IV Sessione

PROSPETTIVE TERAPEUTICHE FARMACOLOGICHE

Moderatrice: **N. Locuratolo**

15.40 Risultati preliminari dello studio Interceptor
P.M. Rossini

16.00 Processo regolatorio dell'approvazione dei nuovi farmaci nella demenza
F. Nonino

16.20 Uso dei farmaci a RNA nelle demenze
M. Denti

16.40 Terapie a RNA per la Demenza Frontotemporale: validazione in un modello neuronale MAPT IVS10+16
I. Brentari

16.50 Declino cognitivo nel paziente diabetico: ruolo del trattamento con i "più nuovi" ipoglicemizzanti orali
M.R. Rizzo

Università degli Studi della Campania *Luigi Vanvitelli*

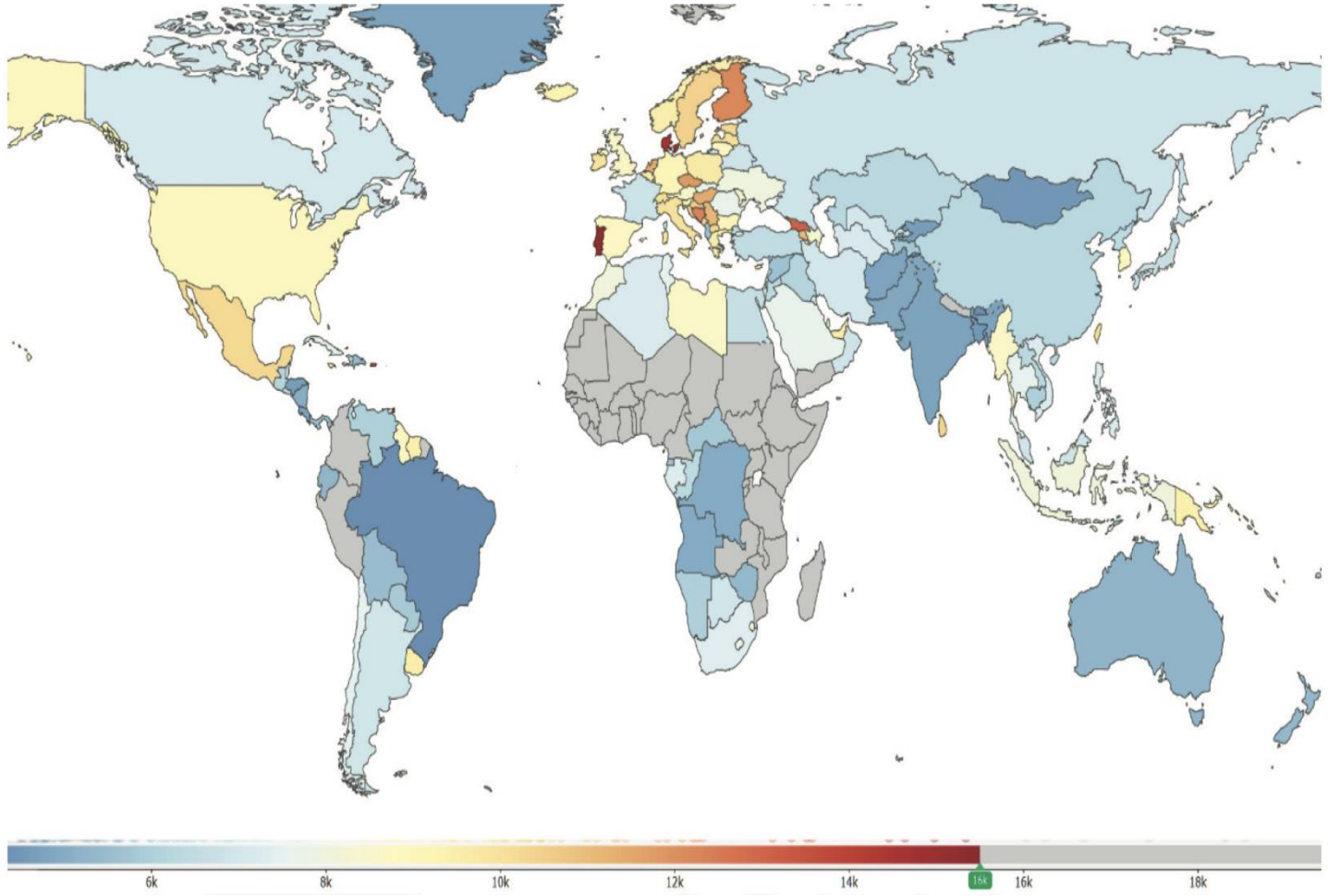
ATLANTIS PRESS

Journal of Epidemiology and Global Health
Vol. 10(1); March (2020), pp. 107–111
DOI: https://doi.org/10.2991/jegh.k.191028.001; ISSN 2210-6006; eISSN 2210-6014
https://www.atlantis-press.com/journals/jegh

Research Article

Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends

Ci sono circa 463 milioni di persone affette da diabete nel mondo (9,3%), e si stima che saranno circa 578 milioni (10,2%) entro il 2030 e 700 milioni entro il 2045 (10,9%)



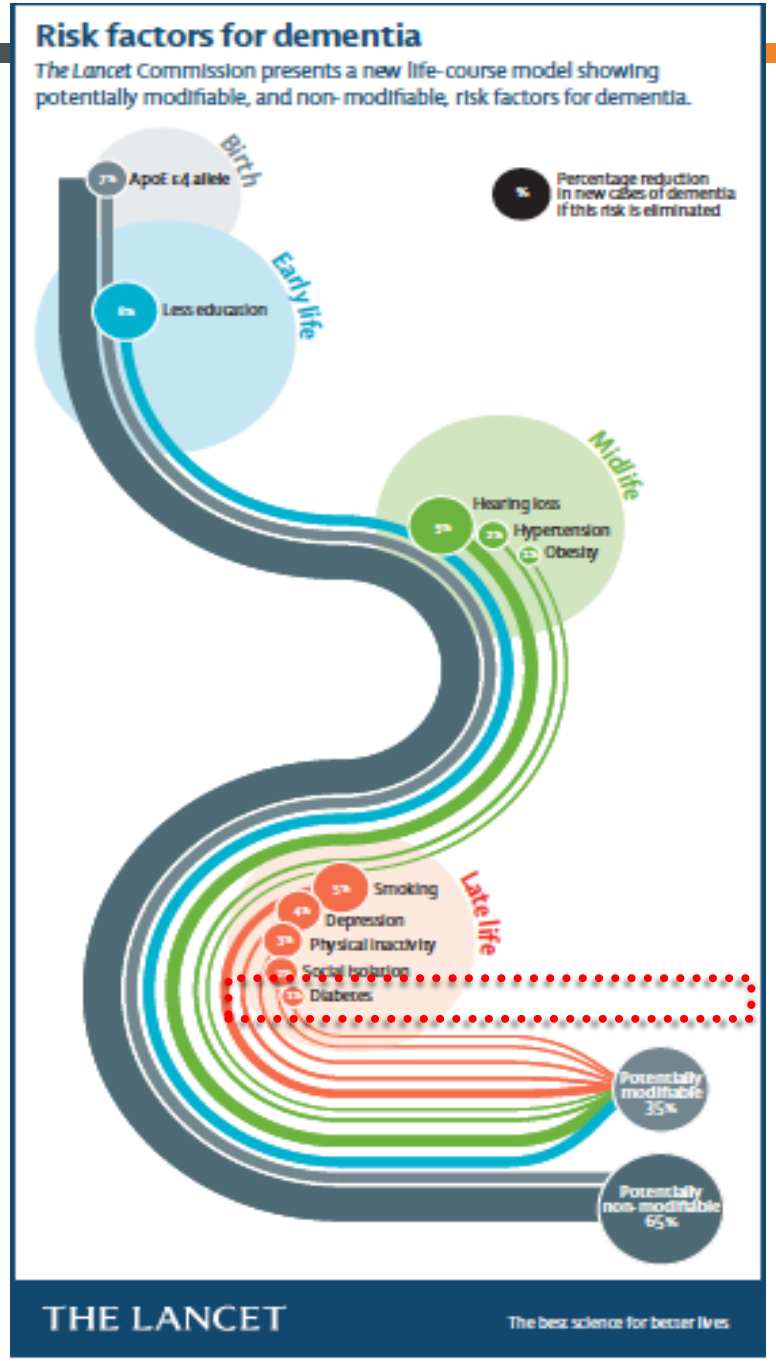
Global distribution of DIABETES MELLITUS TYPE 2 prevalence

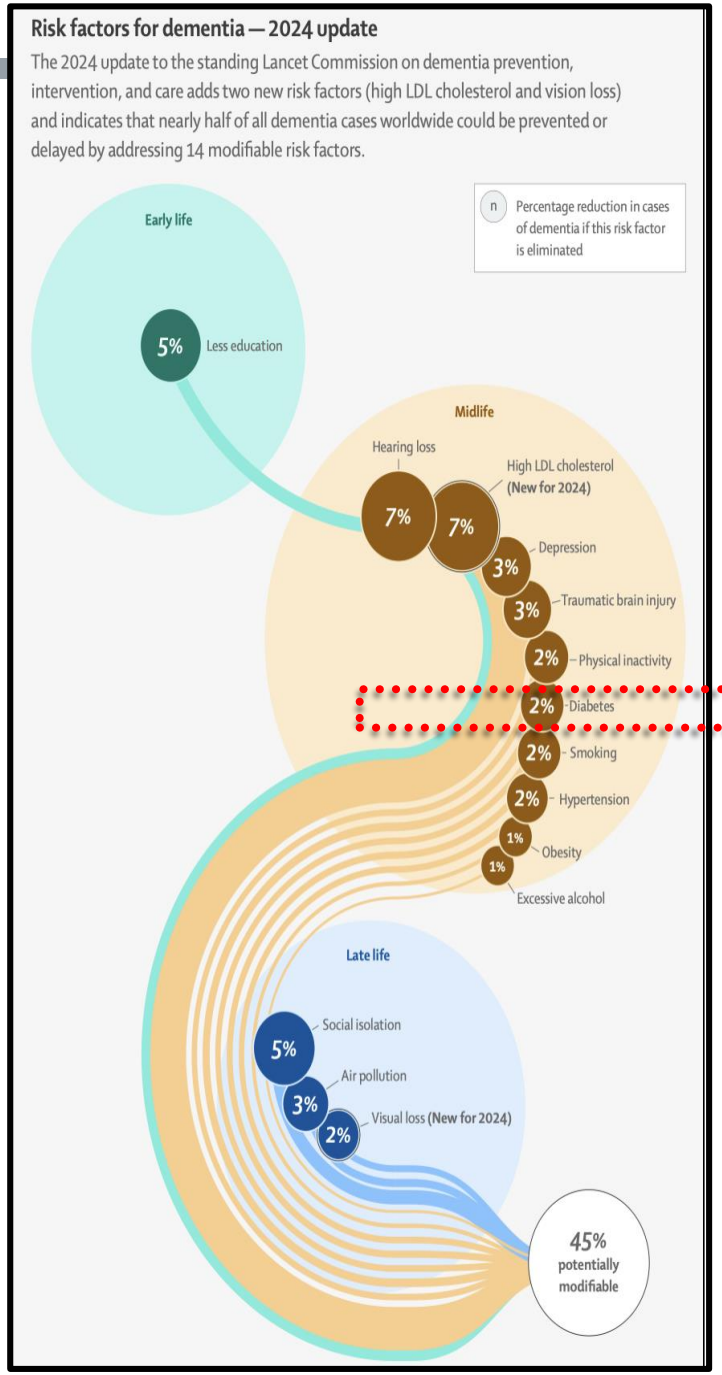
Note: Colors indicate prevalence rates per 100,000 population in 2017

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

The majority of dementia cases are sporadic with unknown etiology, although several risk factors contribute to its development





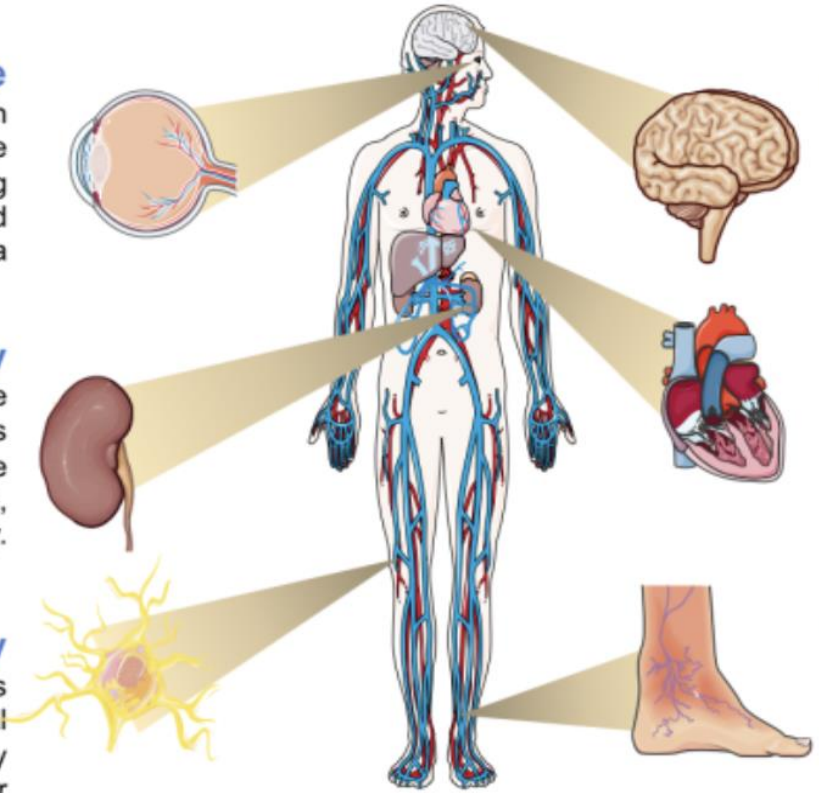
Major Complications of Diabetes

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

PSYCHOLOGIC TESTS APPLIED TO DIABETIC PATIENTS

W. R. MILES, Ph.D.; H. F. ROOT, M.D.

Arch Intern Med. 1922;30(6):767-777.

Diabetes is well known to exert an important influence on the central nervous system. Kraus[1] recently summarized the more common neurologic lesions, and the psychoses occasionally associated with diabetes have been the subject of numerous studies.

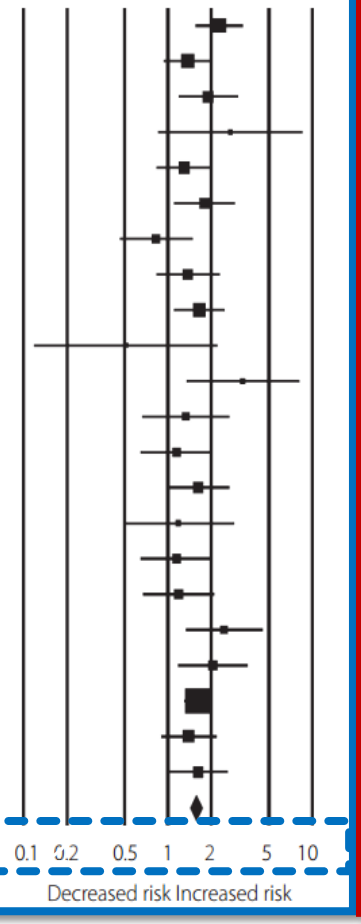
The diabetic patient, on his own part, complains of loss of memory and of poor ability to concentrate the attention. So far as we are aware, there are no objective data which either substantiate or contradict this clinical picture in reference to attention and memory. We have undertaken to gain some light as to the extent of the impairment if such exists, comparing diabetic patients as a group with controls who are of about the same mental status.

DIABETES AND RISK OF DEMENTIA:
A META-ANALYSIS OF PROSPECTIVE OBSERVATIONAL STUDIES

Alzheimer's disease

Study name	Risk ratio	Lower limit	Upper limit
Leibson (Males), 1997	2.27	1.55	3.32
Leibson (Females), 1997	1.37	0.94	2.00
Ott, 1999	1.90	1.18	3.05
Tyas, 2001	2.70	0.85	8.56
MacKnight, 2002	1.30	0.83	2.03
Peila, 2002	1.80	1.10	2.93
Hassing, 2002	0.83	0.46	1.49
Honig, 2003	1.38	0.83	2.28
Arvanitakis, 2004	1.65	1.10	2.47
Borenstein (APOE +), 2005	0.51	0.12	2.21
Borenstein (APOE –), 2005	3.31	1.35	8.12
Hayden, 2006	1.33	0.66	2.68
Akomolafe, 2006	1.15	0.64	2.05
Irie, 2008	1.62	0.98	2.67
Toro, 2009	1.18	0.49	2.87
Raffatin, 2009	1.15	0.64	2.06
Xu, 2009	1.19	0.67	2.11
Ahtiluoto, 2010	2.45	1.32	4.53
Ohara, 2011	2.05	1.18	3.58
Kimm (Males), 2011	1.60	1.29	1.98
Cheng, 2011	1.40	0.90	2.17
Li, 2011	1.62	1.00	2.62
	1.56	1.41	1.73

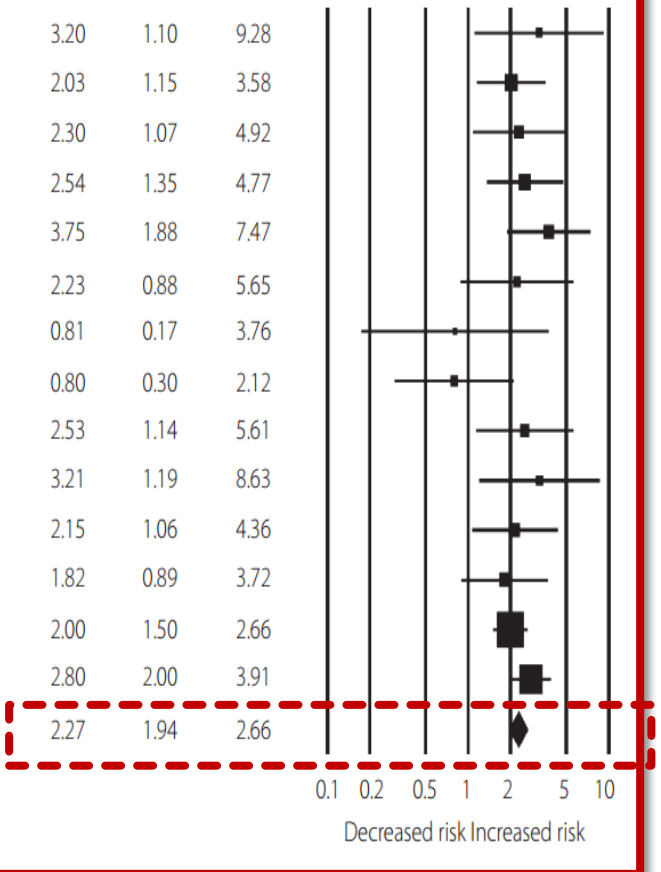
Risk ratio and 95% CI



Vascular dementia

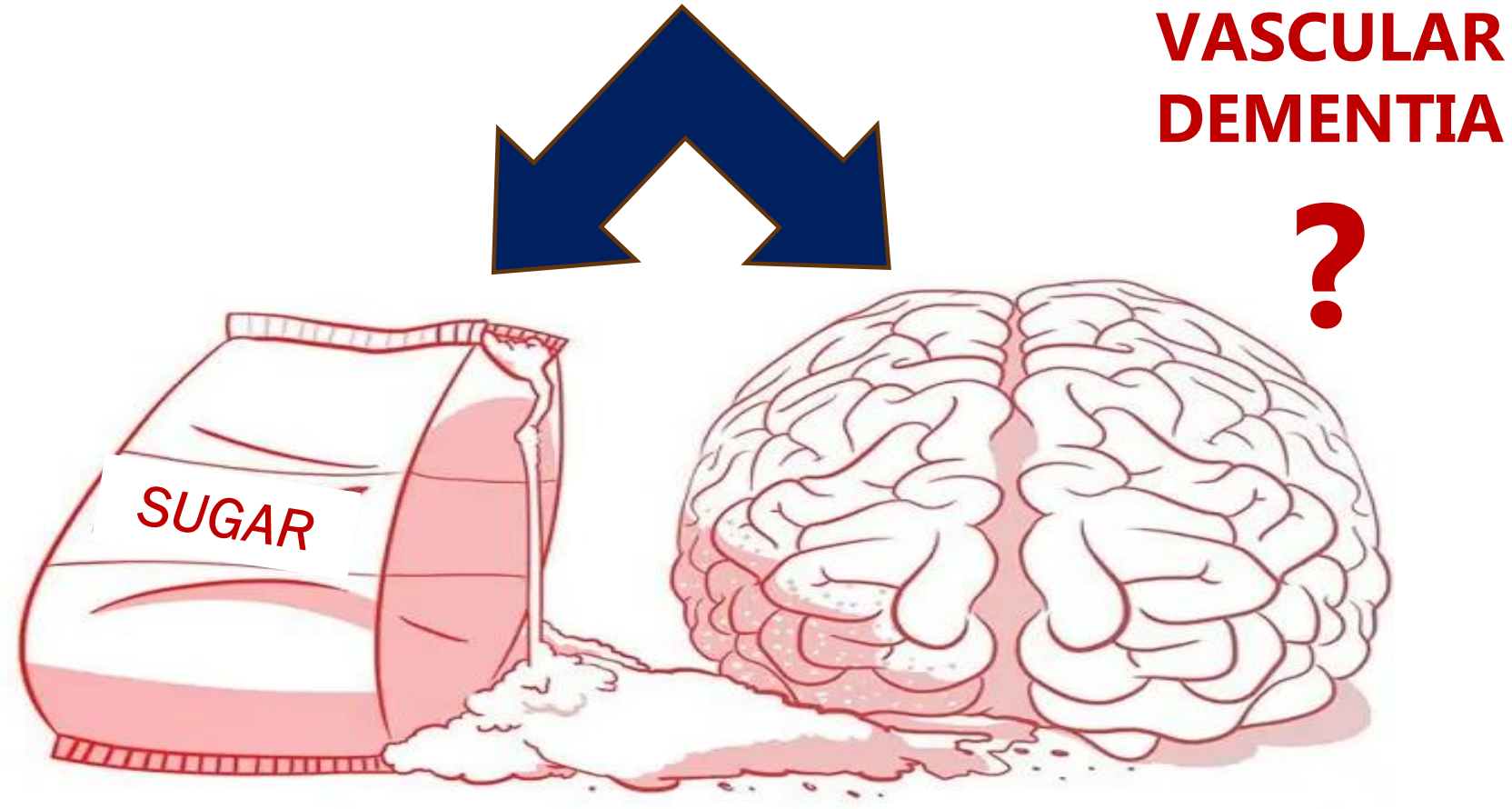
Study name	Risk ratio	Lower limit	Upper limit
Posner, 2002	3.20	1.10	9.28
MacKnight, 2002	2.03	1.15	3.58
Peila, 2002	2.30	1.07	4.92
Hassing, 2002	2.54	1.35	4.77
Lin, 2006	3.75	1.88	7.47
Hayden, 2006	2.23	0.88	5.65
Akomolafe, 2006	0.81	0.17	3.76
Irie, 2008	0.80	0.30	2.12
Raffatin, 2009	2.53	1.14	5.61
Xu, 2009	3.21	1.19	8.63
Ahtiluoto, 2010	2.15	1.06	4.36
Ohara, 2011	1.82	0.89	3.72
Kimm (Males), 2011	2.00	1.50	2.66
Kimm (Females), 2011	2.80	2.00	3.91
	2.27	1.94	2.66

Risk ratio and 95% CI



Journal of Diabetes Investigation Volume 4 Issue 6 November 2013

How diabetes can lead to dementia

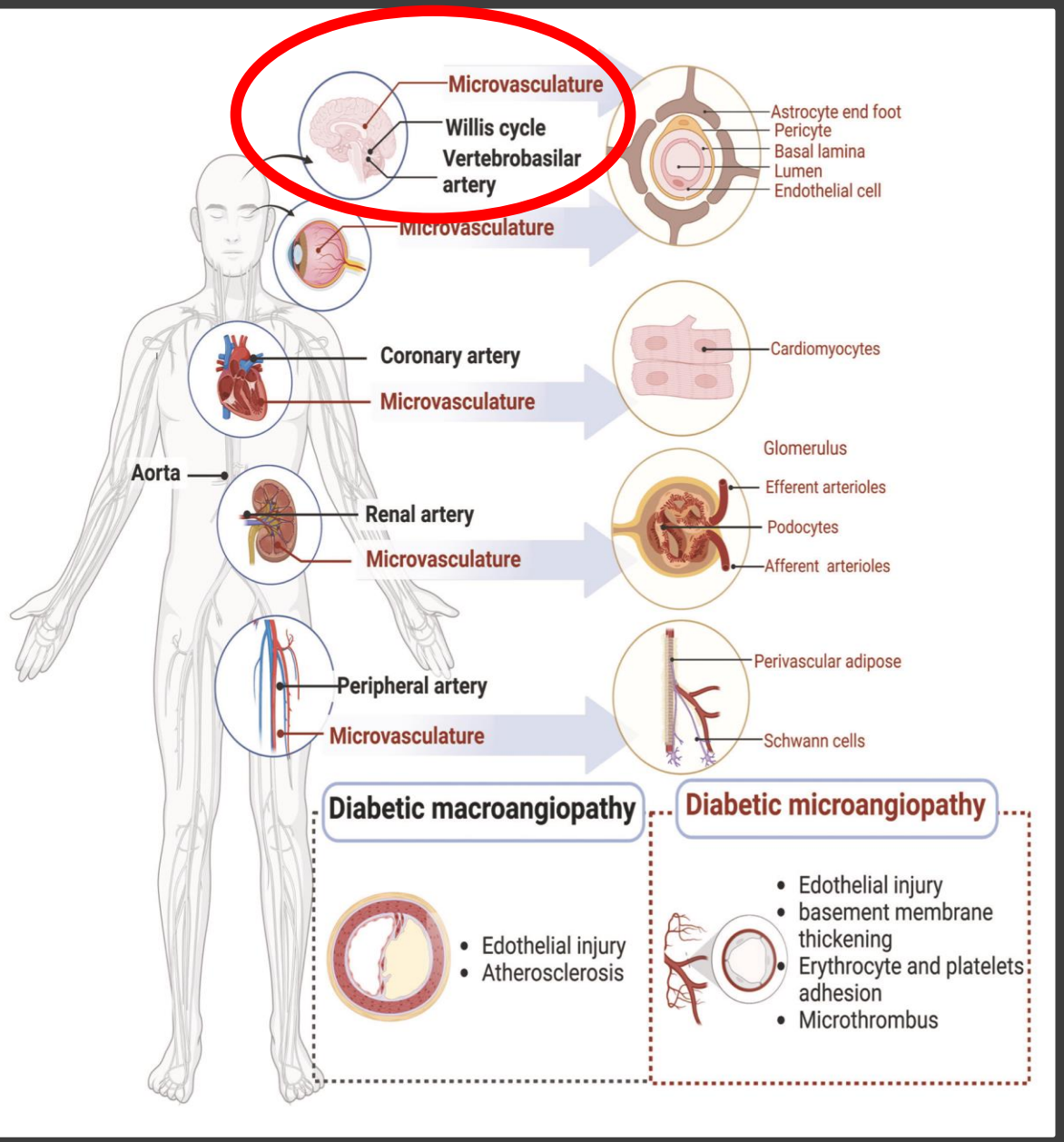


Signal Transduction and Targeted Therapy (2023)8:152

ım/sigtrans

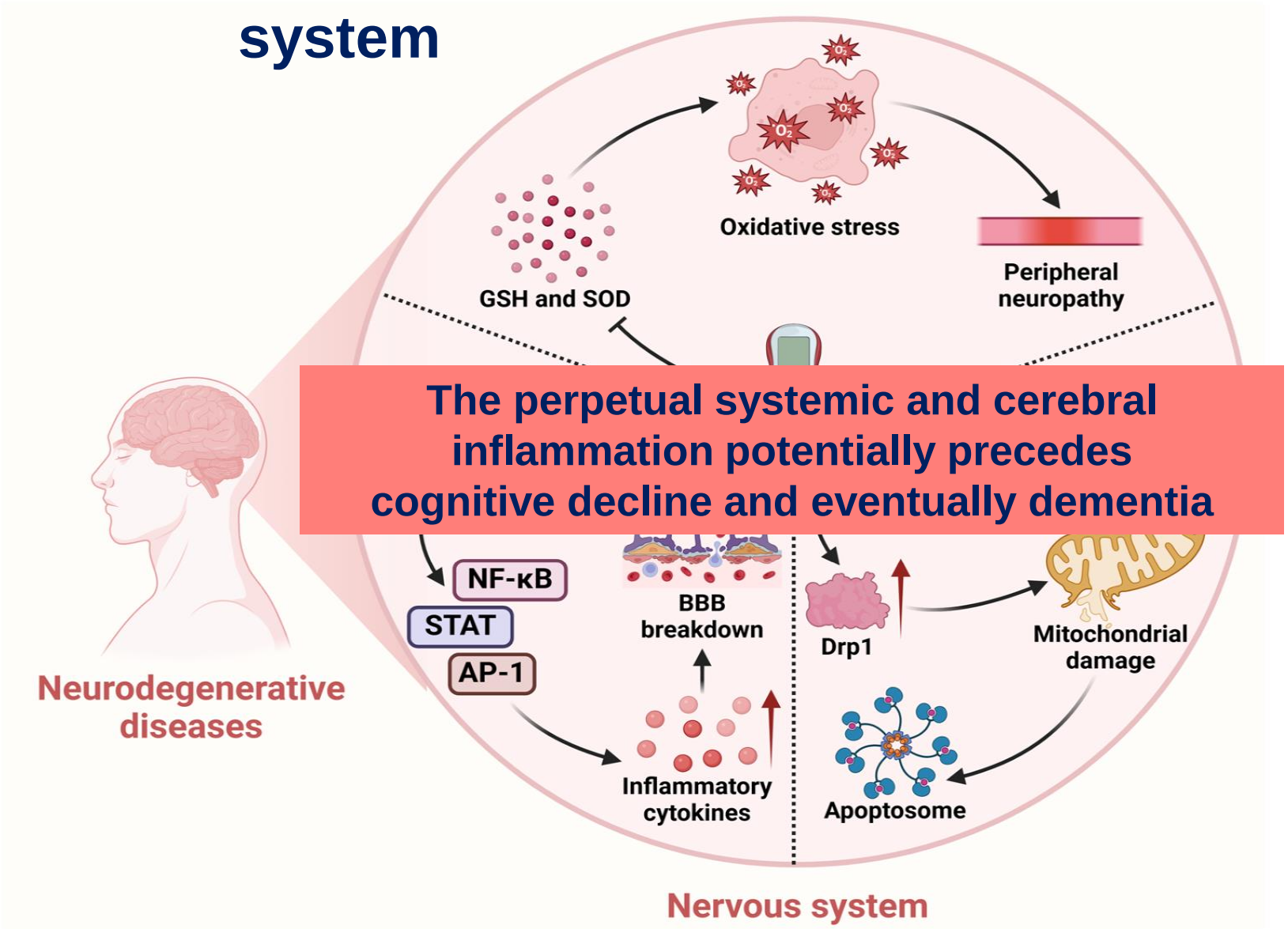
REVIEW ARTICLE OPEN

Diabetic vascular diseases: molecular mechanisms and therapeutic strategies



Diabetes mellitus affects the nervous system

Type 2 diabetes, due to the hyperglycemia, promote endothelial dysfunction and microvascular insufficiency, which can lead to vascular dementia even in the absence of macrovascular insults, through mechanisms involving ischemia, blood–brain barrier leakage, disruptions in white matter integrity, uncontrolled ROS, oxidative stress. RAGE and inflammation



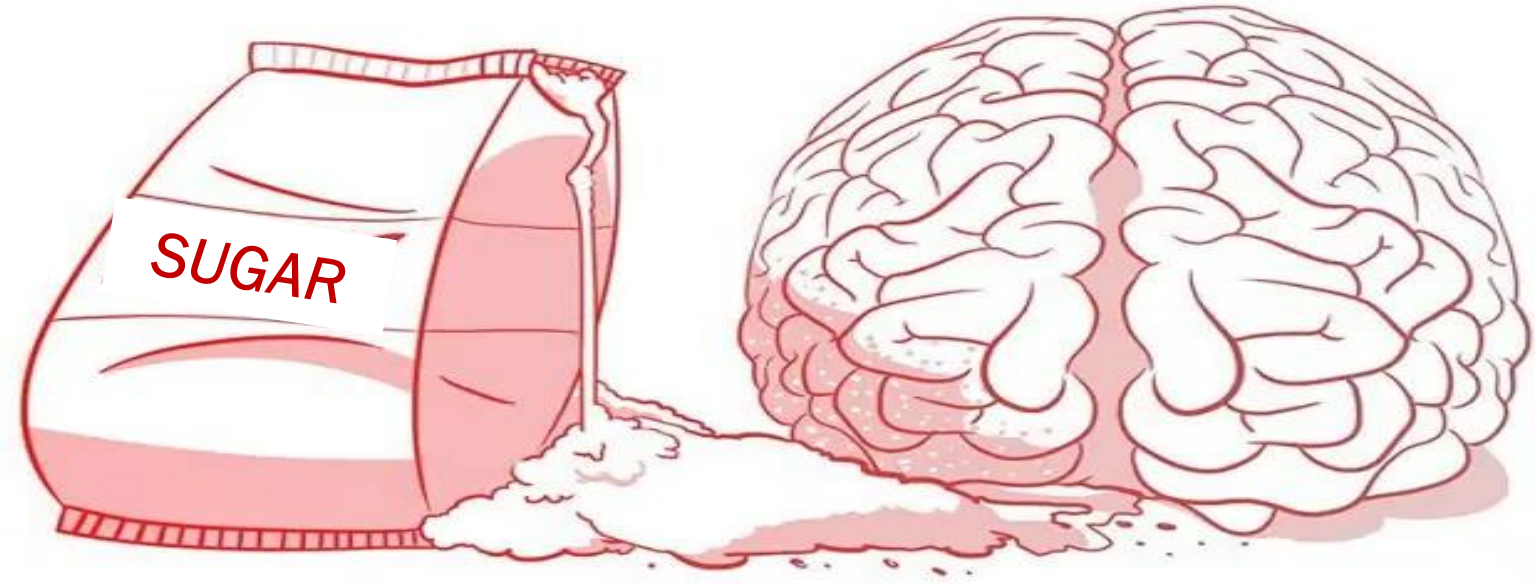
Mei et al – Translation neurodegeneration- 2024

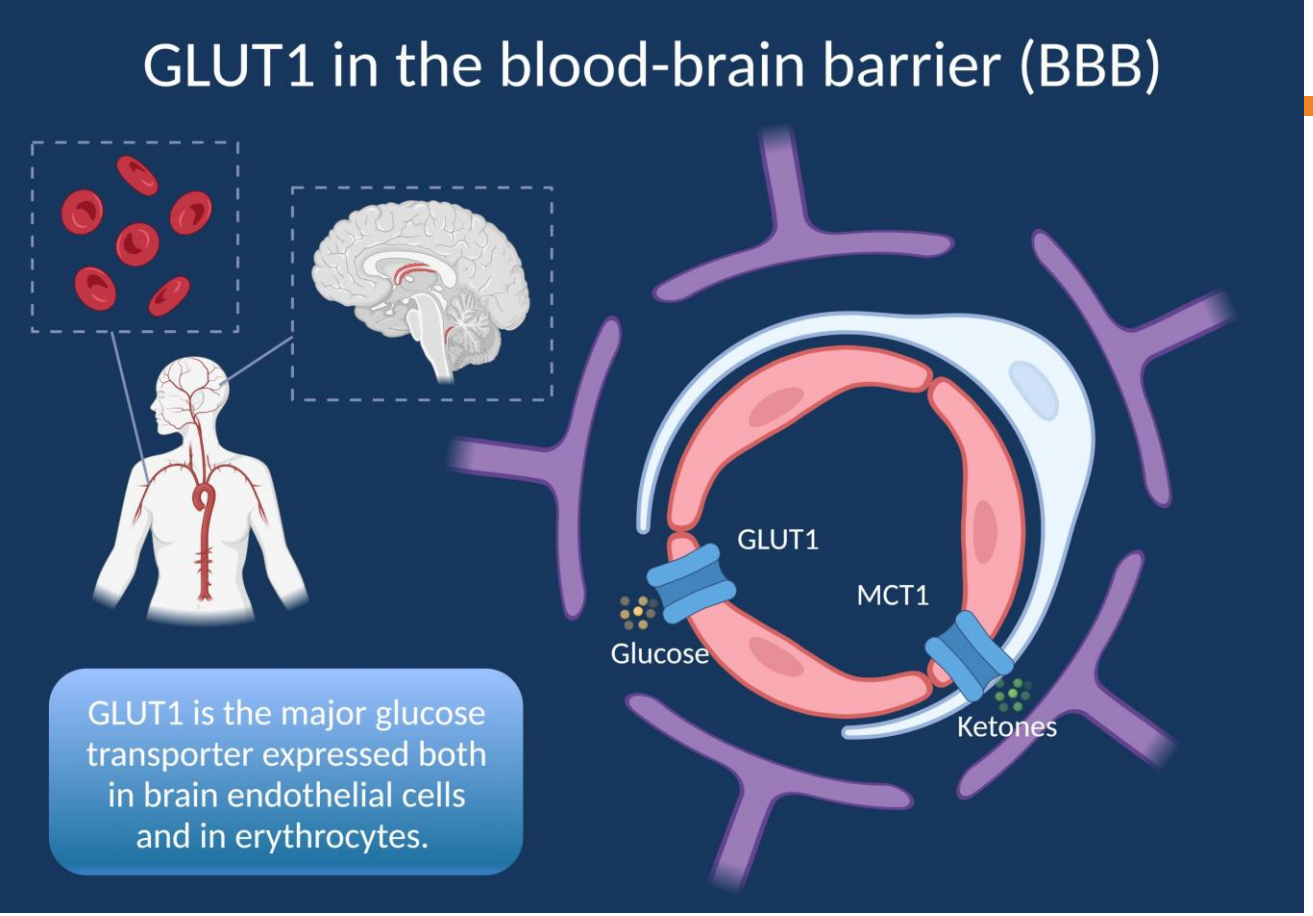
How diabetes can lead to dementia

DEGENERTIVE DEMENTIA

?

VASCULAR DEMENTIA

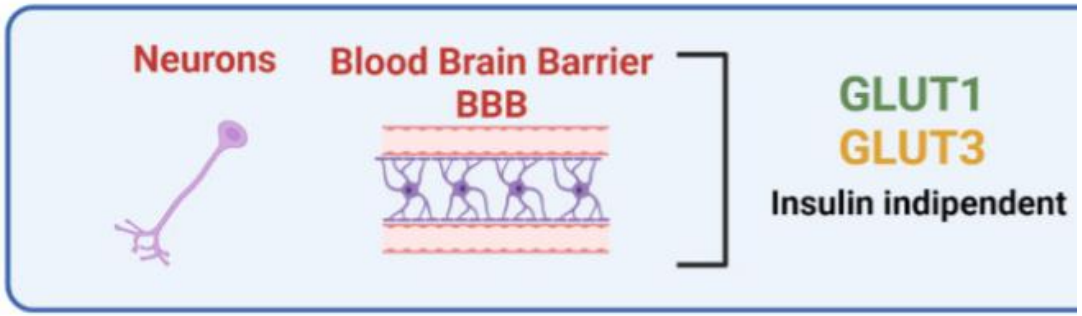




GLUT1: Mainly involved in glucose transport across the BBB and into astrocytes.

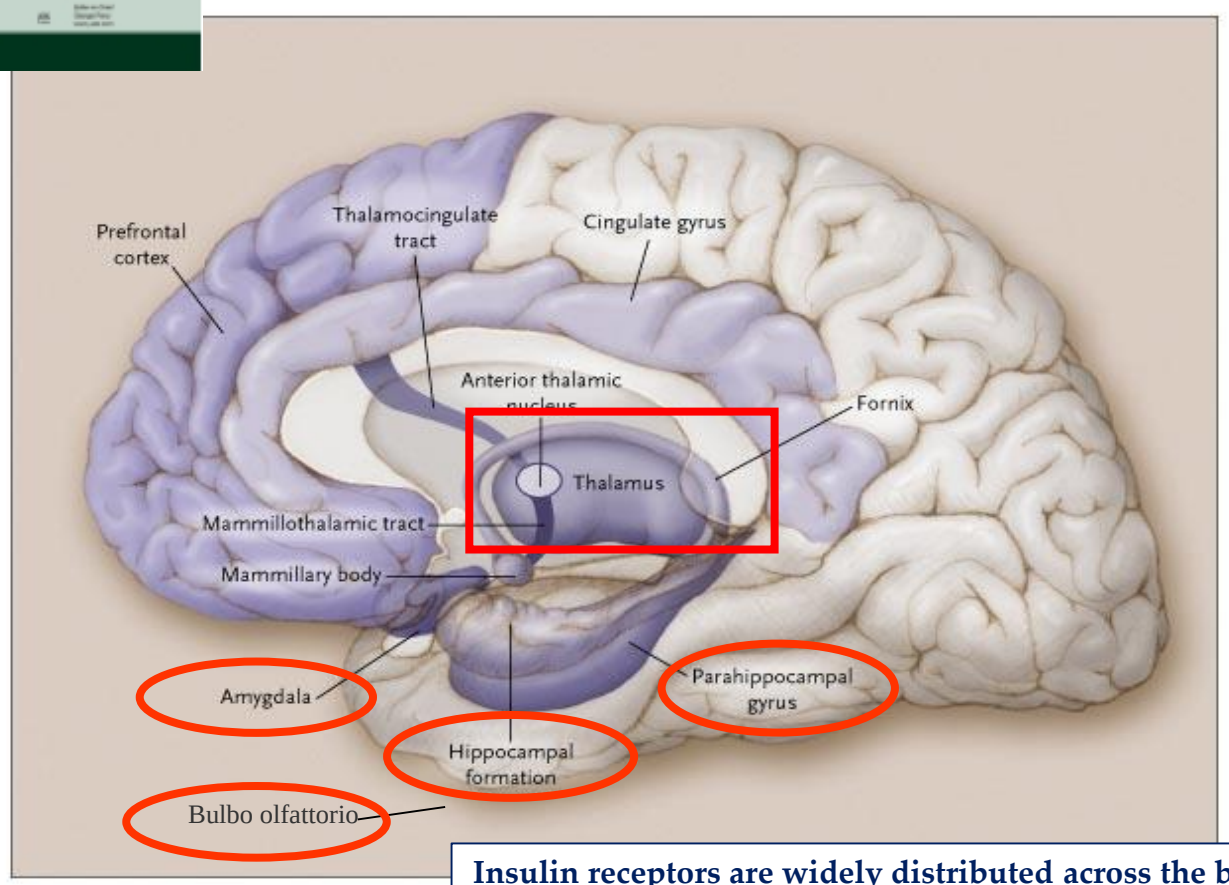
GLUT2: Specialized in glucose sensing and regulation, particularly in astrocytes and some neurons.

GLUT3: Predominant glucose transporter in neurons, ensuring high-affinity glucose uptake.

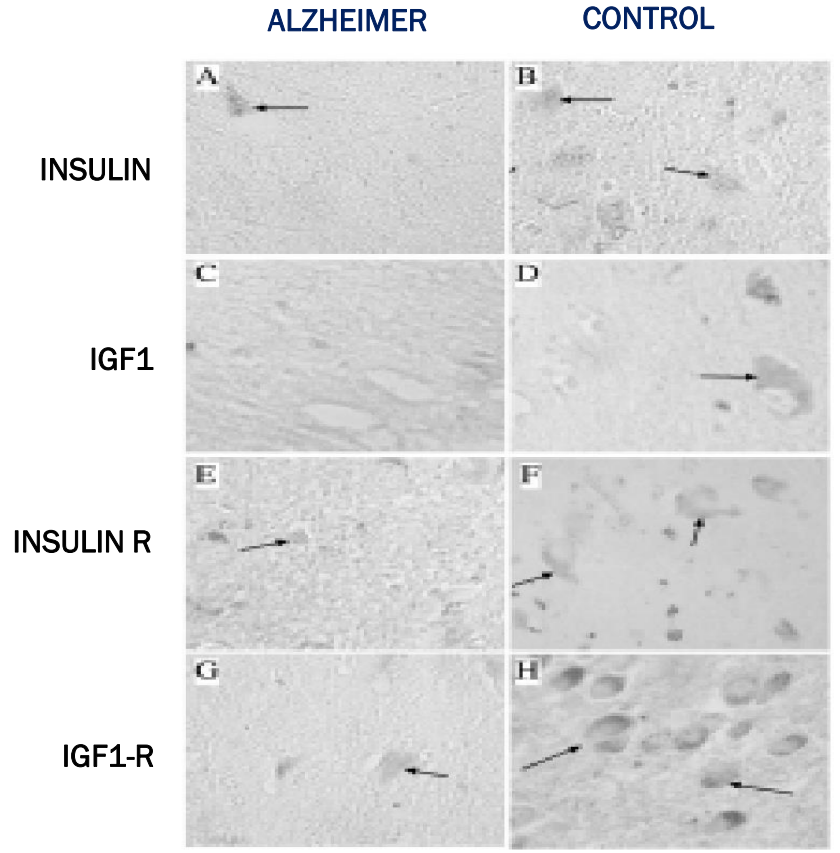


Garcia-Serrano AM, Duarte JMN. Brain Metabolism Alterations in Type 2 Diabetes: What Did We Learn From Diet-Induced Diabetes Models? Front Neurosci 14: 229, 2020. doi: 10.3389/fnins.2020.00229.

INSULIN AND INSULIN RECEPTORS IN NCS

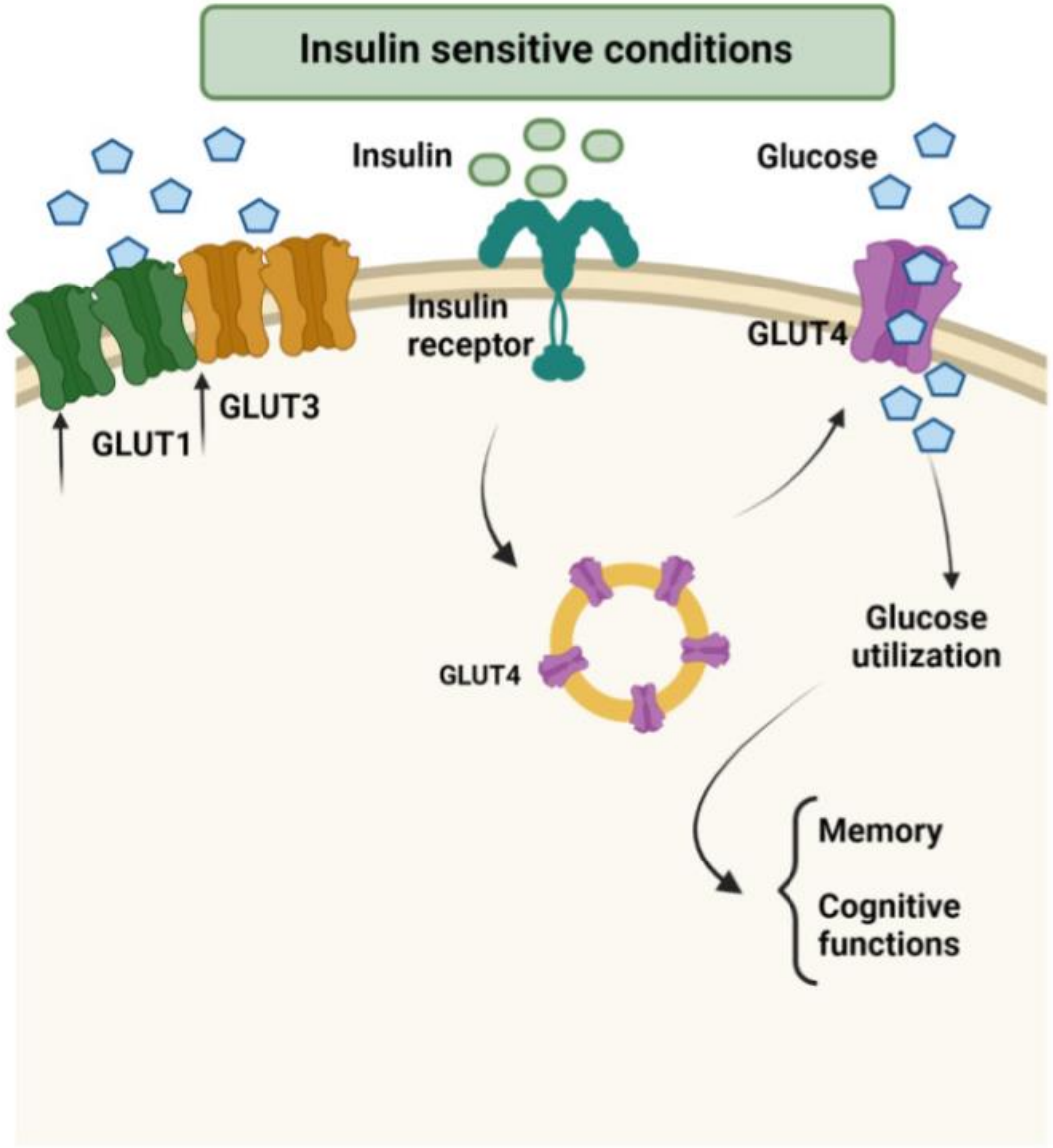


Insulin receptors are widely distributed across the brain, with high concentrations in areas such as the cerebral cortex, hippocampus, amygdala, and cerebellum



Localization of insulin (A–B), IGF-I (C–D), insulin receptor (E–F), and IGF-I receptor (G–H) immunoreactivity in AD and aged control hippocampus using immunohistochemical staining.

Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM. JAD 2005 Feb;7(1):63-80


Insulin sensitive conditions
Insulin
Glucose
Insulin receptor
GLUT4
GLUT1
GLUT3
GLUT4
Glucose utilization
Memory
Cognitive functions

IDE

«Insulin Degrading Enzyme»

NEUROBIOLOGY of AGING

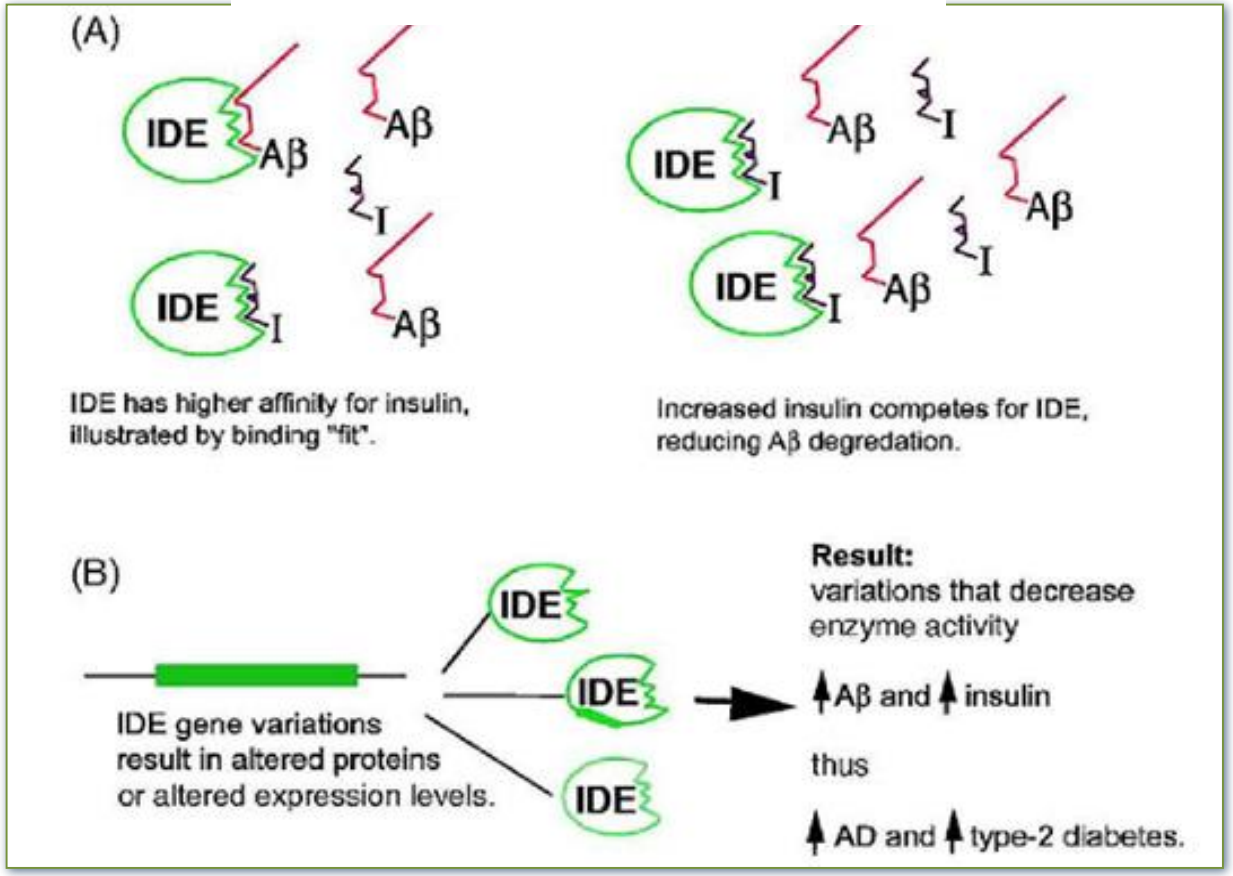
Wei Qiao Qiu, Marshal F. Folstein

Neurobiology of Aging
Volume 27, Issue 2 , Pages 190-198 , February 2006

Insulin, insulin-degrading enzyme and amyloid-β peptide in Alzheimer's disease: review and hypothesis

Abstract

Clinical and epidemiological studies have found that type 2 diabetes, and hyperinsulinaemia, increased the risk of developing Alzheimer's disease (AD) in the elderly. The link between hyperinsulinaemia and AD may be insulin-degrading enzyme (IDE). This enzyme degrades both insulin and amylin, peptides related to the pathology of type 2 diabetes, along with amyloid-β peptide (Aβ), a short peptide found in excess in the AD brain. We review the current evidence, which suggests that hyperinsulinaemia may elevate Aβ through insulin's competition with Aβ for IDE. Genetic studies have also shown that IDE gene variations are associated with the clinical symptoms of AD as well as the risk of type 2 diabetes. The deficiency of IDE can be caused by genetic variation or by the diversion of IDE from the metabolism of Aβ to the metabolism of insulin. It is intriguing to notice that both hyperinsulinaemia and IDE gene variations are related to the risk of AD when the Apolipoprotein E4 (ApoE4) allele, the major risk factor of late-onset AD, is not present. Further studies of the role of IDE in the pathogenesis of AD, which may uncover potential treatment target, are much needed.



A) Hyperinsulineamia increases the levels of Abeta because elevated insulin competes with Abeta for IDE. This results in a relative deficiency of IDE

B) IDE gene variations cause altered IDE proteins such as in GK rat or decreased expression levels

Both conditions (A) and (B) can cause the deficiency of IDE and lead to type 2 diabete and Alzheimer's disease

Acta Psychiatrica Scandinavica / Volume 119, Issue 4 / p. 252-265

Free Access

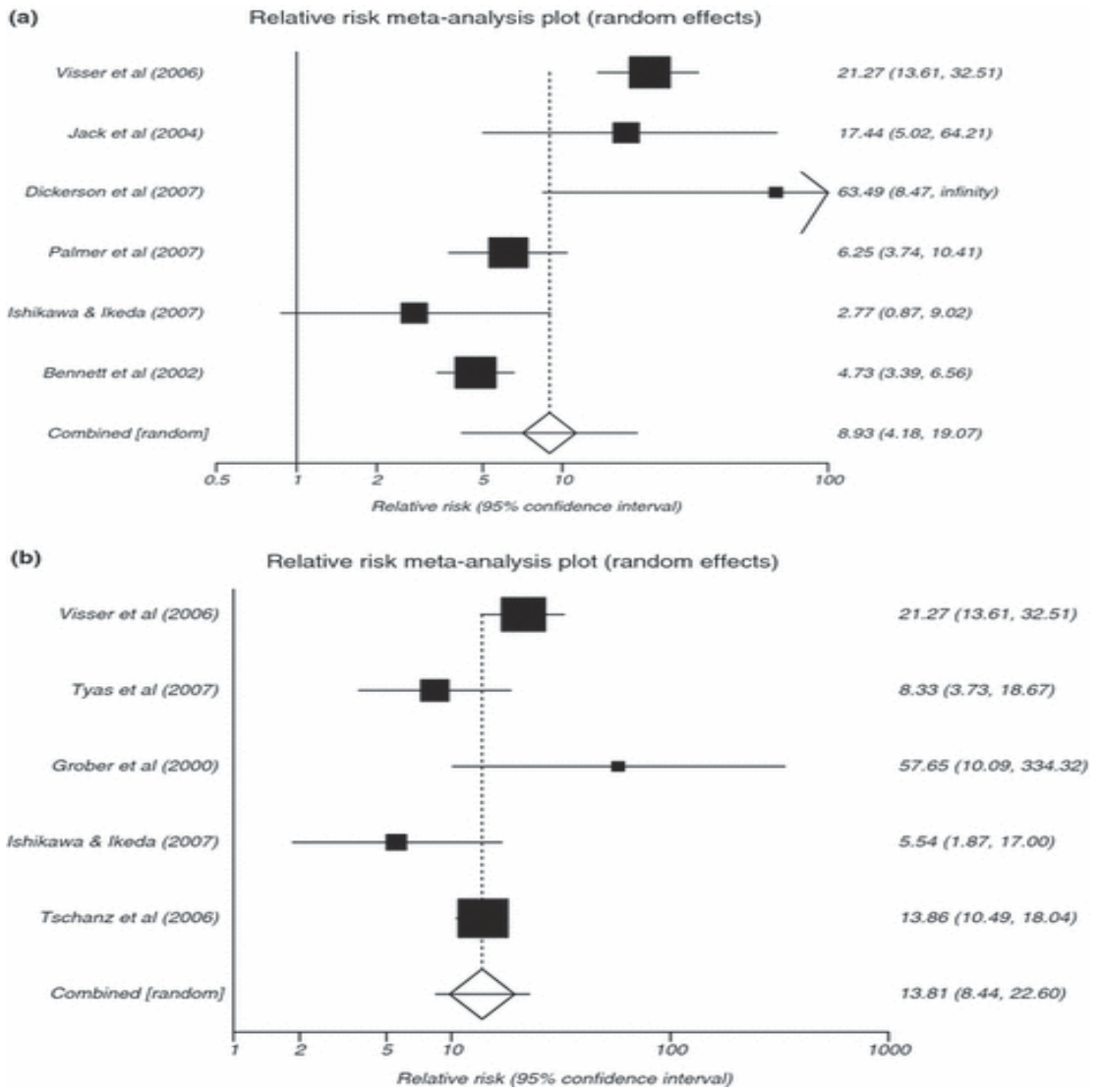
Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies

A. J. Mitchell, M. Shiri-Feshki

First published: 03 March 2009

Mild cognitive impairment (MCI) is a premorbid risk factor for dementia representing a transitional state with objective cognitive impairment but with functional independence maintained.[3] However, the annual rate of progression to dementia ranges from only 8% in clinical trials[4] to 13% in large registries.[5] Furthermore, the objective cognitive impairment that defines MCI can be reversible, with rates of reversion to normal cognition (NC) as high as 16% within 1 year[6] and additional reversions thereafter.[7-9] Thus, the prognostic utility of MCI as an early marker of dementia may benefit from the incorporation of additional features to improve specificity.

Relative risk of Alzheimer's disease



Relative risk of dementia

Axis indicates the relative risk of conversion to dementia in those with MCI vs. those without. The size of the boxes represent the size of the sample in the study.

ORIGINAL ARTICLES

Reversion From Mild Cognitive Impairment to Normal Cognition

A Meta-Analysis

Malek-Ahmadi, Michael MSPH

Author Information

Alzheimer Disease & Associated Disorders 30(4):p 324-330, October–December 2016. |

Spontaneous Reversion of Mild Cognitive Impairment to Normal Cognition: A Systematic Review of Literature and Meta-Analysis

Marco Canevelli, MD • Giulia Grande, MD • Eleonora Lacorte, MSci • ... Claudio Mariani, MD • Giuseppe Bruno, PhD • Nicola Vanacore, PhD • J Am Med Dir Assoc. 2016 Oct 1;17(10):943-8.

International Journal of Geriatric Psychiatry

09 June 2019 |

REVIEW ARTICLE

Factors for predicting reversion from mild cognitive impairment to normal cognition: A meta-analysis

Mild cognitive impairment (MCI) is a premorbid risk factor for dementia representing a transitional state with objective cognitive impairment but with functional independence maintained.[3] However, the annual rate of progression to dementia ranges from only 8% in clinical trials[4] to 13% in large registries.[5] Furthermore, the objective cognitive impairment that defines MCI can be reversible, with rates of reversion to normal cognition (NC) as high as 16% within 1 year[6] and additional reversions thereafter.[7-9] Thus, the prognostic utility of MCI as an early marker of dementia may benefit from the incorporation of additional features to improve specificity.

Original Investigation

April 27, 2021

Association Between Age at Diabetes Onset and Subsequent Risk of Dementia

Claudio Barbiellini Amidei, MD[1,2]; Aurore Fayosse, MSc[1]; Julien Dumurgier, PhD[1,3]; et al

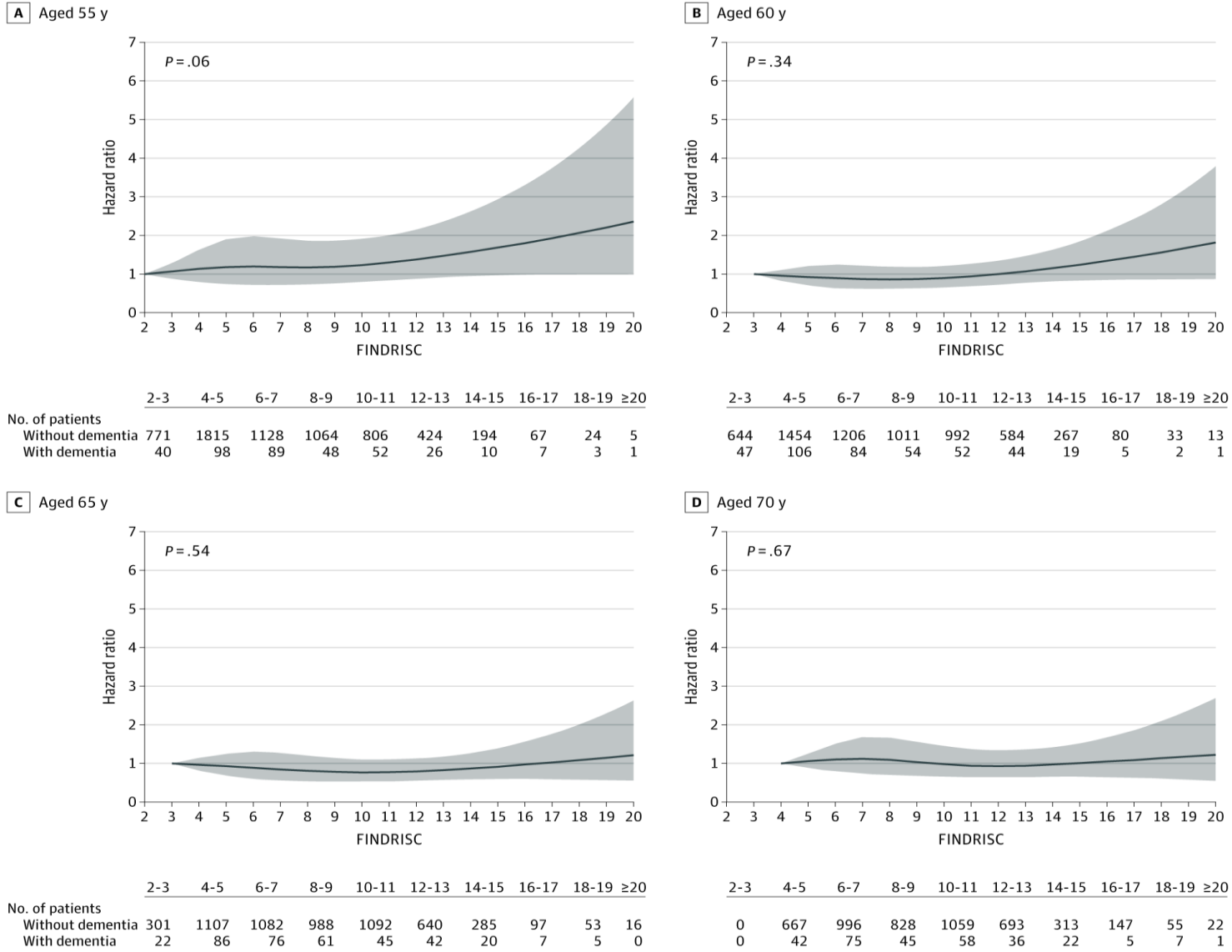
» Author Affiliations | Article Information

JAMA. 2021;325(16):1640-1649. doi:10.1001/jama.2021.4001

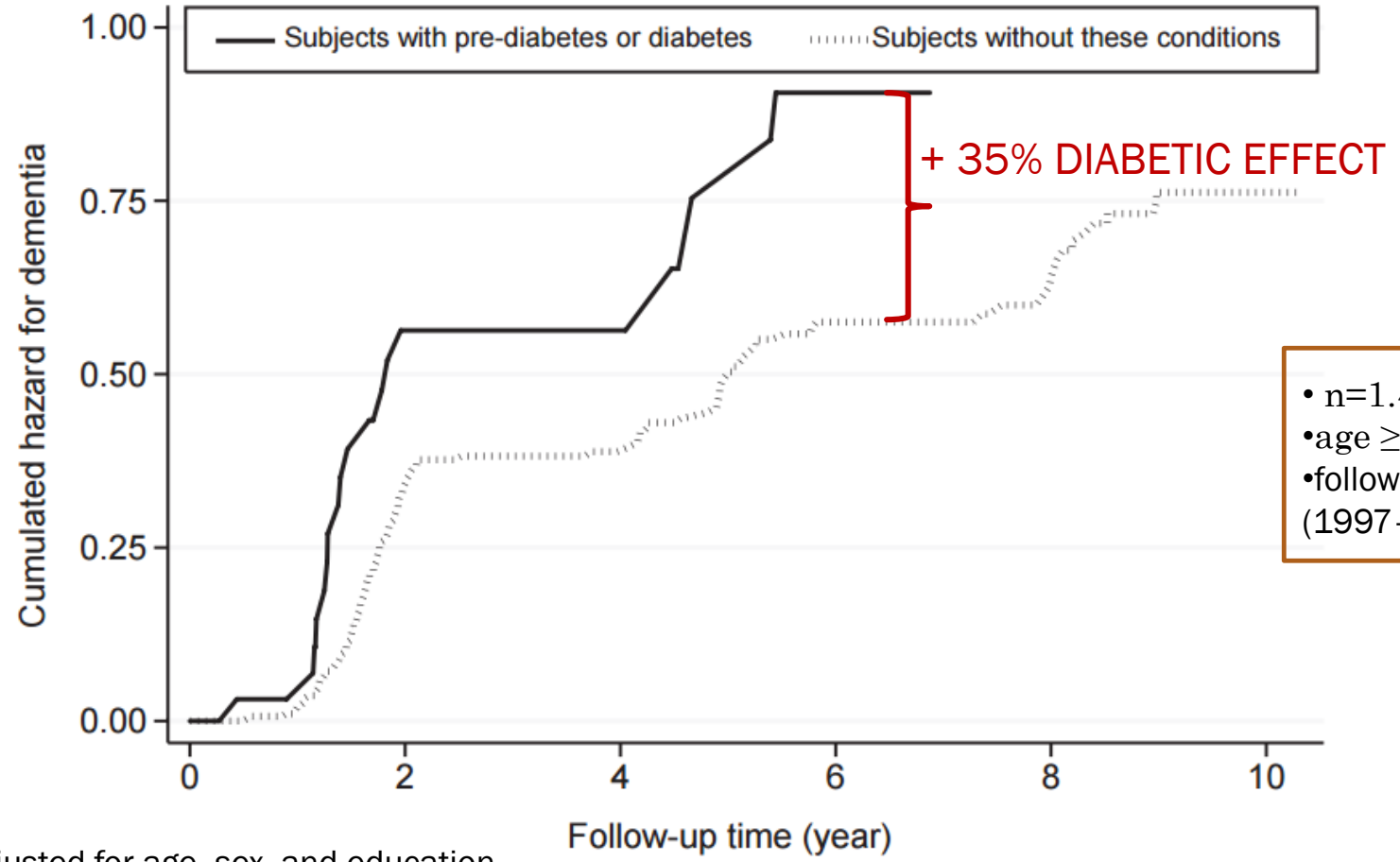
In this longitudinal cohort study with a median follow-up of 31.7 years, younger age at onset of diabetes was significantly associated with higher risk of subsequent dementia.

The Finnish Diabetes Risk Score includes age, family history of diabetes, personal history of elevated blood glucose, fruit and vegetable consumption, blood pressure medication, physical activity, body mass index, and measured waist circumference

Association of Finnish Diabetes Risk Score at Ages 55, 60, 65, and 70 Years With Incidence of Dementia



ACCELERATE PROGRESSION FROM MILD COGNITIVE IMPAIRENT (MCI) TO DEMENTIA IN PEOPLE WITH DIABETES



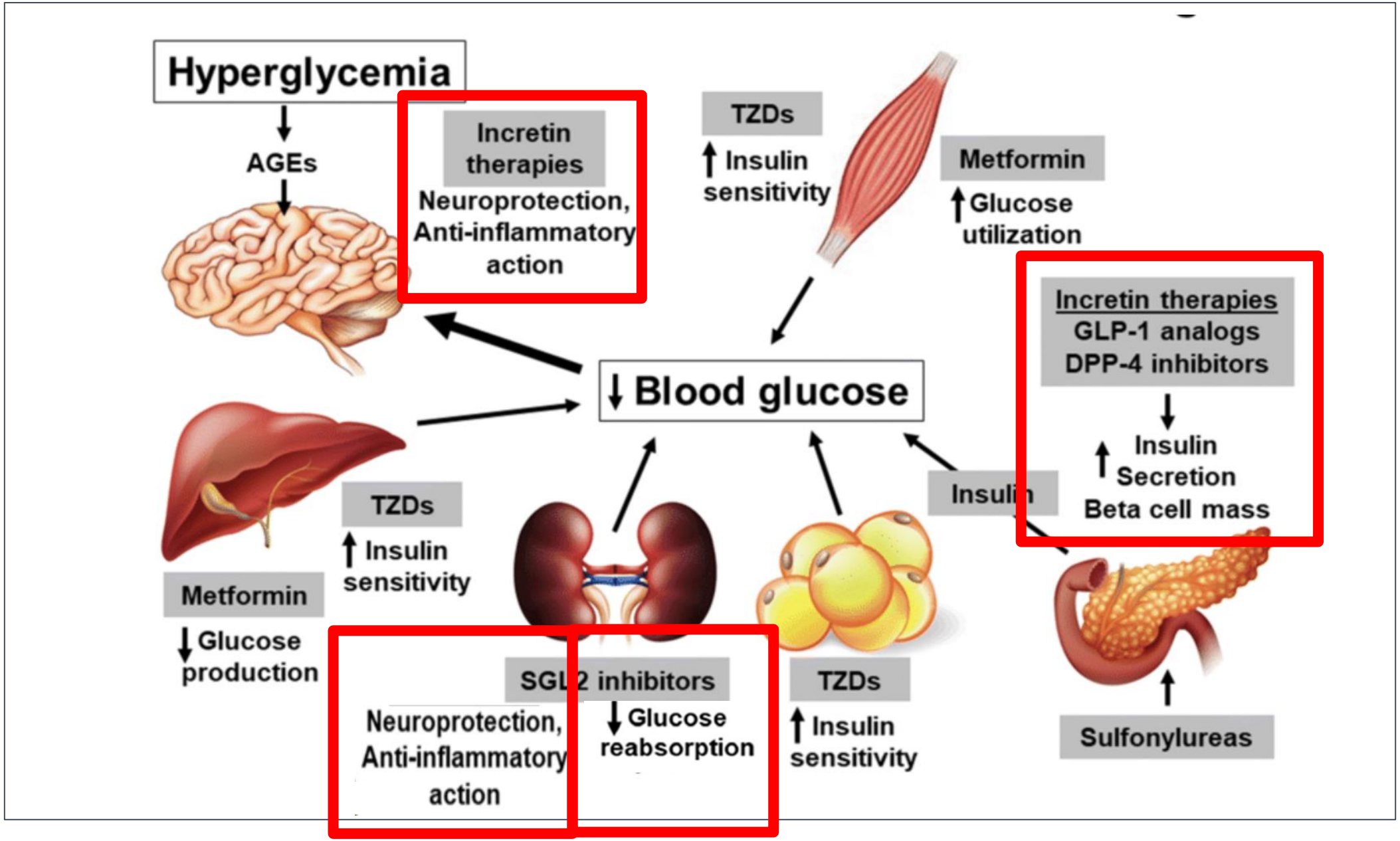
- n=1.435 pz;
- age ≥75 years;
- followed for 9 years (1997–1998) ;

Adjusted for age, sex, and education

Weili Xu, et al. Diabetes, 2010

Mechanisms of action of antidiabetic drugs

Overall, the antidiabetic drugs showed to have beneficial actions in the brain either directly or indirectly



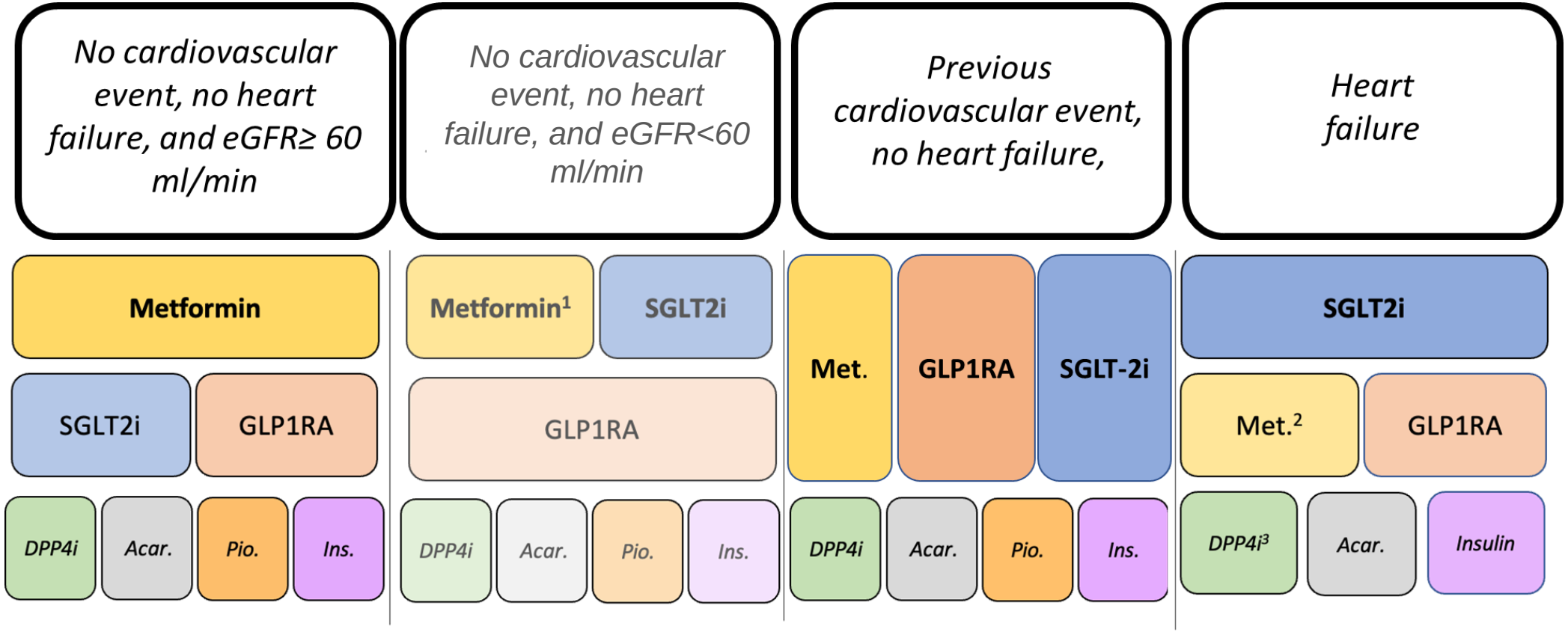
Anit Tyagi, Subbiah Pugazhenthi-Targeting Insulin Resistance to Treat Cognitive Dysfunction *Mol Neurobiol*. 2021 June ; 58(6): 2672–2691. doi:10.1007/s12035-021-02283-3.

"It's important to emphasise that the benefit of a drug reducing the risk of developing a disease is quite separate from any suggestion that the drug might be useful in treating that disease".

"The best way to reduce your risk of lung cancer, for example, is to stop smoking. Once you have lung cancer, however, stopping smoking is insufficient to treat it!!!!"

Italian guidelines for the treatment of T2DM

Drug therapy



[1,2] *If metformin is not contraindicated.*

[3] *With the exception of saxagliptin which is not indicated for patients with heart failure.*

The recommendation for patients with eGFR< 60ml/min is weak (few studies on this population) and therefore is written with a lighter type

We recommend to deprescribe sulfonylureas and glinides.

Mannucci E et al. for SID and AMD. *Acta Diabetol*, 2023

Metformin use is associated with a reduced risk of cognitive impairment in adults with diabetes mellitus: A systematic review and meta-analysis

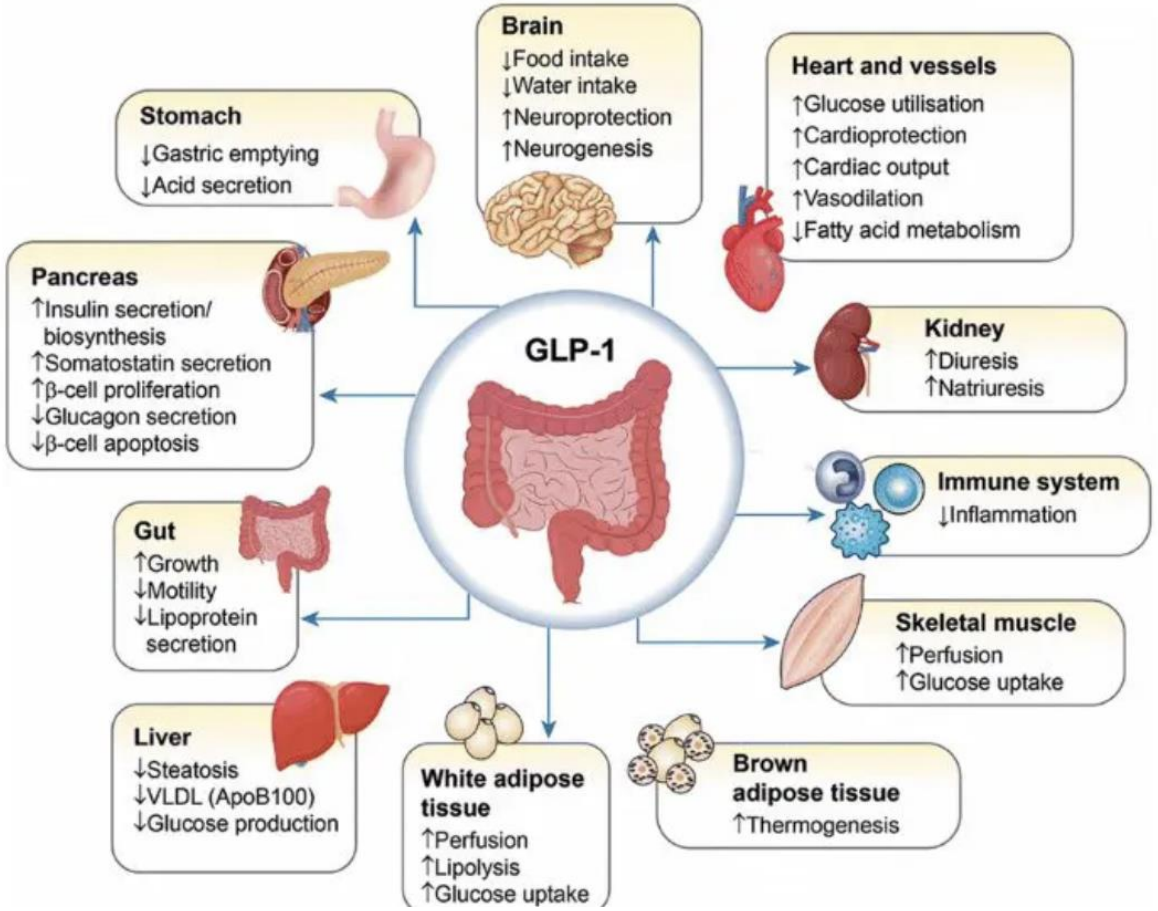
frontiers | Frontiers in Neuroscience

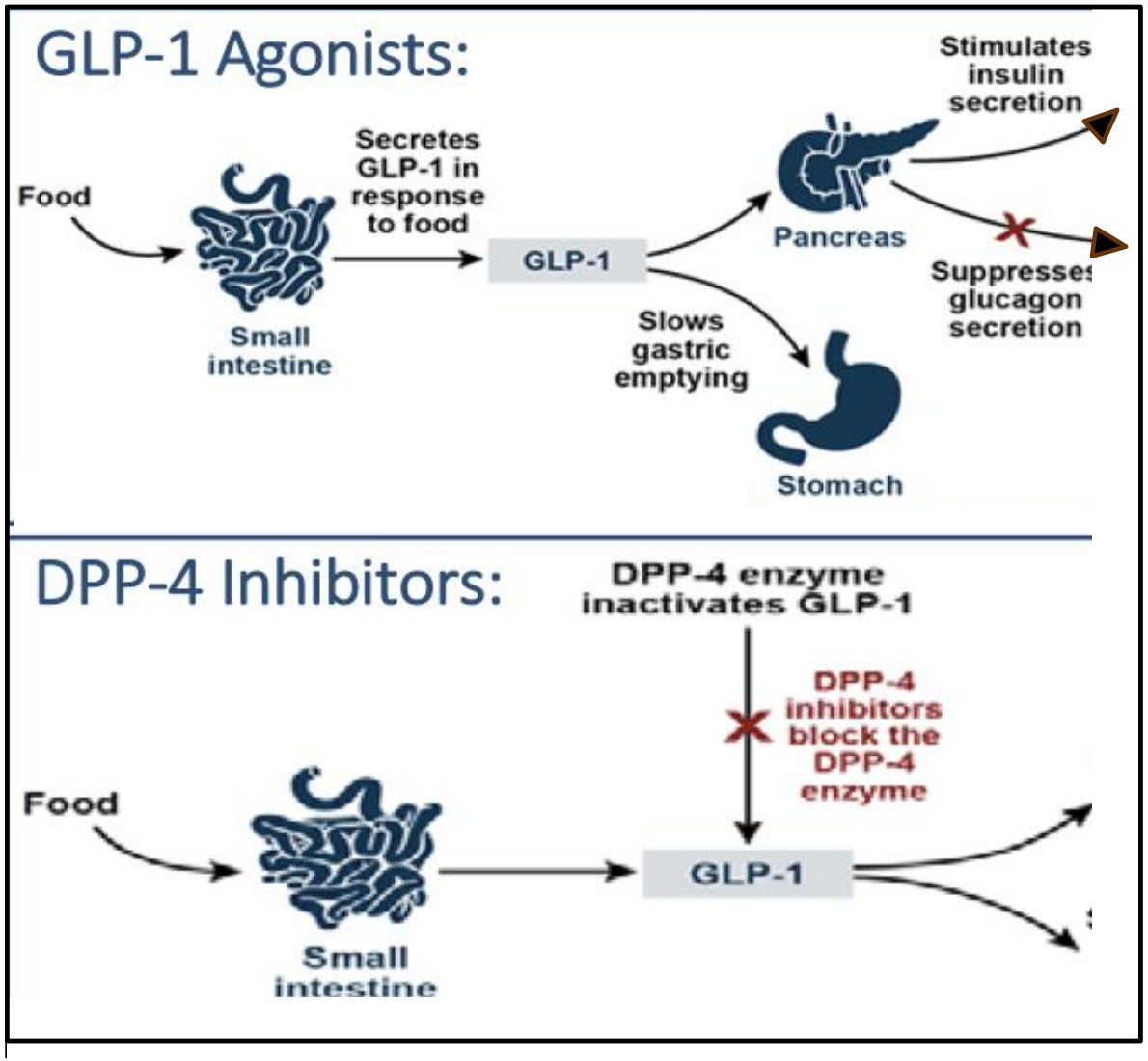
TYPE Systematic Review
PUBLISHED 25 August 2022
DOI 10.3389/fnins.2022.984559

Results: A systematic search identified 1,839 articles, of which 28 (17 cohort, 8 case-control, and 3 cross-sectional studies) were included in the meta-analysis. Metformin reduced the occurrence of cognitive impairment in patients with diabetes [unadjusted hazard ratio (*HR*) = 0.67, 95% *CI*: 0.62–0.73; adjusted hazard ratio (a*HR*) = 0.92, 95% *CI*: 0.85–0.99]. In addition, the use of metformin was associated with a decreased risk of dementia (*HR* = 0.64, 95% *CI*: 0.59–0.69; *aHR* = 0.90, 95% *CI*: 0.84–0.96), while a random-effects meta-analysis indicated no significant effect of metformin on the risk of Alzheimer's disease (AD) (*HR* = 0.85, 95% *CI*: 0.60–1.22; *aHR* = 1.10, 95% *CI*: 0.95–1.28).

Conclusion: Metformin therapy decreased the occurrence risk of cognitive decline in patients with diabetes mellitus. Moreover, the use of metformin by adults with diabetes for the prevention of dementia, but not AD, is supported by the available evidence.

INCRETIN

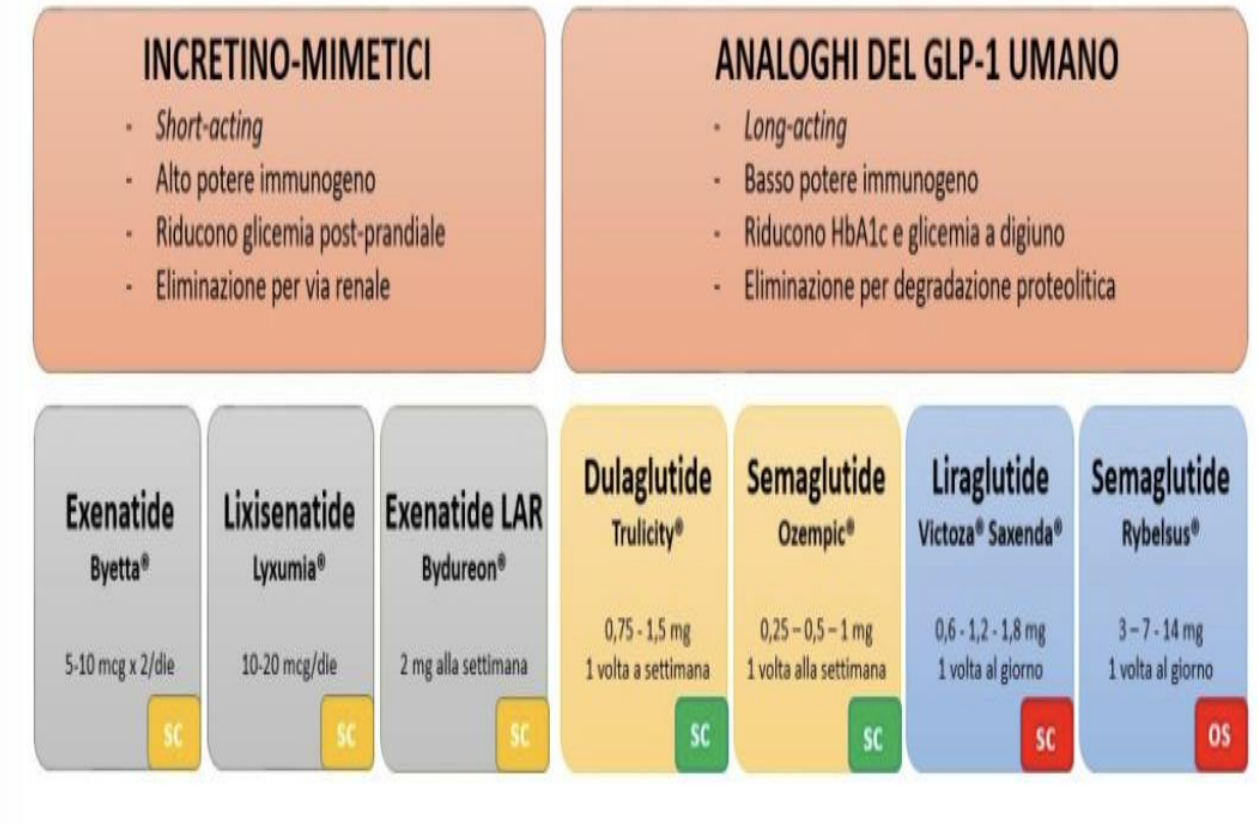

Brain
↓Food intake
↓Water intake
↑Neuroprotection
↑Neurogenesis
Heart and vessels
↑Glucose utilisation
↑Cardioprotection
↑Cardiac output
↑Vasodilation
↓Fatty acid metabolism
Stomach
↓Gastric emptying
↓Acid secretion
Pancreas
↑Insulin secretion/ biosynthesis
↑Somatostatin secretion
↑β-cell proliferation
↓Glucagon secretion
↓β-cell apoptosis
GLP-1
Kidney
↑Diuresis
↑Natriuresis
Immune system
↓Inflammation
Gut
↑Growth
↓Motility
↓Lipoprotein secretion
Skeletal muscle
↑Perfusion
↑Glucose uptake
Liver
↓Steatosis
↓VLDL (ApoB100)
↓Glucose production
White adipose tissue
↑Perfusion
↑Lipolysis
↑Glucose uptake
Brown adipose tissue
↑Thermogenesis


GLP-1 Agonists:
Food
Secretes GLP-1 in response to food
Small intestine
GLP-1
Stimulates insulin secretion
Pancreas
Suppresses glucagon secretion
Slows gastric emptying
Stomach
DPP-4 Inhibitors:
DPP-4 enzyme inactivates GLP-1
DPP-4 inhibitors block the DPP-4 enzyme
Food
Small intestine
GLP-1

DPP4-I

Drug	Brand	Doses	Notes
Alogliptin	Vipidia	25 mg, 12.5 mg and 6.25 mg	Recommended dose 25 mg once daily
Linagliptin	Trajenta	5 mg	Recommended dose 5 mg once daily; can be taken with or without food
Saxagliptin	Onglyza	2.5 mg, 5 mg	Recommended dose 5 mg once daily; reduce dose to 2.5 mg if eGFR <45
Sitagliptin	Januvia	25 mg, 50 mg and 100 mg	Can be taken with or without food
Vildagliptin	Galvus	50 mg	Recommended dose 50 mg twice daily (50 mg once daily if eGFR <45) Not recommended in hepatic dysfunction; perform LFTs before initiating
Saxagliptin + metformin	Komboglyze	2.5/1000 mg, 5/1000 mg or 5/2000 mg	2.5/1000 mg, 5/1000 mg or 5/2000 mg once daily with evening meal
Sitagliptin + metformin	Janumet	50/500 mg and 50/1000 mg	50/500 mg twice daily, with meals Can increase to 50/1000 mg twice daily (maximum dose), with meals

GLP1-RA

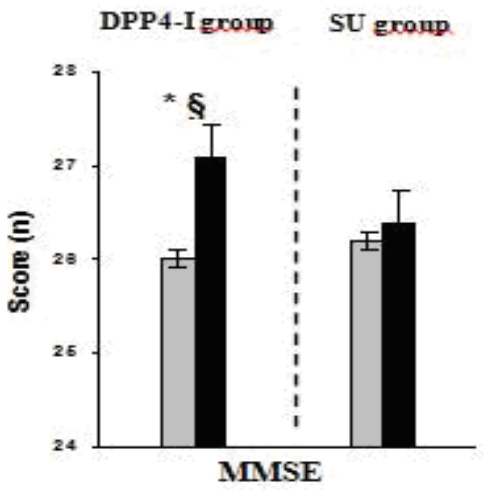


Dipeptidyl Peptidase-4 Inhibitors Have Protective Effect on Cognitive Impairment in Aged Diabetic Patients With Mild Cognitive Impairment

Maria Rosaria Rizzo, Michelangela Barbieri, Virginia Boccardi, Edith Angellotti, Raffaele Marfella, and Giuseppe Paolisso

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 September;69(9):1122–1131
doi:10.1093/gerona/glu032

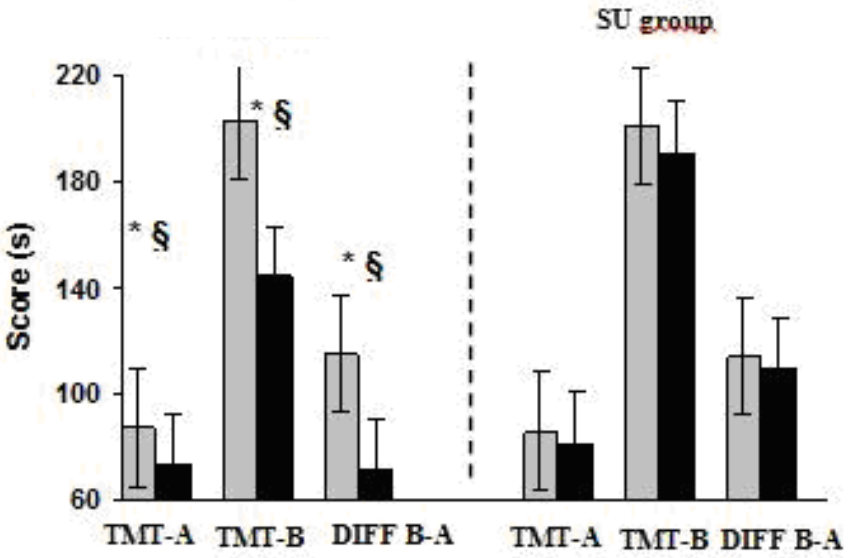
After 2 years of therapy, all baseline variables related to cognition were significantly improved after DPP-4I therapy but not after SU therapy

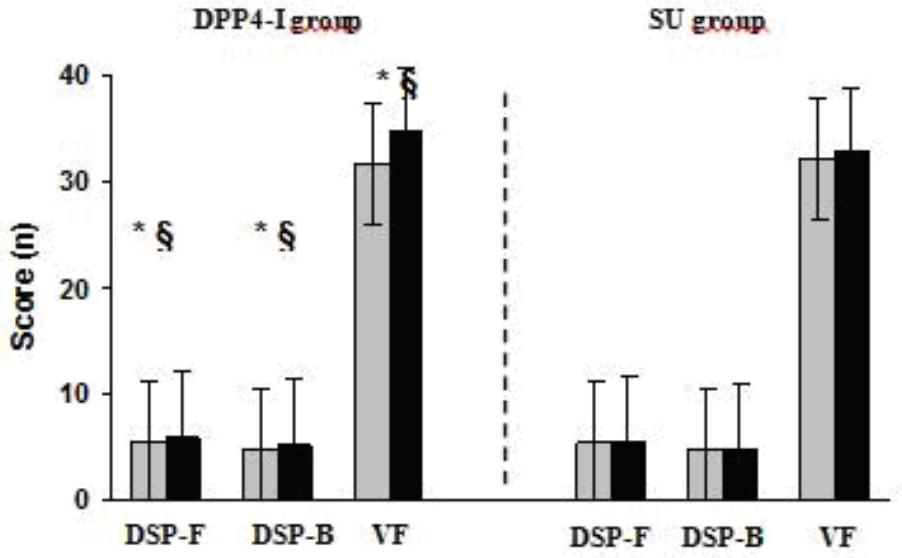


After 2 yrs of therapy
Baseline

* *P<0.05 Baseline vs 2 years of therapy*

§ *P<0.05 DPP4-I vs SU group after 2 yrs of therapy*





Pharmacological Research 186 (2022) 106550

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/yphrs

Novo N

20 years of science on GLP-1 & Alzheimer's Disease

1992 — **Widespread GLP-1R expression reported in the brain**
Neuropeptides 1992; 21:143–146

1996 — **GLP-1 is a neuro-transmitter**
Nature 1996;379:69–72

2002 — **First scientific paper in AD on neuronal protection**
JPET 2002;302:881–88

2003 — **Paper in *Nature Medicine* on GLP-1's physiological role in cognition**
Nature Medicine 2003;9:1173–9

2010-2014 — **Novo Nordisk's work on liraglutide using animal models**
Alzheimer's Dis 2015;4:877–88
Brain Res J 2016;1634,158–70
PloS One 2016:11(7):e0158205

2017 — **First clinical study in AD, showing effect on FDG-PET. Funding and drug by Novo**
Sci Rep 2017;7:17490

2018 — **Paper in Nature Medicine around GLP-1 & Parkinson's Disease, with commentary on neuroinflammatory effects as relevant also in AD**
Nature Medicine 2018;24:900–2
Nature Medicine 2018;24:931–38
Human genetic studies increasingly show neuroinflammation as relevant to target in AD
Alzheimer's Dis 2015;4:877–88
Brain Res J 2016;1634,158–70
PloS One 2016:11(7):e0158205

2020 — **GLP-1 reduces blood brain barrier extravasation**
Nature Comm. 2020;11:4413

2021 — **Novo Nordisk data with semaglutide on neuroinflammation**
Oral presentation at ADPD, 2021
Targeting neuroinflammation recognized as a treatment option of sporadic AD
Lancet 2021; 397:1577–159

2005: 1st approval for Diabetes

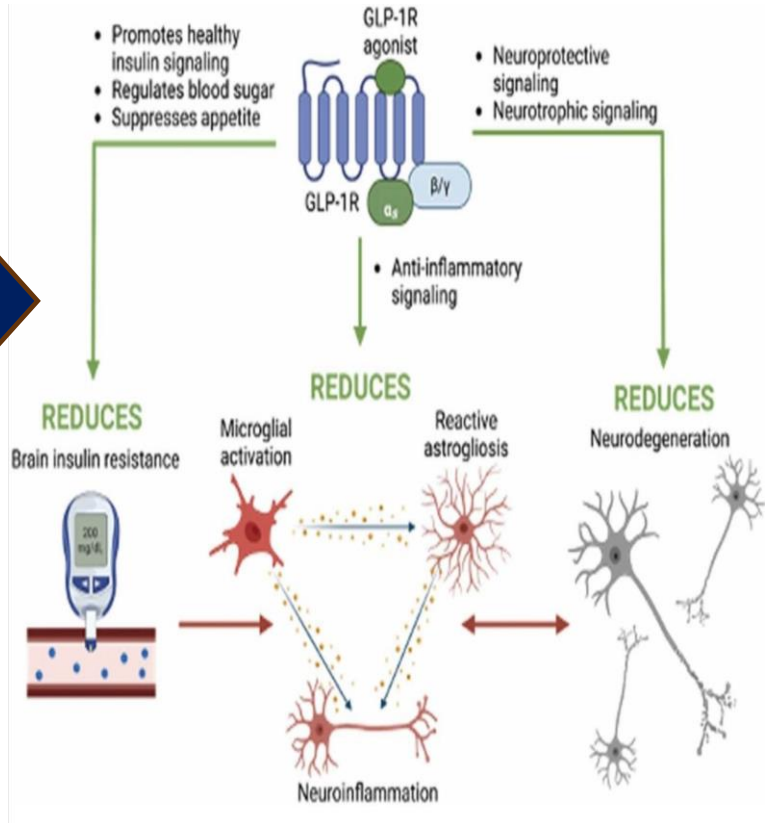
2014: 1st approval for Obesity

2016: 1st Cardiovascular & Diabetic Kidney Disease risk reduction
NEJM 2016; 375:311-322

2021: EVOKE/EVOKE+ Oral semaglutide phase 3a initiations in AD

AD, Alzheimer's Disease; FDG-PET, fluorodeoxyglucose -positron emission tomography; GLP-1, glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment



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DEMENTIA AND BEHAVIORAL NEUROLOGY: TREATMENTS 2 | April 9, 2024 |

Baseline Characteristics from Evoke and Evoke+: Two Phase 3 Randomized Placebo-controlled Trials of Oral Semaglutide in Patients with Early Alzheimer's Disease (P11-9.013)

Philip Scheltens, Alireza Atri, Howard Feldman, Oskar Hansson, Filip Knop, Mary Sano, Claus Dethlefsen, Peter Johannsen, Teresa León, Charlotte Thim Hansen, and Jeffrey Cummings | AUTHORS INFO & AFFILIATIONS

April 9, 2024 issue • 102 (17_supplement_1) • https://doi.org/10.1212/WNL.0000000000205079

Novo Nordisk®

Two phase 3 trials were initiated in Q2 2021 with oral semaglutide 14 mg in Alzheimer's Disease

Alzheimer's Disease

Large unmet need within Alzheimer's Disease with ~85 million people living with mild cognitive impairment and dementia

evoke and evoke+ trials have been initiated with 1,840 patients in each trial with a total of 3,680 patients

Objective

To confirm superiority of oral sema vs placebo on the change in cognition and function in people with early Alzheimer's disease

Primary endpoint

Change in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) score from baseline to end of 104 weeks of treatment

Inclusion criteria

- Early Alzheimer's Disease (mild cognitive impairment or mild dementia)
- Mini-Mental State Examination (MMSE) ≥ 22/30
- Age between 55-85 years
- evoke+ has at least 20% with small vessel pathology

Source: Alzheimer's Association report: 2020 Alzheimer's disease facts and figures, 2020 (16:391-460).
AD: Alzheimer's disease; QD: Once-daily; MCI: mild cognitive impairment; Note: CDR-SB ratings are utilising in six domains are summed to provide a clinical measure = Sum of Boxes. These are: memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care. CDR-SB Scores range from 0 to 18 with higher scores representing greater impairment

DOI: 10.1002/alz.042909

DRUG DEVELOPMENT

POSTER PRESENTATIONS

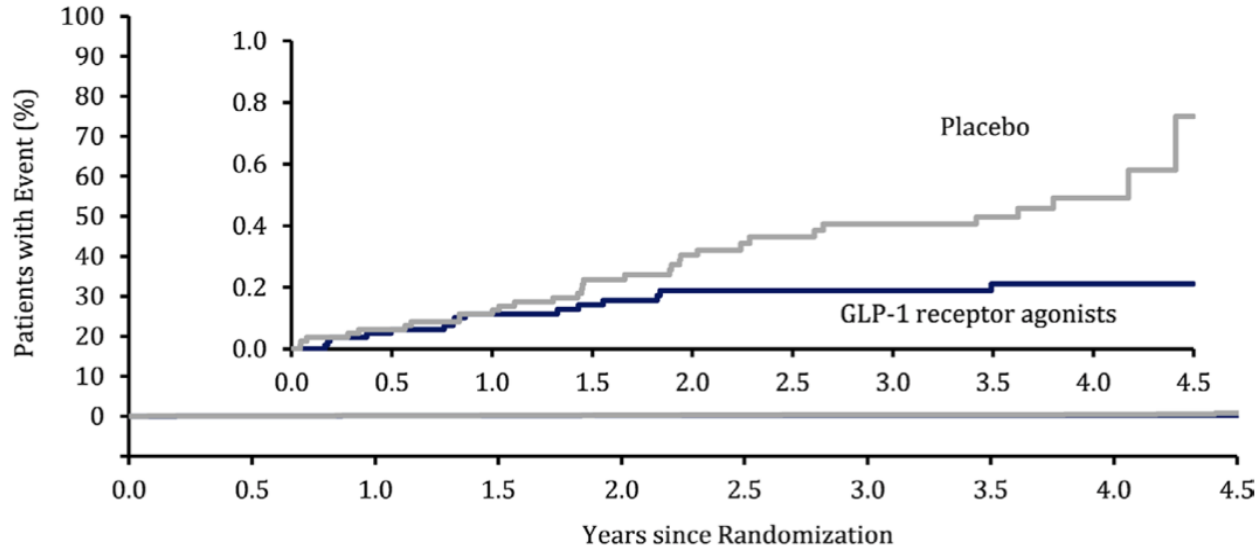
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Human/Human trials: Other

Liraglutide and semaglutide: Pooled post hoc analysis to evaluate risk of dementia in patients with type 2 diabetes

Conclusion: *Post-hoc* analysis based on pooled data from three double-blinded CVOTs suggests, albeit with a low number of events, a reduced risk of dementia with liraglutide or semaglutide treatment in patients with type 2 diabetes.

Figure. Time to dementia with GLP- 1 receptor agonists versus placebo in pooled data from CVOTs



No. at risk										
GLP-1RA	7907	7852	7763	6479	6064	4441	4373	4312	1716	483
Placebo	7913	7843	7740	6438	6016	4394	4321	4251	1700	460

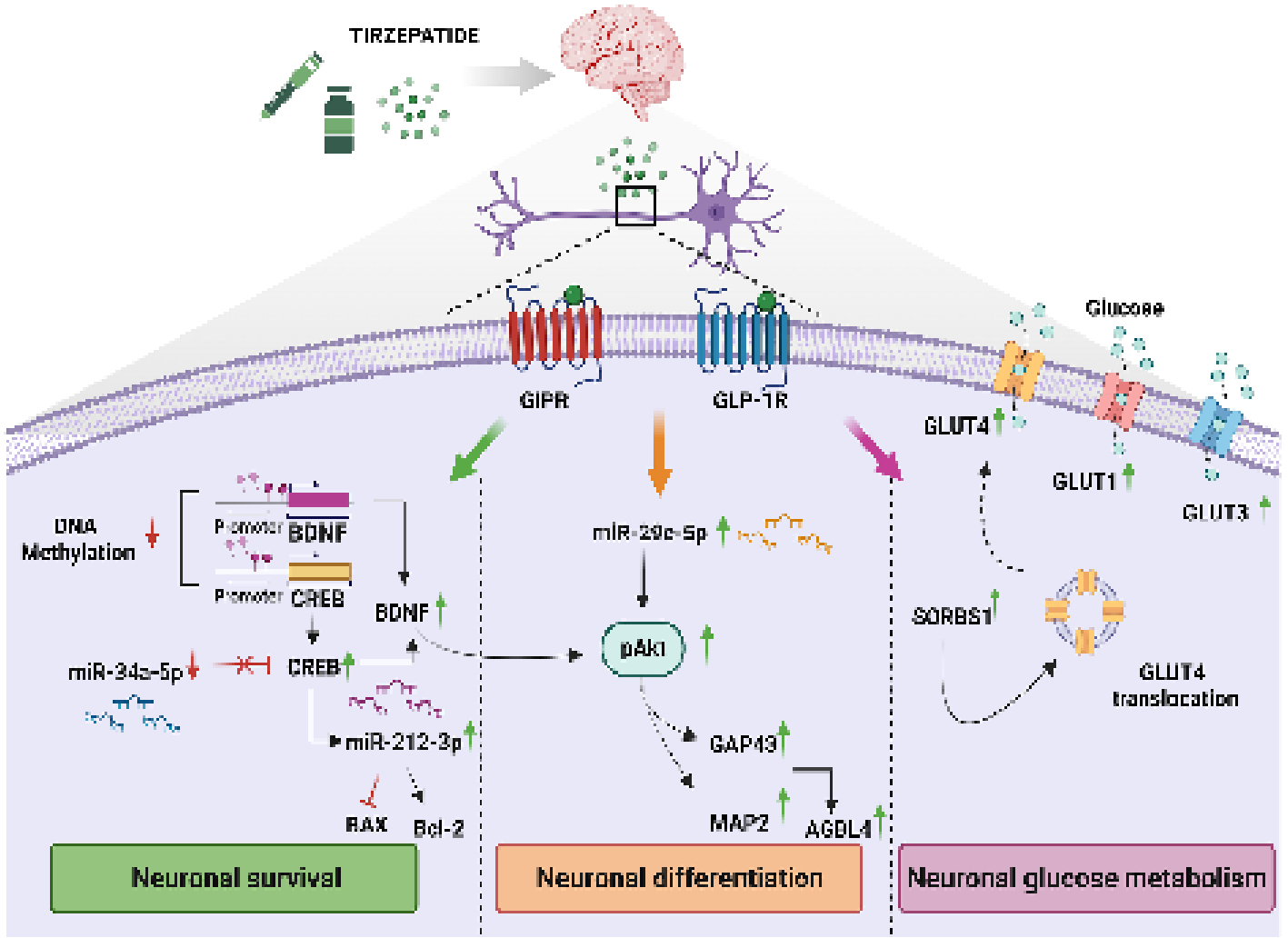
Alzheimer's Dement. 2020;16(Suppl. 9):e042909. https://doi.org/10.1002/alz.042909

Tirzepatide prevents neurodegeneration through multiple molecular pathways

Fontanella *et al.*
Journal of Translational Medicine (2024) 22:114
https://doi.org/10.1186/s12967-024-04927-z

In this study, the authors elucidated the molecular processes underlying the protective effect of Tirzepatide (TIR), a dual glucose-dependent insulinotropic polypeptide receptor agonist (GIP-RA)/ GLP-1RA, against learning and memory disorders.

The results firstly demonstrate the potential role of TIR in ameliorating high glucose-induced neurodegeneration and overcoming neuronal insulin resistance by targeting molecular and epigenetic modulators of neuronal growth, apoptosis, differentiation, and survival.

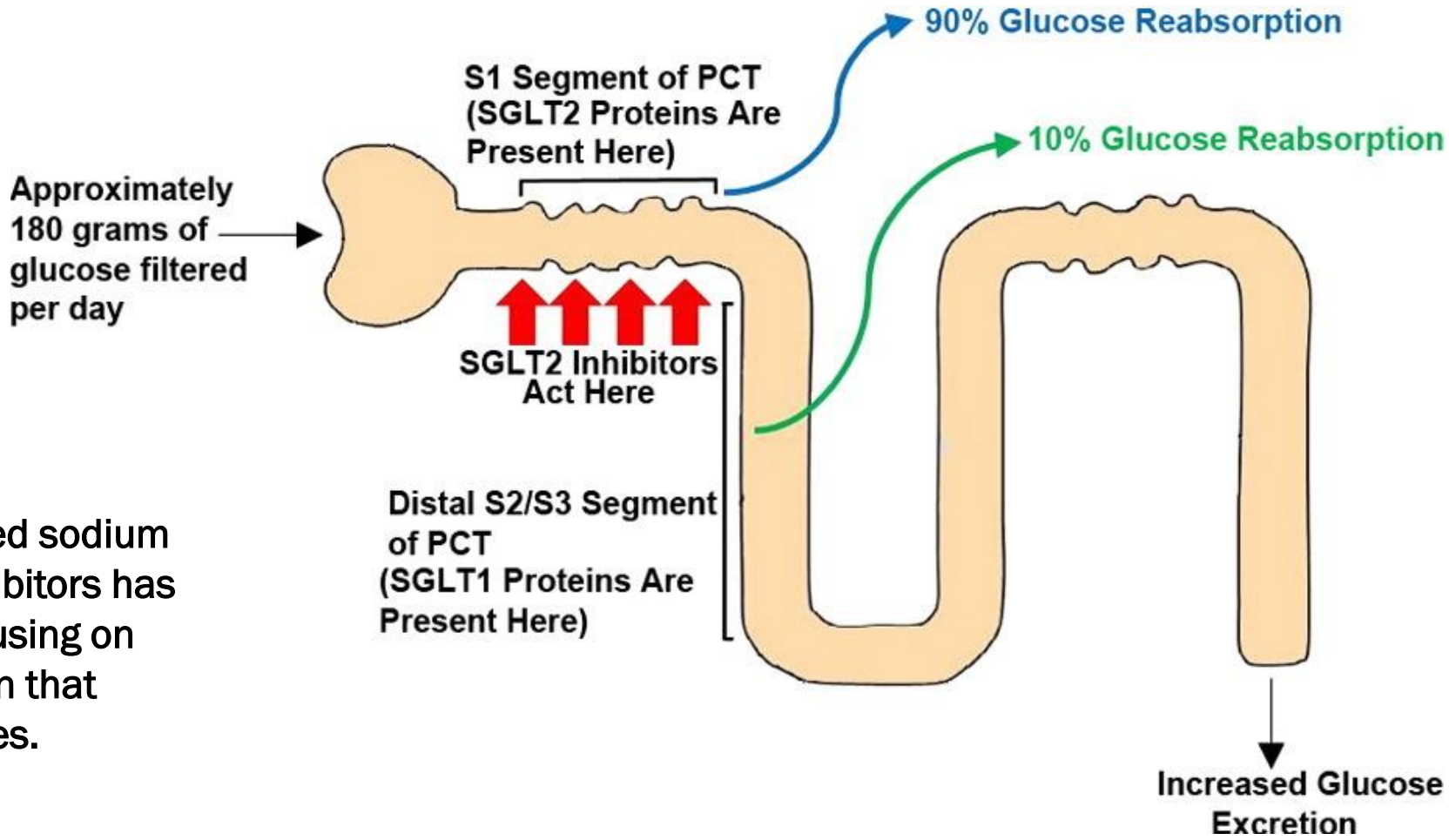


European Journal of Pharmaceutical Sciences
Volume 93, 10 October 2016, Pages 244-252

Review

Sodium glucose CoTransporter 2 (SGLT2) inhibitors: Current status and future perspective

New class of anti-diabetic drugs called sodium glucose co-transporter 2 (SGLT2) inhibitors has a unique mechanism of action focusing on inhibition of glucose reabsorption that separates it from other classes.



Review

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

RIZZO MR et al.

Pharmacological Research 176 (2022) 106062

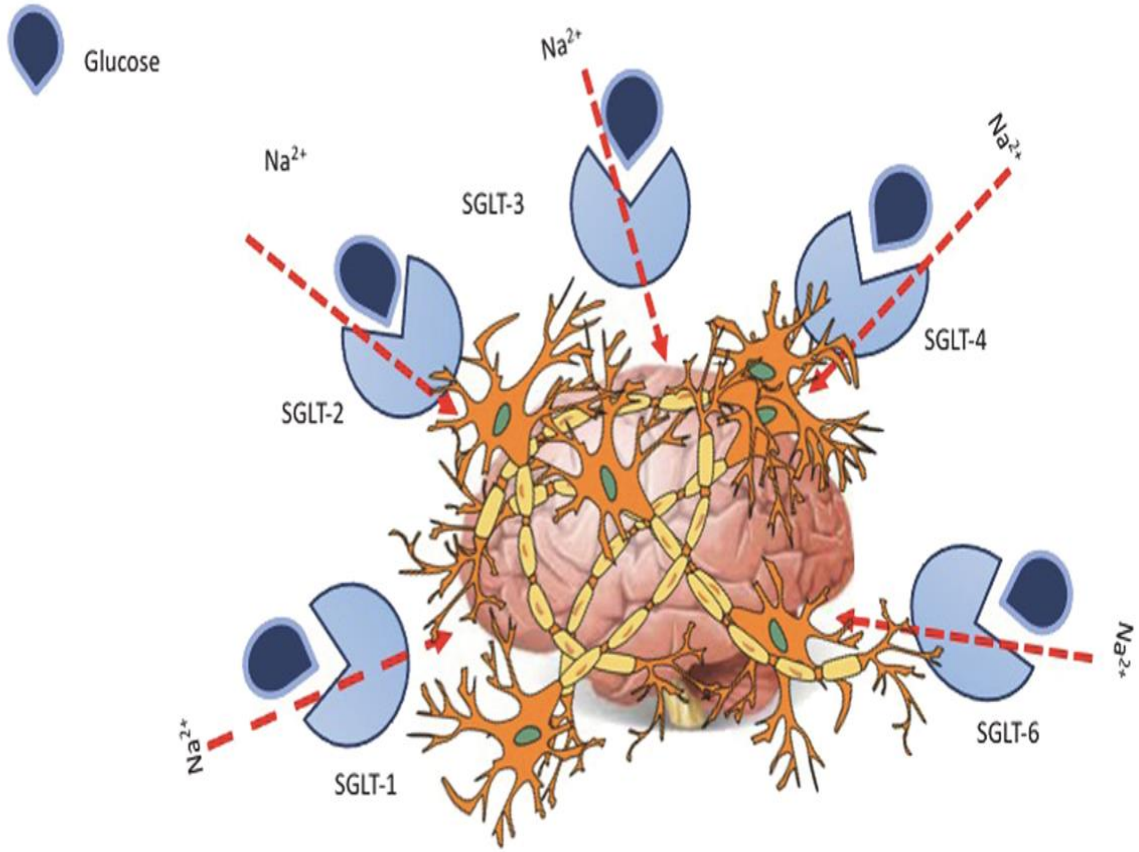
The principal SGLTs expressed in the brain.

Sodium glucose cotransporters (SGLTs) are fundamental in the mechanism of glucose entry into the brain cell.

SGLTs transport glucose into the cell along a sodium gradient.

SGLT1, SGLT2, SGLT3, SGLT4, SGLT6 have been identified in the brain.

The distribution of the brain-expressed SGLTs differs strongly and, unfortunately, not all brain SGLTs have been studied extensively.



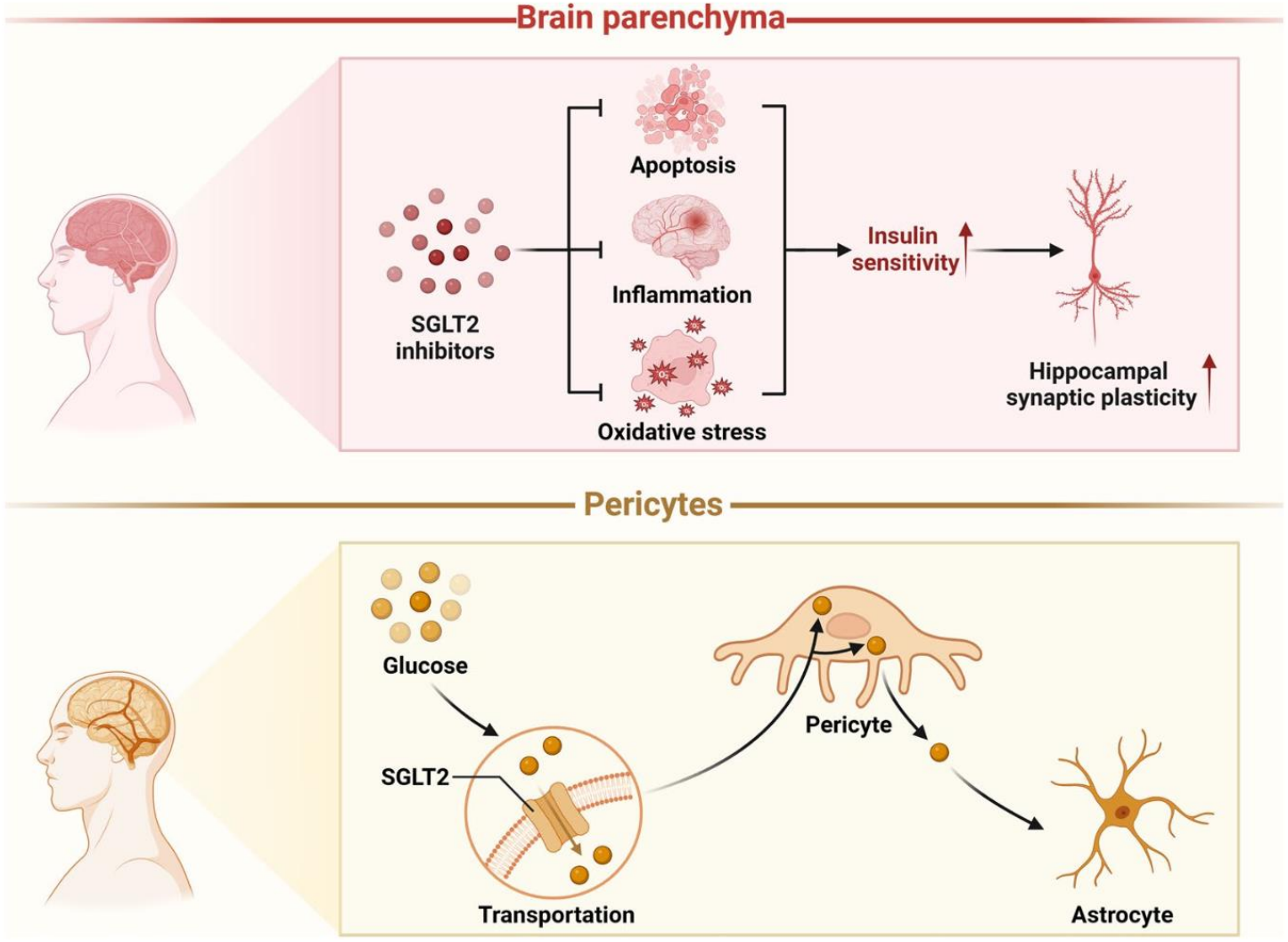
Mei et al. Translational Neurodegeneration (2024) 13:41
https://doi.org/10.1186/s40035-024-00431-y

Translational
Neurodegeneration

Physiological roles of SGLT2 in the brain.

REVIEW Open Access

SGLT2 inhibitors: a novel therapy for cognitive impairment via multifaceted effects on the nervous system



SGLT2 is mainly expressed in pericytes and brain parenchyma.

SGLT2 expressed in pericytes facilitates glucose transport to support their nourishment and metabolic functions, with the additional role of distributing glucose to adjacent astrocytes.

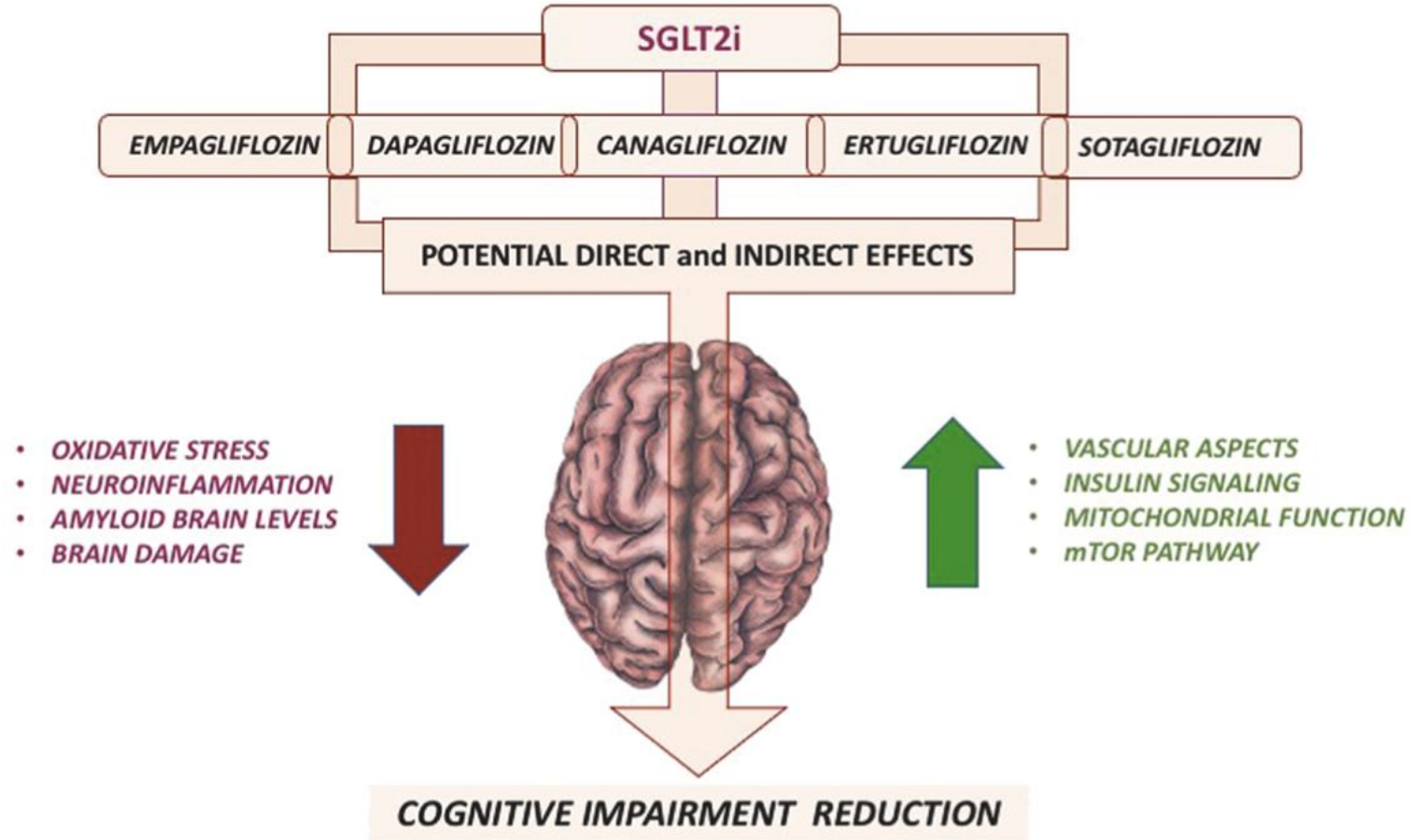
SGLT2 inhibitors enhance insulin sensitivity in the brains of obese rats by mitigating inflammation, apoptosis, and oxidative stress, markedly improving hippocampal synaptic plasticity

Review

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

RIZZO MR et al.

Pharmacological Research 176 (2022) 106062

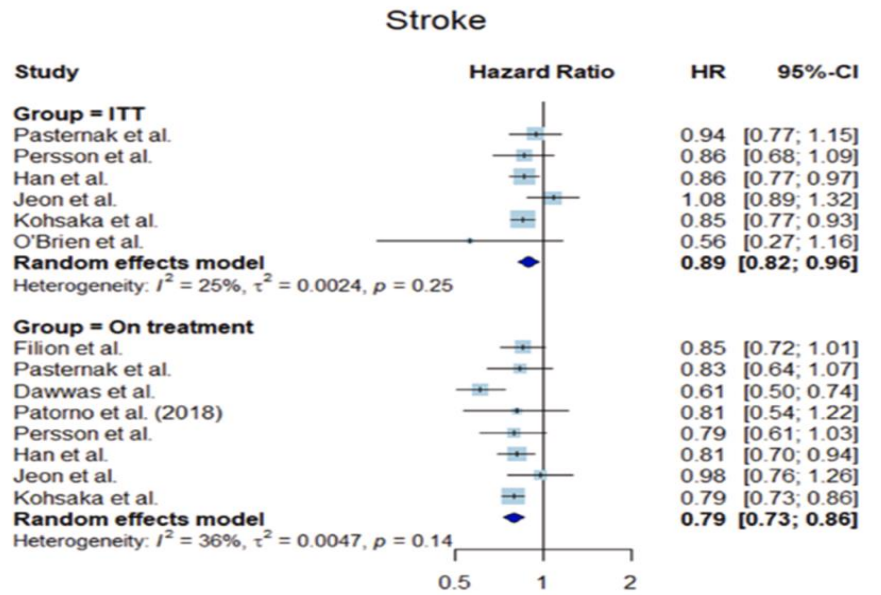


SGLT-2 inhibitors reduce the risk of cerebrovascular/cardiovascular outcomes and mortality: A systematic review and meta-analysis of retrospective cohort studies

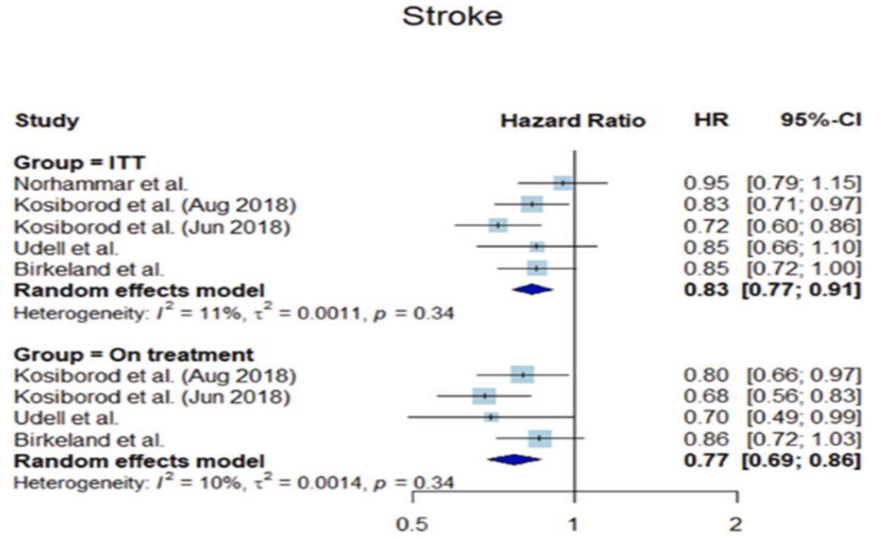
Mascolo et al - Pharmacological Research 172 (2021)

Risk of stroke with SGLT2 inhibitors compared to DPP-4 inhibitors (A) and non-SGLT2 inhibitors (B)..

A



B



ITT: Intention to treat; OT : On treatment analyses

A total of 20 registry-based cohort studies were identified, of which 13 considered the comparison with DPP-4 inhibitors, and 7 the comparison with non-SGLT2 inhibitors.

Evaluated the stroke with a total of 4633 retrievable outcome events, of which 1978 occurred in the SGLT2 inhibitor group and 2655 occurred in the DPP-4inhibitor group.

SGLT2 inhibitors were associated with a significant reduction in the hazard for stroke
(HR, 0.89; 95%CI, 0.82–0.96; Fig. 2A)

Risk of dementia after initiation of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in adults aged 40-69 years with type 2 diabetes: population based cohort study

the bmj | *BMJ 2024;386:e079475* | *doi: 10.1136/bmj-2024-*

OBJECTIVE

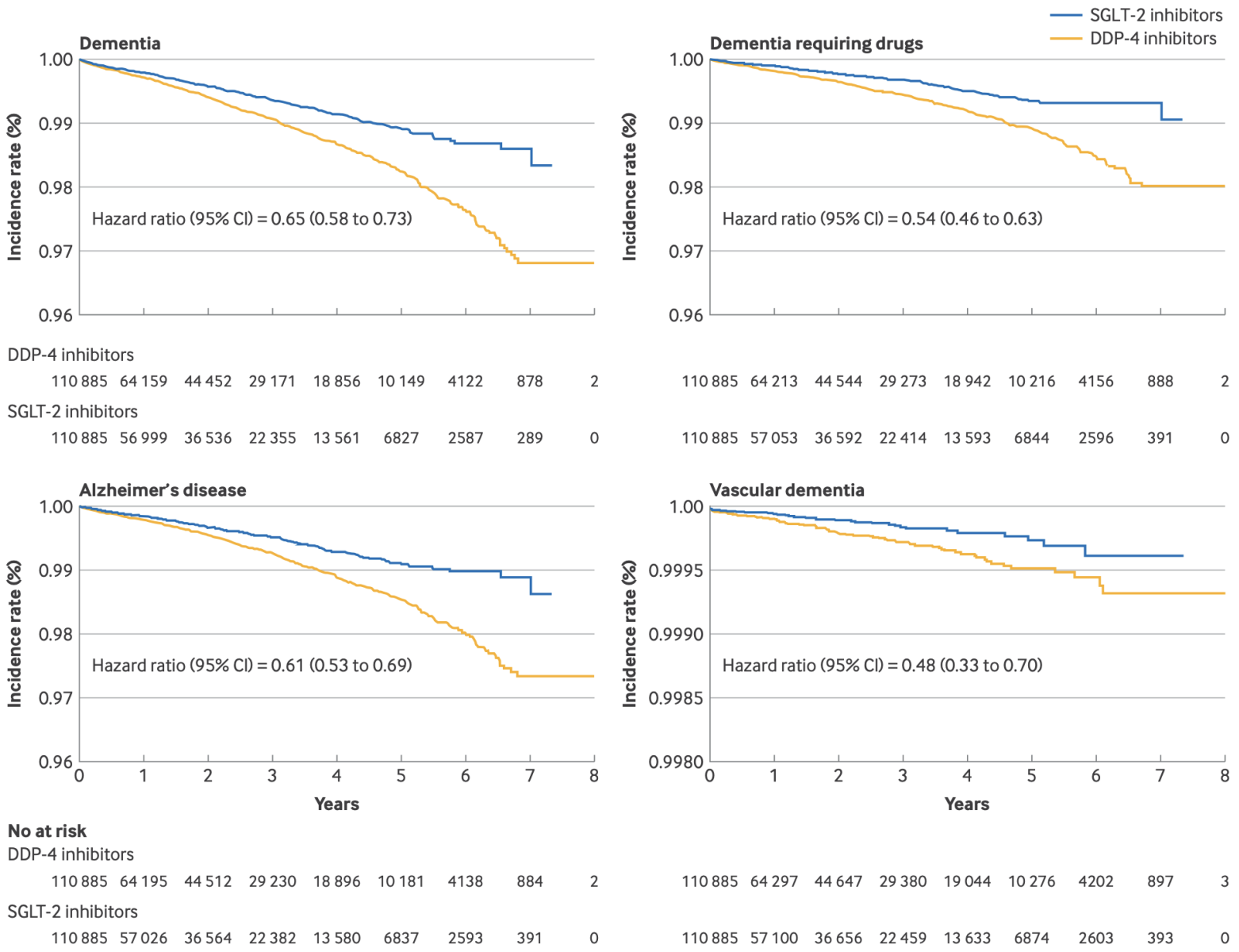
To compare the risk of dementia associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors in adults aged 40-69 years with type 2 diabetes.

MAIN OUTCOME MEASURES

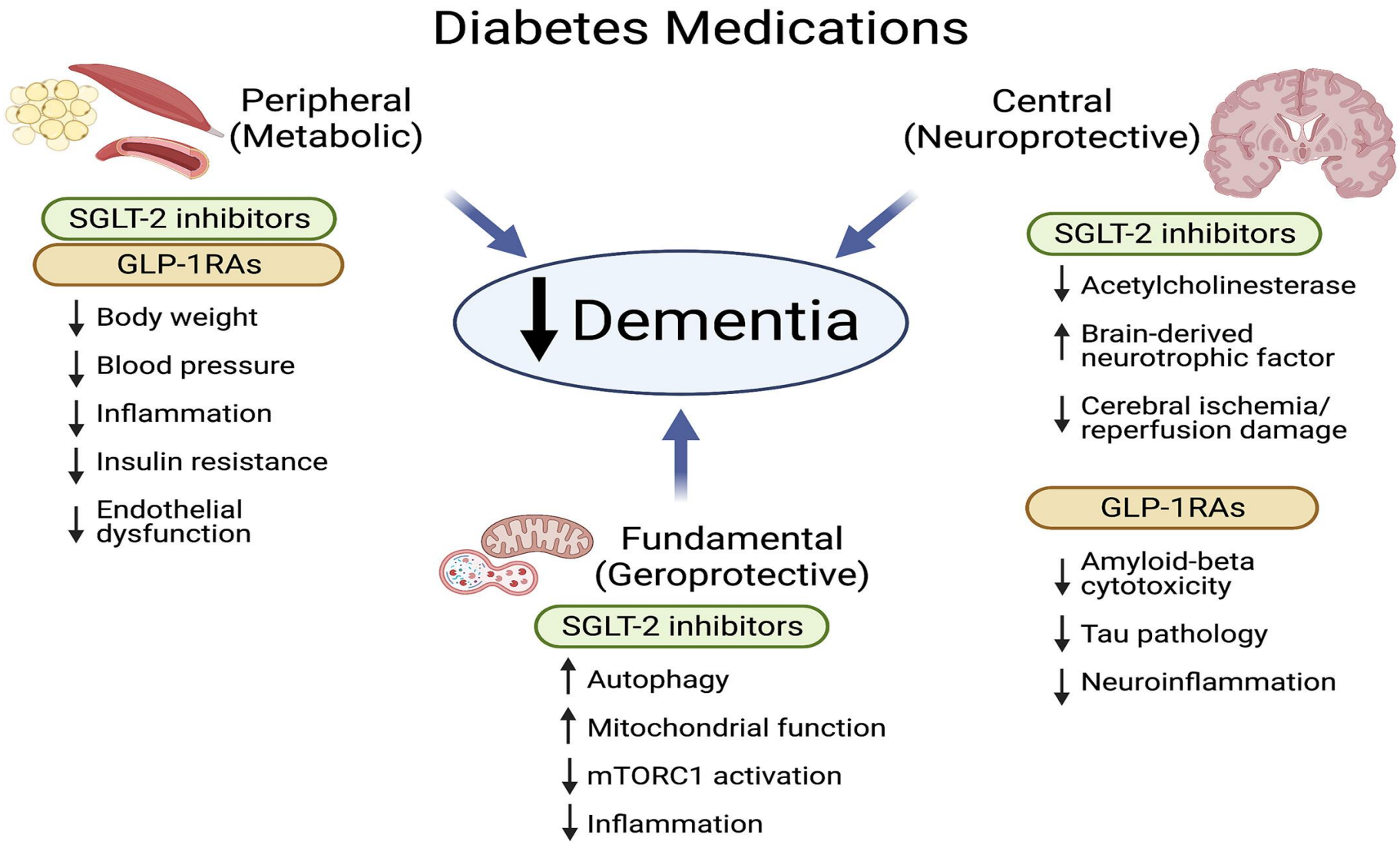
The primary outcome was new onset dementia. Secondary outcomes were dementia requiring drug treatment and individual types of dementia, including Alzheimer's disease and vascular dementia.

CONCLUSION

SGLT-2 inhibitors might prevent dementia, providing greater benefits with longer treatment. As this study was observational and therefore prone to residual confounding and informative censoring, the effect size could have been overestimated. Randomised controlled trials are needed to confirm these findings.



Is it time to purpose protective diabetes medications for prevention of dementia?



J American Geriatrics Society, Volume: 71, Issue: 7, Pages: 2041-2045, First published: 25 May 2023, DOI: (10.1111/jgs.18405)