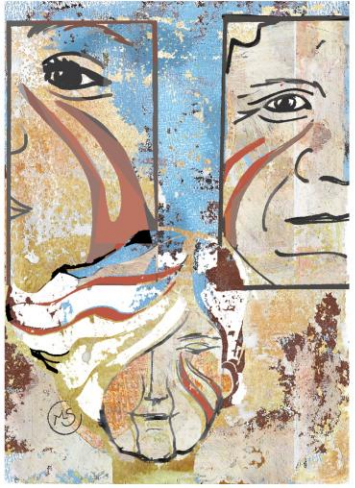


17·20 Dicembre 2025 Napoli

70° CONGRESSO NAZIONALE SIGG

LIBERI E LONGEVI

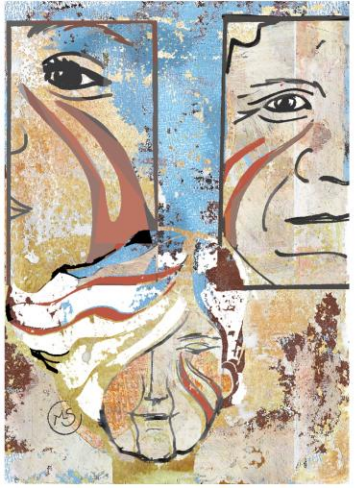
Università degli Studi di Napoli Federico II
Polo Didattico di **SCAMPIA**

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

FUNZIONE ENDOCRINA E DEMENZA

FABIO MONZANI

TAVOLO INTERSOCIETARIO SIGG–SIE–AME di ENDOCRINOLOGIA GERIATRICA



17·20 Dicembre 2025 Napoli

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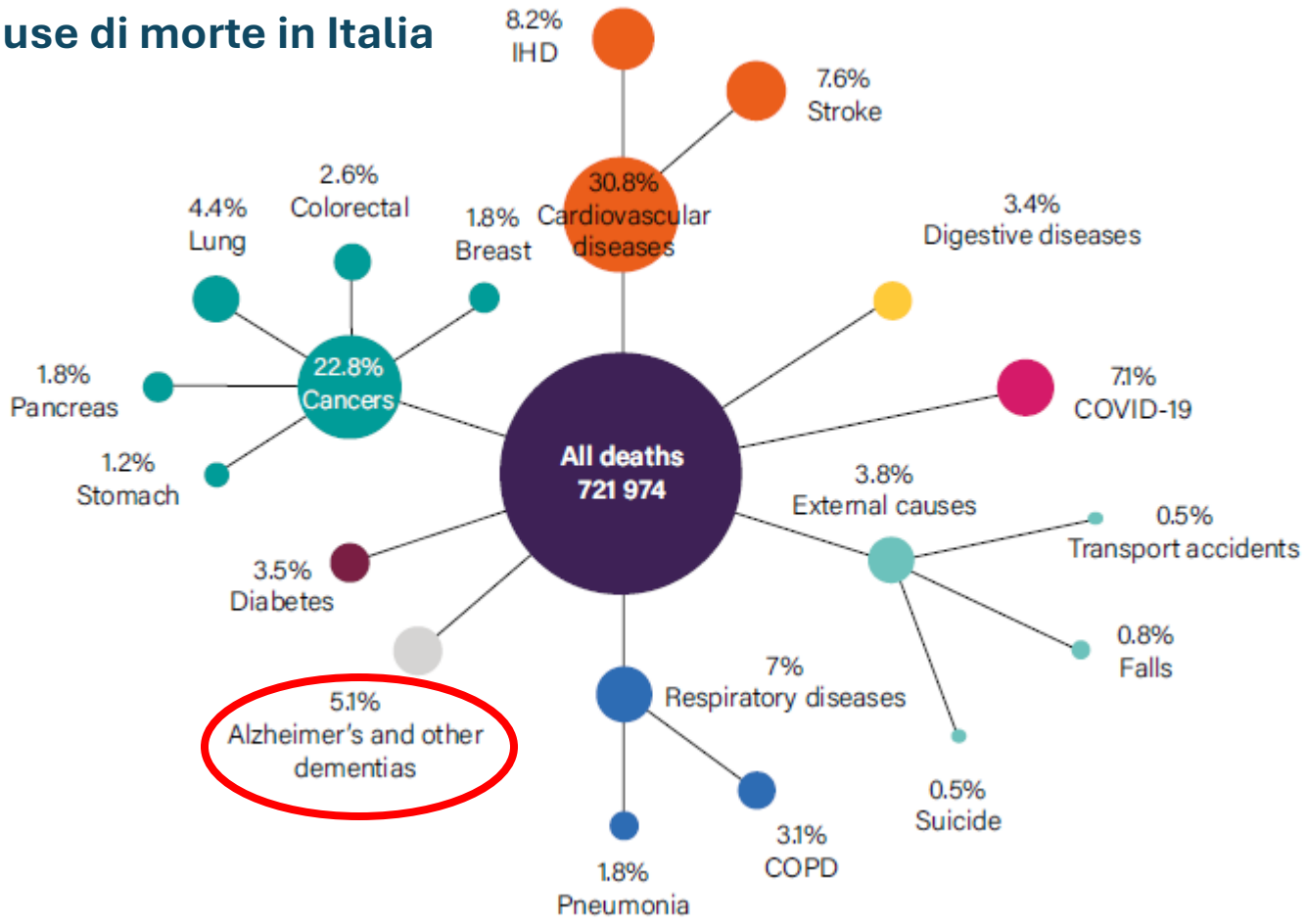
NIENTE DA DICHIARARE

DEMENZA: LE DIMENSIONI DEL PROBLEMA

Cause di morte in Italia

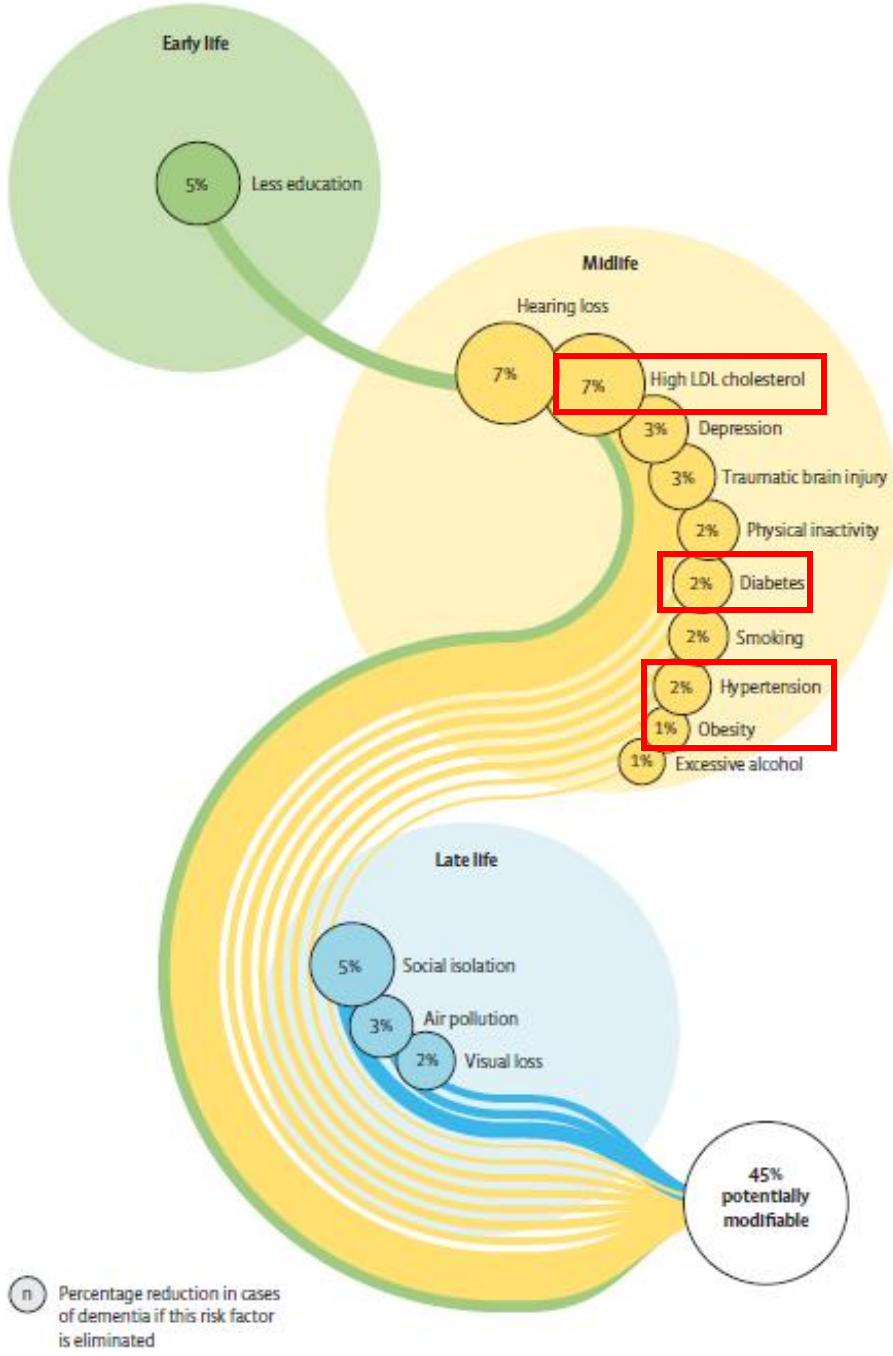


In Italia (2024) circa 1150000 casi (98%>65 aa, 2/3 donne), circa 950000 MCI

Dati preliminari studio europeo Ai-Mind

10% dei soggetti con MCI è progredito verso una forma di demenza in 24 mesi,
20% ha mostrato un declino cognitivo consistente, pur ancora in una condizione di MCI.

Source: Eurostat (hlth_cd_aro); Data refer to 2022.



www.thelancet.com Vol 404 August 10, 2024

DECADIMENTO COGNITIVO ED ALTERAZIONI ENDOCRINE

Variazioni nelle funzioni del sistema endocrino sono state progressivamente correlate alla patogenesi della Malattia di Alzheimer o ad altre demenze.
Anamnesi positiva per diabete, insulino resistenza ed iperinsulinismo sono state largamente associate con lo sviluppo o la progressione della demenza.

Tra le varie patologie endocrine, tuttavia, la relazione più largamente riconosciuta è quella tra le funzioni cognitive e gli ormoni tiroidei

European Journal of Neurology 2010, **17:** 1236–1248 doi:10.1111/j.1468-1331.2010.03040.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for the diagnosis and management of Alzheimer's disease

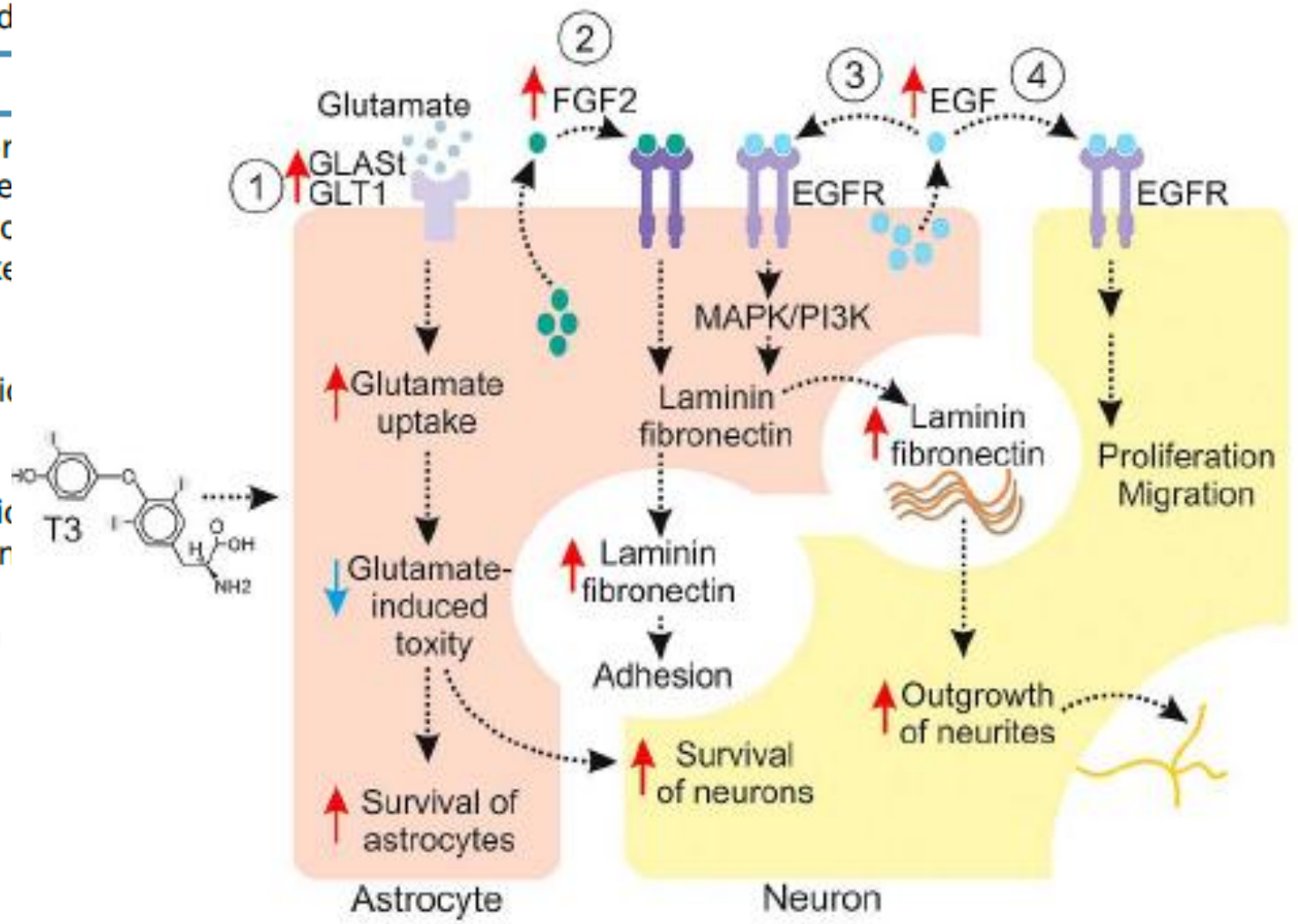
J. Hort[a], J. T. O'Brien[b], G. Gainotti[c], T. Pirttila[d,†], B. O. Popescu[e], I. Rektorova[f], S. Sorbi[g] and P. Scheltens[h] on behalf of the EFNS Scientist Panel on Dementia

Most expert opinion advises to screen for vitamin B12, folate,
***thyroid stimulating hormone**, **calcium**, **glucose**, complete blood cell*
count, renal and liver function abnormalities

The impact of autoimmune thyroid disease on cognitive and psychiatric disorders: focus on clinical, pre-clinical and molecular studies

Table 1 TH-regulated

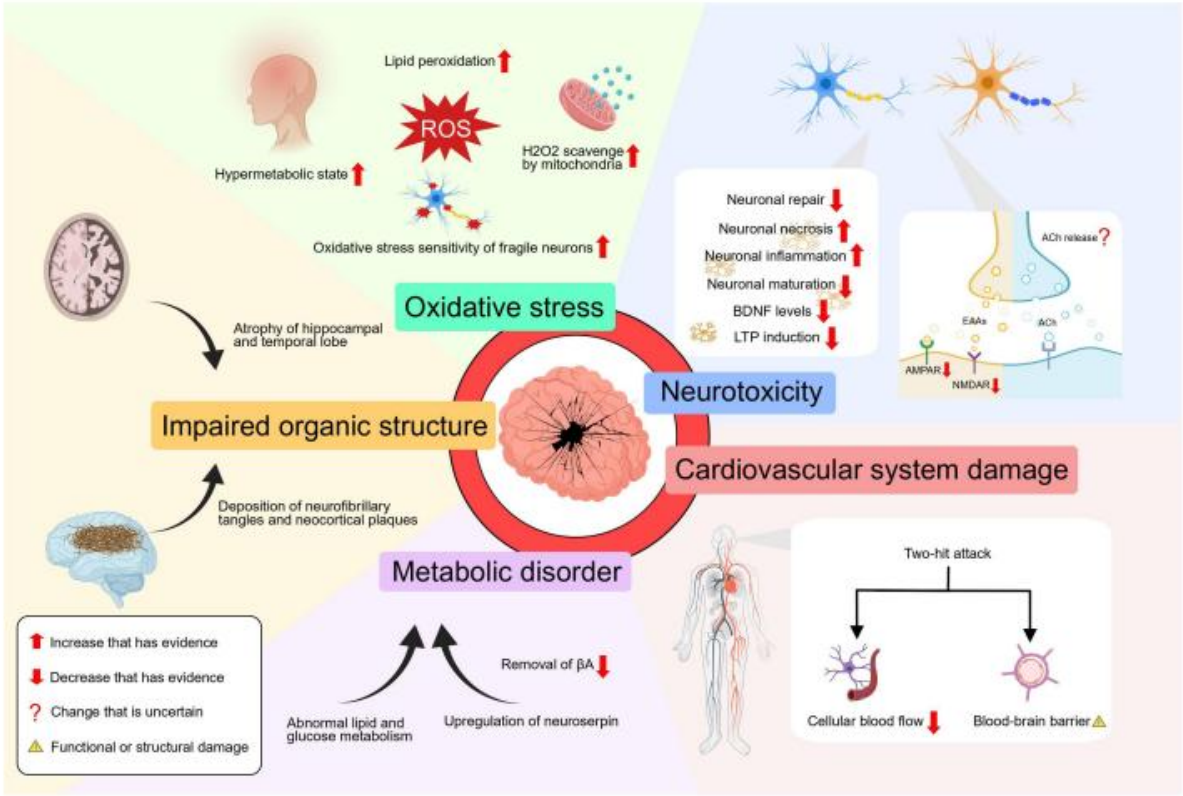
Gene/protein	Ref
APP/amyloid precursor	(57)
BDNF/Brain-derived ne	(58, 59)
DAB1/DAB adaptor pro	(60)
ELAVL4 (HuD)/ELAV like	(61)
FN1 (fibronectin)	(62)
GAP43/neuromodulin	(63)
GFAP/glial fibrillary acid	(62)
IL1-R	(64)
Laminin	(65, 66)
NR3C1 (GR)/Glucocortic	(63, 67)
NRGN (RC3)/neurogran	(63, 68, 69)
RELN/reelin	(61)
SERPINI1/neuroserpin	(70)
SLC1A2/GLT-1	hat mediates (71)
SLC1A3/GLASt	hat mediates (71)
SYN1/synapsin I	(58)
S100B/S100beta	(62)



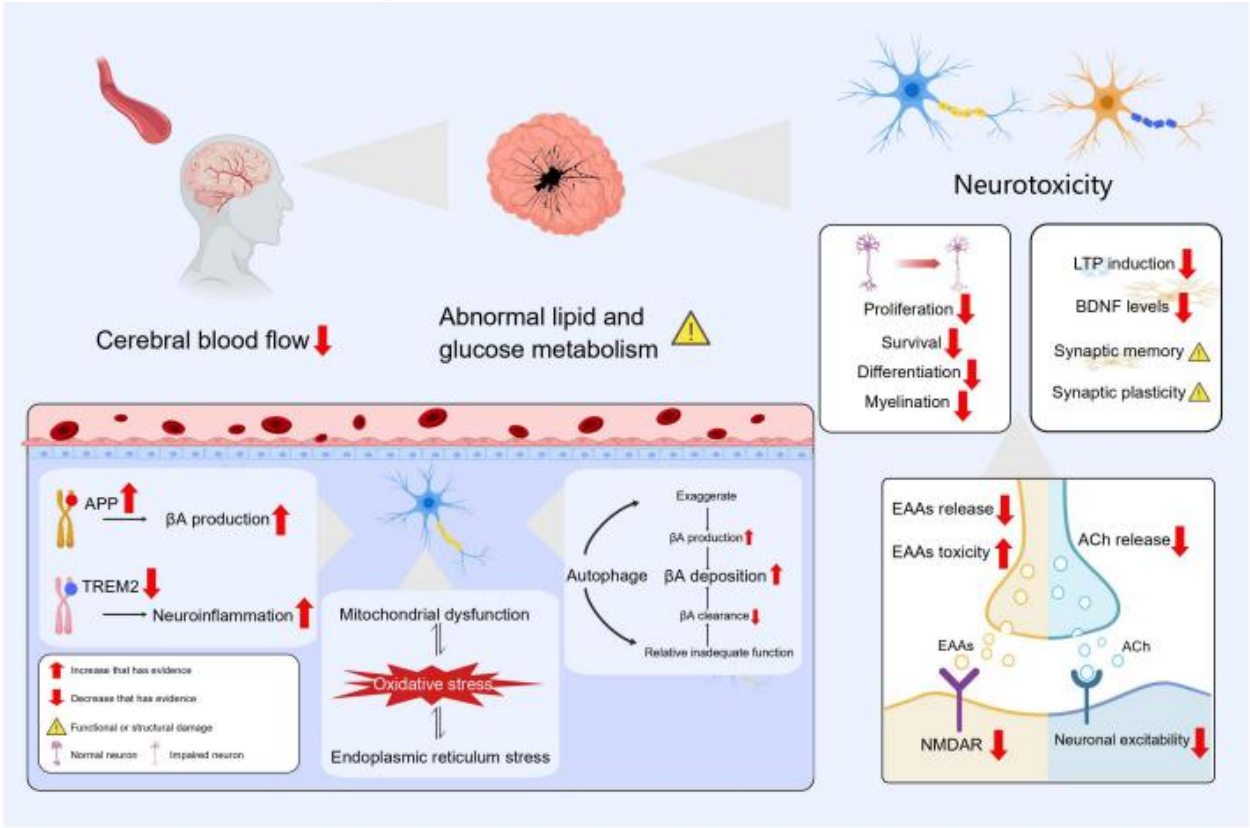
Piekiełko-Witkowska A et al European Thyroid Journal 2025

DECADIMENTO COGNITIVO E DISFUNZIONE TIROIDEA

Ipertiroidismo



Ipotiroidismo



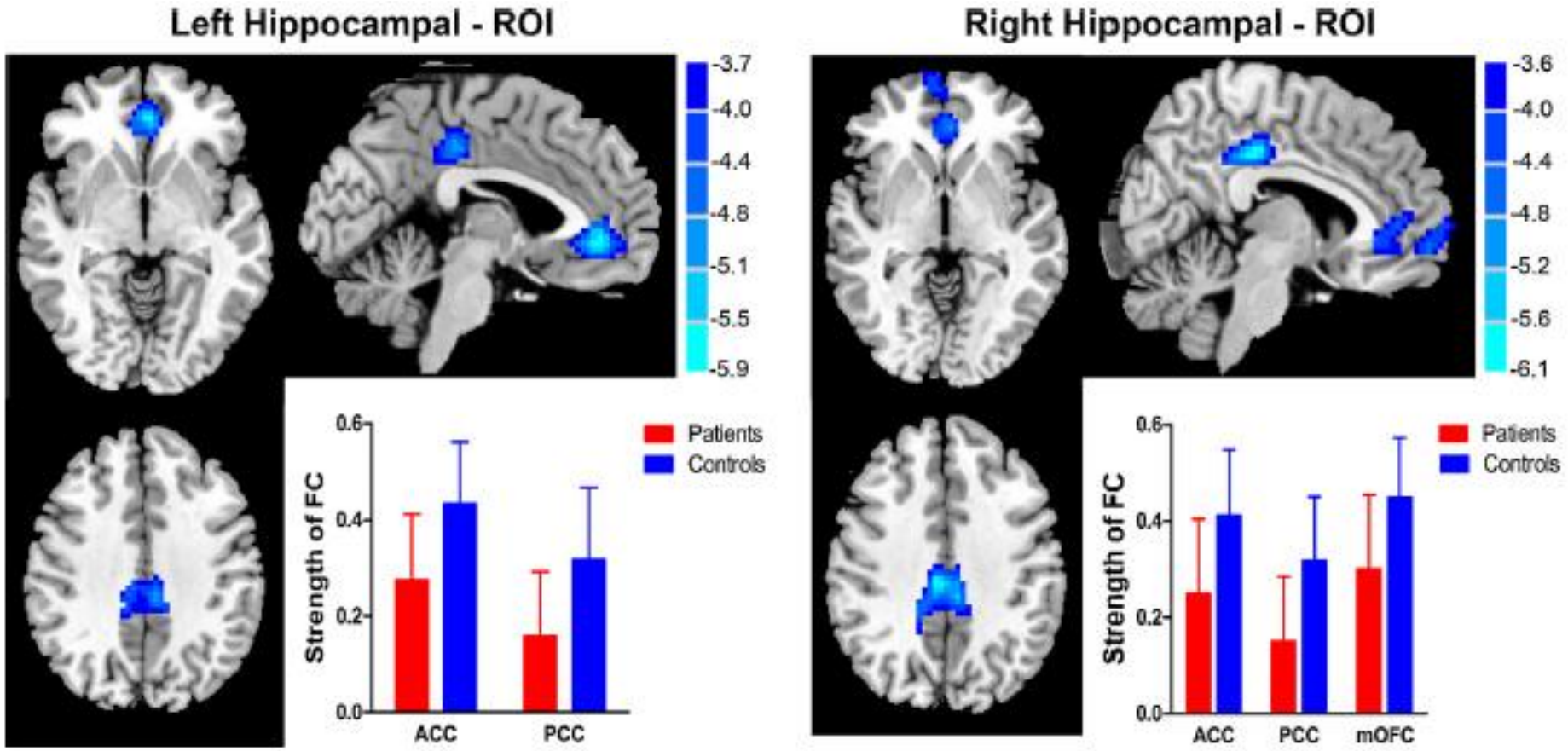
Incrementa stress ossidativo e deposito di proteine patologiche; Incrementa neuroinfiammazione
Compromette normale riparazione cellulare neuronale (>atrofia, <metabolismo glucidico, <colina)

Tossicità glutamatergica per >sensibilità allo stesso e riduzione dei recettori
Neurotossicità soprattutto ippocampale con neurodegenerazione; <colina

Front Endocrinol (Lausanne). 2024 Feb 14;15:1354372

DECADIMENTO COGNITIVO ED ALTERAZIONI ENDOCRINE: ORMONI TIROIDEI

Disrupted functional connectivity of the hippocampus in patients with hyperthyroidism: Evidence from resting-state fMRI



L'ippocampo è ricco di recettori per gli ormoni tiroidei

Lo studio mostra una ridotta connettività tra ippocampo, corteccia del cingolo anteriore e posteriore bilaterale, corteccia orbitofrontale mediale

Zhang W et al. 2014, Eur Journ of Rad, Vol 83, Issue 10, 2014, 1907-13

Disfunzione tiroidea e deficit cognitivo/demenza

Reviews e meta-analisi (2015–2025)

Pasqualetti G et al., JCEM (2015) Metanalisi	Ipotiroidismo subclinico	Associazione presente <75 aa; assente ≥75 aa, correlazione con livelli TSH
Rieben C et al., JCEM (2016) Metanalisi	Ipotiroidismo + Ipertiroidismo subclinico	Nessuna associazione significativa
van Vliet NA et al., JAMA Intern Med (2021) Metanalisi	Ipotiroidismo + Ipertiroidismo subclinico	Nessuna associazione significativa
Ma L-Y et al., Front Aging Neurosci (2023) Metanalisi	Ipotiroidismo + Ipertiroidismo (conclamato + subclinico)	Associazione complessiva con alta variabilità (eterogeneità alta; definizioni tiroidee non uniformi)
Alšauskė SV et al., Medicine (2024) Review sistematica	Ipotiroidismo + Ipertiroidismo (conclamato + subclinico)	Associazione riportata ma non uniforme
Liu Q et al., Brain & Behavior (2024) Metanalisi	Ipertiroidismo subclinico	Associazione positiva (rischio aumentato di demenza con TSH soppresso (<0.1 mU/L); risultati più forti negli anziani
Piekiełko-Witkowska A et al., Eur Thyroid J (2025) Review sistematica	ATD (Hashimoto, Graves)	Associazione plausibile ma indiretta evidenze su vie immuno-infiammatorie; legame con disturbi cognitivi/psichiatrici, ma senza stime quantitative solide

Treatment of Hypothyroidism That Contains Liothyronine is Associated With Reduced Risk of Dementia and Mortality

Table 5. Multivariable regression analyses comparing levothyroxine (LT4) therapy with LT4 + LT3 or DTE (follow-up to 20 years)

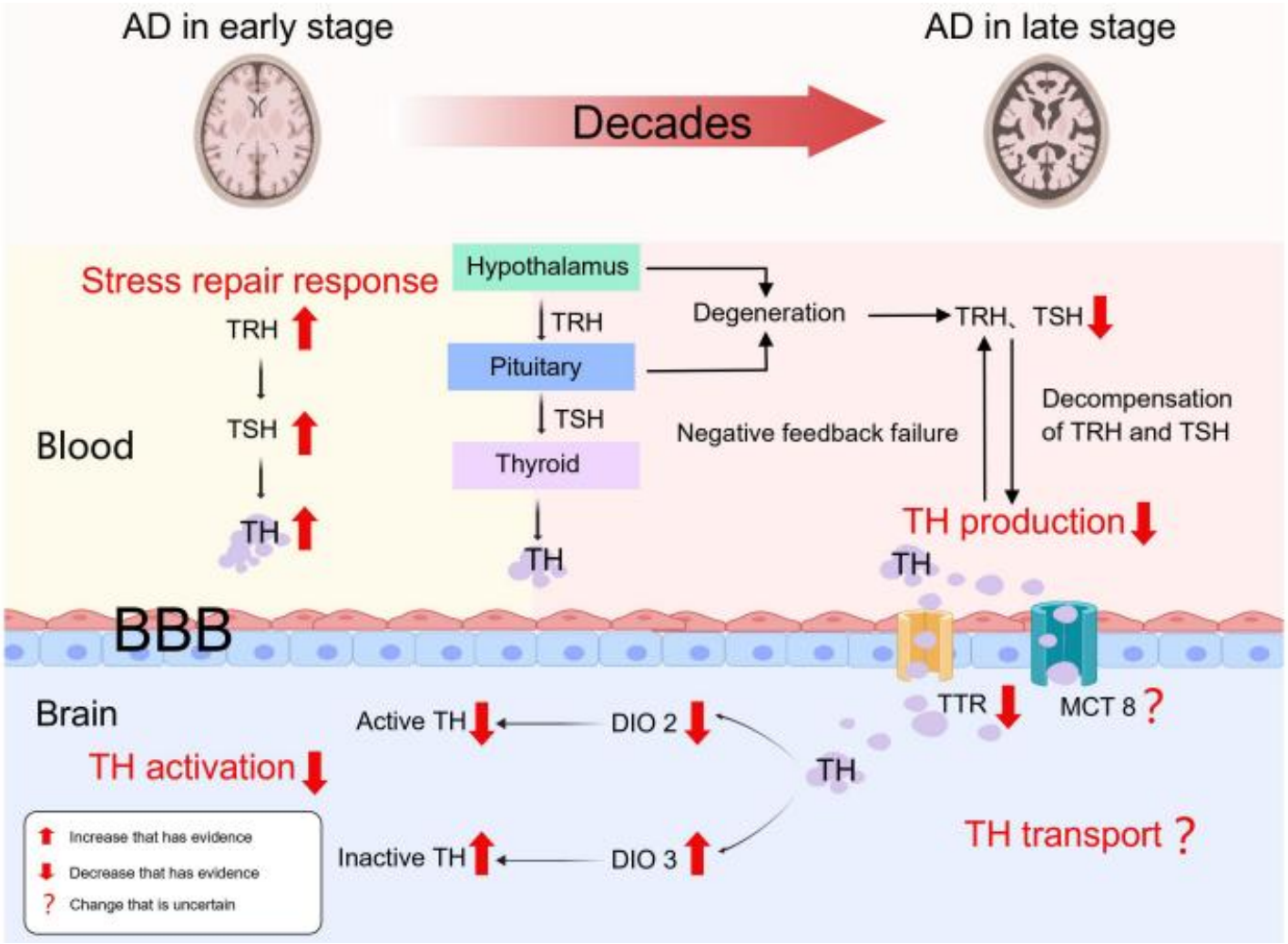
		Any Dementia		Vascular Dementia		Alzheimer's disease		Mortality	
		HR	CI 95%	HR	CI 95%	HR	CI 95%	HR	CI 95%
	Unadjusted	1.94	1.85-2.04	1.94	1.76-2.22	1.82	1.68-1.96	1.94	1.87-2.01
Model 1	Age	1.29	1.23-1.35	1.32	1.17-1.49	1.21	1.11-1.32	1.52	1.47-1.58
Model 1	Gender (male)	1.27	1.21-1.34	1.29	1.15-1.46	1.22	1.12-1.34	1.43	1.38-1.49
Model 1	Nicotine dependence	1.28	1.21-1.34	1.30	1.15-1.47	1.21	1.11-1.32	1.49	1.43-1.54
Model 1	Alcohol use disorder	1.28	1.22-1.35	1.31	1.17-1.48	1.21	1.10-1.32	1.52	1.46 -1.58
Model 1	Ever Hospitalized	1.29	1.23-1.36	1.32	1.17-1.49	1.21	1.11-1.32	1.53	1.47-1.58
Model 1	**Model 1**	**1.28**	**1.22-1.34**	**1.36**	**1.21-1.53**	**1.22**	**1.12-1.33**	**1.42**	**1.36-1.47**
Model 2	Diabetes	1.26	1.19-1.32	1.27	1.12-1.43	1.20	1.10-1.31	1.44	1.39-1.50
Model 2	Dyslipidemia	1.28	1.22-1.35	1.31	1.16-1.47	1.21	1.11-1.32	1.52	1.47-1.58
Model 2	Hypertension	1.27	1.21-1.34	1.27	1.13-1.44	1.21	1.11-1.32	1.48	1.42-1.53
Model 2	Obesity	1.28	1.22-1.35	1.32	1.17-1.49	1.21	1.10-1.32	1.53	1.47-1.58
Model 2	Atrial fibrillation	1.29	1.22-1.35	1.32	1.17-1.48	1.21	1.10-1.32	1.51	1.46 -1.57
Model 2	Depression	1.33	1.26-1.39	1.37	1.22-1.54	1.25	1.14-1.36	1.55	1.49-1.61
Model 2	**Model 2**	**1.30**	**1.24-1.37**	**1.36**	**1.20-1.53**	**1.22**	**1.12-1.33**	**1.41**	**1.35-1.46**
Model 3	TSH	1.29	1.23-1.36	1.34	1.18-1.50	1.22	1.12-1.33	1.52	1.46 -1.57
Model 3	TSH < 0.45	1.35	1.28-1.43	1.32	1.17-1.49	1.23	1.12-1.34	1.51	1.45 -1.57
Model 3	TSH > 7	1.28	1.22-1.35	1.32	1.17-1.49	1.21	1.10-1.32	1.52	1.47 -1.59
Model 3	CRP	1.35	1.29-1.43	1.34	1.18-1.51	1.21	1.11-1.32	1.56	1.50 -1.62
Model 3	Hemoglobin	1.35	1.29-1.43	1.33	1.18-1.50	1.23	1.12-1.35	1.54	1.48-1.60
Model 3	Vitamin B12	1.37	1.30-1.45	1.39	1.23-1.57	1.28	1.17-1.39	1.56	1.50-1.62
Model 3	HbA1c	1.29	1.22-1.35	1.39	1.18-1.50	1.21	1.11-1.32	1.53	1.47-1.59
Model 3	**Model 3**	**1.35**	**1.28-1.41**	**1.41**	**1.26-1.58**	**1.24**	**1.15-1.35**	**1.57**	**1.51-1.63**
Model 4	**Model 4**	**1.30**	**1.24-1.36**	**1.30**	**1.16-1.46**	**1.23**	**1.13-1.33**	**1.39**	**1.34-1.44**
Model 5	**Model 5**	**1.34**	**1.27-1.40**	**1.36**	**1.21-1.52**	**1.28**	**1.18-1.39**	**1.41**	**1.36-1.46**

Cox proportional hazards model: All individual variables and models were adjusted for age. Model 1: additionally adjusted for gender (male), nicotine dependence, alcohol use disorder, and hospitalization history. Model 2: additionally adjusted for diabetes, dyslipidemia, obesity, atrial fibrillation, and depression. Model 3: additionally adjusted for TSH, CRP, hemoglobin, vitamin B12, and HbA1c. Model 4: adjusted for all variables in models 1 and 2. Model 5: fully adjusted for all the above variables. All evaluated variables showed a P value < .0001.

Retrospective cohort study (TriNetX data combined with a comprehensive systematic review, meta-analysis, and meta-regression analysis), comparing **1.26 million patients with hypothyroidism (on LT4, LT4 + T3, or desiccated thyroid extract) to 3.32 million controls**

DECADIMENTO COGNITIVO ED ALTERAZIONI TIROIDEA
UN ALTRO PUNTO DI VISTA

Thyroid dysfunction as a results of Alzheimer's disease



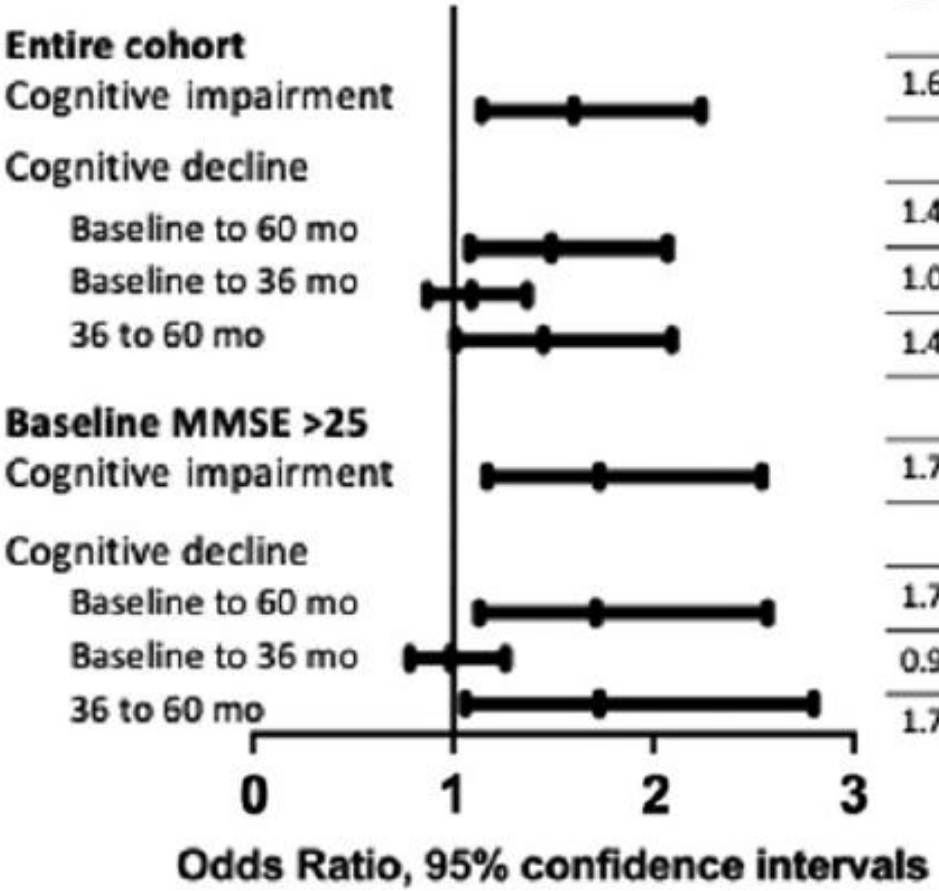
Front Endocrinol 2024;15:1354372

Most clinical and preclinical studies indicate the associations between hyperthyroidism and increased risk of dementia, while reports on hypothyroidism provide variable data.

- Crucial omitted topics include the presence of **autoimmunity and the potential impact of obesity and microbiota**.
- **Hypothyroidism** is often associated with **weight gain**, while fat tissue is an important source of **inflammatory cytokines** that can affect brain function.
- The **gut microbiota is altered in AITD** patients, which can contribute to cognitive and mood impairments through the gut–microbiota–brain axis.
- **Obesity alters gut microbiota**, which further adds to the complexity of potential interrelations between AITD, gut microbiota, and brain function.

Piekiełko-Witkowska A et al European Thyroid Journal 2025

Changes in Serum Thyroid Function Predict Cognitive Decline in the Very Old: Longitudinal Findings from the Newcastle 85+ Study



Odds ratio	p value	Participant number (n)
1.60 (1.14-2.24)	0.006	250
1.49 (1.08-2.07)	0.016	250
1.09 (0.87-1.37)	0.460	346
1.45 (1.01-2.09)	0.049	249
1.77 (1.19-2.61)	0.004	208
1.71 (1.13-2.57)	0.011	208
0.99 (0.78-1.26)	0.967	277
1.73 (1.06-2.80)	0.027	208

Of the 642 participants at baseline (58.1% women), 348 (54.2%) and 276 (43%) were alive to have their thyroid function tests repeated at 36 and 60 months, respectively.

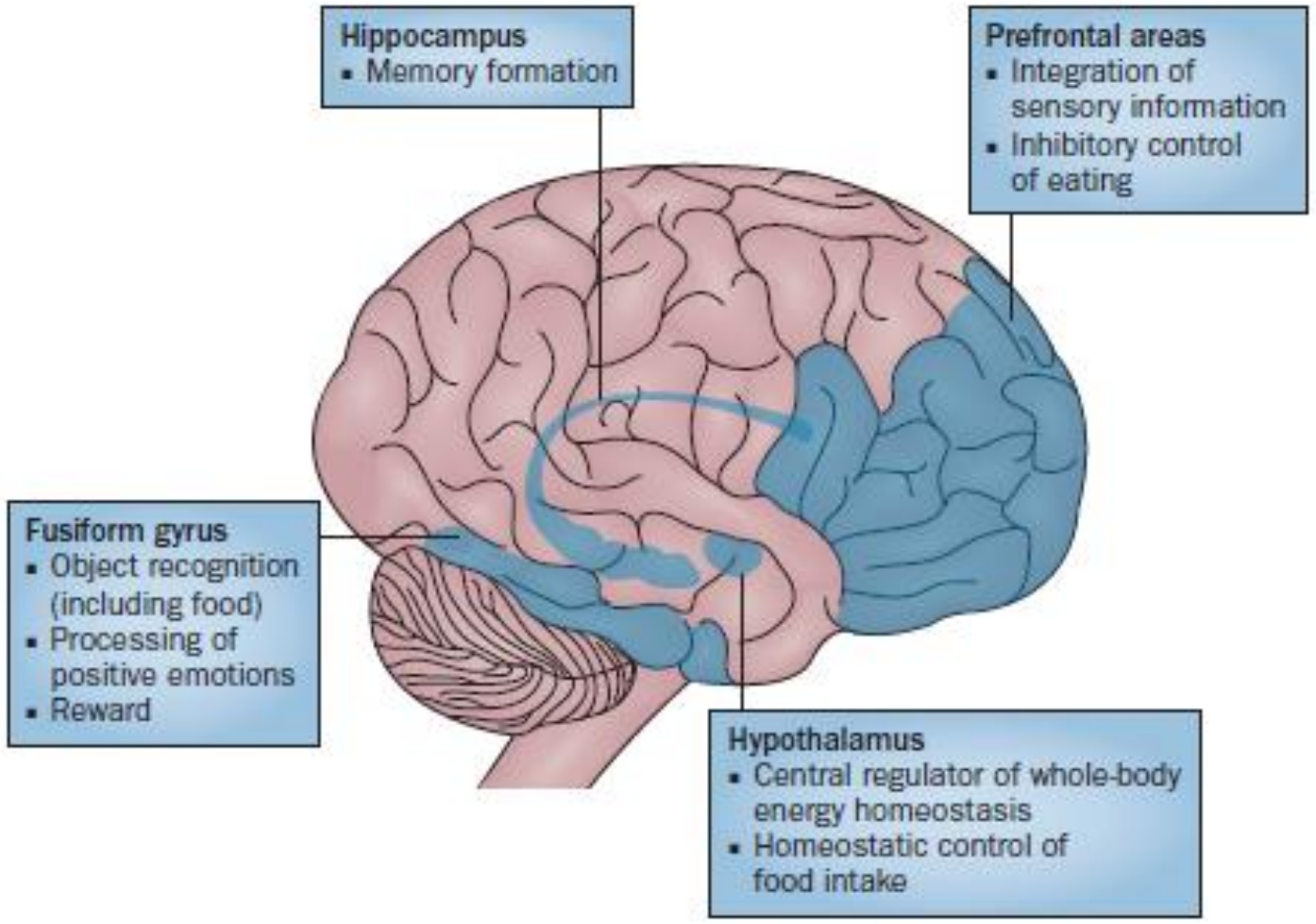
As a whole, 221 (63.5%) showed a decreasing TSH trajectory with time (at least <0.1 mU/L).

Subjects with a falling TSH also showed a reduction in serum FT_4 over time

Cognitive status was defined as normal when MMSE scores were ≥26, whereas incident cognitive impairment was defined as an MMSE score crossing the 25 points threshold. A decline in MMSE score ≥3 points is considered to be a clinically meaningful change in cognitive function

Gan EH et al. Thyroid 2021

INSULINA E SNC



PROLIFERAZIONE E DIFFERENZIAZIONE CELLULARE

Funzione trofica in proliferazione e differenziazione cellulare oltre che nella crescita neuritica nelle fasi dello sviluppo

EFFETTO NEUROPROTETTIVO

L'insulina è un potente agente neuroprotettivo che agisce prevalentemente vs apoptosis, tossicità della beta amilode, stress ossidativo ed ischemia

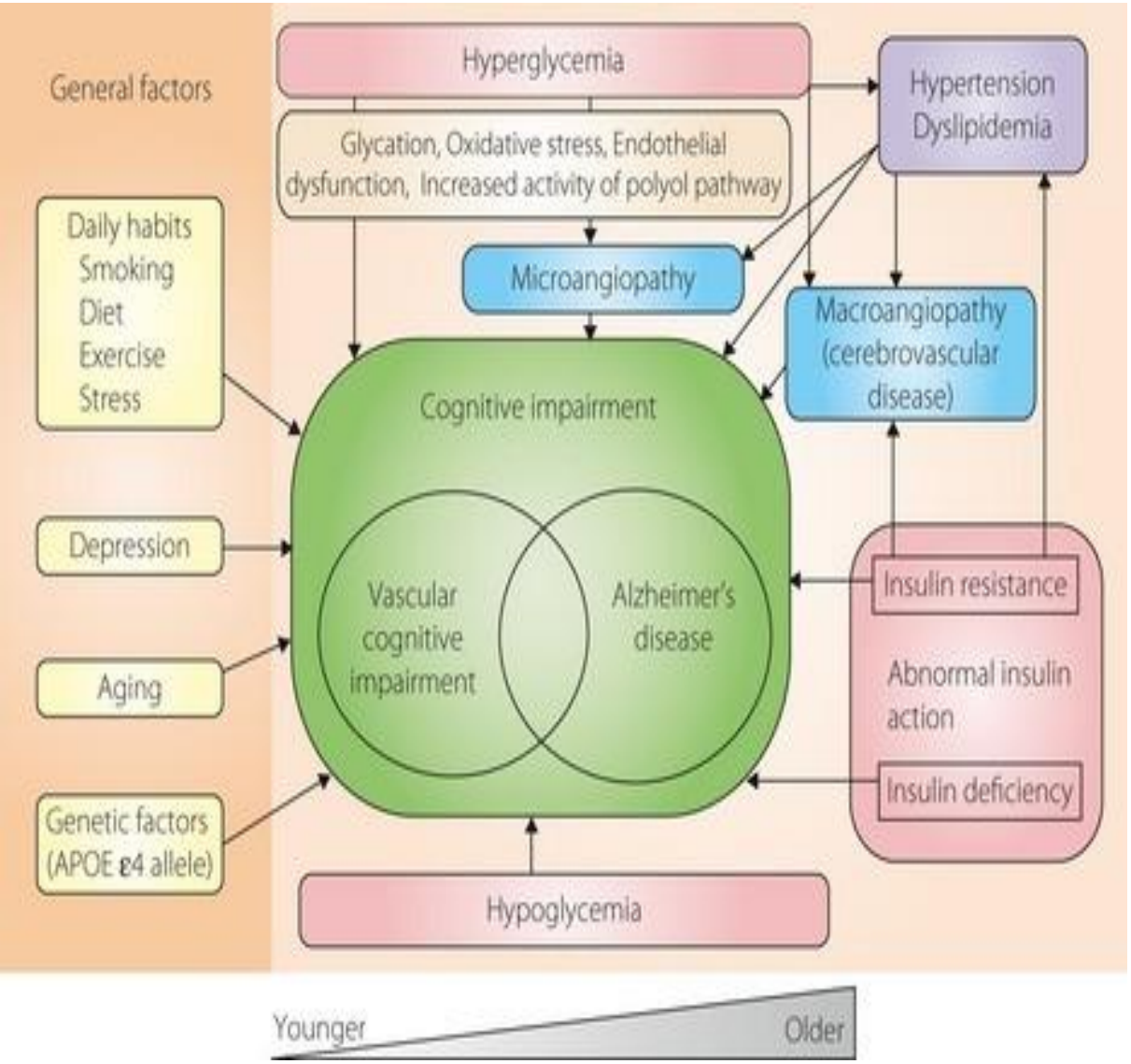
EFFETTO NEUROMODULATORIO

L'insulina agisce sia a livello elettrofisiologico che sulla concentrazione e funzione di diversi neurotrasmettitori

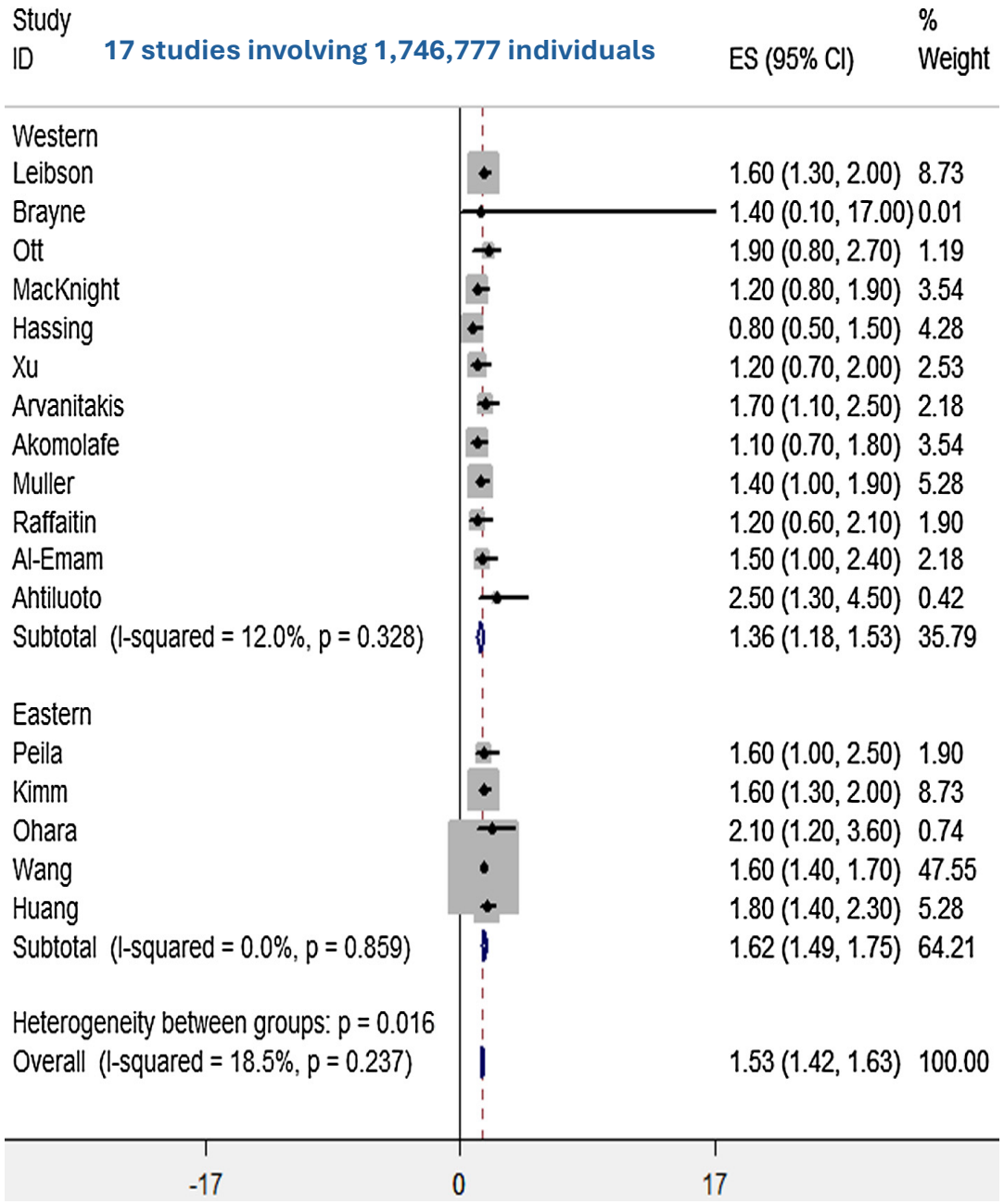
Heni, M. et al. Nat. Rev. Endocrinol. 11, 701–711 (2015)

Blàsquez et al, Front Endocrinol (Lausanne), 2014 Oct 9;5:161

An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease

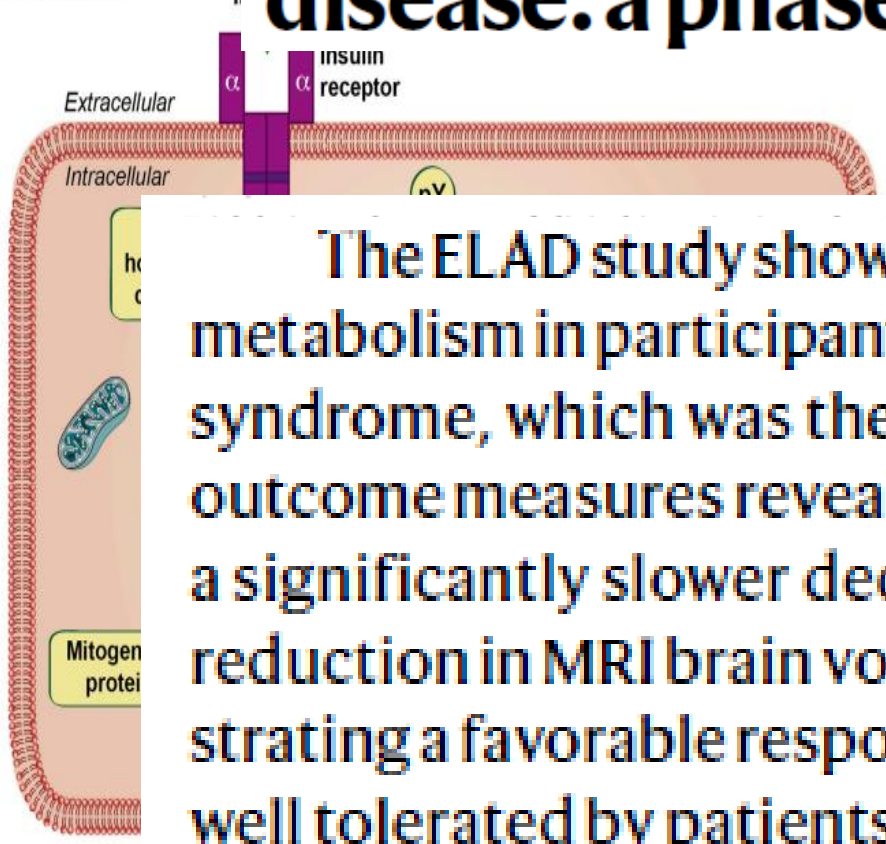


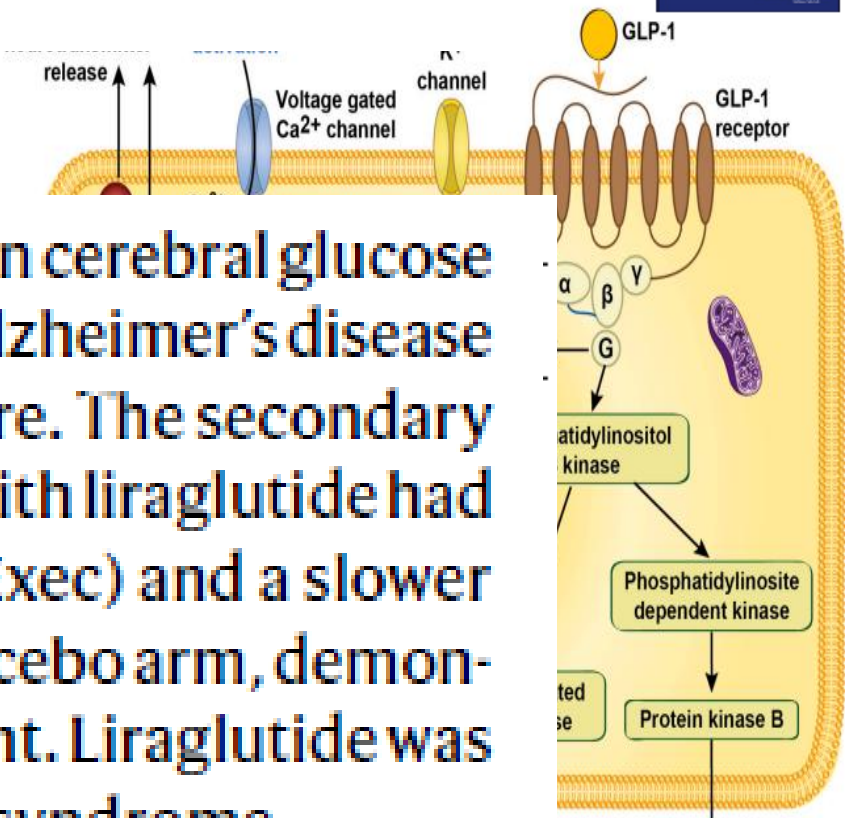
Zhang J et al. Diabetes Res Clin Pract. 2017



Article Edison P, Femminella MG et al Nature Medicine 2025 https://doi.org/10.1038/s41591-025-04106-7

Liraglutide in mild to moderate Alzheimer's disease: a phase 2b clinical trial





The ELAD study showed no significant changes in cerebral glucose metabolism in participants with mild to moderate Alzheimer's disease syndrome, which was the primary outcome measure. The secondary outcome measures revealed that patients treated with liraglutide had a significantly slower decline in cognition (ADAS-Exec) and a slower reduction in MRI brain volume compared to the placebo arm, demonstrating a favorable response to liraglutide treatment. Liraglutide was well tolerated by patients with Alzheimer's disease syndrome.

Neuroprotection / Memory formation / Brain development and function

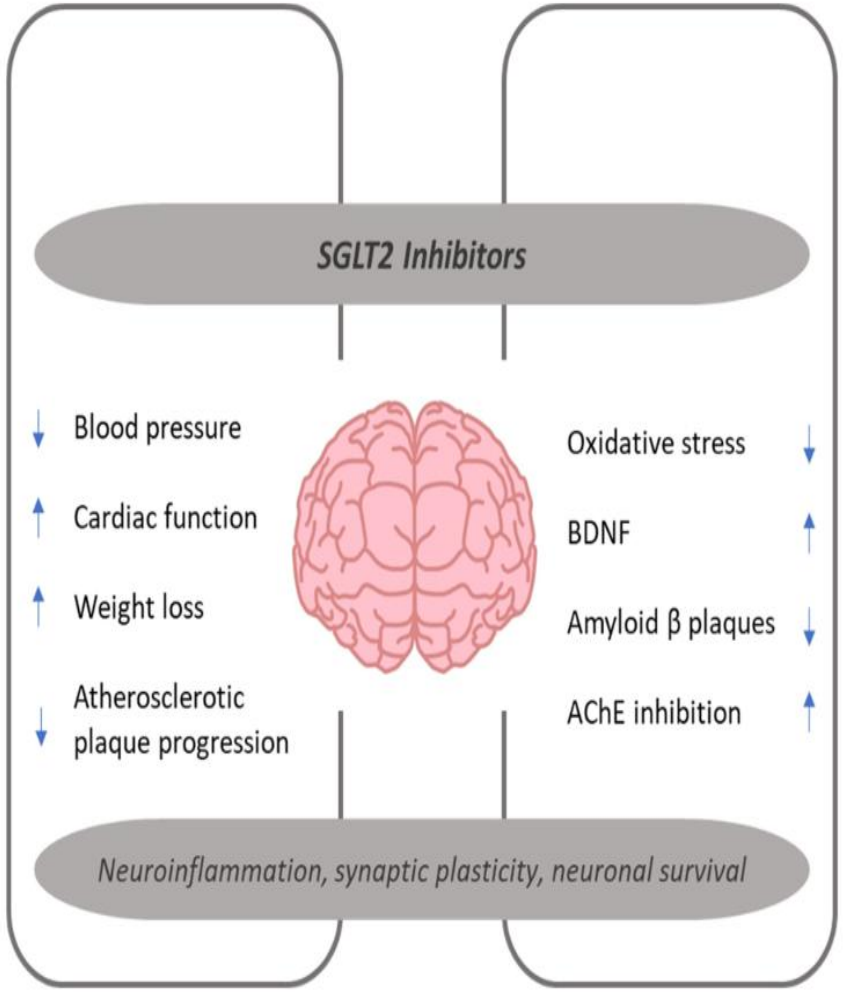
+ Autophagy	– Apoptosis
+ Cell growth and repair	– Oxidative stress
+ Gene transcription	– Tau hyperphosphorylation
+ Long term potentiation	
+ Neuronal growth	

Neuronal development / Neuroprotection / Memory formation

+ Long term potentiation	– Inflammation
+ Memory formation	– Apoptosis
+ Neuronal development	– α-synuclein
+ Cell survival	– Insulin resistance
+ Neurogenesis	– Tau hyperphosphorylation
+ Autophagy	– Amyloid deposition
+ Mitochondrial function	– Oxidative stress

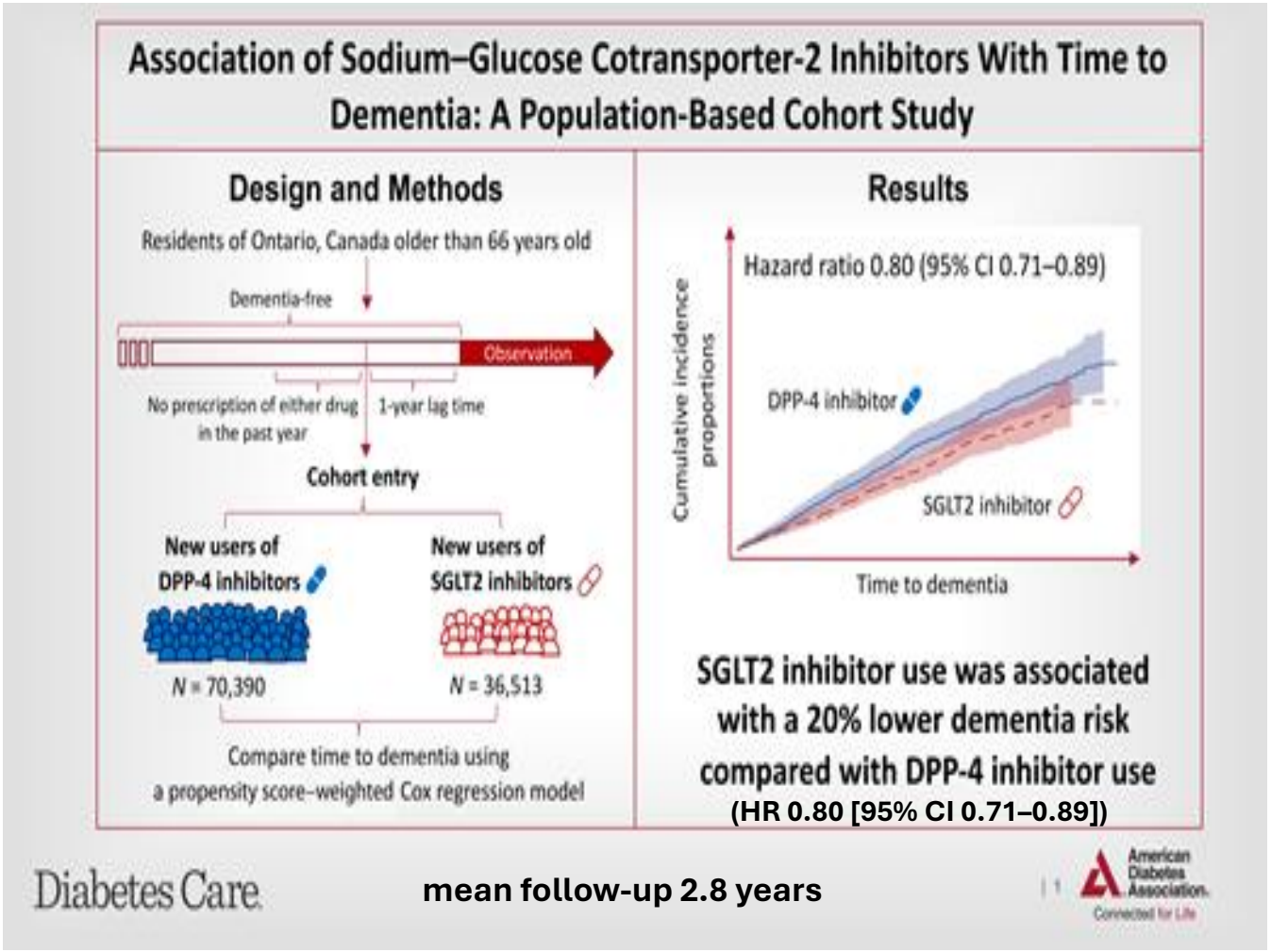
Nowel J et al. Ageing Research Reviews 2023

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



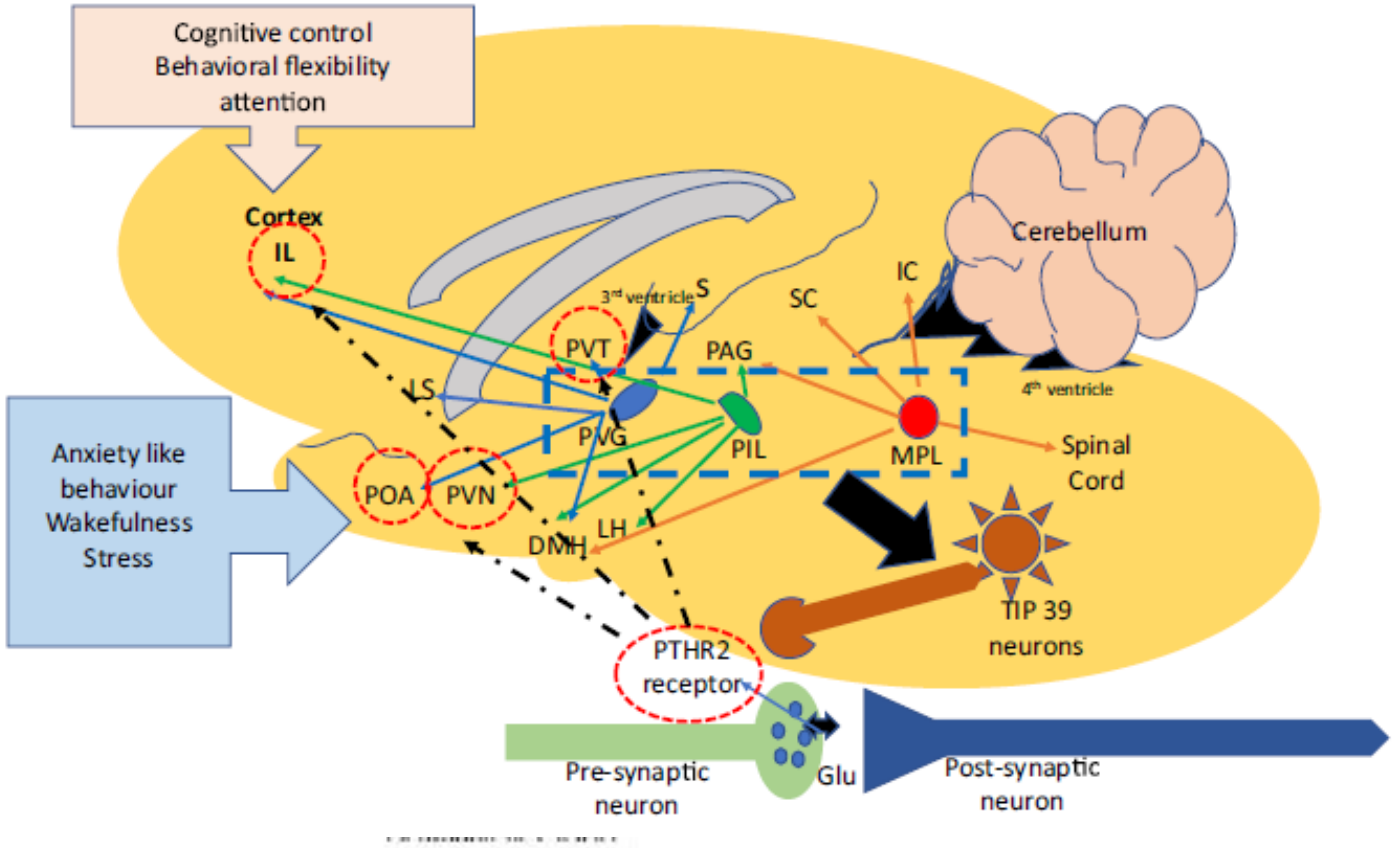
Nowel J et al. Ageing Research Reviews 2023

106,903 Ontario residents aged ≥66 yrs, new users of an SGLT2*i* or a DPP-4*i*.



Che-Yuan Wu et al.Diabetes Care. 2022

DECADIMENTO COGNITIVO ED IPERPARATIROIDISMO



E' la terza più comune patologia endocrina.
Sintomi classici solo nel 20% dei casi

I restanti casi manifestano spesso sintomi aspecifici: **fatica, ansia, difficoltà nella concentrazione, declino cognitivo, sintomi psicotici e ridotta qualità di vita**

Il Ca ha un ruolo nel metabolismo delle monoamine, modulando **metabolismo dopaminergico ed acetilcolinergico**

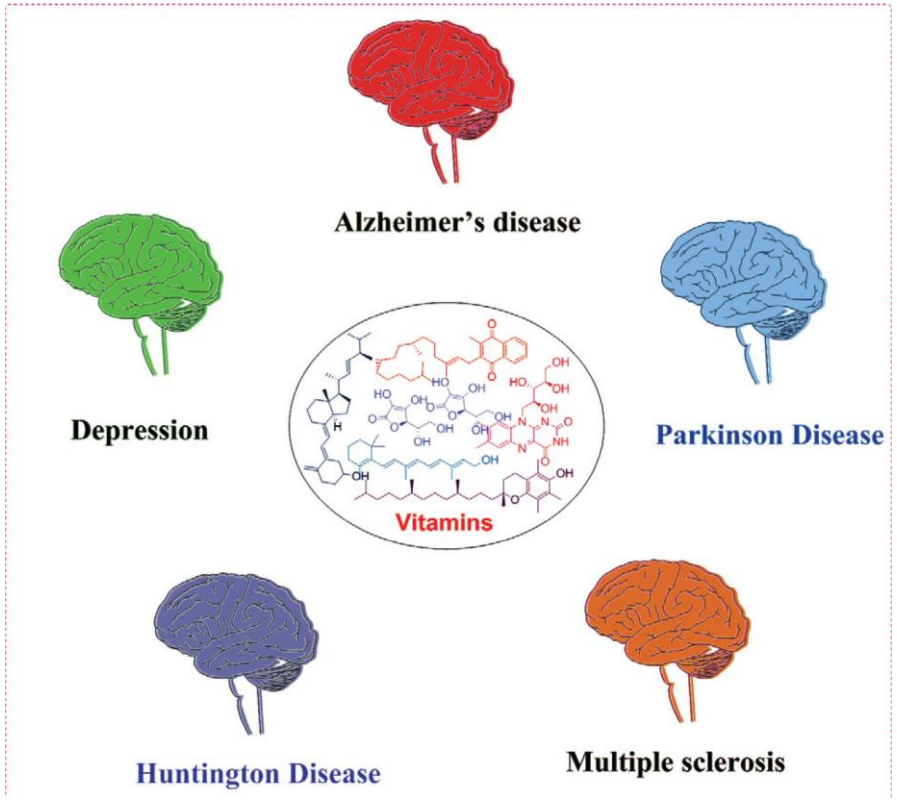
Meccanismo ancora non conosciuto: **effetto diretto del PTH** (TIP-39-PTHR2) o **indiretto tramite ipercalcemia e deficit Vit. D attiva**?

Coker LH et al Annals of Surgery 2005

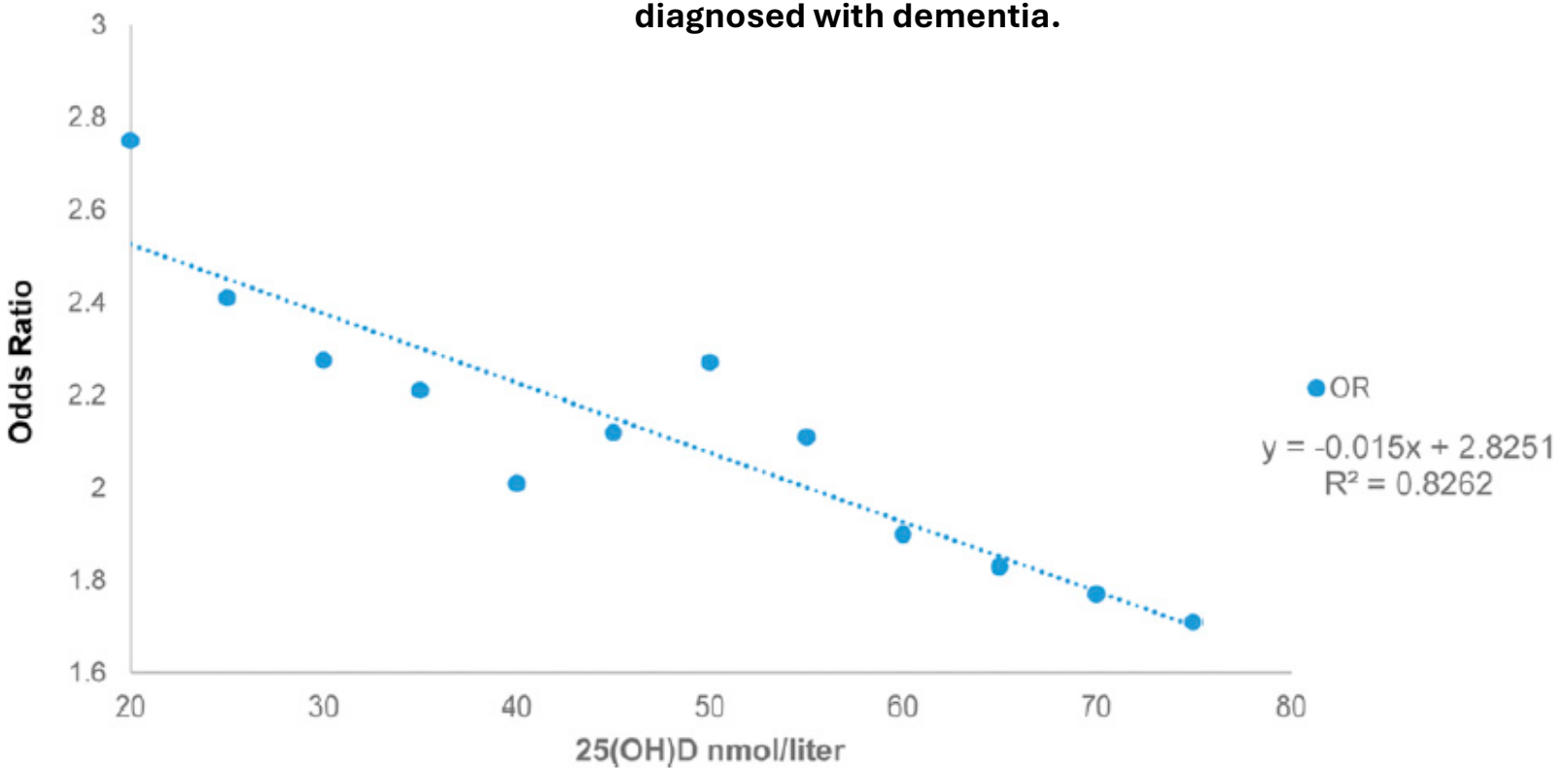
Chandran M et al. Reviews in Endocrine and Metabolic Disorders 2022

Nisson IL. J Intern Med, 2019.

Vitamin D Insufficiency is Associated with Higher Incidence of Dementia, a Large Community-Based Retrospective Cohort Study



4278 patients (57% women) from the Clalit Health Services database; During the17 yrs follow-up period (2002 -2019) 133 patients (3%) were diagnosed with dementia.



Age and-gender adjusted odds ratios for dementia according to vitamin D levels. Odds ratios for the risk of dementia, for different hydroxy vitamin D cutoff levels, calculated vs. sufficient levels (≥75 nmol/l)

Kumar RR et al. CNS & Neurological Disorders Drug Targets 2022

Kiderman D et al. Journal of Geriatric Psychiatry and Neurology 2023

Cognitive deficits in primary hyperparathyroidism – what we know and what we do not know: A narrative review

Study	Study design	Follow up length	Sample size	Country	Global cognitive function	Memory	Executive function	Attention
Perrier et al. [49]	RCT	6 months	18	USA		=	=	=
Chiang et al. [46]	Pre-post	380 days	40	Australia		=		
Cogan et al. [58]	Pre-post	4 months	12	USA		=	=	
Dotzenrath et al. [50]	Pre-post	6 months	52	Germany	>	>		
Goya et al. [59]	Pre-post	6 months	39	India	=	=		
Numann et al. [51]	Pre-post	4 months	20	USA		>		
Roman et al. [47]	Pre-post	4 weeks	41	USA		>		
Walker et al. [38]	Pre-post	6 months	128	USA		>		>
Babinska et al. [52]	Pre-post	18 months	70	Poland		>		
Casella et al. [53]	Pre-post	1 month	16	Italy			>	>
Mittendorf et al. [54]	Pre-post	4 weeks	47	USA			>	>
Prager et al. [55]	Pre-post	12 weeks	20	Austria		>		
Roman et al. [56]	Pre-post	6 months	159	USA		>		
Benge et al. [48]	Pre-post	1 month	67	USA	>			
Liu et al. [60]	Pre-post	6 months	43	USA	=			
Zanocco et al. [61]	Pre-post	3 weeks	44	USA	=		=	
Walker et al. [57]	Pre-post	6 months	46	USA	>	>	=	

The symbol = denotes no statistically significant difference between pre and post study for cognition. The symbol > denotes improvement in cognition post-surgery, with statistical significance. Unmarked boxes denote that cognition was not analysed in the study

Currently there is a lack of high-quality evidence to establish a direct causal relationship between PTH and cognitive impairment.

Though the available studies, limited though they are, suggest that cognitive impairment PHPT **is more likely to be associated with raised PTH levels per se and not with hypercalcaemia,**

It is possible that **vitamin D deficiency** if present in patients with PHPT, **could contribute to aberrations in cognitive function**

Chandran M et al. Rev Endocr Metab Disord 2022

Hong et al. Alzheimer's Research & Therapy (2023) 15:136
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Alzheimer's
Research & Therapy

RESEARCH Open Access

Risk of dementia in primary aldosteronism compared with essential hypertension: a nationwide cohort study

Namki Hong[1†], Kyoung Jin Kim[2†], Min Heui Yu[3], Seong Ho Jeong[4], Seunghyun Lee[5], Jung Soo Lim[5*] and Yumie Rhee[1*]

Studio di registro dal National Health Insurance Claim database in Korea (2003–2017)

3,687 pazienti con iperaldosteronismo primario (età media 56±10 aa), di cui 1339 trattati con surrenectomia, 2348 con antagonisti del recettore mineralcorticoide (MRA) **No diagnosi di demenza al baseline**
Match per sesso ed età in rapporto 1:4 con pazienti ipertesi (14741)

DECADIMENTO COGNITIVO ED IPERALDOSTERONISMO

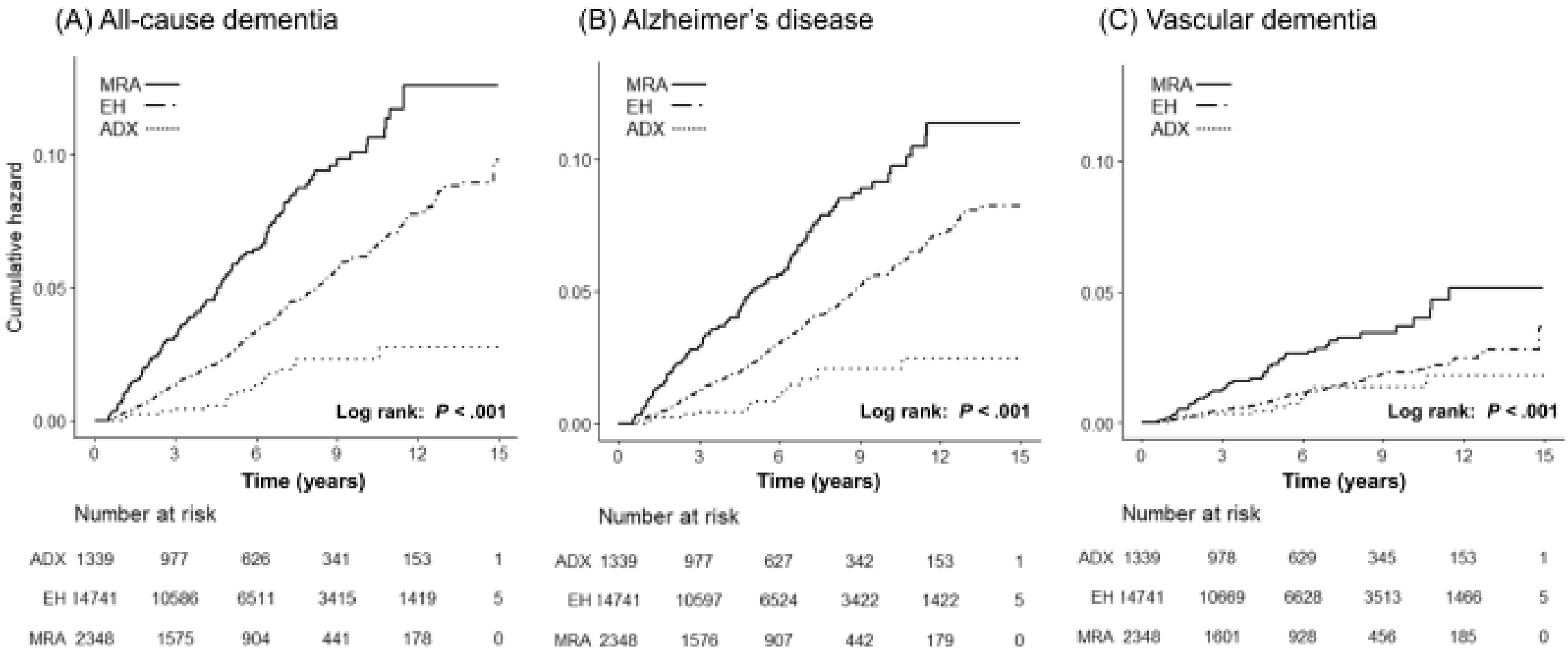


Fig. 2 Kaplan–Meier survival curves for (**A**) all-cause dementia, (**B**) Alzheimer's disease, and (**C**) vascular dementia according to PA treatment groups (ADX group vs MRA group) compared to their EH matches after treatment initiation. Abbreviations: ADX indicates adrenalectomy; EH, essential hypertension; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism

Hong et al. Alzheimer's Research & Therapy (2023)

DECADIMENTO COGNITIVO ED IPERALDOSTERONISMO

Table 2 Comparing risks for dementia between patients with PA and their EH matches after treatment initiation

	Number of events	Person-years	Cumulative incidence/1,000 person-years	Univariable Cox regression		Multivariable Cox regression[a]					
						Model 1		Model 2		Model 3	
				HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
All-cause dementia											
EH (reference)	522	88,156	5.92	1.00		1.00		1.00		1.00	
PA (Total)	156	20,953	7.45	**1.26 (1.05–1.51)**	0.011	**1.26 (1.06–1.52)**	0.011	0.90 (0.74–1.10)	0.317	1.20 (0.95–1.51)	0.134
PA (ADX)	18	8317	2.16	**0.35 (0.22–0.57)**	< 0.001	**0.35 (0.22–0.57)**	< .0001	**0.28 (0.17–0.46)**	< 0.001	0.69 (0.41–1.15)	0.157
PA (MRA)	138	12,637	10.92	**1.88 (1.56–2.27)**	< 0.001	**1.87 (1.55–2.26)**	< .0001	**1.30 (1.06–1.61)**	0.013	**1.31 (1.03–1.67)**	0.027
Alzheimer disease											
EH (reference)	475	88,257	5.38	1.00		1.00		1.00		1.00	
PA (Total)	140	20,979	6.67	**1.24 (1.03–1.50)**	0.027	**1.24 (1.02–1.50)**	0.029	0.87 (0.71–1.08)	0.209	1.17 (0.91–1.49)	0.220
PA (ADX)	16	8322	1.92	**0.34 (0.20–0.56)**	< 0.001	**0.34 (0.20–0.56)**	< .0001	**0.27 (0.16–0.45)**	< 0.001	0.68 (0.40–1.18)	0.172
PA (MRA)	124	12,657	9.80	**1.85 (1.51–2.26)**	< 0.001	**1.84 (1.51–2.25)**	< .0001	**1.26 (1.01–1.58)**	0.039	1.27 (0.99–1.63)	0.062
Vascular dementia											
EH (reference)	169	89,192	1.89	1.00		1.00		1.00		1.00	
PA (Total)	65	21,207	3.06	**1.64 (1.23–2.18)**	0.001	**1.64 (1.23–2.19)**	0.001	1.16 (0.85–1.60)	0.352	**1.59 (1.07–2.36)**	0.020
PA (ADX)	12	8338	1.44	0.76 (0.42–1.37)	0.358	0.78 (0.43–1.40)	0.404	0.64 (0.35–1.16)	0.141	1.45 (0.75–2.81)	0.265
PA (MRA)	53	12,869	4.12	**2.21 (1.62–3.02)**	< 0.001	**2.19 (1.61–2.99)**	< 0.001	**1.48 (1.05–2.10)**	0.026	**1.62 (1.08–2.45)**	0.020

Abbreviations: *ADX* adrenalectomy, *CI* confidence interval, *EH* essential hypertension, *HR* hazard ratio, *MRA* mineralocorticoid receptor antagonist, *PA* primary aldosteronism

[a] Model 1: age, sex, and income; Model 2: model 1 + baseline comorbidities (diabetes mellitus, dyslipidemia, chronic kidney disease, atrial fibrillation, non-fatal stroke, and non-fatal myocardial infarction); Model 3: model 2 + prescribed medications (angiotensin II receptor antagonists/angiotensin-converting-enzyme inhibitor (ARB/ACE inhibitor), β-blocker, calcium channel blocker (CCB), diuretics, statins, and antithrombotics)

Maggiore carico di comorbidità e FR CV nei pazienti con iperaldosteronismo primario

Follow up min 6 mesi, max 15 anni, medio 5.2 anni

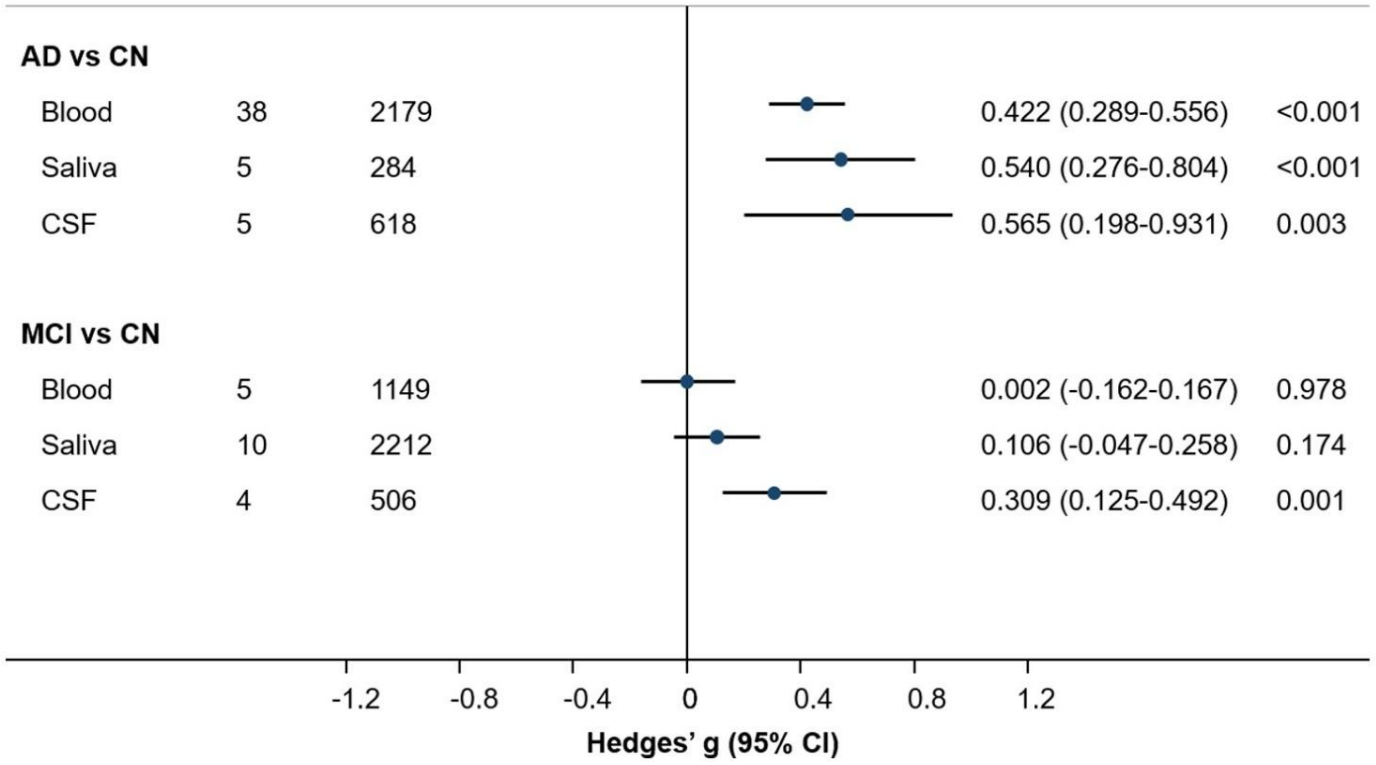
Hong et al. Alzheimer's Research & Therapy (2023)

Cortisol hypersecretion and the risk of Alzheimer's disease: A systematic review and meta-analysis

Bang Zheng [a], Roy Tal [a], Zhirong Yang [b], Lefkos Middleton [a c], Chinedu Udeh-Momoh [a d]

17,245 participants from 57 cross-sectional studies and 19 prospective cohort studies

Cortisol sample type	No. of studies	Pooled sample size	Hedges' g (95% CI)	*P* value
AD vs CN				
Blood	38	2179	0.422 (0.289-0.556)	<0.001
Saliva	5	284	0.540 (0.276-0.804)	<0.001
CSF	5	618	0.565 (0.198-0.931)	0.003
MCI vs CN				
Blood	5	1149	0.002 (-0.162-0.167)	0.978
Saliva	10	2212	0.106 (-0.047-0.258)	0.174
CSF	4	506	0.309 (0.125-0.492)	0.001



Highlights

- Patients with Alzheimer's disease had higher morning cortisol level than controls.
- Clinically meaningful AD-related increases of morning cortisol level were quantified.
- People with mild cognitive impairment had higher CSF cortisol than normal controls.
- High cortisol is associated with accelerated cognitive decline in people with MCI.
- Predictive value of cortisol for cognitive decline in preclinical adults is unclear.

Ageing Research Reviews
Volume 64, December 2020, 101171

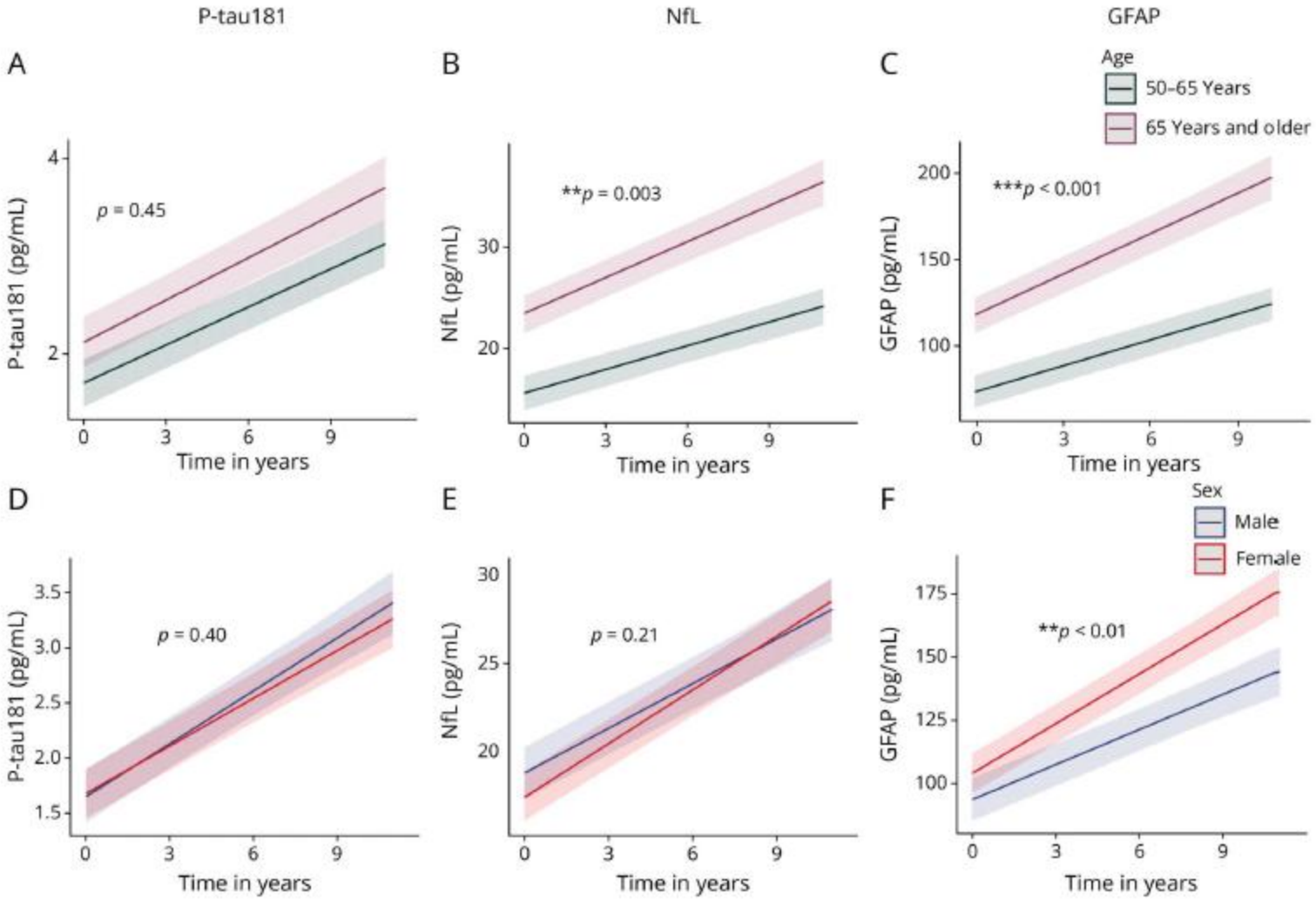
Review > Inflammopharmacology. 2025 May;33(5):2641-2656.
doi: 10.1007/s10787-025-01734-w. Epub 2025 Apr 18.

Impact of corticoid receptors on Alzheimer's disease: a neuroendocrine perspective

Falguni Goel [1], Daksh Kumar [2], Anushka Sharma [2]

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that has been strongly associated with changes in corticoid receptor function and HPA axis dysregulation. This review gives an overview of the complex role of GC and MC receptors in AD, especially how chronic exposure to elevated cortisol contributes to hippocampal degeneration, oxidative stress, and cognitive decline. Specific emphasis lies with cortisol, brought to the attention of neurotoxicity, and relates it to Cushing syndrome with chronic hyper-cortisolism simulating cognitive and structural impairments seen in AD. The impact of HPA axis over-activity in AD pathology is presented, demonstrating its contribution to neuro-inflammation and possible utilization as a biomarker for disease progression. This review further includes pharmacological strategies that modulate corticoid receptors for the reduction of GC-induced neurotoxicity and includes selective GR antagonists and MR agonists. Lifestyle modifications, which modulate HPA activity, are the other non-pharmacological approach to managing AD. Finally, novel drugs and interventions targeting the regulation of GC, anti-inflammatory pathways, as well as attenuation of oxidative stress are emerging strategies. Such a strategy implies that it is possible that receptor activity balance can delay or arrest AD progression.

Association of Nonmodifiable Risk Factors With Alzheimer Disease Blood Biomarkers in Community-Dwelling Adults in the ESTHER Study



This population-based study on dementia biomarkers [1,026 participants (1:1 with/without dementia during FU) aged 50–75 years at baseline followed over 17 years] found that **NfL was dependent on age while GFAP on age, sex, and menopause status. GFAP levels and rate of increase were especially higher in premenopausal women**

Stoker H et al. Neurology 2025

Sex Hormones and Risk of Incident Dementia in Men and Postmenopausal Women

Result: A total of 186,296 men (mean age: 56.68 years, SD: 8.18) and 126,109 postmenopausal women (mean age: 59.73 years, SD: 5.78) were included. After 12.0 (IQR: 11.0-13.0)-year follow-up, 3874 (2.08%) male participants and 2523 (2.00%) female participants developed dementia. Men in the highest quintile of free testosterone levels had a reduced risk of all-cause dementia (HR: 0.63, 95%CI: 0.56-0.71) and AD (0.49, 0.60-0.72) compared to those in the lowest quintile. Conversely, men in the highest quintile of SHBG levels had an increased risk of all-cause dementia (1.47, 1.32-1.64) and AD (1.32, 1.11-1.58) compared to those in the lowest quintile. Among postmenopausal women, those in the fourth quintile of free testosterone levels exhibited a lower risk of all-cause dementia (0.84, 0.78-0.95) and AD (0.76, 0.63-0.91). Higher SHBG was linked to an increased incidence of all-cause dementia (1.35, 1.28-1.55) and AD (1.52, 1.25-1.85) in menopausal women.

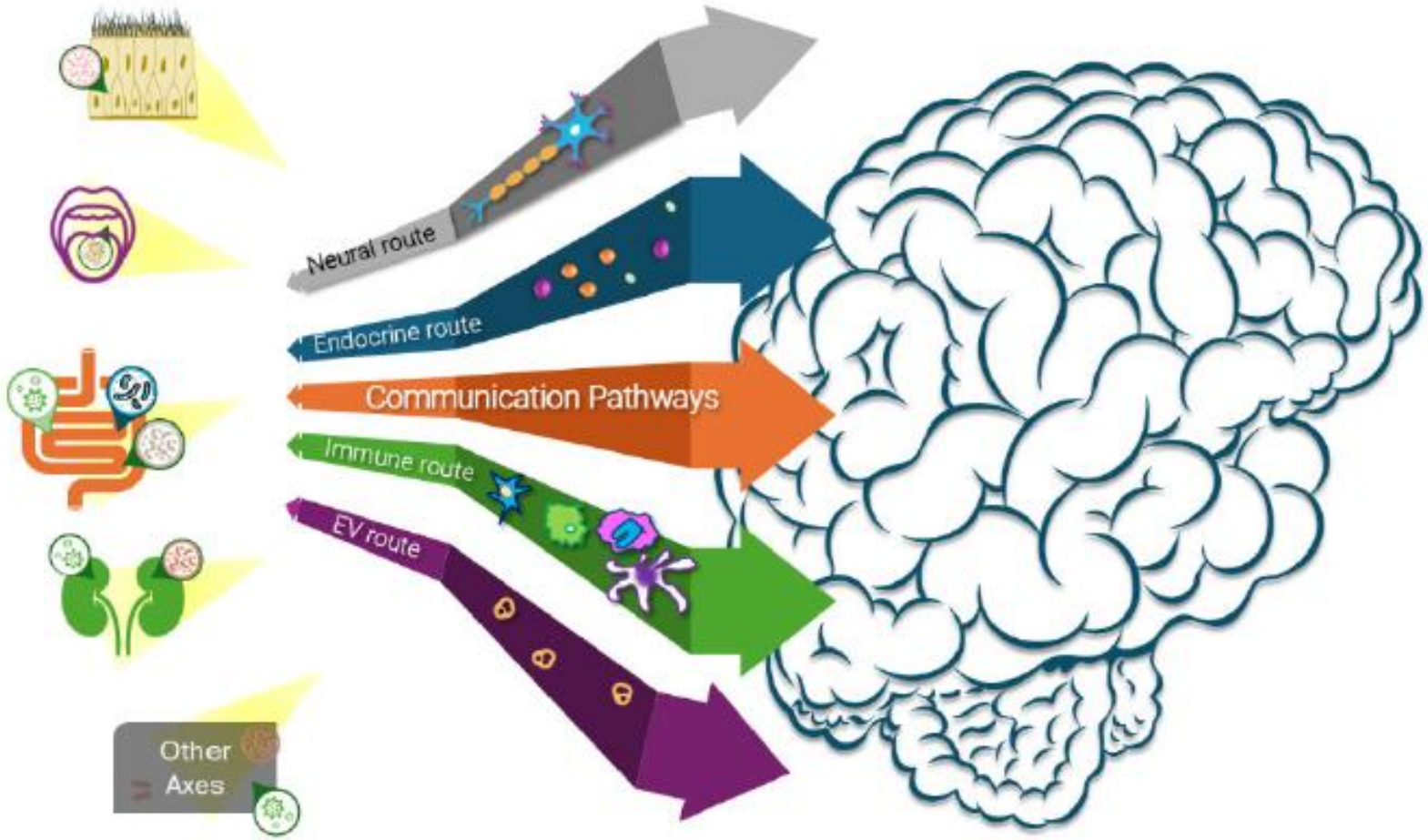
Conclusion: Our findings revealed that higher SHBG and lower free testosterone concentrations seem to be associated with higher incidence of all-cause dementia and AD and further studies must be done to determine causality.

Data from UK Biobank

Zhao Y et al. Clin Endocrinol 2025

Neurodegeneration as Ecosystem Failure: A New Paradigm for Prevention and Treatment

International Journal of Molecular Sciences



Multi-Route Communication in Organ–brain Axes.

Peripheral organs communicate with the brain through **multiple pathways**: **neural routes** (vagus nerve, cranial nerves), **endocrine signaling** (hormones, metabolites), **immune routes** (cytokines, infiltrating cells), and extracellular vesicle **(EV) trafficking carrying pathological cargo**, including **misfolded proteins** and **microbial components**.

Bidirectional communication allows brain pathology to propagate back to peripheral organs, establishing the feedback loops that characterize ecosystem failure.

The convergence of multiple routes explains how peripheral dysfunction rapidly becomes systemic neurodegeneration.

TAKE HOME MESSAGES

- Le disfunzioni endocrine possono contribuire allo sviluppo ed evoluzione dei disturbi cognitivi e comportamentali sia direttamente (recettoriale/nucleare →ormoni tiroidei, insulina, GLP1, PTH?, Vitamina D?) che indirettamente (stress ossidativo/vascolare, modificazione del microbiota intestinale, neuro infiammazione)

- Le disfunzioni tiroidee ed il diabete mellito (insulinoresistenza) sono le endocrinopatie più comunemente correlate al rischio di deficit cognitivo e demenza.

- L'iperparatiroidismo deve sempre essere valutato a fronte di comparsa improvvisa di disturbi cognitivo-comportamentali

- Anche l'iperfunzione surrenalica sembra conferire un maggior rischio di sviluppare demenza, verosimilmente per la stretta relazione con I maggiori fattori di rischio cardiovascolare

- Esiste una interazione bidirezionale tra il SNC e gli organi periferici, incluso il sistema endocrino, con multipli circuiti a feed-back coinvolti nello sviluppo di insufficienza multiorgano (periferica e del SNC)

- **L'endocrinogeriatria può, quindi, rappresentare un'importante strumento per l'individuazione di profili di rischio di demenza, contribuendo alla prevenzione e/o al rallentamento dell'evoluzione clinica di una malattia multifattoriale, sempre più diffusa ed invalidante come la demenza**