

Convegno **SID-AMD Toscana**

Pisa, 10 Giugno 2023

Diabete e funzione cognitiva: la salvaguardia della salute complessiva della persona con diabete

Giuseppe Daniele

Dipartimento di Medicina Clinica e Sperimentale

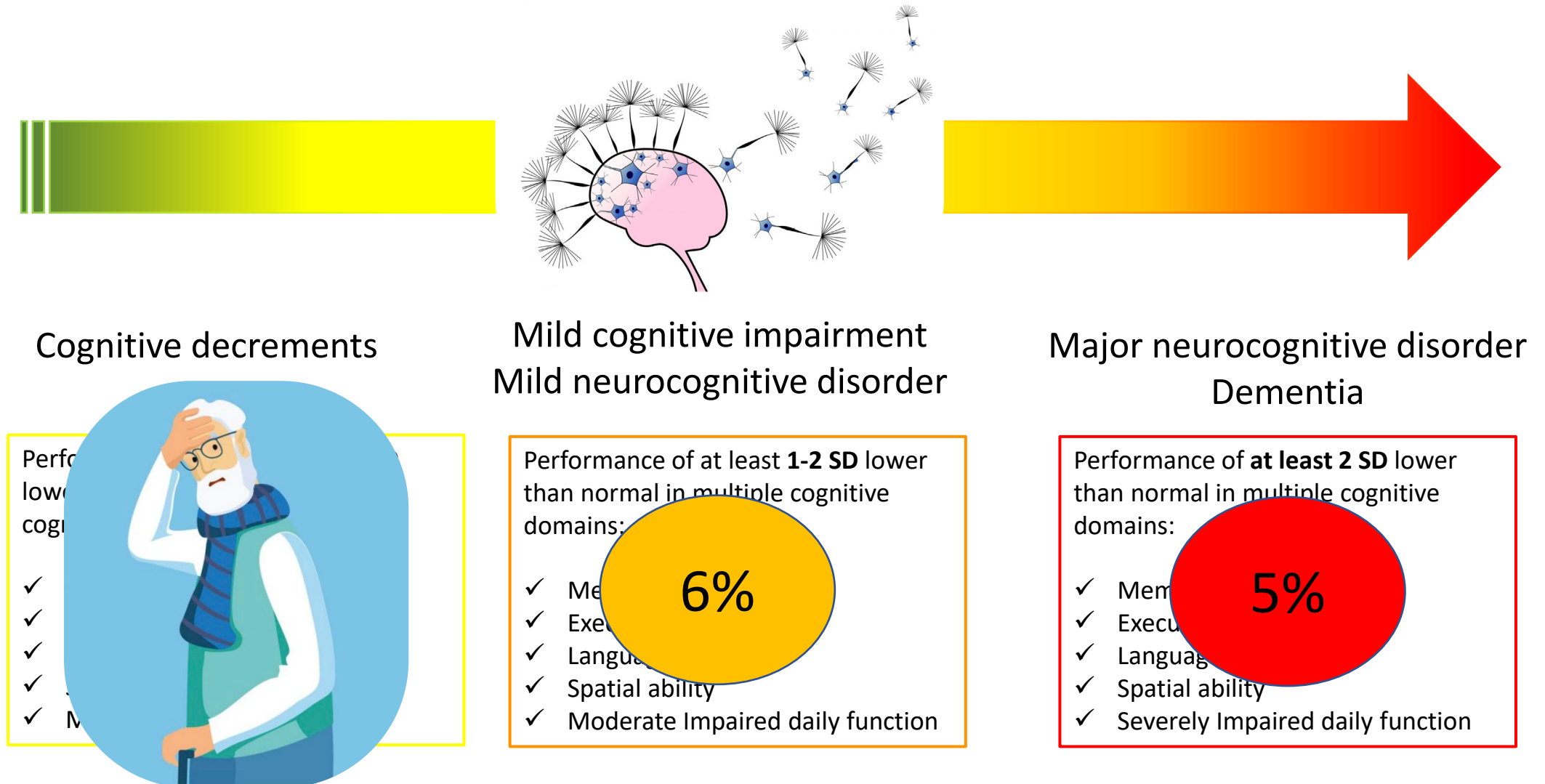
Università di Pisa



Conflitti di interesse

Nessun conflitto di interessi da dichiarare

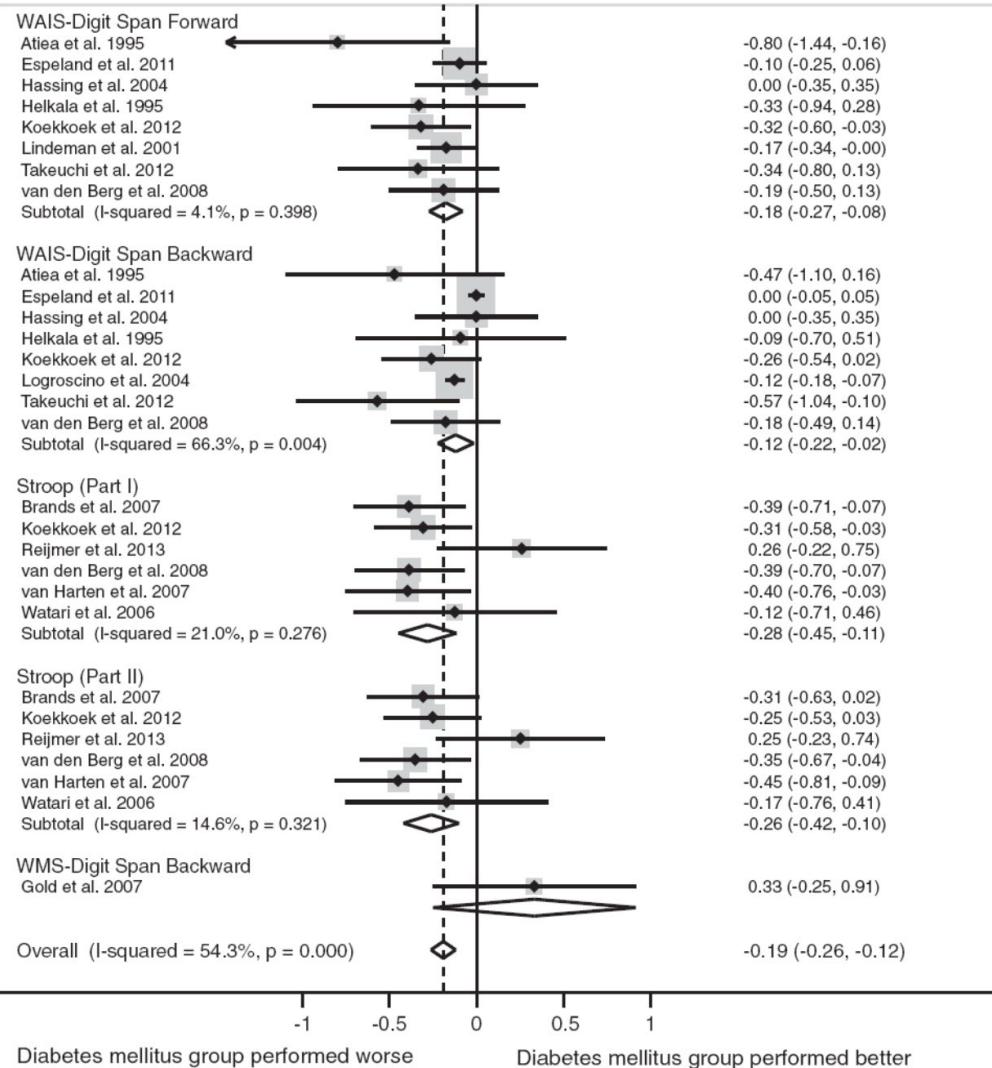
Diabetes and Cognitive Decline Spectrum



Magnitude of Cognitive Dysfunction in Type 2 Diabetes

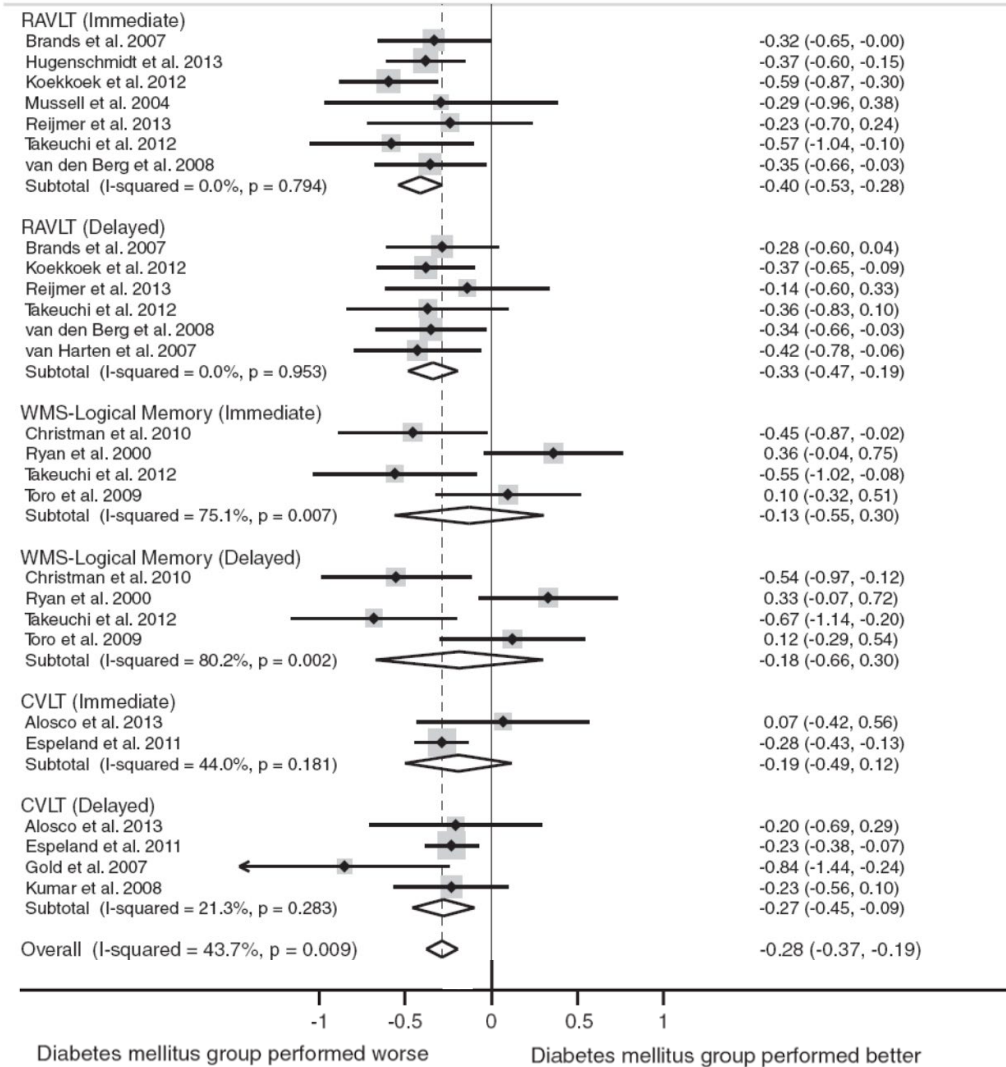
Attention/Concentration Tests

Effect Size (95% CI)



Verbal Memory Tests

Effect Size (95% CI)



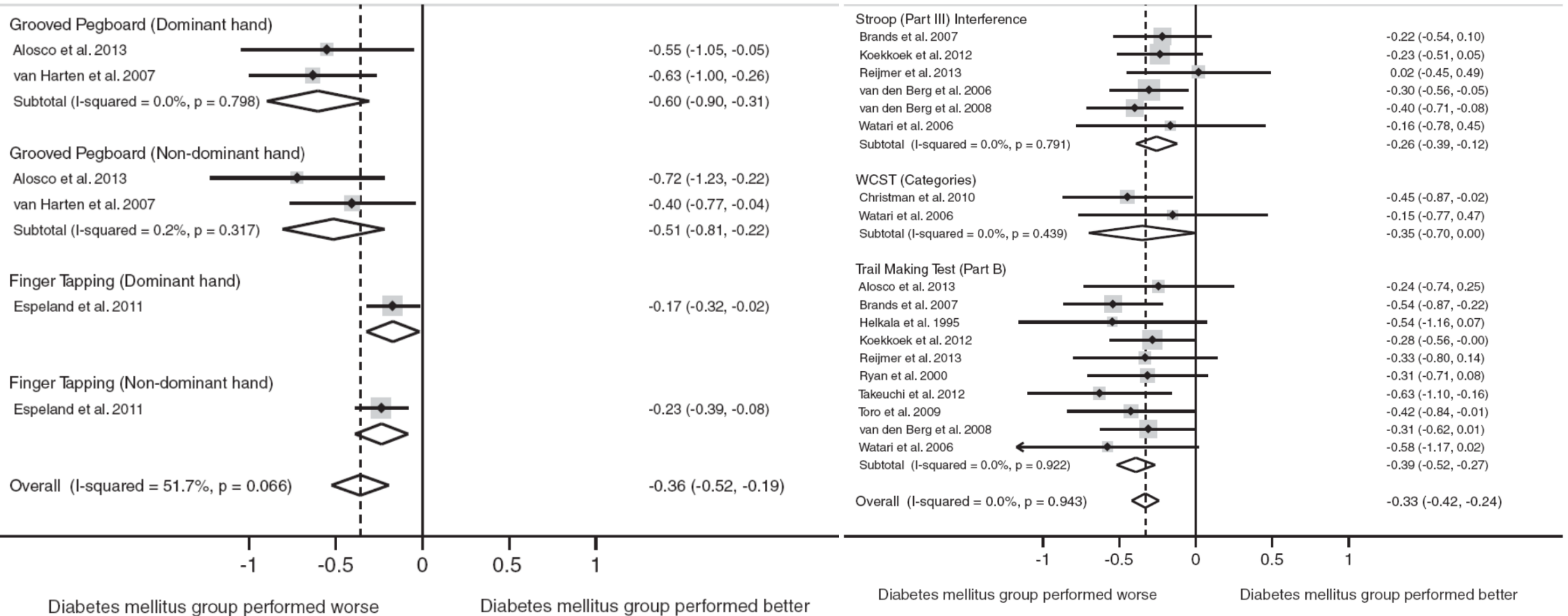
Magnitude of Cognitive Dysfunction in Type 2 Diabetes

Motor Function Tests

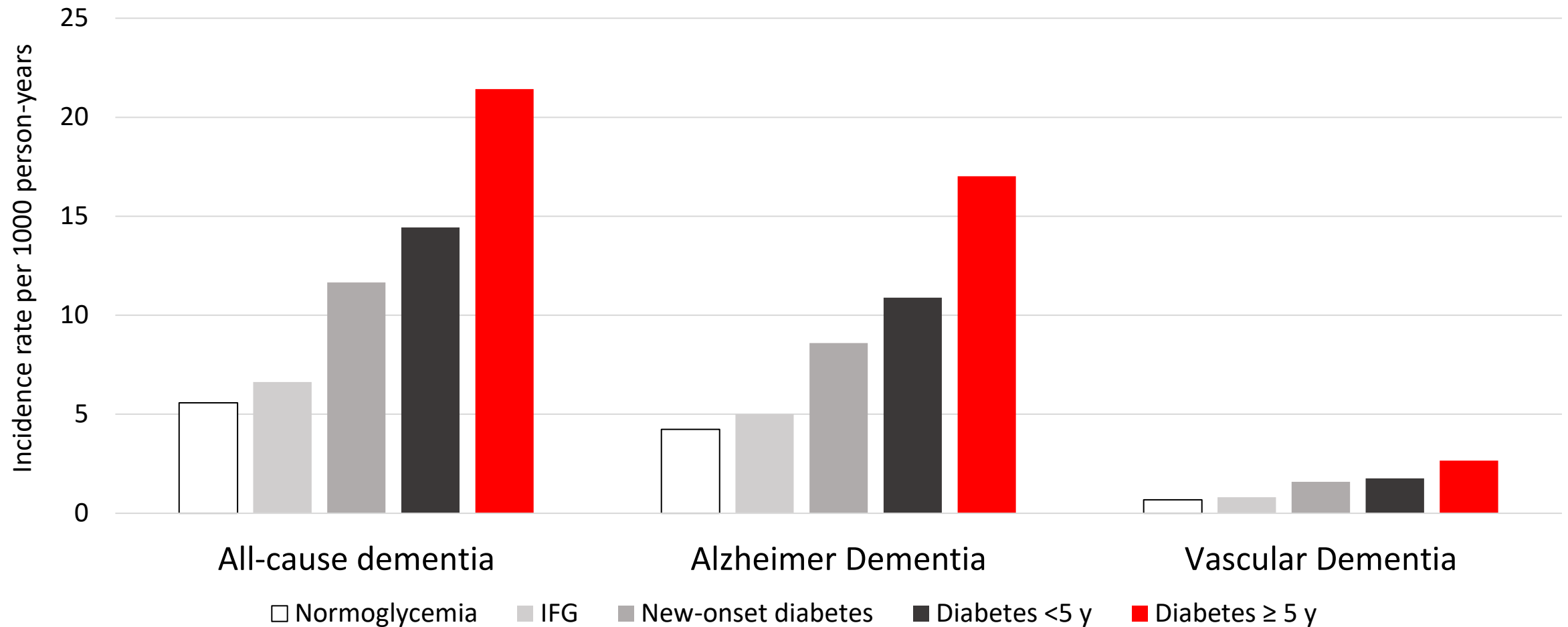
Effect Size (95% CI)

Executive Function Tests

Effect Size (95% CI)

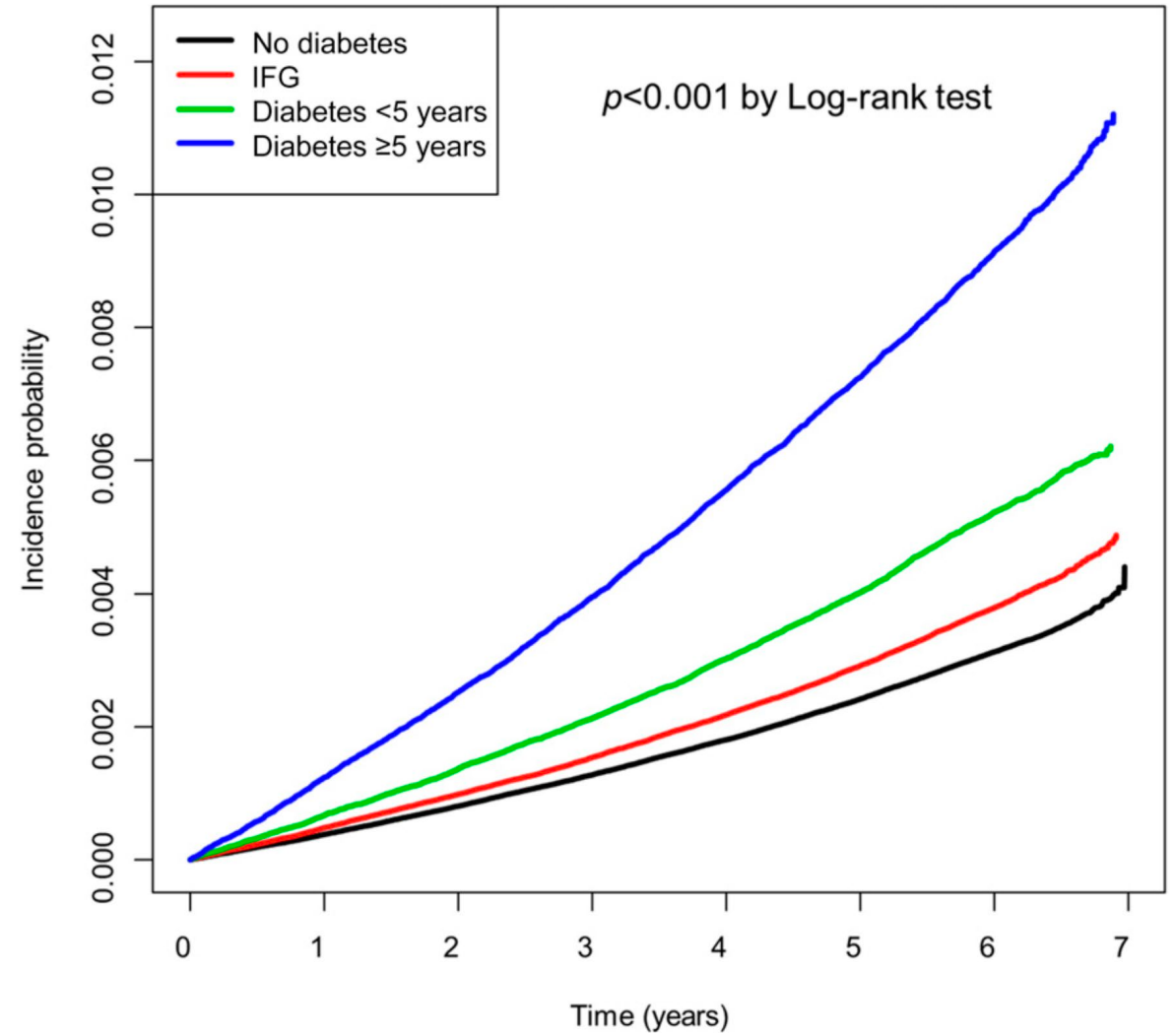
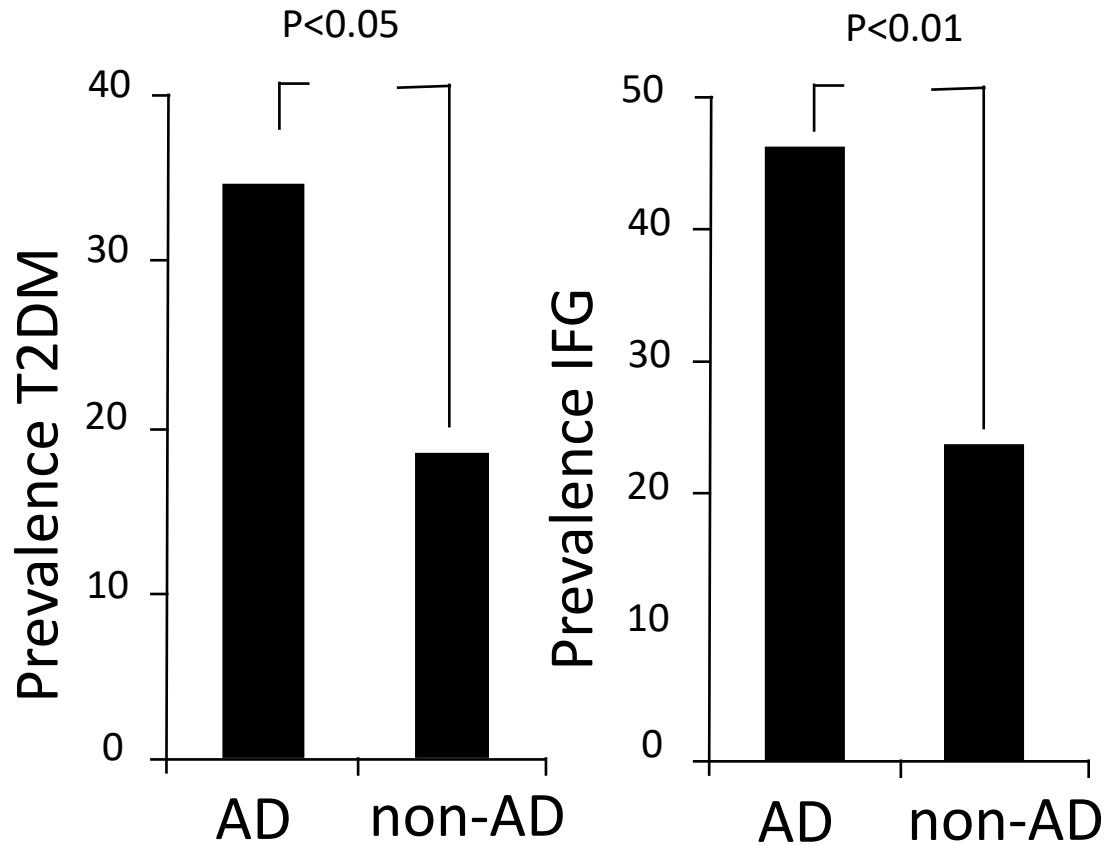


Incidence rates of dementia according to glycemic status and duration of diabetes

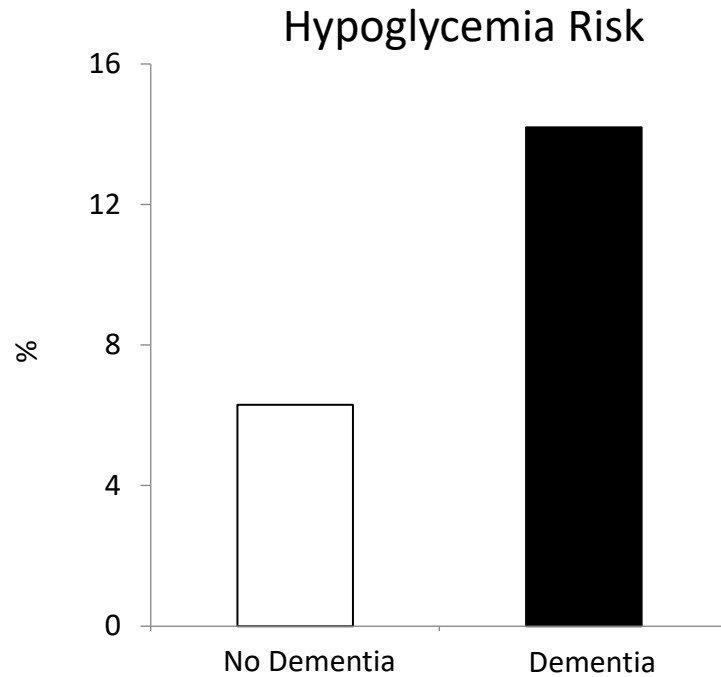


Model: adjusted for age, sex, smoking, drinking, exercise, BMI, hypertension and dyslipidemia

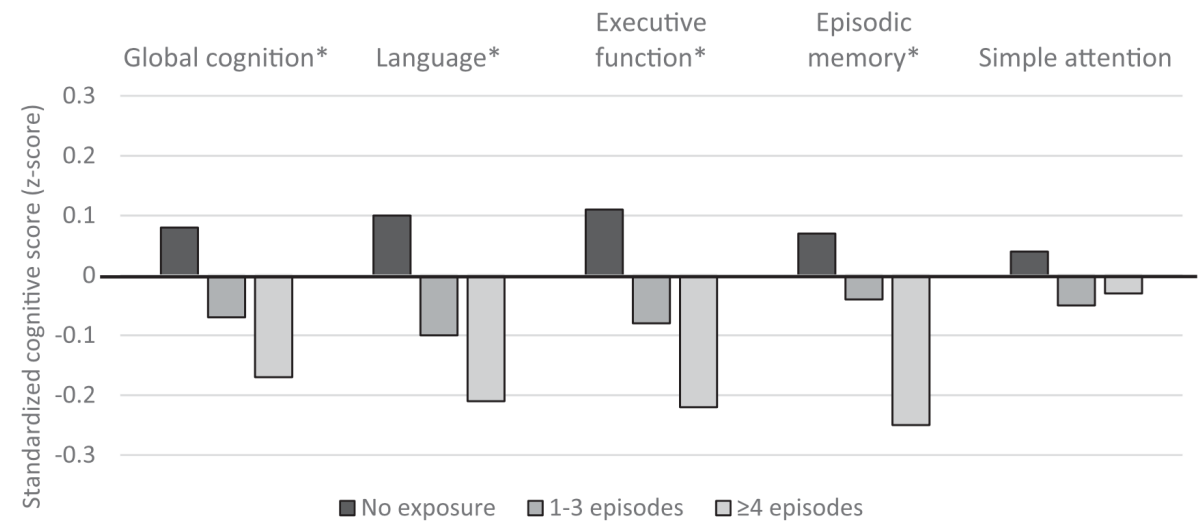
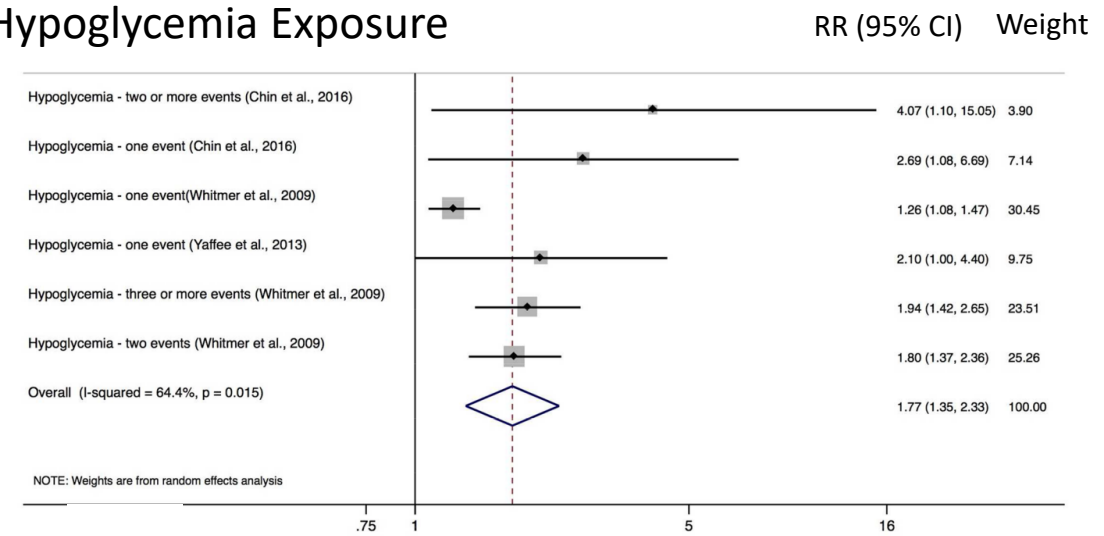
Metabolic and Neurodegenerative Diseases: a two-way connection



Cognitive Dysfunction, Dementia and Hypoglycemia



Hypoglycemia Exposure



The Effect of Cognitive Dysfunction on Diabetes Self-Care

Affected Behavior	Impact on Diabetes Self Care
Memory Loss	Forget to: ✓ Monitor Glucose ✓ Take medications ✓ Take insulin injections ✓ Eat on time ✓ Eat before exercise ✓ Attend clinic visits
Problem solving difficulty	Unable to integrate into practice new instructions Unable to recognize or treat hypoglycemia
Difficulty stopping old behavior and starting new behavior	Refuse any new therapy Errors when old routines are changed
Difficulty with mental flexibility	Feel anxious regarding “failing” the treatment plans Too much focus on diabetes management

	MMSE 0-23	MMSE 24-30	Adjusted odds Ratio (95% CI)	P
n	113	283		
Management of diabetes, n (%)				
<i>Patient solely responsible for self-medication</i>	49 (44)	242 (86)	7.14 (4.35,12.5)	<0.001
<i>Patient solely responsible for self-monitoring of blood and/or urine glucose</i>	67 (60)	247 (87)	3.70 (2.22,6.25)	<0.001
Use of Health/Social Service, n (%)				
<i>Hospitalized in the past years</i>	47 (42)	71 (25)	0.45 (0.28, 0.72)	0.001
<i>Help received with personal care</i>	49 (43)	57 (20)	0.43 (0.26, 0.70)	0.001
<i>Living in residential/nursing home</i>	20 (18)	6 (2)	0.16 (0.06, 0.42)	<0.001
Functional status (mean, SD)				
<i>Barthel ADL score</i>	15.6 (5.6)	18.9 (2.3)	1.22 (1.12, 1.32)	<0.001
<i>Extended ADL score</i>	9.6 (5.6)	15.4 (5.1)	1.16 (1.11, 1.20)	<0.001
<i>Diabetes Knowledge Questionnaire (mean)</i>	5.6 (5.6)	8.7 (3.5)	1.25 (1.15, 1.35)	<0.001

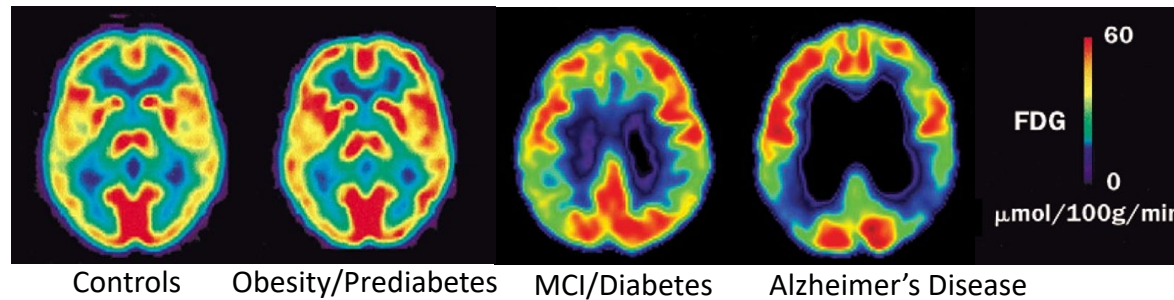
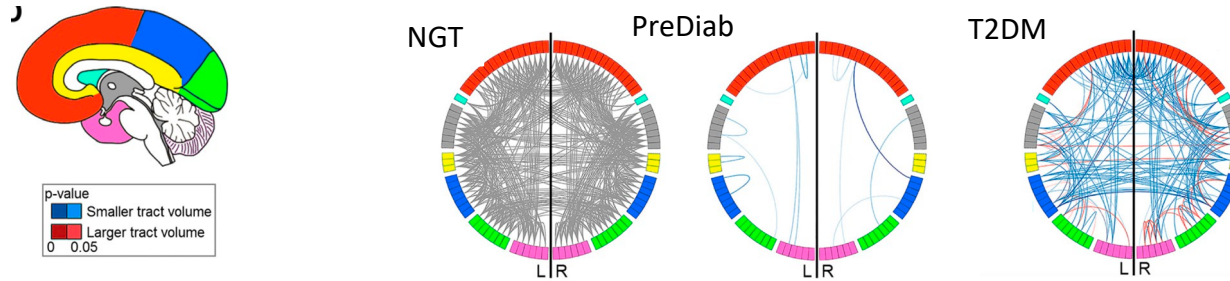
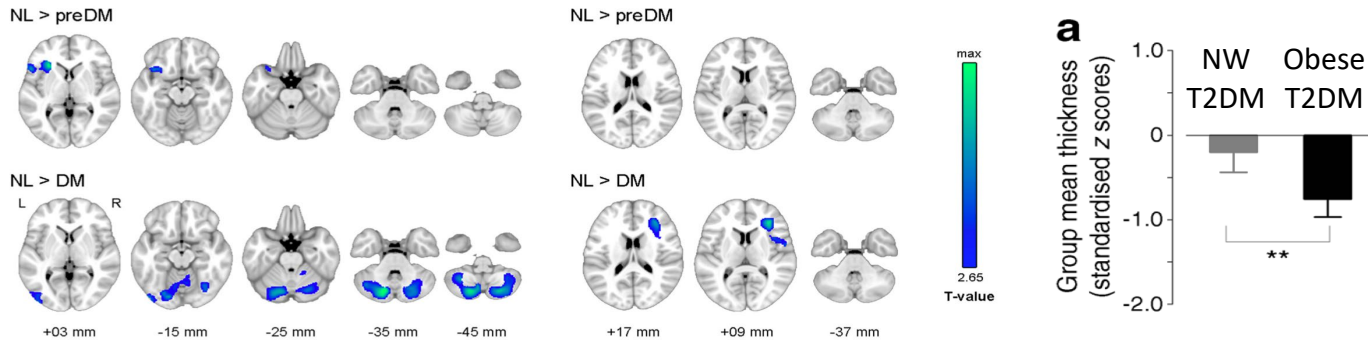
Odds ratios are adjusted for age and sex

Brain effects of obesity and Type 2 Diabetes

Obesity



Diabetes



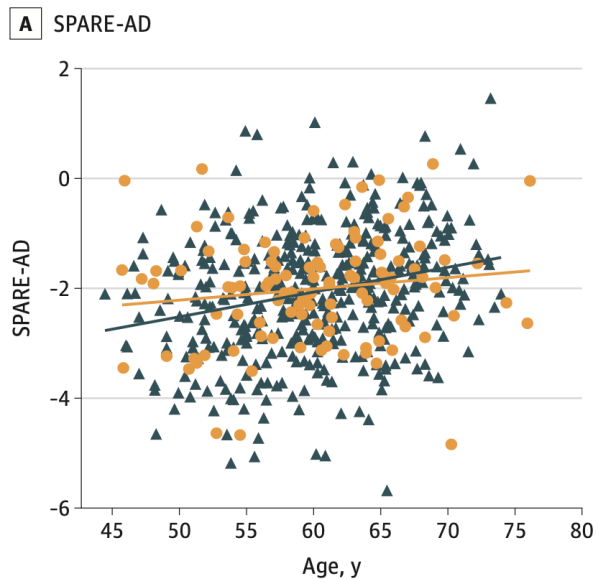
Normal Cognitive Function

Cognitive Decrements

Mild cognitive impairment

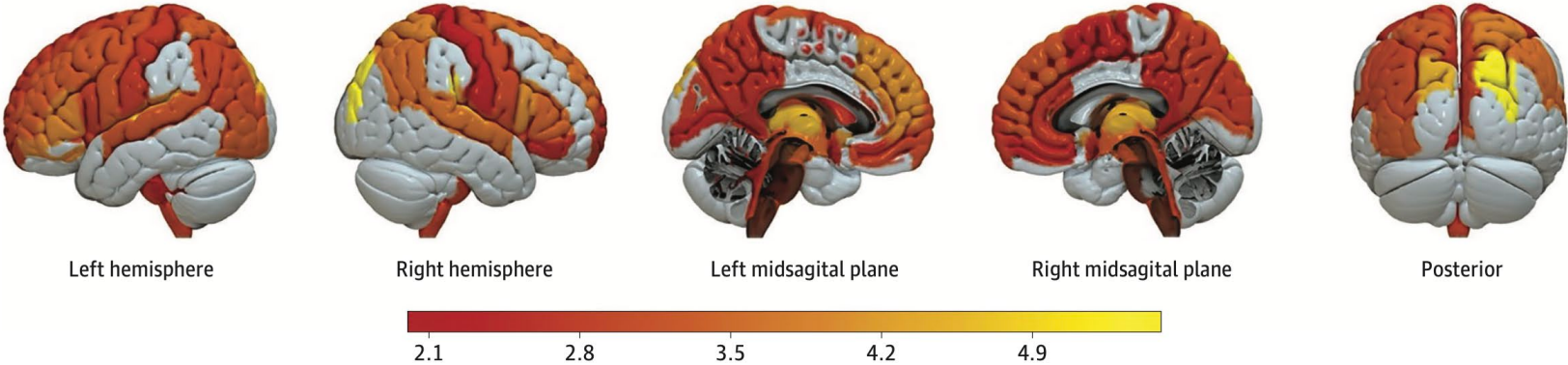
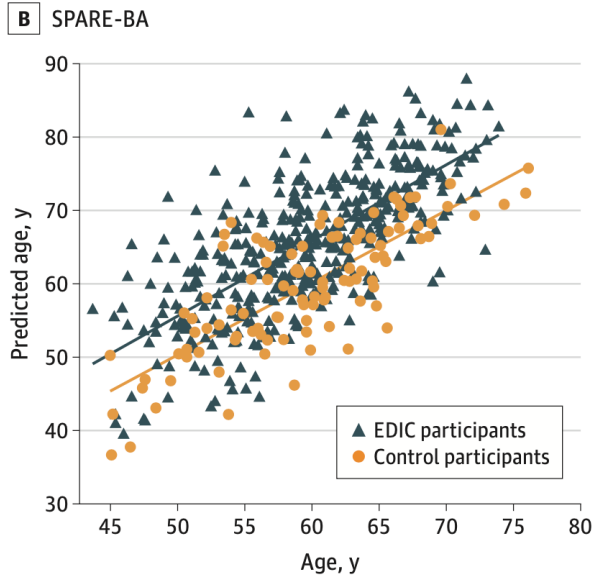
Major neurocognitive disorder

Brain effects of Type 1 Diabetes

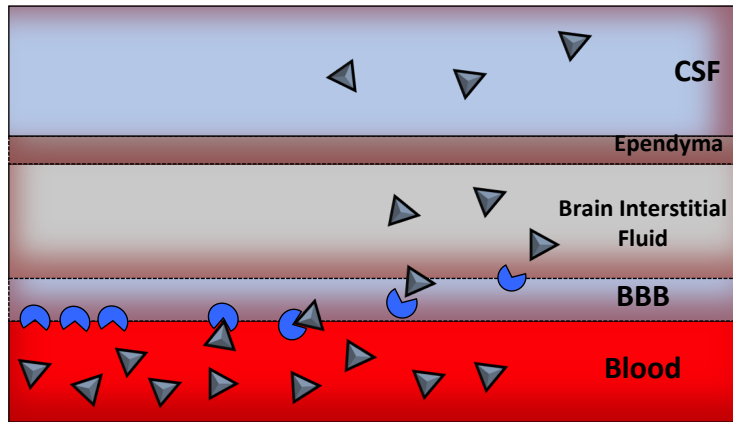


DCCT - EDIC MRI study – Mean follow-up 36 years

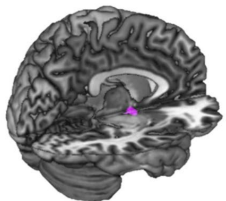
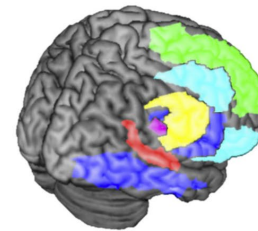
Cohort	Immediate memory ^a			Delayed recall ^a			Psychomotor and mental efficiency ^a		
	β (SE)	<i>t</i>	<i>P</i> value	β (SE)	<i>t</i>	<i>P</i> value	β (SE)	<i>t</i>	<i>P</i> value
EDIC participants, <i>n</i> = 415									
SPARE-AD	-0.13 (0.04)	-3.26	.001	-0.11 (0.01)	-2.44	.02	-0.17 (0.05)	-3.66	<.001
SPARE-BA	-0.01 (0.01)	-0.72	.47	-0.01 (0.01)	-1.65	.1	-0.04 (0.01)	-4.96	<.001
Controls, <i>n</i> = 94									
SPARE-AD	-0.16 (0.11)	-1.4	.16	-0.133 (0.12)	-1.12	.27	-0.12 (0.10)	-1.26	.21
SPARE-BA	-0.03 (0.02)	-1.4	.16	-0.04 (0.02)	-2.16	.03	0.006 (0.02)	0.35	.73



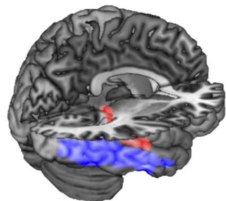
Brain insulin action and brain insulin resistance



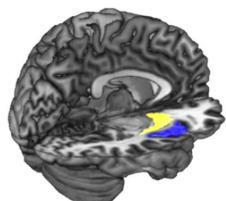
Saturable, receptor-mediated process



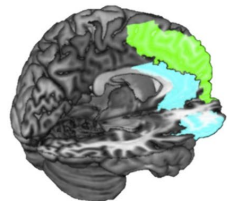
Homeostasis
Hypothalamus



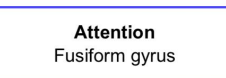
Memory
Hippocampus



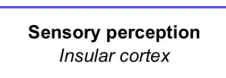
Reward
Striatum



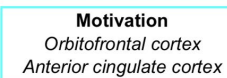
Inhibition
Lateral prefrontal cortex



Attention
Fusiform gyrus



Sensory perception
Insular cortex



Motivation
Orbitofrontal cortex
Anterior cingulate cortex

Neuronal Metabolism
Neuronal Development
Synaptic Efficacy
Neuronal Firing
Neuronal Survival

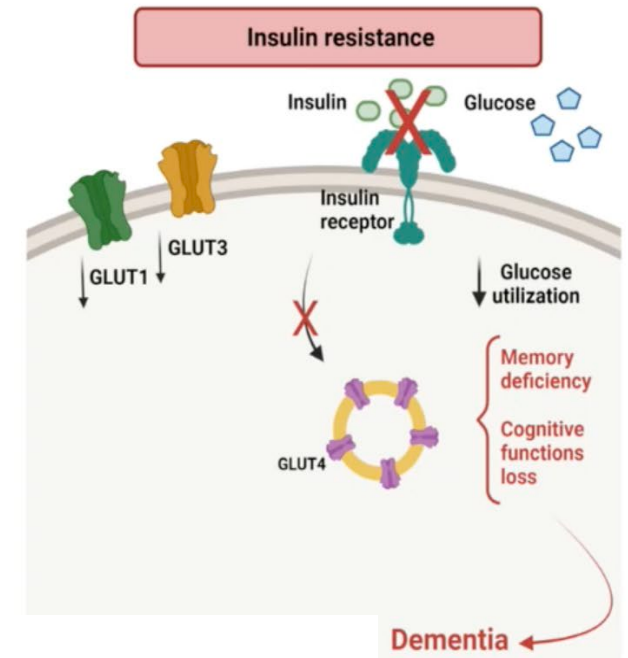
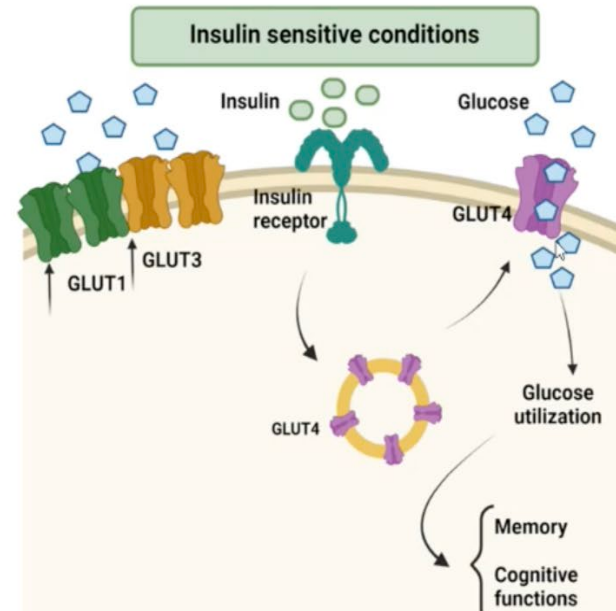
Local Insulin Sources

- Local Energy on demand
- Local Suppression of Excitation

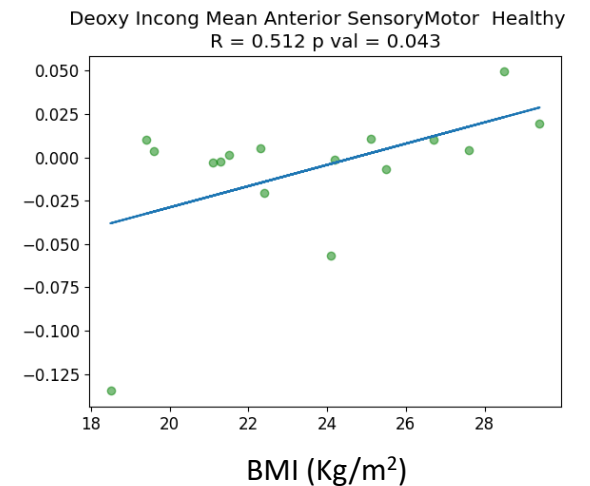
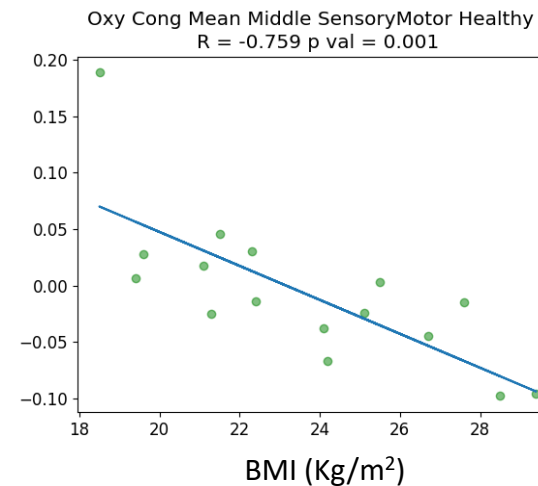
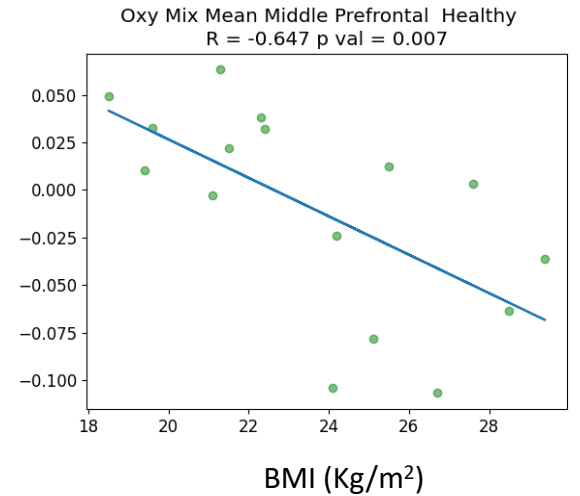
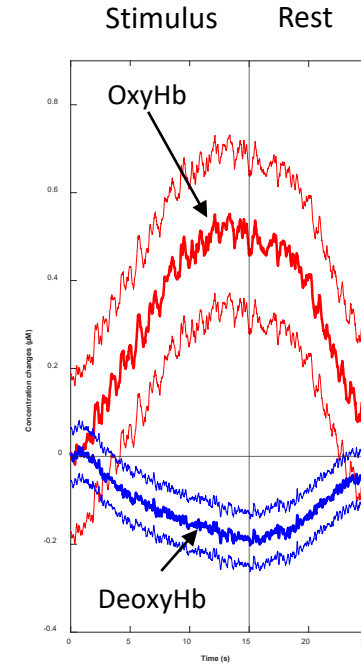
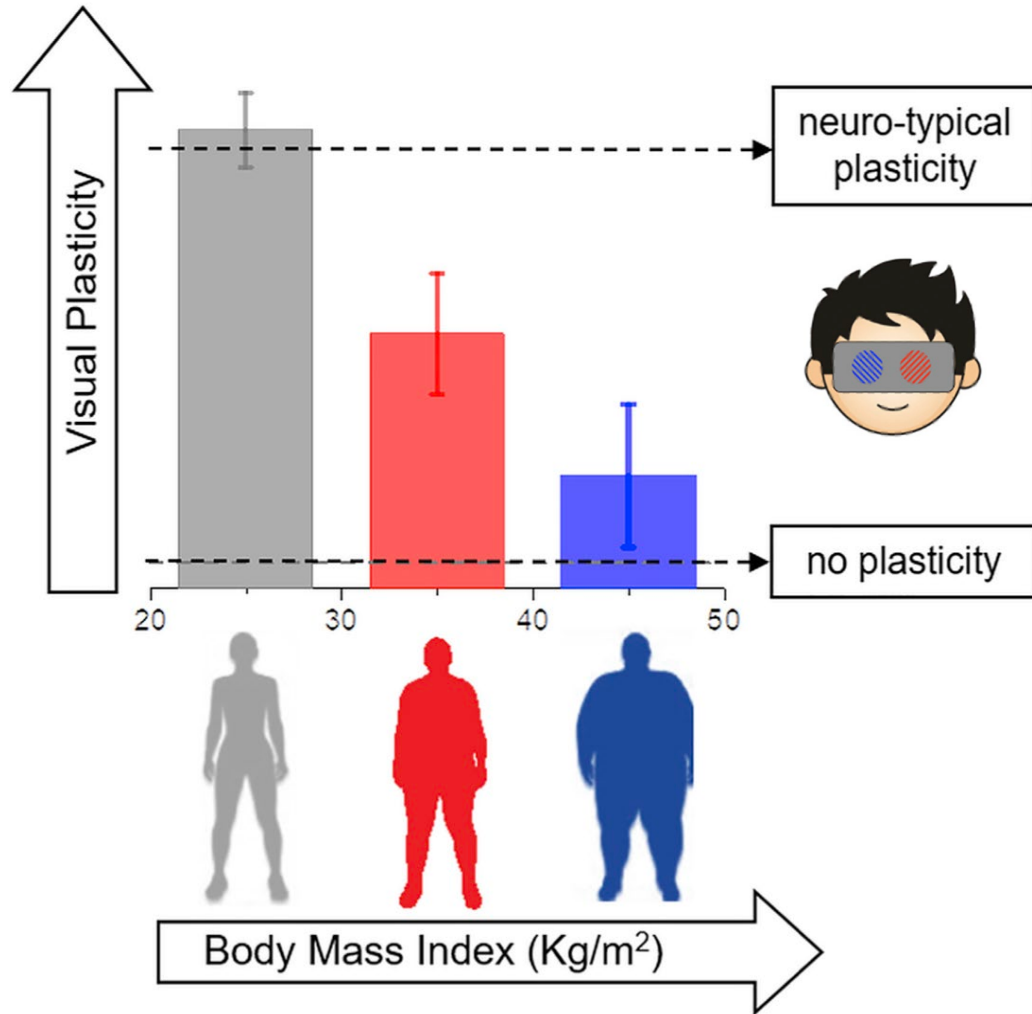
BBB

← Pancreatic Insulin

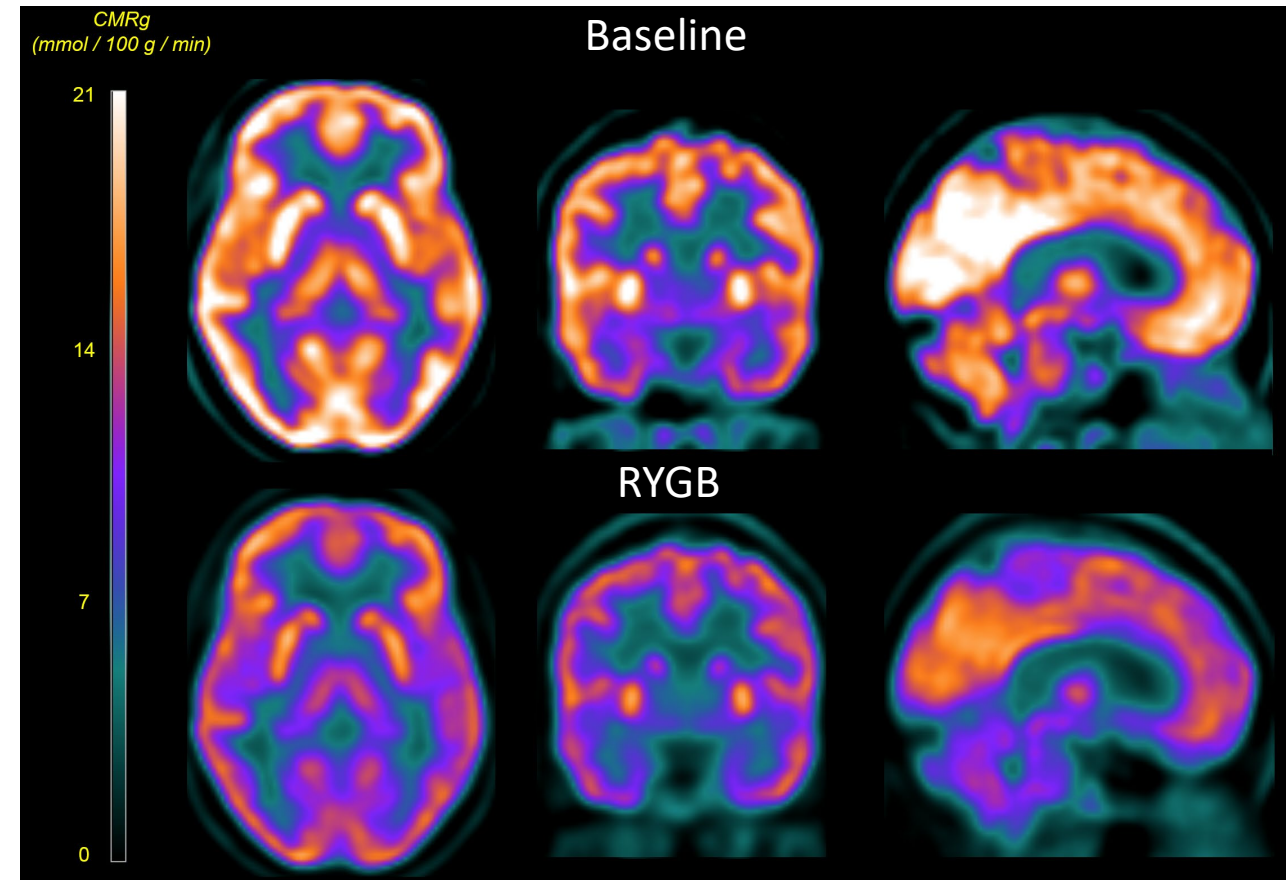
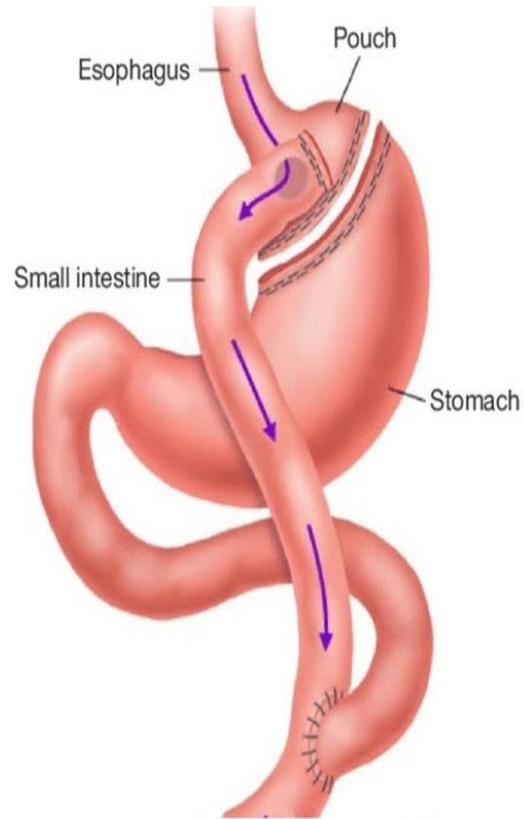
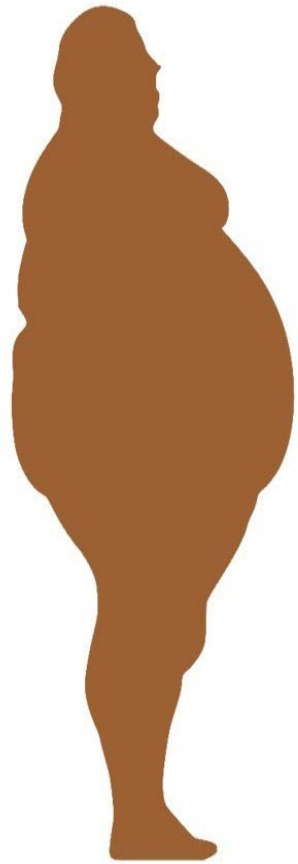
- ✓ Chronic peripheral hyperinsulinemia downregulates BBB transporters



Insulin Sensitivity and Neuroplasticity



Insulin Sensitivity and Brain Metabolism



Exposure to Pollution and Cognitive Function

Oxidative Stress
Neurotoxicity
Neuroinflammation
BBB & NVU Damage

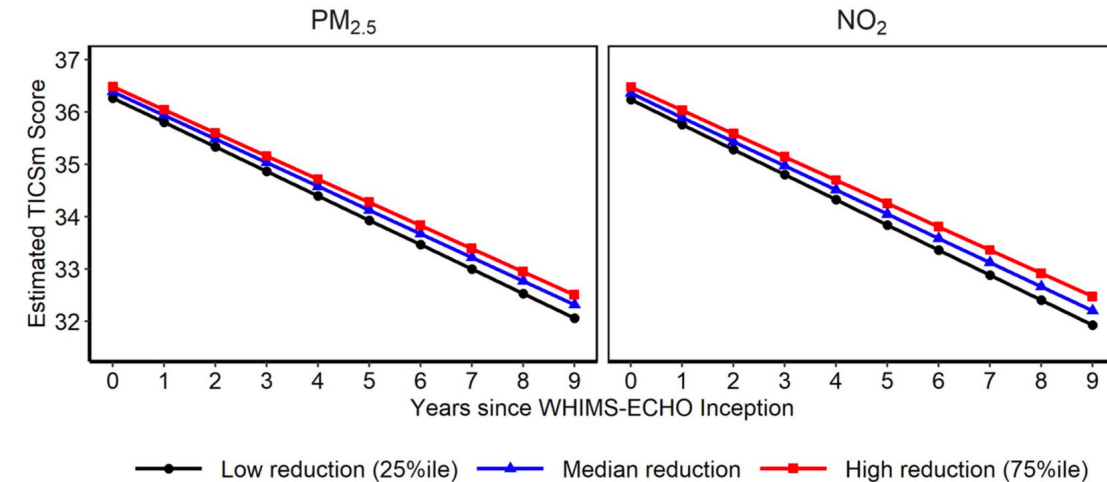
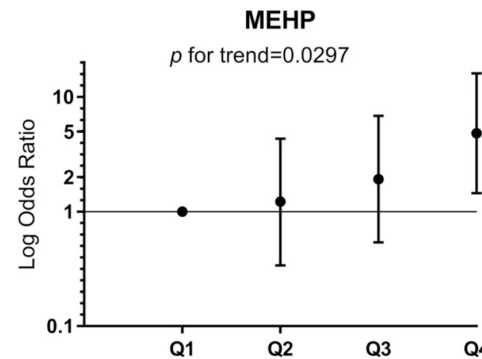
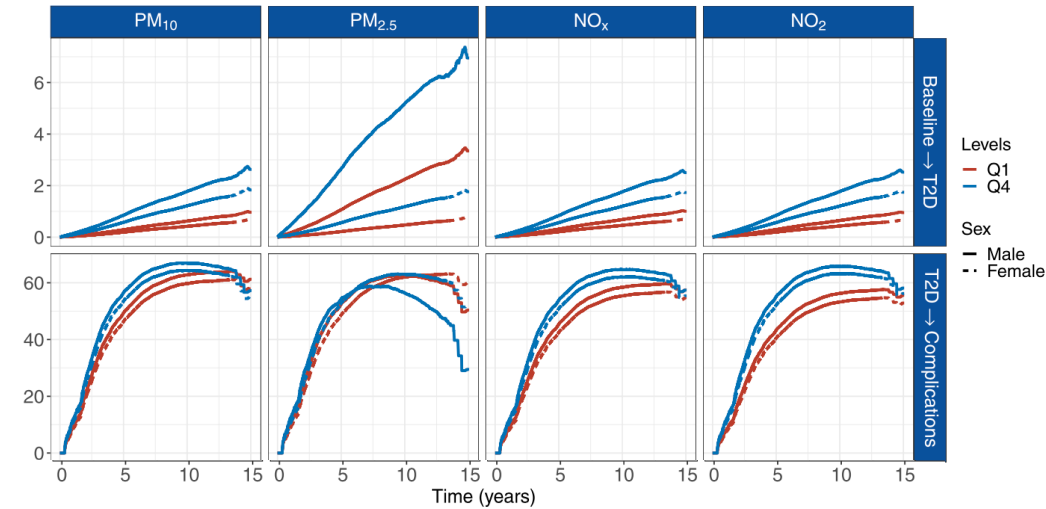
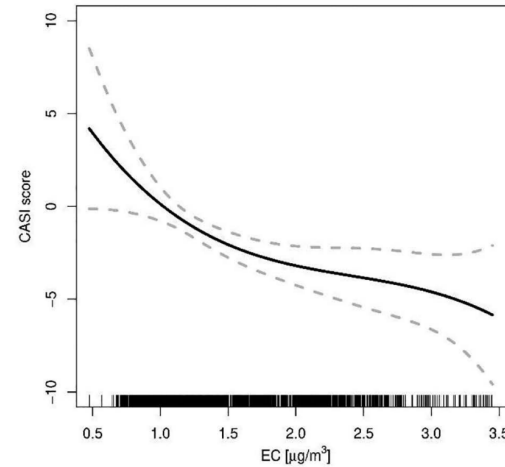
Nose-to-Brain Route

Circulation & BBB

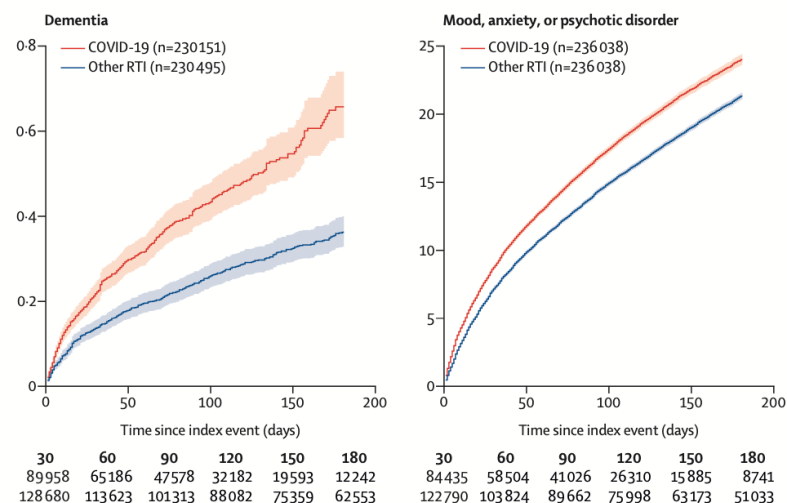
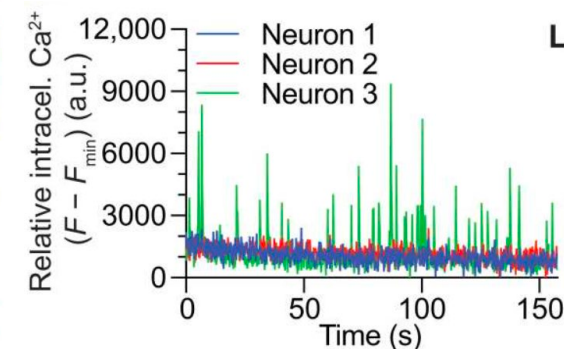
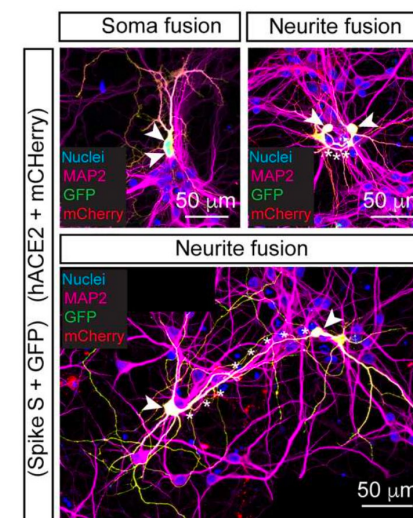
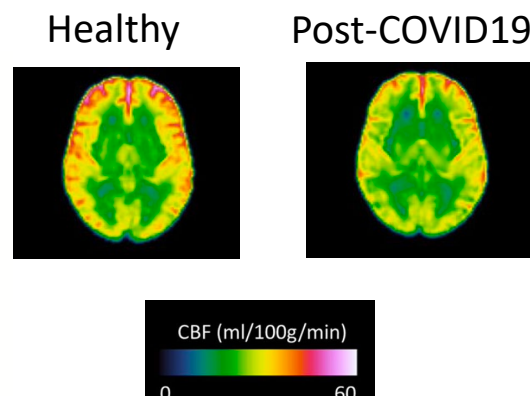
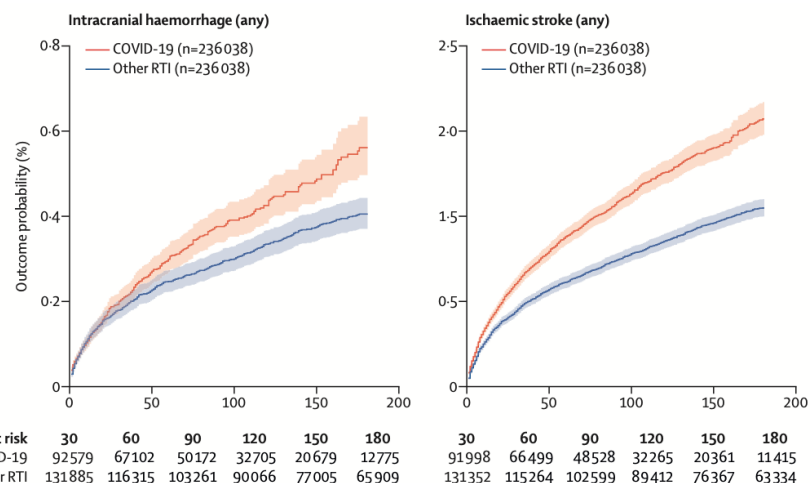
Particulate matters

- PM_{2.5} (Elemental carbon)
- NO_x/NO₂
- Si
- SO₄⁻²

Circulation



Exposure to COVID-19 and Cognitive Function

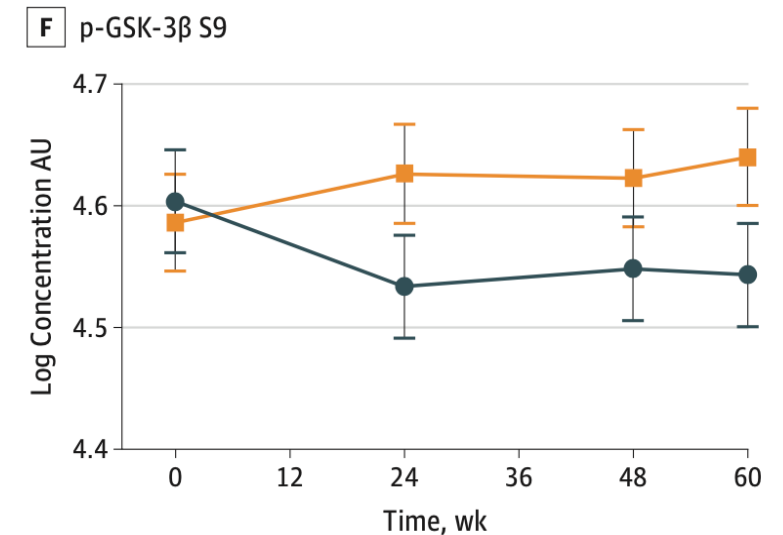
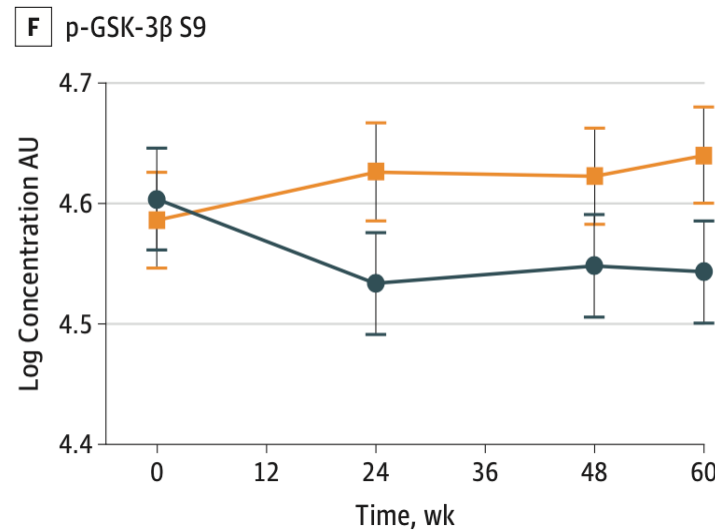
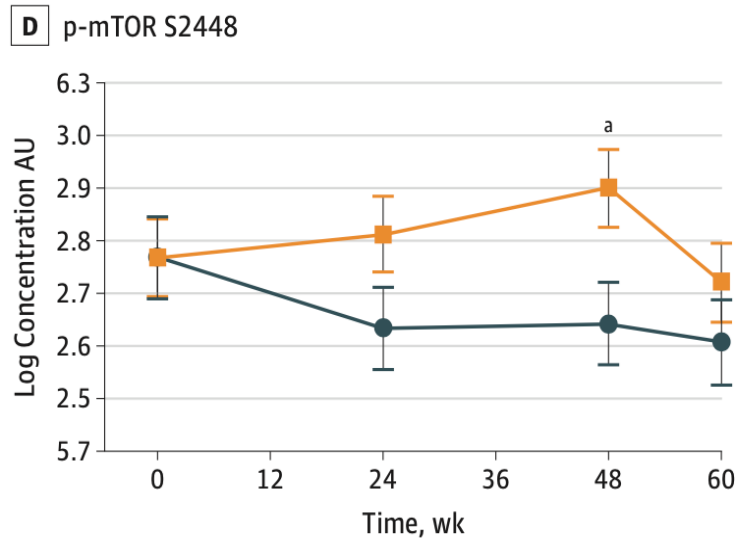
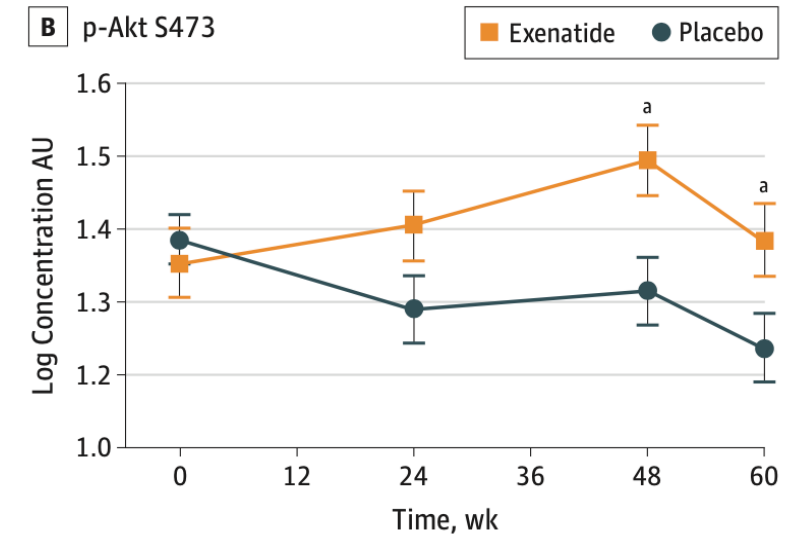
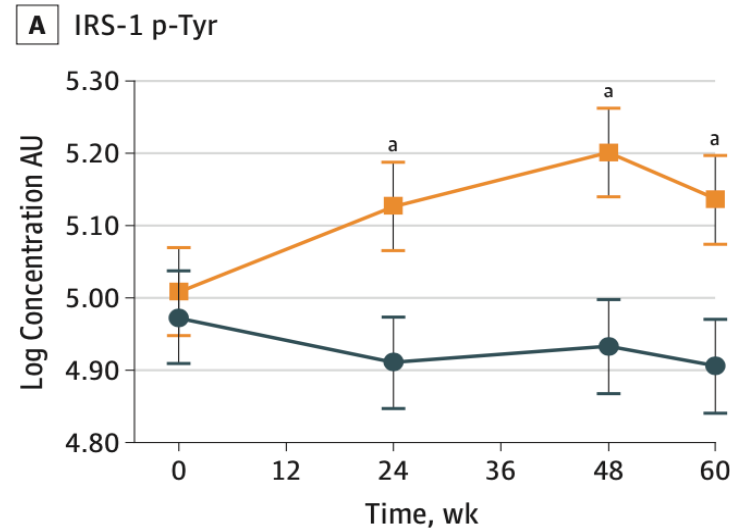
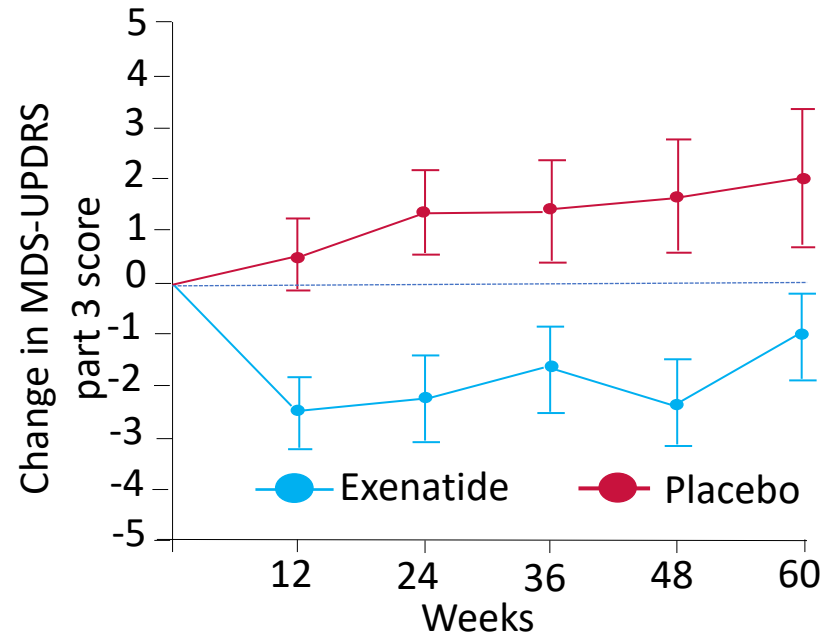


	Group with diabetes (n = 145)	Group without diabetes (n = 290)
Age, mean (SD), years	70.2 (13.2)	70.2 (13.4)
Sex, n (%)		
Male	90 (62.1)	180 (62.1)
Female	55 (37.9)	110 (37.9)
BMI, mean (SD), kg/cm ² *	27.1 (4.1)	25.7 (3.9)
Functional limitations, n (%)	Group with diabetes (n = 145)	Group without diabetes (n = 290)
Limitation in		
Occupational activities	18 (12.4)	46 (15.9)
Leisure/social activities	59 (40.7)	100 (34.5)
Basic activities of daily life	34 (23.4)	66 (22.8)
Instrumental activities of daily life	45 (31.0)	87 (30.0)
HADS-D (0–21), mean (SD)	5.3 (4.5)	5.2 (4.6)
Depressive symptoms (HADS-D ≥ 10 points), n (%)	32 (22.1)	52 (17.9)
HADS-A (0–21), mean (SD)	5.4 (5.3)	5.0 (4.6)
Anxiety symptoms (HADS-A ≥ 12 points), n (%)	30 (20.7)	49 (16.9)
PSQI (0–21), mean (SD)	6.9 (3.8)	6.2 (3.9)
Poor sleep quality (PSQI ≥ 8 points), n (%)	55 (37.9)	90 (31.0)

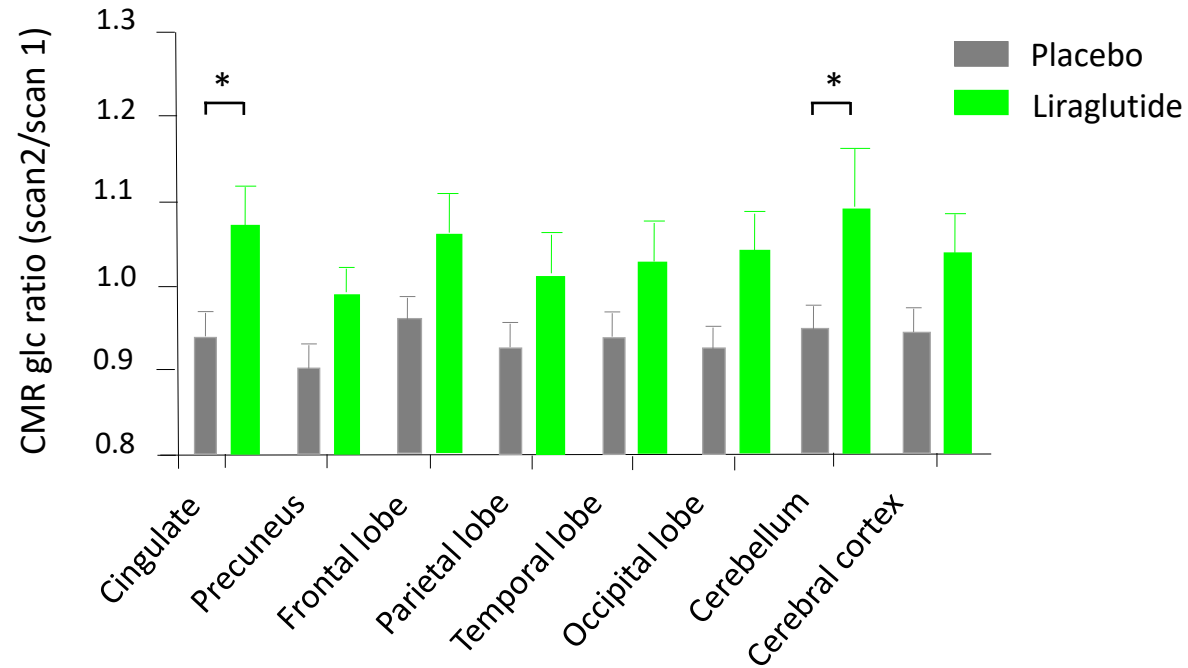
Can Pharmacological treatments Prevent or Delay the Brain Impact of Diabetes?

Type 2 Diabetes Study	Patients Characteristics	Treatment	Follow-up	Outcome
ACCORD-MIND	2977 patients aged >55 years	Intensive treatment (HbA1c ≤42 mmol/mol)	2.8 years	No difference in cognitive performance and decline Reduced rate of brain atrophy
ADDITION-Cognition	183 patients aged 50-70 years	Intensive multifactorial treatment	3.2 years	No difference in cognitive performance and decline
ADVANCE	11.140 patients ≥55 years with a history of major macrovascular or microvascular disease or one other cardiovascular risk factor	HbA1c < 48 mmol/mol with gliclazide and Perindopril-indapamide	5 years	No difference in risk of cognitive decline or dementia
CARMELINA-COG	1545 patients with Type 2 Diabetes	Linagliptin 5 mg	2.5 years	No effect on cognitive decline
REWIND	8828 patients with Type 2 Diabetes	Dulaglutide 1.5 mg once a week vs placebo	5.4 years	14% reduction in substantive cognitive impairment

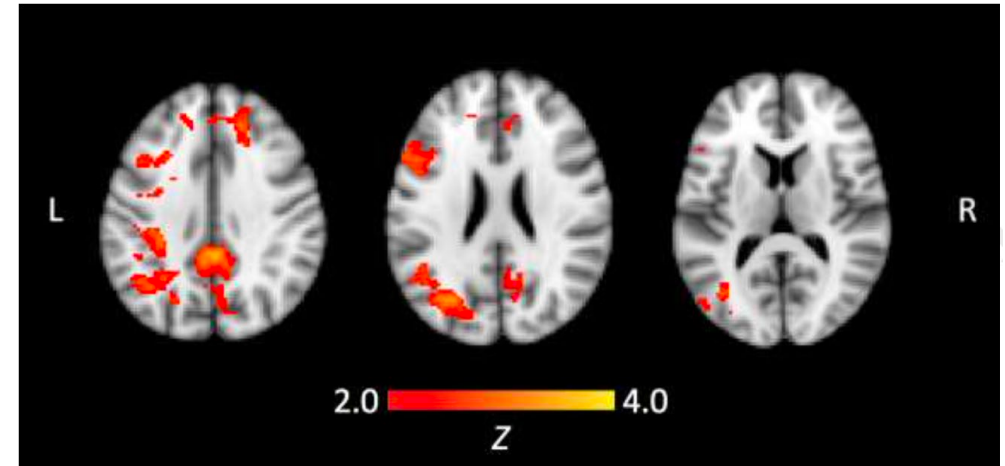
GLP-1Ras treatment and Parkinson Disease



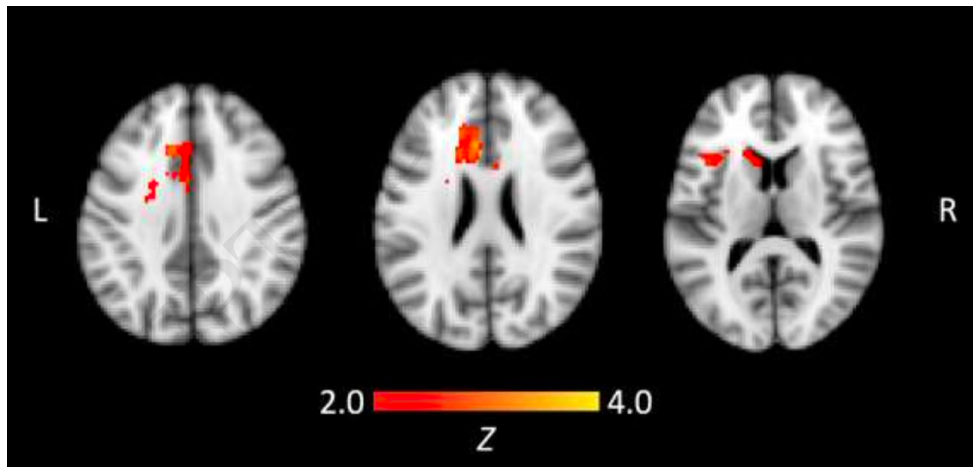
GLP-1Ras treatment and Alzheimer Disease



Connectivity with Hippocampus



Connectivity and plasma glucose



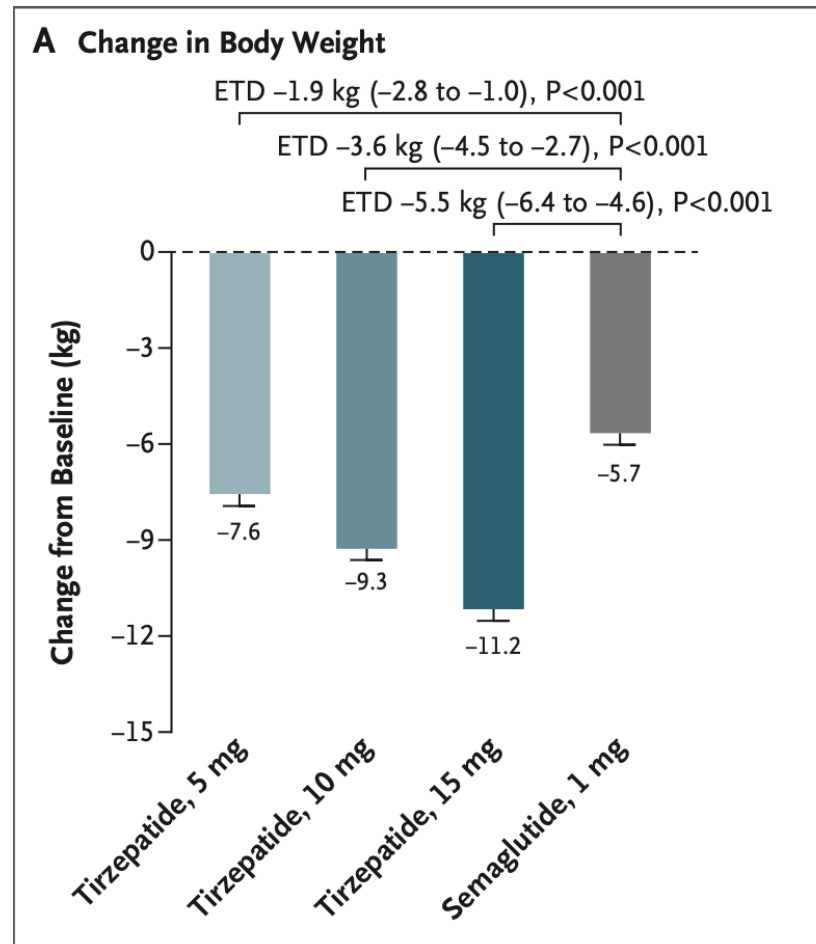
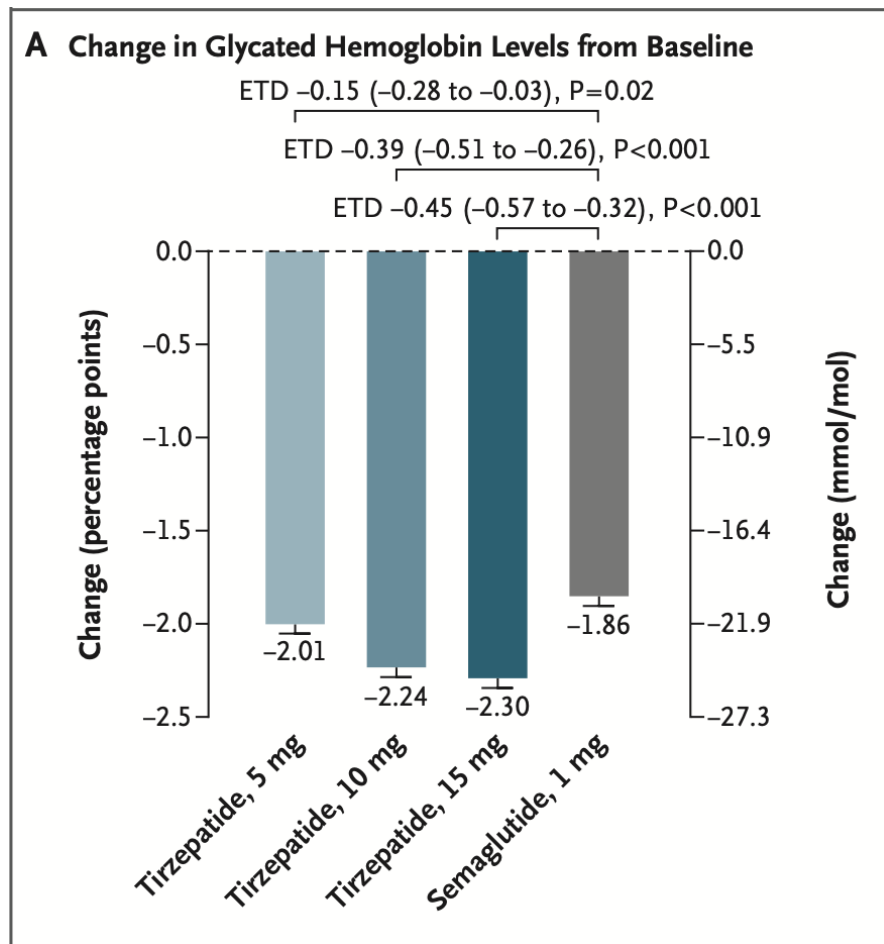
ELAD Study

Liraglutide

1. cognitive impairment
2. temporal lobe atrophy
3. cortical grey matter atrophy

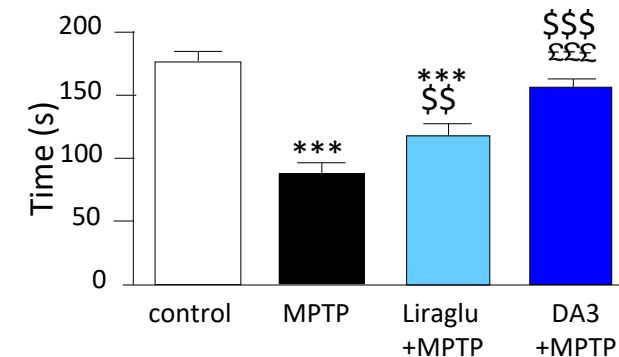


Dual agonists and Neurodegenerative Diseases

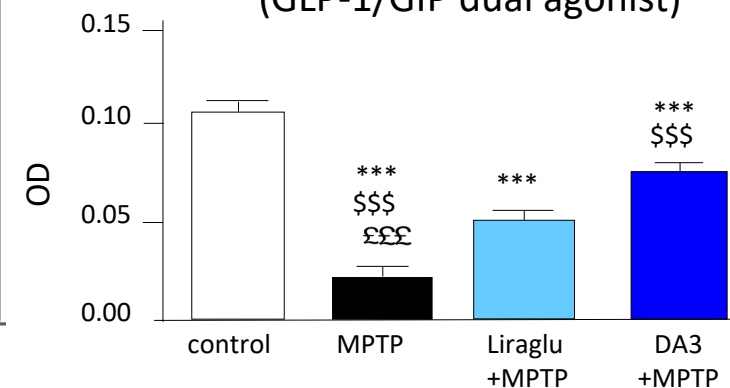


● Tirzepatide, 5 mg ▼ Tirzepatide, 10 mg ◆ Tirzepatide, 15 mg ○ Semaglutide, 1 mg

Motor Performance
(GLP-1/GIP dual agonist)



Dopamine Synthesis
(GLP-1/GIP dual agonist)



Dementia prevention and intervention

	Relative risk for dementia (95% CI)	Risk factor prevalence
Early Life (<45 years)		
Less education	1.6 (1.3-2.0)	40.0%
Midlife (age 45-65 years)		
Hearing loss	1.9 (1.4-2.7)	31.7%
Traumatic Brain Injury	1.8 (1.5-2.2)	12.1%
Hypertension	1.6 (1.2-2.2)	8.9%
Alcohol (>21 units/week)	1.2 (1.1-1.3)	11.8%
Obesity	1.6 (1.3-1.9)	3.4%
Later Life (age>65 years)		
Smoking	1.6 (1.2-2.2)	27.4%
Depression	1.9 (1.6-2.3)	13.2%
Social isolation	1.6 (1.3-1.9)	11.0%
Physical Inactivity	1.4 (1.2-1.7)	17.7%
Diabetes	1.5 (1.3-1.8)	6.4%
Air pollution	1.1 (1.1-1.1)	75%

Potentially
modifiable
40%



Risk unknown
60%

Risk Evaluation and Diagnosis of Cognitive Dysfunction in Type 2 Diabetes

