LUNDS UNIVERSITET

Diabetologiskt vårmöte
Göteborg
15–17 april 2026

Nyheter om diabetes och hjärnan
- mekanismer och behandlingsmöjligheter

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Inst. Kliniska vetenskaper Malmö

Lunds universitet

Inga jäv att deklarera för denna presentation

14. Årets tema: Hjärnan

T1D, särskilt vid tidig debut, är kopplat till kognitiva nedsättningar. Ketoacidos vid debut och långvarig hyperglykemi är riskfaktorer för både strukturell och funktionell hjärnpåverkan. Hypoglykemi kan ge akut konfusion, inlärningssvårigheter, exekutiva svårigheter eller medvetslös het. Återkommande perioder med medvetslöshet av lågt blodsocker kan ge bestående hjärnpåverkan. T1D är också associerat med mikrovaskulära förändringar i hjärnan, vilket kan bidra till kognitiv försämring.

T2D är kopplat till ökad risk för depression, kognitiv nedsättning, demens och neurodegenerativa sjukdomar, medan T1D främst påverkar kognitiv funktion, särskilt vid tidig debut och högt HbA1c. Mekanismerna är komplexa och involverar både metabola och vaskulära faktorer.

När det gäller sjukdomsprogression så föreligger stor individuell variation; kardiovaskulär riskfaktorbörda, livsstil, kost och utbildning kan påverka förloppet.

Diabetes och nedsatt kognition/demens

- Ett kliniskt problem
- Ett behandlingsdilemma
- Ett hälsoekonomiskt problem
- Ett mänskligt problem

- En vetenskaplig utmaning…

Relativ risk (RR) för demens vid diabetes (typ 1 och 2)

- All demens: RR 1.51 (95% CI: 1.31-1.74)
- Vaskulär demens: RR 2.48 (2.08-2.96)
- Alzheimers sjukdom: RR 1.46 (1.20-1.77)

Cheng G *et al.* Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J. 2012; 42(5):484-91.

T1D

Dementia Risk in People With Type 1 Diabetes and Associated Risk Factors: A Nationwide, Register-Based Cohort Study

Objective

To assess (1) risk of all-cause dementia and dementia subtypes and (2) associated risk factors in individuals with type 1 diabetes

Methods

Type 1 diabetes from the Swedish National Diabetes Register (*n* = 43,440)

Matched control individuals from the Swedish general population (*n* = 217,109)

Outcome: all-cause dementia and dementia subtypes

Results

All-cause dementia: *n* = 530 (1.2%) in type 1 diabetes and *n* = 1,867 (0.9%) matched control individuals

All-cause dementia risk: hazard ratio **2.02 (95% CI 1.83–2.23)**

Dementia subtypes risk:

Alzheimer disease:	hazard ratio 1.38 (95% CI 1.13–1.69)
Vascular dementia:	hazard ratio 3.73 (95% CI 3.07–4.52)
Non-Alzheimer–nonvascular dementia:	hazard ratio 1.87 (95% CI 1.63–2.15)

Risk factors for all-cause dementia in individuals with type 1 diabetes:

	Age (1 year)	Single status	HbA_{1c} (10 mmol/mol)	Higher education	Systolic blood pressure (10 mmHg)	History of stroke/TIA
hazard ratio (95% CI)	1.14 (1.13–1.15)	1.56 (1.23–1.97)	1.10 (1.03–1.18)	0.66 (0.55–0.79)	1.07 (1.02–1.13)	2.65 (1.91–3.67)

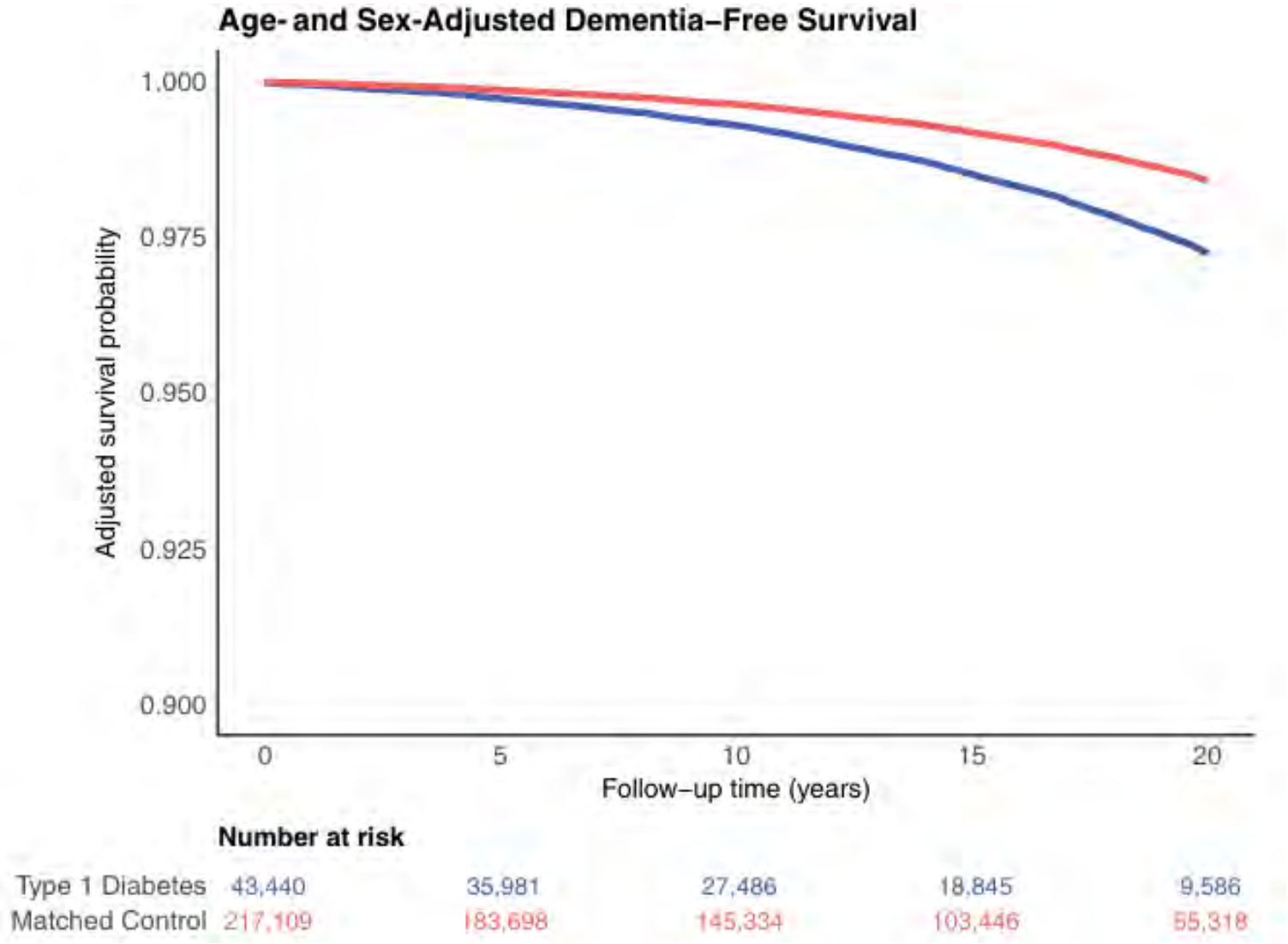
Conclusion

Risk of all-cause dementia and dementia subtypes is higher in individuals with type 1 diabetes compared to matched control individuals.

NDR NATIONELLA DIABETESREGISTRET

Jances M, *et al*. Diabetes Care. 2025;48(11):1888-1895.

T1D



Survival curve of **all-cause dementia** in individuals with **type 1 diabetes** and matched control individuals. Blue line indicates individuals with type 1 diabetes, and red line indicates age-, sex-, and county-matched control individuals. Follow-up time is used as the time scale.

Jances M, *et al*. Diabetes Care. 2025;48(11):1888-1895.

Mental resiliens hos T1D escapers – varför?

- Mildare typ 1 diabetes, partiellt bevarad beta-cell funktion?
- God följsamhet till behandling, väl utvecklade vårdkontakter
- Bevarad neurobiologisk struktur och funktion i CNS
- Kognitiv funktion relativt väl bevarad trots lång diabetesduration
- God förmåga att hantera kronisk sjukdomsbörda (”coping”)
- Personlighet (”social skills”, extroversion?)
- Okända faktorer, genetik

Eske C Gertje, Pontus Tideman, Peter M Nilsson (2026)

Elin Dybjer

Typ 2-diabetes och incident demens i befolkningskohorten Malmö Kost Cancer

	HR (95% CI)	p
All-cause dementia	1.46 (1.20-1.77)	**<0.001**
Mixed dementia	1.61 (1.12-2.30)	**0.010**
Vascular dementia	1.84 (1.32-2.58)	**<0.001**
Alzheimer's disease	1.26 (0.84-1.89)	0.272

- N=29 139
- Medelålder 55 år vid baslinjen 1991-2014

Adjusted for age, sex, education, smoking, alcohol consumption, physical activity, SBP, BMI, ApoB/ApoA-ratio, history of CVD (stroke or coronary event), use of anti-hypertensive medication and use of lipid-lowering treatment.

Dybjer E, et al. *Brain Commun.* 2023; 5(2):fcad054.

Risk för nedsatt kognition

- Ökad även vid prediabetes[1]
- Ökad med ökande blodsockernivå i befolkningen (linjärt samband)[2]

1. Biessels GJ, et al. Lancet Diabetes Endocrinol 2014
2. Dybjer E, et al. BMC endocrine disorders. 2018;18(1):91.

Elin Dybjer

Befolkningsstudie från Malmö: kognitiva testresultat vid normoglykemi, prediabetes och diabetes

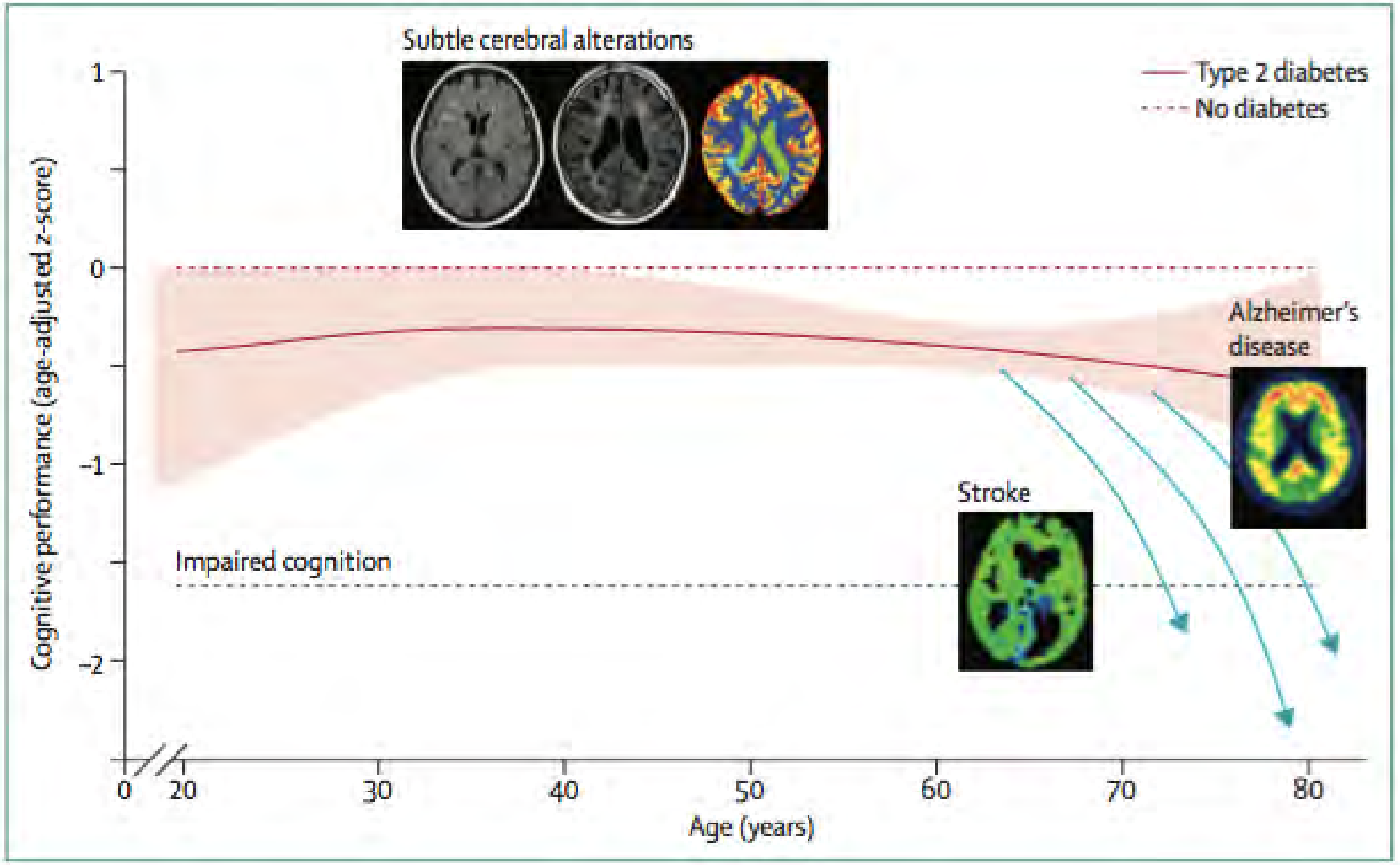
	MMSE (p/100)	AQT test time (s)
Normal glucose tolerance	**80.4 (79.7-81.1)**	**130.8 (129.5-132.2)**
Pre-diabetes	**78.5 (77.6-79.4)****	**133.8 (132.0-135.5)***
Diabetes	**78.4 (77.2-79.5)****	**136.0 (133.8-138.2)***

N= 2994, medelålder 72 år

*p<0.05, **p<0.01 of difference in mean test results between NGT (reference) and each other category. Adjusted for age, sex, education, physical activity, smoking and alcohol consumption

Dybjer E, *et al.* BMC Endocr Disord. 2018;18(1):91.

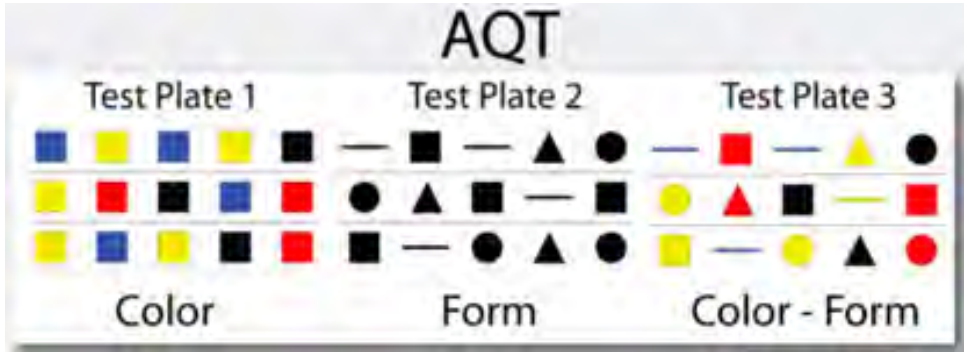
Subtil påverkan på kognitionen genom hela livet vid typ 2-diabetes

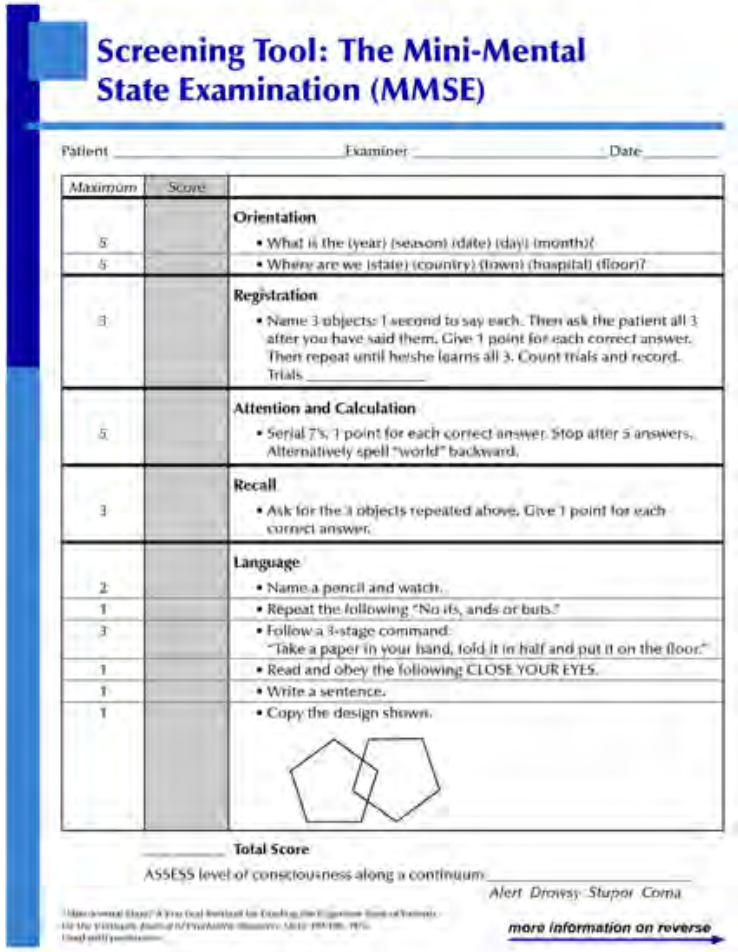


Biessels GJ, *et al.* Lancet Diabetes Endocrinol 2014

Kognitiva domäner som påverkas vid diabetes

- Global kognitiv funktion
- Processing speed
- Exekutiv funktion
- Minne





Screening Tool: The Mini-Mental State Examination (MMSE)

Patient _____ Examiner _____ Date _____

Maximum	Score	
5		**Orientation** • What is the (year) (season) (date) (day) (month)? • Where are we (state) (country) (town) (hospital) (floor)?
3		**Registration** • Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat until he/she learns all 3. Count trials and record. Trials _____
5		**Attention and Calculation** • Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
3		**Recall** • Ask for the 3 objects repeated above. Give 1 point for each correct answer.
2		**Language** • Name a pencil and watch.
1		• Repeat the following "No ifs, ands or buts."
3		• Follow a 3-stage command: "Take a paper in your hand, fold it in half and put it on the floor."
1		• Read and obey the following CLOSE YOUR EYES.
1		• Write a sentence.
1		• Copy the design shown.

_____ **Total Score**

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

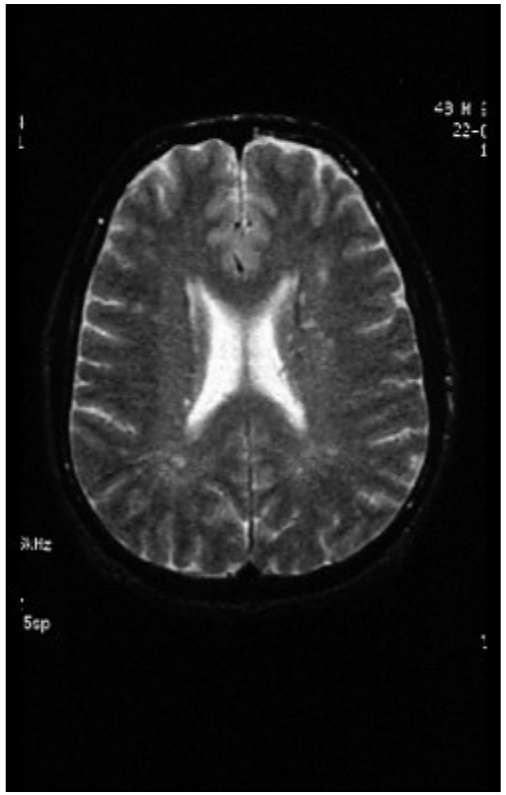
more information on reverse

Dybjer E, *et al.* BMC Endocrine Dis. 2018;18(1):91.

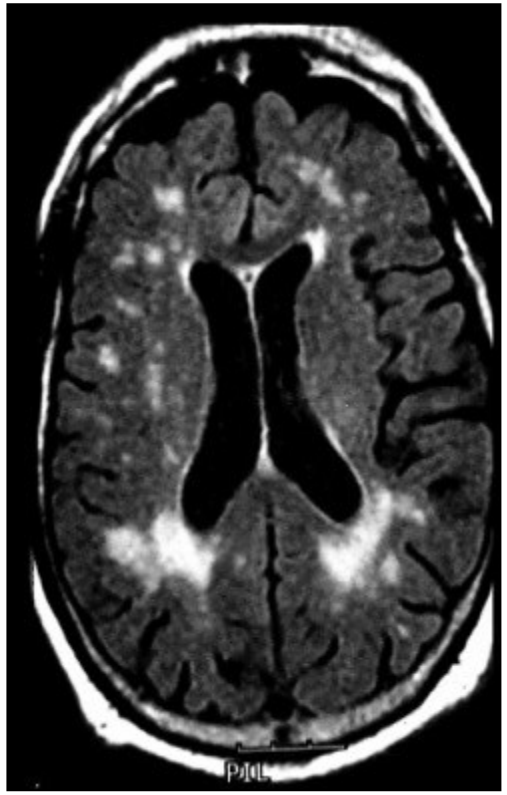
Patofysiologi

Förändringar i hjärnan vid diabetes

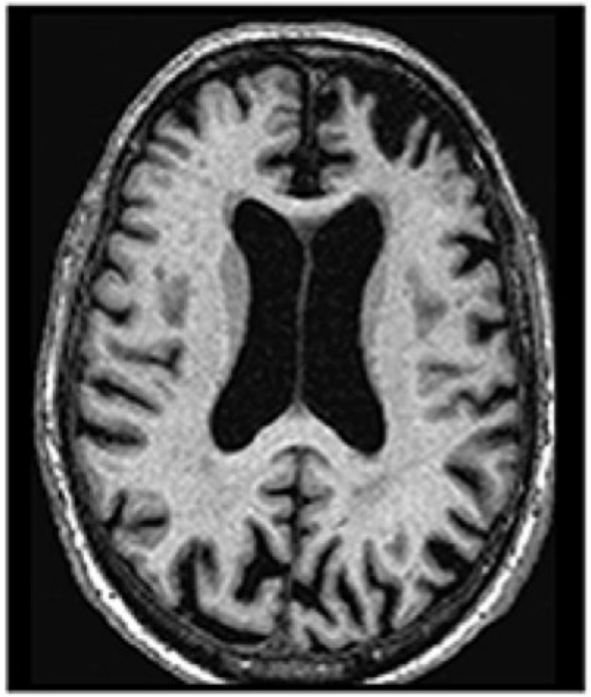
Confluent periventricular hyperintensities



Lacunar infarcts and leucoaraiosis

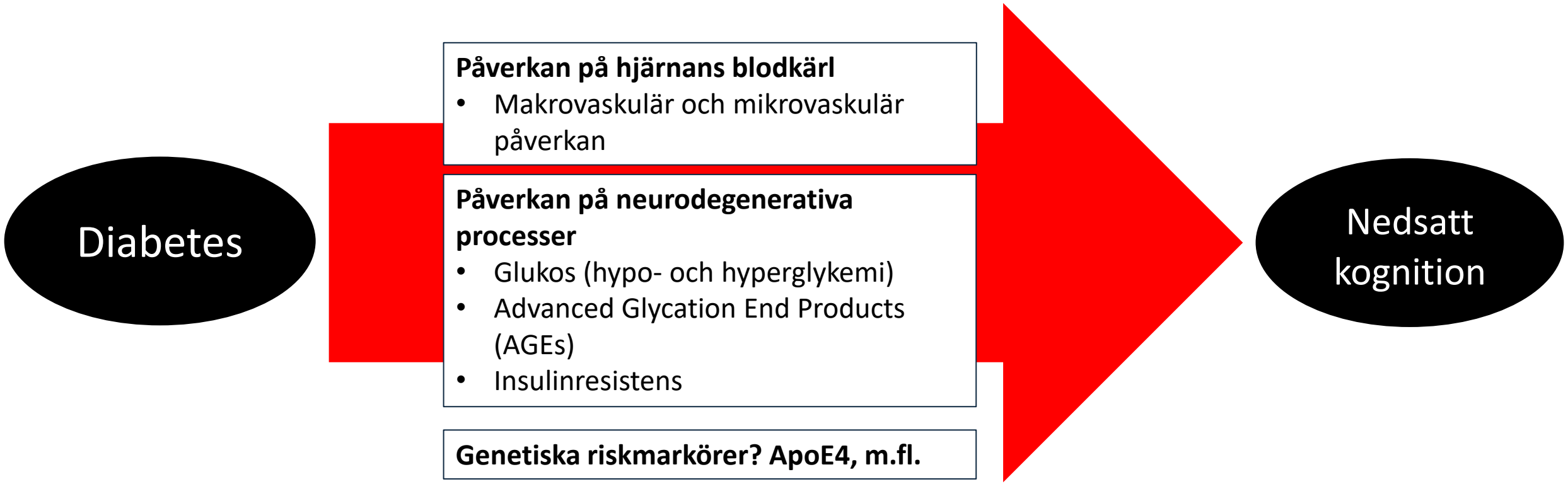


Brain atrophy

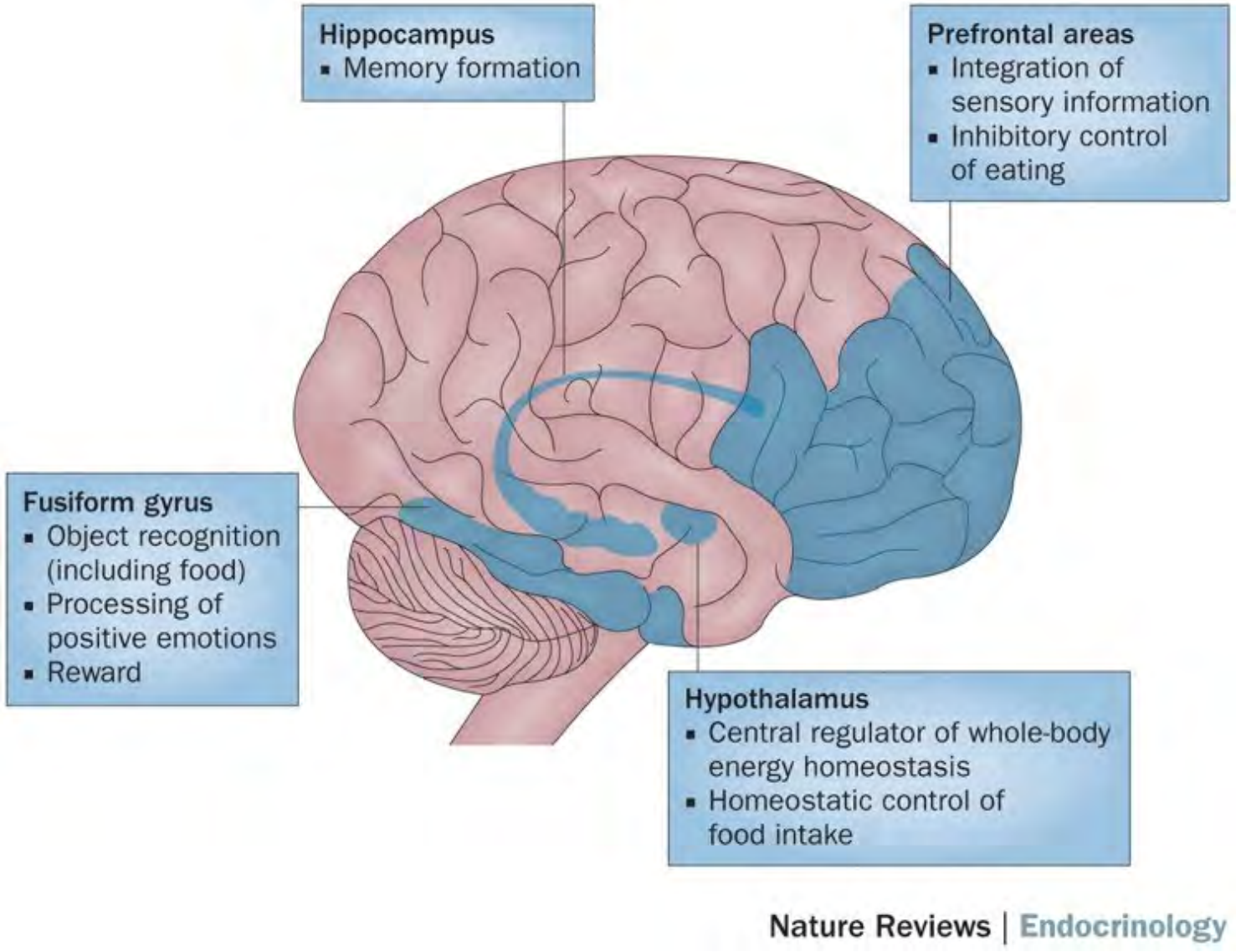


Biessels GJ, *et al.* Lancet Diabetes Endocrinol 2014

Möjliga mekanismer (hypoteser)

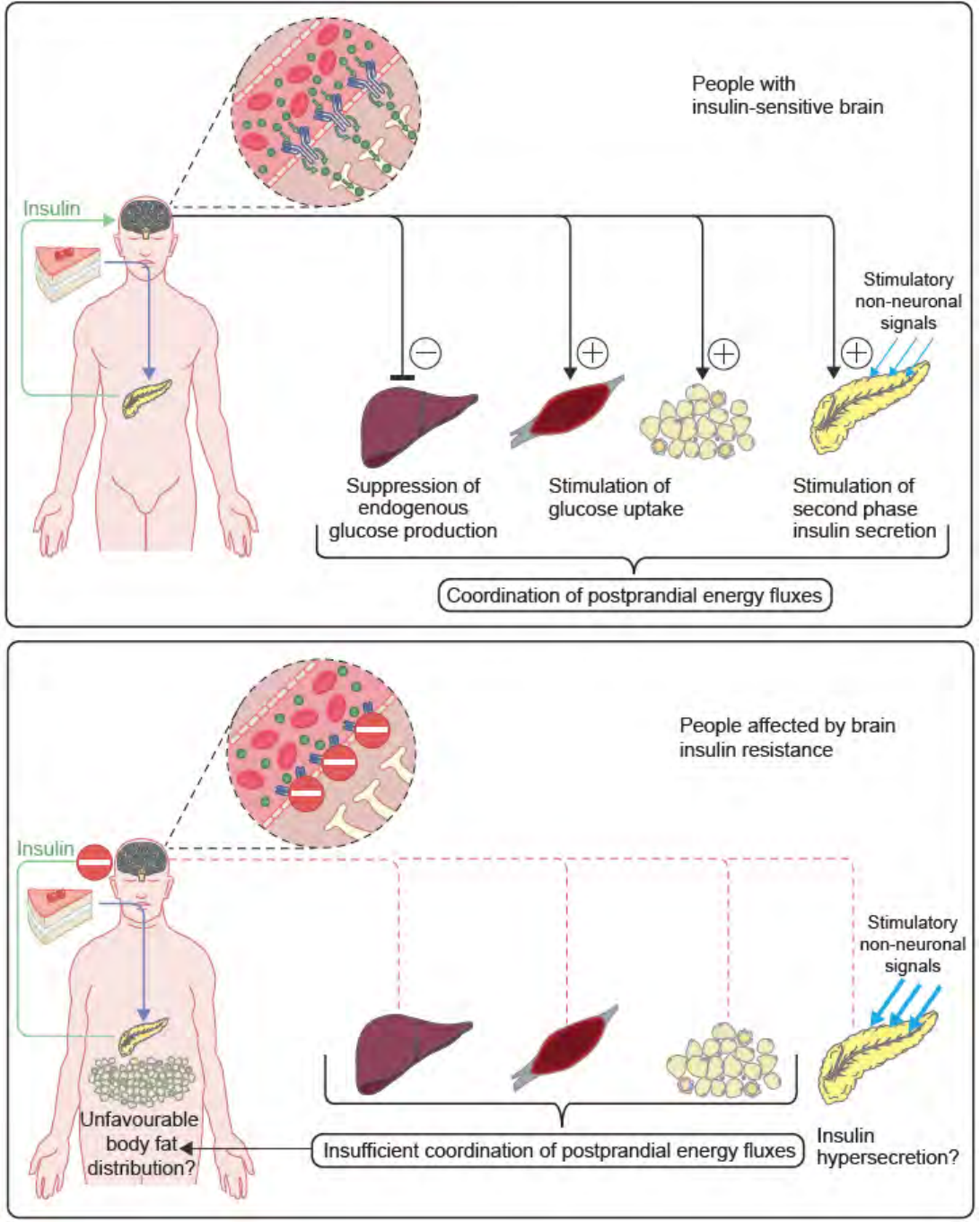


Insulinkänsliga områden i hjärnan

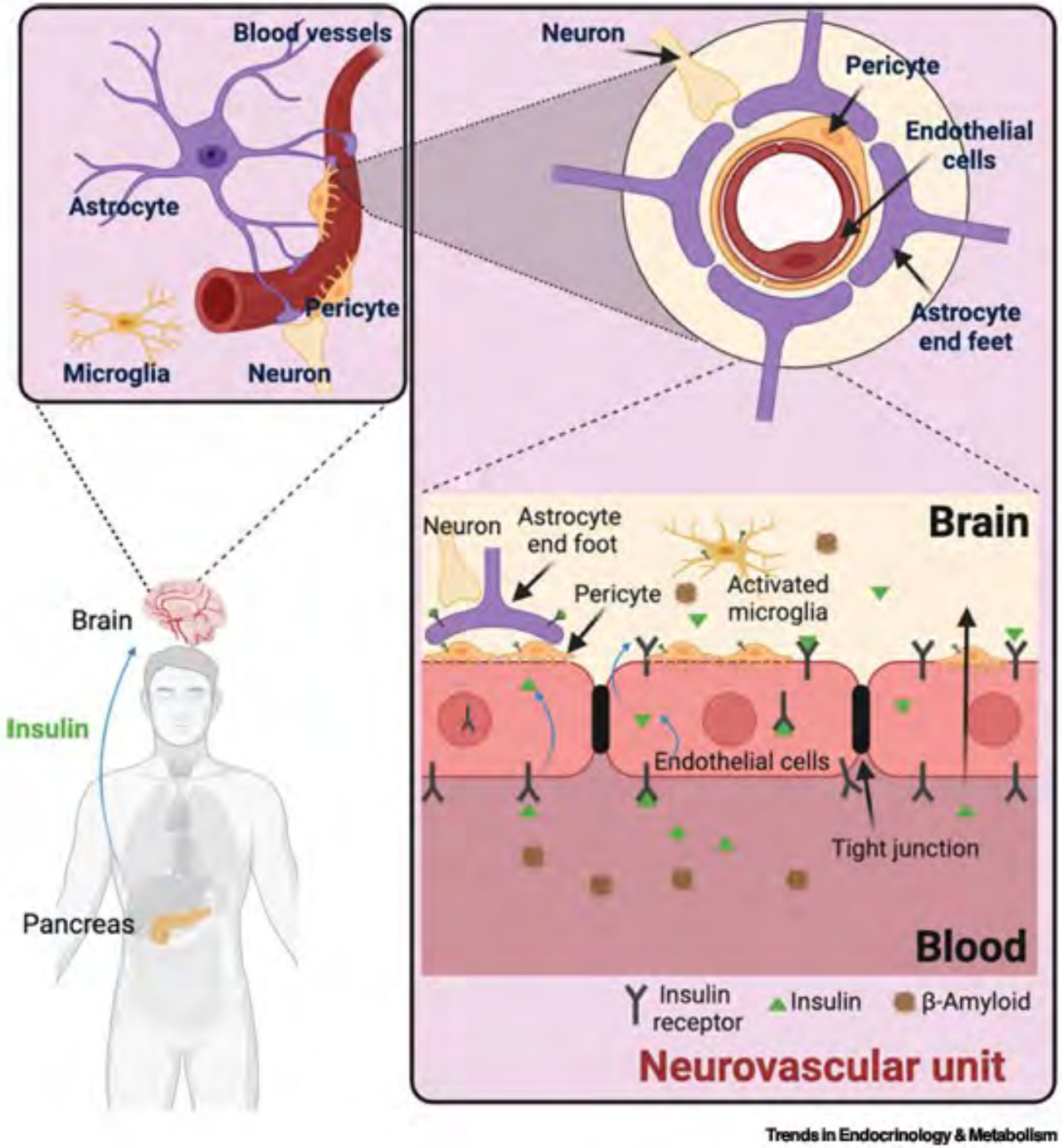


Prof Martin Heni,
Minkowski-pristagare
EASD 2022

Insulinresistens i hjärnan – påverkar perifer metabolism



Heni M. Diabetologia 2024



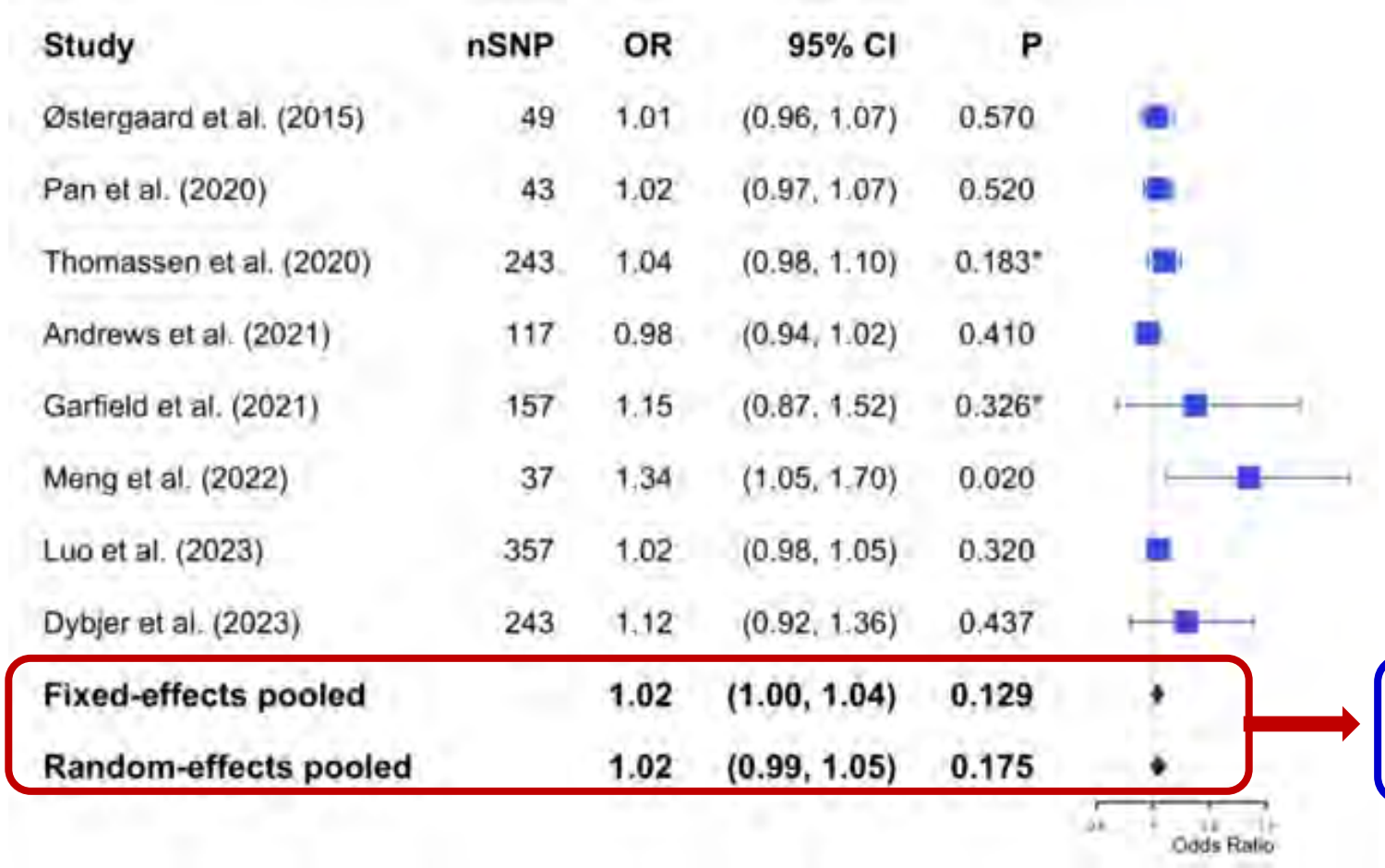
Peripheral–central axis at the neurovascular unit (NVU). Pancreas-derived insulin crosses the blood–brain barrier (BBB), which is a part of the NVU.

The insulin receptor (IR) is expressed in all cell types of the NVU but is most abundantly expressed in brain endothelial cells. While this receptor is critical for signaling within brain endothelial cells, it is not required for insulin transport across the BBB.

Chen W, *et al*. Trends Endocrinol Metab. 2026; 37(1):17-30.

Systematic Review

Evaluating the Causal Association Between Type 2 Diabetes and Alzheimer's Disease: A Two-Sample Mendelian Randomization Study



The pooled results of the **Mendelian Randomization genetic analysis** between type 2 diabetes mellitus and Alzheimer's disease (based on fixed effect model with heterogeneity I2 = 31.3%).

No causality proven between T2D and risk of Alzheimer Disease (AD)

Han S, *et al*. Biomedicines. 2025; 13(5):1095.

Behandling

Mia Kivipelto, KI

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

We screened 2654 individuals 2009-2011 and randomly assigned 1260 to the intervention group (n=631) or control group (n=629).

A multidomain intervention could **improve or maintain cognitive functioning** in at-risk elderly people from the general population.

Ngandu T, *et al*. Lancet. 2015; 385(9984):2255-63.

Preserved muscle function as a protective factor against cognitive decline: Longitudinal results from the FINGER study

Interpretation:

Our findings suggest that **muscle function may serve as an early marker of neurocognitive resilience**, even before any intervention or cognitive decline.

Further, preserved baseline muscle function, particularly **lower-limb strength, predicts more favorable cognitive trajectories** over two years in older adults at risk for cognitive decline.

Borda MG, *et al*. Alzheimers Dement. 2026; 22(1):e71043.

Impact of multidomain lifestyle intervention on dynamics of cognitive frailty: post hoc analysis of the FINGER trial

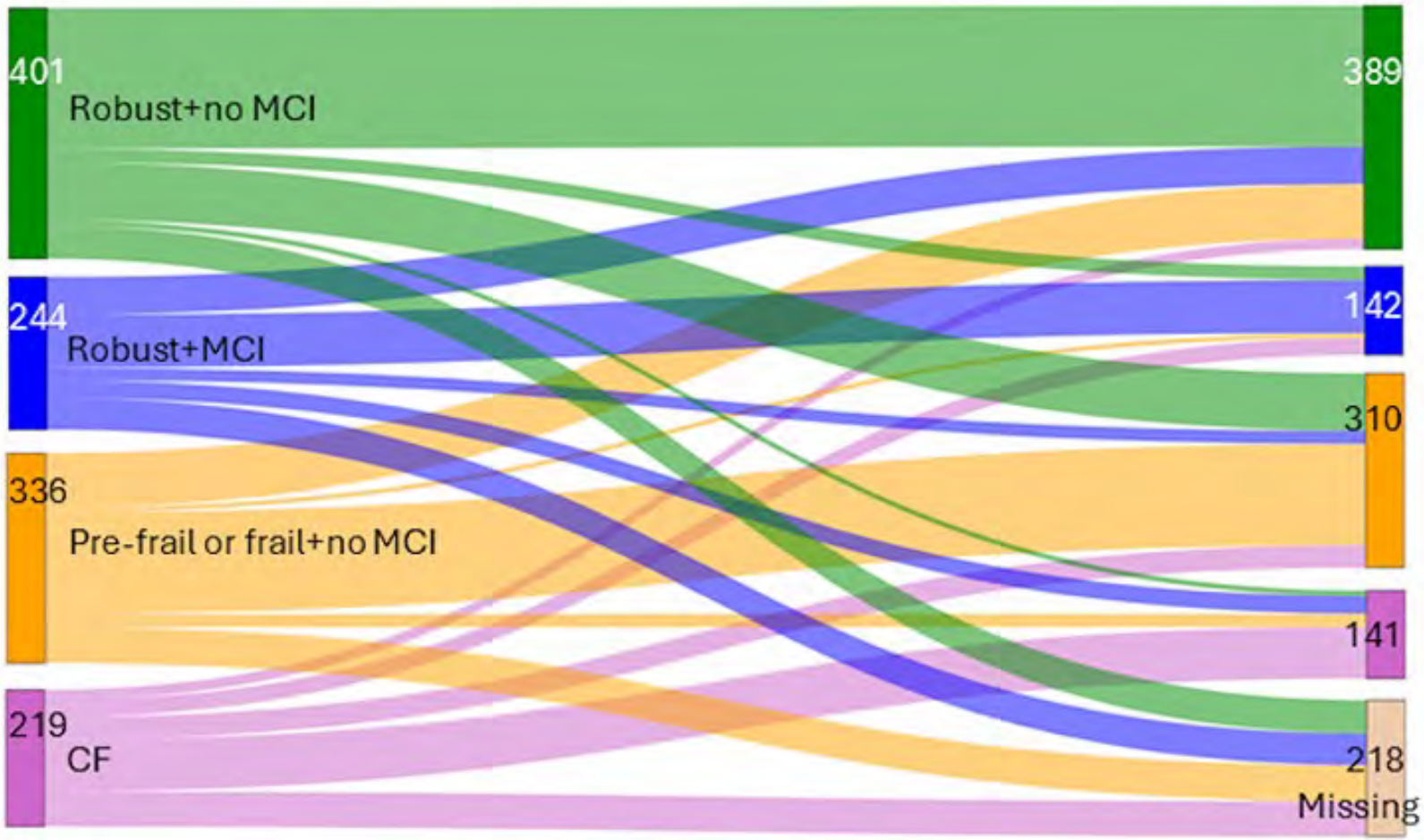


Diagram showing the **transition of participants between cognitive and physical frailty states** **from baseline to the 2-year follow-up**. The figure visualizes the flow of all participants **(n = 1200**) with available baseline frailty status and NTB total z-score data through 4 mutually exclusive baseline categories: Healthy (no MCI or pre-frailty/frailty), MCI only, pre-frail/frail only, and CF.
CF, cognitive frailty; **MCI,** mild cognitive impairment

Pöyhönen J, *et al*. J Gerontol A Biol Sci Med Sci. 2026;81:glaf275.

Cognitive dysfunction in diabetes – the 'forgotten' diabetes complication: a narrative review

Table 1. Published and ongoing randomized clinical trials regarding effects of treatment for the prevention of impairment of brain functions in diabetic patients.

Study	Target group	Intervention	Outcome	Comment
ACCORD-MIND ACCORDION [49]	T2D	Intensive vs. standard glucose control	No differences in cognition or dementia	Part of a larger study that was prematurely terminated
CAROLINA-Cognition [36]	T2D	Linagliptin vs. glimepiride	No difference in cognitive decline	Interpretation difficult due to lack of placebo arm
REWIND [35]	T2D	Dulaglutide vs. placebo	Dulaglutide better than placebo in preventing cognitive decline	A post hoc analysis of a larger study, hypothesis-generating
EVOKE https://clinicaltrials.gov/ct2/show/NCT04777396	T2D	Semaglutide vs. placebo	Ongoing	
DRINN https://beta.clinicaltrials.gov/study/NCT02847403	Pre-diabetes	Exenatide vs. placebo	Ended 2021	Not published
MET-FINGER [50] https://clinicaltrials.gov/study/NCT05109169	Mixed	Metformin + lifestyle vs. placebo	Ongoing	

Sjöholm Å, Bennet L, Nilsson PM. *Scand J Prim Health Care*. **2025**; 43(2):448-454.

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

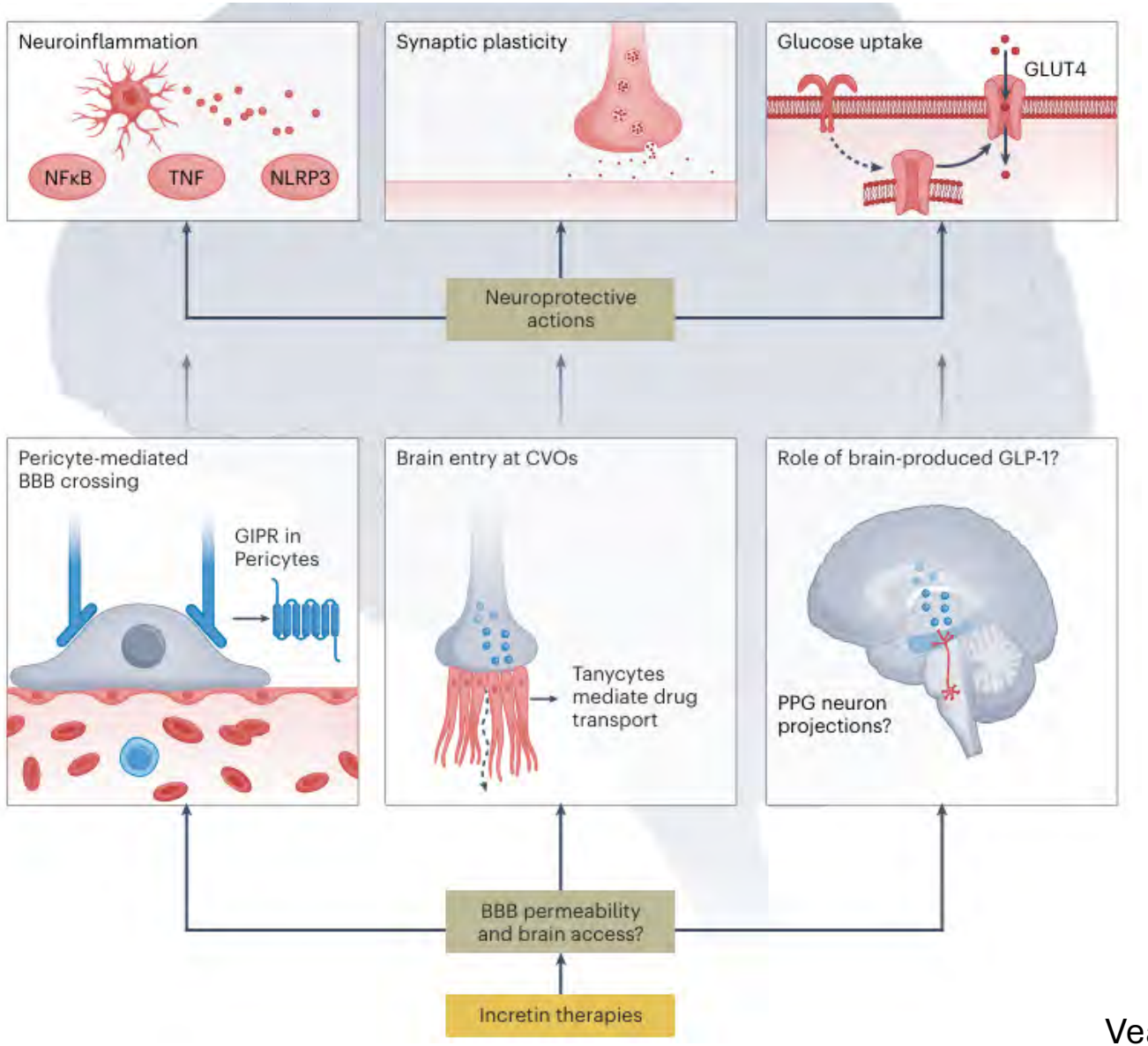
South Korea: 110 885 propensity score matched pairs of adults with type 2 diabetes aged 40-69 years who were initiators of either an SGLT-2 inhibitor or a DPP-4 inhibitor. **Observational study.**

These findings indicate a **35% relative reduction in overall dementia risk among SGLT-2 inhibitor users**.

The risk reduction associated with SGLT-2 inhibitors was consistently observed across different types of dementia,including **Alzheimer'sdisease** (hazard ratio **0.61**, 95% CI 0.53 to 0.69) and **vascular dementia** (HR **0.48**, 0.33 to 0.70). Additionally, the effect seemed more pronounced with longer treatment duration.

Shin A, *et al.* BMJ. **2024**; 386:e079475.

Incretin-based therapeutics for the treatment of neurodegenerative diseases



Mechanisms of action of incretin mimetics in the brain. Following peripheral administration, **GLP-1R agonists and GLP-1R–GIPR co-agonists** are thought to cross the BBB to a limited extent and access the brainstem and certain hypothalamic regions via circumventricular organs (CVOs) or pericyte-mediated transport.

In the brain, incretin mimetics exert **anti-inflammatory actions, modulate glucose uptake and promote synaptic plasticity.**

Vear A, *et al.* Nat Metab. **2025**; 7(4):679-696.

The effect of glucagon-like peptide 1 (GLP-1) receptor agonists on cognition: A systematic review of systematic reviews and meta-analyses

Results:
Nine systematic reviews and meta-analyses examining the effect of GLP-1 RAs on cognitive function in adults with T2DM were included.

Evidence suggests that GLP-1 RAs are associated with a reduction in overall cognitive decline in adults with T2DM and dementia/AD. Replicated findings from meta-analyses indicated that GLP-1 RAs improved performance on cognitive assessments (total learning; $p = 0.039$; $p < 0.00001$). Some meta-analyses observed a change in cognitive measures but lacked sufficient statistical significance ($p > 0.05$).

Conclusions:
GLP-1 RAs positively affect cognitive function in AD patients with T2DM. However, their efficacy on disparate cognitive domains requires further replication in larger scale controlled clinical trials.

Ballum H, *et al*. J Affect Disord. **2026** Jun 1;402:121310.

Effects of GLP-1 receptor agonists on vascular dementia: a systematic review and meta-analysis

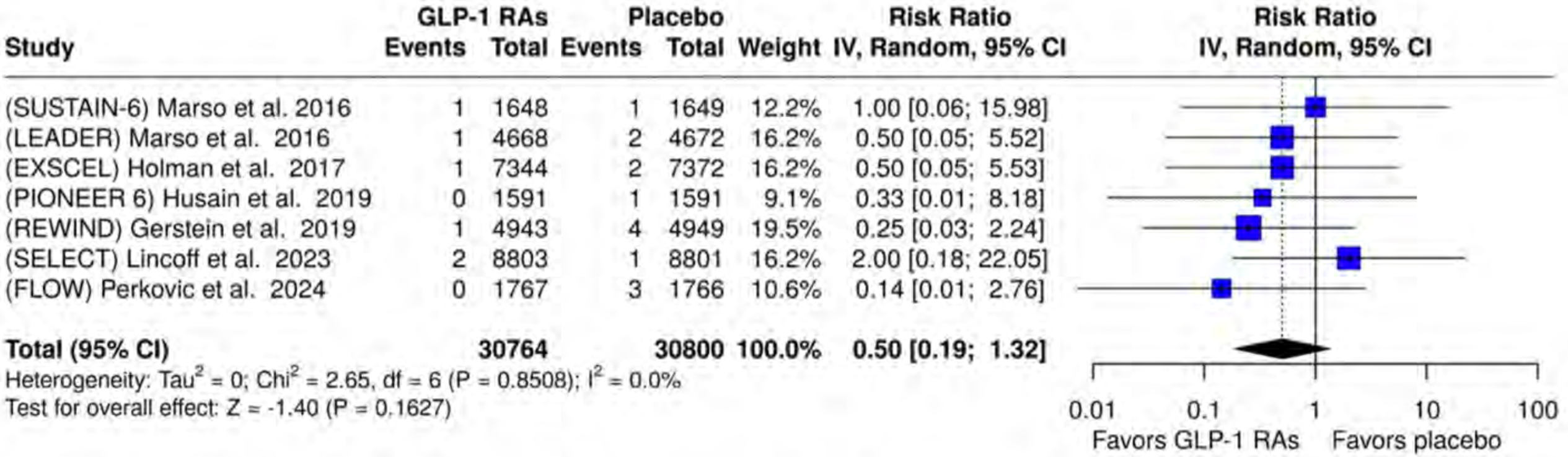


Fig. 2. Forest plot comparing the risk of incident VaD in patients with T2DM or overweight/obesity treated with GLP-1 RAs vs. placebo.

Stefanou MI, *et al*. J Diabetes Complications. **2026** Mar;40(3):109271.

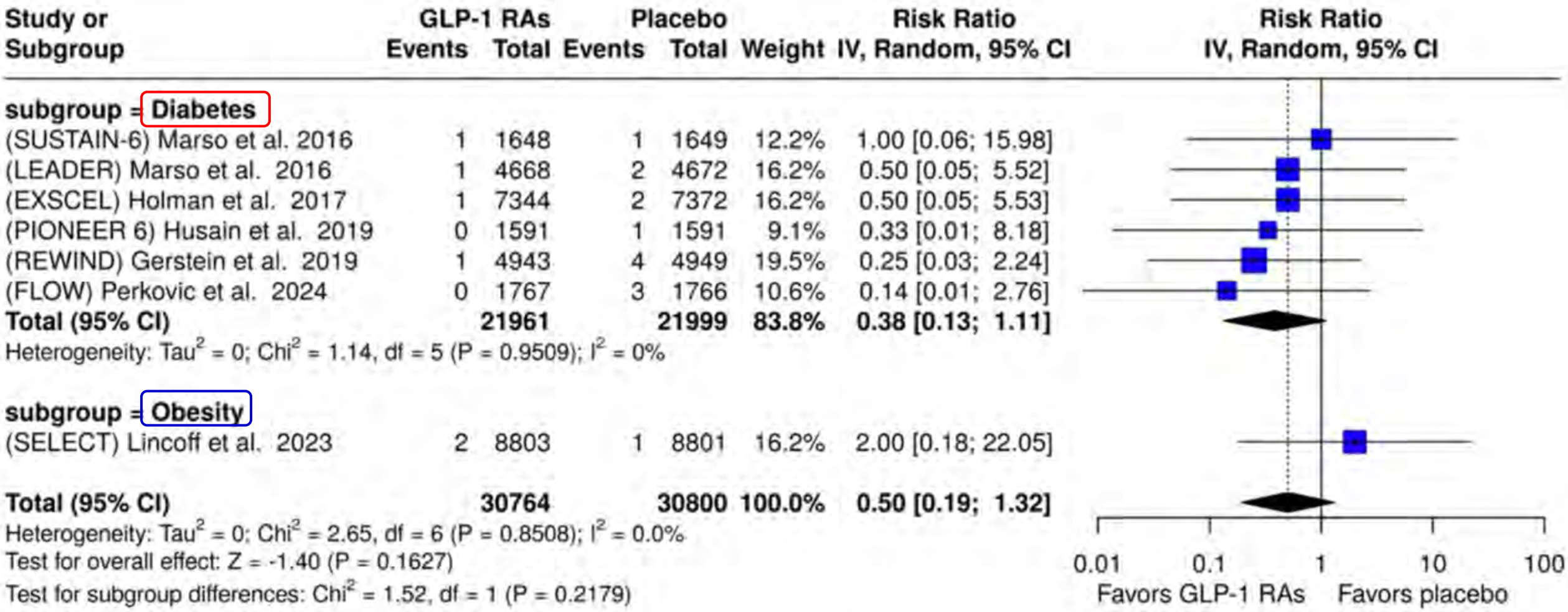


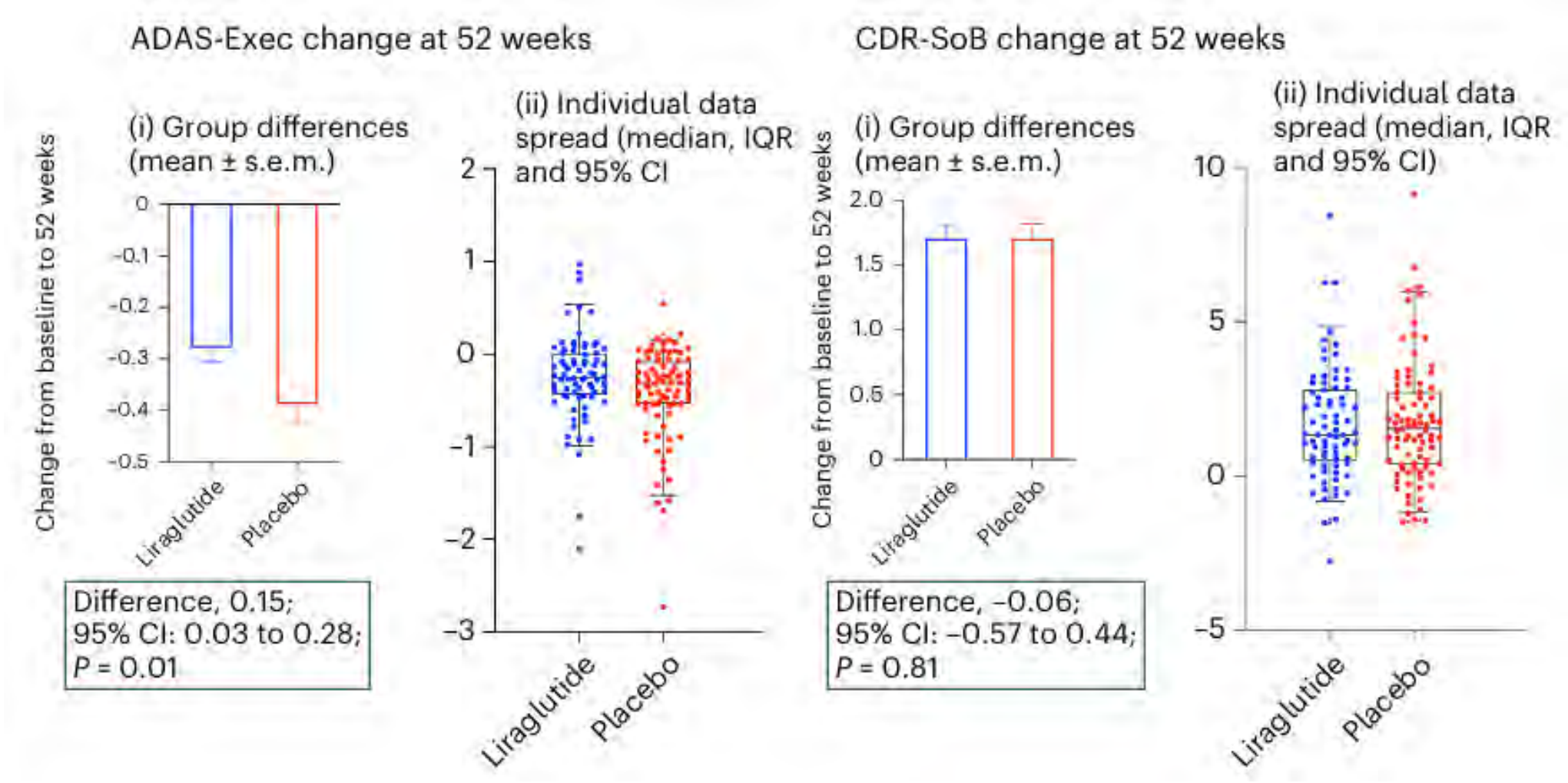
Fig. 3. Forest plot comparing the risk of incident VaD in subgroup analysis stratified by patient population (T2DM vs. overweight/obesity).

Stefanou MI, *et al*. J Diabetes Complications. 2026 Mar;40(3):109271.

ELAD Study

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

N= 204, RCT, 52 weeks



ADAS-Exec: Alzheimer's Disease Assessment Scale-Executive domain

CDR-SoB: Clinical Dementia Rating-Sum of Boxes

Edison P, *et al.* Nat Med. 2026; 32(1):353-361.

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.

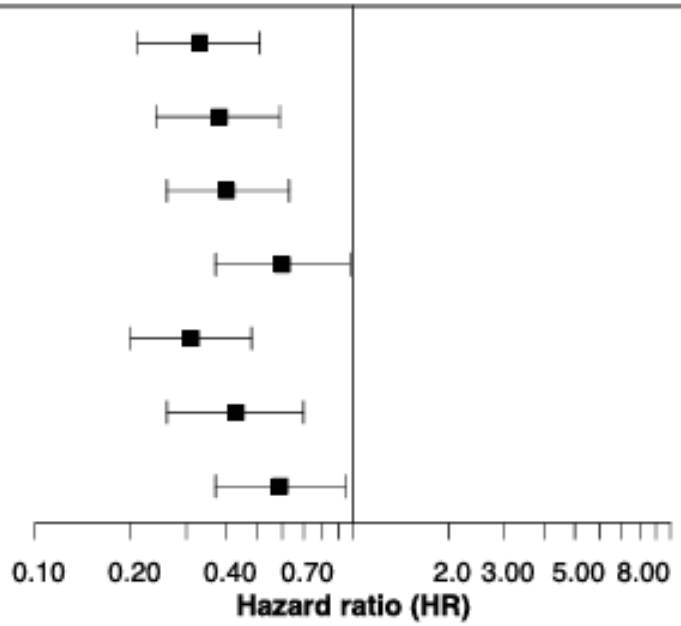
The *secondary outcome* measures revealed that patients treated with liraglutide had a significantly **slower decline in cognition (ADAS-Exec)** and a **slower reduction in MRI brain volume** compared to the placebo arm, demonstrating a favorable response to liraglutide treatment.

Edison P, *et al.* Nat Med. 2026; 32(1):353-361.

Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US

Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (comparison between matched semaglutide vs other antidiabetes medications groups)

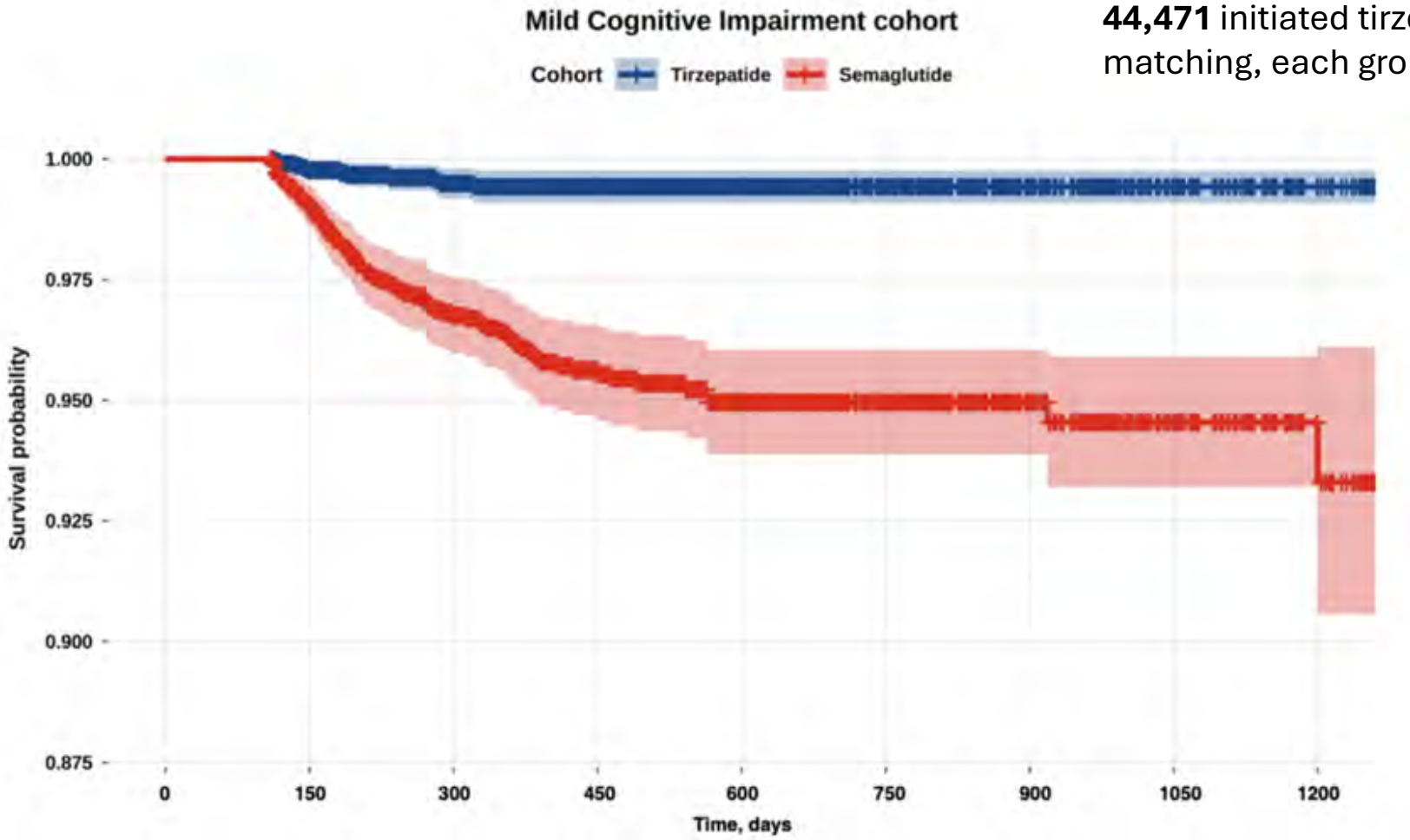
Size/Group	Exposure group	Comparison group	Exposure Group Cases (overall risk)	Comparison Group Cases (overall risk)	HR (95% CI)
17,087	Semaglutide	Insulin	27 (0.16%)	73 (0.43%)	0.33 (0.21 to 0.51)
17,080	Semaglutide	Metformin	27 (0.16%)	68 (0.40%)	0.38 (0.24 to 0.59)
15,878	Semaglutide	DPP–4i	27 (0.17%)	62 (0.39%)	0.40 (0.26 to 0.63)
15,288	Semaglutide	SGLT2i	26 (0.17%)	40 (0.26%)	0.60 (0.37 to 0.98)
16,503	Semaglutide	SU	27 (0.16%)	80 (0.49%)	0.31 (0.20 to 0.48)
10,847	Semaglutide	TZD	24 (0.22%)	51 (0.47%)	0.43 (0.26 to 0.70)
17,029	Semaglutide	Other GLP–1RAs	27 (0.16%)	44 (0.26%)	0.59 (0.37 to 0.95)



Wang W, *et al*. Alzheimers Dement. 2024; 20(12):8661-8672.

Tirzepatide versus semaglutide for the prevention of mild cognitive impairment, dementia, and Alzheimer's disease in type 2 diabetes: A real-world, retrospective cohort study

290,606 patients initiated **semaglutide** and **44,471** initiated tirzepatide. After propensity score matching, each group included **44,470 patients.**



Journal of Diabetes and Its Complications 40 (2026) 109306

evoke
evoke+

Efficacy and safety of oral semaglutide 14 mg (flexible dose) in early-stage symptomatic Alzheimer's disease (evoke and evoke+): two phase 3, randomised, placebo-controlled trials

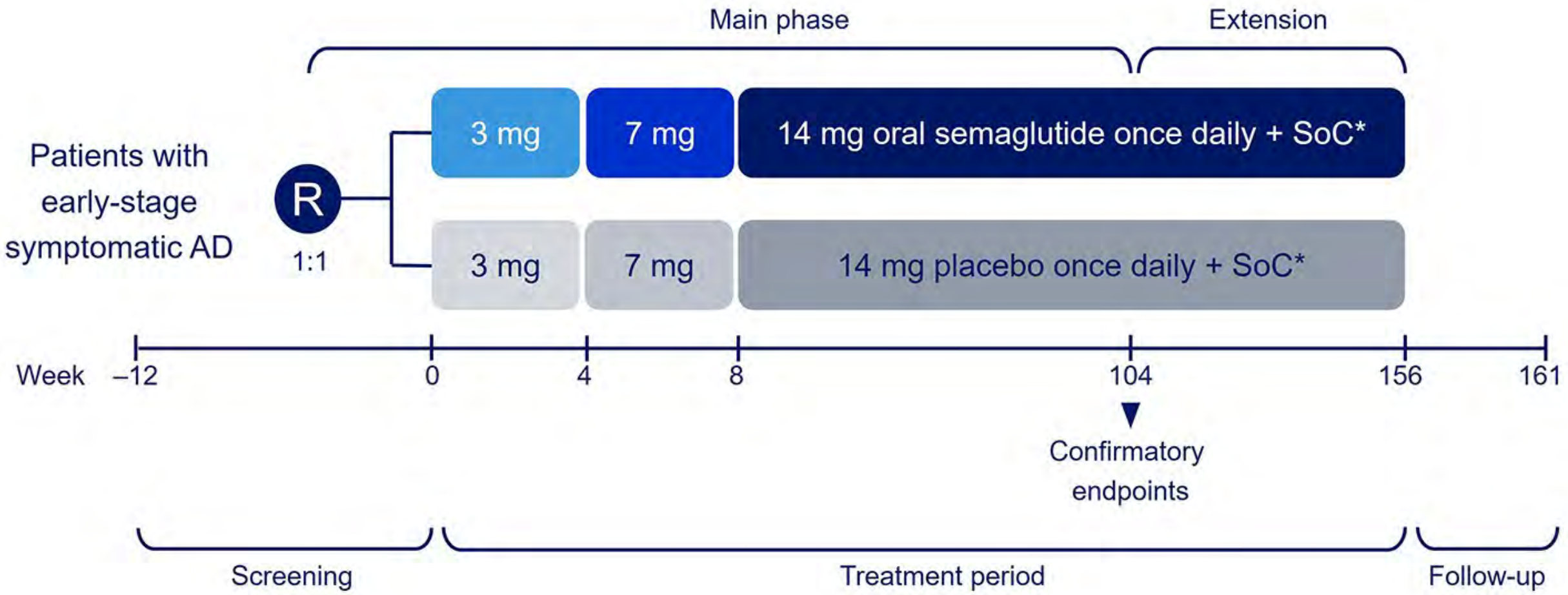
evoke and **evoke+** were multicentre, randomised, double-blind, placebo-controlled phase 3 trials conducted across **566 sites in 40 countries**.

The trials assessed the efficacy and safety of oral semaglutide up to 14 mg once daily in **participants with amyloid-confirmed Alzheimer's disease, aged 55–85 years,** with mild cognitive impairment or mild dementia due to Alzheimer's disease. **In evoke+, participants with significant small vessel pathology were included**.

Participants were randomly assigned (1:1) to **once-daily semaglutide 14 mg (flexible dose) or placebo for up to 156 weeks.**

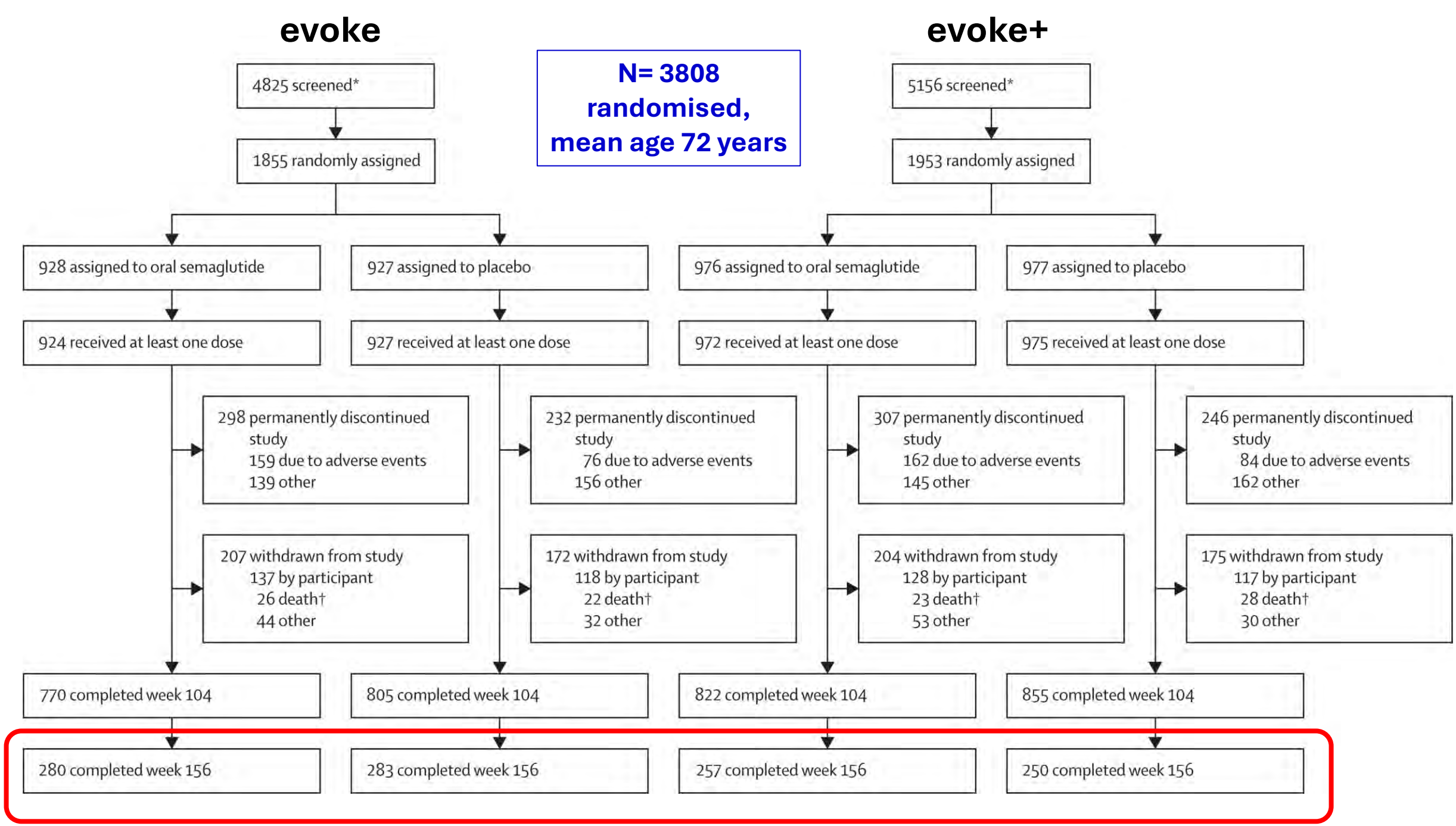
Cummings JL,...**Hansson O**.... *et al*. Lancet. **2026**:S0140-6736(26)00459-9.

Trial design of evoke/evoke+



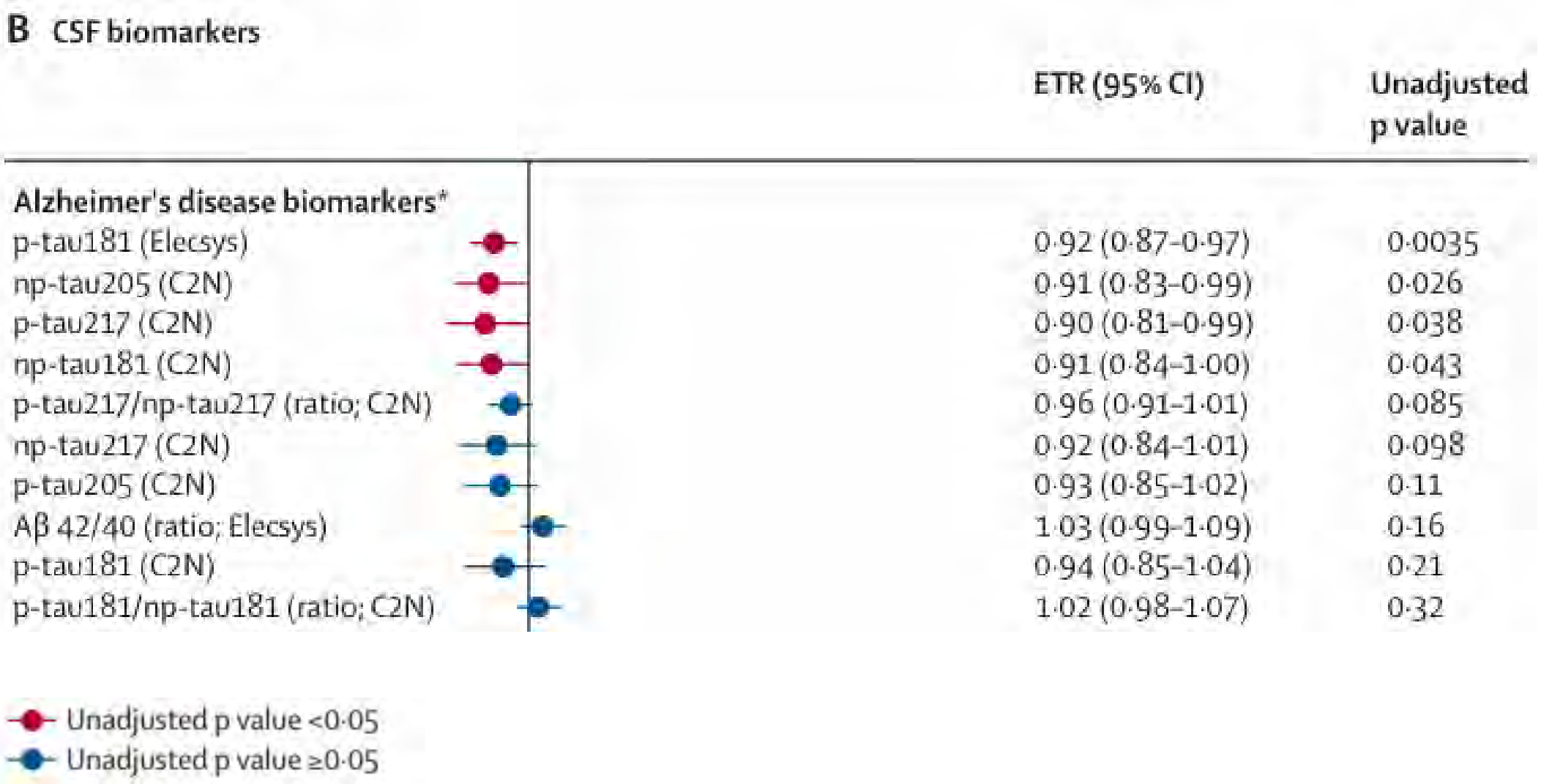
OBS! Few patients (10-16%) with diabetes!

Cummings JL, *et al*. Lancet. **2026**:S0140-6736(26)00459-9.


evoke
evoke+
N= 3808 randomised, mean age 72 years
4825 screened*
1855 randomly assigned
5156 screened*
1953 randomly assigned
928 assigned to oral semaglutide
927 assigned to placebo
976 assigned to oral semaglutide
977 assigned to placebo
924 received at least one dose
927 received at least one dose
972 received at least one dose
975 received at least one dose
298 permanently discontinued study
159 due to adverse events
139 other
232 permanently discontinued study
76 due to adverse events
156 other
307 permanently discontinued study
162 due to adverse events
145 other
246 permanently discontinued study
84 due to adverse events
162 other
207 withdrawn from study
137 by participant
26 death†
44 other
172 withdrawn from study
118 by participant
22 death†
32 other
204 withdrawn from study
128 by participant
23 death†
53 other
175 withdrawn from study
117 by participant
28 death†
30 other
770 completed week 104
805 completed week 104
822 completed week 104
855 completed week 104
280 completed week 156
283 completed week 156
257 completed week 156
250 completed week 156

Changes in CSF biomarkers in the CSF sub-study (evoke)

B CSF biomarkers



	ETR (95% CI)	Unadjusted p value
Alzheimer's disease biomarkers*		
p-tau181 (Elecsys)	0·92 (0·87–0·97)	0·0035
np-tau205 (C2N)	0·91 (0·83–0·99)	0·026
p-tau217 (C2N)	0·90 (0·81–0·99)	0·038
np-tau181 (C2N)	0·91 (0·84–1·00)	0·043
p-tau217/np-tau217 (ratio; C2N)	0·96 (0·91–1·01)	0·085
np-tau217 (C2N)	0·92 (0·84–1·01)	0·098
p-tau205 (C2N)	0·93 (0·85–1·02)	0·11
Aβ 42/40 (ratio; Elecsys)	1·03 (0·99–1·09)	0·16
p-tau181 (C2N)	0·94 (0·85–1·04)	0·21
p-tau181/np-tau181 (ratio; C2N)	1·02 (0·98–1·07)	0·32

ETR= estimated treatment ratio

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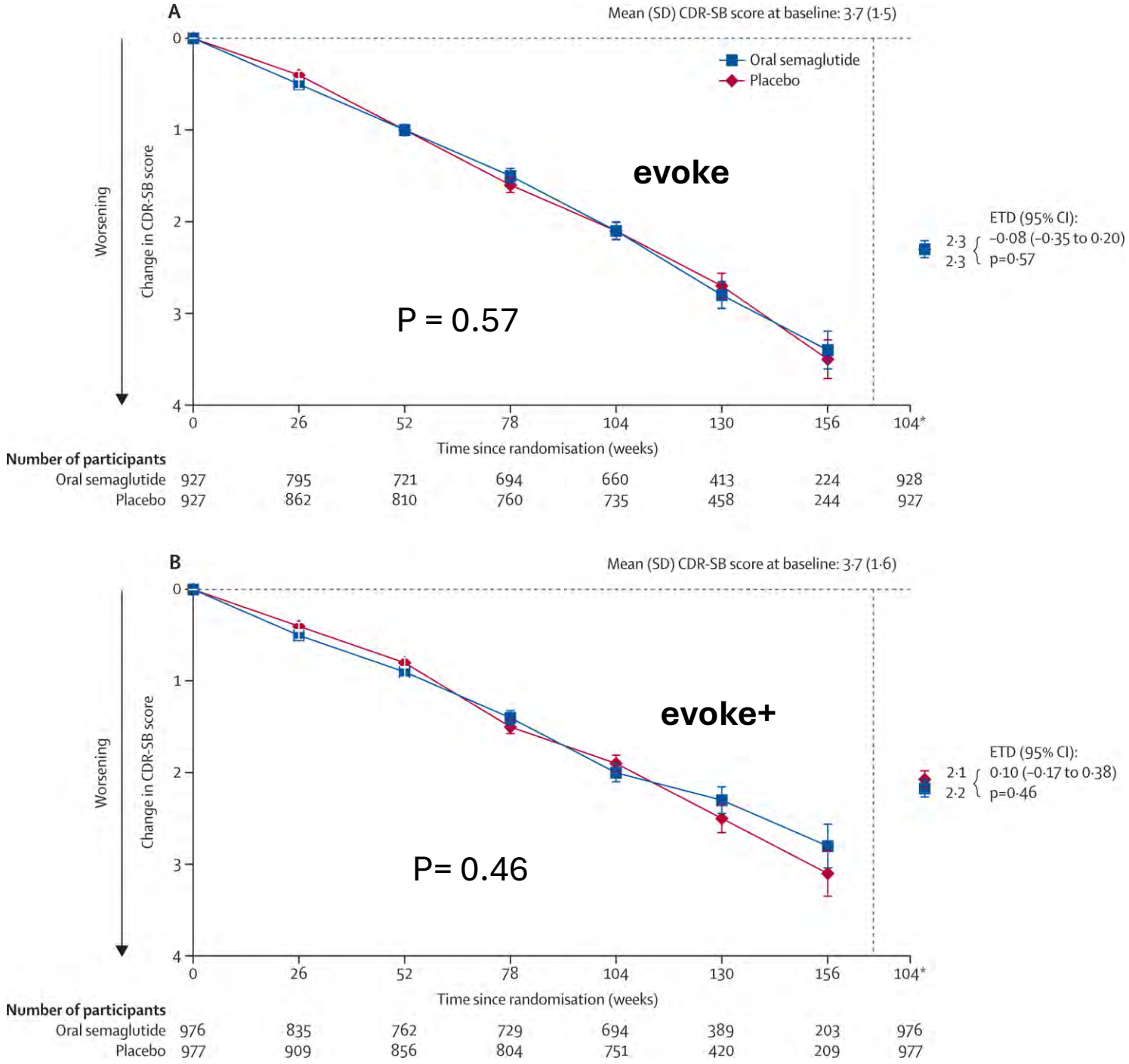
Change in **CDR-SB** score from baseline up to week 104 for **evoke** (A) and **evoke+** (B)

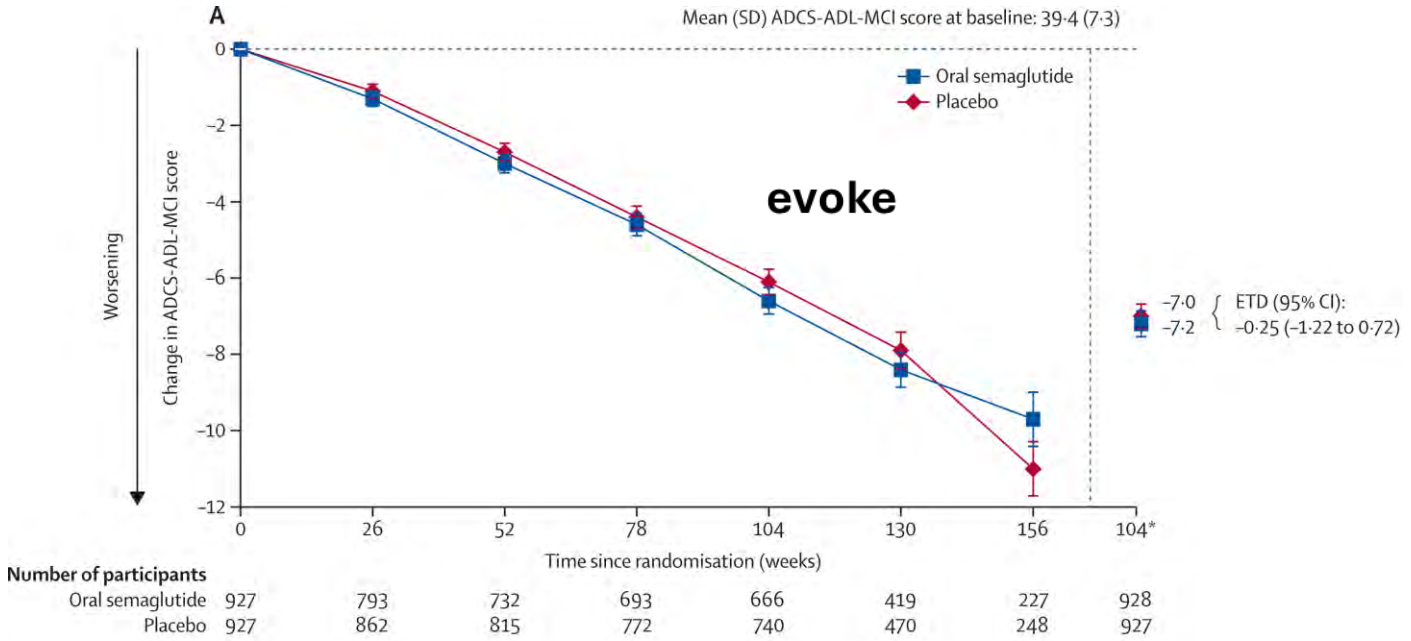
CDR-SB= Clinical Dementia Rating—Square (sum) of Boxes.

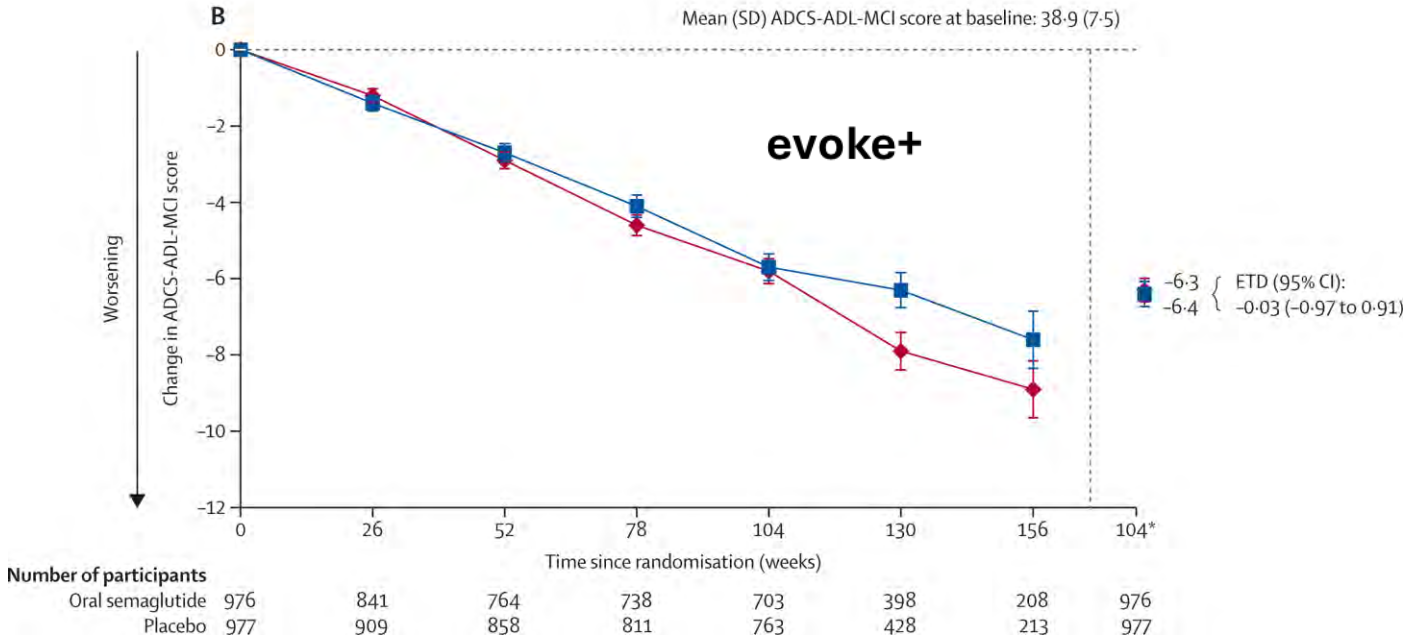


Cummings JL, *et al*. Lancet. **2026**:S0140-6736(26)00459-9.

Change in **ADCS-ADL-MCI** score from baseline up to week 104 for **evoke** (A) and **evoke+** (B)

ADCS-ADL-MCI= Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment





Cummings JL, *et al*. Lancet. **2026**:S0140-6736(26)00459-9.

THE LANCET

Interpretation

Oral semaglutide was not efficacious in slowing clinical progression in participants with early Alzheimer's disease. Safety and tolerability of semaglutide in early Alzheimer's disease is consistent with studies in other indications.

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International commentaries after evoke/evoke+

"Together, global expert responses suggest a strategic pivot toward **preventing disease before symptoms appear**, deploying multi-mechanism combinations, and continuing to probe metabolic pathways, while recognizing that semaglutide itself does not alter symptomatic AD."

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Sammanfattning

- **Diabetes typ 1** och **typ 2** är associerade med hög risk för **nedsatt kognition** samt **ökad demensrisk** i observationsstudier. Genetiska studier antyder ett kausalt samband med vaskulär demens men inte med Alzheimer demens
- Behandling med **livsstil** förefaller kunna minska kognitiv nedgång (FINGER) och flera observationsstudier anger minskad risk för nedsatt kognition och demens vid behandling med **SGLT-2i** och **GLP-1 RA** läkemedel
- I en stor RCT (**evoke, evoke+**) kunde man inte påvisa minskad risk för kognitiv nedgång hos patienter med tecken på tidig Alzheimer demens (Lancet, 2026)
- I den **kliniska praktiken** kan det bli aktuellt att utvärdera kognitionssvikt hos riskpatienter med diabetes (dålig metabol kontroll, lång diabetesduration, hög ansamling av riskfaktorer, lägre utbildningsnivå, familjär förekomst av minnessjukdomar). En **anpassad pedagogik** kan behövas vid kognitionssvikt