Diabete e decadimento cognitivo
Implicazioni terapeutiche

DIA-PAVIA 2, 12 Dicembre 2020

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Diabetes and Alzheimer's disease
Outline

- Epidemiology and shared genetic factors
- Insulin signaling in the brain
- Insulin resistance (IR) and glycaemic control: impact on NDG
- Treatment: current evidence
- Future perspectives

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Archives of Medical Research 43 (2012) 600–608

REVIEW ARTICLE

Epidemiology of Dementias and Alzheimer's Disease

Ana Luisa Sosa-Ortiz,[a] Isaac Acosta-Castillo,[a] and Martin J. Prince[b]

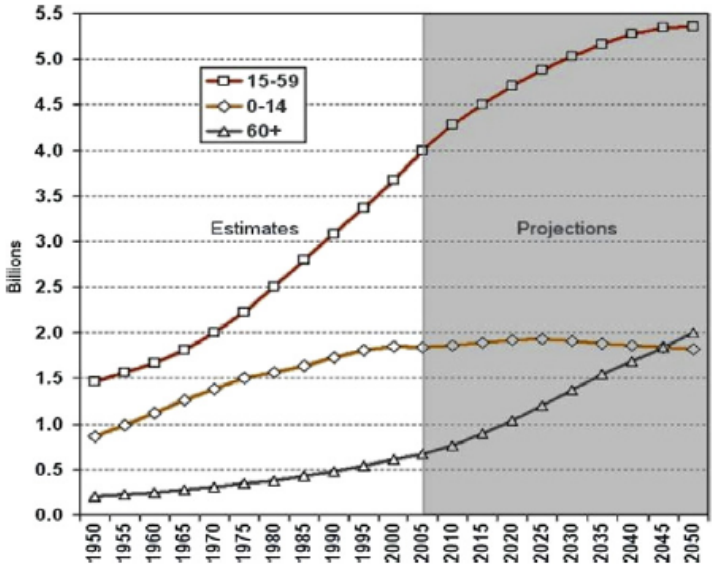


Figure 1. World population by age groups, 1950–2050. Source: World Population Prospects. Fact Sheet, Series A. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (7).

There are currently 35.6 million people world-wide with dementia, which will **double** to 65.7 million by 2030 and more than **triple** to 115 million by 2050 *(WHO report, 2012).*

AD accounts for up to 80% of dementias

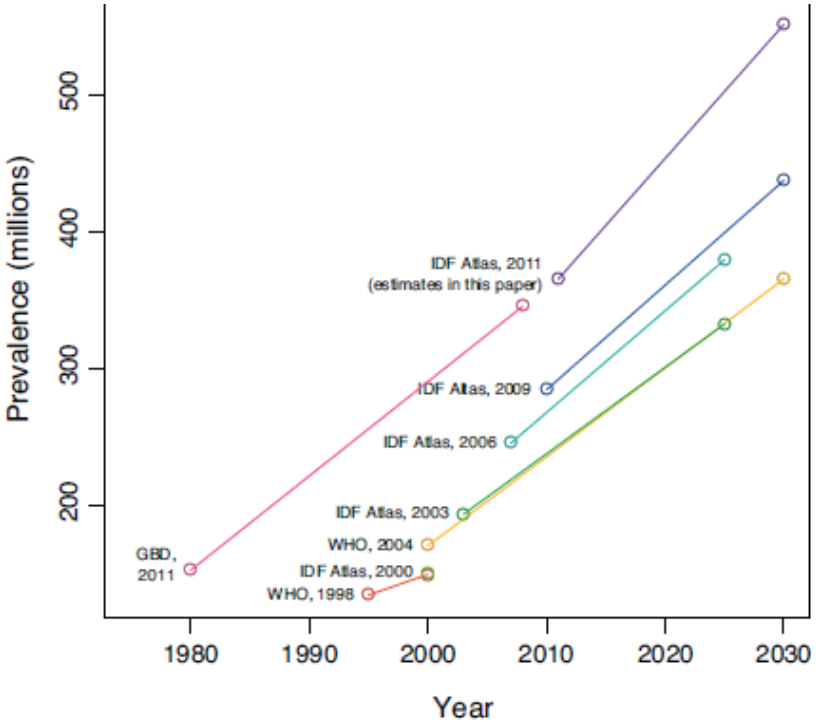
Table 1. Total population >60 years of age, crude estimated prevalence of dementia (2010), estimated number of people with dementia (2010, 2030 and 2050) and proportionate increases (2010–2030 and 2010–2050) by GBD regions

GBD region	Population >60 years of age (millions 2010)	Crude estimated prevalence (%, 2010)	Number of people with dementia (millions)			Proportionate increases (%)	
			2010	2030	2050	2010–2030	2010–2050
Asia	406.6	3.9	15.9	33.0	60.9	107.0	282.0
Europe	160.2	6.2	10.0	14.0	18.7	40.0	87.0
The Americas	120.7	6.5	7.8	14.8	27.1	89.0	246.0
Africa	71.1	2.6	1.9	3.9	8.7	111.0	370.0
World	758.5	4.7	35.6	65.7	115.4	85.0	225.0

GBD, global burden of disease. Source: World Alzheimer Report 2009 (15).

DIABETES RESEARCH AND CLINICAL PRACTICE 94 (2011) 311–321

IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030



366 million people currently have diabetes mellitus world-wide, and this number is expected to reach 552 million by 2030

and estimated diabetes numbers by region among adults aged 20–79 years for the years 2011 and 2030.

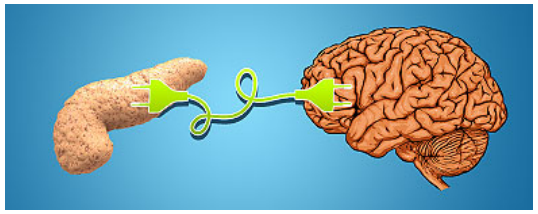
	2011			2030			
	Population (000s)	Cases (000s)	Adjusted prevalence (%)[a]	Population (000s)	Cases (000s)	Adjusted prevalence (%)[a]	Increase
AFR	387	14.7	5	658	28	5.9	90.5
EUR	651	52.6	6	671	64	7.1	21.7
MENA	359	32.8	12.5	542	60	14.3	82.9
NAC	322	37.7	11.1	386	51.2	12.6	35.8
SACA	290	25.1	8.6	376	39.9	10.1	59
SEA	856	71.4	8.6	1188	120.9	10.5	69.3
WP	1544	131.9	10.1	1766	187.9	11.6	42.5
World	4409	366.2	8.3	5587	551.9	9.9	185.7

[a] Age-standardized to the world population.

Epidemiological similarities between diabetes and Alzheimer's disease

Type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD) are both conditions:

- Age-related
- With increasing worldwide incidence
- Complex, multi-factorial
- Chronic

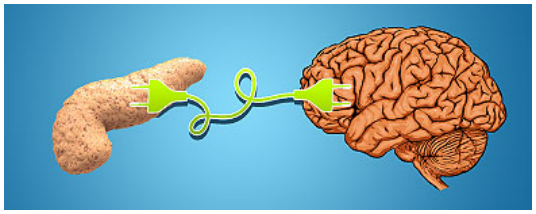


Kukull et al., Arch Neurol 2002

Similarities between diabetes and Alzheimer's disease

Type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD) are both conditions:

- Age-related
- With increasing worldwide incidence
- Complex, multi-factorial
- Chronic
- Characterised by IR, increased inflammation, impaired energy metabolism, increased oxidative stress



Kukull et al., Arch Neurol 2002;
Bedse, Front. Neurosci 2015

Epidemiological evidence

In a longitudinal cohort study, lasting up to 9 years, the risk of AD was 65% higher in persons with diabetes than in non-diabetic controls *(Arvanitakis, Arch Neurol 2004);*

In a community-based controlled study (*Mayo Clinic AD Patient Registry)* frank diabetes or glucose intolerance might be present in up to 80% of patients with AD *(Janson, Diabetes 2004).*

Longer diabetes duration is associated with a higher risk of dementia *(Ott, Neurology 1999; Bruce, Diabetes Care 2008; Bruce, Diabetologia 2008).*

There is a positive association between DM2 and mild cognitive impairment (MCI), and an accelerated progression from MCI to dementia in DM2 *(Alagiakrishnan, Am J Geriatr Psychiatry 2012).*

Diabetes Mellitus and Risk of Developing Alzheimer Disease

Results From the Framingham Study

Abimbola Akomolafe, MD, MPH, MS; Alexa Beiser, PhD; James B. Meigs, MD, MPH; Rhoda Au, PhD; Robert C. Green, MD, MPH; Lindsay A. Farrer, PhD; Philip A. Wolf, MD; Sudha Seshadri, MD

(REPRINTED) ARCH NEUROL/VOL 63, NOV 2006 WWW.ARCHNEUROL.COM

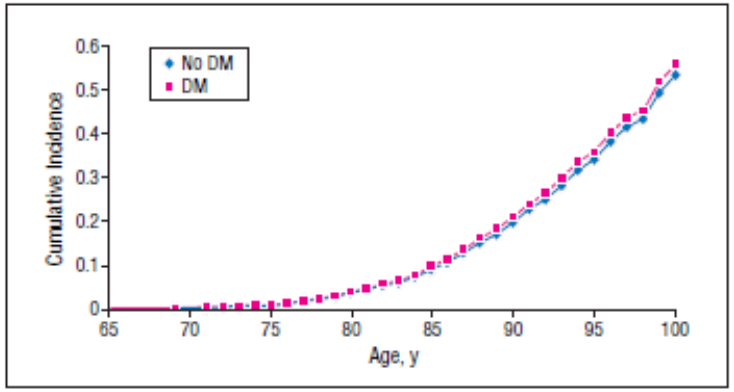


Figure 1. Cumulative incidence of Alzheimer disease in entire sample: comparison of groups with and without diabetes mellitus (DM), adjusted for age and sex.

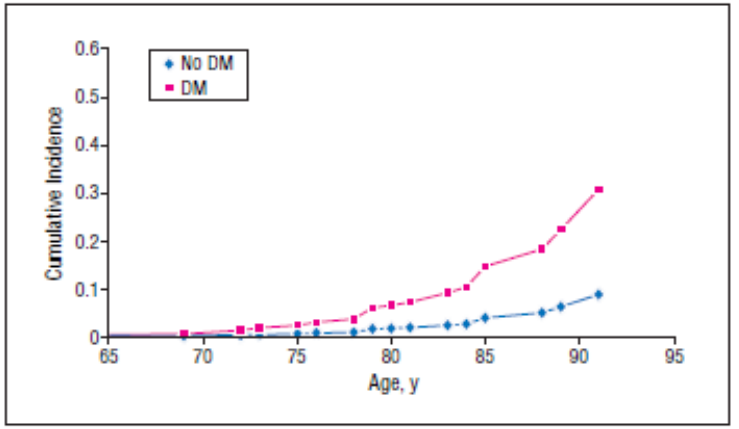


Figure 2. Cumulative incidence of Alzheimer disease in low-risk group: comparison of persons with and without diabetes mellitus (DM), adjusted for age and sex.

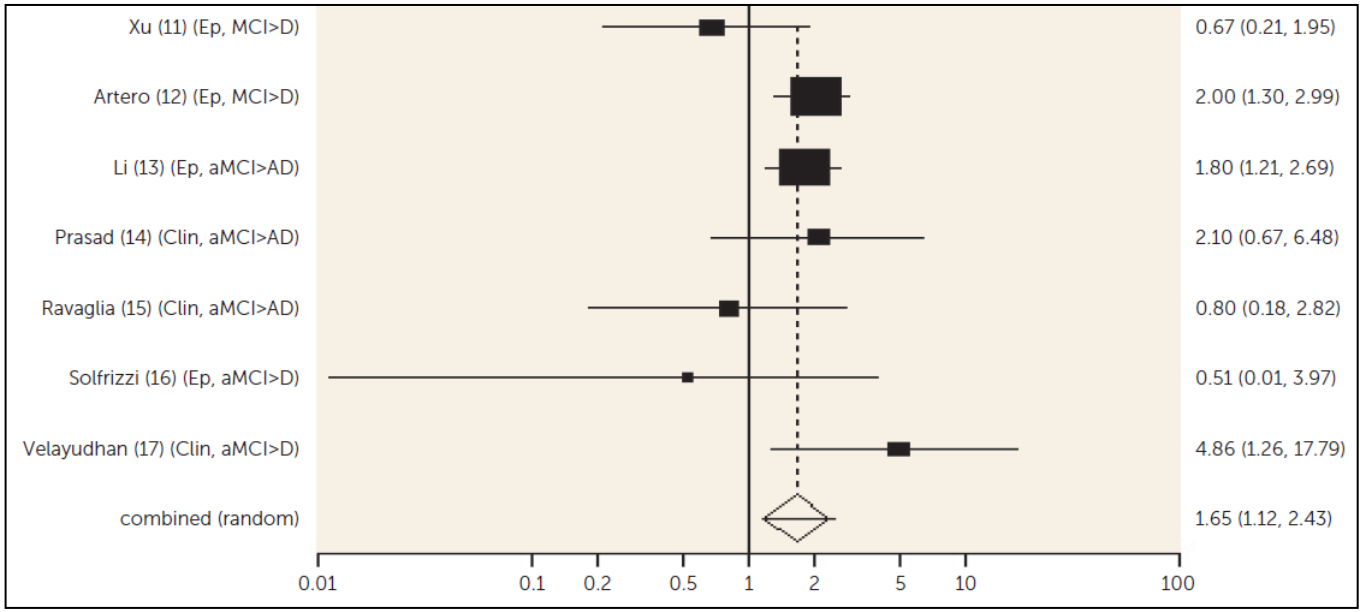
DM was not an independent risk factor for AD in the overall Framingham Study sample, but it was **a strong independent risk factor for AD** among persons at a relatively lower initial risk (those who were APOE ε4 negative and did not have a plasma tHcy level in the highest age- and sex-specific quartile), **raising the RR for AD by 3- to 5- fold in this group.**

Am J Psychiatry 2015;

Modifiable Predictors of Dementia in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis

Claudia Cooper, Ph.D., M.R.C.Psych., Andrew Sommerlad, M.R.C.Psych., Constantine G. Lyketsos, M.D., M.H.S., Gill Livingston, M.D., F.R.C.Psych.

76 eligible articles

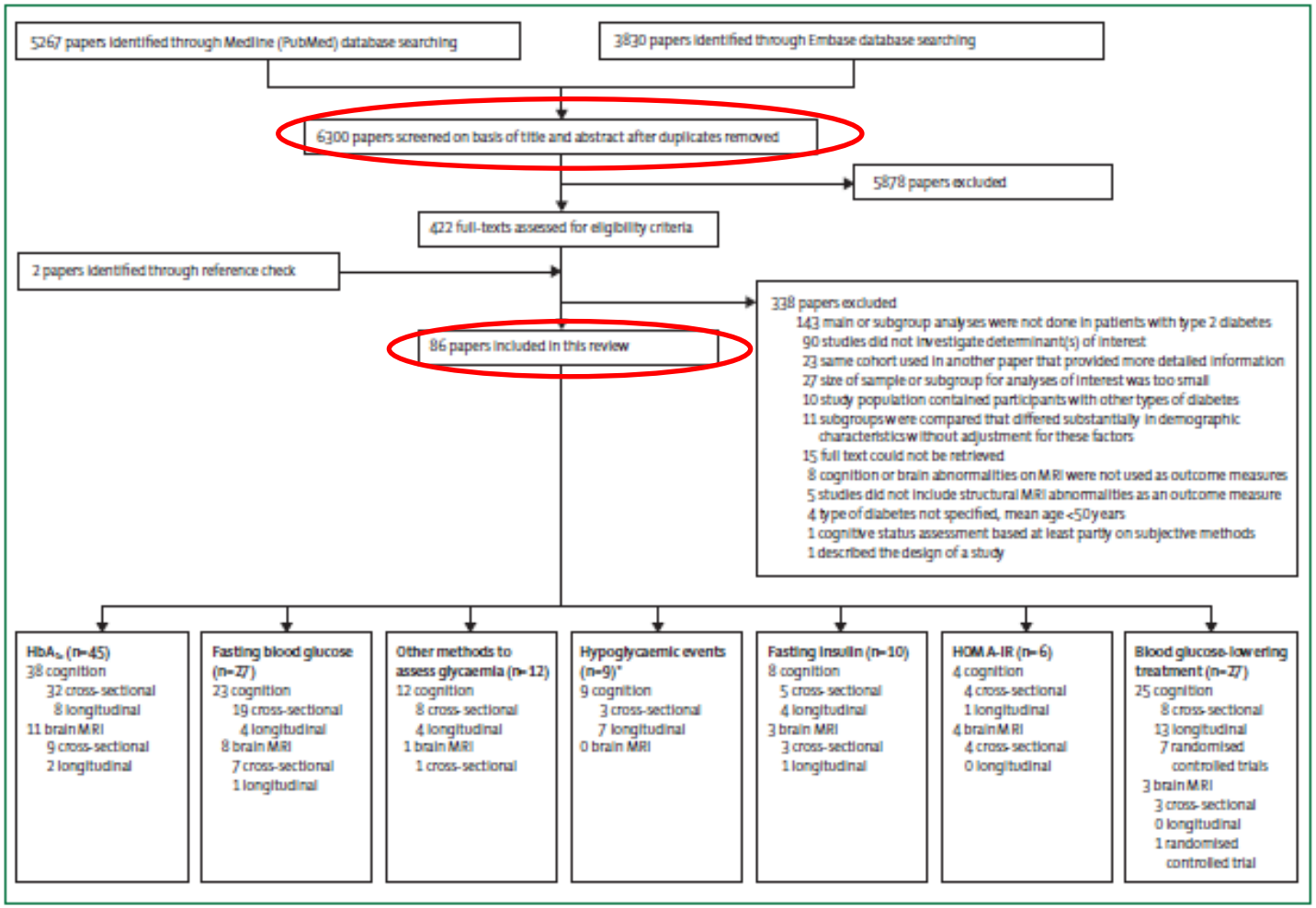


Diabetes and prediabetes increased risk of conversion from amnestic MCI to AD; risk in treated versus untreated diabetes was lower in one study. Diabetes was also associated with increased risk of conversion from any-type or nonamnestic MCI to all-cause dementia. **Mediterranean diet** decreased the risk of conversion.

Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review

Lancet Diabetes Endocrinol 2014

Stefan L C Geijselaers, Simone J S Sep, Coen D A Stehouwer, Geert Jan Biessels



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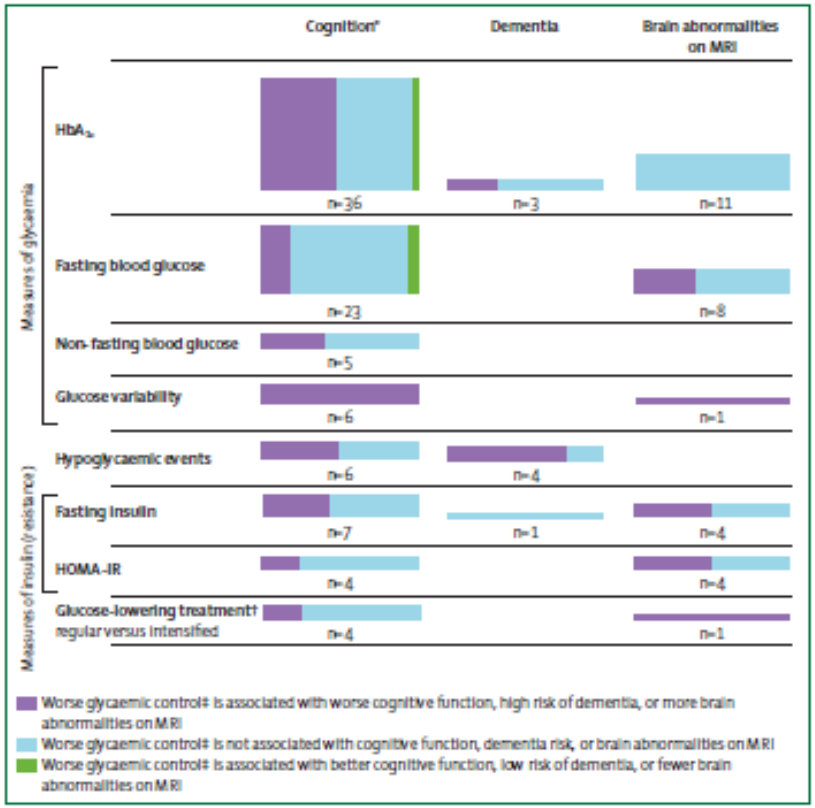

Measures of glycaemia are **negatively associated** with scores on cognitive tests in type 2 diabetes, particularly **increased HbA1c concentration** and **acute glucose fluctuations**, but not fasting blood glucose concentrations.

No clear conclusions about the association between measures of insulin concentration and IR and cognitive performance in type 2 diabetes.

Other factors might contribute to the onset and progression of cerebral changes in type 2 diabetes, starting **with vascular risk factors** (eg, hypertension, dyslipidaemia, and obesity) associated with cognitive decline in the general population and more prevalent in type 2 diabetes.

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

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

Review

Shared genetic etiology underlying Alzheimer's disease and type 2 diabetes

Ke Hao [a,b], Antonio Fabio Di Narzo [a,b], Lap Ho [c], Wei Luo [a,d], Shuyu Li [a,b], Rong Chen [a,b], Tongbin Li [e], Lauren Dubner [c], Giulio Maria Pasinetti [c,f,*]

Overlap of GWAS signals for AD and T2D.

(A)

Comparison	GWAS p-value threshold	Overlap OR	Overlap p-value	Number of overlap SNPs	N of overlap SNPs with consistent risk allele	% SNPs with consistent risk allele	p-Value of risk allele consistency
AD *vs.* T2D	1.00E−06	2.87	2.95E−01	1	0	0	1.00E+00
	1.00E−05	4.8	1.05E−02	4	0	0	1.25E−01
	1.00E−04	9.94	4.45E−18	27	2	7.41	5.65E−06
	1.00E−03	3.19	1.02E−15	68	7	10.29	7.39E−12
	1.00E−02	1.48	6.93E−28	927	395	42.61	7.66E−06
	1.00E−01	1.04	1.70E−10	35,719	18,085	50.63	1.73E−02

(B)

GWAS p-value threshold	Consistent risk allele			Divergent risk allele		
	Number of overlap SNP	Overlap OR	Overlap p-value	Number of overlap SNP	Overlap OR	Overlap p-value
1.00E−06	0	–	1	1	8.25	1.15E−01
1.00E−05	0	–	1	4	13.18	2.86E−04
1.00E−04	2	1.33	5.65E−06	25	21.68	1.31E−24
1.00E−03	7	0.46	7.39E−12	61	5.82	2.72E−26
1.00E−02	395	1.2	7.66E−06	532	1.72	1.43E−29

GWAS studies support **disease concordance between T2D and AD**, and provide information for the design of future novel therapeutic approaches, for a **subpopulation of T2D subjects with genetic disposition to AD,** that could benefit T2D and reduce the risk for subsequent development of AD.

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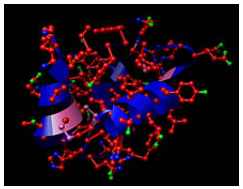
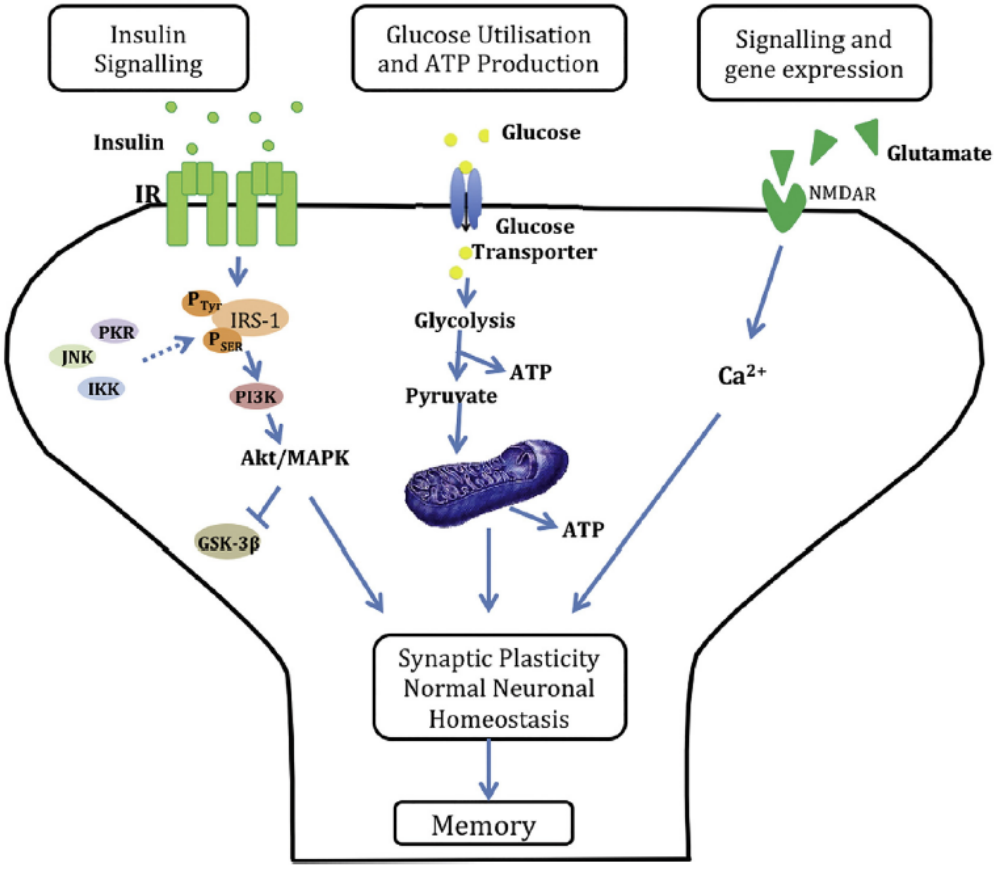
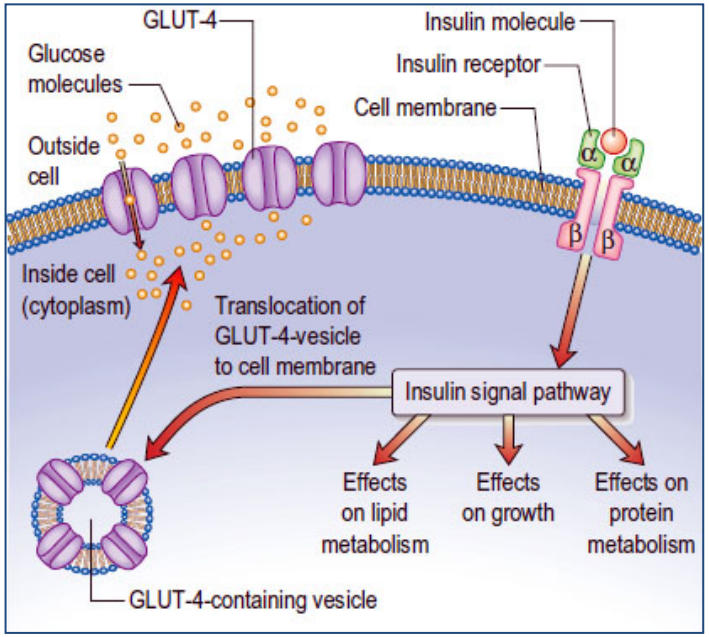
Insulin signaling in the brain







Verdile et al., Neurobiol. Aging, 2015

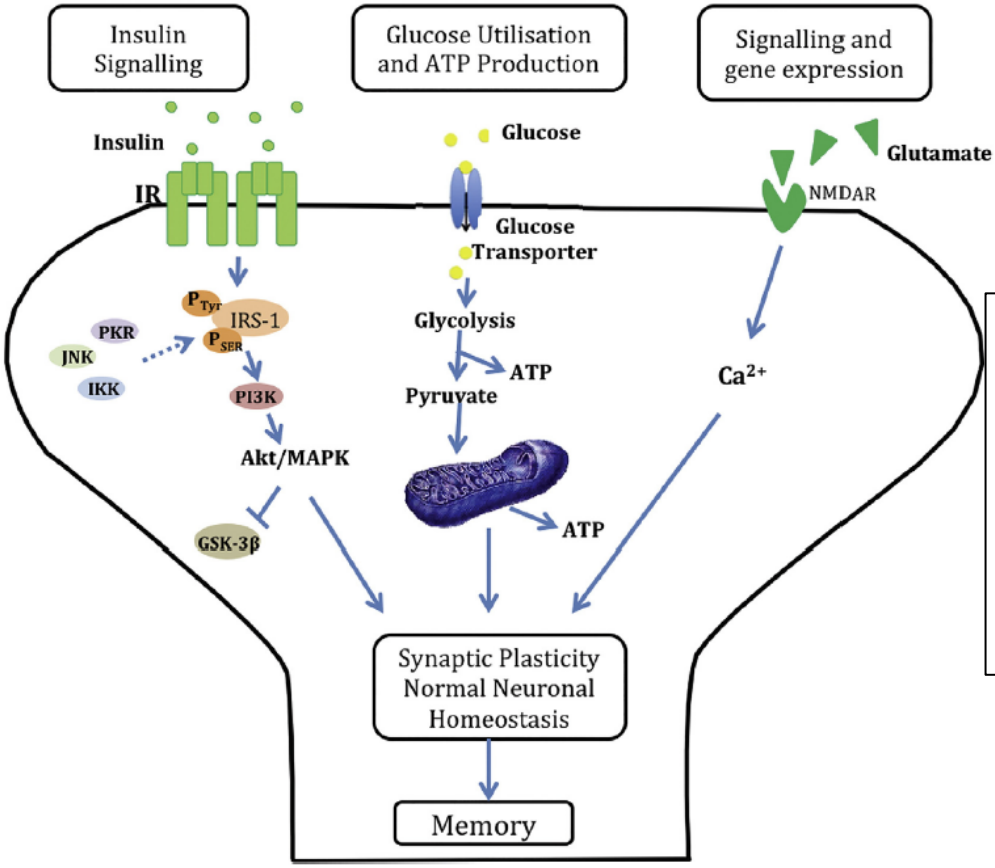
Insulin signaling is altered in AD

Subjects/Tissue	Components of insulin signaling system	Observation	References
ALZHEIMER'S DISEASE			
AD human patients/Hippocampus, cortex, and cerebellum	IGF-II Mannose -6-phosphate receptor	Unchanged	Kar et al., 2006
AD human patients/frontal, temporal, parietal, and occipital cortex	Insulin IR c-peptide levels	- Strong insulin immunoreactivity in pyramidal neurons compared to age-matched controls - Unchanged insulin and c-peptide levels - Increased IR density - No significant difference in IGF-1binding	Frolich et al., 1998
AD human patients/frontal cortex, hippocampus, hypothalamus	Insulin IGF-1 IGF-2 receptor mRNA	↓ IR and IGF-1R mRNA in hippocampus and hypothalamus ↓ insulin and IGF-2 mRNA in hippocampus and hypothalamus and IGF-1 in frontal cortex ↓ insulin, IGF-1, IR and IGF-1R-positive neurons in hippocampus ↓ IR and IGF-1R protein in hippocampus ↓ tyrosyl-phosphorylated IR, IGF-1R and IRS-1 in hippocampus, cortex and hypothalamus ↓ IRS-2 protein in hippocampus Impaired IRS-1 signaling in hippocampus and hypothalamus (↓pS6-associated IRS-1) ↓ pAkt and pGSK-3b	Steen et al., 2005
AD human patients/Plasma, serum	IGF-1 IGFBPs	↑ total and unbound IGF-1 levels ↑ serum and CSF levels of IGF-1 and IGFBPs	Vardy et al., 2007; Salehi et al., 2008
AD human patients/CSF	Insulin	↓ insulin in mild AD patients ↓ insulin in MCI women - Positive correlation of insulin with $A\beta_{1-42}$ levels and cognitive score	Gil-Bea et al., 2010
AD human patients/Temporal cortex	IGF-1R IGFBP-2	Unaltered IR protein levels however altered its distribution in AD neurons ↑ IGF-1R;↓IGFBP-2 ↑ IGF-1R surrounding and within plaques and in astrocytes ↓ IRS-1and IRS-2 protein levels ↑ phosphoIRS-1 levels near NFTs	Moloney et al., 2010
AD human brain tissue/ cynomolgus monkeys (i.c.v. injection of Aβ oligomer/AβPP-PS1 Tg mice	IRS-1	↑ IRS-1pSer636/639 levels in hippocampus ↑ IRS-1pSer636/639 levels were observed in neurons targeted by Aβ	Bomfim et al., 2012
AD human patients, triple transgenic mouse model, Cultured rat hippocampus neurons (Aβ oligomer insult)	IRS-1	↑ active JNK and IRS-1pSer616 levels Redistribution of IRS-1pSer616 expression from nucleus to cytosol in AD human patients and 3×Tg-AD ↑ IRS-1pSer616 colocalized with NFTs Aβ oligomer induced expression of IRS-1pSer616 in hippocampal neurons culture	Ma et al., 2009

Insulin signaling is altered in AD (ctd.)

Subjects/Tissue	Components of insulin signaling system	Observation	References
AD human patients/cortex and hippocampus	Insulin IGF-1 IRS-1	- Unchanged basal levels of insulin and IGF-1 signaling molecules - Trend to increase IRS-1 levels in hippocampus - ↓In responses to insulin signaling in the IR→IRS-1→PI3K signaling pathway and greater → in responses to IGF-1 in the IGF-1R→IRS-2→PI3K signaling pathway in AD - IRS-1 pS616 and IRS-1 pS636/639 correlated positively with Aβ plaques and negatively associated with memory	Talbot et al., 2012
AD human patients/frontal cortex	Insulin IGF-1 IRS-2	↓ Insulin, IGF-1 and IGF-2 receptor mRNA and polypeptide mRNA in AD ↓ binding of ^{125}I labled insulin, IGF-1 and IGF-2	Rivera et al., 2005
Hippocampal and cortical neuronal cultures S.D. Rats (soluble Aβ oligomer insult)	IR Tyr phosphorylation	Soluble Aβ oligomer inhibits IR activity (IR Tyr phosphorylation) ↑ Akt serine473 phosphorylation (Akt-pSer473)	Zhao et al., 2008
AD human patients/plasma	IGF-1	↓ plasma IGF-1 level in familial AD patients carrying the swedish AβPP 670/671 mutation	Mustafa et al., 1999
AD human patients/serum and CSF	IGF-1 IGF-2 IGFBP	↑ IGF-2 in both AD serum and CSF ↑ IGF-1 in AD serum ↑ IGFBPs in the CSF of the AD patients	Tham et al., 1993
AD human patients/CSF and plasma	Insulin	↓ CSF insulin and CSF-to-plasma insulin ratio ↑ plasma insulin	Craft et al., 1998
AD human patients/cortex	Insulin signaling	↓ total and phosphorylated components of insulin-PI3K-Akt signaling in AD	Liu et al., 2011
AD human patients/cortex and hippocampus	IRS-1	↑ IRS1-pS^{616}, IRS1-pS^{312}, Akt-pS^{473} in AD Co-expression of IRS1-pS^{616} with pathological tau neurons	Yarchoan et al., 2014
AD human patients/plasma	Insulin	↑ plasma insulin after oral glucose tolerance test in AD patients ↑ CSF insulin levels	Fujisawa et al., 1991
Tg2576 mice of AD	IGF	↓ serum IGF levels	Carro et al., 2002

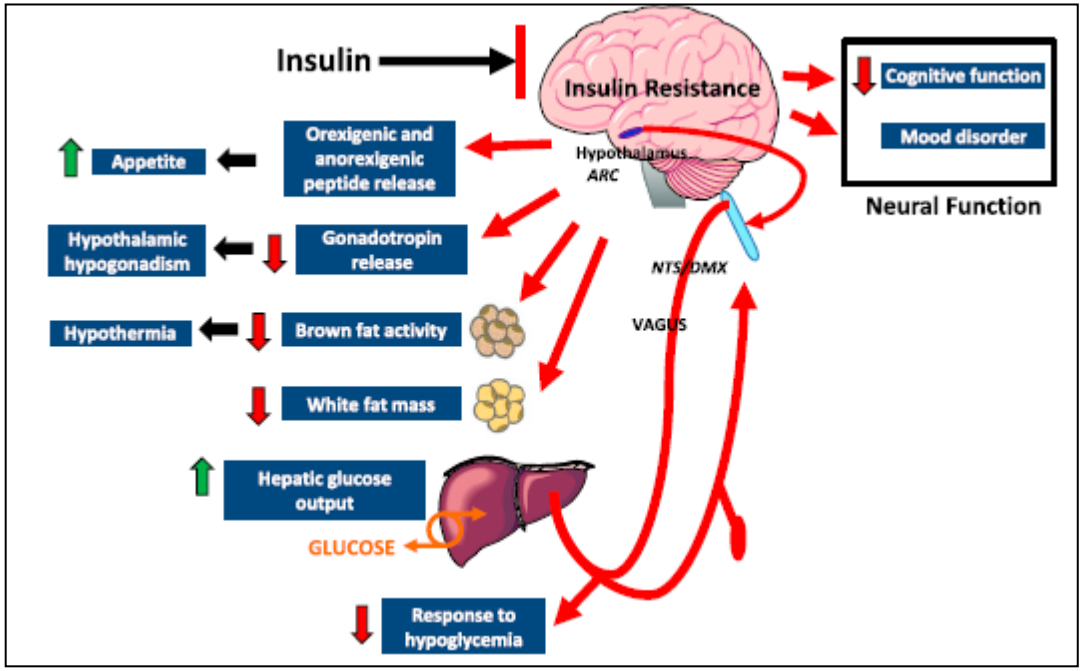
Insulin signaling is altered in AD



- **Reduced brain IR sensitivity**
- **IR and IRS-1 hyperphosphorylation**
- **Reduced IR and IGF-1R expression**
- **Reduced CSF insulin levels** (controv.)

Watson and Craft, 2003; Rivera et al., 2005; Steen et al., 2005; Holscher and Li, 2010; Talbot et al., 2012; de La Monte, 2012c; Freiherr et al., 2013.

Consequences of altered insulin signaling (IR) in the brain



Effects of insulin signaling in the brain on central and peripheral function. Brain insulin resistance results in increased food intake, hypothalamic hypogonadism, hypothermia, decreased white fat mass, increased hepatic glucose output, impaired response to hypoglycemia, and impaired neural function.
ARC, arcuate nucleus; DMX, dorsal motor vagal nucleus; NTS, nucleus of the solitary tract.

Kleinridders et al., 2014

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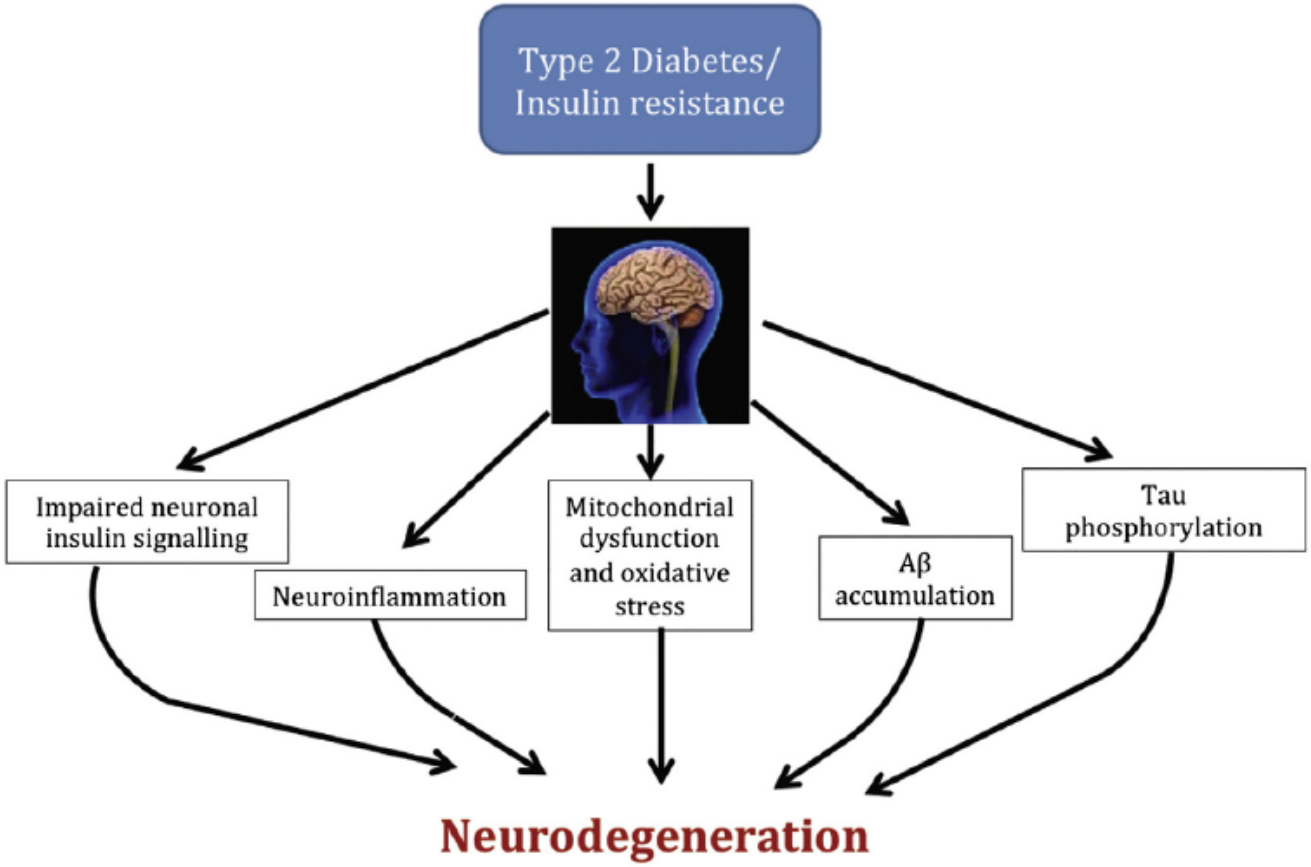
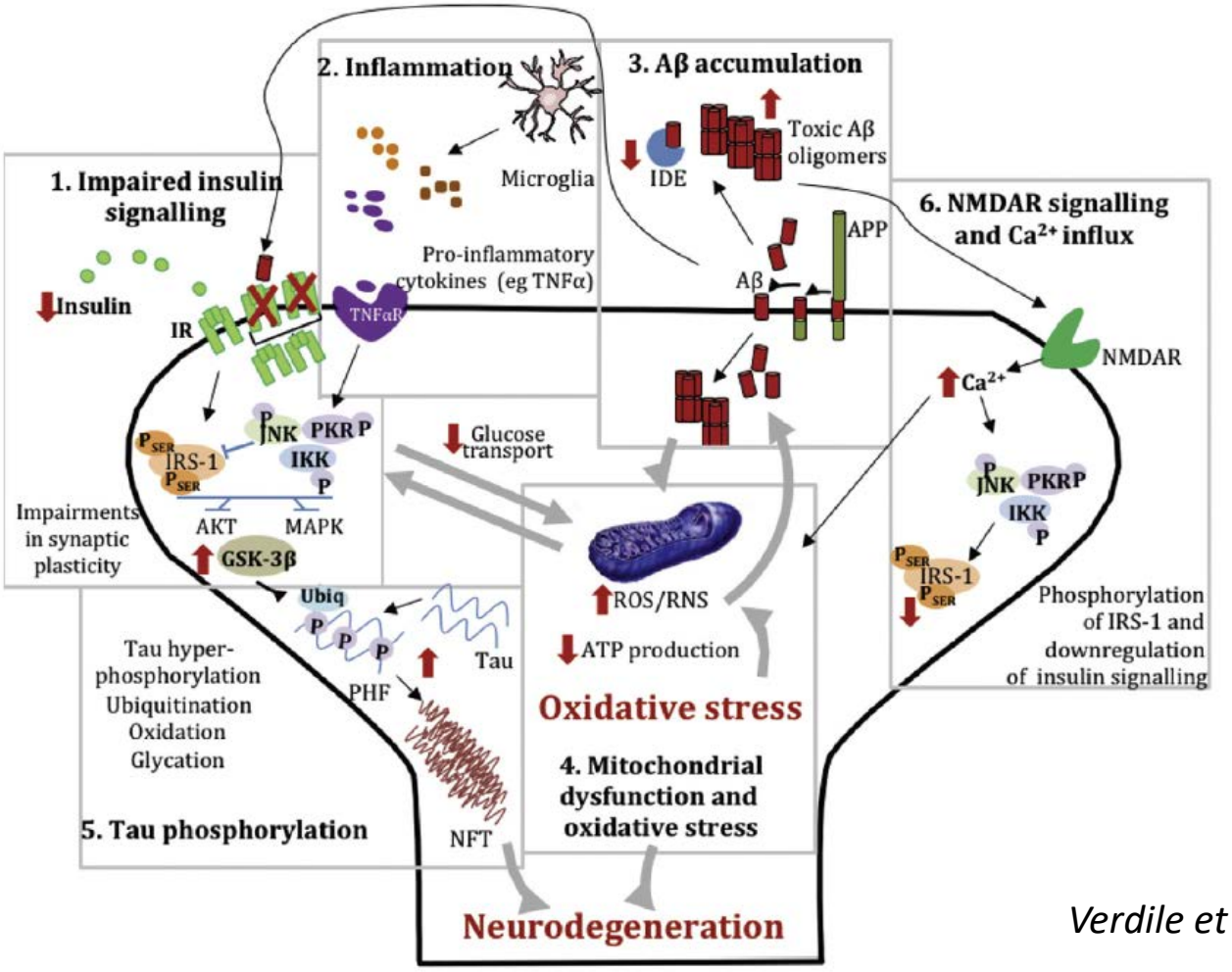
Contribution of type-2 diabetes/IR to neurodegeneration



Verdile et al., 2015

Contribution of type-2 diabetes/IR to neurodegeneration



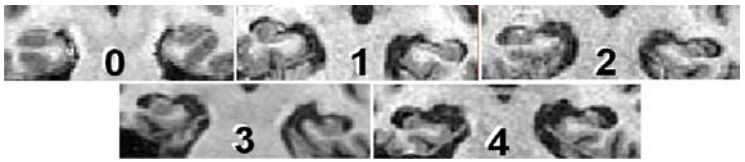
Verdile et al., 2015

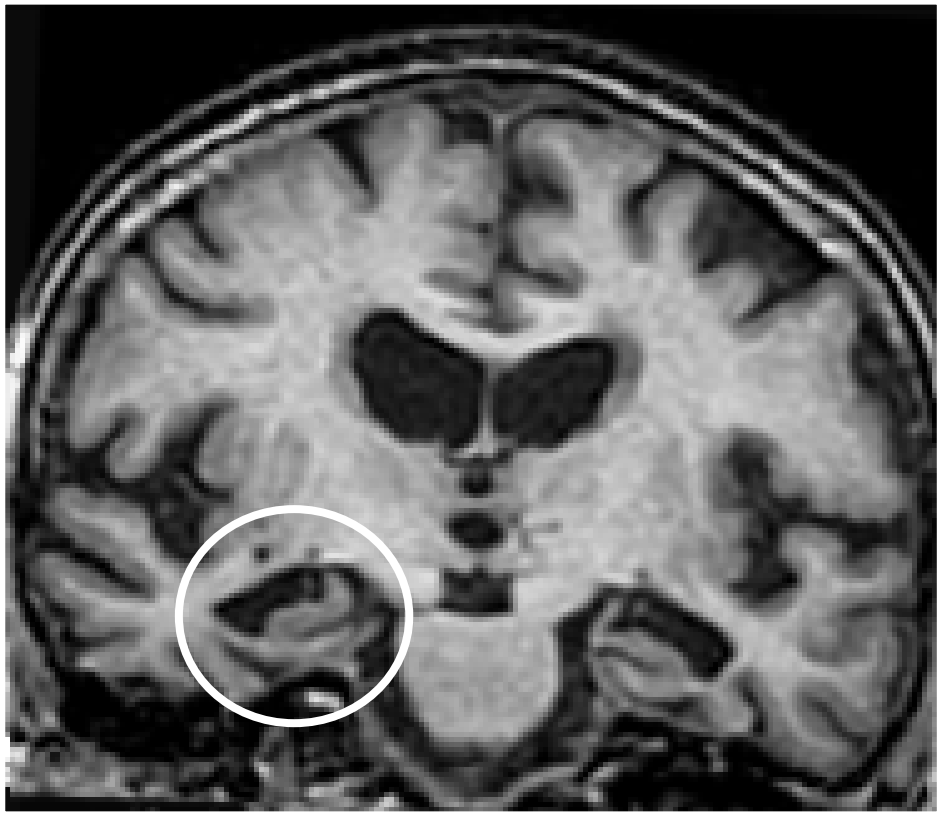
IR is associated with brain atrophy: MRI

Atrophy in Alzheimer's disease

Prodromal AD	15%
Mild dementia	25%
Moderate dementia	40%

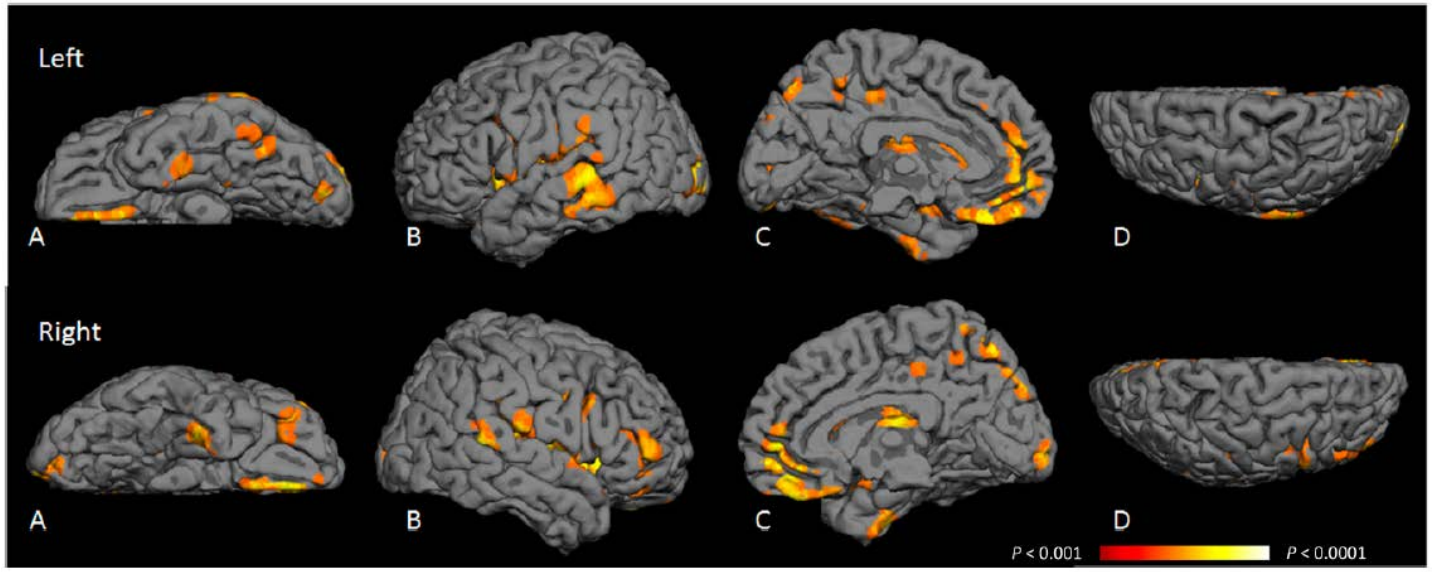
	Choroid fissure width	Temporal horn width	Hippocampus height
0	N	N	N
1	↑	N	N
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓





The rate of brain atrophy **in T2D is up to 3 times faster** than in normal aging *(Van Elderen, 2010)*

IR is associated with brain atrophy: VBM



Probability map of location of gray matter atrophy attributable to T2DM.
VBM: voxels highlighted are those areas most likely to have gray matter atrophy attributable to T2DM, with a false discovery rate P<0.001 (orange) to P<0.0001 (yellow).
Hyppocampus is included in these areas.

Moran et al., 2013

Original Investigation

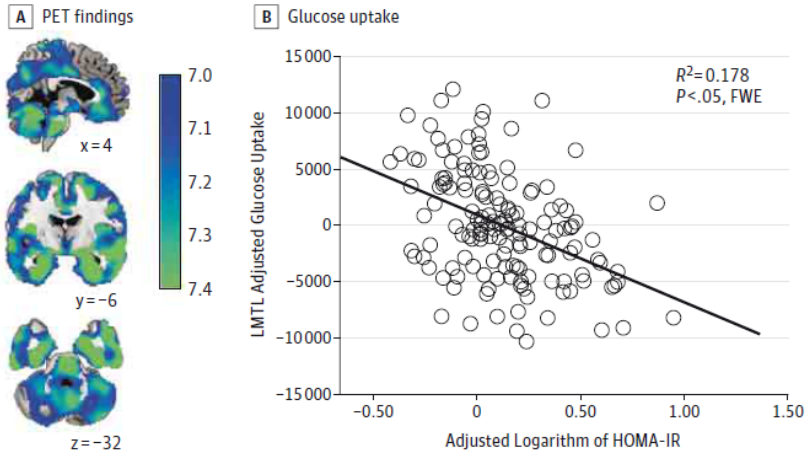
Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease

Auriel A. Willette, PhD; Barbara B. Bendlin, PhD; Erika J. Starks, BS; Alex C. Birdsill, PhD; Sterling C. Johnson, PhD; Bradley T. Christian, PhD; Ozioma C. Okonkwo, PhD; Asenath La Rue, PhD; Bruce P. Hermann, PhD; Rebecca L. Koscik, PhD; Erin M. Jonaitis, PhD; Mark A. Sager, MD; Sanjay Asthana, MD

18-FDG PET

JAMA 2015

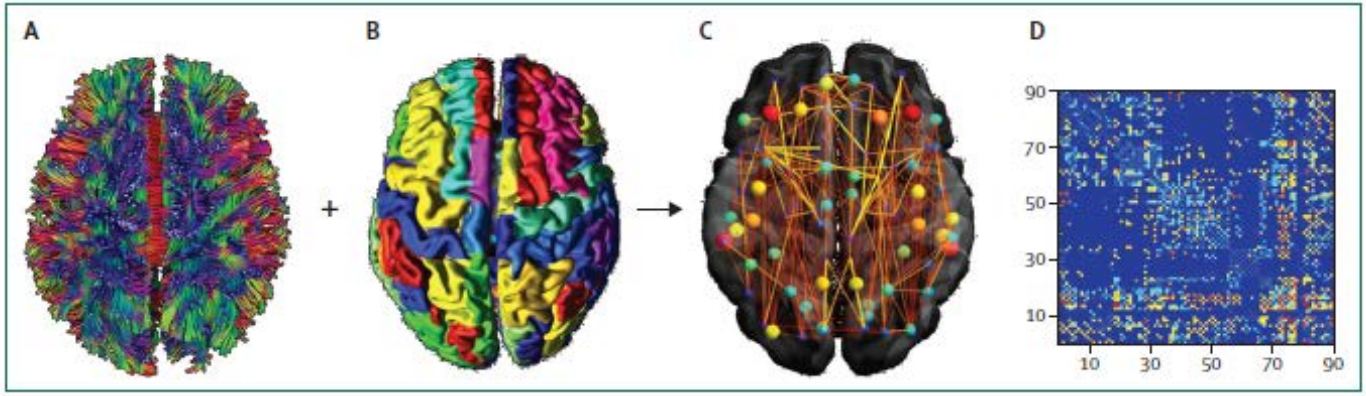
Figure 2. Association Between Higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Lower Regional Uptake of Fludeoxyglucose F 18 (FDG) in Positron Emission Tomography (PET)



Participants included 150 late middle-aged adults. A, The FDG-PET results are displayed on 3-dimensional cross-sections of temporal, parietal, and frontal regions, with images oriented in neurologic space. The color bar depicts *t* values. B, Glucose uptake values (measured in arbitrary units) were adjusted by the following covariates: age, sex, parental history of Alzheimer disease, apolipoprotein E ε4 genotype, and glucose metabolism in the reference region. Circles indicate individual participants; line, the linear regression fit across all participants. FWE indicates familywise error correction; LMTL, left medial temporal lobe.

A link between increased IR and decreased glucose uptake/ metabolism (FDG-PET) in several brain areas, particularly robust in the left **medial temporal lobe**, which in turn may predict worse memory performance.

IR is associated with loss of brain connectivity on DTI

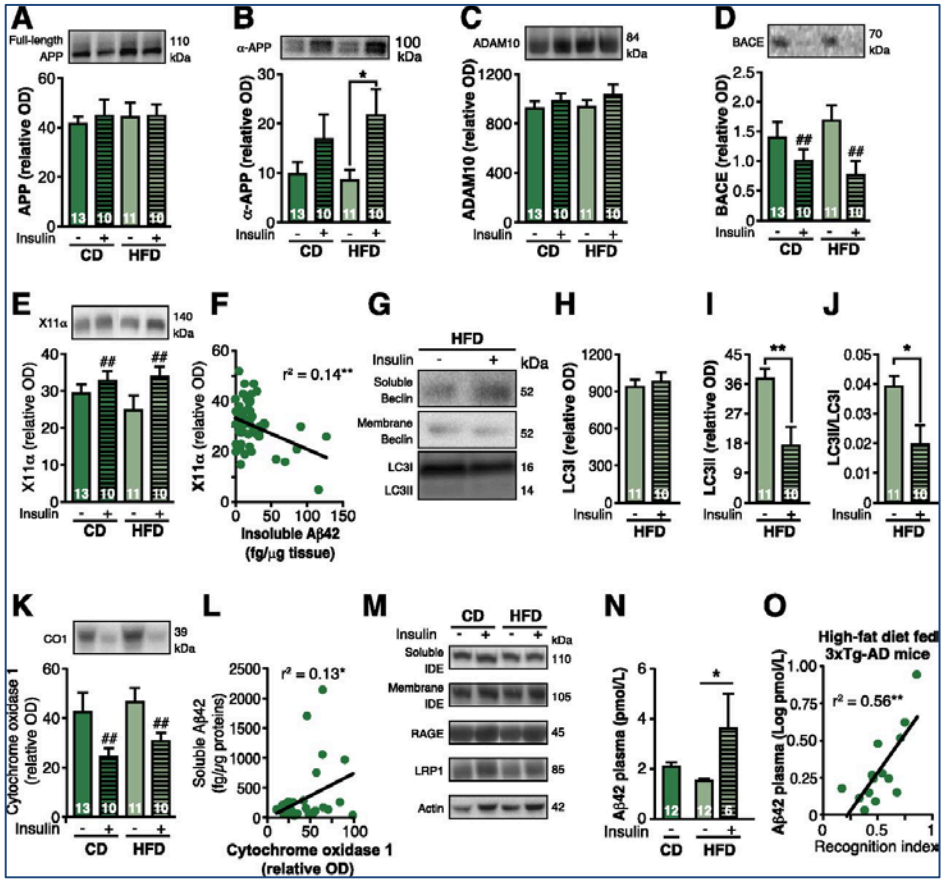


Cerebral white matter networks reconstructed from diffusion tensor imaging (DTI) scans with graph theory. A) DTI-based fibre tracts form the edges (connections) of the network
B) Parcellated cortical and subcortical regions form the nodes (90 in total). C) Weighted brain network obtained, which can be represented by D) a 90x90 connectivity matrix.

Brain changes in T2D patients are strongly correlated with cognitive functioning, independent of MRI markers of atrophy and small vessel disease.

(Reimer et al, 2013)

IR promotes the accumulation of beta-amyloid



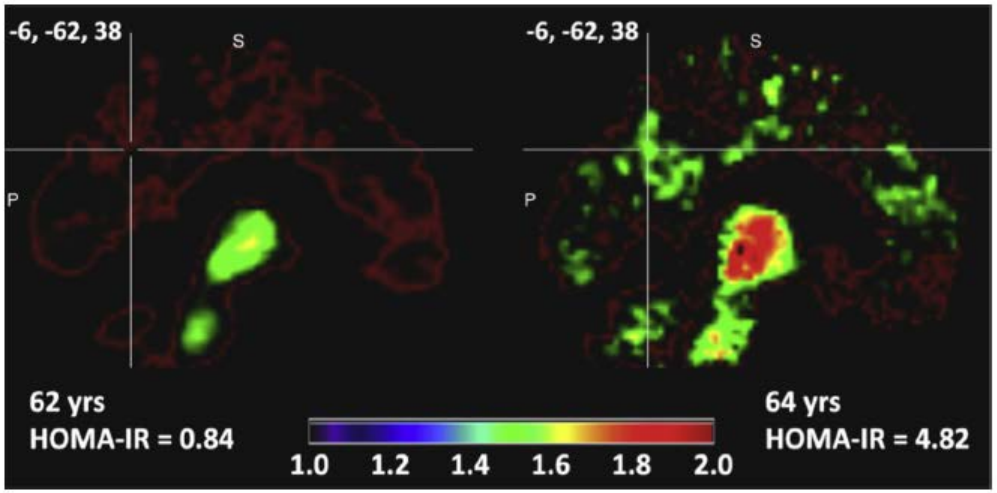
When insulin resistance is induced in 3xTg AD-model transgenic mice or in diabetic obese mice (db/db, leptin mutant mice) through feeding a high fat diet, the mice exhibit **increased levels of brain Aβ and key enzymes that generate Aβ (BACE and γ-secretase)**

Vandal et al., 2014

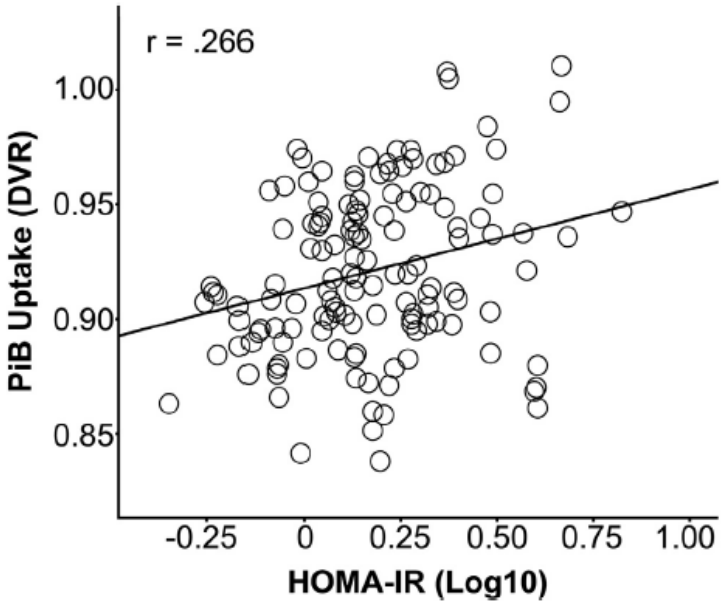
Insulin resistance predicts brain amyloid deposition in late middle-aged adults

Alzheimer's & Dementia 11 (2015) 504-510

Auriel A. Willette[a,b,c,†], Sterling C. Johnson[a,b,d,e], Alex C. Birdsill[a,b], Mark A. Sager[b,e],

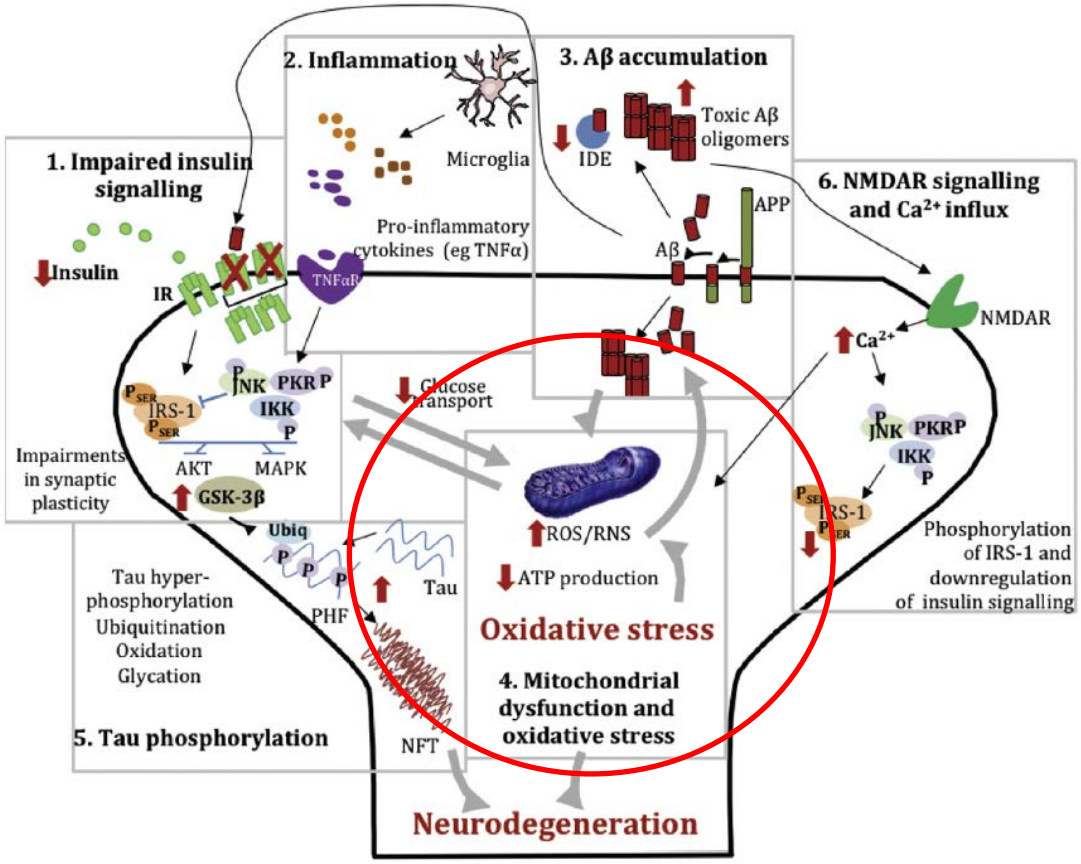


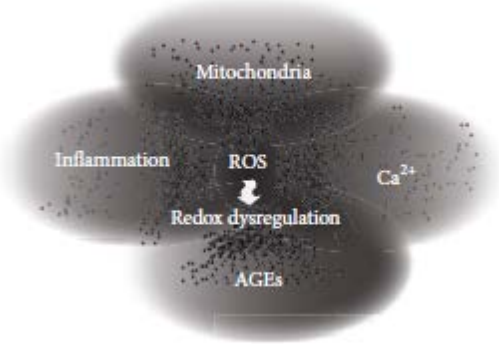
PiB, amyloid load according to HOMA, sagittal plane



In participants with normoglycemia but not hyperglycemia, higher insulin resistance corresponded to higher PiB uptake in **frontal and temporal areas**, reflecting increased amyloid deposition. The first human study to demonstrate that insulin resistance may contribute to amyloid deposition in brain regions affected by AD.

IR reduces glucose utilization and promotes oxidative stress





Oxidation of several enzymes involved in glycolisis and Krebs cycle in AD and 2TD.

Mitochondria dysfunction is an **early** event in AD: cause of consequence of IR?

The oxidative stress processes associated with both T2D and AD represent the **major underlying link of these conditions**: using the same oxidative stress-dependent mechanisms, T2D and AD may feedback on each other.

J Neurol Neurosurg Psychiatry 2015

RESEARCH PAPER

CSF lactate levels, τ proteins, cognitive decline: a dynamic relationship in Alzheimer's disease

C Liguori,[1,2] A Stefani,[2,3] G Sancesario,[2,3] G M Sancesario,[4] M G Marciani,[2,3] M Pierantozzi[2]

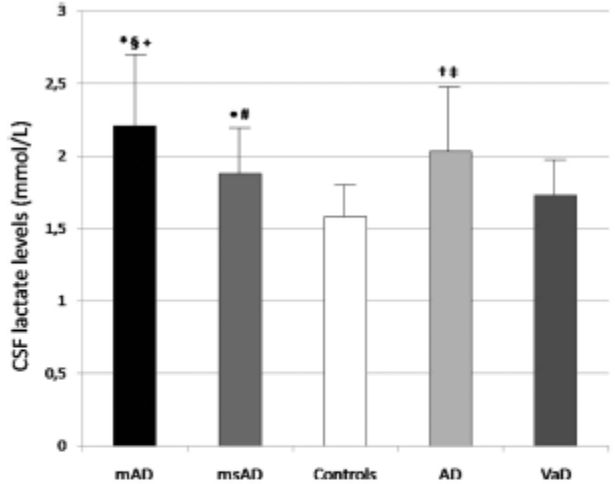


Figure 1 Cerebrospinal fluid (CSF) lactate levels of Alzheimer's disease (AD), vascular dementia (VaD) and control groups. Bars with whiskers show means and SDs. †AD versus controls, p<0.0001; ‡AD vs VaD, p<0.0001; *mild AD (mAD) versus moderate–severe (msAD), p<0.0001; §mAD versus controls, p<0.0001; +mAD versus VaD, p<0.001; •msAD versus controls, p<0.0001; #msAD versus VaD, p<0.05.

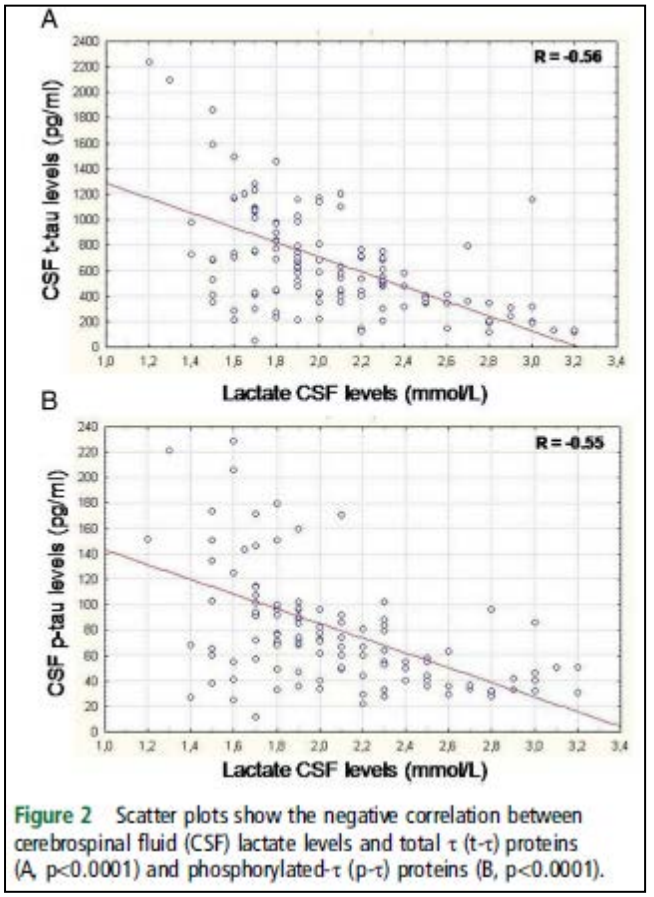


Figure 2 Scatter plots show the negative correlation between cerebrospinal fluid (CSF) lactate levels and total τ (t-τ) proteins (A, p<0.0001) and phosphorylated-τ (p-τ) proteins (B, p<0.0001).

Reciprocal relationship between the alteration of neuronal energy metabolism (increased CSF lactate concentration), the severity of AD neurodegenerative processes (CSF t-τ and p-τ proteins), and cognitive inpairment (MMSE) The damage of energetic cellular metabolism in AD may involve not only mitochondria but also glycolysis.

IR, hyperinsulinaemia and obesity cause neuroinflammation and increase neuroinflammation in AD

Heneka, Lancet Neurol 2015

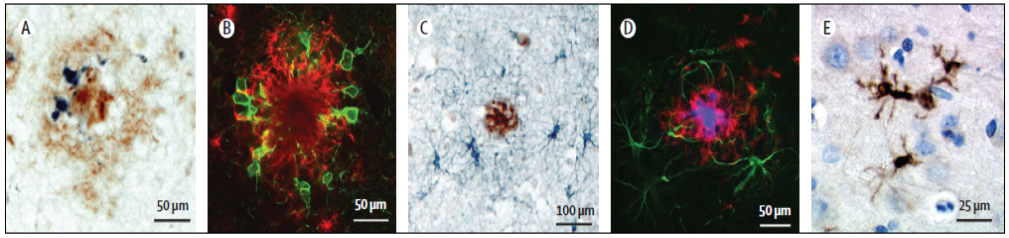
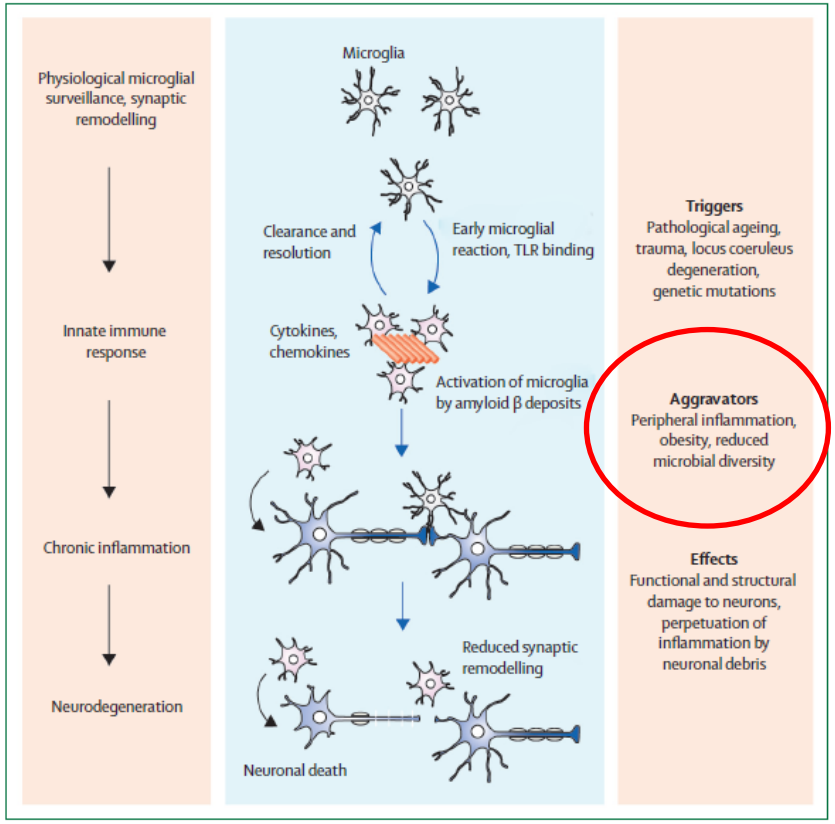
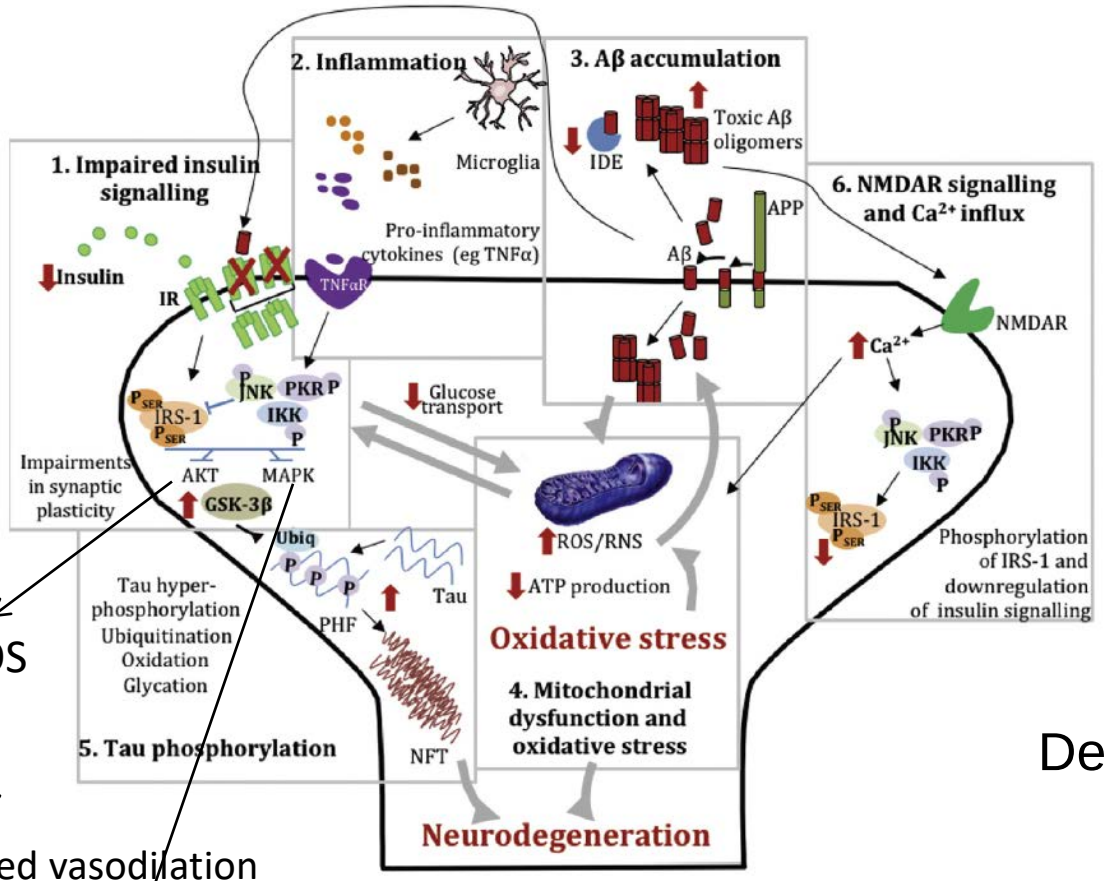


Figure 2: **Changes in microglia and astroglia in Alzheimer's disease**
Microglia and astroglia are key players in the inflammatory response: changes in microglia and astroglia are evident in the post-mortem brains of patients with Alzheimer's disease and in animal models of the disorder. (A) CD11b-positive microglia (blue) within an amyloid β (Aβ) deposit (brown) in the parietal cortex of a brain section from a patient with Alzheimer's disease. (B) Activated, IBA1-positive microglia (green) at an Aβ plaque site (red) in a brain section from an APP/PS1 transgenic mouse. (C) GFAP-positive astrocytes (blue) surround the site of Aβ deposition (brown) in the parietal cortex of a brain section from a patient with Alzheimer's disease. (D) GFAP-positive astrocytes (green) at an Aβ plaque site (red) in a brain section from an APP/PS1 transgenic mouse. (E) Interleukin-1β-positive microglia (brown) in the frontal cortex of a brain section from a patient with Alzheimer's disease.

Physiological functions of microglia, (tissue surveillance and synaptic remodelling), are compromised when microglia sense pathological amyloid β accumulations. **Triggers and aggravators** promote sustained exposure and immune activation, (cytokines) perpetuation of chronic neuroinflammation (RAGE), and eventually NDG



IR reduces cerebral blood flow: vasoconstriction



eNOS

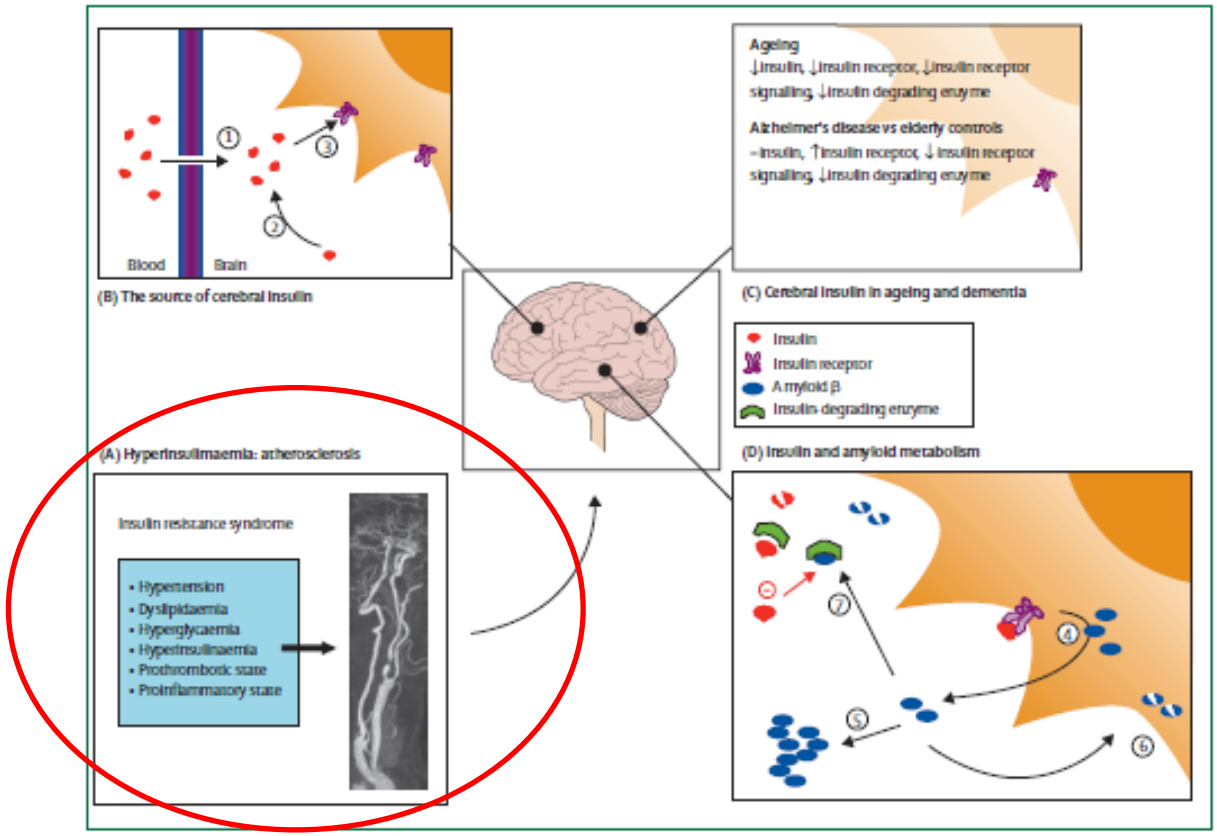
↓

Reduced vasodilation

Relative increase in ET ⟶ Increased vasoconstriction

Decreased RBF in AD

IR reduces cerebral blood flow: atherosclerosis



Biessels, 2006

Hyperinsulinaemia, in the context of IR, is a risk factor for artherosclerosis (A). Insulin is transported actively across the BBB (1), may be produced locally in the brain (2), and via IRs (3)—modulates food-intake and energy homeostasis (B). Ageing is associated with changes in insulin and its receptor in the brain, and these may be even more pronounced in AD(C). Insulin also affects amyloid metabolism (D): it stimulates the secretion of amyloid (4) into the extracellular space where it can aggregate with other proteins to form senile plaques (5). Alternatively, excessive amyloid can be cleared through endocytosis (6), or through direct extracellular proteolytic degradation by insulin-degrading enzyme IDE (7).

Diabetes and Alzheimer's disease
Outline

- Epidemiology and shared genetic factors
- Insulin signaling in the brain
- Insulin resistance (IR) and glycaemic control: impact on NDG
- Treatment: current evidence
- Future perspectives

Intranasal insulin improves memory function: animals

Subjects	Intranasal insulin duration/dose	Main result	References
S.D. rats—streptozotocin induced AD model	5 IU for 6 days	Insulin administration significantly reduced the Aβ levels without altering peripheral glucose levels	Subramanian and John, 2012
Streptozotocin induced-rat model of type 2 diabetes	2U insulin intranasally/4 weeks 6.7 U/kg (s.c.)/4 weeks	Decreased Akt activation and increased tau phosphorylation and GSK-3β activation was found in T2D rat brains. Intranasal insulin treatment normalized Akt and GSK-3β and reduced tau phosphorylation in diabetic rats s.c. insulin had minimal effect of tau phosphorylation and GSK-3β	Yang et al., 2013
3 × Tg-AD mice	1.75 U/7 days	Intranasal insulin administration restored insulin signaling, ↑ synaptic proteins, and ↓ Aβ40 level and microglia activation in the brains of 3 × Tg-AD mice. Glucose transporters and tau-phosphorylation is unchanged	Chen et al., 2014c
3 × Tg-AD mice	1.75 U/7 days Propofol 250 mg/kg (i.p.)	Insulin treatment attenuated propofol-induced hyperphosphorylation of tau, promoted brain insulin signaling. Resulted in down-regulation of several tau protein kinases, including cyclin-dependent protein kinase 5, calcium/calmodulin-dependent protein kinase II, and c-JunN-terminal kinase and up-regulation of protein phosphatase 2A	Chen et al., 2014b

Experimental Neurology 261 (2014) 610–619

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Regular Article

Intranasal insulin restores insulin signaling, increases synaptic proteins, and reduces Aβ level and microglia activation in the brains of 3xTg-AD mice

Yanxing Chen [a,b,1], Yang Zhao [a,c,1], Chun-ling Dai [a], Zhihou Liang [d], Xiaoqin Run [e], Khalid Iqbal [a], Fei Liu [a], Cheng-Xin Gong [a,*]

Daily intranasal administration of insulin for 7 days

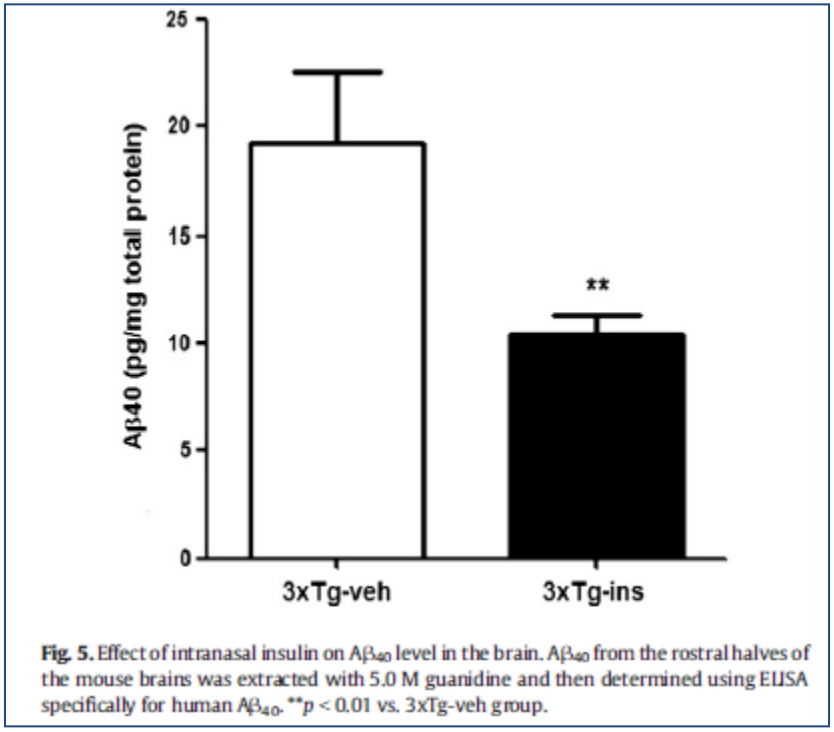


Fig. 5. Effect of intranasal insulin on $A\beta_{40}$ level in the brain. $A\beta_{40}$ from the rostral halves of the mouse brains was extracted with 5.0 M guanidine and then determined using ELISA specifically for human $A\beta_{40}$. $^{**}p < 0.01$ vs. 3xTg-veh group.

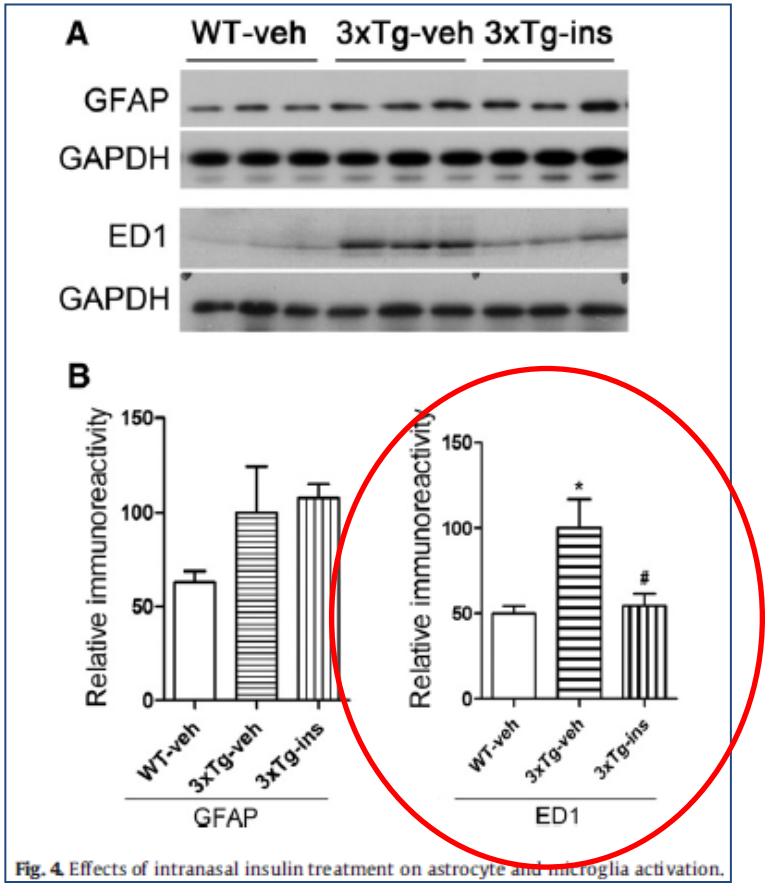
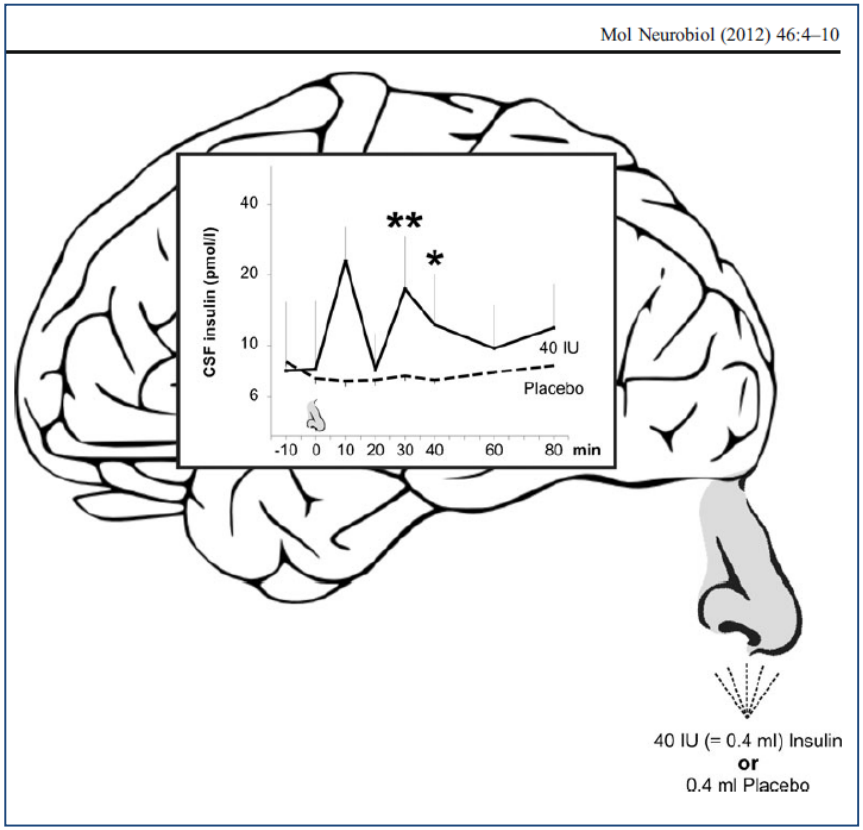


Fig. 4. Effects of intranasal insulin treatment on astrocyte and microglia activation.

Intranasal insulin improves memory function: humans

Subjects	Intranasal insulin duration/dose	Main result	References
Healthy humans	4 × 40 IU/day, for 8 weeks	Intranasal intake of insulin enhanced long-term declarative memory and positively affected mood in humans without causing systemic side effects like hypoglycaemia.	Benedict et al., 2004
Healthy humans	4 × 40 IU/day, for 8 weeks; insulin and rapid-acting insulin analog insulin aspart	Declarative memory was improved in insulin and insulin aspart groups compared to placebo group without altering glucose levels. Insulin aspart treated subjects performed even better that those of insulin treated group	Benedict et al., 2007
Healthy humans	Single dose of regular human insulin 160 IU	Hippocampus-dependant memory and working memory were improved in women where as men did not benefit from acute insulin treatment	Benedict et al., 2008; Krug et al., 2010
MCI and mild AD patients	20 or 40 IU of insulin acute treatment	Acute intranasal insulin administration improved verbal memory in AD and MCI subjects without the APOE- ε4 allele	Reger et al., 2006
MCI and AD patients	10, 20, 40, or 60 IU for 5 days	10, 20, and 40 IU of insulin improved declarative memory only in APOE-ε4 negative patients Memory facilitation generally peaked at the 20 IU dose ↑ Aβ42 levels for memory-impaired adults from saline to 10 IU regardless of APOE-ε4 status Intranasal insulin did not affect peripheral glucose or insulin levels	Reger et al., 2008a
MCI and AD patients	20 IU BID intranasal insulin treatment for 21 days	Insulin-treated subjects retained more verbal information and improved attention and functional status Insulin treatment raised fasting plasma $A\beta_{40}/A\beta_{42}$ ratio	Reger et al., 2008b
MCI and mild to moderate AD patients	20 or 40 IU for 4 months	Treatment with 20 IU of insulin improved delayed memory Both dosages preserved caregiver-rated functional ability and general cognition Unchanged $A\beta_{42}$ and tau levels after insulin treatment	Craft et al., 2012
AD patients with ApoE4 allels	Rapid acting insulin	Rapid acting insulin failed to have an acute impact on cognition in ApoE4 carriers with AD	Rosenbloom et al., 2014
MCI and mild AD patients	20 or 40 IU of insulin detemir for 21 days	High dose (40 IU) improved visuospatial and verbal working memory for all participant High dose improved memory for adults with MCI and AD who were APOE-ε4 positive patients APOE-ε4 carriers taking high dose also improved peripheral insulin resistance APOE-ε4 negative patients taking high dose experiences increased peripheral insulin resistance	Claxton et al., 2015

Intranasal insulin effects: CSF concentrations



Concentrations of insulin in cerebrospinal fluid (CSF) before and within 80 min after i.n. administration of human insulin (40 IU; solid lines) and placebo (dashed lines) with a nasal spray atomizer.

- **Rapid delivery** of insulin to CNS (bypassing BBB) via bulk flow along olfactory and trigeminal perivascular channels, and **slower delivery** via olfactory bulb axonal transports
- **No invasive administration**
- **Avoidance of adverse side effects**
- **Relatively high bioavailability**
- **Avoidance of first- pass effect**

Benedict et al, 2004 and 2012

Intranasal insulin effetcs: a memory enhancer?

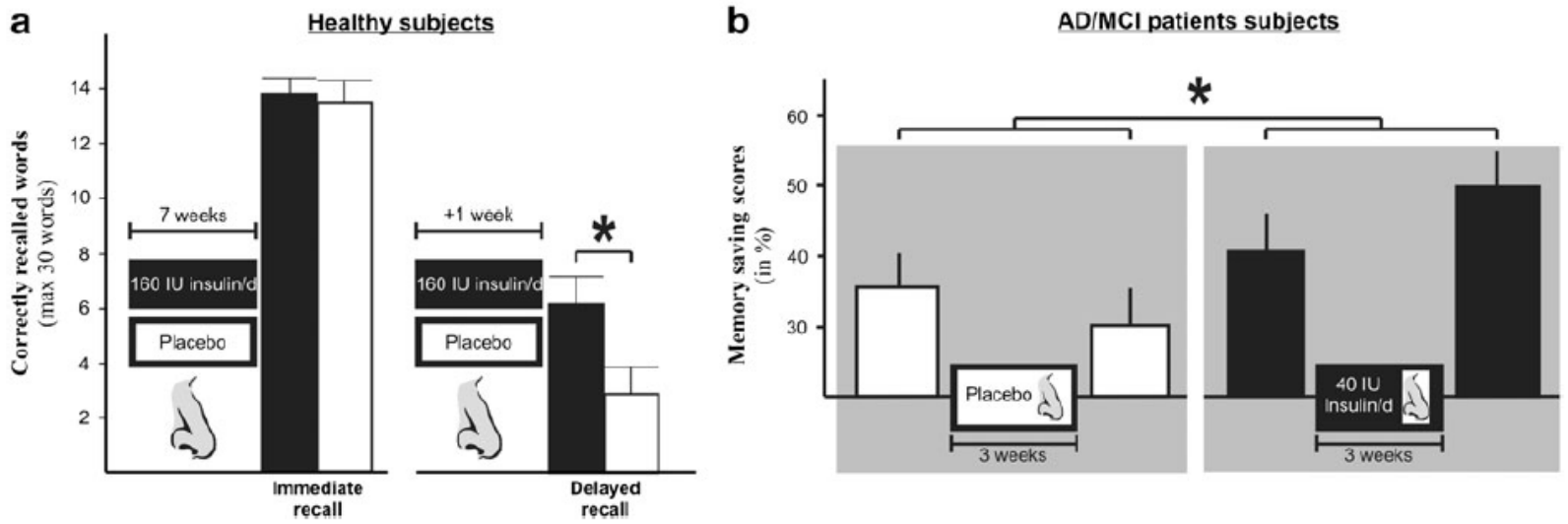


Fig. 2 a Intranasal insulin improves memory in humans [data from [32]]. Immediate and delayed word list recall in healthy humans following 7 (immediate recall) and 8 weeks (delayed recall) of intranasal administration of regular human insulin (160 IU/day, *black bars*, $n=19$) and placebo (*white bars*, $n=19$), respectively. Immediate recall was tested 3 min after the auditory presentation of 30 nouns (e.g., car, tree, and chocolate). Delayed recall of the same list of nouns was tested after one more week of treatment. Baseline adjusted means ± SEM are indicated. b Intranasal insulin improves memory in patients with MCI or in the early stages of AD [data from [55]]. Mean memory saving scores (±SEM) in patients with early stage Alzheimer's disease and mild cognitive impairment (MCI) at baseline (day 0) and after 21 days of treatment with placebo ($n=12$) and insulin (2×20 IU/day; $n=13$), respectively. Insulin-treated patients showed increased memory savings over the 21-day period relative to placebo. *P value smaller than 0.05

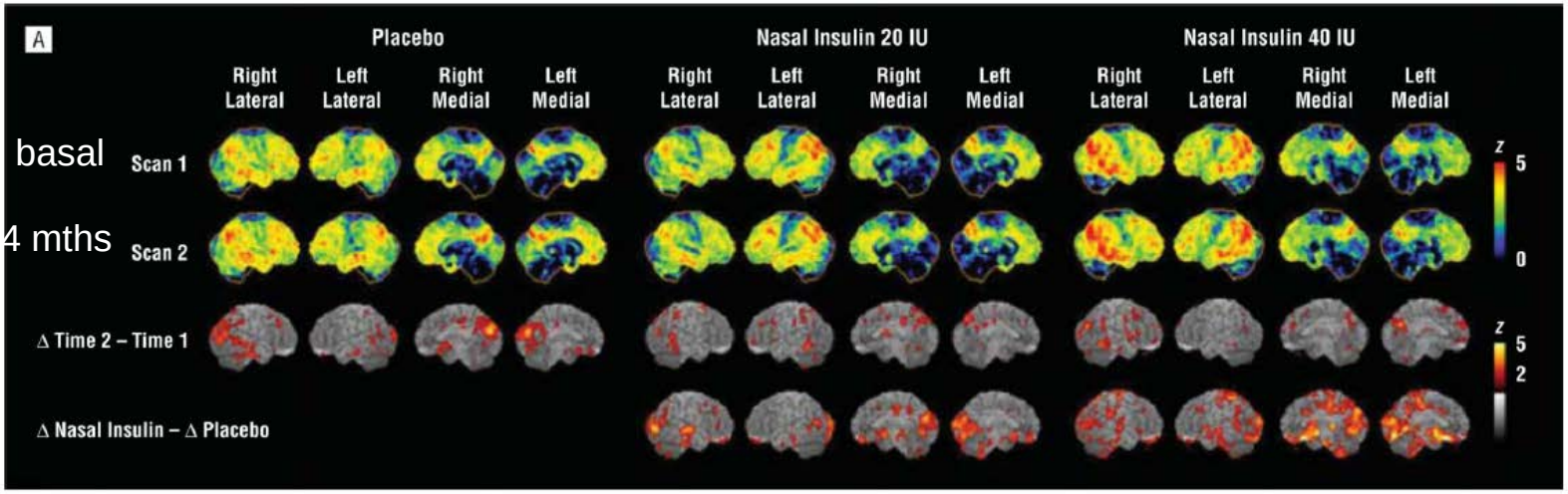
Rapidly absorbed insulin aspart, and long-acting insulin detemir even stronger effects

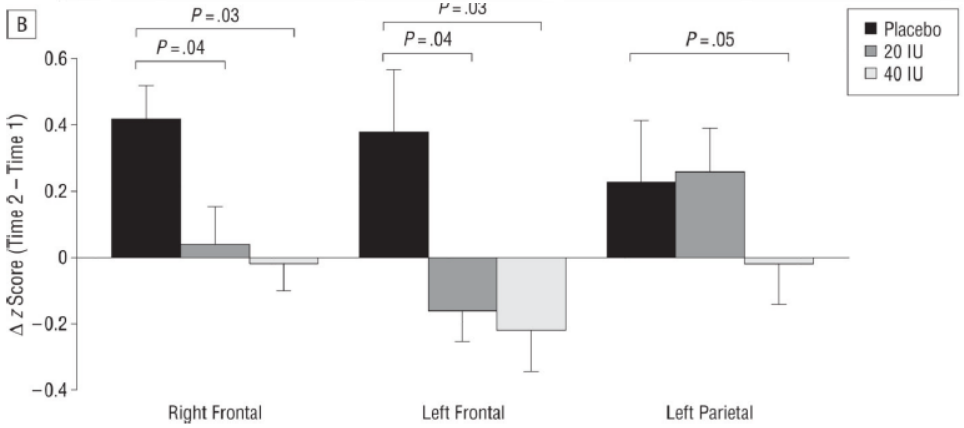
Benedict et al, 2004, 2007 and and 2012; Reger et al. 2008, Claxton 2015

Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment

Suzanne Craft, PhD, Laura D. Baker, PhD, Thomas J. Montine, MD, PhD, Satoshi Minoshima, MD, PhD, G. Stennis Watson, PhD, Amy Claxton, PhD, Matthew Arbuckle, BA, Maureen Callaghan, MD, Elaine Tsai, MD, Stephen R. Plymate, MD, Pattie S. Green, PhD, James Leverenz, MD, Donna Cross, PhD, and Brooke Gerton, MD

Arch Neurol. 2012 January ; 69(1): 29–38.





4-month treatment

A, Areas of hypometabolism at baseline (scan 1) and month 4 (scan 2), along with changes in hypometabolism (Δ time 2 − time 1) The red and orange colors indicate areas of greater hypometabolism from time 1 to time 2, and from placebo group to insulin groups. B, Change in mean regional *z* scores. Reduced activity over time for the placebo group compared with the 40-IU dose insulin group.

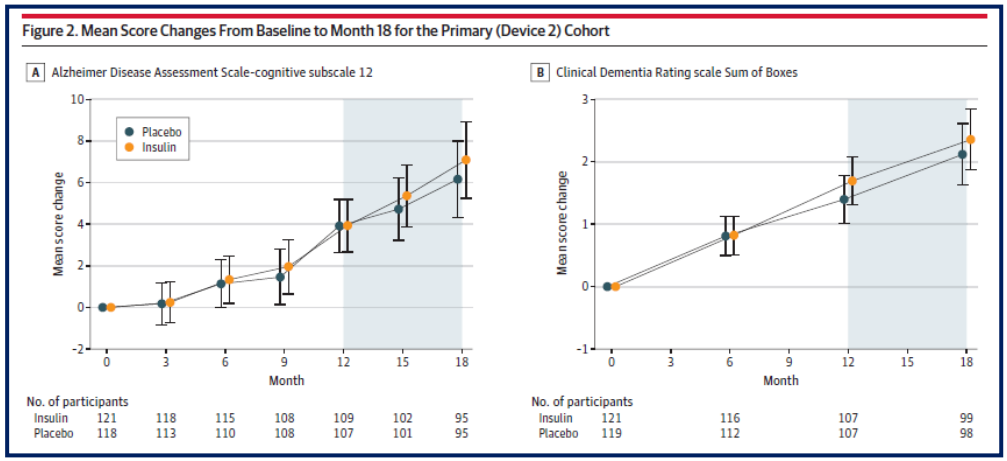
JAMA Neurology | Original Investigation

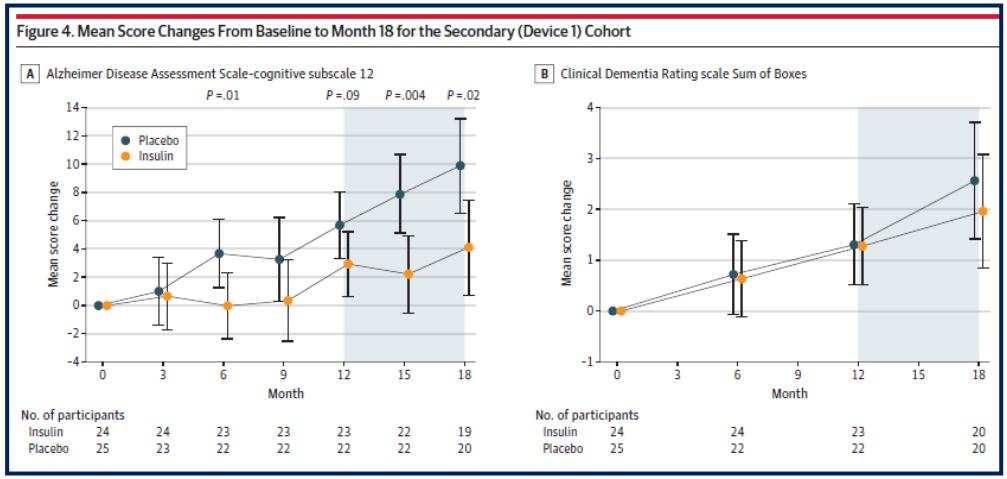
Safety, Efficacy, and Feasibility of Intranasal Insulin for the Treatment of Mild Cognitive Impairment and Alzheimer Disease Dementia

A Randomized Clinical Trial

SNIFF STUDY 2020

Suzanne Craft, PhD; Rema Raman, PhD; Tiffany W. Chow, MD; Michael S. Rafii, MD; Chung-Kai Sun, MS; Robert A. Rissman, PhD; Michael C. Donohue, PhD; James B. Brewer, MD, PhD; Cecily Jenkins, PhD; Kelly Harless, BS; Devon Gessert, BS; Paul S. Aisen, MD





Intranasal **40 IU** insulin (Humulin-RU-100; Lilly) or placebo, daily **for 12 months** (blinded phase) followed by a 6-month open-label extension (49 and later further 240 pts).

No benefits of for any outcome (clinical / biochemical /MR imaging).

Further investigation is needed with intranasal delivery **devices** increasing insulin levels in the CNS. The indirectly measured access is an **insufficient standard** and the access of insulin to the CNS needs to be directly shown, i.e measuring acute increases in CSF, or alternatively by administering labelled insulin and measuring brain distribution with PET.

Insulin sensitizers

Metformin

- acts via AMPactivated kinase (AMPK) in liver and other tissues, increasing insulin sensitivity.

- crosses the BBB (Labuzek et al., 2010; Nath et al., 2009)

- reduces phosphorylation of tau (Gupta et al., 2011) and promotes dephosphorylation of tau (Kickstein et al., 2010).

- in vivo attenuates cognitive impairment and AD-like pathology in obese, leptin resistant mice (Li et al.,2012).

- **After pilot studies in subjects in non-diabetic MCI (NCT00620191) and AD (NCT01965756), with unclear results, a phase 2 trial for patients with MCI and AD is currently underway (NCT04098666).**

Insulin sensitizers

Thiazolinediones

- Increase insulin sensitivity by activating gene expression of the glucose transporter (GLUT-4) via PPAR-γ receptor

- inhibit inflammatory gene expression, reduce Aβ deposition and exhibit other neuroprotective effects (Landreth, 2007; Neumann , 2008 Jiang , 2008, Kummer, 2014).

- **Rosiglitazone** (4 mg/day) for 6 months in mild AD or MCI showed improvement in memory and modulation of plasma Aβ levels (Watson et al., 2005) but a larger phase 3 trial failed (Harrington et al., 2011)

- **Pioglitazone i**n mild AD with type 2 diabetes improved cognition and cerebral blood flow (Sato et al., 2011). Longer (18 month) treatment in non-diabetic AD patients failed (Geldmacher et al., 2011). The TOMMORROW Study (NCT01931566), a phase 3 trial in 3500 cognitively normal subjects based on their APOE genotype (to delay MCI) was terminated due to lack of efficacy.

GLP-1 receptor agonists

- GLP-1 (glucagon-like peptide 1) receptor agonists stimulate insulin secretion and increase peripheral insulin sensitivity.

- In the brain, GLP-1 receptor agonists increase cell proliferation and growth, protect against excitotoxic cell death and apoptosis, increase hippocampal neuronal density, protect against insulin receptor loss and synaptic dysfunction, reduce hyperphosphorylated tau.

- Subcutaneous daily administration of **liraglutide i**n 18 patients with AD for 26 weeks prevented the decline of brain glucose metabolism compared with placebo but had no effect on cognition or Aβ burden.

- **An ongoing phase 2, randomised, placebo-controlled clinical trial of 12 months of daily liraglutide treatment in patients with AD is examining treatment effects on FDG-PET (primary outcome), and cognitive performance (NCT01843075).**

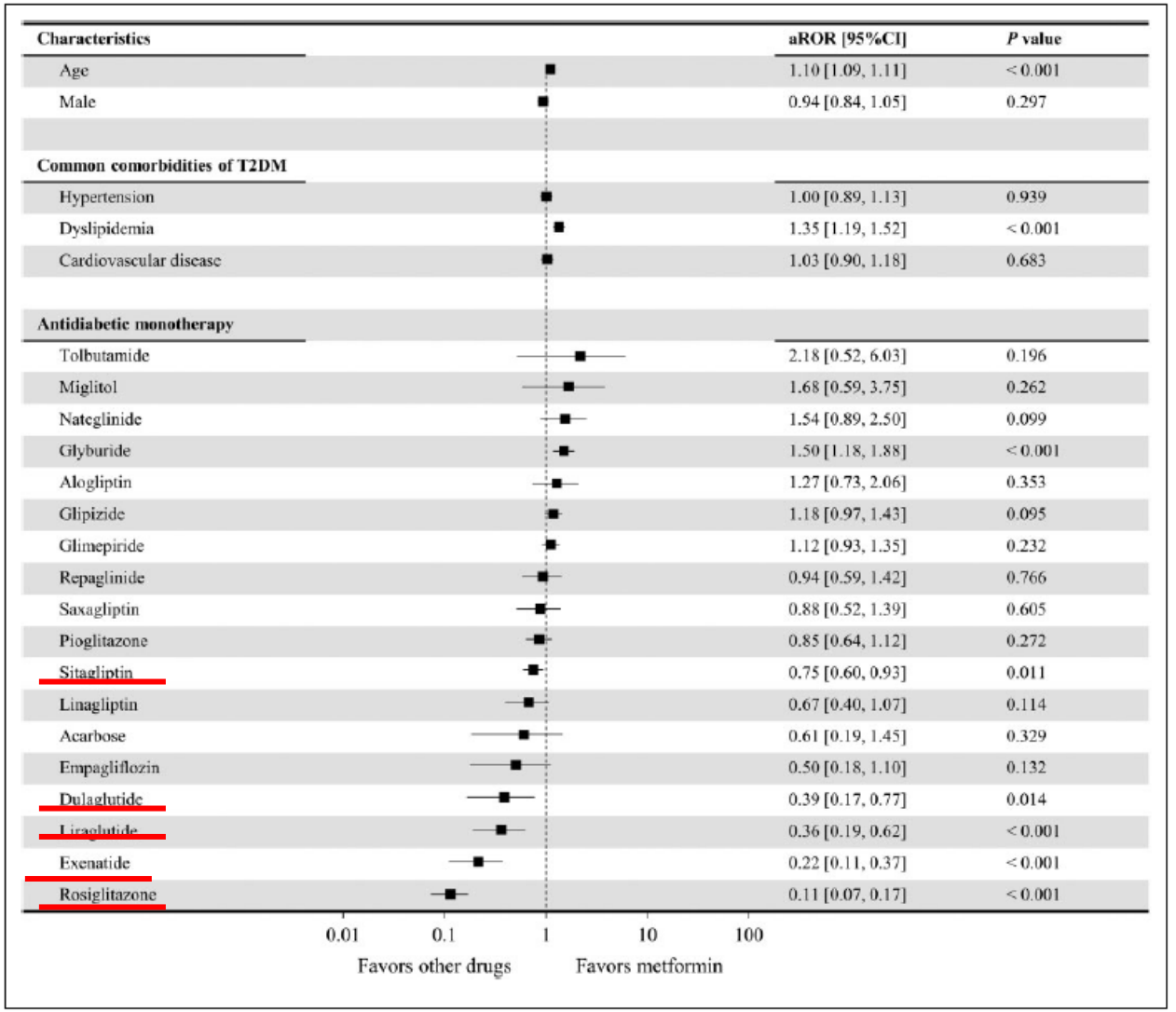
Meta-analysis of pro-cognitive effects of antidiabetic agents vs placebo for AD/MCI

	Comparisons				Heterogeneity test		
Subgroup	k[a]	Z	*P*-value	Pooled SMD [95%CI] (random-effects model)	Q	*P*-value	I^2, %
Overall	29	4.85	<.001	−0.49 [−0.69, −0.29]	260.41	<.001	89.2
Cognitive measurements							
ADAS-Cog	17	1.98	.048	−0.08 [−0.15, −0.001]	21.62	.156	26.0
MMSE	4	4.84	<.001	−3.30 [−4.63, 1.96]	31.3	<.001	90.4
WMS-IV	1	0.54	.589	−0.19 [−0.87, 0.50]	.		.
Memory scores	7	1.62	.106	−0.45 [−1.00, 0.10]	23.17	.001	74.1
Antidiabetic agents							
Intranasal insulin	9	2.75	.006	−0.97 [−1.66, −0.27]	72.39	<.001	88.9
20 IU	4	1.29	.198	−0.71 [−1.80, 0.37]	31.84	<.001	90.6
40 IU	5	2.29	.022	−1.19 [−2.21, −0.17]	38.56	<.001	89.6
Pioglitazone	5	1.87	.062	−0.47 [−0.96,0.02]	10.55	.032	62.1
15 to 30 mg	3	3.38	.001	−0.82 [−1.29, −0.34]	2.8	.247	28.5
45 mg	2	0.24	.811	0.06 [−0.40, 0.51]	0	.957	0
Rosiglitazone	11	1.9	.057	0.06 [−0.12, 0.002]	4.86	.9	0
2 mg	4	1.75	.08	−0.08 [−1.67, 0.009]	2.85	.416	0
4 mg	2	0.3	.761	−0.04 [−0.29, 0.21]	1.02	.312	2.3
8 mg	5	0.9	.37	−0.04 [−0.13, 0.05]	0.61	.962	0
Metformin 1000 mg	1	0.87	.383	0.22 [−0.27, 0.71]	.	.	.
Sitagliptin 100 mg	1	7.92	<.001	−2.31 [−2.88, −1.74]	.	.	.
Liraglutide 1.8 mg	2	1.06	.291	−3.15 [−8.98, 2.69]	67.53	<.001	98.7

[a] k = number of comparisons. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; MMSE, the Mini Mental State Evaluation; WMS, Wechsler Memory Scale.

(Cao et al., 2018)

Risk of developing AD in T2DM patients on antidiabetic drugs compared to metformin



Characteristics	aROR [95%CI]	*P* value
Age	1.10 [1.09, 1.11]	< 0.001
Male	0.94 [0.84, 1.05]	0.297
Common comorbidities of T2DM		
Hypertension	1.00 [0.89, 1.13]	0.939
Dyslipidemia	1.35 [1.19, 1.52]	< 0.001
Cardiovascular disease	1.03 [0.90, 1.18]	0.683
Antidiabetic monotherapy		
Tolbutamide	2.18 [0.52, 6.03]	0.196
Miglitol	1.68 [0.59, 3.75]	0.262
Nateglinide	1.54 [0.89, 2.50]	0.099
Glyburide	1.50 [1.18, 1.88]	< 0.001
Alogliptin	1.27 [0.73, 2.06]	0.353
Glipizide	1.18 [0.97, 1.43]	0.095
Glimepiride	1.12 [0.93, 1.35]	0.232
Repaglinide	0.94 [0.59, 1.42]	0.766
Saxagliptin	0.88 [0.52, 1.39]	0.605
Pioglitazone	0.85 [0.64, 1.12]	0.272
Sitagliptin	0.75 [0.60, 0.93]	0.011
Linagliptin	0.67 [0.40, 1.07]	0.114
Acarbose	0.61 [0.19, 1.45]	0.329
Empagliflozin	0.50 [0.18, 1.10]	0.132
Dulaglutide	0.39 [0.17, 0.77]	0.014
Liraglutide	0.36 [0.19, 0.62]	< 0.001
Exenatide	0.22 [0.11, 0.37]	< 0.001
Rosiglitazone	0.11 [0.07, 0.17]	< 0.001

Akimoto et al., 2020

66.085 pts studied

GLP-1 receptor agonists (exenatide, liraglutide, dutaglutide) and **rosiglitazone** reduce the risk of AD

Diabetes and Alzheimer's disease
Outline

- Epidemiology and shared genetic factors
- Insulin signaling in the brain
- Insulin resistance (IR) and glycaemic control: impact on NDG
- Treatment: current evidence
- Future perspectives

Neuroprotective Properties of Linagliptin

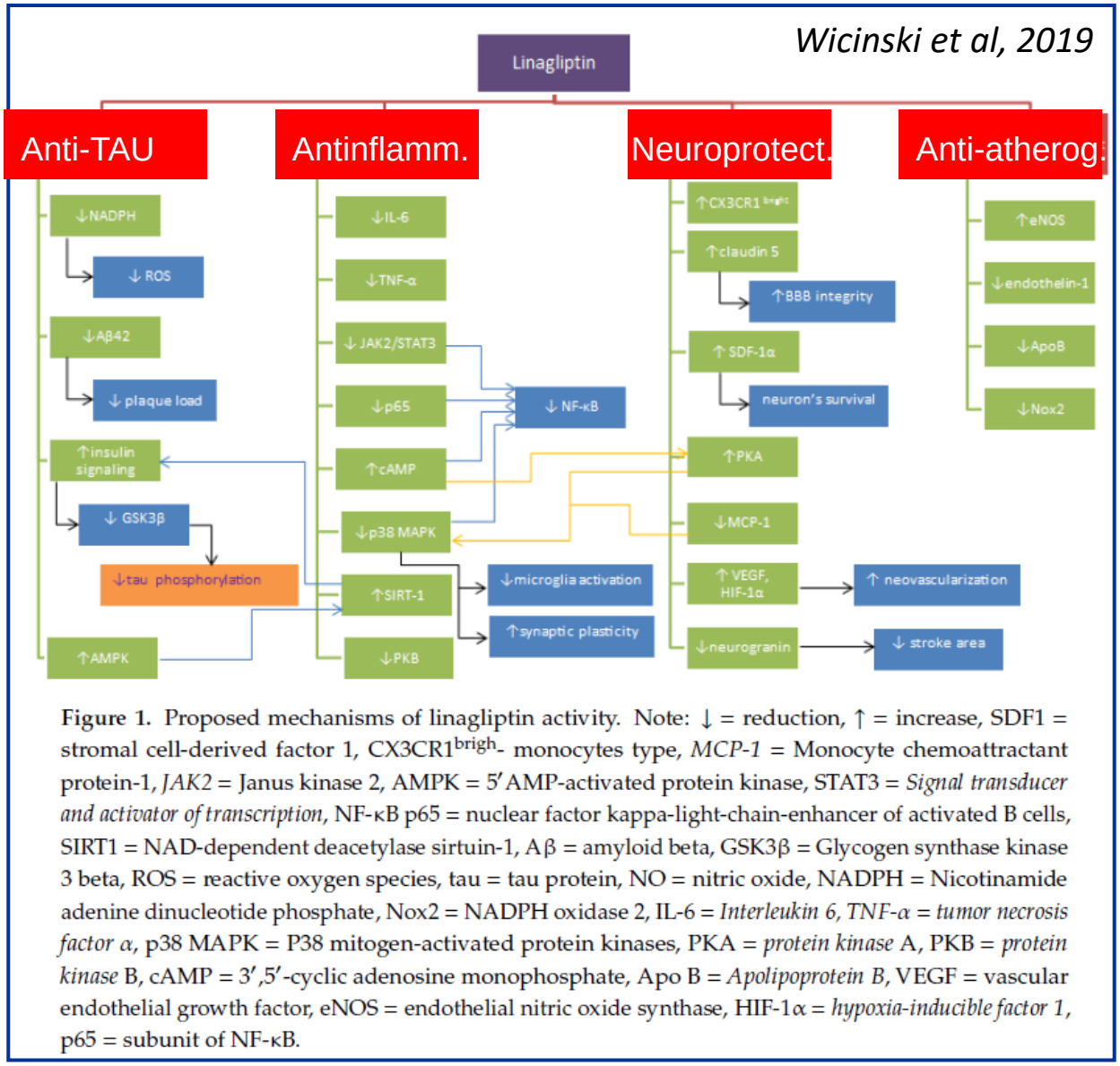
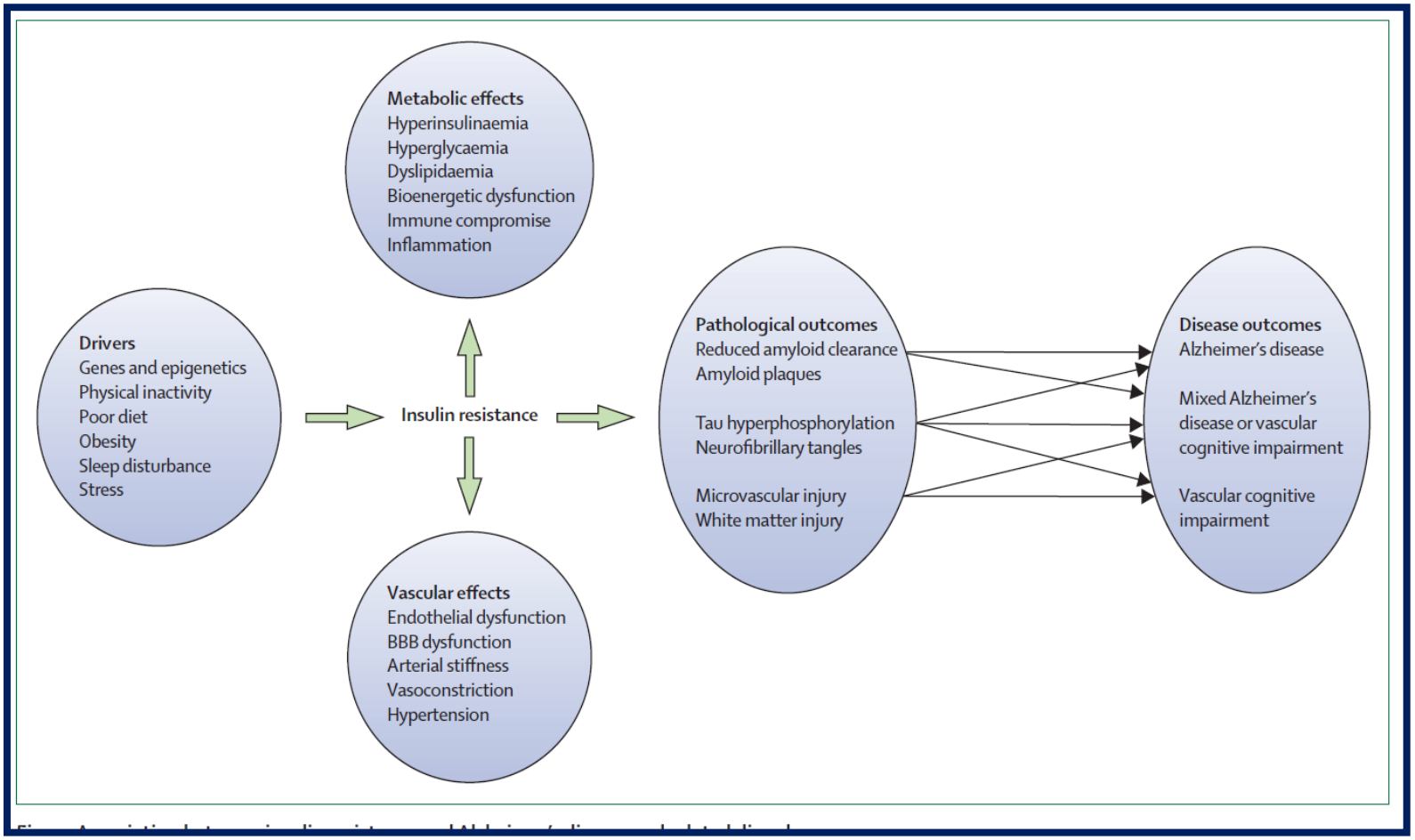


Figure 1. Proposed mechanisms of linagliptin activity. Note: ↓ = reduction, ↑ = increase, SDF1 = stromal cell-derived factor 1, CX3CR1^{brigh}- monocytes type, *MCP-1* = Monocyte chemoattractant protein-1, *JAK2* = Janus kinase 2, AMPK = 5′AMP-activated protein kinase, STAT3 = *Signal transducer and activator of transcription*, NF-κB p65 = nuclear factor kappa-light-chain-enhancer of activated B cells, SIRT1 = NAD-dependent deacetylase sirtuin-1, Aβ = amyloid beta, GSK3β = Glycogen synthase kinase 3 beta, ROS = reactive oxygen species, tau = tau protein, NO = nitric oxide, NADPH = Nicotinamide adenine dinucleotide phosphate, Nox2 = NADPH oxidase 2, IL-6 = *Interleukin 6*, *TNF-α* = *tumor necrosis factor α*, p38 MAPK = P38 mitogen-activated protein kinases, PKA = *protein kinase* A, PKB = *protein kinase* B, cAMP = 3′,5′-cyclic adenosine monophosphate, Apo B = *Apolipoprotein B*, VEGF = vascular endothelial growth factor, eNOS = endothelial nitric oxide synthase, HIF-1α = *hypoxia-inducible factor 1*, p65 = subunit of NF-κB.

Dipeptidyl peptidase 4 (DPP-4) inhibitor (decrease in glucagon and glucose)

IR, AD and related disorders



Too many variables interplaying, it is mandatory to be **earlier** and more **specific.**

Lancet Neurol 2020; 19: 758–66