SFD Vårmöte

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Kognitiv svikt och diabetes

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Diabetes och demens

- Ett växande kliniskt problem
- Ett vårdtyngdsproblem
- Ett mänskligt problem

- En vetenskaplig utmaning…

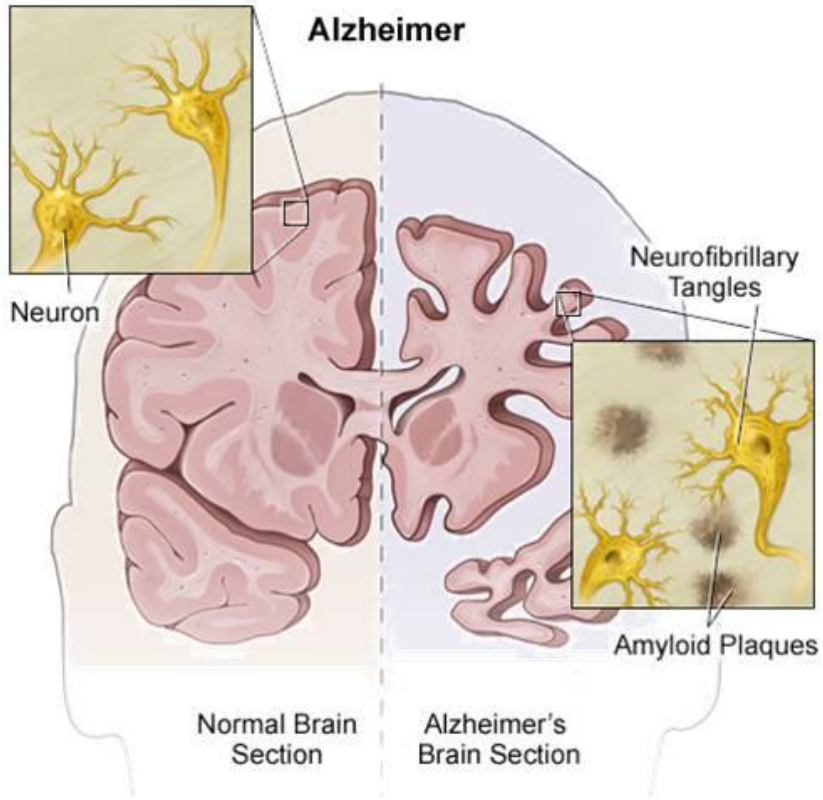
Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006; 5: 64–74.

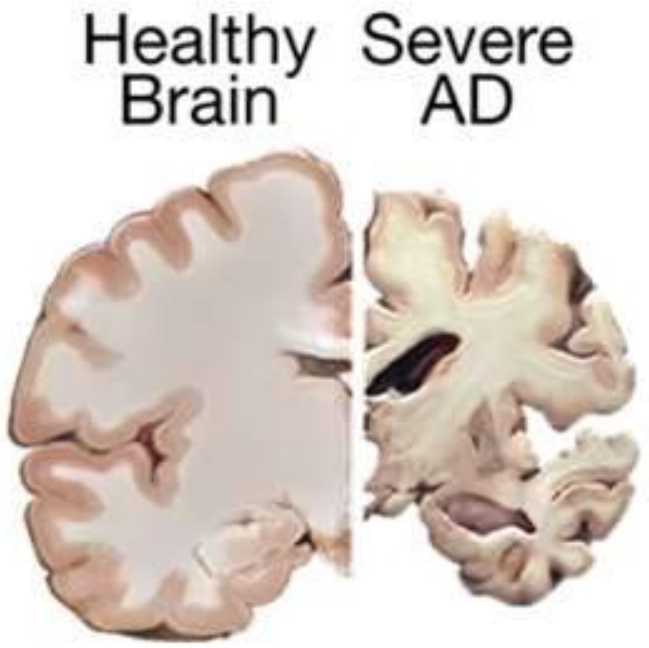
Riskmarkörer för demensutveckling

- Ålder
- Ärftlighet (*ApoE4* genetisk markör)
- Hypertoni
- Metabola syndromet
- Låg utbildning
- Dålig livsstil (alkohol, rökning)

- Störd glukos/insulin omsättning i CNS?

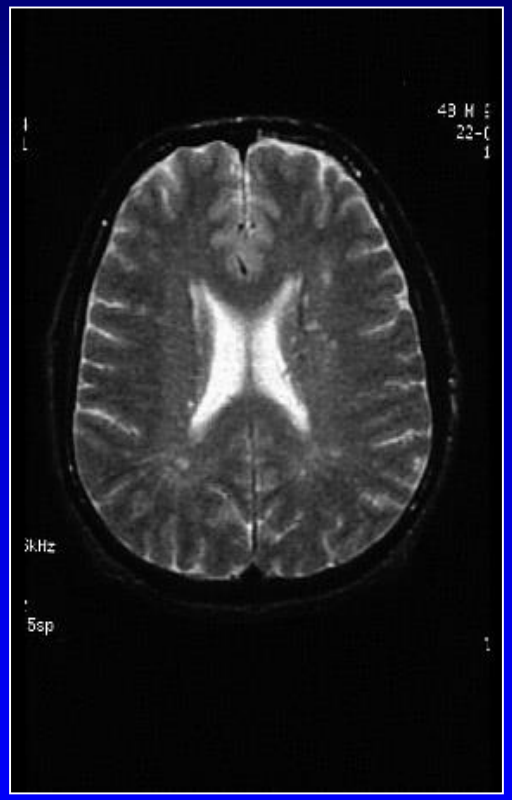
Impact on our brain…





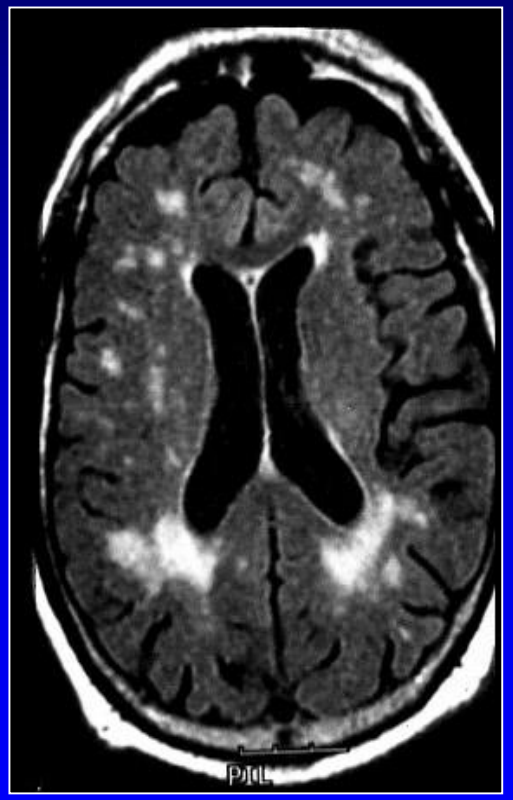
Consequences of Vascular Structural Changes in Hypertension

Confluent periventricular hyperintensities



Brain MRI: axial plane
T_2 - weighted image

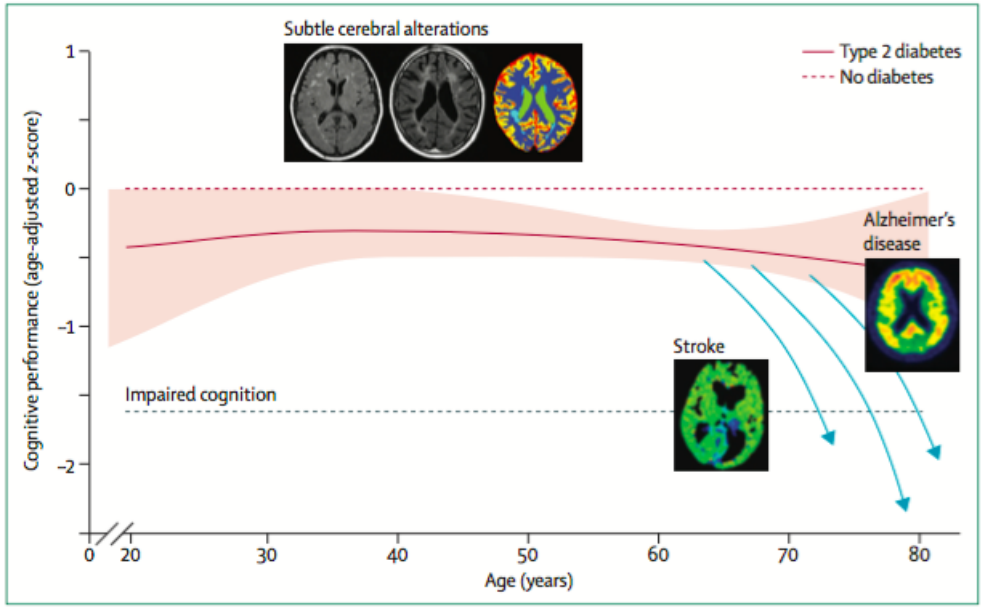
Lacunar infarcts and leucoaraiosis



Brain MRI: axial plane
FLAIR image

Diabetes and cognitive impairment

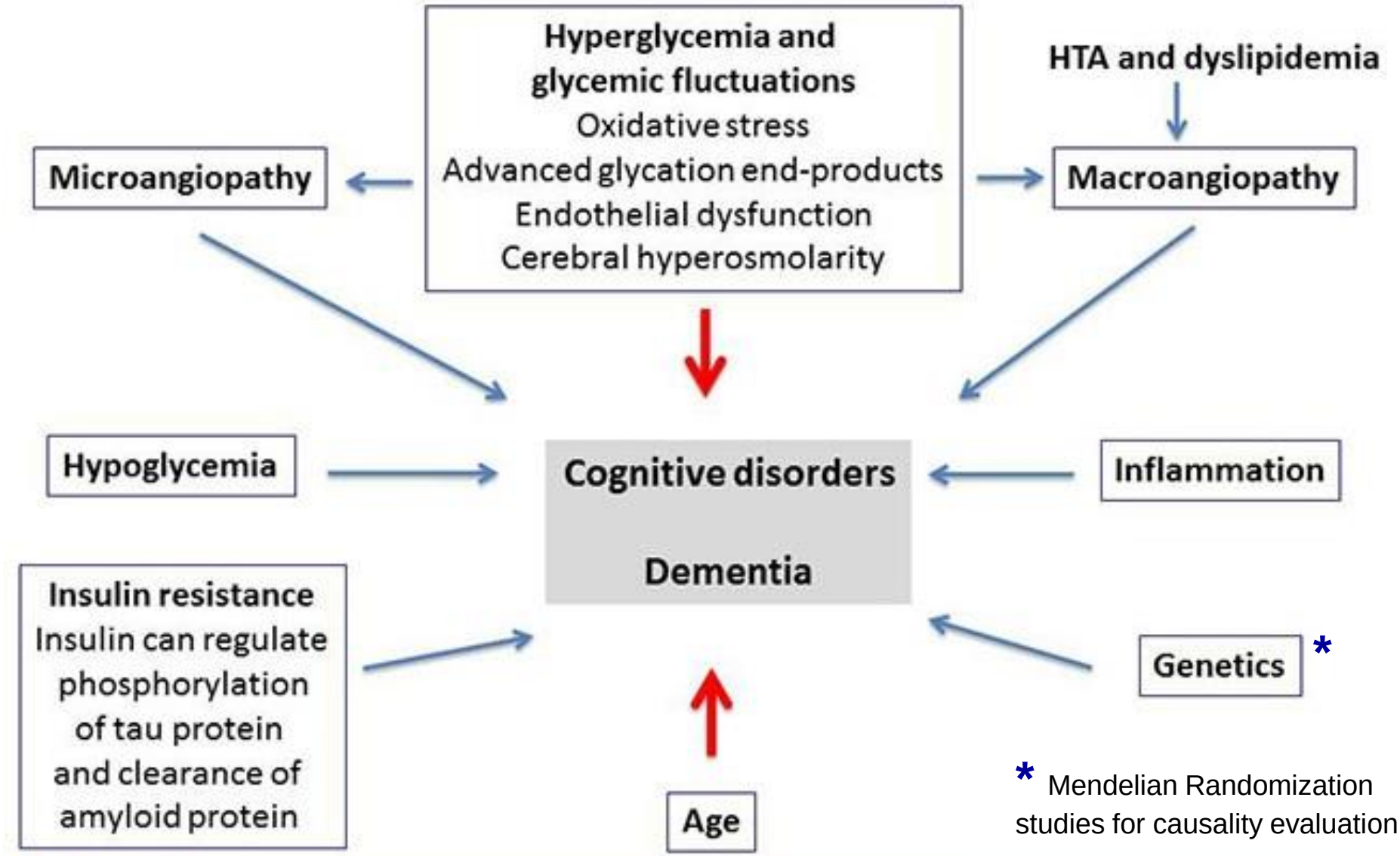
- T2D doubles the risk of **dementia** [1]
  - RR 2.48 (95% CI: 2.08-2.96) for vascular dementia
  - RR 1.46 (1.20-1.77) for Alzheimer's Disease (AD)
- Over the life-course: **mild cognitive decrements** that develop slowly over time [2]
- Cognitive domains affected: processing speed, executive function, memory
- MRI shows:
  - global atrophy
  - cerebral small-vessel disease manifestations



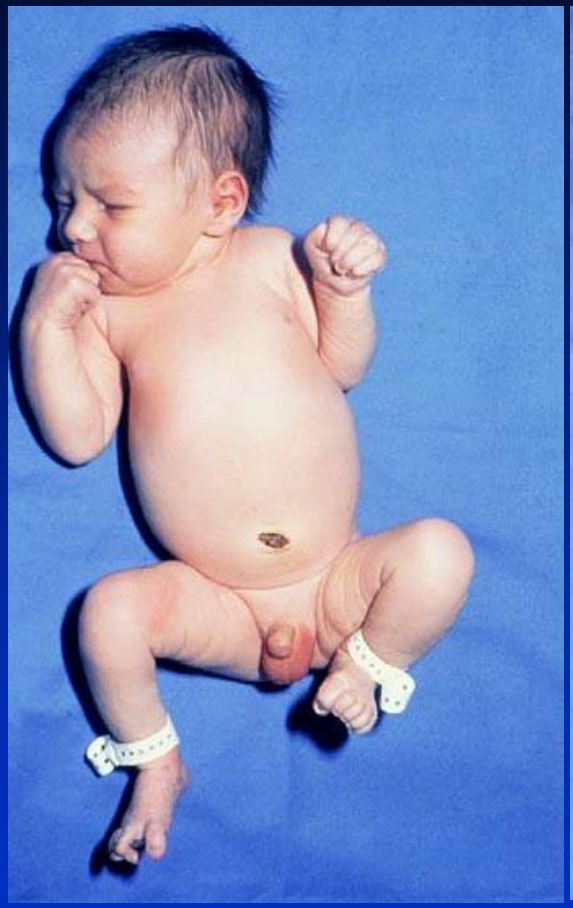
1 Cheng G, *et al.* Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J* 2012; **42:** 484–91.

2 Biessels GJ, *et al.* Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol 2014; 2:246–255

Diabetes and the Brain – Impaired cognition and dementia risk



Birth weight and adult disease



8.5 lbs

5.5 lbs

low birth weight (LBW)

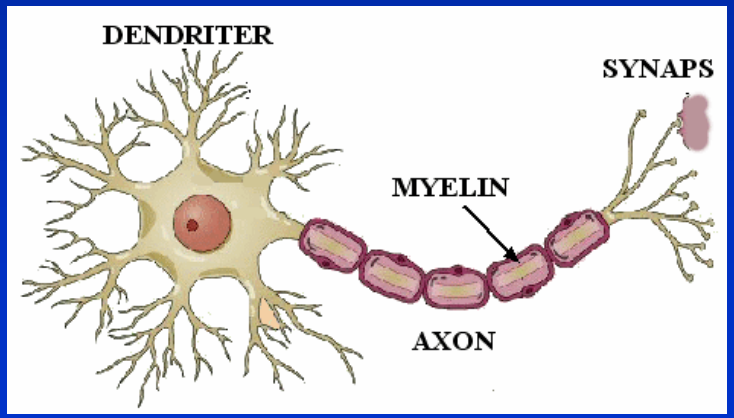
→

- hypertension
- type 2 diabetes
- hyperlipidaemia
- insulin resistance
- metabolic syndrome
- vascular dysfunction
- coronary heart disease (CHD)

- osteoporosis
- depression and other psychopathologies
- dementia?

LBW: caused by impaired fetal growth or preterm delivery

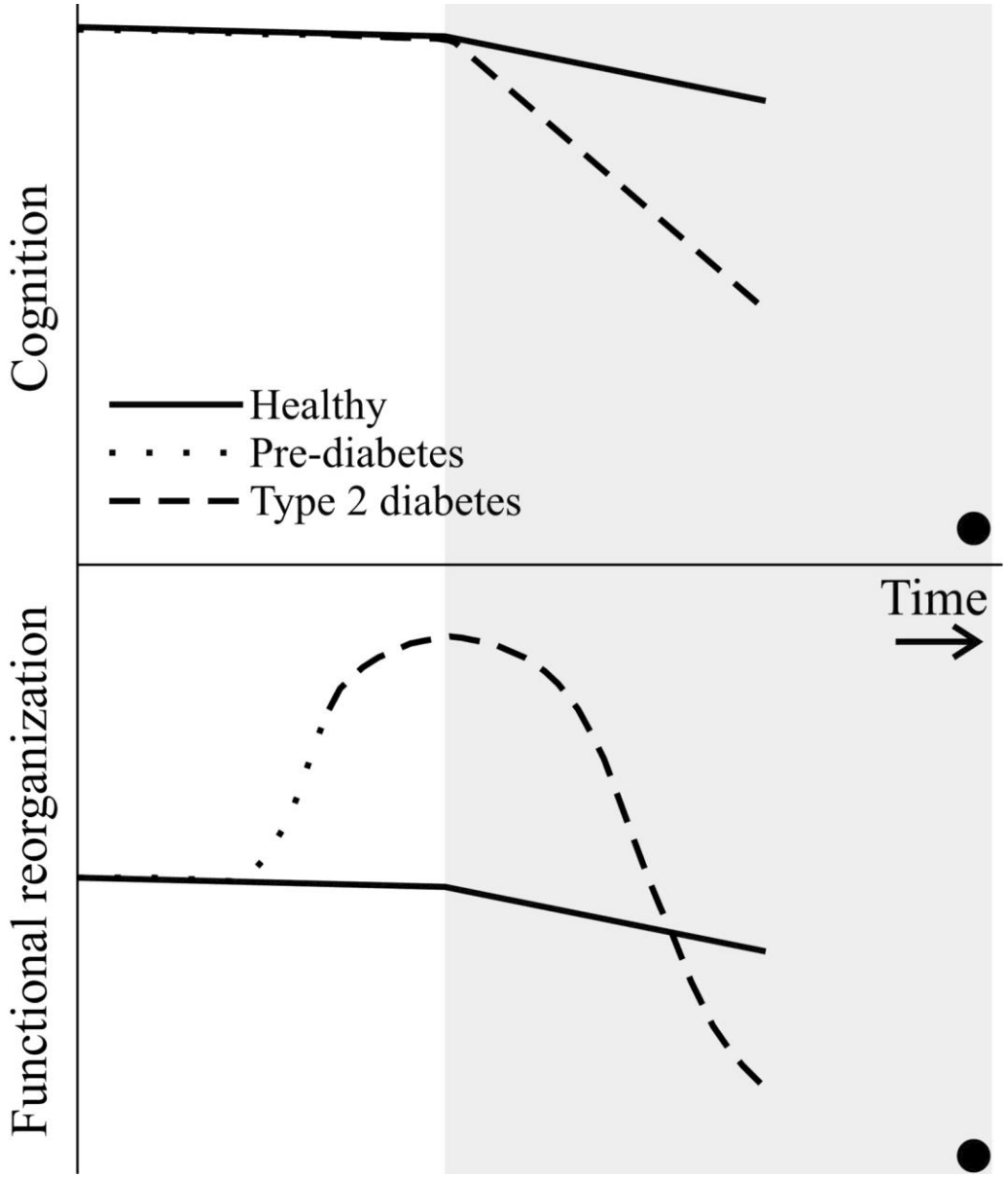
Neurokognitiv utveckling och kognitiv reserv
Av betydelse för hälsa, sjukdom och livsförlopp hos vuxna



Myelinisering

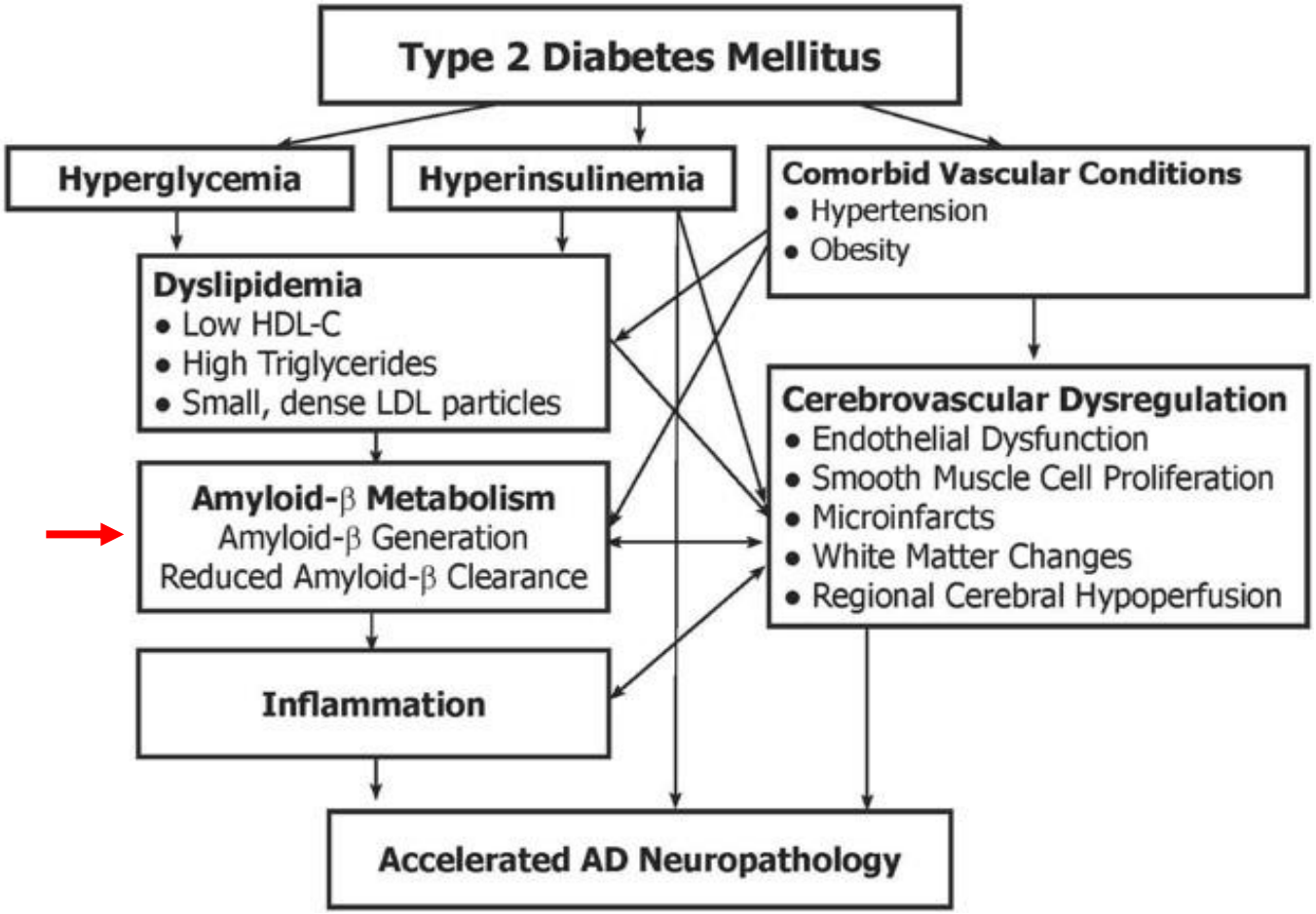
Problemlösning

Hypothetical overview of cognitive performance and functional reorganization over time



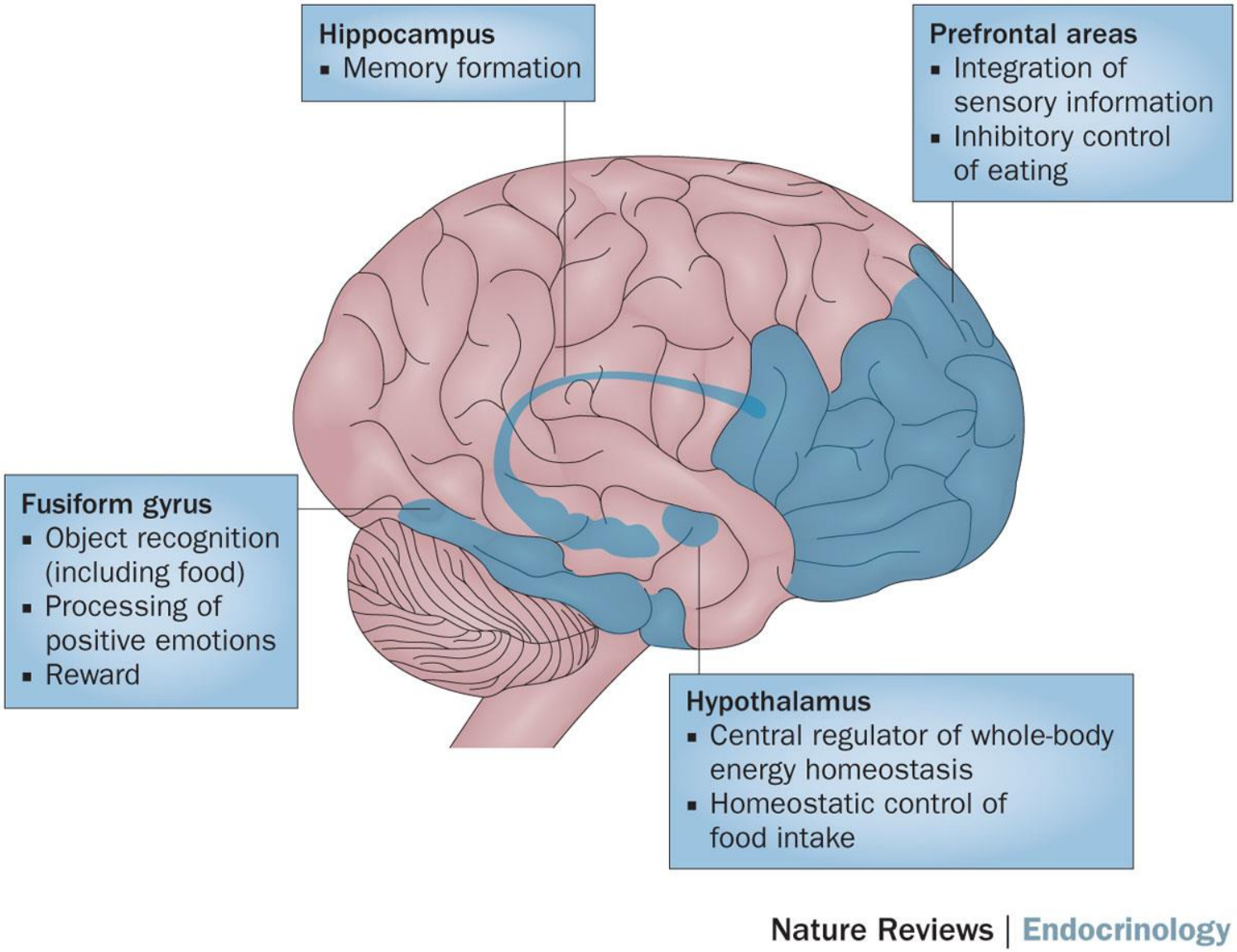
Frank C.G. van Bussel *et al.* Diabetes 2016;65:2404-2413

T2DM & Alzheimer's disease pathology



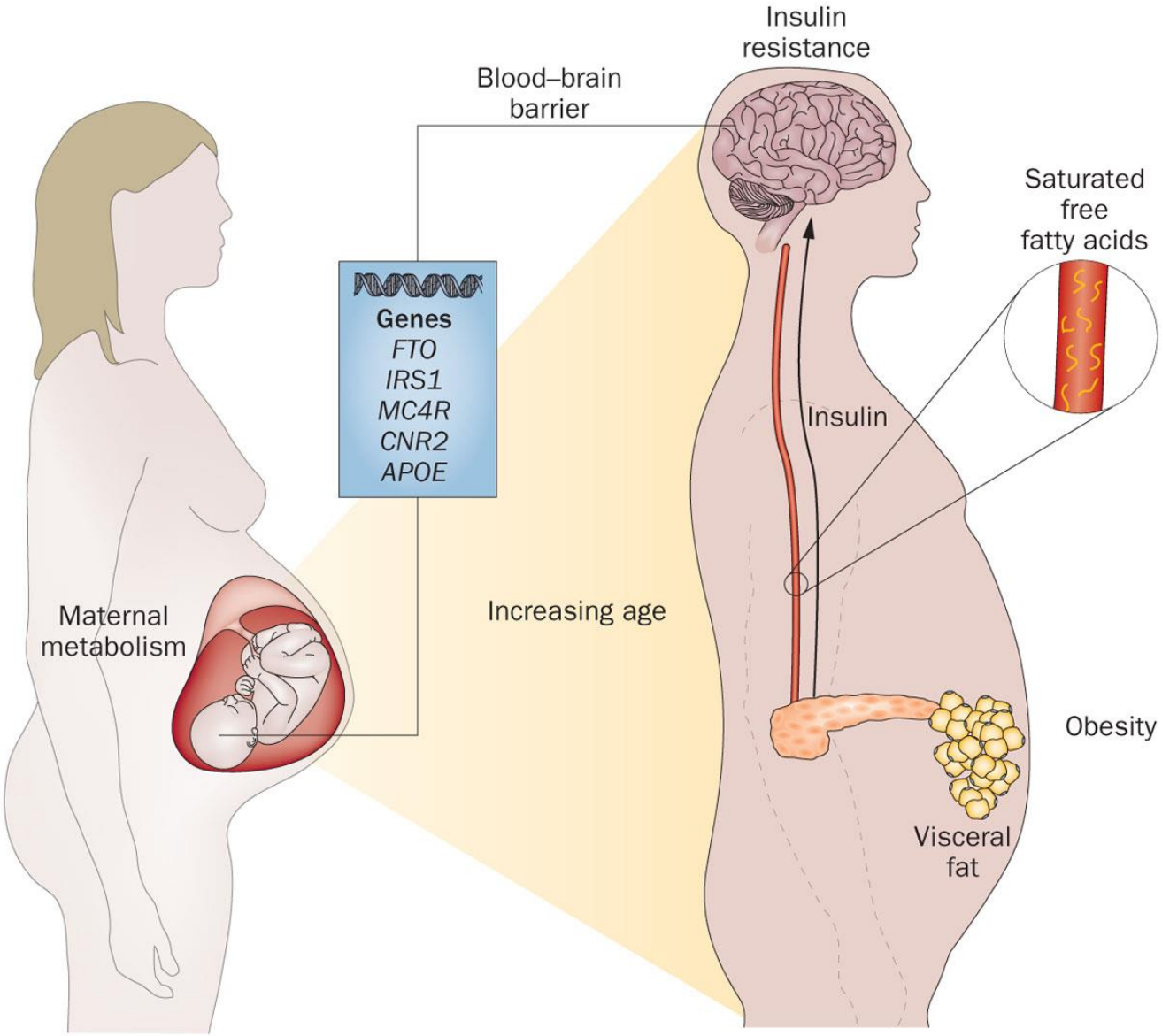
Carlsson, J Alzheimer's Dis 2010; 20:711-22

Insulin-sensitive brain areas in humans



Heni, M. *et al.* Impaired insulin action in the human brain: causes and metabolic consequences *Nat. Rev. Endocrinol.* 2015

Possible causes of brain insulin resistance



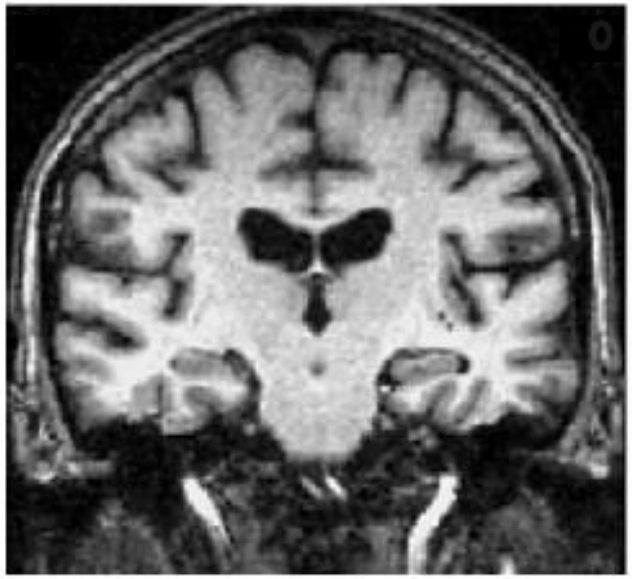
Markers of glucose metabolism and cognitive impairment

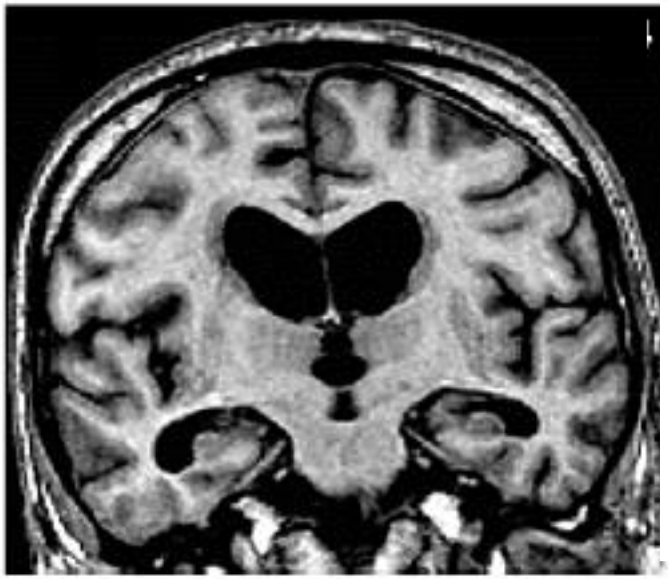
- Markers associated with cognitive impairment in previous studies:
  - Fasting glucose [1]
  - Insulin [2]
  - Skin-autofluorescence Advanced Glycation End Products (sf AGE) [3]

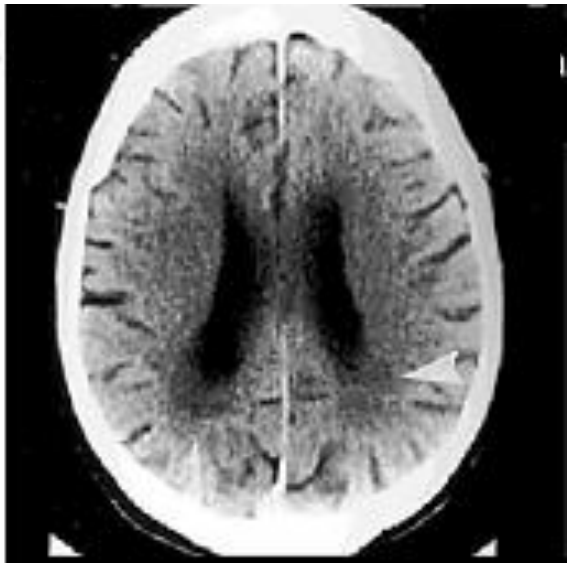
- May have neuroprotective effects (animal studies):
  - Glucagon-like peptide 1, GLP-1 (stimulates insulin secretion in pancreatic beta-cells) [4]

1. Backeström A, et al. Glucose but not insulin or insulin resistance is associated with memory performance in middle-aged non-diabetic women: a cross-sectional study. Diabetol Metab Syndr. 2015 Mar 15;7:20. doi: 10.1186/s13098-015-0014-7. eCollection 2015.
2. Kuusisto J,et al. Essential hypertension and cognitive function. The role of hyperinsulinemia. Hypertension. 1993 Nov;22(5):771-9.
3. P. J. J. Spauwen, et al. Associations of Advanced Glycation End-Products With Cognitive Functions in Individuals With and Without Type 2 Diabetes: The Maastricht Study. J Clin Endocrinol Metab, March 2015, 100:951–9
4. Matteucci E, Giampietro O. Mechanisms of Neurodegeration in Type 2 Diabetes and the Neuroprotective Potential of Dipeptidyl Peptidase 4 Inhibitors. Curr Med Chem. 2015 Feb 27, online.

Vascular and brain ageing - cognitive decline







normal **atrophy** **microvascular lesion**

No independent association was found between c-f PWV (arterial stiffness) and dementia.
It remains a matter of debate why c-f PWV repeatedly has been associated with **cognitive test results** and markers of cerebral small vessel disease, but not with **dementia.**

Nilsson ED, Elmståhl S, Minthon L, Pihlsgård M, Nilsson PM, Hansson O, Nägga K. J Hypertens. 2017; 35(12):2462-2467.

Svensk forskning inom diabetes, kognition och demens

The Effect of Borderline Diabetes on the Risk of Dementia and Alzheimer's Disease

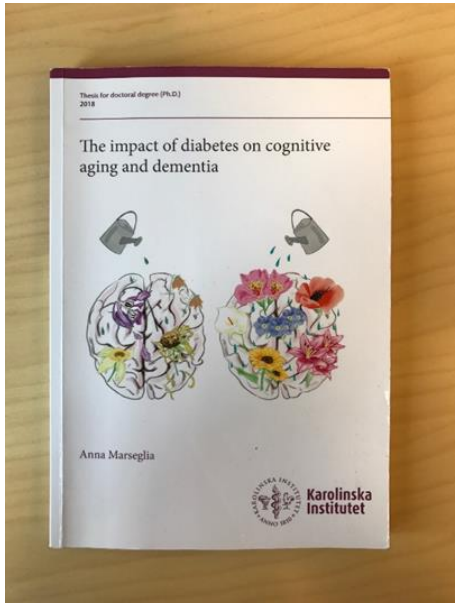
Weili Xu,[1] Chengxuan Qiu,[1] Bengt Winblad,[1,2] and Laura Fratiglioni[1,2]

TABLE 3
Adjusted HR of dementia and Alzheimer's disease for the combined effect of borderline diabetes and blood pressure, BMI, or *APOE* ϵ4 allele

Joint exposure status	Borderline diabetes	At risk (*n*)	Dementia*	Alzheimer's disease*
Systolic blood pressure (mmHg)†				
<180	No	899	1.00 (Ref.)	1.00 (Ref.)
<180	Yes	38	1.54 (0.93–2.58)	1.63 (0.94–2.82)
≥180	No	207	1.00 (0.74–1.34)	0.98 (0.70–1.38)
≥180	Yes	8	4.41 (1.08–17.99)	6.27 (1.53–25.80)
BMI ≥30 (kg/m^2)†				
No	No	1,079	1.00 (Ref.)	1.00 (Ref.)
No	Yes	40	1.52 (0.91–2.53)	1.57 (0.89–2.79)
Yes	No	52	1.00 (0.58–1.73)	1.15 (0.64–2.08)
Yes	Yes	2	1.62 (0.23–11.69)	1.75 (0.24–12.68)
APOE ϵ4†				
No	No	623	1.00 (Ref.)	1.00 (Ref.)
No	Yes	18	2.28 (1.31–3.98)	2.52 (1.35–4.70)
Yes	No	257	1.41 (1.11–1.80)	1.56 (1.19–2.05)
Yes	Yes	6	0.60 (0.08–4.32)	0.86 (0.12–6.21)

Data are HRs (95% CIs) unless otherwise indicated. *HRs and 95% CIs estimated with adjustment for age, sex, education, follow-up survival status, baseline MMSE score, stroke, heart disease, diastolic blood pressure, and antihypertensive drug use and, if applicable, for systolic blood pressure and BMI. †Twenty-one subjects for blood pressure readings, 143 subjects for BMI, and 269 subjects for *APOE* genotypes had missing values.

Anna Marseglia



From THE AGING RESEARCH CENTER
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THE IMPACT OF DIABETES ON COGNITIVE AGING AND DEMENTIA

Anna Marseglia

Stockholm 2018

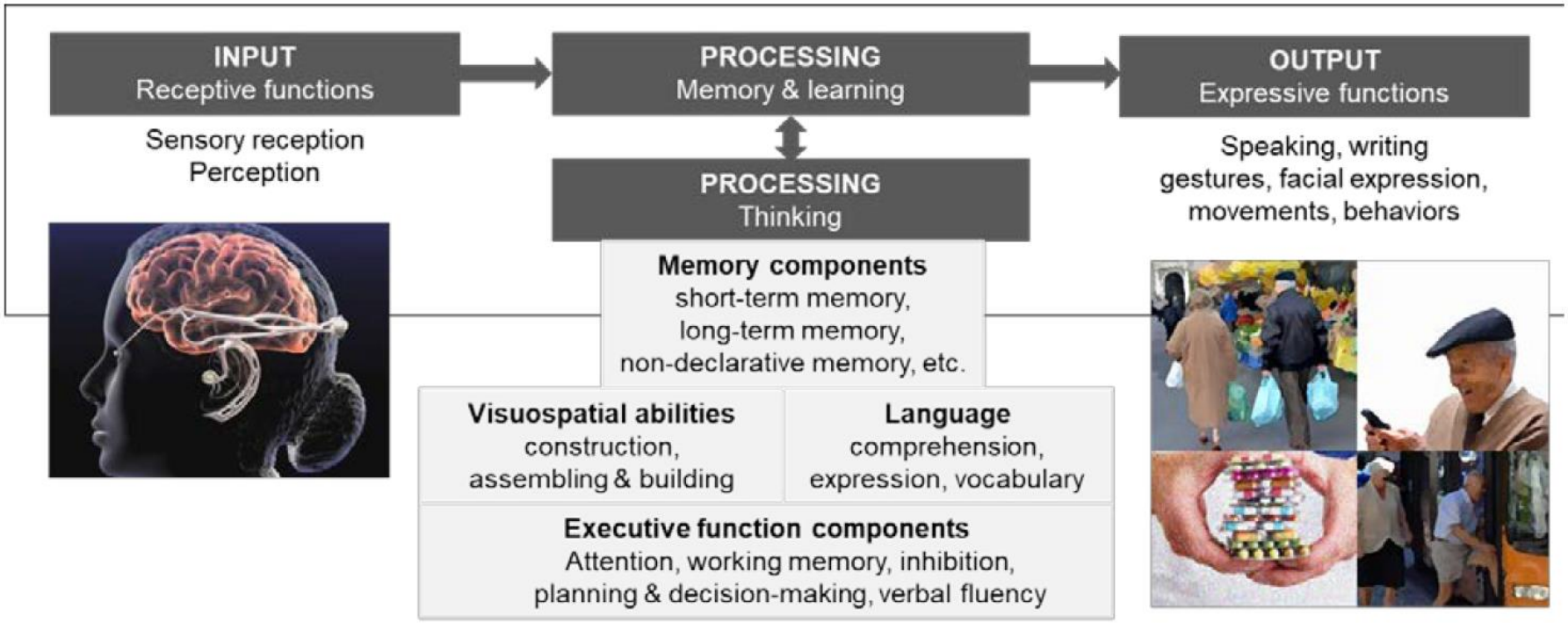


Figure 1. The relationship between brain receptive functions, brain cognitive processes, and daily life behaviors is analogous to the relationship between computer input, processing, and output.

Marseglia A. (Thesis), KI 2018

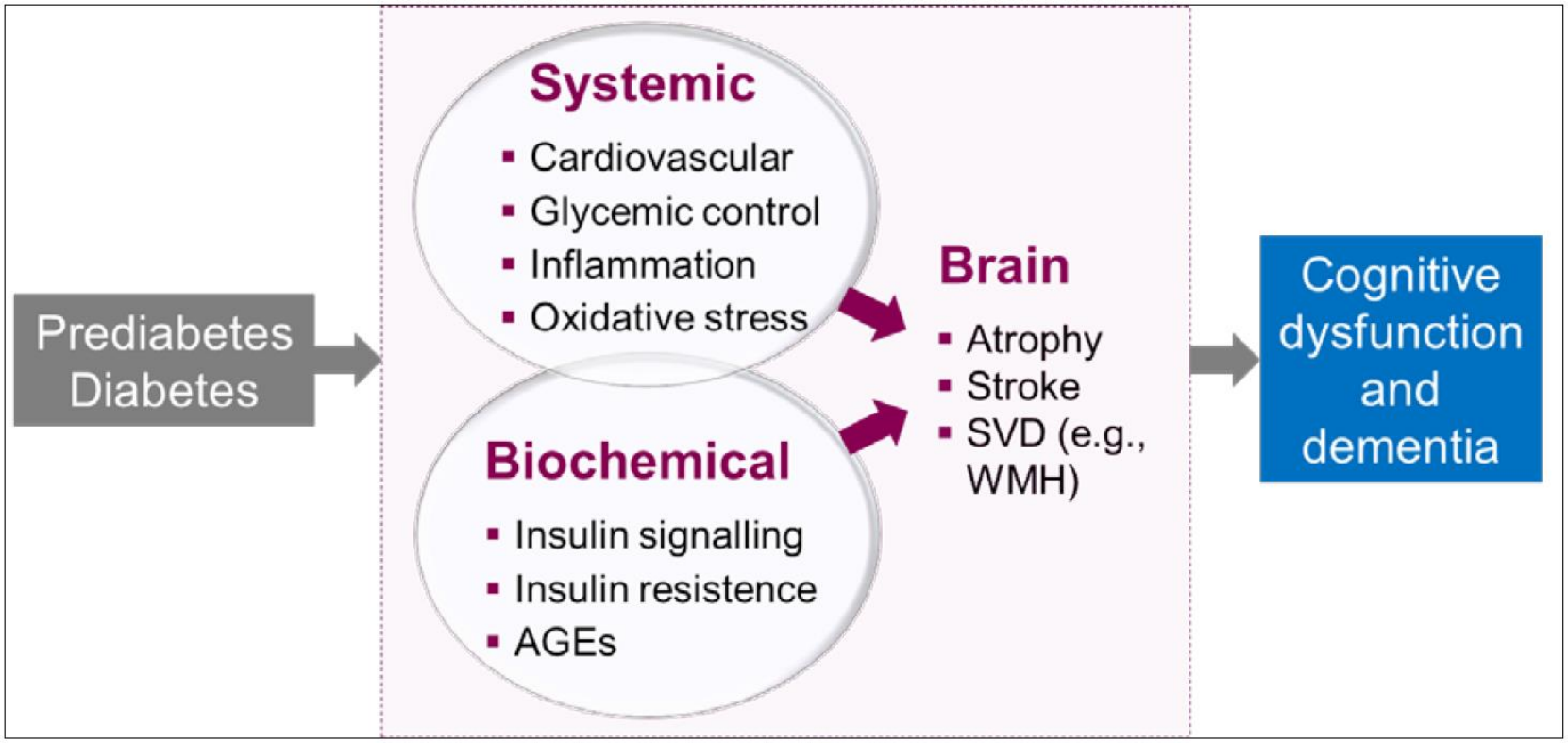


Figure 2. Multifactorial pathways underlying cognitive dysfunction and dementia in people with diabetes.

Marseglia A. (Thesis), KI 2018

Research hypotheses

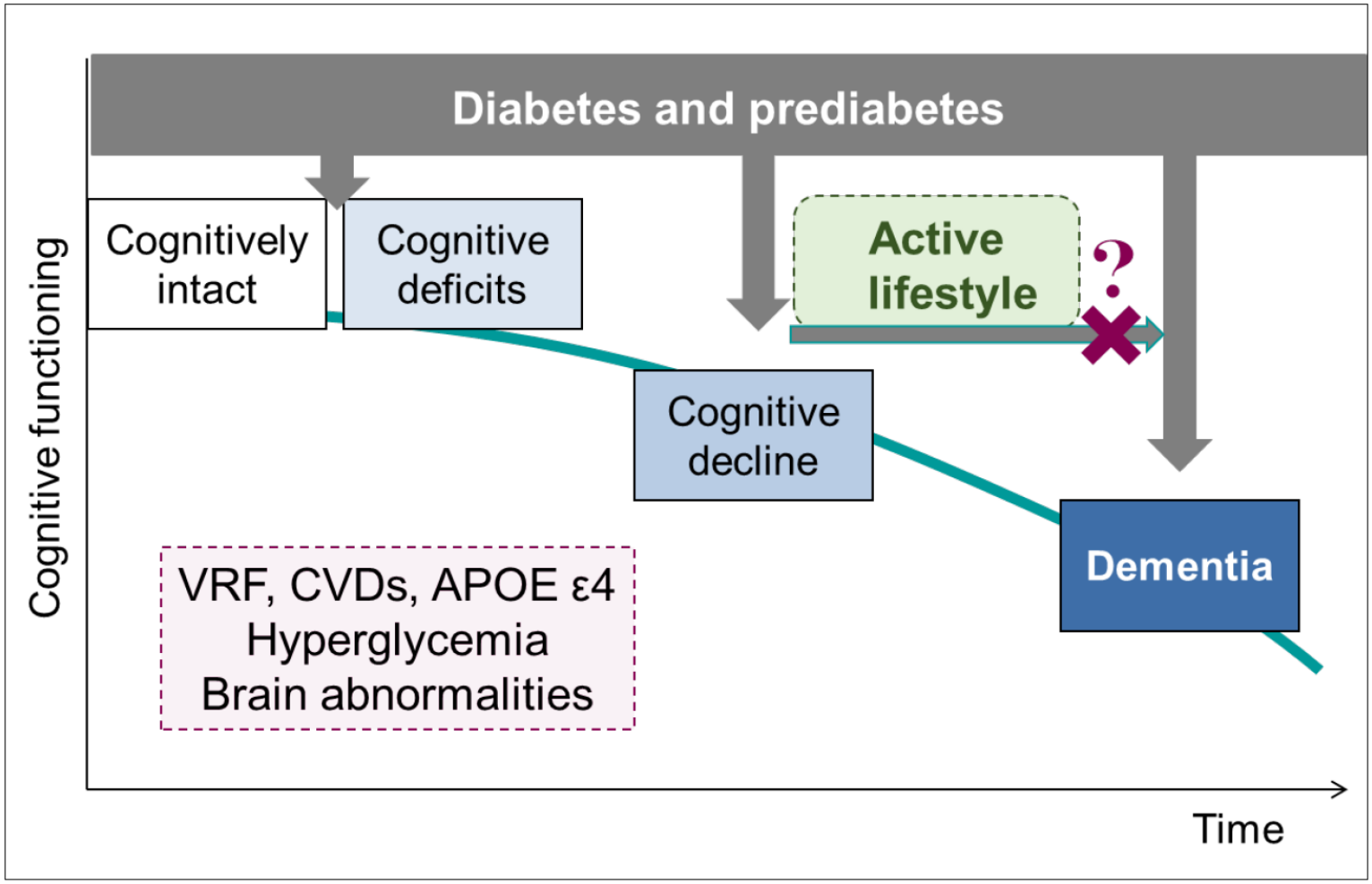


Figure 3. Schematic representation of the research hypothesis.
Abbreviations: *APOE* ε4, apolipoprotein E gene-ε4 allele; CVDs, cardio- and cerebrovascular disorders; VRF, vascular risk factors.

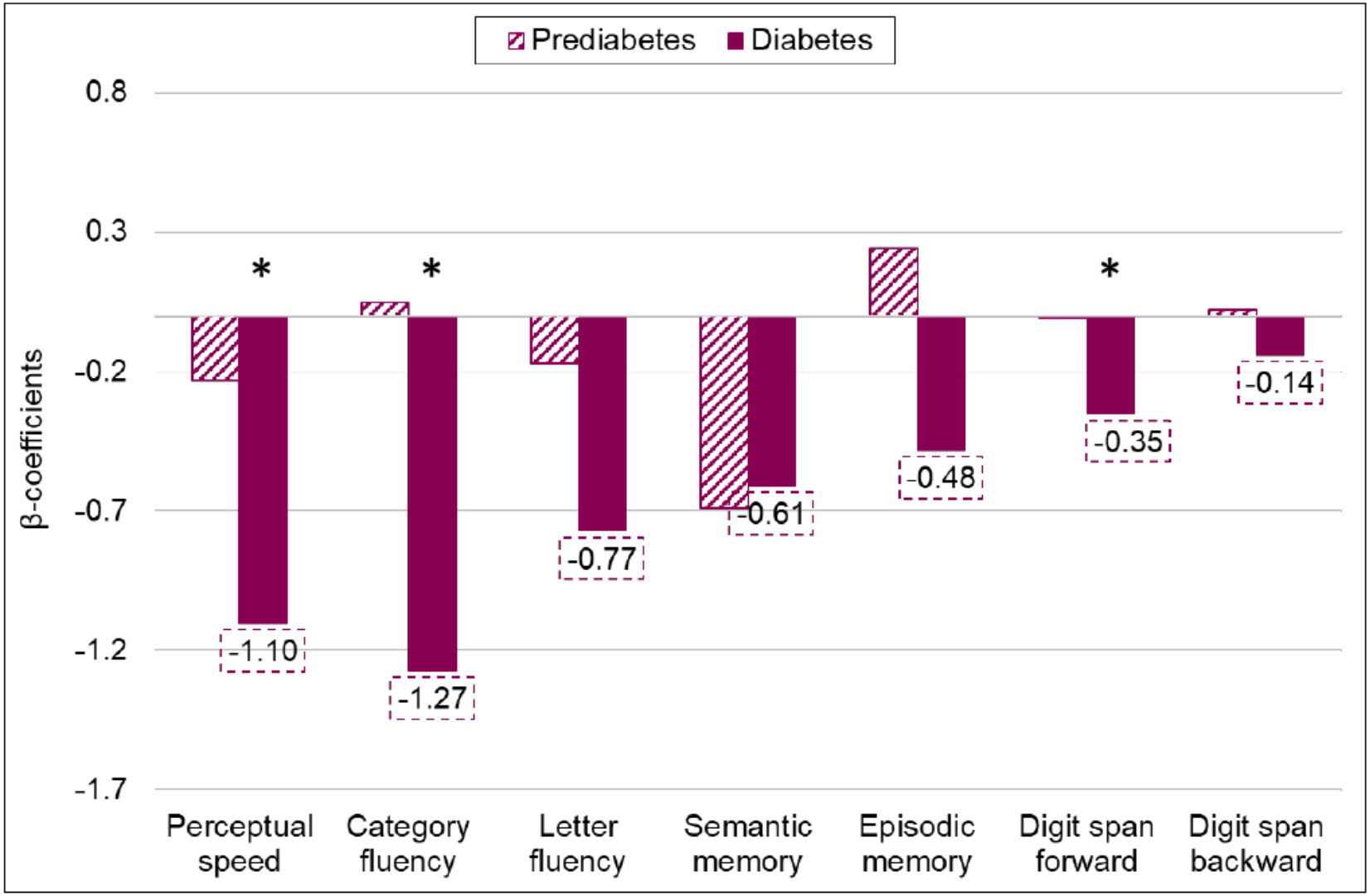
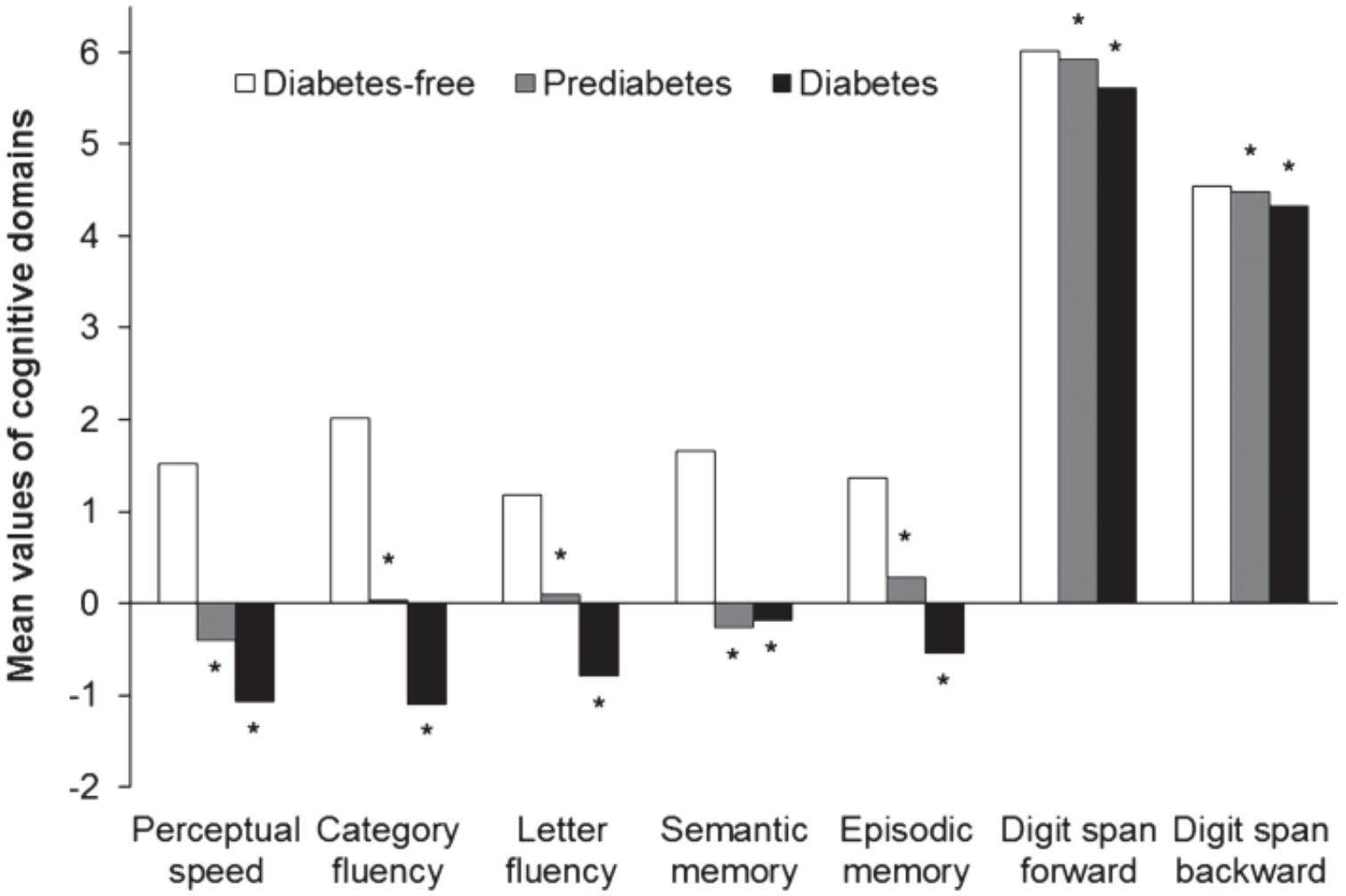


Figure 7. Association between prediabetes and diabetes and performance across cognitive domains.

Marseglia A. (Thesis), KI 2018

Early Cognitive Deficits in Type 2 Diabetes: A Population-Based Study



Cognitive characteristics of the study sample by diabetes. Pairwise multiple comparisons: *p<0.05 (reference group included diabetes-free participants). All latent factor scores were multiplied by 100.

Marseglia A, et al, J Alzheimers Dis. 2016; 53(3):1069-78.

MRI

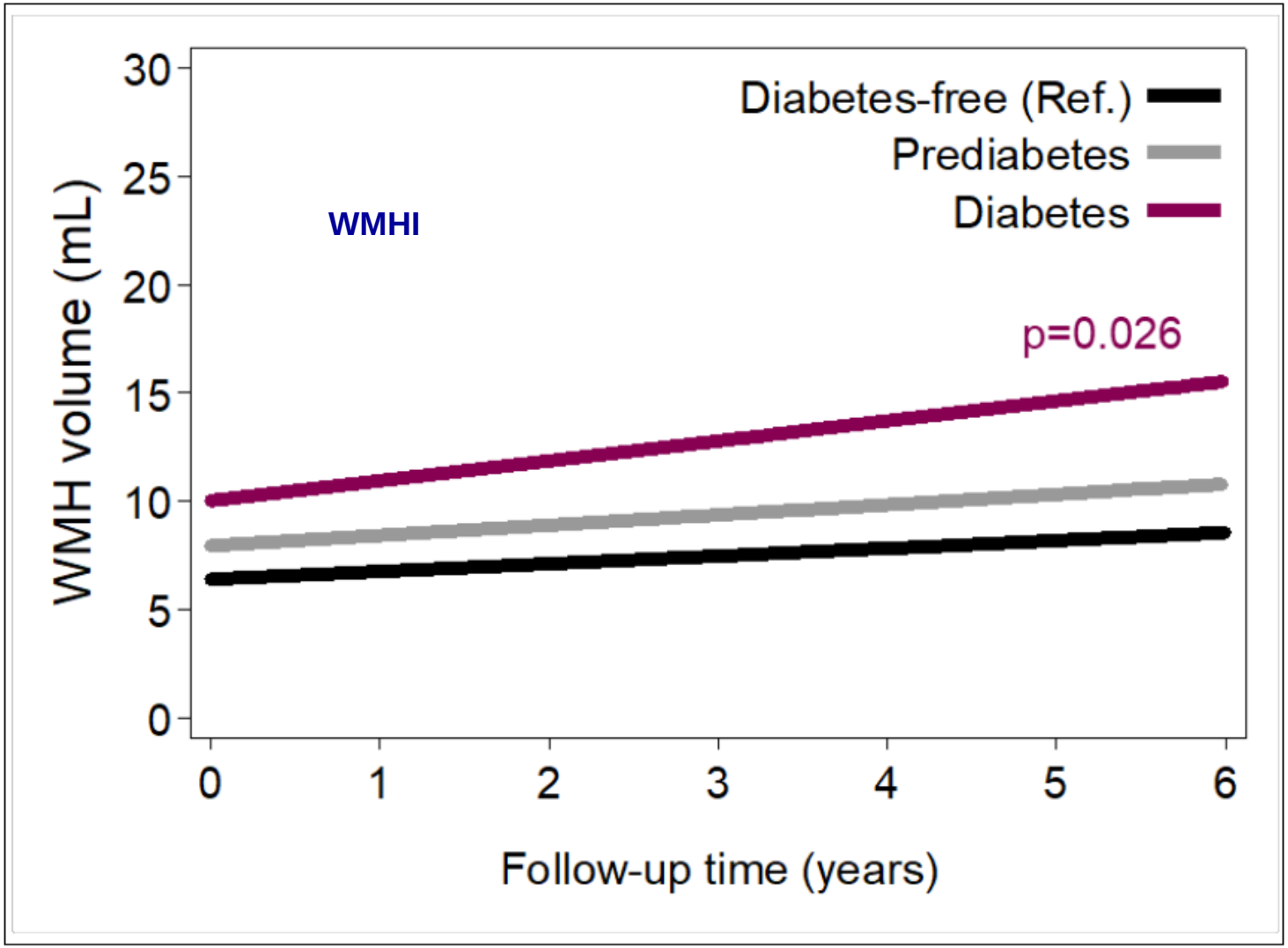


Figure 10. Trajectories of change in the volume of white matter hyperintensities over six years by diabetes status.

Marseglia A. (Thesis), KI 2018

Table 7. Incidence rates of all-cause dementia, Alzheimer's disease, vascular dementia, and mixed dementia (per 1000 person-years) by diabetes status and hazard ratios and 95% confidence intervals of the association between dementia, prediabetes, and diabetes.

Dementia	No. events/ Person-year	IR (95% CI)	Cox regression models	
			HR (95% CI) *	*p*
All-cause				
Diabetes-free	121/9368	13.3 (11.2–15.9)	Reference	
* Prediabetes	88/5517	16.0 (12.9–19.7)	0.97 (0.72–1.30)	0.835
Diabetes	37/1339	27.6 (20.0–38.1)	2.23 (1.49–3.33)	0.000
AD				
Diabetes-free	67/9068	7.39 (5.85–9.39)	Reference	
* Prediabetes	49/5517	8.88 (6.71–11.8)	0.97 (0.66–1.43)	0.894
Diabetes	12/1339	8.96 (5.09–15.8)	1.34 (0.69–2.59)	0.388
VaD				
Diabetes-free	10/9068	1.10 (0.59–2.05)	Reference	
* Prediabetes	7/5517	1.27 (0.60–2.66)	1.20 (0.44–3.33)	0.718
Diabetes	8/1339	5.97 (2.99–11.9)	7.11 (2.21–22.9)	0.001
Mixed				
Diabetes-free	12/9068	1.32 (0.75–2.33)	Reference	
* Prediabetes	15/5517	2.72 (1.64–4.51)	1.39 (0.63–3.05)	0.410
Diabetes	6/1339	4.48 (2.01–9.97)	2.55 (0.90–7.23)	0.078

* Adjusted for baseline age, sex, education, smoking, BMI, CVD, and *APOE* ε4.

Abbreviations: AD, Alzheimer's disease; *APOE* ε4, apolipoprotein E gene-ε4 allele; BMI, body mass index; CI, confidence interval; CVD, cardio- and cerebrovascular disorders; HR, hazard ratio; IR, incident rate; Mixed, mixed dementia; VaD, vascular dementia.

*** Pre-diabetes determined by HbA1c 5.7-6.5% (not OGTT)**

Marseglia A. (Thesis), KI 2018

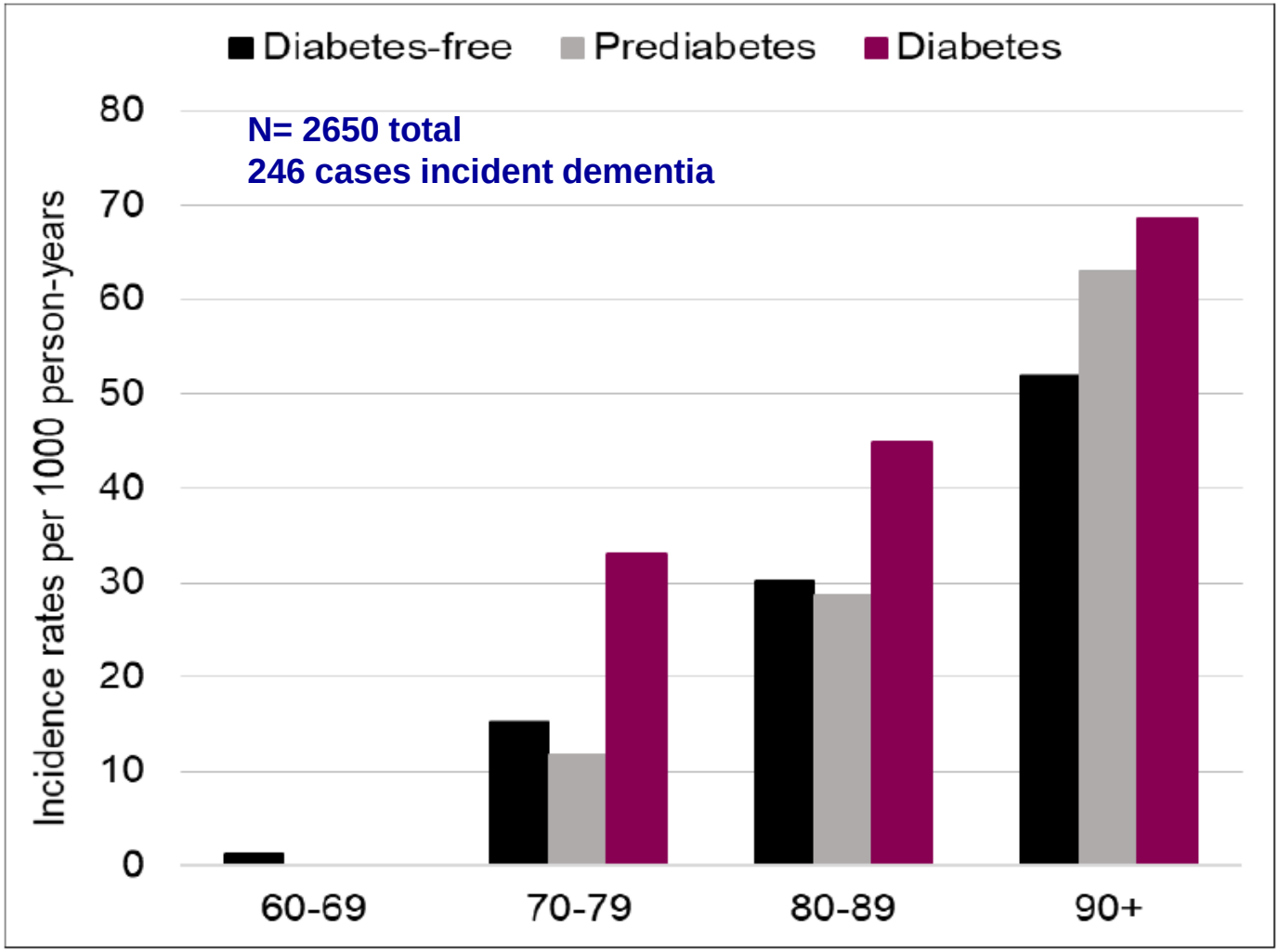


Figure 11. Age-specific incidence rates of dementia per 1000 person-years by diabetes status.

Less risk associated with active lifestyle and better social networks (modifying factors), Paper IV

Marseglia A. (Thesis), KI 2018

Associations between pre-diabetes, diabetes and cognitive outcomes?

- **Cross-sectional, population-based study**
- **Malmö Diet and Cancer Study Cardiovascular cohort Re-examination 2007-2012 (MDC-CV Re-exam)**
- **N= 2994, mean age 72 years**

Glucometabolic categories based on Oral Glucose Tolerance Test (OGTT):

Normoglycaemia (NGT)
Pre-diabetes
Diabetes, short duration
Diabetes, long duration
(diagnosis at baseline, >13 years ago)

?

Cognitive test results

MMSE total score
AQT total score

MMSE memory score
AQT part 1-2 (processing speed)
AQT part 3 (executive functioning)

Adjustment models:
Model 1. demographics (age, sex, education)
Model 2. demographics + lifestyle factors (smoking, alcohol intake, physical activity,)
Model 3. demographics + lifestyle factors + cardiovascular factors (systolic BP, heart rate, total cholesterol, waist circumference, smoking, alcohol intake, physical activity, medications, pulse-wave velocity)

Dybjer E, *et al.* BMC Endocr Disord. 2018 Dec 4;18(1):91.

Elin Dybjer

Pre-diabetes and diabetes are independently associated with adverse cognitive test results: a cross-sectional, population-based study

Elin Dybjer[1*], Peter M. Nilsson[1], Gunnar Engström[1], Catherine Helmer[2] and Katarina Nägga[3,4]

Table 3 Multiple linear regression analyses of linear relationships between *fasting* and *2 h-glucose* respectively and cognitive test results

	Model 1		Model 2	
	B	*p*	B	*p*
All participants				
Fasting glucose (*n* = 2991)				
MMSE total score	−5.325	**< 0.001**	−2.720	0.135
AQT total score	0.087	**< 0.001**	0.034	0.188
2 h-glucose (n = 2671)				
MMSE total score	−2.147	**0.012**	−1.787	**0.046**
AQT total score	0.033	**0.006**	0.023	0.072
All without diabetes				
Fasting glucose (*n* = 2484)				
MMSE total score	−8.323	**0.001**	−5.860	**0.030**
AQT total score	0.098	**0.004**	0.035	0.360
2 h-glucose (*n* = 2433)				
MMSE total score	−2.961	**0.005**	−2.563	**0.019**
AQT total score	0.042	**0.004**	0.030	**0.046**

Model 1: Adjusted for age, sex, education, physical activity level, smoking habits and alcohol consumption
Model 2: Adjusted for factors in Model 1 and cardiovascular factors: Systolic blood pressure, heart rate, c-f PWV, waist circumference, total cholesterol levels and medications (anti-hypertensive, anti-diabetic and lipid-lowering treatment)

Dybjer E, *et al.* BMC Endocr Disord. 2018 Dec 4;18(1):91.

Results

- **Declining trends** in cognitive test results across glucometabolic categories

- **Pre-diabetes and short-term diabetes**: small differences in results compared to the group with normoglycaemia
  - In line with the fact that **early stages of diabetes** are associated with **mild cognitive decrements** that develop slowly over the life-course

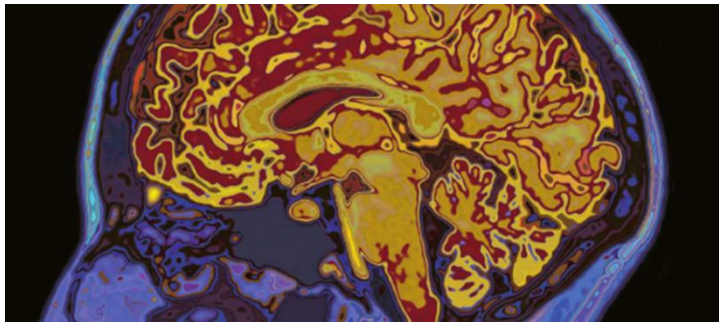
- **Long-term-diabetes**: Clinically relevant differences (17.8 seconds slower at AQT test and 1.7 MMSE points worse than the group with normoglycaemia, $p<0.001$)
  - In line with the fact that duration of diabetes is a predictor of cognitive outcome

- After additional adjustment for cardiovascular factors, long-term diabetes was still associated with worse cognitive test results
  - Cardiovascular factors cannot (on their own) explain the associations between diabetes and cognitive outcomes

Dybjer E, *et al.* BMC Endocr Disord. 2018 Dec 4;18(1):91.

Typ 1-diabetes och kognitiva utfall

- Effektstorleken av diabetes på kognitiva utfall verkar vara mycket liten.
  - Marginellt sämre grundskole- och gymnasiebetyg och IQ (svenska studier)
- Domäner som kan påverkas: intelligens, uppmärksamhet, snabbhet, minne.
- Annorlunda bild på MRI - men ej kunnat härledas till skillnad i kognitiv prestationsförmåga.
- Diabetesrelaterade faktorer som kan bidra:
  - Hypoglykemier (inte alla studier visar detta)
  - Kronisk hyperglykemi (mer övertygande)
  - Ketoacidos
  - Tidig debut
  - Hormonella förändringar i puberteten



Typ 1-diabetes och risk för diabeteskomplikationer

- Vikten av **tidig glykemisk kontroll** och anpassad **insulinbehandling** avseende risk för **komplikationer** (njur-, ögon- och nervkomplikationer) studerats under de senaste decennierna
  - Exempel: Amerikanska DCCT (Diabetes Control and Complications Trial), 1983-1993 (n=1441) och uppföljande EDIC (the Epidemiology of Diabetes Interventions and Complications study), 1994 (n=96)

- **Färre studier med lång uppföljningstid**
  - **Svensk longitudinell kohortstudie** med T1D-patienter följda sedan 60-talet vid Universitetssjukhuset i Linköping (Nordwall e*t al* 2009).
    - n=269, T1D-diagnos 1961-85. Följdes till slutet av 90-talet.
    - Diabetesduration och HbA1c = prediktorer för retinopati och nefropati

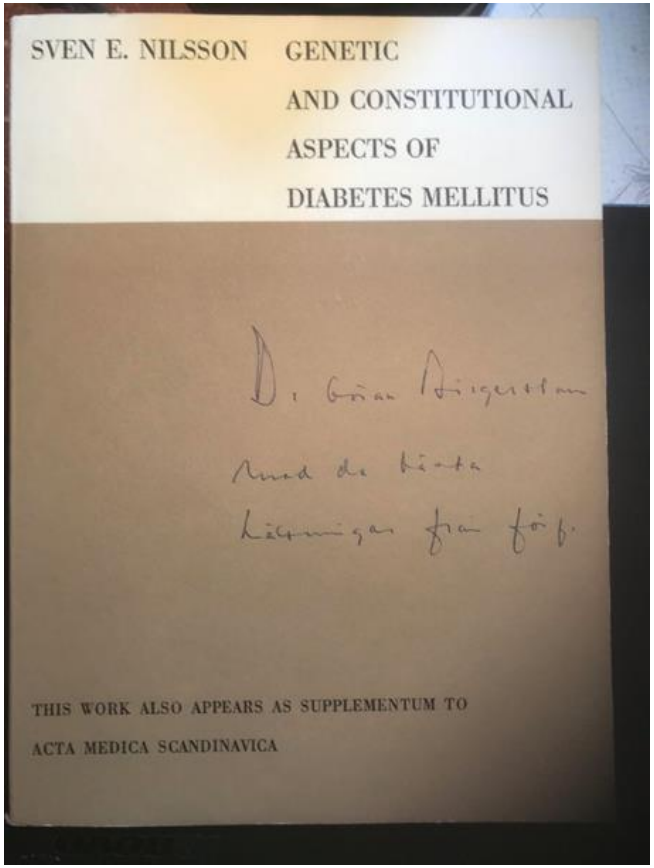
- **Många studier om mortalitet och hjärtkärlsjukdom vid T1D**
  - Kvinnor med T1D har 40% ökad risk för ”all cause mortality” och dubbelt så hög risk för död i hjärtkärlsjukdom jämfört med män

Typ 1-diabetes och risk för demens

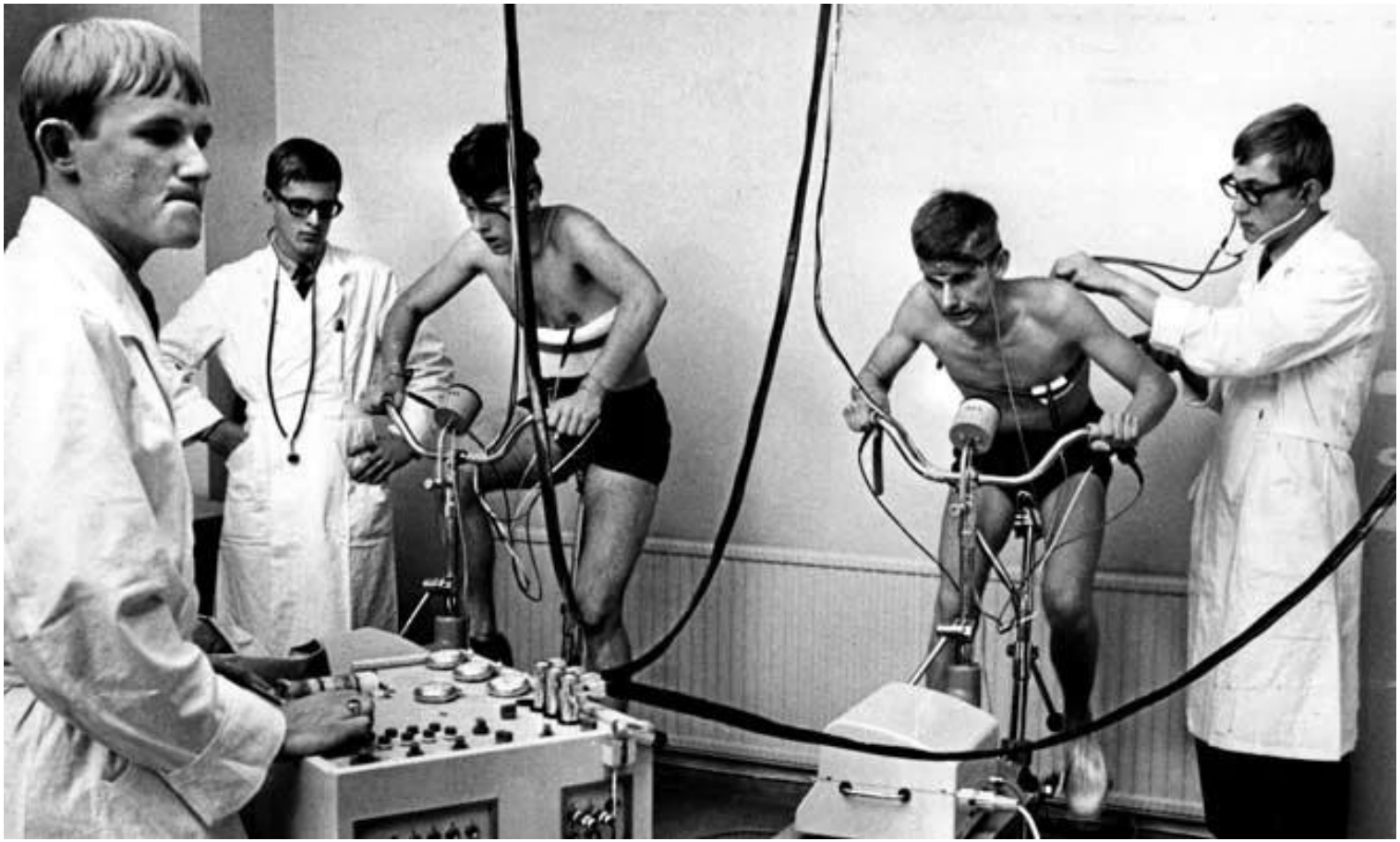
- **Färre studier. Några exempel:**
  - Retrospektiv journalstudie från England:
    - The overall RR for dementia in people admitted to hospital with type 1 diabetes was 1.65 (95% CI 1.61, 1.68)
  - Populationsbaserad kohortstudie från Taiwan (N=1100):
    - The relative risk of developing dementia (118-314%) in patients with type 1 DM was much higher than the -previously reported relative risk (15-28%) associated with type 2 DM.
  - Amerikansk fall-kontrollstudie (n=150): lång duration >50 år av T1D -> sämre kognitiva testresultat

1. Smolina K, et al. Risk of dementia in patients hospitalised with type 1 and type 2 diabetes in England, 1998-2011: a retrospective national record linkage cohort study. Diabetologia. 2015 May;58(5):942-50.
2. Kuo CL, et al. Population-Based Cohort Study on Dementia Risk in Patients with Type 1 Diabetes Mellitus. Neuroepidemiology. 2018;50(1-2):57-62.
3. Musen G, et al. Cognitive Function Deficits Associated With Long-Duration Type 1 Diabetes and Vascular Complications. Diabetes Care. 2018 Jun 5.

Sven Nilsson (1929-2009) disputerade på en avhandling *”Genetic and constitutional aspects of diabetes mellitus”* vid Lunds universitet 1962 (*Acta Med Scand*: supplement 375, Lund 1962).



Värnpliktsmönstring i Kristianstad 1967



Sven Nilsson tog initiativ till en screeningundersökning vid mönstring som omfattade **119 manliga patienter med typ 1-diabetes** (födda 1934-1942) som identifierades genom journalgenomgång från medicinkliniker i Skåne 1959-1960. Dessa representerade 90% av skånska män med typ 1-diabetes i denna ålder.

Som **kontrollpersoner** rekryterades vid mönstringsundersökning 1959 i Kristianstad följande manliga kontroller:

- 237 individer med en positiv familjehistoria för diabetes
- 238 individer utan känd familjehistoria för diabetes

Totalt utgjordes materialet av **594 individer.**

Behandlingsaspekter

Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy

*Lenore J Launer, Michael E Miller, Jeff D Williamson, Ron M Lazar, Hertzel C Gerstein, Anne M Murray, Mark Sullivan, Karen R Horowitz, Jingzhong Ding, Santica Marcovina, Laura C Lovato, James Lovato, Karen L Margolis, Patrick O'Connor, Edward W Lipkin, Joy Hirsch, Laura Coker, Joseph Maldjian, Jeffrey L Sunshine, Charles Truwit, Christos Davatzikos, R Nick Bryan, for the ACCORD MIND investigators**

N= 2977

	Intensive-treatment group	Standard-treatment group	Difference in means*
Stroop test			
Baseline†	32·0	32·0	..
20 months	30·87 (30·16 to 31·57)	31·46 (30·77 to 32·16)	−0·60 (−1·59 to 0·40); p=0·2375
40 months	31·45 (30·73 to 32·17)	32·06 (31·34 to 32·77)	−0·61 (−1·62 to 0·40); p=0·2383
40-month change	−0·55 (−1·27 to 0·17)	0·06 (−0·66 to 0·77)	..
MMSE			
Baseline†	27·39	27·39	..
20 months	27·26 (27·14 to 27·38)	27·27 (27·15 to 27·39)	−0·01 (−0·18 to 0·16); p=0·9268
40 months	27·05 (26·93 to 27·17)	27·06 (26·93 to 27·18)	−0·01 (−0·18 to 0·16); p=0·9328
40-month change	−0·34 (−0·46 to −0·22)	−0·33 (−0·46 to −0·21)	..
TBV (cm^3)			
Baseline†	927·5	927·5	..
40 months‡	914·4 (912·5 to 916·4)	909·8 (908·0 to 911·6)	4·6 (2·0 to 7·3); p=0·0007
40-month change	−13·0 (−15·0 to −11·1)	−17·7 (−19·5 to −15·9)	..

TBV: Total Brain Volume

Launer LJ, *et al*. Lancet Neurol. 2011;10:969-77.

Rationale and design of the CAROLINA® - cognition substudy: a randomised controlled trial on cognitive outcomes of linagliptin versus glimepiride in patients with type 2 diabetes mellitus

Geert Jan Biessels[1*], Jolien Janssen[1,2], Esther van den Berg[1,3], Bernard Zinman[4], Mark A. Espeland[5], Michaela Mattheus[6], Odd Erik Johansen[7] and on behalf of the CAROLINA® investigators

Discussion: Between December 2010 and December 2012, 6042 patients were randomised and treated with either linagliptin (5 mg) or glimepiride (1-4 mg) once daily in CAROLINA®. Cognitive tests were conducted in nearly 4500 participants at baseline and are scheduled for two subsequent assessments, after 160 weeks of follow-up and end of follow-up. This substudy of the ongoing CAROLINA® trial will establish if linagliptin is superior to glimepiride in the prevention of accelerated cognitive decline in patients with type 2 diabetes mellitus. Final results are expected in 2019.

Trial registration: ClinicalTrials.gov Identifier: NCT 01243424.

Final results are awaited in late 2019

Biessels *et al. BMC Neurology* (2018) 18:7

February 14th 2019 – PRESS RELEASE

Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced **CAROLINA®** (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) met its primary endpoint, defined as **non-inferiority** for Tradjenta® (linagliptin) versus glimepiride in time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (3P-MACE).

CAROLINA is the only active-comparator cardiovascular outcome trial for a dipeptidyl peptidase-4 (DPP-4) inhibitor. The trial evaluated the cardiovascular safety of Tradjenta (5 mg once daily) compared with the sulfonylurea glimepiride, on top of standard of care, in **6,033 adults with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease**. The study assessed Tradjenta safety over the longest period ever studied in a DPP-4 inhibitor cardiovascular outcome trial, with a median follow-up of more than 6 years. The overall safety profile of Tradjenta in CAROLINA was consistent with previous data, and no new safety signals were observed.

People with type 2 diabetes have an increased risk of cardiovascular disease, and despite recent advancements in treatment options, cardiovascular disease remains the leading cause of death for this population. Together with **CARMELINA®**, which demonstrated **similar long-term cardiovascular safety compared with placebo** in adults with type 2 diabetes at high risk for cardiovascular and/or kidney disease, CAROLINA confirms the long-term overall safety profile of Tradjenta in a broad range of adults with type 2 diabetes

To be presented at ADA, June 2019

Reducing your risk for diabetes and dementia
The importance of healthy lifestyle

- What's good for your heart is good for your brain. Living a **healthy lifestyle** that promotes cardiovascular health will benefit your brain.

- Eat a healthy diet rich in vitamin D, folate, and B1, B6 and B12 vitamins
- Exercise regularly – both your body and mind
- Stay **socially active** and challenge yourself daily
- Protect your head when playing sports

Sammanfattning

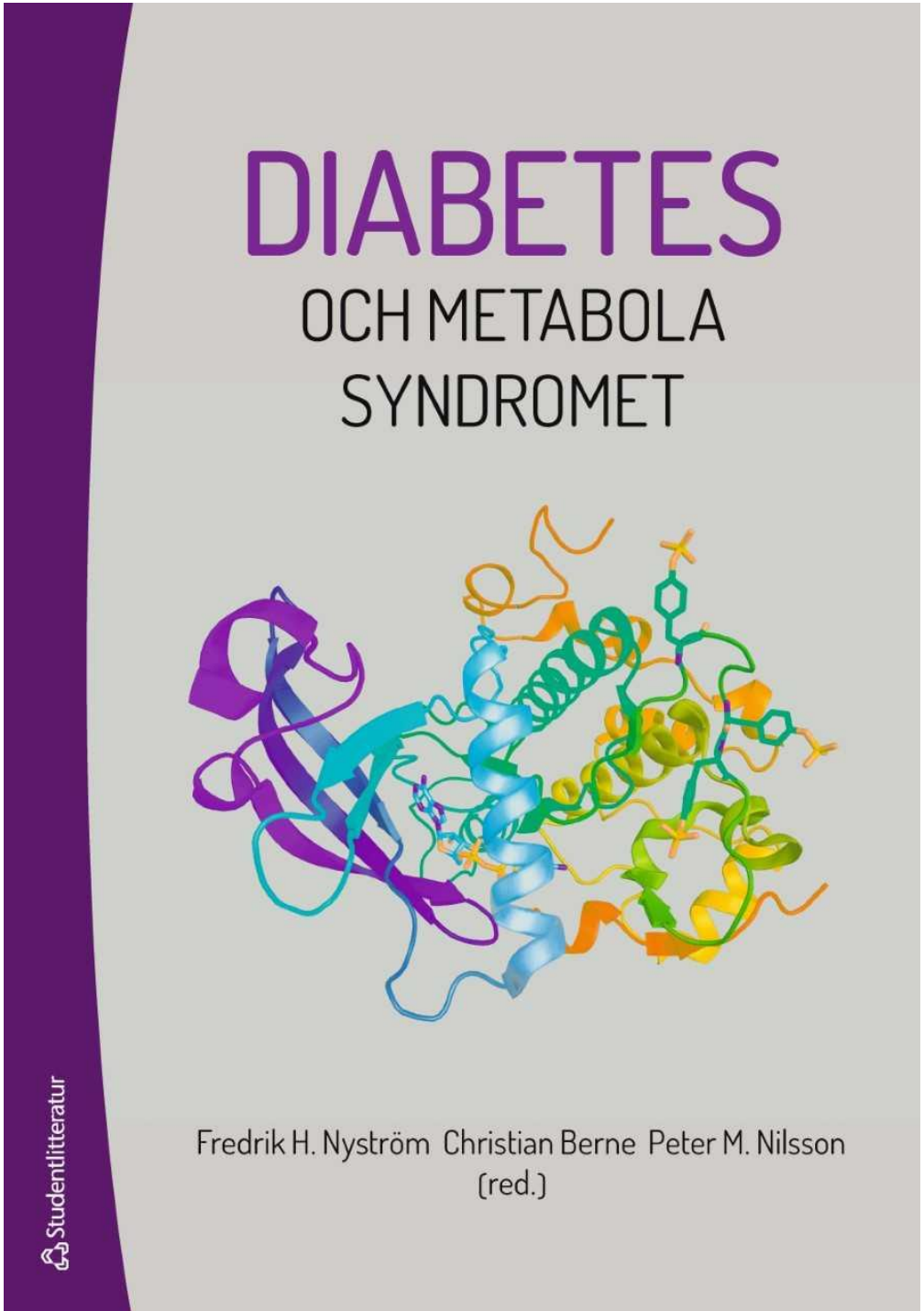
- Patienter med diabetes löper en ökad risk för kognitionsnedsättning samt utveckling av demens, både av vaskulär och Alzheimer typ

- Orsaken kan vara inflytandet av vaskulära riskfaktorer och *ApoE4* men mycket talar för att det även finns diabetesspecifika bidragande faktorer, som t.ex. hypoglykemier och störd cerebral insulinomsättning

- Insulinresistens och hyperglykemi har associerats till ökad bildning av beta-amyloid, en bidragande faktor vid utveckling av Alzheimer demens

- Hittillsvarande försök att förebygga demens med antidiabetes-behandling har inte varit framgångsrik (ACCORD-MIND)

PN, ED 2019



Kapitel 10.

Diabetes, kognition och demens

Elin Dybjer & Peter M Nilsson

Studentlitteratur AB, mars 2019