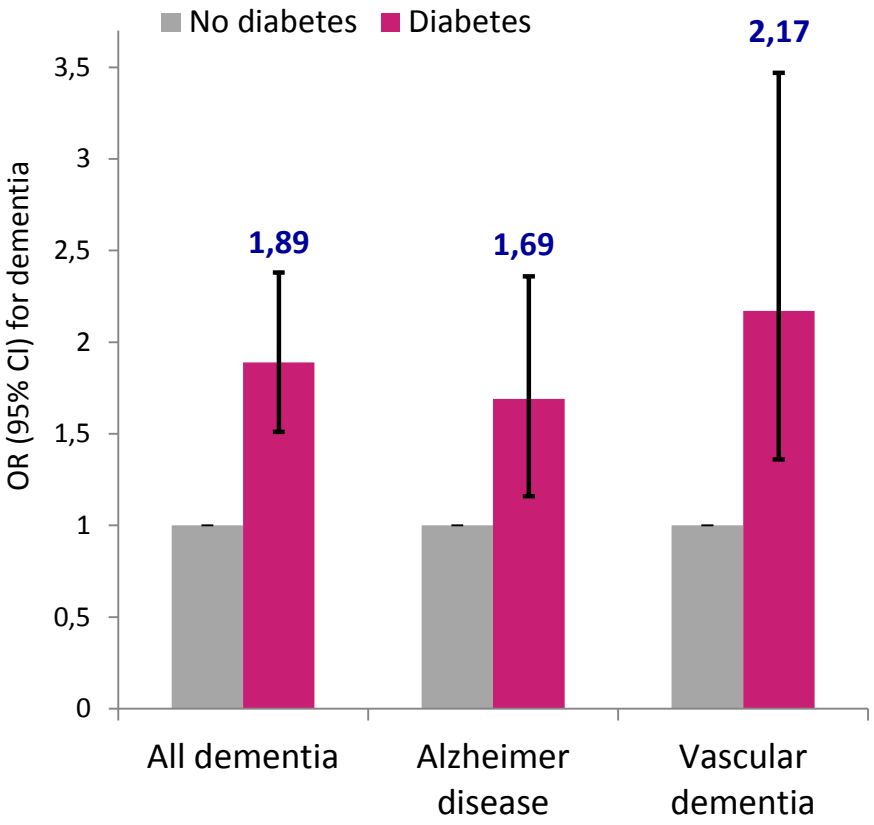

Normal Aging
Everyone experiences slight cognitive changes during aging
Preclinical
• Silent phase: brain changes without measurable symptoms
• Individual may notice changes, but not detectable on tests
• "A stage where the patient knows, but the doctor doesn't"
MCI
• Cognitive changes are of concern to individual and/or family
• One or more cognitive domains impaired significantly
• Preserved activities of daily living
Mild
Moderate
Moderately Severe
Severe
Dementia
• Cognitive impairment severe enough to interfere with everyday abilities
Cognitive Decline
Time (Years)

Rischio di sviluppare demenza in relazione al disturbo uditivo

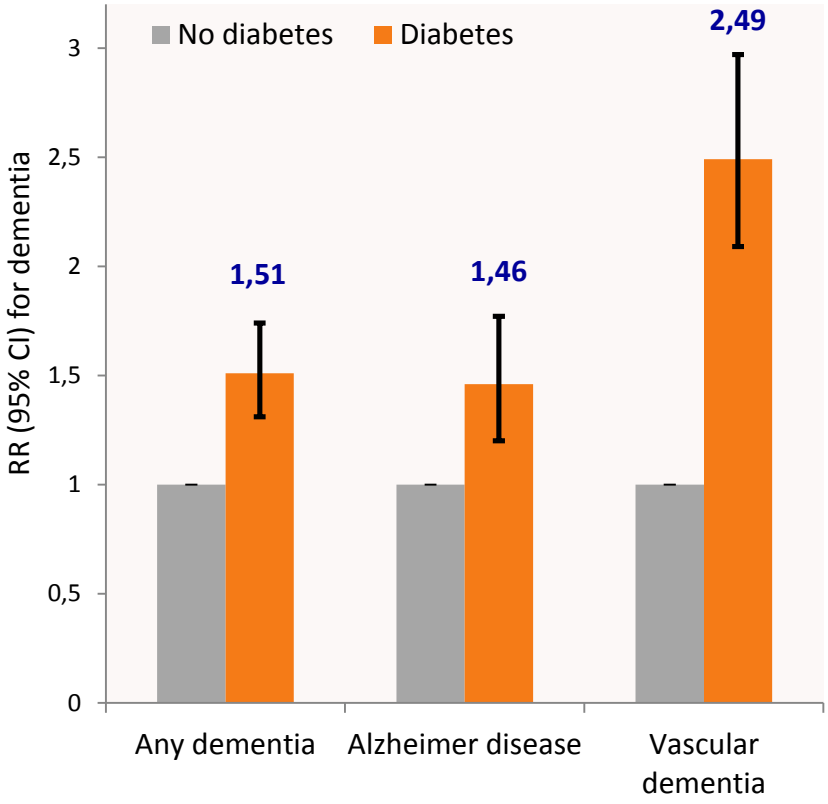


Rischio di sviluppare demenza in relazione al diabete di tipo 2

T2DM is associated with increased risk of dementia

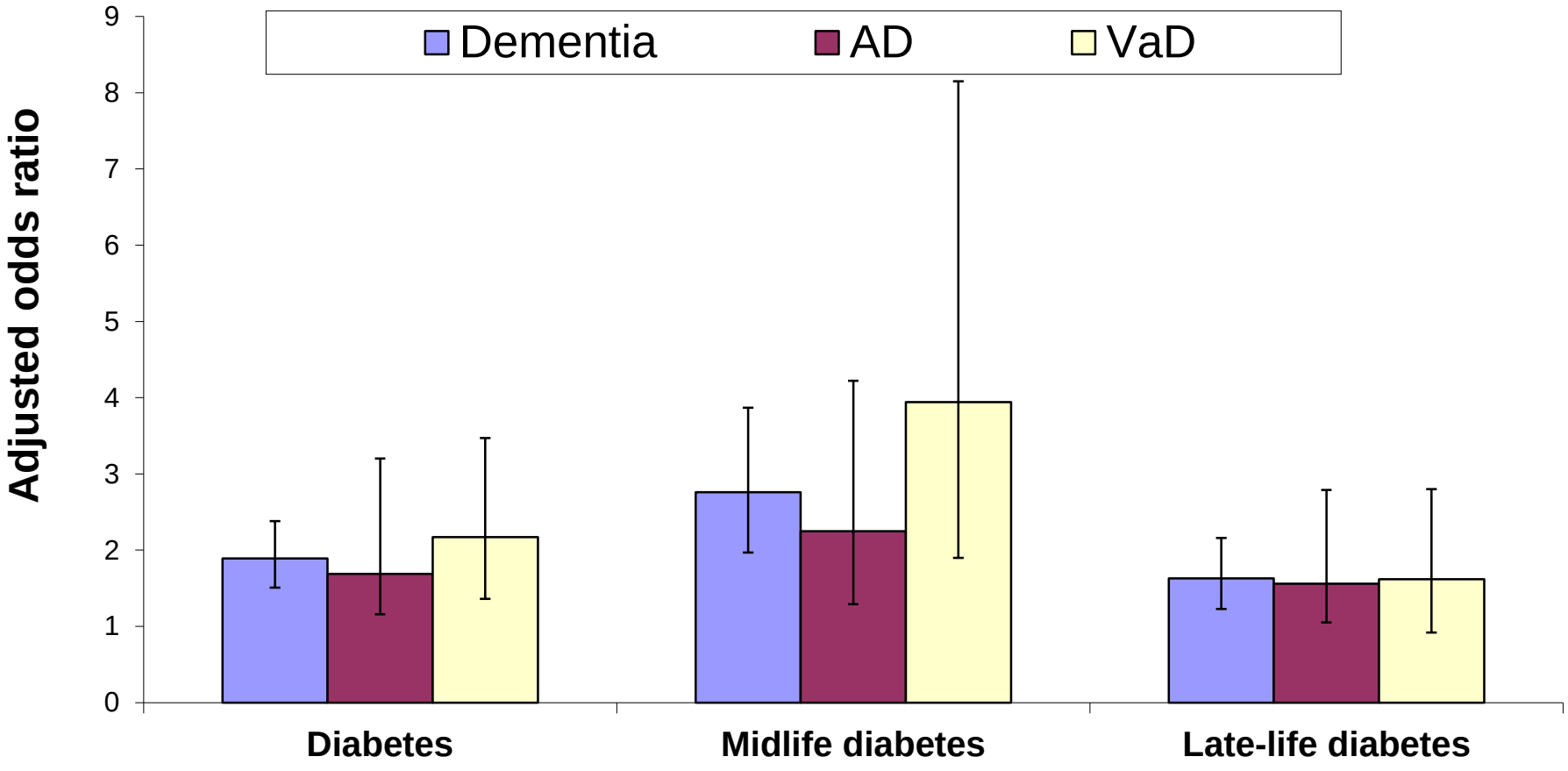


Xu et al., *Diabetes* 2009; 58:71-7



Cheng et al., *Intern Med J* 2012; 42:484-91

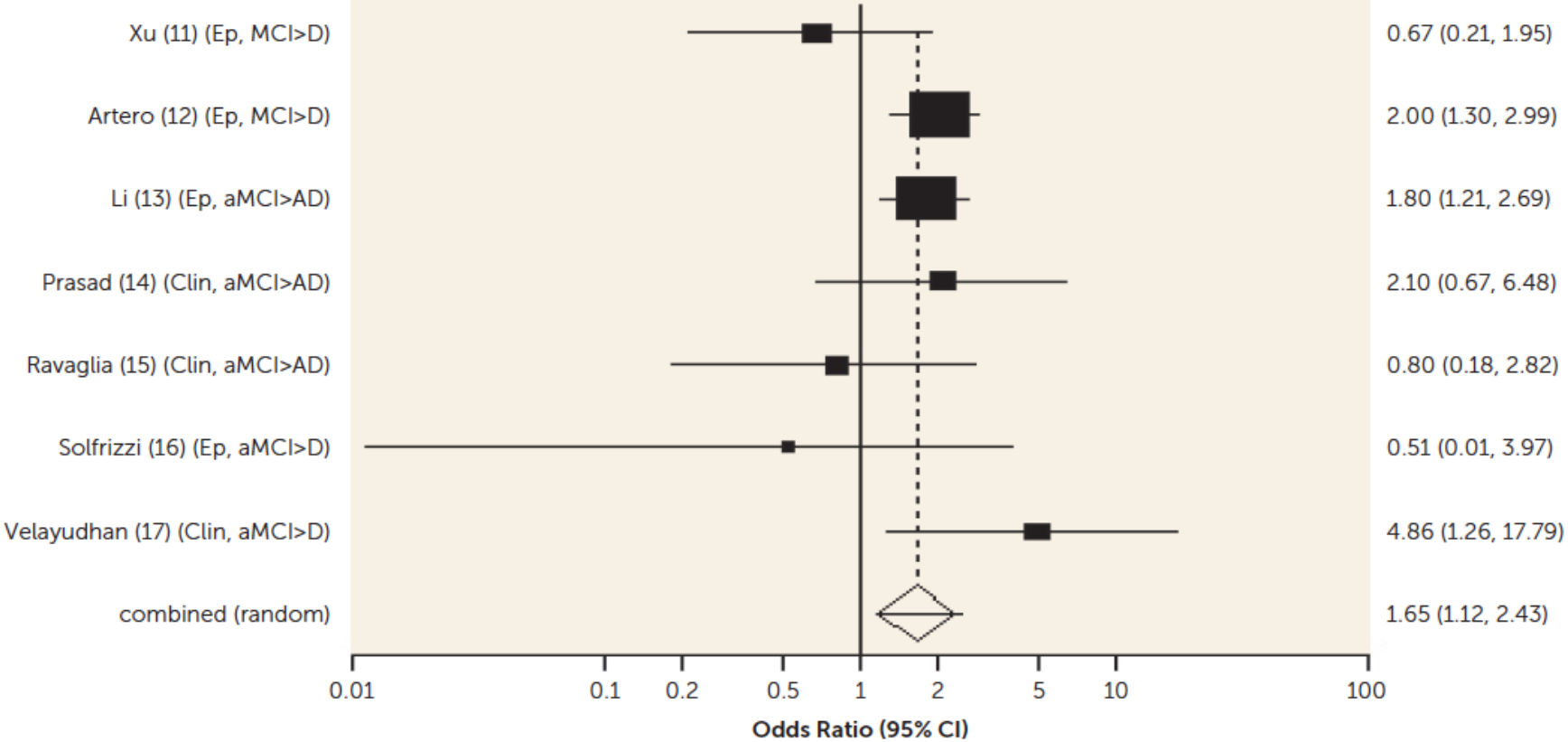
Il diabete in età adulta raddoppia il rischio di demenza



Xu et al, Diabetes 2010

Rischio di progressione per MCI a demenza in relazione al diabete di tipo 2

FIGURE 1. Meta-Analysis Plot for Diabetes as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

Cooper et al, Am J Psych 2015

Malattie croniche e Comorbidità con il disturbo uditivo

Diabetes

- High blood glucose causes tiny blood vessels in the inner ear to break, disrupting sound reception.
- Mechanisms related to neuropathic or microvascular factors, inflammation, or hyperglycemia causes an association between diabetes and hearing loss.
- Up to 30% of adults with diabetes will experience hearing loss.

Thyroid disease

- Hypothyroidism (under active thyroid) causes hearing loss that may be conductive, sensorineural or mixed in nature, although it is primarily sensorineural.
- Most losses are flat, bilateral, symmetrical with no vestibular involvement.
- Hearing loss may increase with severity of hypothyroidism.

Chronic Kidney disease

- The kidney and blood supply in the inner ear share physiologic, ultrastructural and antigenic similarities.
- CKD shows a higher prevalence of hearing loss among older adults.
- Diabetes is the cause of 44% of the cases of chronic renal disease.

Cardiovascular disease

- Inadequate blood supply and trauma to inner ear blood vessels can contribute to hearing loss.
- Hearing loss appeared in almost 80% of the people who had suffered from a cardiovascular disease.
- A stroke is a vascular trauma in the brain affecting the nervous system, motor and thought processes. Strokes can decrease hearing on the affected side of the brain.
- Broad research has shown negative influence of impaired cardiovascular health on both peripheral and central auditory systems.

Alzheimer's / Dementia Neurology

- Significantly higher % of people with ALZ may have hearing loss than normally aging peers.
- Research has shown that use of hearing aids has helped to reduce ALZ-related problems.
- Study at John Hopkins University reported patients with hearing loss had up to 5X higher risk of dementia than patients with no hearing problems.

HSC

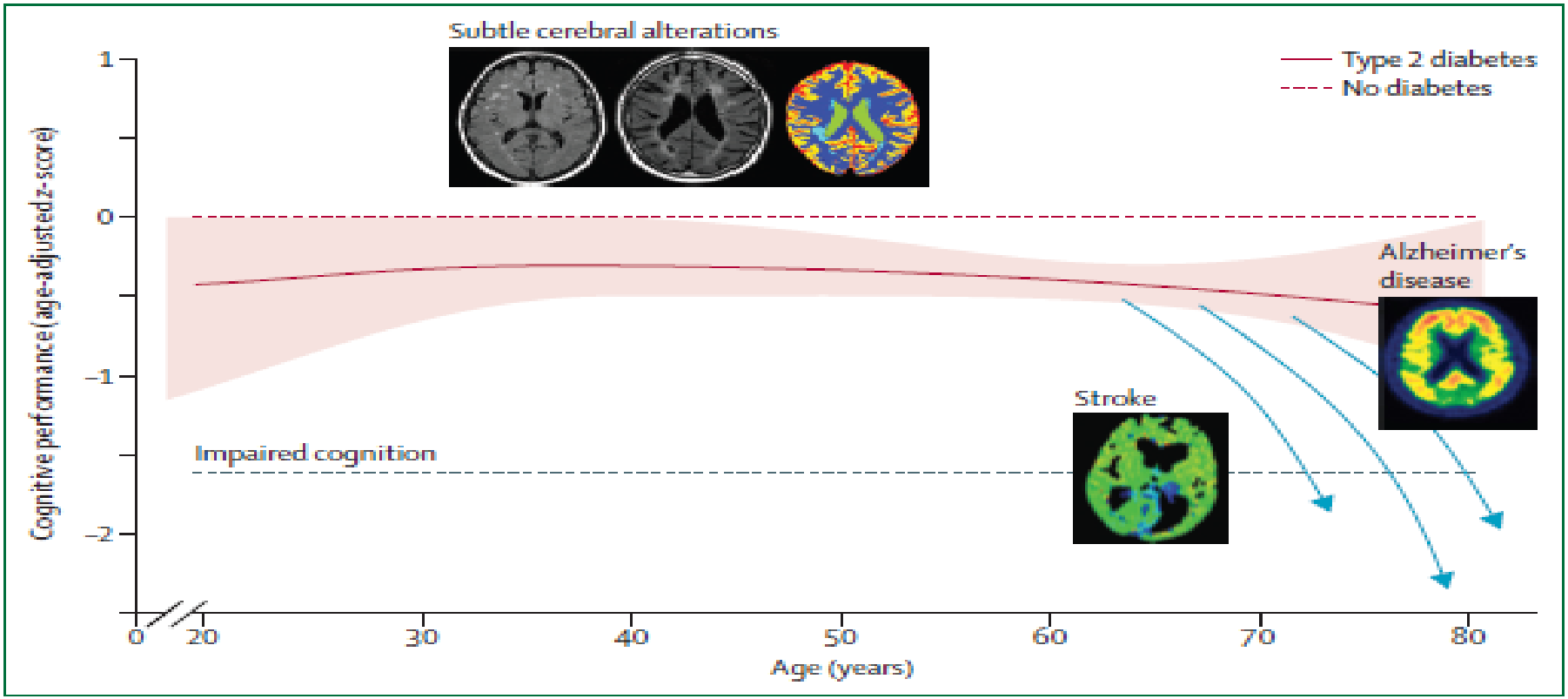
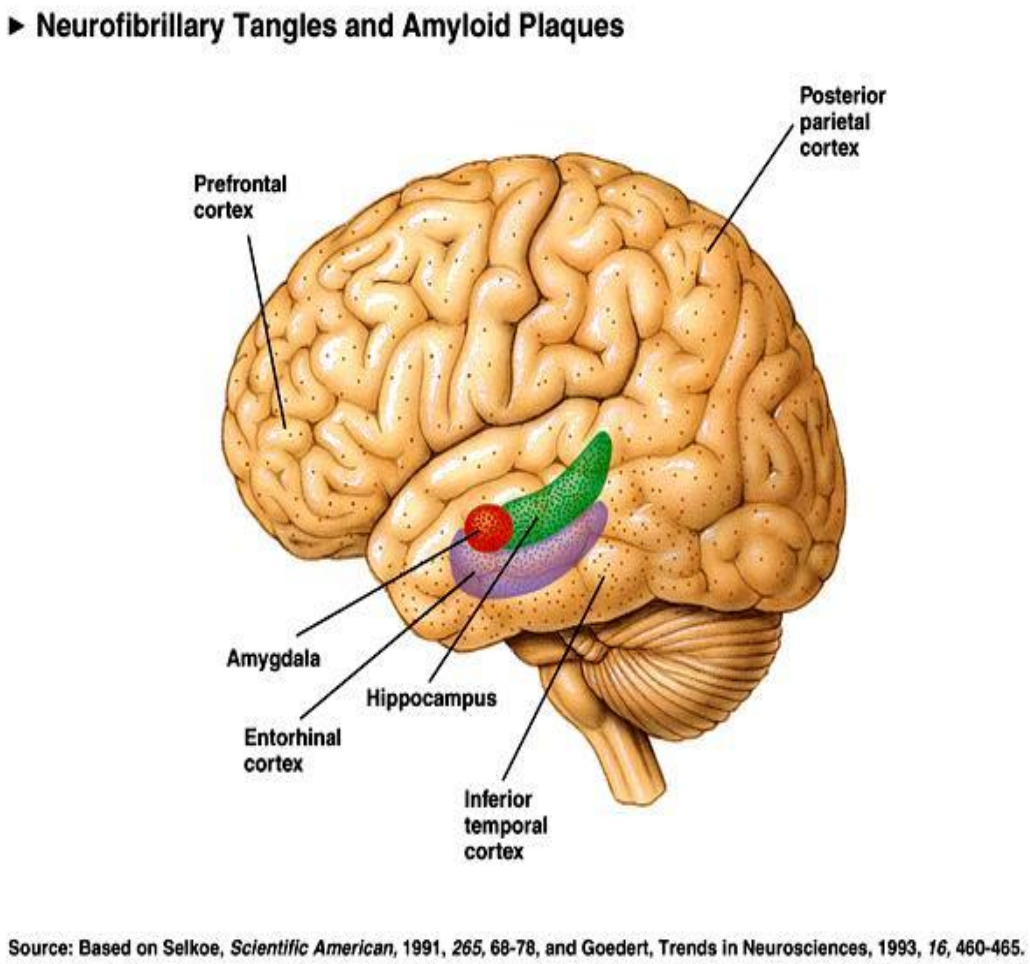


Figure 4: **Cerebral changes underlying cognitive trajectories in type 2 diabetes**
Slight cognitive decrements are related to subtle cerebral alterations including slight atrophy, disturbed white matter integrity, and vascular lesions (the picture shows two MRI scans and a segmentation of different brain tissues). These changes progress slowly, from midlife onwards, drawing on the reserve capacity of the brain. This progress increases vulnerability to the consequences of further incidents later in life, particularly (silent) stroke (the picture shows a left thalamic infarct on CT perfusion) and Alzheimer's-type abnormalities (the picture shows a PIB-PET amyloid scan, reproduced from Jack and colleagues,[79] by permission of Elsevier.) Individuals with such a combined burden of multiple abnormalities will have accelerated cognitive decline. Blue arrows indicate hypothetical cognitive trajectories of individual patients with multiple abnormalities.

Biessels et al, Lancet Diabetes Endocrinol 2014, 2: 246-255

AD è il diabete tipo 3



Insulin and IGF I are significantly reduced in the frontal cortex, hippocampus and hypothalamus – all areas that are affected by the progression of AD. 'Type 3 diabetes', accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlaps with T2DM

SM de la Monte & JR Wands, J Diabetes Science & Tech, 2008

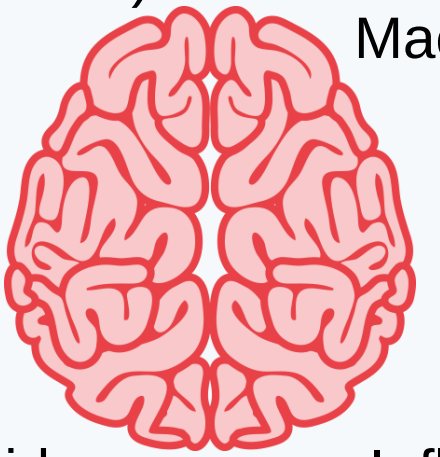
Diabete e disturbo cognitivo

Glycemic control
(hyper- & hypoglycemia)

Microvascular diseases

Macrovascular diseases

Hyperinsulineamia



Hypertension

Depression

Genetic predisposition

Beta amyloid

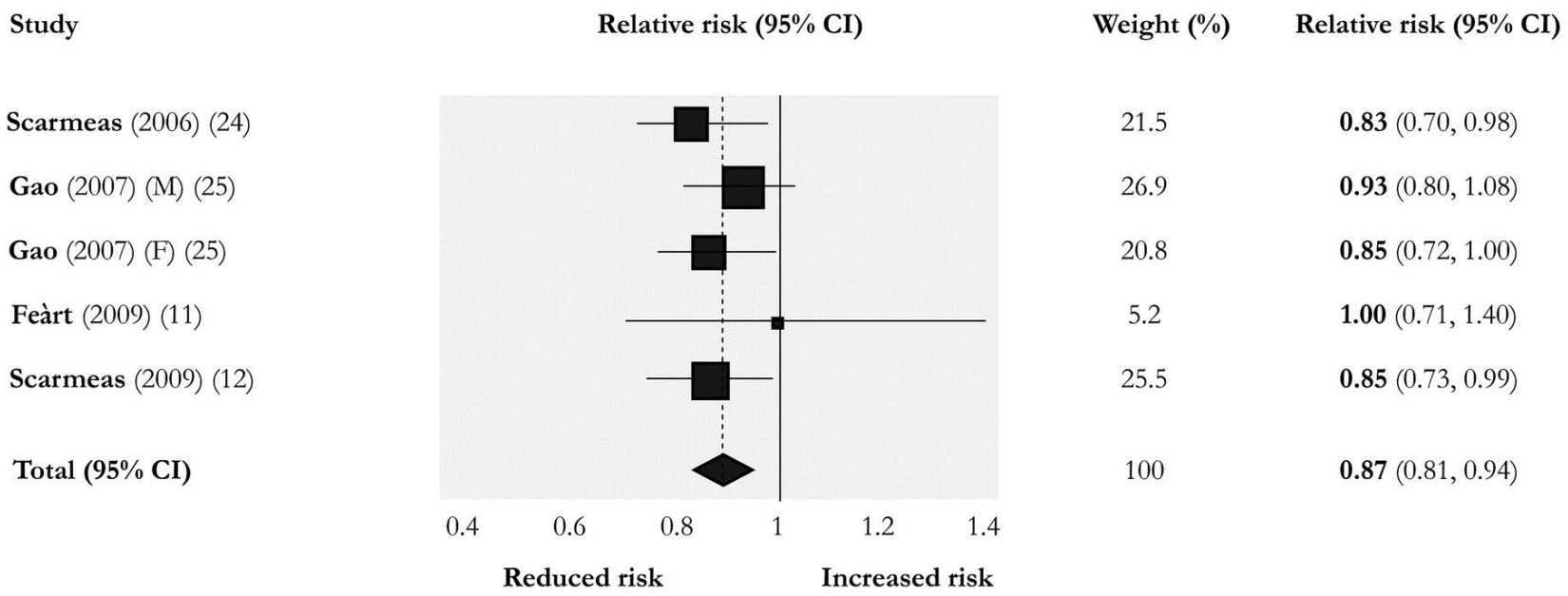
Inflammation

Hearing impairment

Adapted from Strachan et al., *Nat Rev Endocrinol*. 2011

DIETA MEDITERRANEA E DEMENZA

The American Journal of Clinical Nutrition

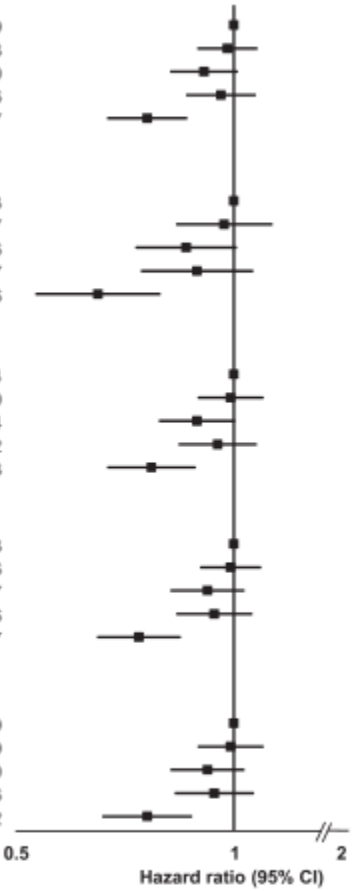


Francesco Sofi et al. Am J Clin Nutr 2010;92:1189-1196

©2010 by American Society for Nutrition

Rischio di MCI in relazione alla dieta

	Hazard ratio	Confidence interval Lower	Upper	Events	Sample size
Overall					
Q1	1.00	-	-	987	5459
Q2	0.98	0.89	1.08	1012	5498
Q3	0.91	0.82	1.02	952	5570
Q4	0.96	0.85	1.07	966	5646
Q5	0.76	0.66	0.86	782	5687
Excl decline in 1st 2 years of follow-up					
Q1	1.00	-	-	461	4933
Q2	0.97	0.83	1.13	471	4957
Q3	0.86	0.73	1.01	442	5606
Q4	0.89	0.74	1.06	447	5127
Q5	0.65	0.53	0.79	341	5246
Excl those with composite outcome					
Q1	1.00	-	-	809	4604
Q2	0.99	0.89	1.10	847	4690
Q3	0.89	0.79	1.01	777	4814
Q4	0.95	0.84	1.08	804	4922
Q5	0.77	0.67	0.89	675	5048
Excl those with baseline MMSE <24					
Q1	1.00	-	-	875	4818
Q2	0.99	0.89	1.09	926	5026
Q3	0.92	0.82	1.04	883	5097
Q4	0.94	0.83	1.06	888	5266
Q5	0.74	0.65	0.85	738	5417
Excl those with cancer at baseline					
Q1	1.00	-	-	886	4869
Q2	0.99	0.89	1.10	910	4899
Q3	0.92	0.82	1.04	837	4860
Q4	0.94	0.83	1.07	824	4896
Q5	0.76	0.66	0.88	667	4832

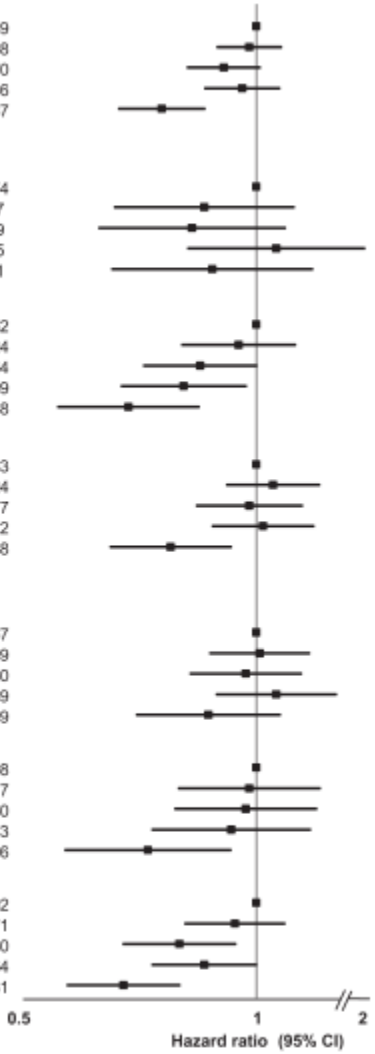


Adjusted HR and 95% CIs for the association between quintiles of diet quality (mAHEI) and cognitive decline, where Q1 represents the unhealthiest diet and Q5 the healthiest diet. The primary analyses are presented as the overall cohort; sensitivity analyses are presented excluding early events (first 2 years of follow-up), those with the composite (cardiovascular) outcome from the primary studies, those with baseline MMSE score <24, and those with cancer at baseline. All HRs adjusted for age, education, sex, trial enrollment (ONTARGET or TRANSCEND), treatment allocation, geographical region, baseline MMSE score, systolic blood pressure, history of stroke/TIA, diabetes mellitus, myocardial infarction, microalbuminuria, macroalbuminuria, serum creatinine, statin therapy, β-blocker therapy, antithrombotic use (antiplatelet or anticoagulant), smoking, body mass index, physical activity, and depression. CI = confidence interval; Excl = excluding; HR = hazard ratio; mAHEI = modified Alternative Healthy Eating Index; MMSE = Mini-Mental State Examination.

Smyth et al, Am A Neurol, 2015

Rischio di MCI in relazione a dieta e attività fisica

	Hazard ratio	Confidence interval Lower	Confidence interval Upper	Events	Sample size
Overall					
Q1	1.00	-	-	987	5549
Q2	0.98	0.89	1.08	1012	5498
Q3	0.91	0.82	1.02	952	5570
Q4	0.96	0.85	1.07	966	5646
Q5	0.76	0.66	0.86	782	5687
Categories of MMSE at baseline					
MMSE <26					
Q1	1.00	-	-	199	1174
Q2	0.86	0.66	1.12	158	977
Q3	0.83	0.63	1.09	134	929
Q4	1.06	0.82	1.38	146	825
Q5	0.88	0.66	1.19	95	651
MMSE 26-28					
Q1	1.00	-	-	333	1752
Q2	0.95	0.80	1.12	315	1724
Q3	0.85	0.71	1.00	301	1764
Q4	0.81	0.67	0.97	268	1709
Q5	0.69	0.56	0.85	227	1748
MMSE >28					
Q1	1.00	-	-	455	2533
Q2	1.05	0.91	1.20	315	1724
Q3	0.98	0.84	1.14	517	2877
Q4	1.02	0.88	1.19	552	3112
Q5	0.78	0.65	0.93	460	3288
Categories of physical activity at baseline					
Sedentary					
Q1	1.00	-	-	474	2467
Q2	1.01	0.87	1.17	426	2109
Q3	0.97	0.82	1.14	367	1880
Q4	1.06	0.89	1.27	317	1539
Q5	0.87	0.70	1.07	209	2009
Moderate activity					
Q1	1.00	-	-	195	1198
Q2	0.98	0.79	1.20	210	1217
Q3	0.97	0.79	1.22	209	1260
Q4	0.93	0.74	1.18	211	1343
Q5	0.73	0.57	0.93	180	1406
High activity					
Q1	1.00	-	-	318	1792
Q2	0.94	0.81	1.09	376	2171
Q3	0.80	0.68	0.95	376	2430
Q4	0.86	0.74	1.01	436	2764
Q5	0.68	0.58	0.81	393	3081



Adjusted HR (95% CI) for the association between quintiles of diet quality and cognitive decline by subgroup of baseline MMSE score and physical activity. Sedentary physical activity defined as active less than once per week, moderate activity defined as active 2 to 4 times per week, high activity defined as active more than 4 times per week. All HRs adjusted for age, education, sex, trial enrollment (ONTARGET or TRANSCEND), treatment allocation, geographical region, baseline MMSE score, systolic blood pressure, history of stroke/TIA, diabetes mellitus, myocardial infarction, microalbuminuria, macroalbuminuria, serum creatinine, statin therapy, β-blocker therapy, antithrombotic use (antiplatelet or anticoagulant), smoking, body mass index, and depression. CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination.

Smyth et al, Am A Neurol, 2015

Cosa fare?

Screening e prevenzione

Diabetes drugs and neurological disorders: new views and therapeutic possibilities

Patrone et al, Lancet Diabetes Endocrinol 2014, 2:256-62

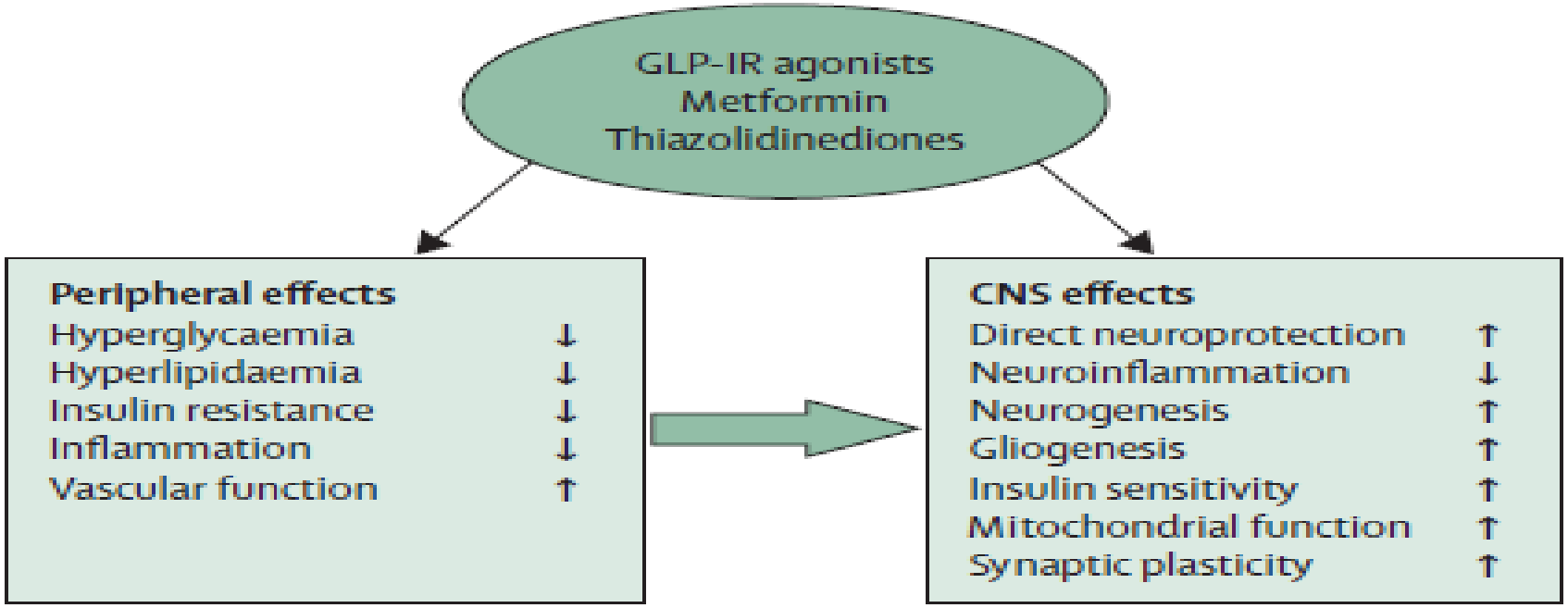


***Figure 1:* Summary of the effects of antidiabetic drugs on the periphery and brain**

Type 2 diabetes affects brain cells in several ways, with mainly negative effects on cell metabolism, neuronal viability, and behaviour. GLP-1R agonists, metformin, and thiazolidinediones can improve glycaemic control in the periphery and counteract organ complications in type 2 diabetes. These drugs also have favourable effects on the CNS. The mechanisms for the actions of these drugs in the brain are being investigated—they could involve direct effects on brain cells (figure 2) or they could act indirectly by positively affecting general whole-body metabolism and the vascular system in the brain.

Studio Predimed

- **Campione:** 7447 adulti a rischio di malattie cardiovascolari

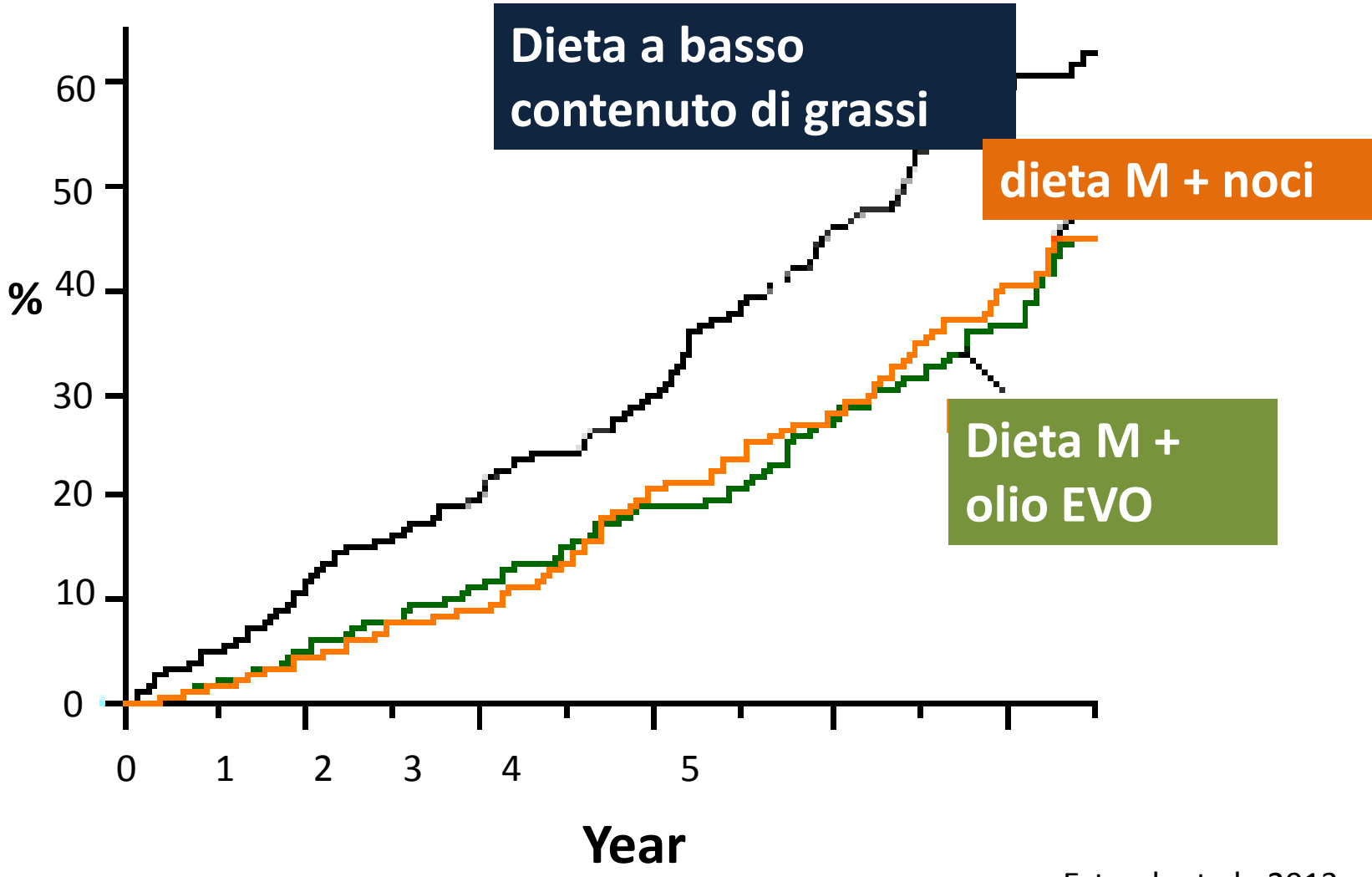
- **gruppi:** Dieta Mediterranea e olio EVO
  Dieta Mediterranea e noci
  Dieta a basso contenuto di grassi

- **Misure:** Morti cardiovascolari, infarto, ictus o diabete, disturbo cognitivo

- **Durata:** 5 anni

Studio PREDIMED

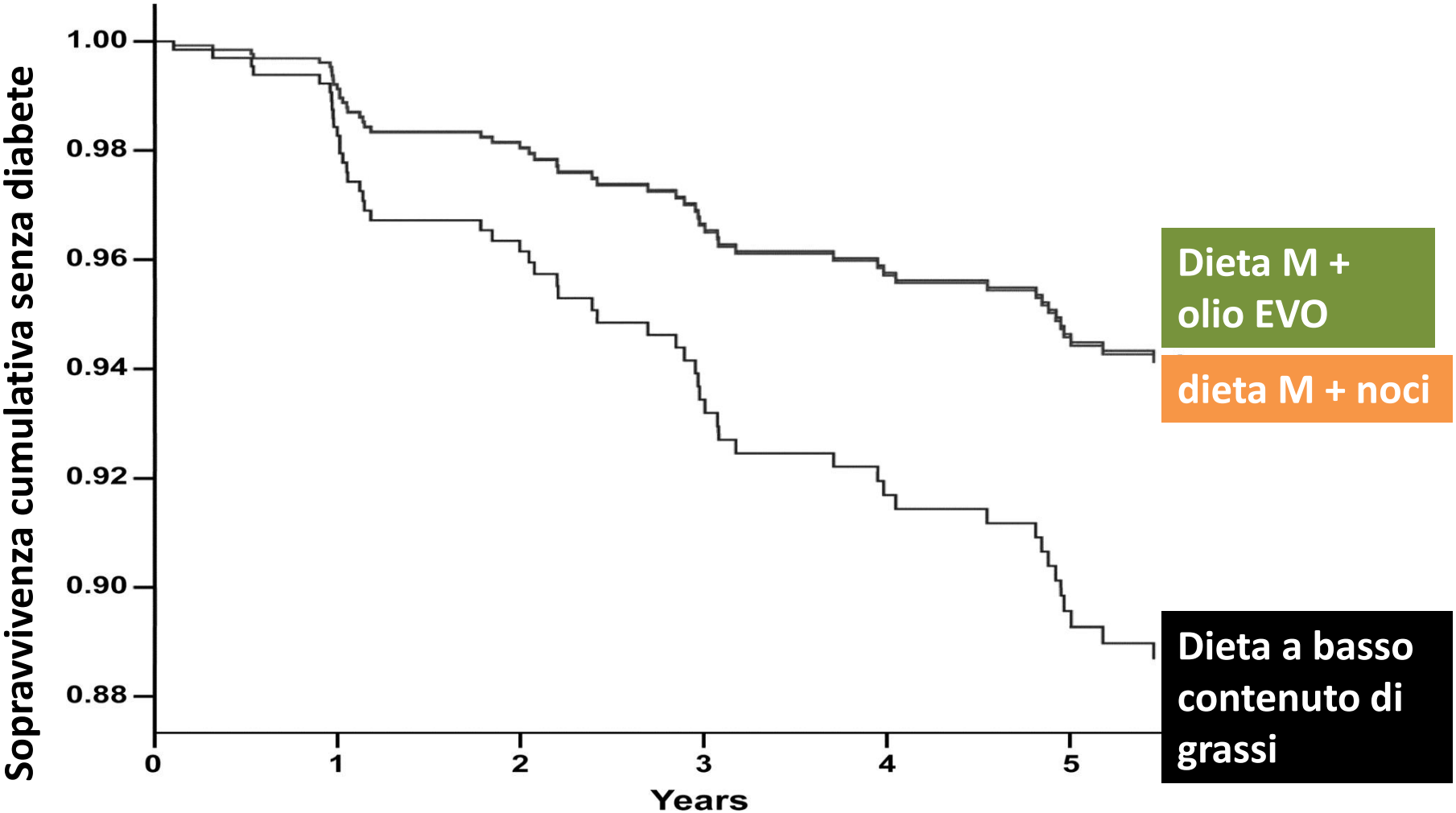
Eventi cardiaci in 5 anni



Estruch et al., 2013

Studio PREDIMED

Sopravvivenza senza diabete in 5 anni (individui non-diabetici)



Salas-Salvadó et al., Diabetes care 2011

PREDIMED Risultati

30% di riduzione nel rischio di mal.cardiaca

52% di riduzione nel rischio di diabete

27% riduzione nel rischio di mal.cardiaca con le statine

30% di riduzione nel rischio di diabete con la metformina

(Taylor et al, 2013; (Knowler et al, 2002)

From: **Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial**

JAMA Intern Med. Published online May 11, 2015. doi:10.1001/jamainternmed.2015.1668

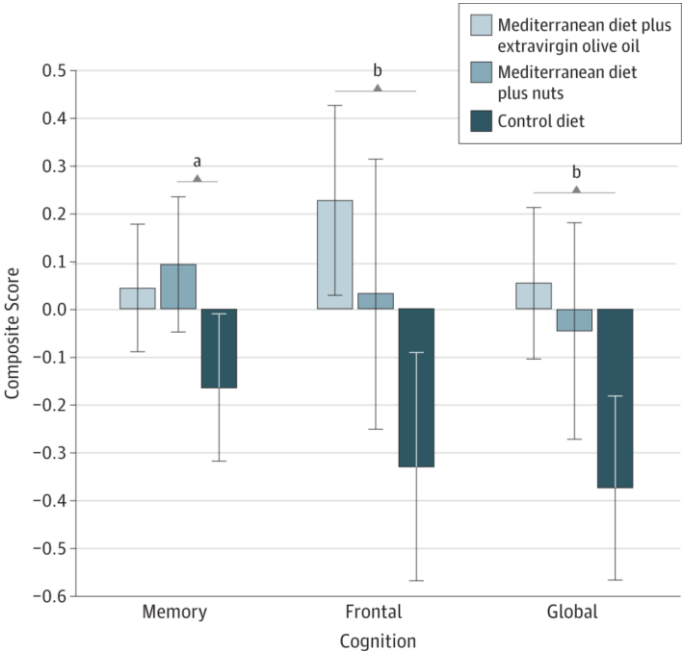


Figure Legend:

Changes in Cognitive Function Measured With Composites by Intervention GroupError bars indicate 95% CIs. P values by analysis of covariance were adjusted for sex, baseline age, years of education, marital status, APOE ε4 genotype, ever smoking, baseline body mass index, energy intake, physical activity, type 2 diabetes mellitus, hyperlipidemia, ratio of total cholesterol to high-density lipoprotein cholesterol, statin treatment, hypertension, use of anticholinergic drugs, and time of follow-up, with the Bonferroni post hoc test. For each cognitive composite, the changes between the 2 Mediterranean arms were not statistically different (P >.99 for all). The changes for memory between the Mediterranean diet plus olive oil and control groups and for frontal and global cognition between the Mediterranean diet plus nuts and control groups had values of P < .25.

Date of download: 6/4/2015
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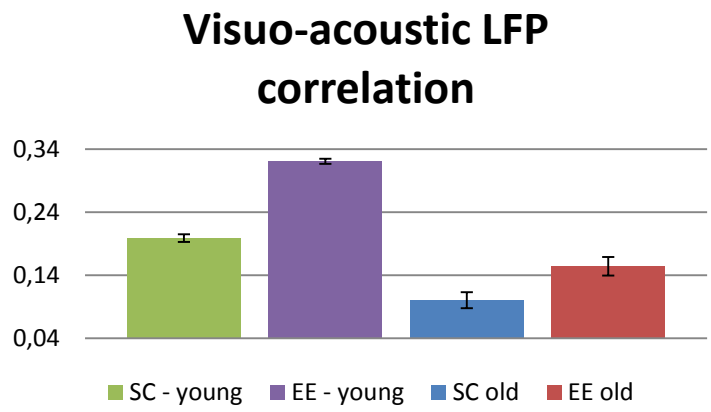
AMBIENTE ARRICCHITO
CONDIZIONI SPERIMENTALI

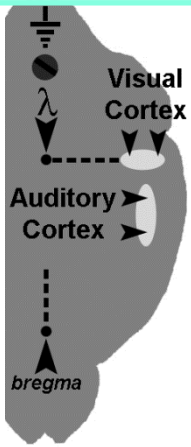
- Condizione di impoverimento

- Condizione standard di laboratorio (non AA).

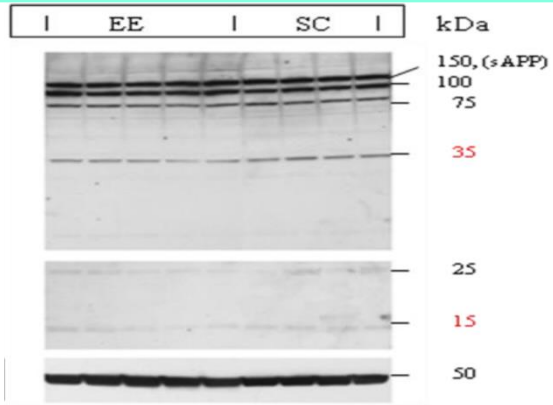
- Condizione sperimentale di “ambiente arricchito” con possibilità di svolgere esercizio fisico (AA).

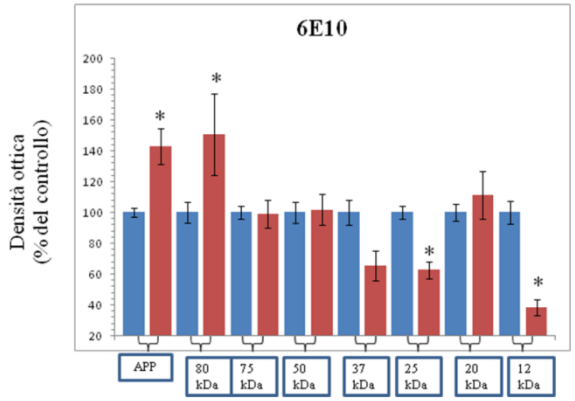
Environmental enrichment restores adult-like functional properties and synthesis of molecules linked to Alzheimer



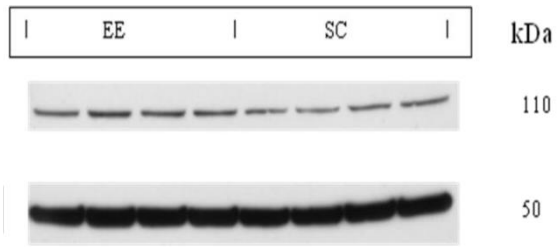


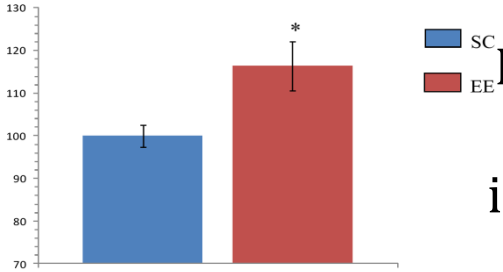
Aged mice subjected to Environmental Enrichment display a higher correlation between primary sensory cortices





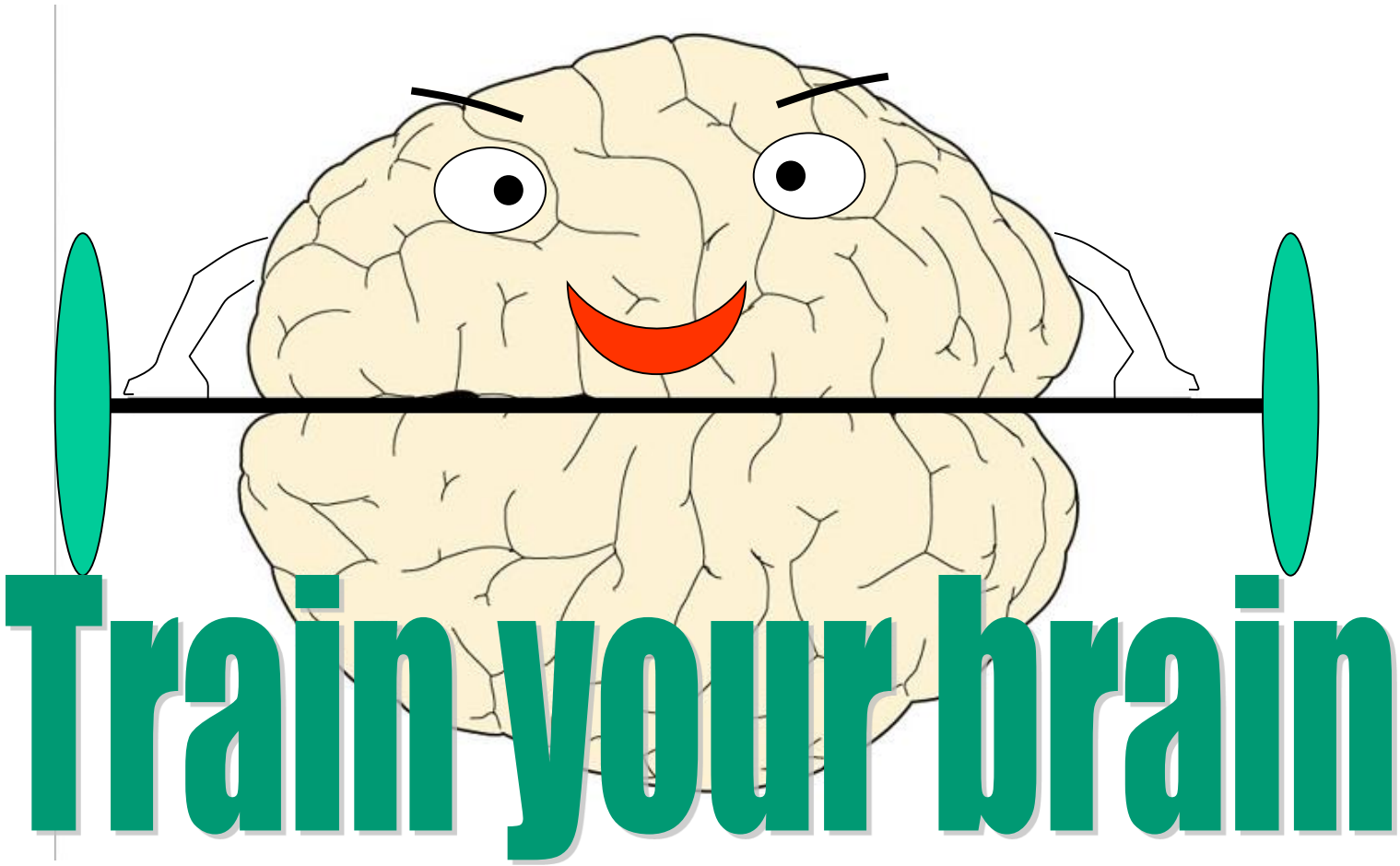
Lower levels of amyloid beta oligomers into the brain parenchyma of enriched, aged mice





Increased synthesis of neprilysin, An Abeta scavenging enzyme, in the brain of enriched, aged mice

M. Mainardi, A. Di Garbo, R. Narducci, M. Caleo, N. Berardi, A. Sale, L. Maffei



Environmental enrichment: a strategy to potentiate brain plasticity and promote brain health acting on **endogenous** factors?

Ambiente arricchito: una cura?

Train the brain: studio clinico e sperimentale sull’efficacia di un training fisico e cognitivo nella dementia

Progetto Train the Brain

Soggetti valutati allo screening n=1000

Screening negativo (esclusi dallo studio)

Screening positivo n atteso 400

Conferma clinica e valutazione cognitiva baseline

No conferma clinica

Valutazione strumentale baseline

Gruppo di intervento n=80 (intervento per 7 mesi)

Gruppo di controllo n=80 (normale attività per 7 mesi)

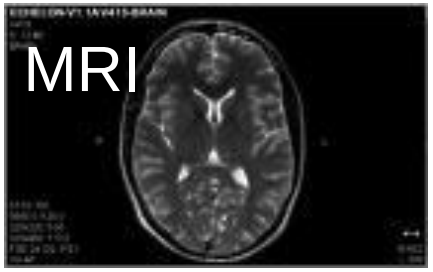
Follow up alla fine dell'intervento e rivalutazione 12 mesi dopo

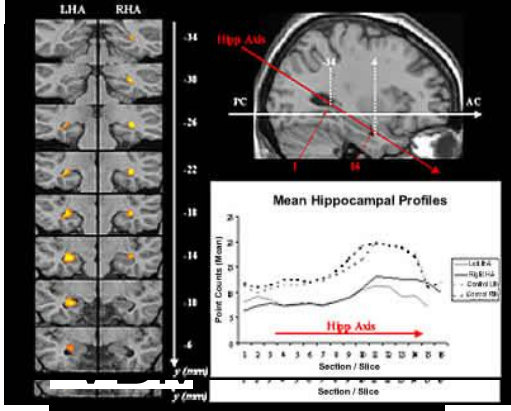
Esercizio fisico aerobico

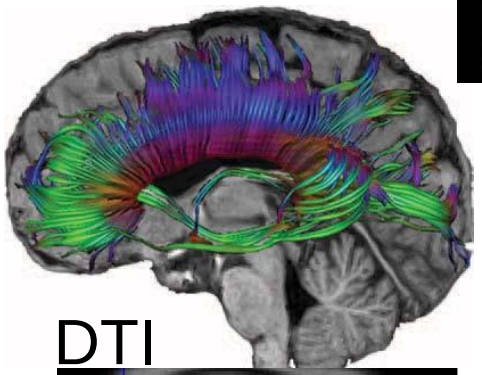
Esercizio fisico ritmico

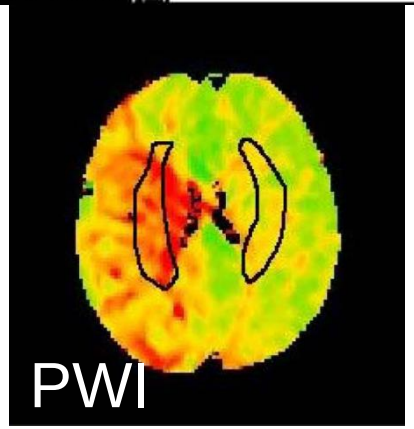
musicoterapia

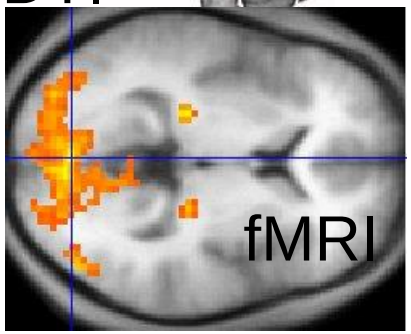
Correlazione dello stato cognitivo con:

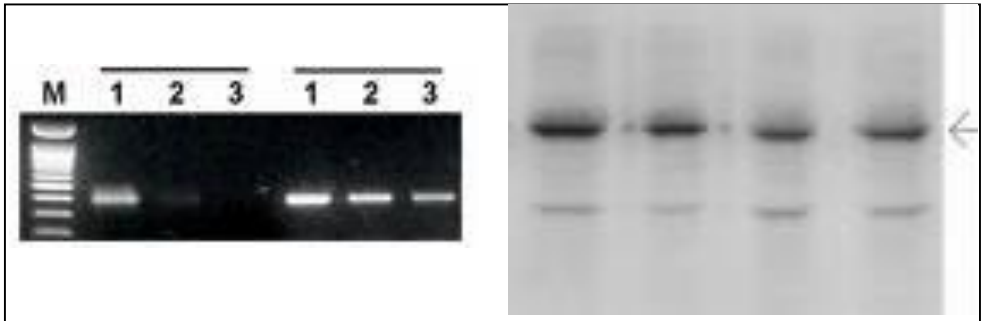


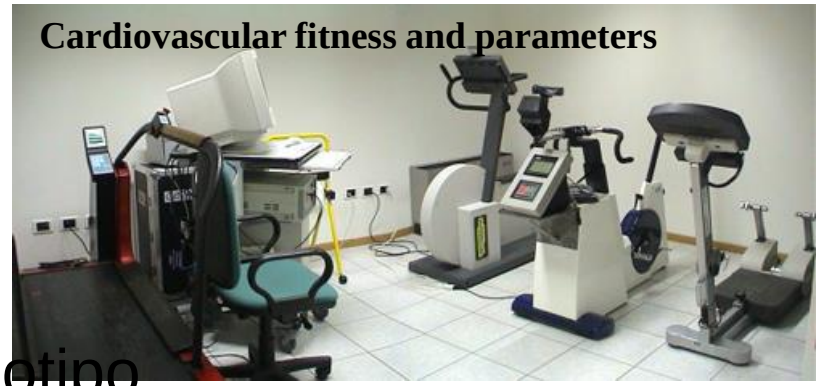






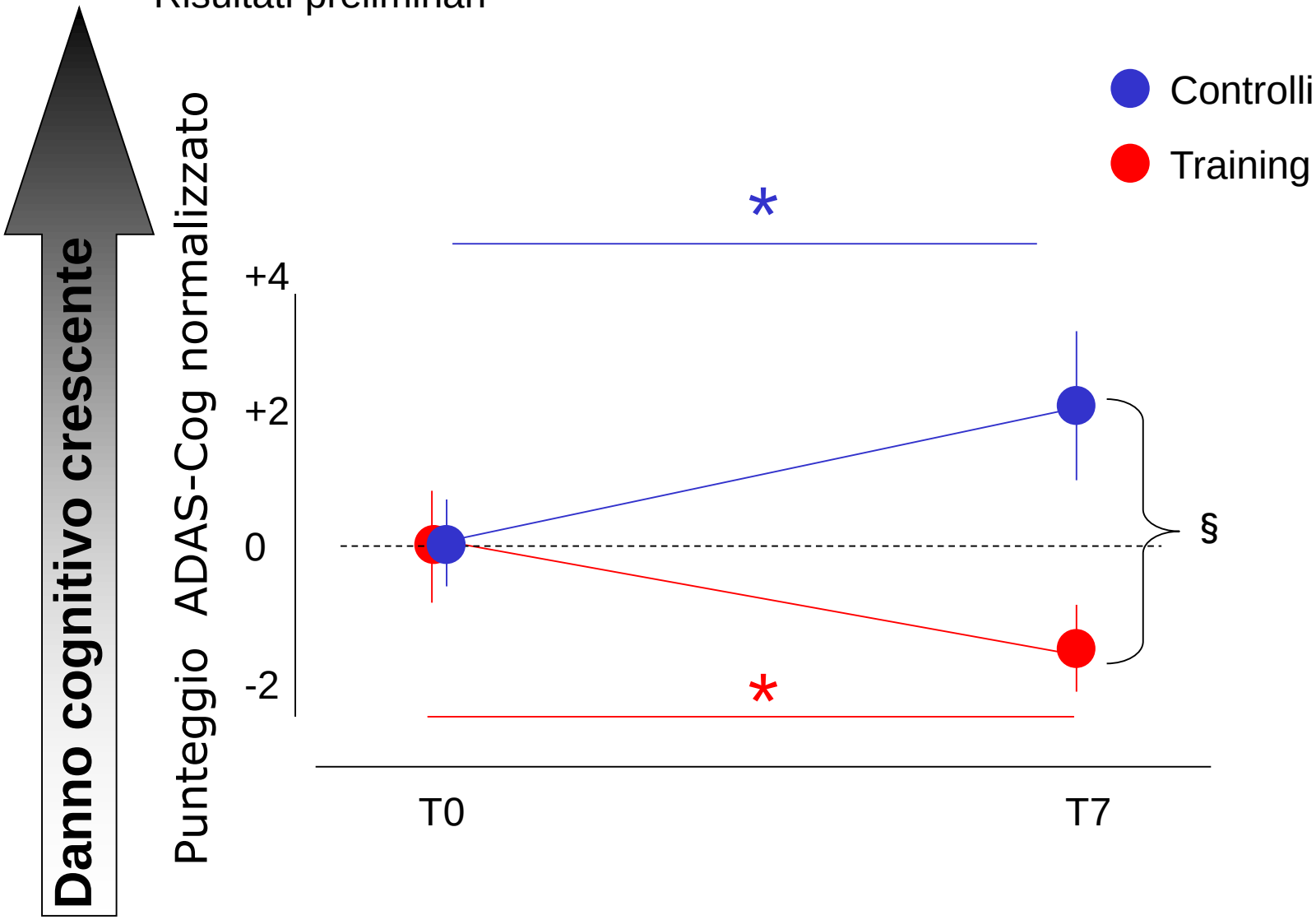




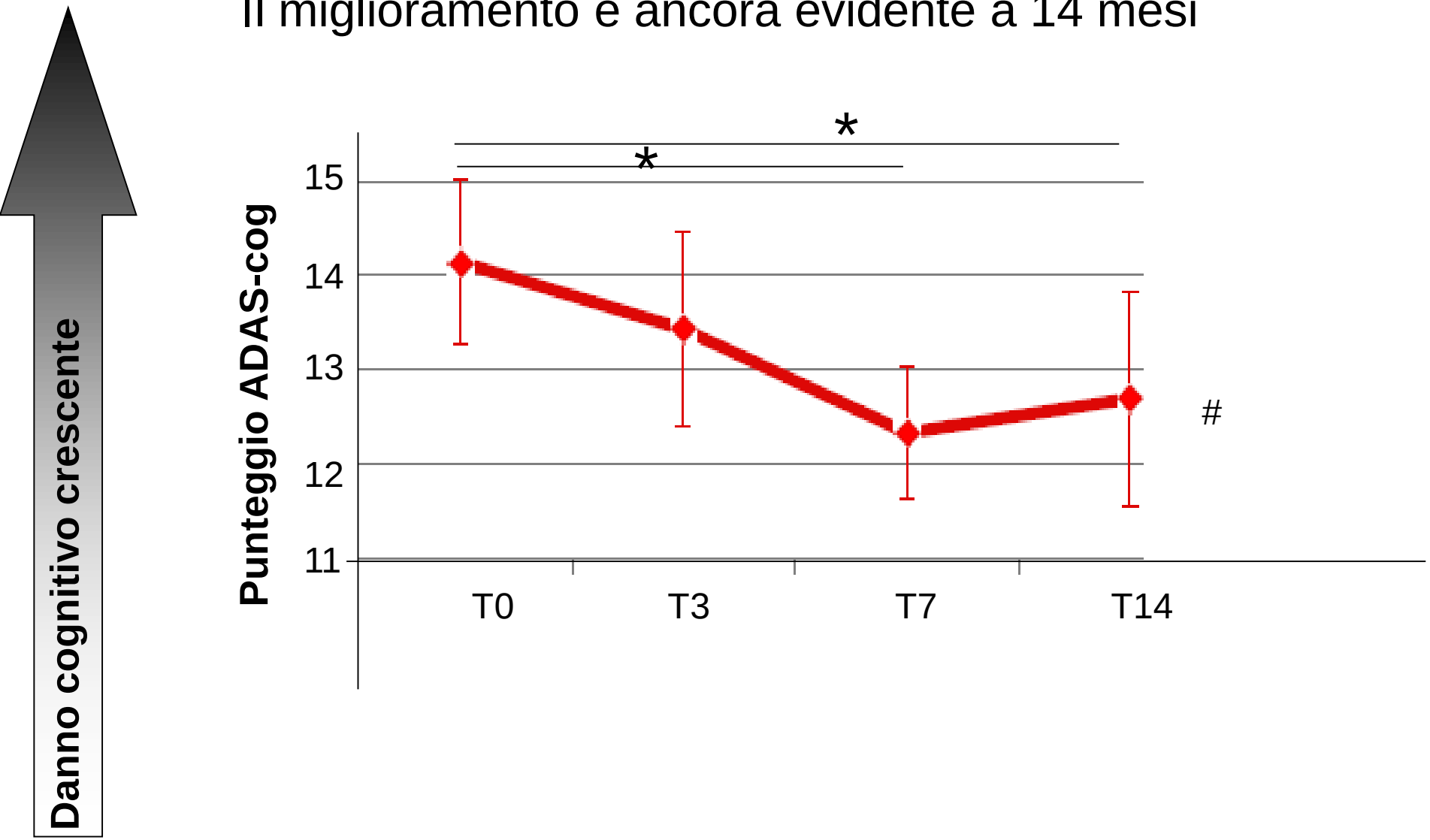


Markers AD, fattori di plasticità, genotipo

Risultati preliminari



Il miglioramento è ancora evidente a 14 mesi



Conclusioni

- Diversi fattori modificabili sono associati al disturbo cognitivo e alla sua progressione a demenza (diabete, disturbo uditivo, dieta, mancanza di attività fisica) ed esiste una plausibilità biologica per tale associazione

- Studi di intervento dimostrano l'efficacia di interventi su alcuni di questi fattori di rischio nel prevenire il disturbo cognitivo e la demenza.

- L'approccio multidimensionale al paziente è l'unico che permette la diagnosi precoce e la messa in atto di interventi efficaci