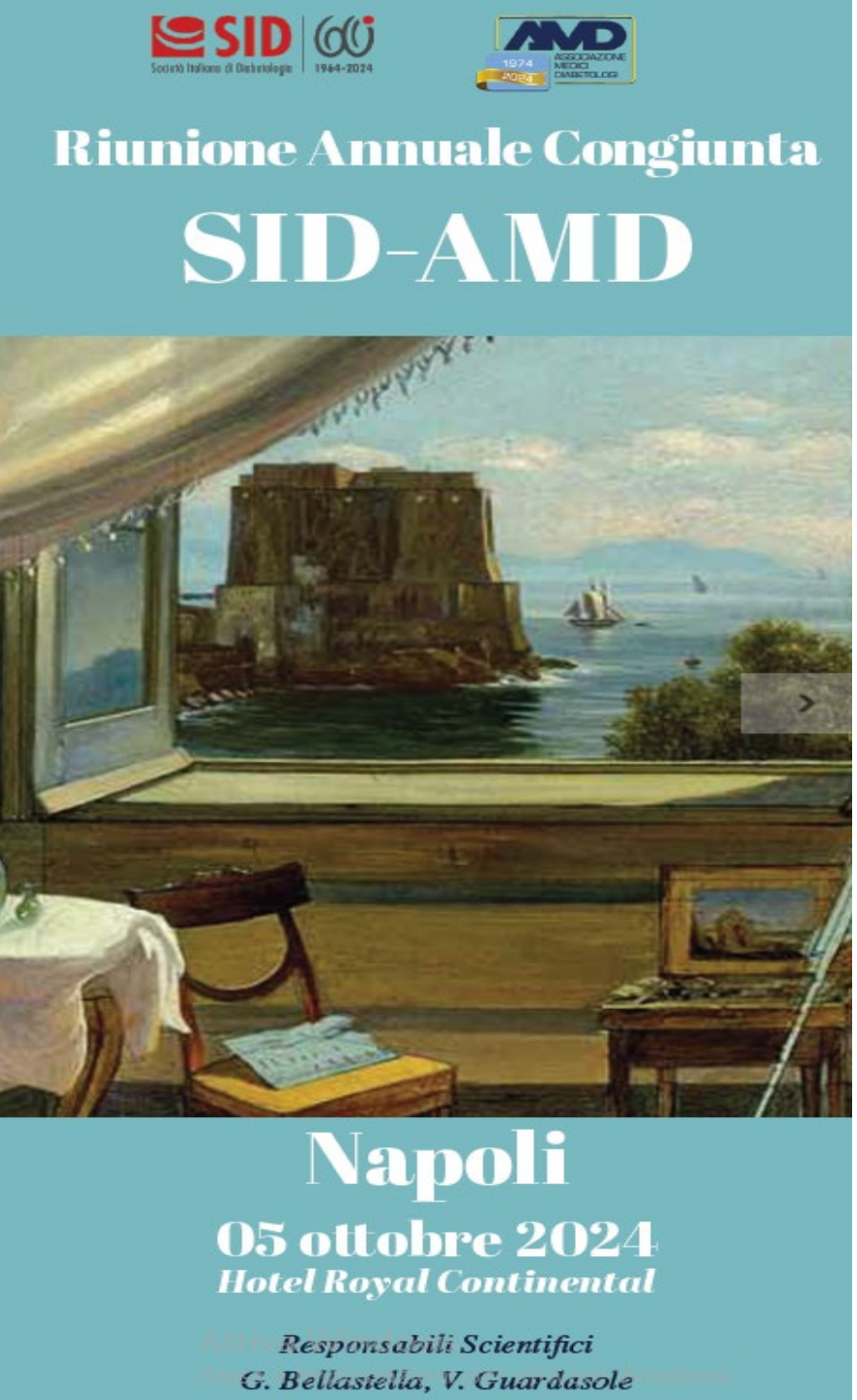


Decadimento cognitivo e diabete

Dott. Masi Stefano
ASL Salerno ed ASL Napoli3sud

Disclosures

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, il Dott. Stefano Masi dichiara di aver ricevuto negli ultimi due anni compensi e/o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

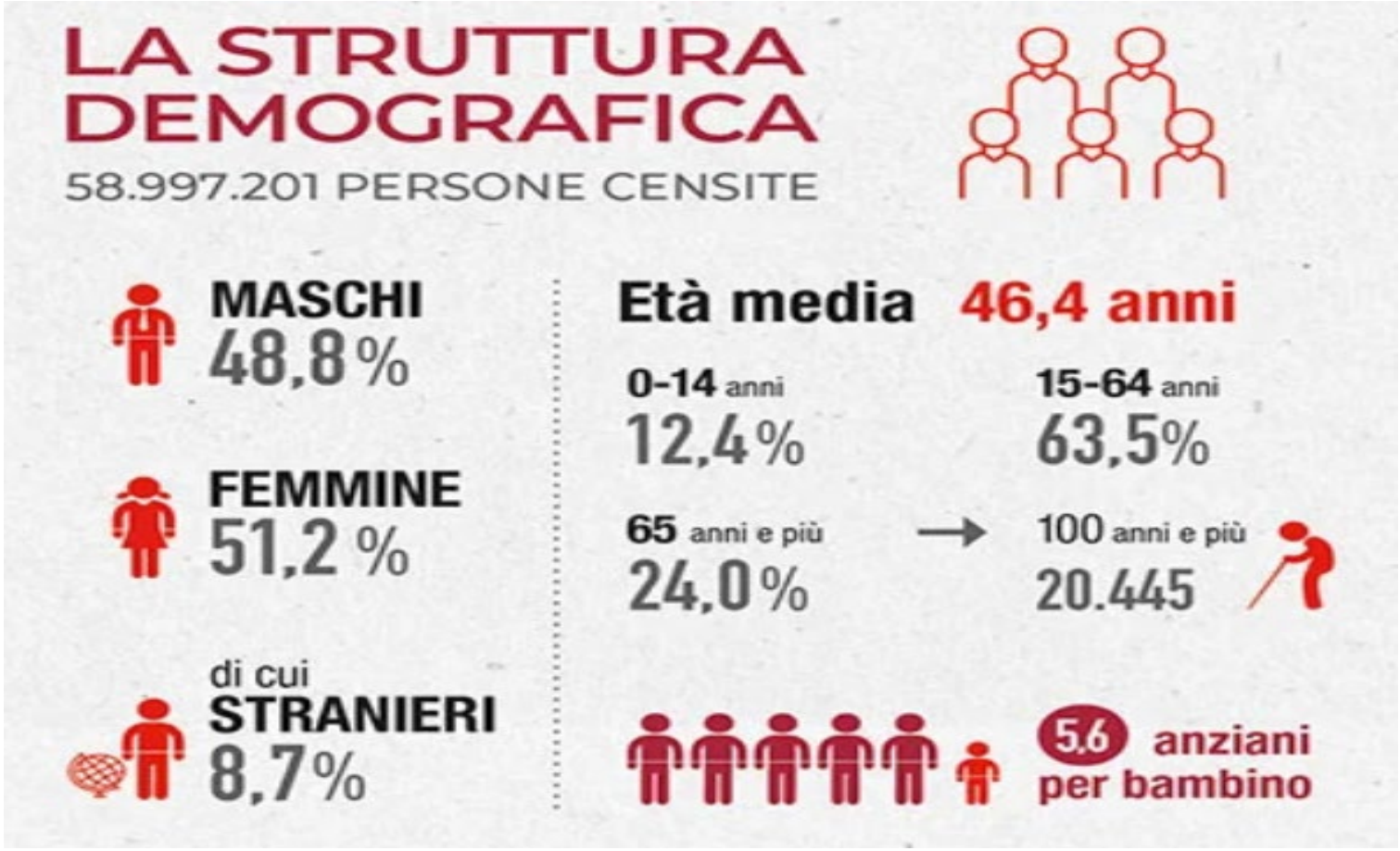
Finanziamenti Ricerca: Nessuno
Relatore convegni: Boehringher Ingelheim, Astra Zeneca, Takeda, Novo Nordisk, Sanofi-Aventis, Abbott, Eli-Lilly
Board Member/Advisory Panel: Nessuno
Stock/Shareholder: Nessuno
Altro: Nessuno

(Dichiaro, altresì, di astenermi nell'ambito della mia relazione dal nominare, in qualsivoglia modo e/o forma, aziende farmaceutiche e/o nomi commerciali di farmaci e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirugici, etc)

In Fede
Stefano Masi

Ultra ottantenni

Popolazione italiana (1)

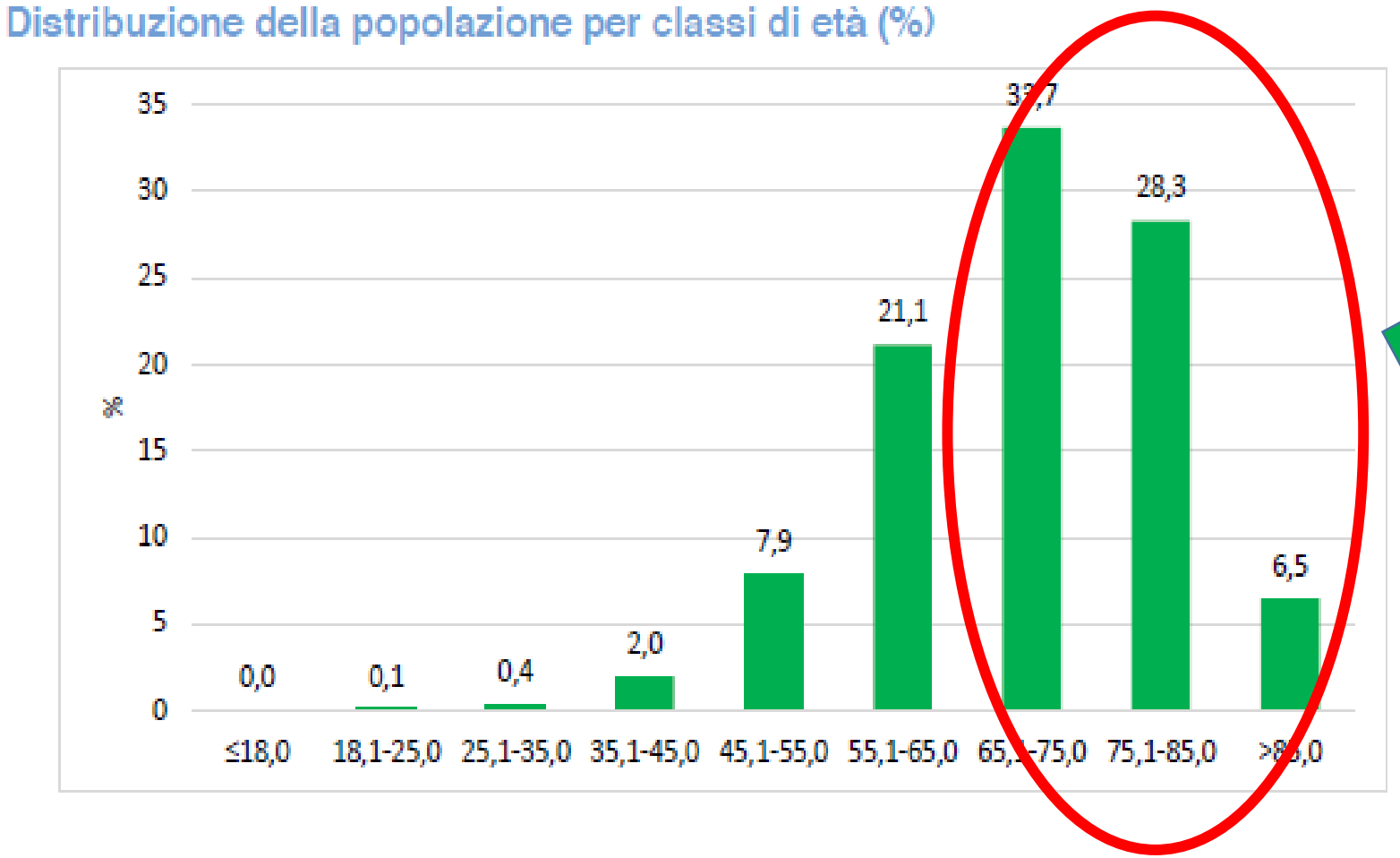


Popolazione italiana (2)

Con 2,2 milioni di italiani con più di 85 anni siamo il Paese più longevo d'Europa

Istat | Istituto Nazionale di Statistica

ANNALI 2023

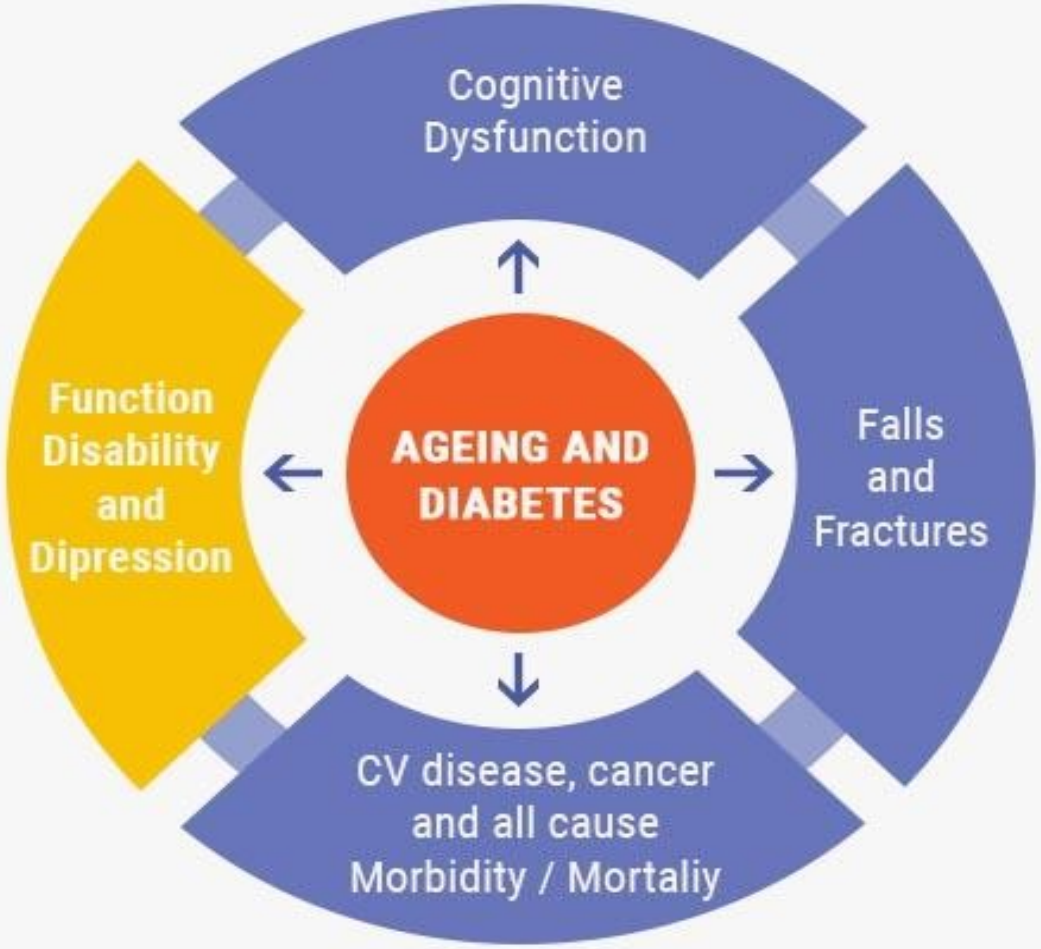


68,5 % popolazione over 65

THE OLDER PATIENT WITH **DIABETES**

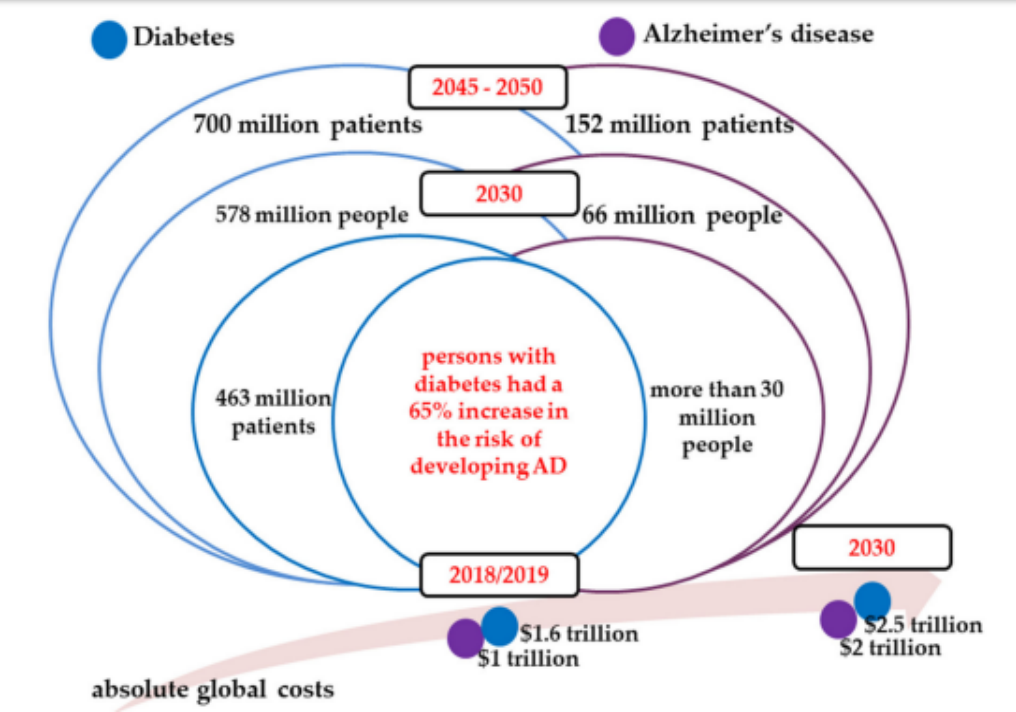
Older person with diabetes are at higher risk than those without diabetes of:

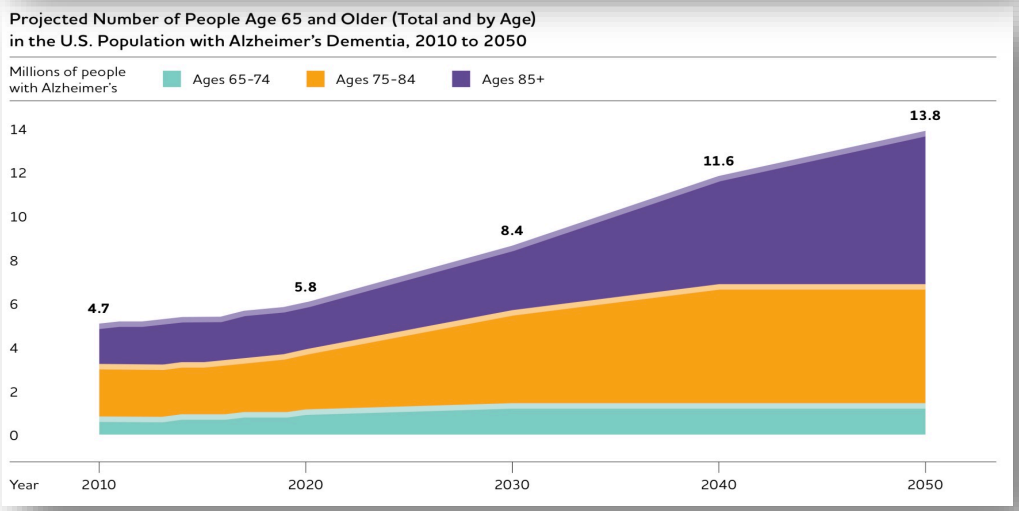
- Cancer mortality and vascular deaths
- **Function Disability**
- Geriatic syndromes: Depression
- Falls and Fractures
- Geriatic syndromes: Cognitive impairment



Cognitive dysfunction should be added to the list of the COMPLICATIONS OF DIABETES, along with Retinopathy, Nephropathy, Neuropathy and Cardiovascular disease.

Global diabetes and Alzheimer's disease (AD) **prevalence estimates** and economic burden for 2018/2019 and projections to 2030 and 2050





Summary relative risks of AD, VD and any dementia among subjects **with diabetes compared with that without**

Metanalisi: 19 Studi Longitudinali
6.184 Soggetti Diabetici
38.530 Soggetti Non Diabetici,

	Heterogeneity test			Random effects		Fixed effects	
	Chi	d.f.	P	RR	95%CI	RR	95%CI
Risk for AD	47.3	15	<0.0001	1.46	1.20–1.77	1.54	1.40–1.70
Risk for VD	6.3	9	0.71	2.49	2.09–2.97	2.48	2.08–2.96
Risk for any dementia	28.9	10	0.001	1.51	1.31–1.74	1.54	1.41–1.67
Risk for mild cognitive impairment	0.1	1	0.76	1.22	1.0–1.45	1.21	1.02–1.45

95%CI, 95% confidence interval; AD, Alzheimer's disease; RR, relative risk; VD, vascular dementia.

The relative risks were **2.48** and **1.46** for **VD** and **AD**, respectively, and for **any dementia** was **1.51** (between those for VD and AD)

G. Cheng, Internal Medicine Journal, 2012

T2D has been established as a risk factor for developing **all-cause dementia** and dementia attributable **to AD**

G. D. Stanciu, J. Clin. Med. 2020, 9, 1713;

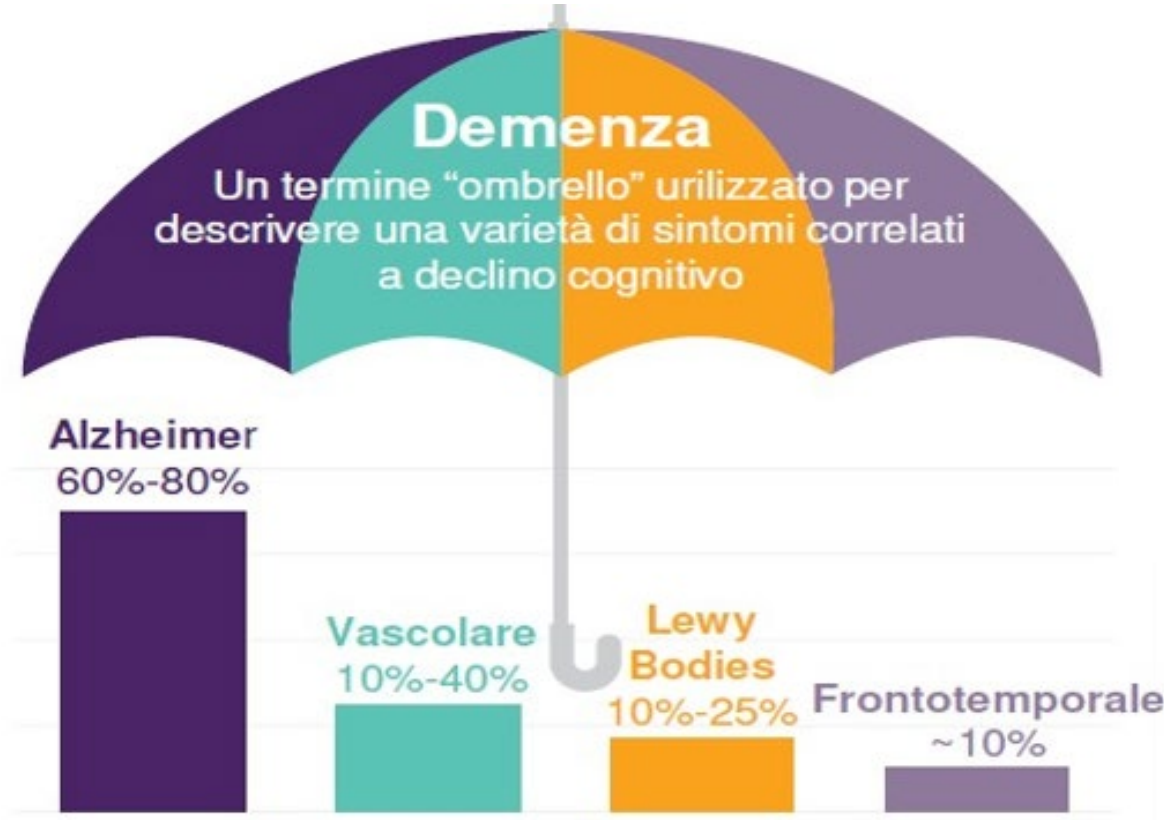
DYSREGULATION OF GLUCOSE HOMEOSTASIS AND RISK OF COGNITIVE DECLINE

Ref.	Methodology	Results
Gudala *et al*[112]	Meta-analysis with 28 prospective observational studies which evaluated the association between diabetes and the risk of developing AD	A 56% risk of developing AD [RR = 1.56 (95%CI: 1.41-1.73), $P < 0.05$] was reported in patients with diabetes
Profenno *et al*[113]	Meta-analysis of 16 cross-sectional studies evaluating the relationship between diabetes and AD	The presence of diabetes significantly and independently increased the risk of AD [OR = 1.54 (95%CI: 1.33-1.79; $P < 0.001$]
Ohara *et al* [114]	Prospective study that evaluated the association between glucose tolerance status and the development of neurocognitive disorders in 1017 individuals ≥ 60 yr	AD incidence was significantly higher in subjects with T2DM compared to subjects with normal tolerance to glucose [HR = 2.05 (95%CI: 1.18 to 3.57), $P = 0.01$]
Xu *et al* [115]	Prospective study that examined the association between diabetes and the different types of neurocognitive disorders in 1248 older adults. Diagnoses were based on the DSM-III-R criteria	Individuals with non-diagnosed diabetes had a HR of 3.29 (95%CI: 1.20-9.01) $P < 0.05$ for AD diagnosis
Xu *et al* [116]	Prospective study that evaluated the association between T2DM and neurocognitive disorders and AD in 1301 older adults	T2DM diagnosis was significantly associated with neurocognitive disorders [HR = 1.5 (95%CI: 1.0-2.1) $P = 0.04$] and AD [HR = 1.3 (95%CI: 0.9-2.1) $P < 0.05$]
Peila *et al* [117]	Prospective study that examines the association between T2DM and neurocognitive disorder incidence in 2574 Japanese-American men. Diagnosis of neurocognitive disorder was performed through physical exam and MRI according to the NINCDS-ADRDA and DSM-IV criteria	T2DM was significantly associated with AD diagnosis [RR = 1.8 (95%CI: 1.1-2.9) $P < 0.05$]
McIntosh *et al*[118]	Prospective study that examined the relationship between T2DM, biomarkers, and the risk for suffering from neurocognitive disorders in 1289 dementia-free participants. AD biomarker levels were measured from the CSF. Neurocognitive disorders were evaluated through the CDRSB	Untreated diabetic individuals had higher levels of p-tau, p-tau/Aβ1-42, and t-tau/Aβ1-42 in their CSF than normoglycemic or prediabetic individuals ($P < 0.05$). The untreated group did not progress to neurocognitive disorder in higher rates than normoglycemic individuals [HR = 1.602 (95%CI: 1.057-2.429); $P = 0.026$]

World J Diabetes 2021 June 15; 12(6): 685-915

In generale la presenza di Diabete di Tipo 2 aumenta il rischio di Demenza di circa il 60% , che può arrivare al 300% in casi di diabete non diagnosticato

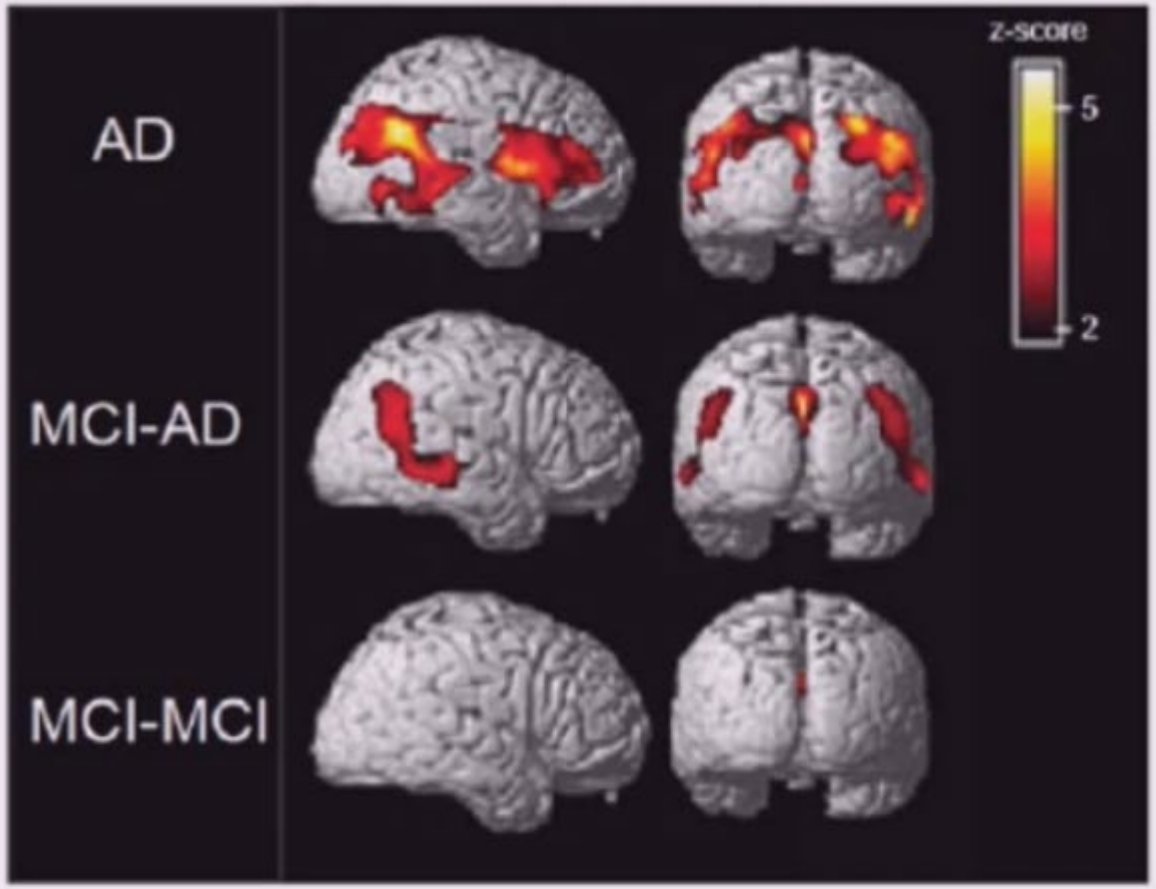
World J Diabetes 2021 June 15; 12(6): 685-915



Altre Demenze: Demenza di Parkinson, di Creutzfeldt-Jakob, da corea di Huntington, da idrocefalo normoteso e da Sindrome di Wernicke-Korsakoff

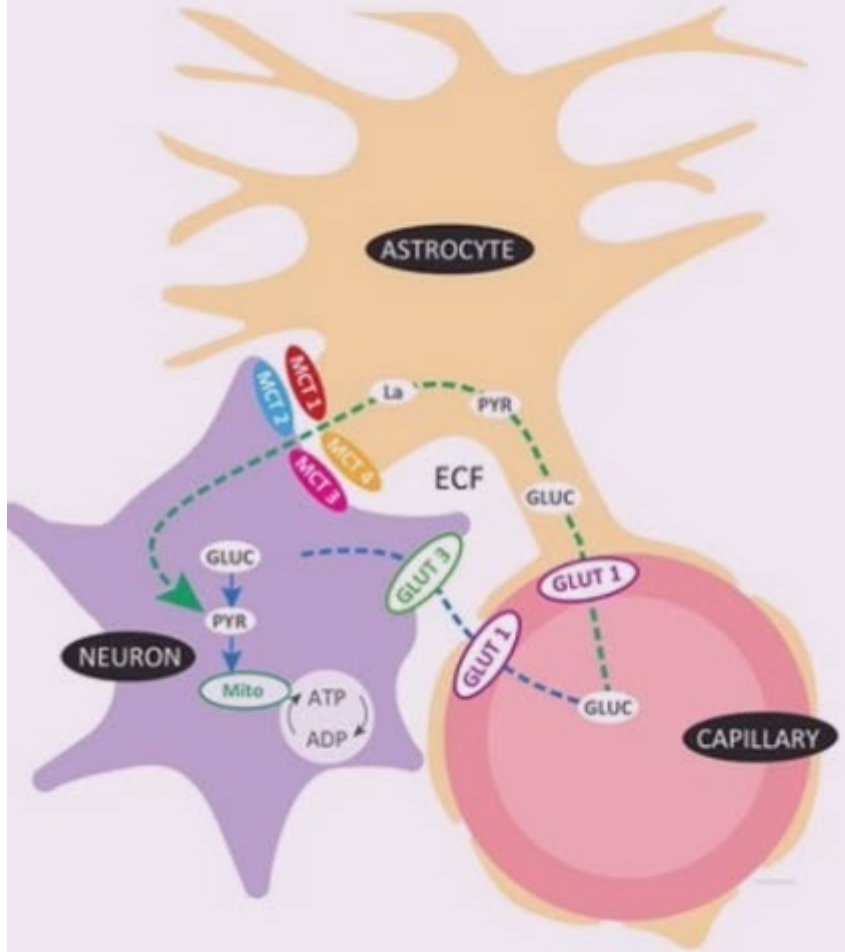
Hypometabolism in Neurodegenerative Diseases

Journal of Neuroscience Research
95:2217–2235 (2017)



Reduced glucose utilization in early stages of neurodegenerative diseases.(A) Regional reductions (compared to healthy controls) in cerebral glucose metabolic rate (CMRglc) observed using positron emission tomography with FDG–PET: in AD patients (AD, top), patients with mild cognitive impairment (MCI) that progressed to AD after 2 years (MCI-AD, middle), and in MCI patients who remained

BRAIN GLUCOSE TRANSPORTERS: IMPLICATIONS FOR NEUROLOGIC DISEASE



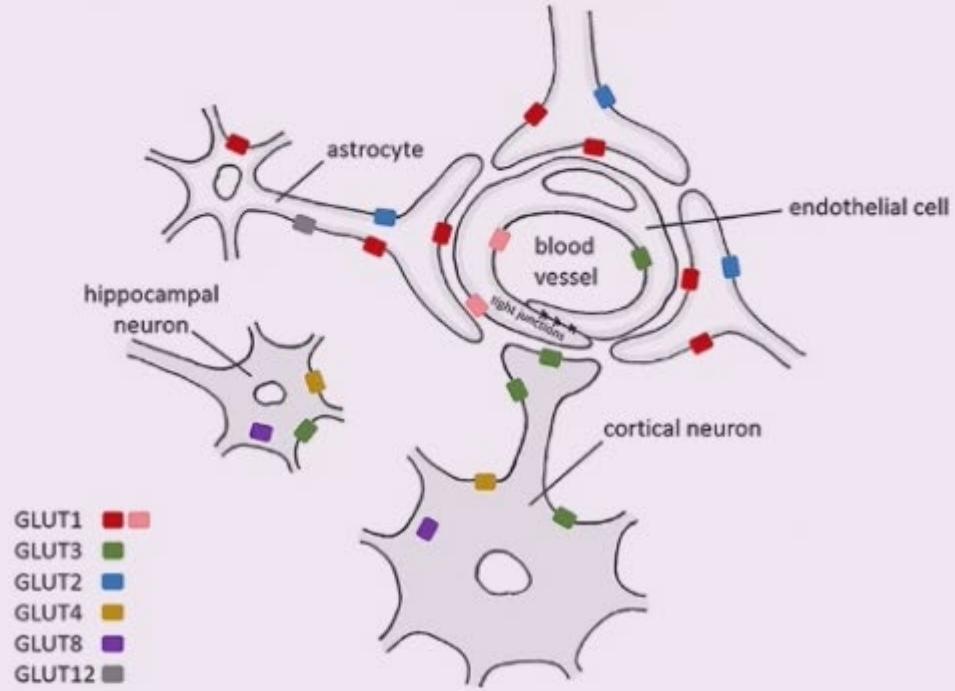


Table 1 | Main glucose transport (GLUT) isoforms in the brain.

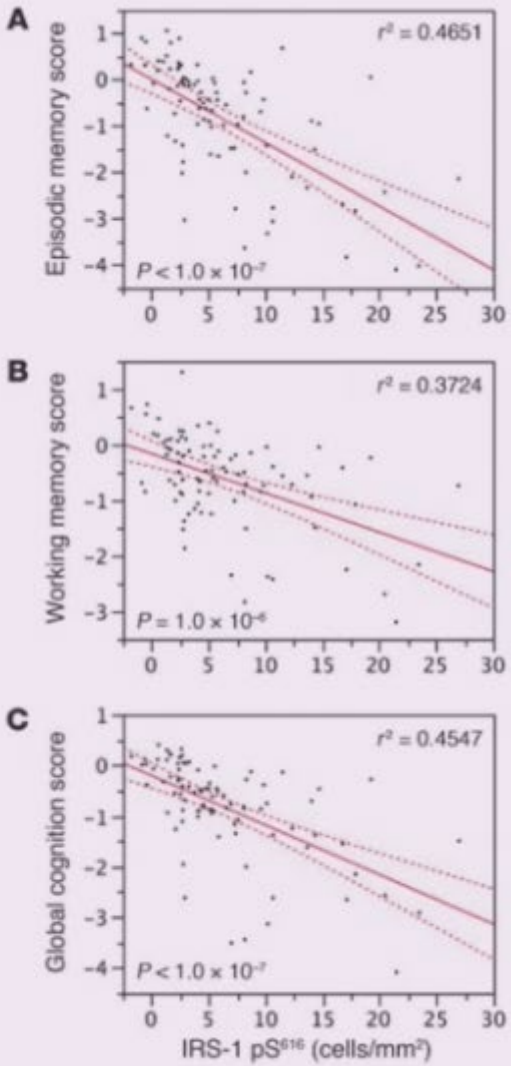
Glucose transport isoforms	Location	Cell types	Abundance	Control
GLUT-1	Ubiquitous	Glia and endothelial	Very abundant	Hypoglycemia, insulin
GLUT-2	Hypothalamus	Neurons, glia, and tanycytes	Limited	
GLUT-3	Cerebellum, striatum, cortex, and hippocampus	Neurons, glia, and endothelial	Very abundant	
GLUT-4	Olfactory bulb, hippocampus (dentate gyrus), and hypothalamus cerebellum	Neurons and glia	Selective areas	Glucose, insulin and exercise training
GLUT-8	Hypothalamus, cerebellum, brainstem, hippocampus, dentate gyrus, amygdala, and primary olfactory cortex	Neurons: bodies and proximal apical dendrites	Limited	Glucose

Front. Neurosci., 20 May 2021

BRAIN INSULIN RESISTANCE IN AD PATIENTS IS ASSOCIATED IRS-1 DYSREGULATION, AND COGNITIVE DECLINE

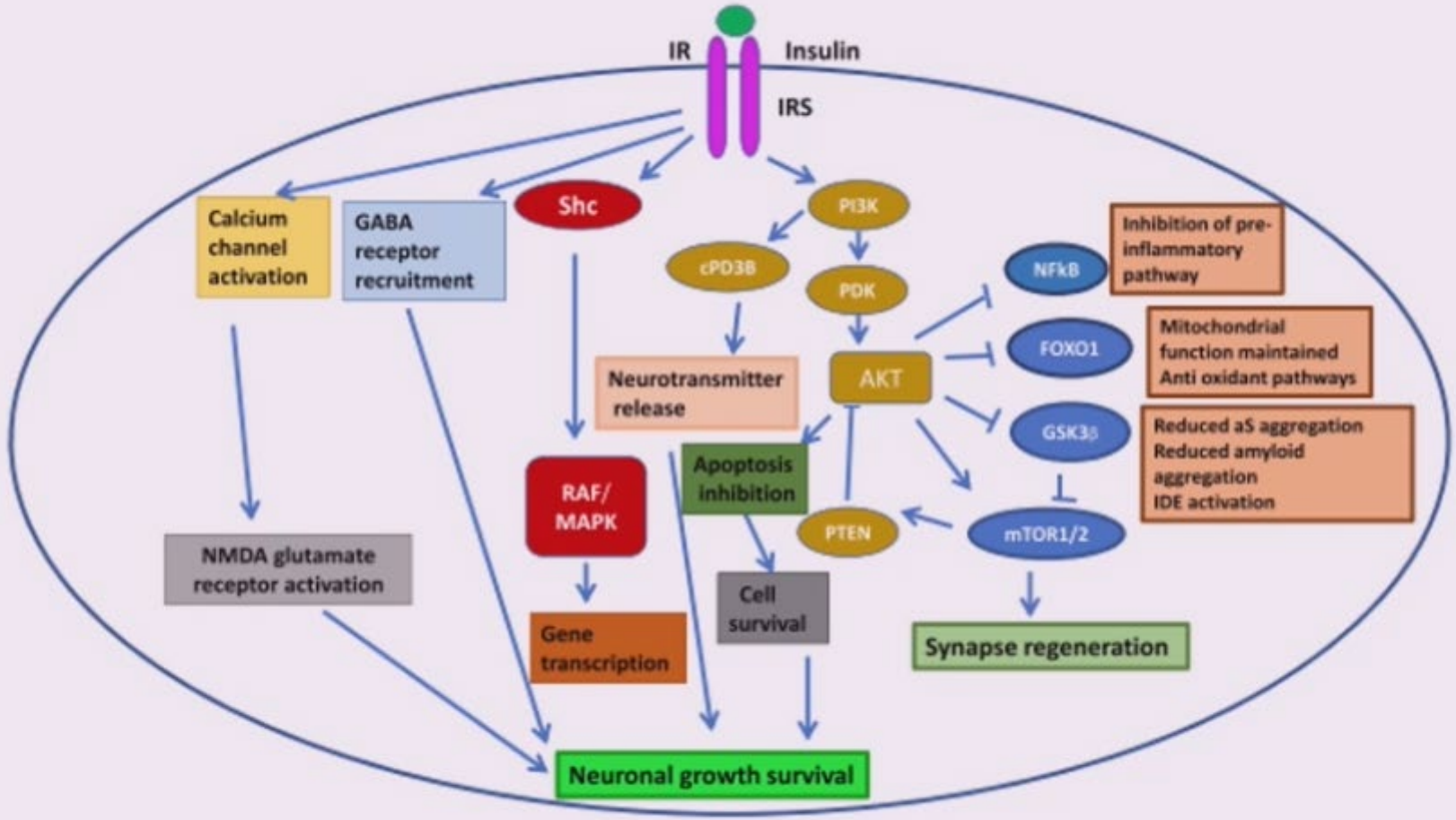
Linear regression prediction of episodic memory scores by CA1 neuronal insulin signaling and regulatory variables adjusted for age, sex, and years of education

Analyte	*N*	Model r^2	Model *F* (*P*)	Parameter estimate	Analyte *t*	Analyte *P*
Age, sex, and education only	89	0.11	$F_{4,85} = 3.36$ (0.02)			
IR/IGF-1Rβ pY	85	0.20	$F_{5,80} = 4.88$ (0.0014)	0.0019	3.41	0.001
IRβ pY^{960}	87	0.18	$F_{5,82} = 4.46$ (0.0026)	0.0017	2.73	0.0078
IRS-1 pY^{612}	84	0.40	$F_{5,79} = 13.29$ ($<1 \times 10^{-6}$)	−0.053	−6.44	$<1 \times 10^{-6}$
IRS-1 pY^{941}	81	0.36	$F_{5,76} = 10.84$ ($<1 \times 10^{-6}$)	−0.049	−5.80	$<1 \times 10^{-6}$
IRS-1 pS^{312}	88	0.34	$F_{5,83} = 10.70$ ($<1 \times 10^{-6}$)	−0.086	−5.38	$<1 \times 10^{-6}$
IRS-1 pS^{616}	88	0.47	$F_{5,83} = 18.04$ ($<1 \times 10^{-6}$)	−0.137	−7.42	$<1 \times 10^{-6}$
IRS-1 $pS^{636/639}$	88	0.29	$F_{5,83} = 8.51$ (2×10^{-6})	−0.038	−4.67	1.1×10^{-5}
PIP3	85	0.32	$F_{5,85} = 9.27$ ($<1 \times 10^{-6}$)	0.017	4.92	4×10^{-6}
$Akt1^{A}$ pS^{473}	63	0.25	$F_{5,58} = 4.92$ (0.0018)	−0.046	−3.23	0.002
Akt2 pS^{474}	67	0.15	$F_{5,62} = 2.68$ (0.0398)	−0.022	−1.48	0.1441
PKCζ/λ $pT^{410/403}$	84	0.36	$F_{5,79} = 10.94$ ($<1 \times 10^{-6}$)	−0.056	−5.61	$<1 \times 10^{-6}$
GSK-3α/β $pS^{21/9}$	65	0.33	$F_{5,59} = 7.44$ (1.8×10^{-5})	−0.00026	−4.44	4×10^{-5}
mTOR pS^{2448}	89	0.37	$F_{5,84} = 12.33$ ($<1 \times 10^{-6}$)	−0.031	−5.93	$<1 \times 10^{-6}$
IKKα/β $pS^{176/180}$	87	0.25	$F_{5,82} = 6.91$ (2×10^{-5})	−0.043	−3.85	0.0002
JNK1/2 pT^{183}/pY^{185}	87	0.27	$F_{5,82} = 7.53$ (7×10^{-6})	−0.025	−4.34	4×10^{-5}
Total Aβ plaque load[B,C]	89	0.21	$F_{5,84} = 5.50$ (0.0006)	−0.93	−3.28	0.0015
Oligomeric Aβ plaque load[B,C]	84	0.26	$F_{5,79} = 7.05$ (1.7×10^{-5})	−0.98	−4.33	4.3×10^{-5}
NFT density[B]	84	0.44	$F_{5,79} = 15.38$ ($<1 \times 10^{-6}$)	−0.089	−6.79	$<1 \times 10^{-6}$
Nitrotyrosine[B]	68	0.33	$F_{5,69} = 10.74$ ($<1 \times 10^{-6}$)	−0.016	−5.03	4×10^{-6}

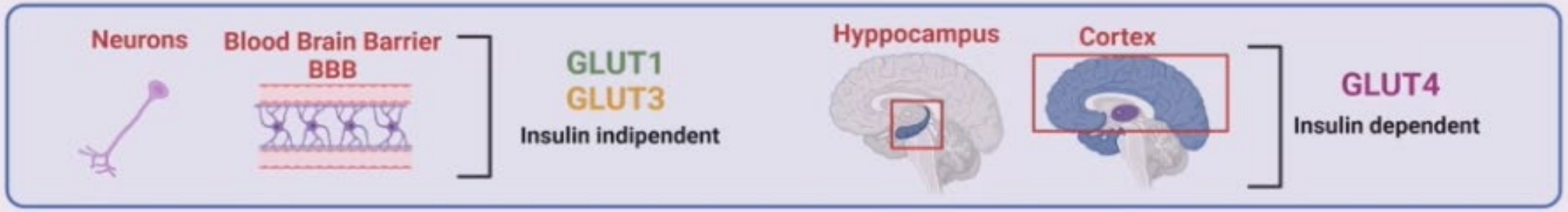


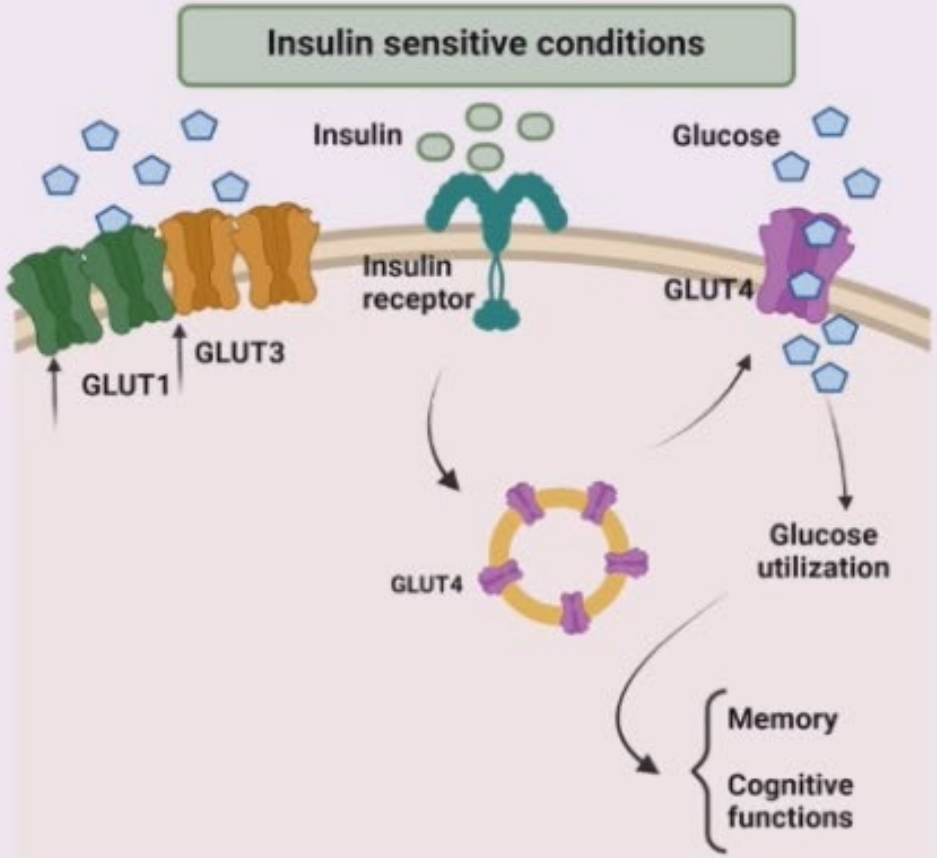
J Clin Invest. 2012;122(4):1316–1338. doi:10.1172/JCI59903

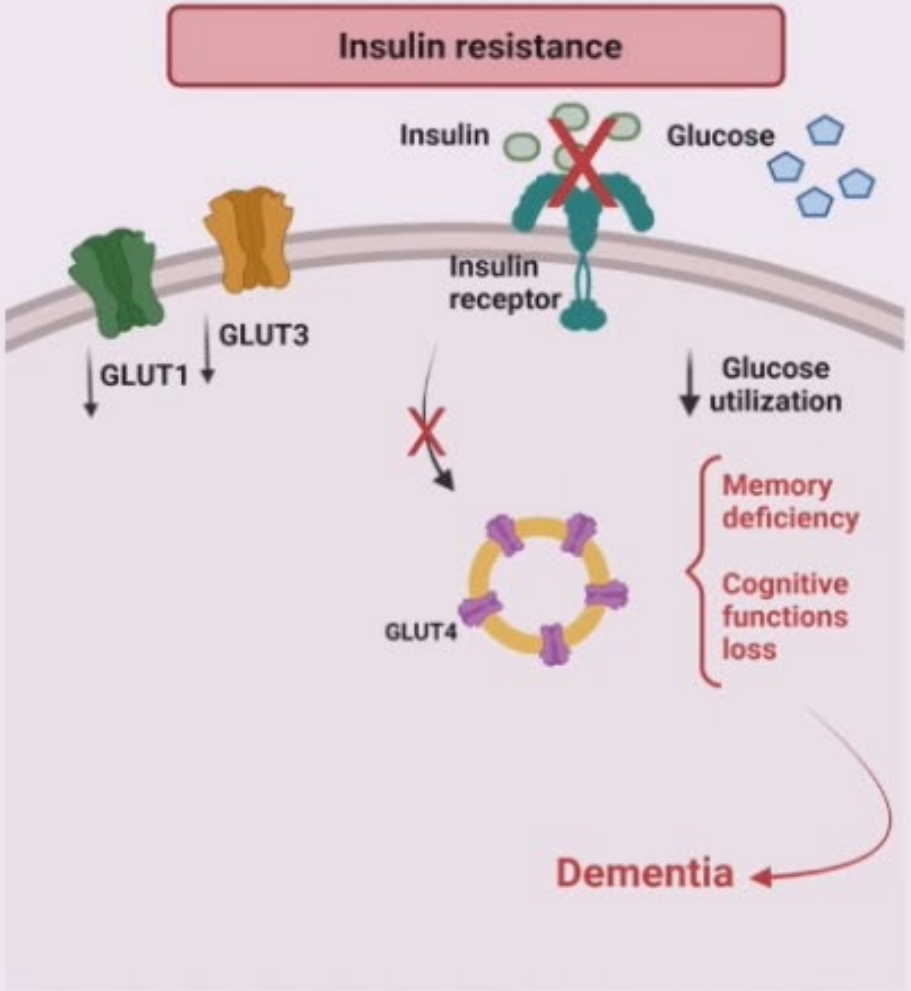
Neuronal Insulin signaling pathway



IBRO Neurosci Rep. 2022 Dec 13;14:57-63. doi: 10.1016/j.ibneur.2022.12.006.



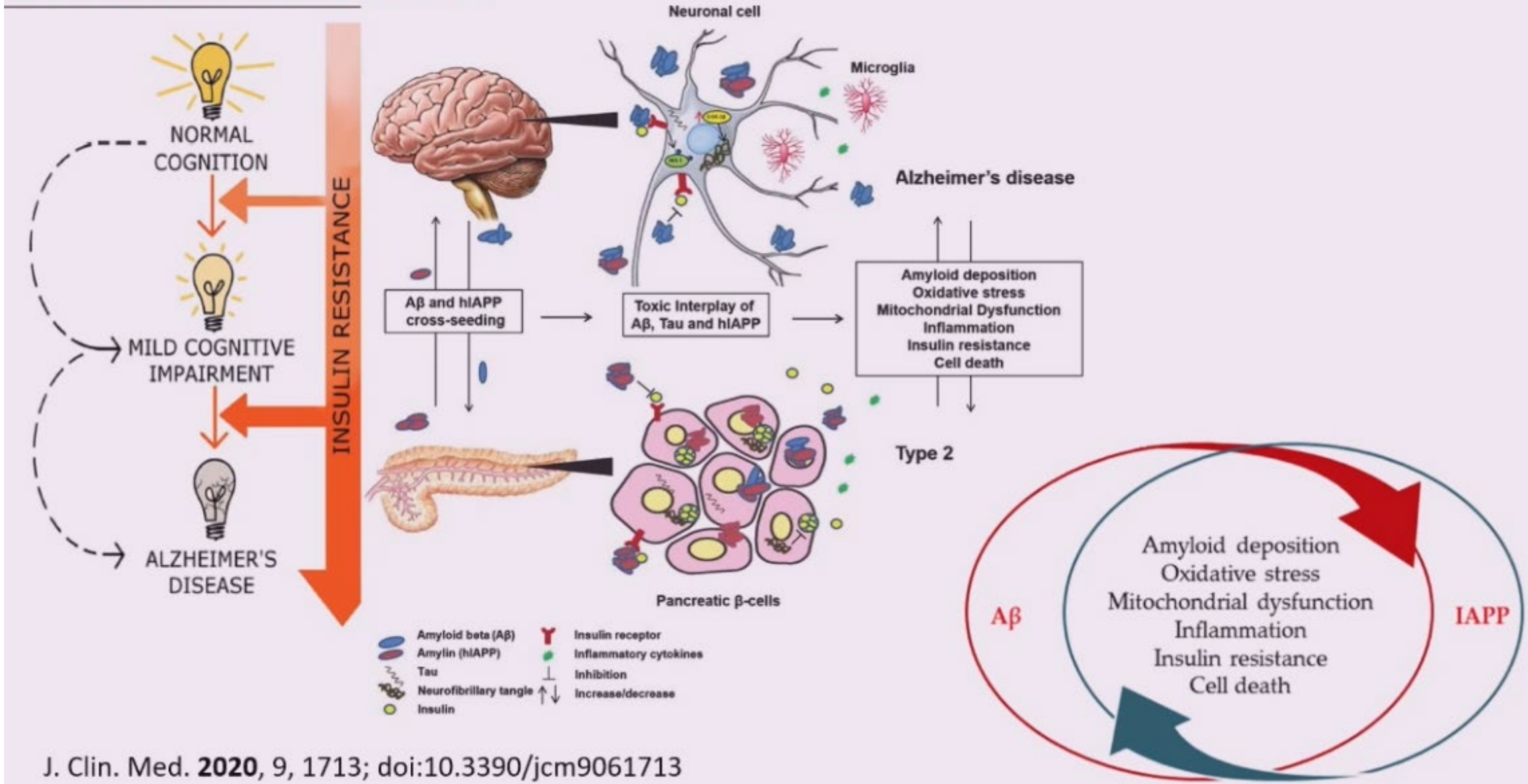




Front. Neurosci. 2020, 14:229.

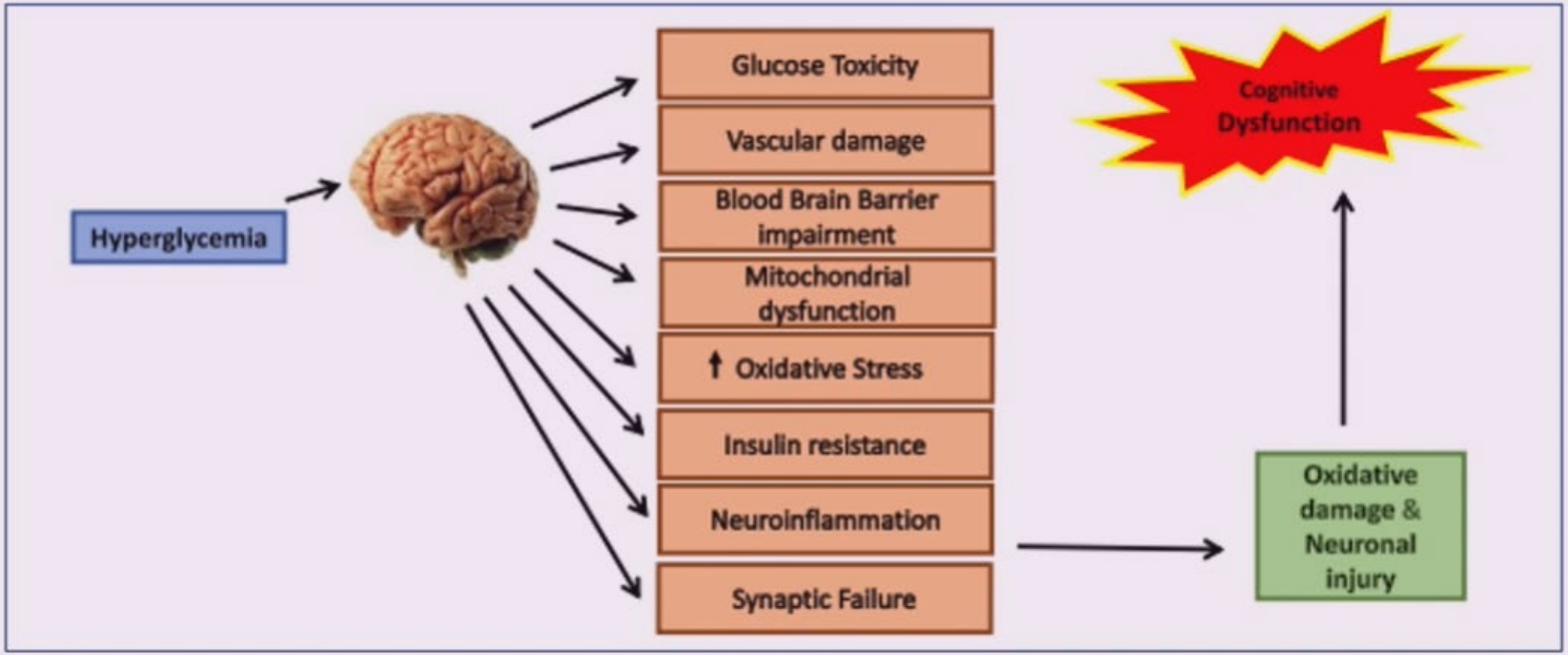
Brain Res. 2009 November 3; 1296: 35–45.

SCHEMATIC REPRESENTATION OF THE CORRELATIONS BETWEEN ISLET AMYLOID POLYPEPTIDE OF DIABETES AND AMYLOID-PEPTIDE FROM ALZHEIMER'S DISEASE



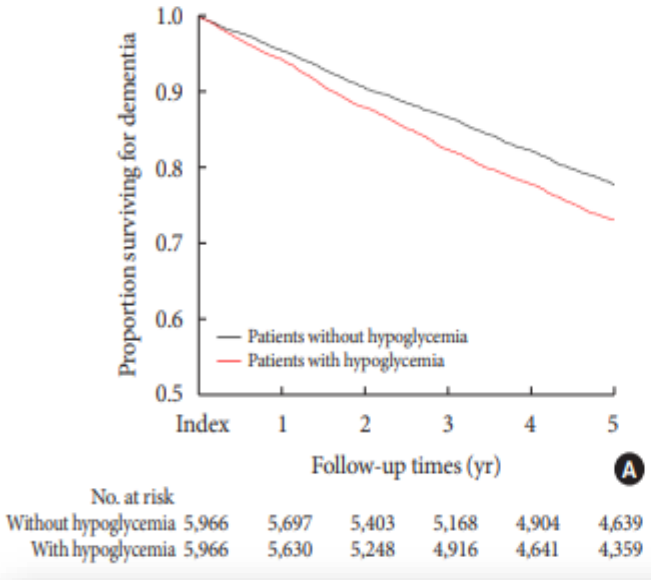
J. Clin. Med. **2020**, 9, 1713; doi:10.3390/jcm9061713

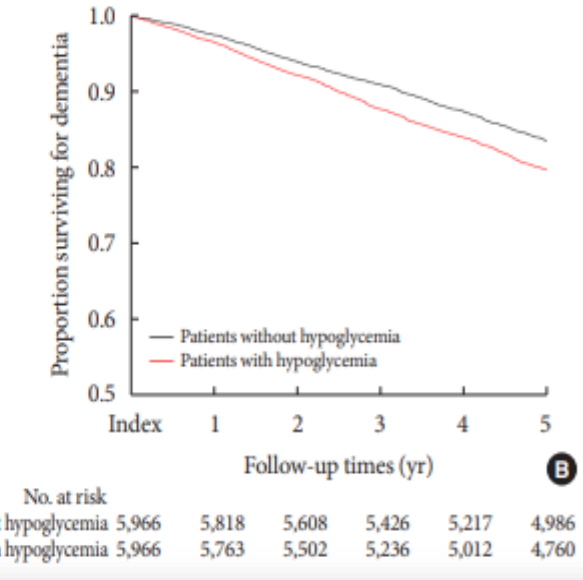
Pathway through which hyperglycemia leads to cognitive impairment



IBRO Neurosci Rep. 2022 Dec 13;14:57-63. doi: 10.1016/j.ibneur.2022.12.006.

Hypoglycemia and Dementia Risk in Older Patients with Type 2 Diabetes Mellitus





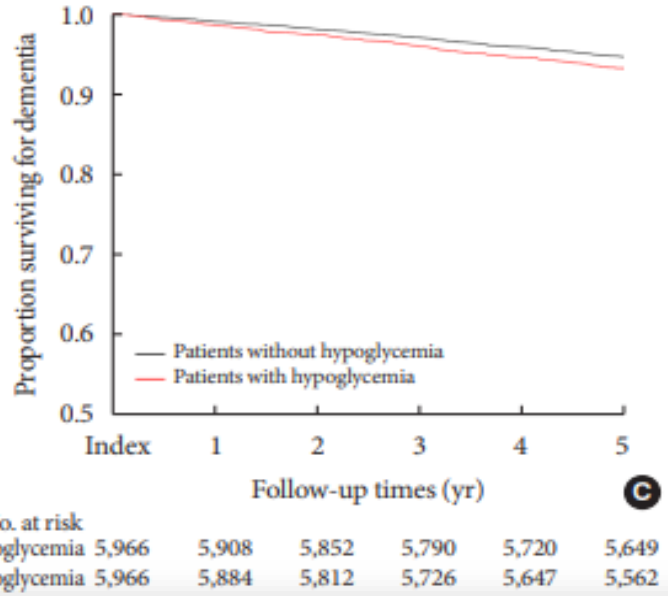


Table 2. The risk of dementia in patients with hypoglycemia compared to patients without hypoglycemia

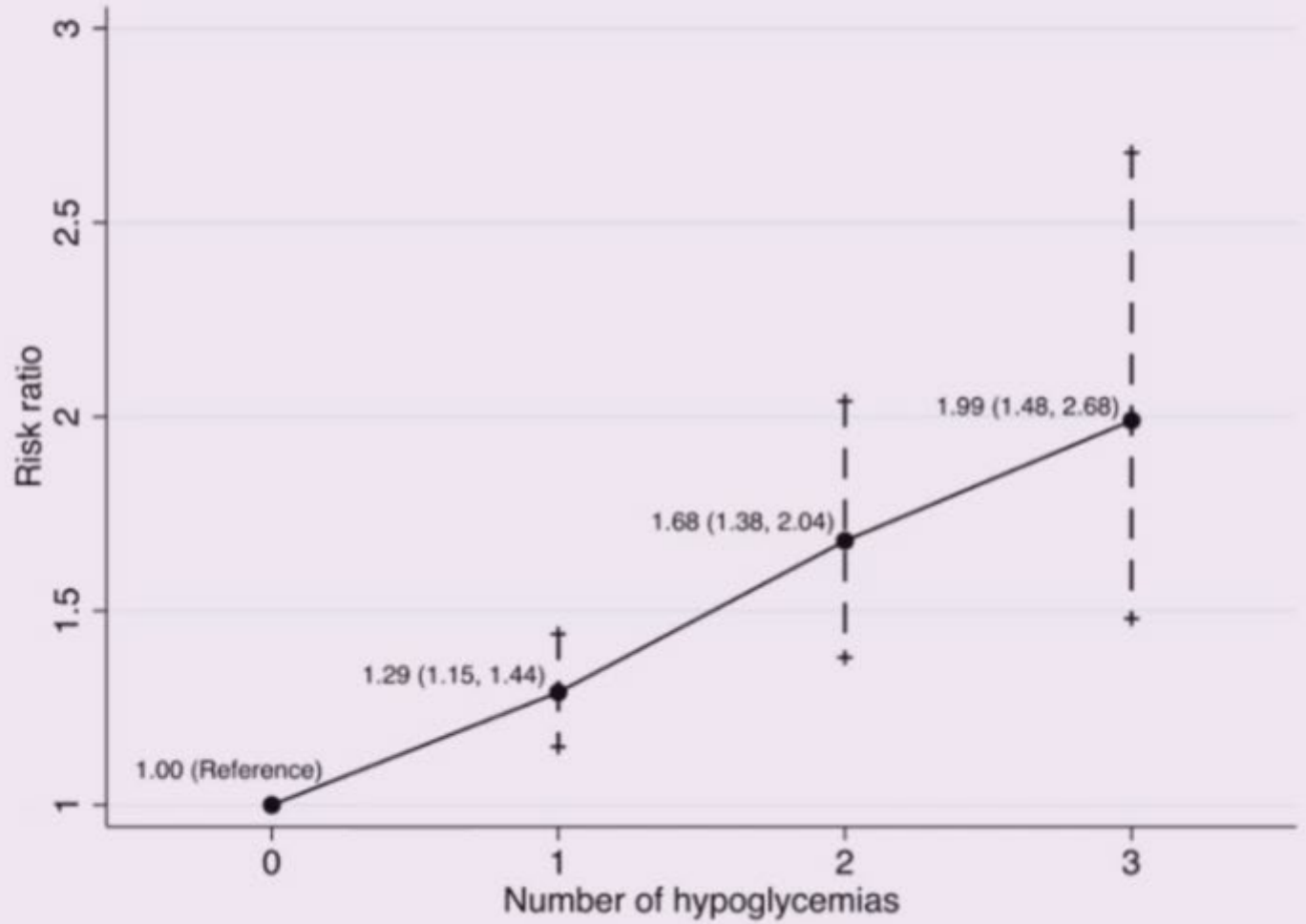
Variable	Number	Events	HR	95% CI	*P* value
All-cause dementia	11,932	2,934	1.254	1.166–1.349	<0.001
Alzheimer's disease	11,932	2,186	1.264	1.162–1.375	<0.001
Vascular dementia	11,932	721	1.286	1.110–1.490	<0.001

Kaplan-Meier plots for (A) all-cause dementia, (B) Alzheimer disease, and (C) vascular dementia in patients with or without underlying hypoglycemia

I. Kim Wium-Andersen. European Journal of Endocrinology (2019) 181, 499–507

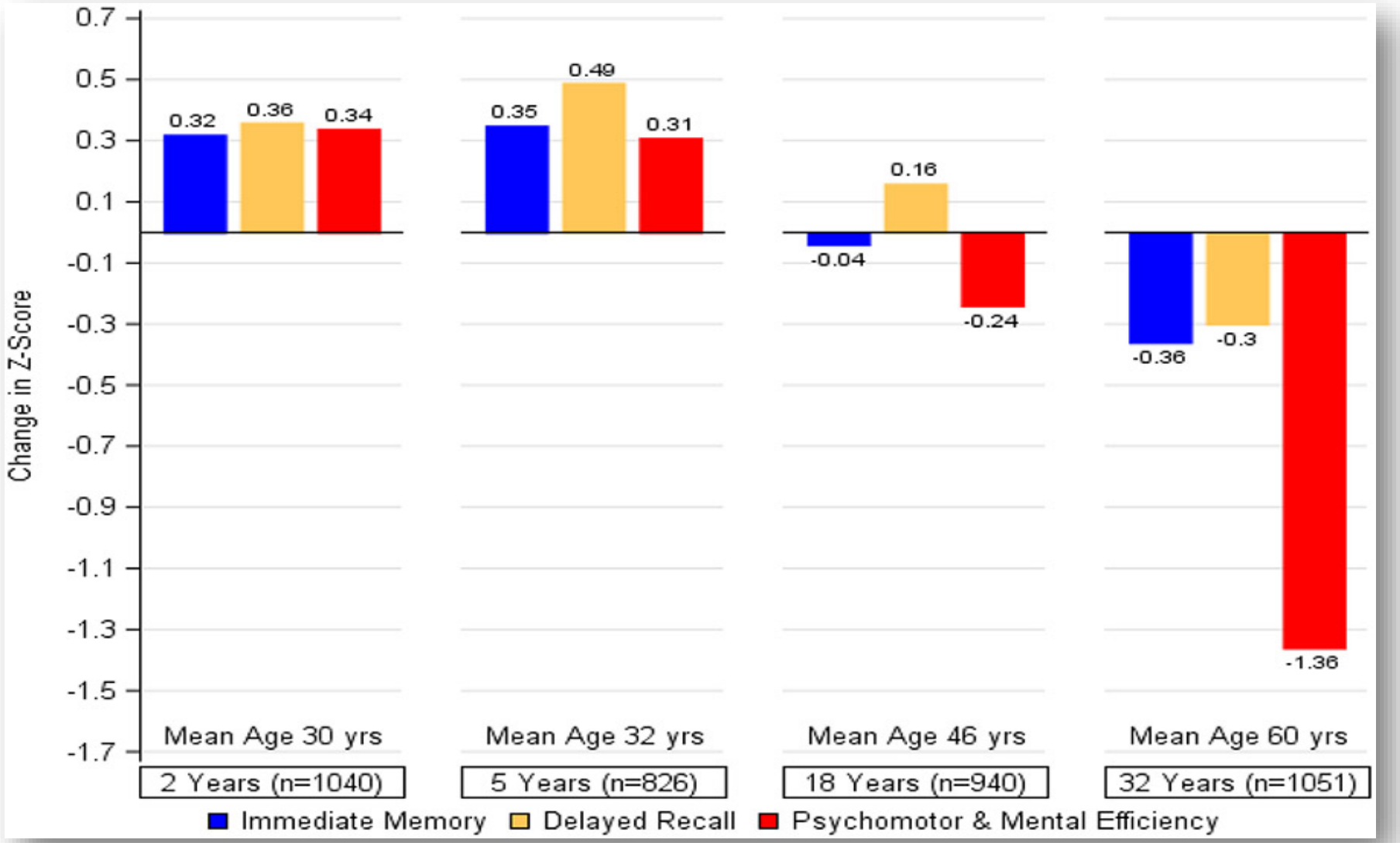
Association between SEVERE HYPOGLYCEMIA and RISK of DEMENTIA in patients with type 2 diabetes mellitus

Diabetes/Metabolism Research and Reviews



Diabetes Metab Res Rev. 2023 Jan 17:e3610. doi: 10.1002/dmrr.3610.

Cognitive Performance Declines in **Older Adults with Type 1** Diabetes: Results from 32 Years of Follow-up in the DCCT/EDIC Study



The bars represent the changes within each of the cognitive domains between testing at DCCT baseline and each follow-up assessment, expressed as changes in **z-scores**.

change was significant over the years within each cognitive domain at p<0·0001.

Alan M. Jacobson, Lancet Diabetes Endocrinol. 2021 July ; 9(7):

- **Declino cognitivo e demenza** sono riconosciuti come **comorbidità e complicanze del diabete mellito**; impattano negativamente sul benessere psico-fisico della persona, sulla Qol e sulla gestione di malattia
- Uno **screening cognitivo**, finalizzato al precoce riconoscimento di MCI e demenza, dovrebbe essere rivolto a tutti gli **individui con DM di età ≥65 anni** e ripetuto regolarmente
- L'**approccio terapeutico ha tre milestones;** dovrebbe tener conto degli obiettivi terapeutici individuali ed evitare il verificarsi di eventi acuti (ipoglicemie o iper-glicemie sintomatiche)

ADA - Standanrd of Care. Diabetes Care 2024;47(1):S244-S257. *Nguyen TT et al. Int J Mol Sci 2020;21(9):3165.*

Contents available at ScienceDirect
Diabetes Research and Clinical Practice
journal homepage: www.elsevier.com/locate/diabres
International Diabetes Federation

The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease

Ahmet Turan Isik[a,*], Pinar Soysal[a], Adnan Yay[b], Cansu Usarel[a]

[a]Center for Aging Brain and Dementia, Department of Geriatric Medicine, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey
[b]Department of Internal Medicine, Izmir Military Hospital, Izmir, Turkey

In conclusione, dopo un follow-up di 6 mesi, mentre la terapia con sitagliptin mostra effetto simile sul controllo glicemico rispetto a insulina e metformina, l'utilizzo di Sita è stato associato ad un miglioramento della funzione cognitiva nei pz DM2 anziani con e senza Alzheimer

4. Discussion

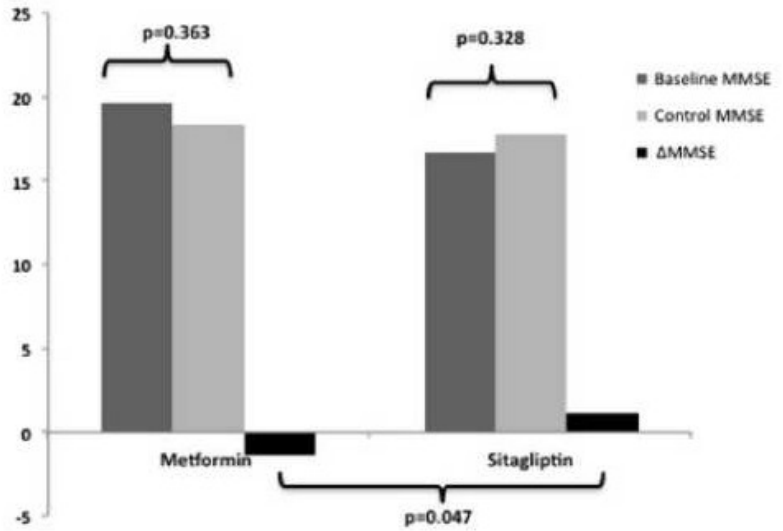


Fig. 2 – Comparison of MMSE scores and mean changes from baseline in MMSE scores in the patients with AD treated with metformin or sitagliptin monotherapy.

Isik AT, Soysal P, Yay A, Usarel C. The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease. **Diabetes Res Clin Pract. 2017** Jan;123:192-198.

Analoghi del GLP-1 e Patologie Neurodegenerative

diabetesresearchandclinicalpractice 200 (2023) 110688

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Diabetes Research and Clinical Practice

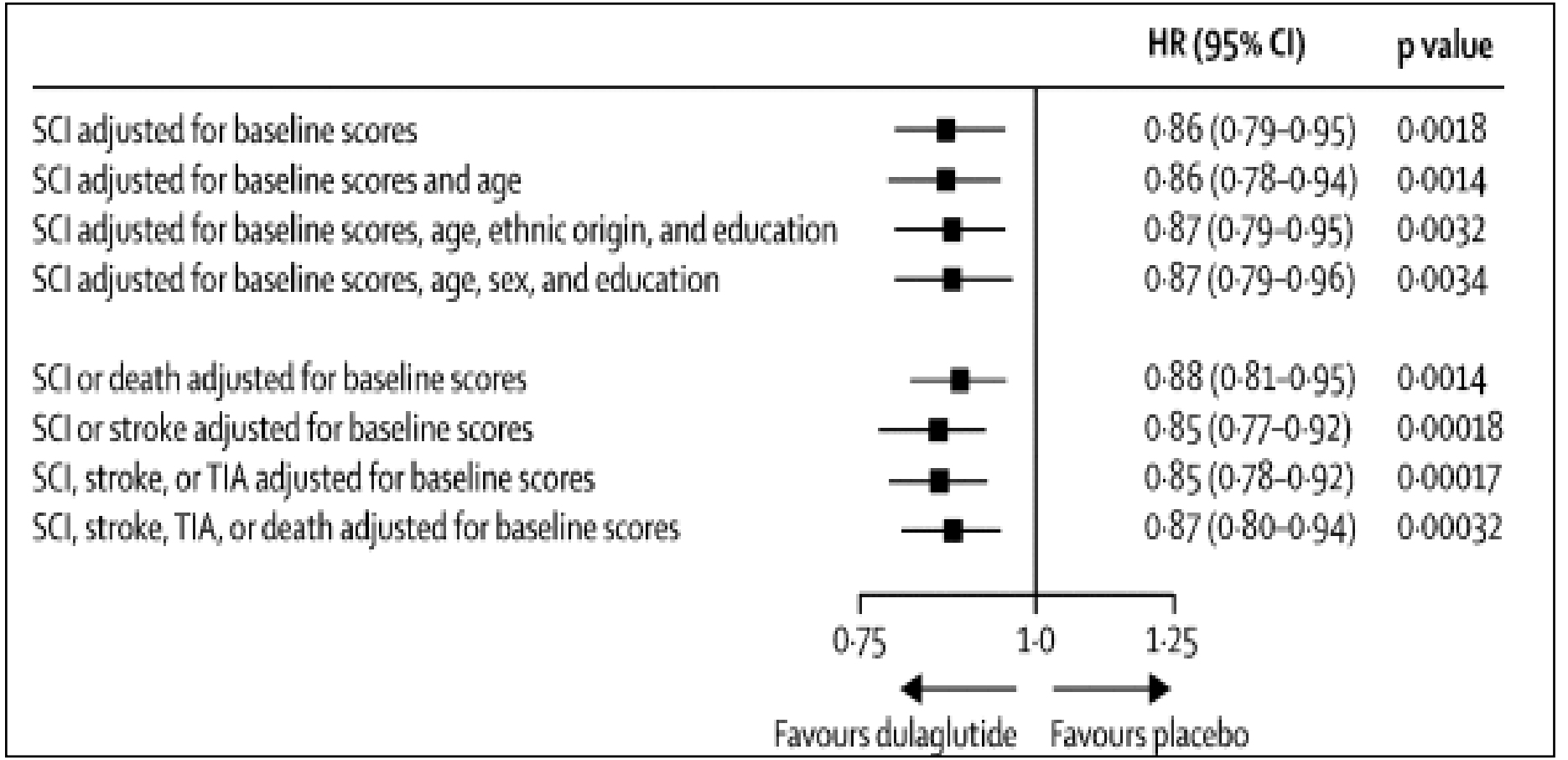
journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Circulating levels of endothelial progenitor cells are associated with better cognitive function in older adults with glucagon-like peptide 1 receptor agonist-treated type 2 diabetes

Miriam Longo [a,b,*], Irene Di Meo [a,c], Paola Caruso [a,b], Maria Francesca Muscio [a,c], Lorenzo Scappaticcio [a,b], Antonietta Maio [a,b], Maria Ida Maiorino [a,b], Giuseppe Bellastella [a,b], Giuseppe Signoriello [d], Filip K. Knop [e,f], Maria Rosaria Rizzo [a,c,1], Katherine Esposito [a,b,1]

[a] Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
[b] Division of Endocrinology and Metabolic Diseases, AOU University of Campania "Luigi Vanvitelli", Naples, Italy
[c] Division of Geriatrics and Internal Medicine, AOU University of Campania "Luigi Vanvitelli", Naples, Italy
[d] Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[e] Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[f] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Dulaglutide mostra un impatto positivo su diversi indicatori di declino cognitivo: post hoc analisi dello studio REWIND



Dulaglutide riduce il rischio di decadimento cognitivo sostanziale (SCI) del 14% rispetto al placebo (HR 0·86, 95% CI 0·79–0·95; p=0·0018).

Substantive cognitive impairment (**SCI = decadimento congitivo sostanziale),** definito come prima evidenza di variazione di punteggio di MoCA (Montreal Cognitive Assessment test) o di DSST (Digit Symbol Substitution Test) di almeno −1.5 devizioni standard.

Cukierman-Yaffeet al. Lancet Neurol 2020; 19: 582–90

Diabetes Care. 2022;46(2):297-304. doi:10.2337/dc22-1705

Association of Sodium–Glucose Cotransporter-2 Inhibitors With Time to Dementia: A Population-Based Cohort Study

Design and Methods

Residents of Ontario, Canada older than 66 years old

Dementia-free

Observation

No prescription of either drug in the past year

1-year lag time

Cohort entry

New users of DPP-4 inhibitors

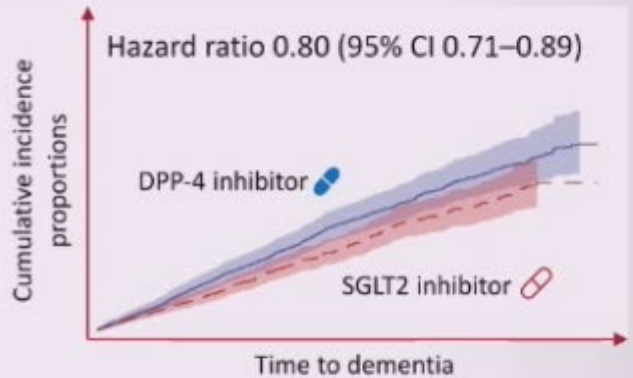
N = 70,390

New users of SGLT2 inhibitors

N = 36,513

Compare time to dementia using a propensity score–weighted Cox regression model

Results



SGLT2 inhibitor use was associated with a 20% lower dementia risk compared with DPP-4 inhibitor use

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Review

Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment

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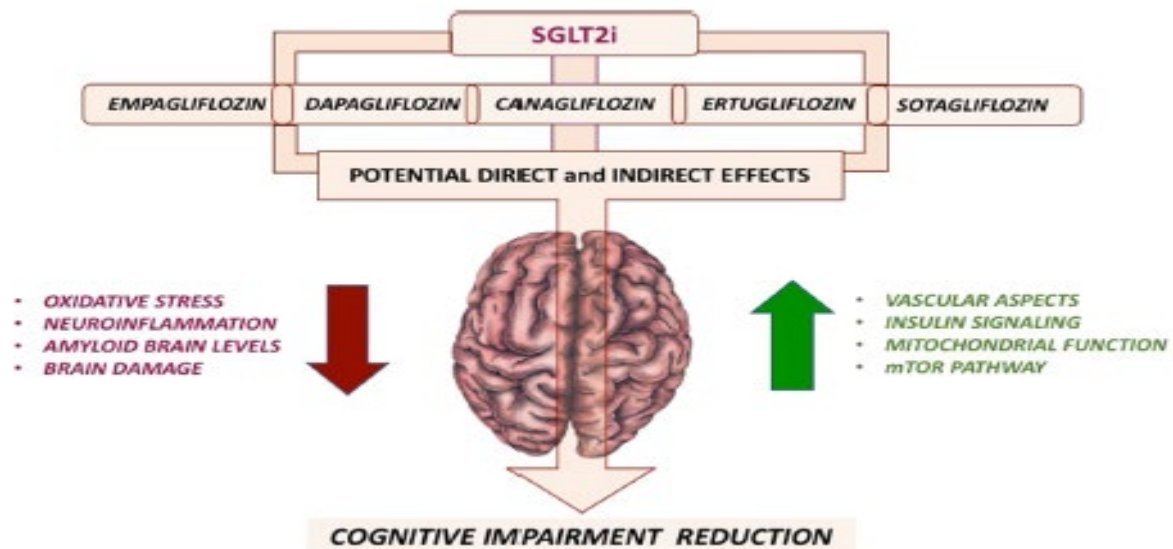

TAKE HOME MESSAGES

- Il link tra diabete e declino cognitivo ha solide basi scientifiche
- L'insulino-resistenza sembra giocare un ruolo chiave
- L'identificazione dei meccanismi molecolari coinvolti rappresenta il punto di partenza per l'individuazione di markers precoci di malattia e di nuovi potenziali target terapeutici.

Thanks for attention