Dementia and Cognitive Decline in Diabetes: A Two-Way relationship?

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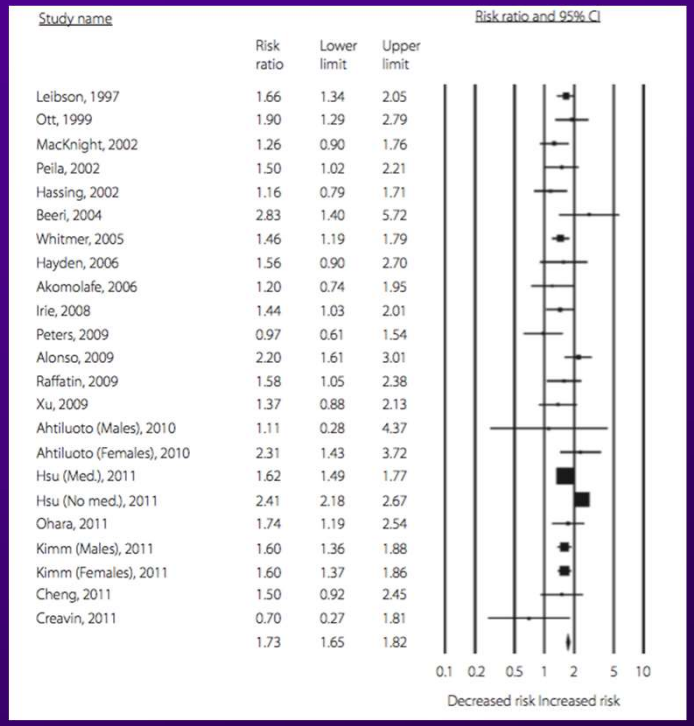
Dementia is More Common in People with Diabetes



Study name	Risk ratio	Lower limit	Upper limit
Leibson, 1997	1.66	1.34	2.05
Ott, 1999	1.90	1.29	2.79
MacKnight, 2002	1.26	0.90	1.76
Peila, 2002	1.50	1.02	2.21
Hassing, 2002	1.16	0.79	1.71
Beeri, 2004	2.83	1.40	5.72
Whitmer, 2005	1.46	1.19	1.79
Hayden, 2006	1.56	0.90	2.70
Akomolafe, 2006	1.20	0.74	1.95
Irie, 2008	1.44	1.03	2.01
Peters, 2009	0.97	0.61	1.54
Alonso, 2009	2.20	1.61	3.01
Raffatin, 2009	1.58	1.05	2.38
Xu, 2009	1.37	0.88	2.13
Ahtiluoto (Males), 2010	1.11	0.28	4.37
Ahtiluoto (Females), 2010	2.31	1.43	3.72
Hsu (Med.), 2011	1.62	1.49	1.77
Hsu (No med.), 2011	2.41	2.18	2.67
Ohara, 2011	1.74	1.19	2.54
Kimm (Males), 2011	1.60	1.36	1.88
Kimm (Females), 2011	1.60	1.37	1.86
Cheng, 2011	1.50	0.92	2.45
Creavin, 2011	0.70	0.27	1.81
	1.73	1.65	1.82

- 28 pooled prospective studies
- RR 1.78 for all-type dementia
- RR 1.56 for Alzheimer's dementia
- RR 2.27 for Vascular dementia

Gudala et al J Diabetes Invest 2013; 4: 640-650

Cardiovascular Disease is Associated with Cognitive Decline

	Standardised β-coefficient* (p-value)
All CVD	-0.09 (0.008)
Stroke	-0.07 (0.036)
Carotid intima media thickness	-0.15 (<0.001)
Ankle brachial pressure index	0.12 (0.001)
NT-ProBNP	-0.12 (0.001)
MI/angina	-0.04 (0.293)

*adjusted for age, sex, baseline cognition, BP, cholesterol, smoking

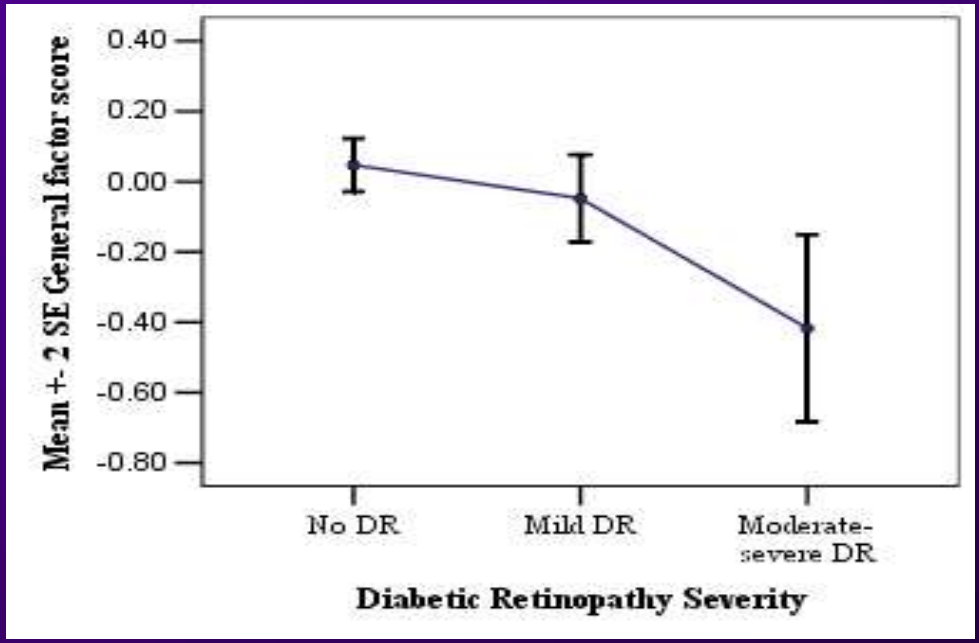
Feinkohl et al Diabetes Care 2013: 36; 2279-86
Feinkohl et al PLoS One 2012: 7; e44569

Cardiovascular Risk Factors and Cognitive Decline

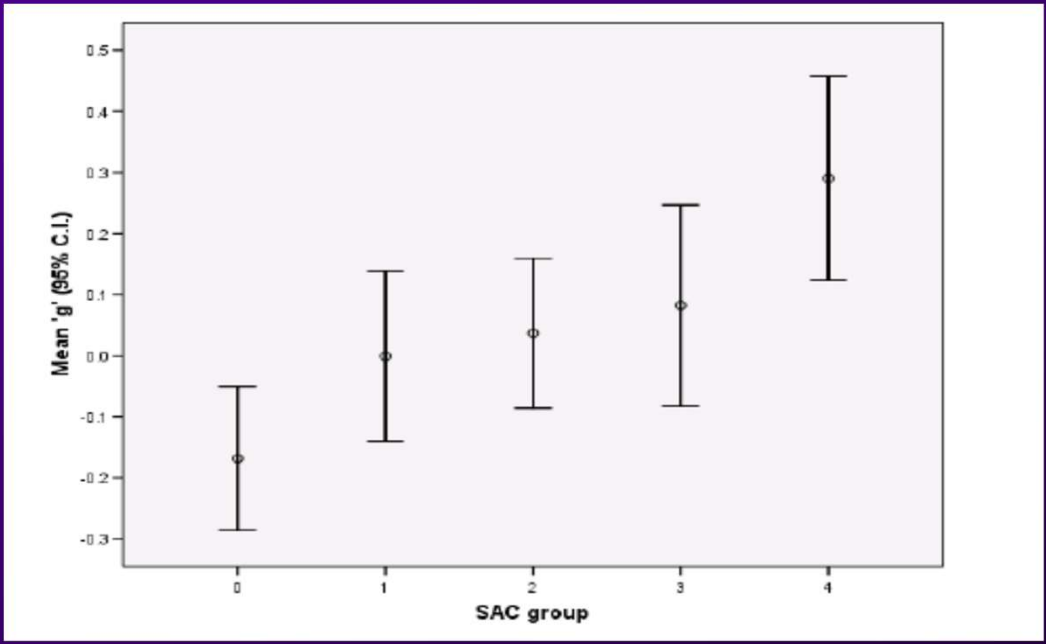
Risk Factor	Effect on Decline in 'g' [Standardised β coefficient (p-value)]	Risk of Accelerated Cognitive Decline [Odds ratio (95% CI)]
Time-weighted blood pressure	-0.07 (0.067)	1.01 (0.99-1.03)
Time-weighted HbA1c	-0.10 (0.005)	1.21 (1.00-1.45)
Smoking (pack years)	-0.14 (<0.001)	1.64 (1.14-2.34)
Cholesterol	0.00 (0.938)	-

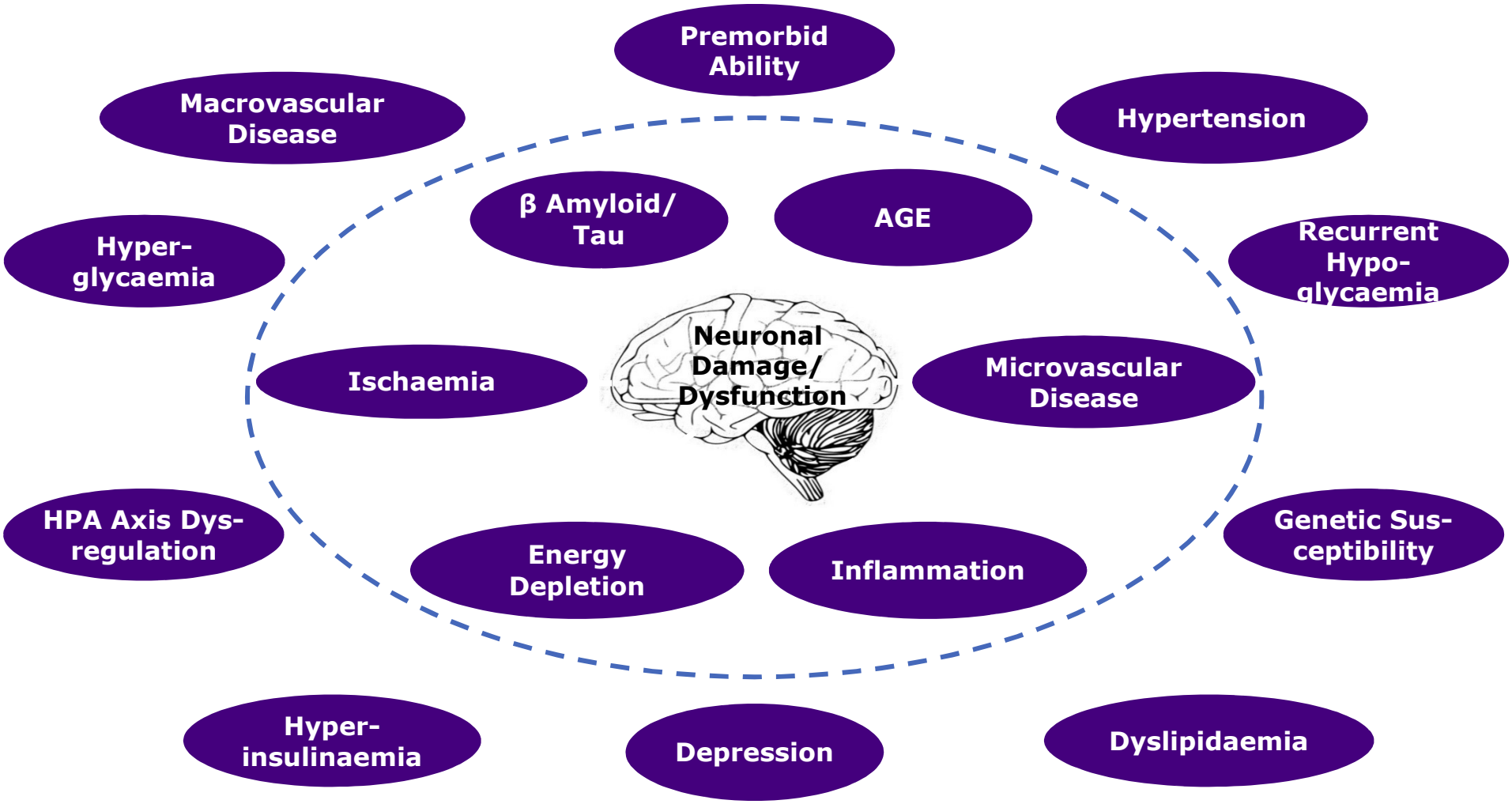
Feinkohl et al, Diabetologia 2015: 58; 1637-45

Retinopathy and Cognitive Decline

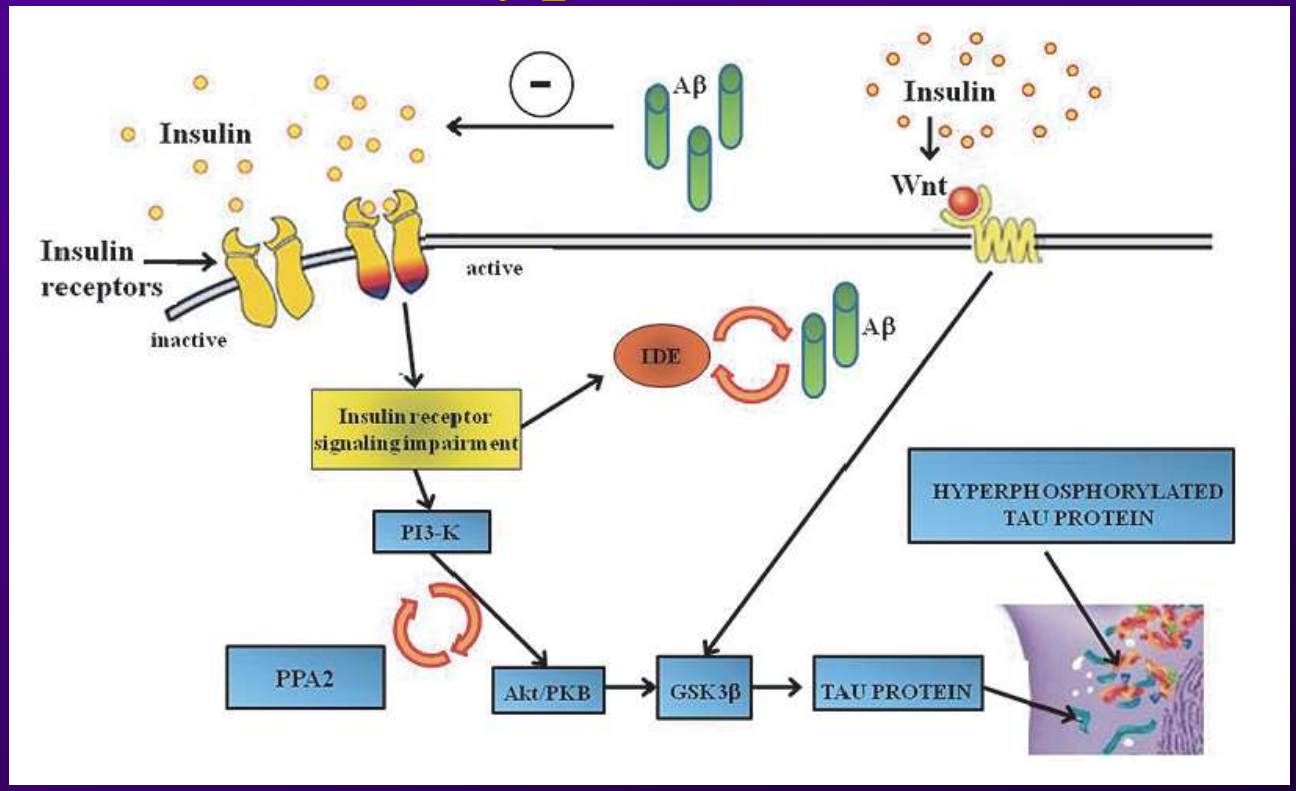


Alcohol and Cognitive Function

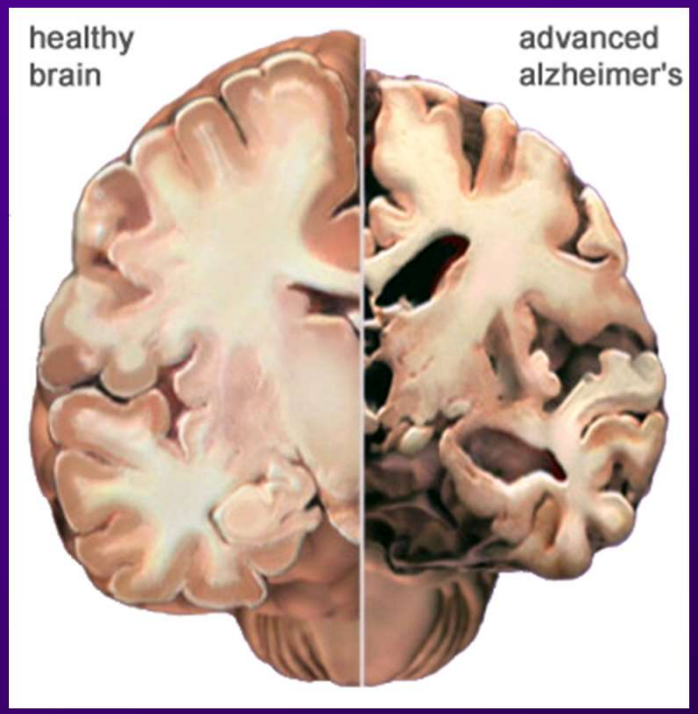



Premorbid Ability
Macrovascular Disease
Hypertension
β Amyloid/ Tau
AGE
Hyper-glycaemia
Recurrent Hypo-glycaemia
Neuronal Damage/ Dysfunction
Ischaemia
Microvascular Disease
HPA Axis Dys-regulation
Genetic Sus-ceptibility
Energy Depletion
Inflammation
Hyper-insulinaemia
Depression
Dyslipidaemia

The ‘Insulin Resistance’ Hypothesis



Hypoglycaemia and Dementia in Type 2 diabetes



- Longitudinal cohort study in 16,667 people with Type 2 diabetes. Mean age 65 years.
- 1465 patients had at least 1 episode of severe hypoglycaemia between 1980-2002 (from hospital records)
- 1822 incident diagnoses of dementia 2003-2007

Whitmer et al JAMA 2009: 301: 1565-1572

Severe Hypoglycaemia is Associated with an Increased Risk of Future Dementia

Number of Episodes of Severe Hypoglycaemia	Hazard Ratio* (95% CI)
1 or more	1.44 (1.25-1.66)
1	1.26 (1.10-1.49)
2	1.80 (1.37-2.36)
3 or more	1.94 (1.42-2.64)

*adjusted for age, sex, BMI, education, 7 year HbA1c, duration of diabetes, comorbidities, diabetes treatments, years of insulin

Whitmore et al JAMA 2009: 301: 1565-1572

DCCT/EDIC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Effect of Diabetes and Its Treatment on Cognitive Function

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group*

The members of the writing committee — Alan M. Jacobson, M.D., and Gail Musen, Ph.D., Joslin Diabetes Center and Harvard Medical School, Boston; Christopher M. Ryan, Ph.D., and Nancy Silvers, R.N., University of Pittsburgh School of Medicine, Pittsburgh; Patricia Cleary, M.S., and Barbara Waberski, M.S., George Washington University, Rockville, MD; Amanda Burwood, B.S., and Katie Weinger, Ed.D., Joslin Diabetes Center, Boston; Meg Bayless, R.N., University of Iowa College of Medicine, Iowa City; William Dahms, M.D. (deceased), Case Western Reserve University, Cleveland; and Judith Harth, R.N., University of Western Ontario Schulich School of Medicine, London, ON, Canada — and the DCCT/EDIC Study Research Group assume responsibility for the overall content and integrity of the article.

*Participants in the DCCT/EDIC Study Research Group are listed in the Appendix.

This article (10.1056/NEJMoa066397) was updated on November 4, 2009, at NEJM.org.

N Engl J Med 2007;356:1842-52.

ABSTRACT

BACKGROUND

Long-standing concern about the effects of type 1 diabetes on cognitive ability has increased with the use of therapies designed to bring glucose levels close to the nondiabetic range and the attendant increased risk of severe hypoglycemia.

METHODS

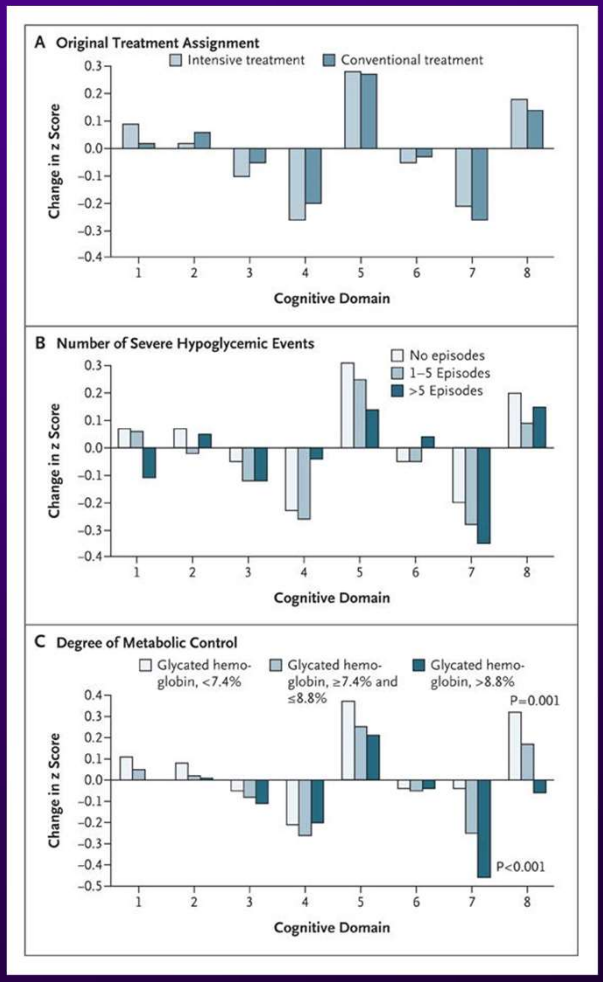
A total of 1144 patients with type 1 diabetes enrolled in the Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study were examined on entry to the DCCT (at mean age 27 years) and a mean of 18 years later with the same comprehensive battery of cognitive tests. Glycated hemoglobin levels were measured and the frequency of severe hypoglycemic events leading to coma or seizures was recorded during the follow-up period. We assessed the effects of original DCCT treatment-group assignment, mean glycated hemoglobin values, and frequency of hypoglycemic events on measures of cognitive ability, with adjustment for age at baseline, sex, years of education, length of follow-up, visual acuity, self-reported sensory loss due to peripheral neuropathy, and (to control for the effects of practice) the number of cognitive tests taken in the interval since the start of the DCCT.

RESULTS

Forty percent of the cohort reported having had at least one hypoglycemic coma or seizure. Neither frequency of severe hypoglycemia nor previous treatment-group assignment was associated with decline in any cognitive domain. Higher glycated hemoglobin values were associated with moderate declines in motor speed (P=0.001) and psychomotor efficiency (P<0.001), but no other cognitive domain was affected.

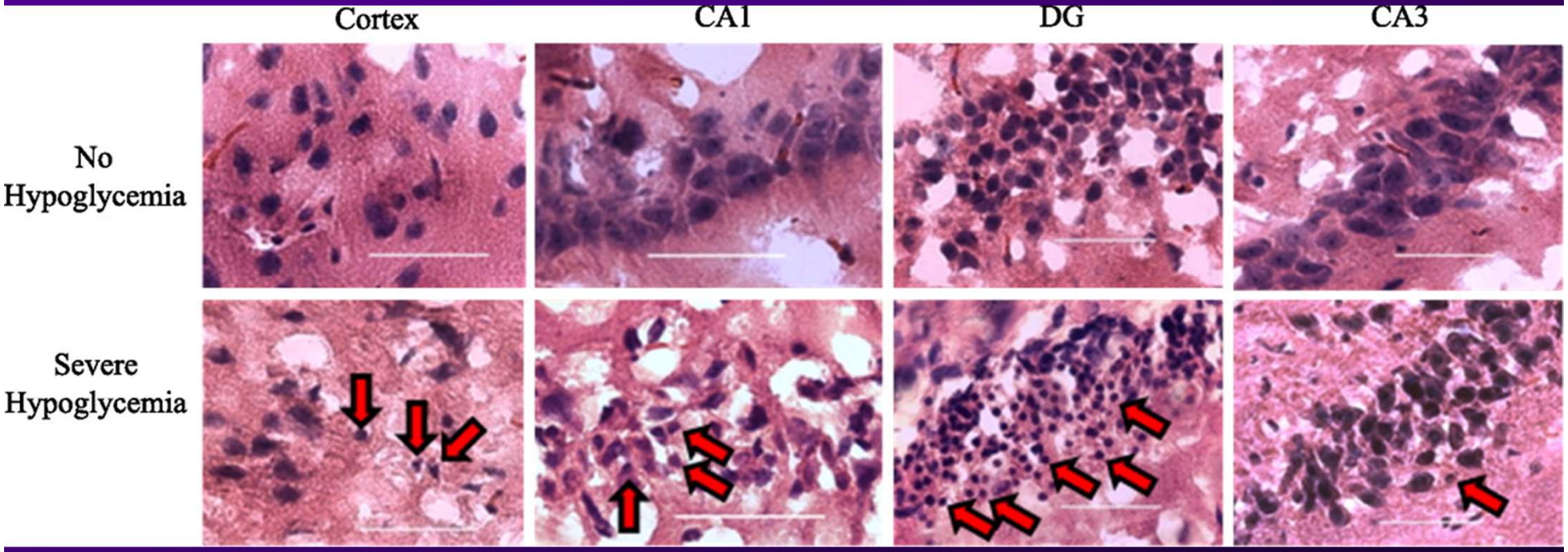
CONCLUSIONS

No evidence of substantial long-term declines in cognitive function was found in a large group of patients with type 1 diabetes who were carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycemia. (ClinicalTrials.gov number, NCT00360893.)



DCCT/EDIC Study Investigators NEJM 2007; 356:1842-1852

Profound Hypoglycaemia Causes Neuronal Death

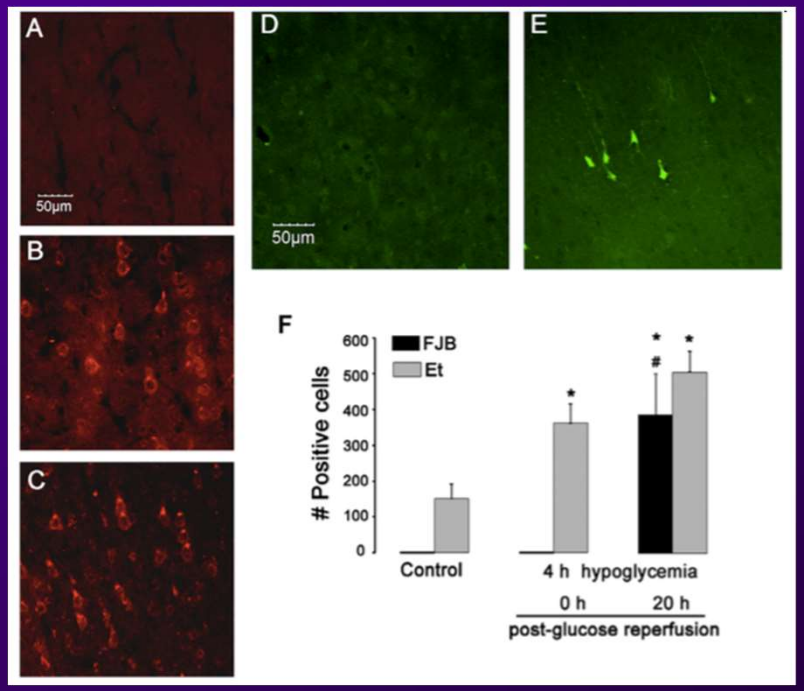


Bree et al Am J Physiol Endocrinol Metab 2009; 297: E194-201

Profound Hypoglycaemia Causes Neuronal Death

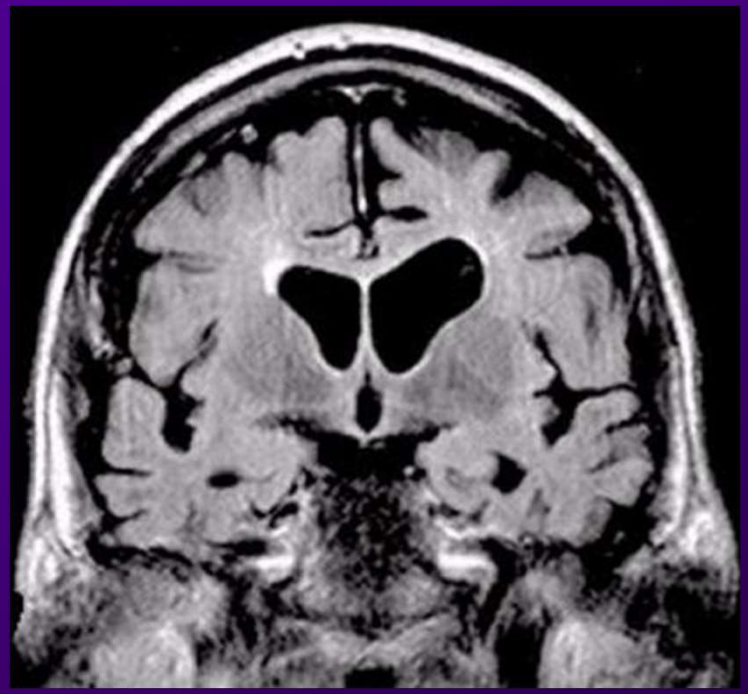
- Cerebral cortex, hippocampus and basal ganglia most vulnerable to hypoglycaemia
- Rats with diabetes get 2.3-fold more neuronal death than non-diabetic animals
- Historically believed that neuronal death only occurred during EEG ‘isoelectricity’

Neuronal Death Does Not Require Coma



Languren et al Neurochemistry International 2013; 63:331-343

Hypoglycaemia and Dementia in Type 2 Diabetes

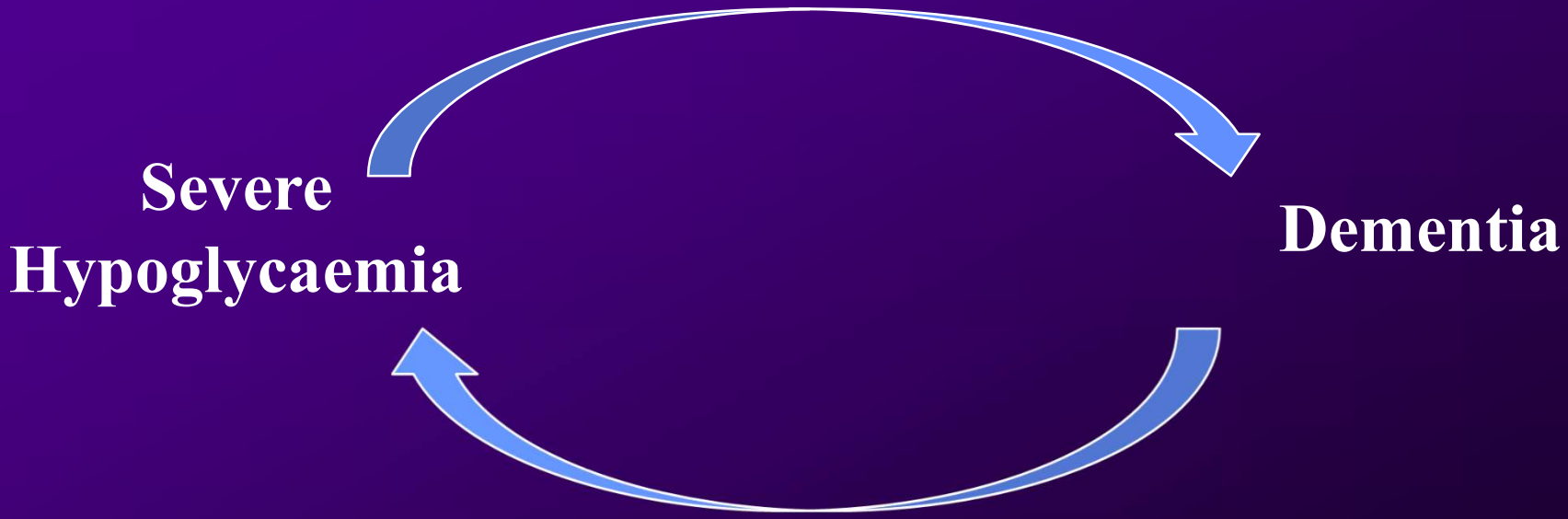


- Longitudinal cohort of 783 adults with Type 2 diabetes, mean age 74 years
- Severe hypoglycaemia associated with a 2.1-fold increased risk of dementia
- Dementia associated with a 2.2-fold increased risk of severe hypoglycaemia

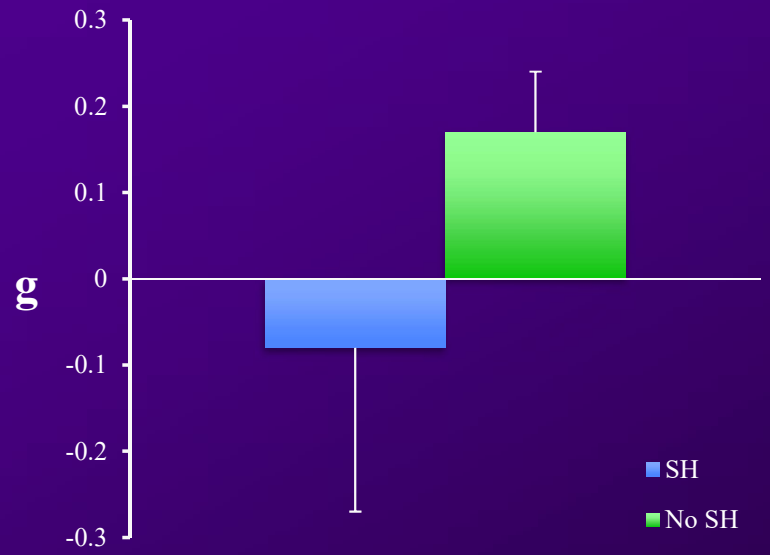
Yaffe et al JAMA Intern Med 2013; 173: 1300-1306

There is a Bi-Directional Relationship Between Severe Hypoglycaemia and Dementia

There is a Bi-Directional Relationship Between Severe Hypoglycaemia and Dementia



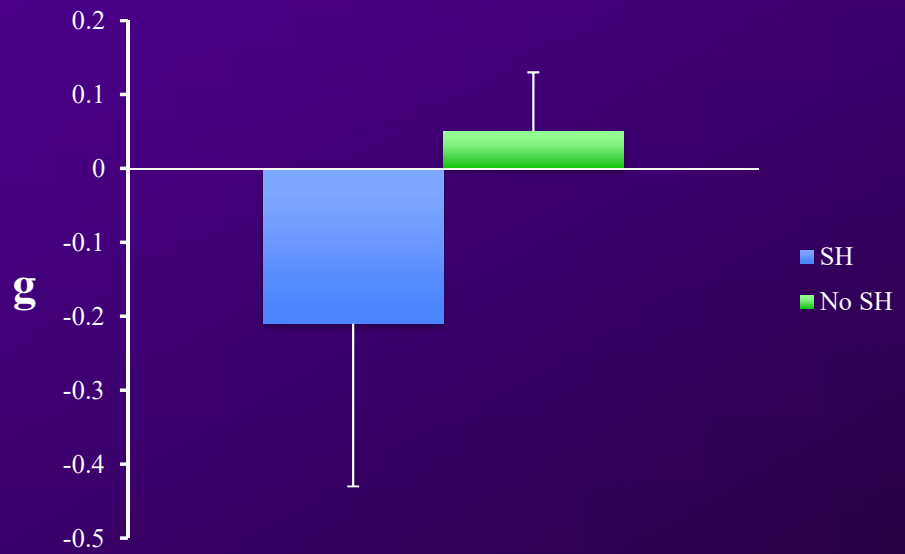
Edinburgh Type 2 Diabetes Study: Baseline Cognition and Incident Severe Hypoglycaemia



Participants in the lowest tertile for ‘g’ were twice as likely to experience an episode of severe hypoglycaemia over 4 years than those in the highest tertile

Feinkohl et al Diabetes Care 2014: 37; 507-15

Edinburgh Type 2 Diabetes Study: Incident Severe Hypoglycaemia and Cognitive Decline



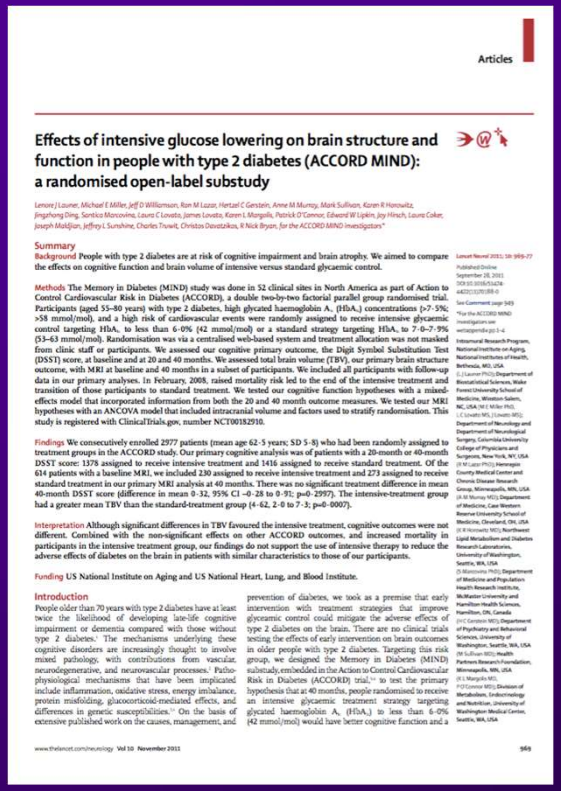
Feinkohl et al Diabetes Care 2014: 37; 507-15

Severe Hypoglycaemia and Dementia: Confounders

People with Type 2 diabetes who have severe hypoglycaemia:

- Are more likely to be treated with insulin
- Have a longer duration of diabetes
- Older
- Have more complications of diabetes

What About RCTs?



Articles

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 Trivedi, Christos Davatzikos, R Nick Bryan, for the ACCORD MIND Investigators*

Summary

Background People with type 2 diabetes are at risk of cognitive impairment and brain atrophy. We aimed to compare the effects on cognitive function and brain volume of intensive versus standard glycaemic control.

Methods The Memory in Diabetes (MIND) study was done in 52 clinical sites in North America as part of Action to Control Cardiovascular Risk in Diabetes (ACCORD), a double two-by-two factorial parallel group randomised trial. Participants (aged 55–80 years) with type 2 diabetes, high glycated haemoglobin A, (HbA_1) concentrations (>7·5%; >58 mmol/mol), and a high risk of cardiovascular events were randomly assigned to receive intensive glycaemic control targeting HbA, to less than 6·0% (42 mmol/mol) or a standard strategy targeting HbA, to 7·0–7·9% (53–63 mmol/mol). Randomisation was via a centralised web-based system and treatment allocation was not masked from clinic staff or participants. We assessed our cognitive primary outcome, the Digit Symbol Substitution Test (DSST) score, at baseline and at 20 and 40 months. We assessed total brain volume (TBV), our primary brain structure outcome, with MRI at baseline and 40 months in a subset of participants. We included all participants with follow-up data in our primary analyses. In February, 2008, raised mortality risk led to the end of the intensive treatment and transition of those participants to standard treatment. We tested our cognitive function hypotheses with a mixed-effects model that incorporated information from both the 20 and 40 month outcome measures. We tested our MRI hypotheses with an ANCOVA model that included intracranial volume and factors used to stratify randomisation. This study is registered with ClinicalTrials.gov, number NCT00182910.

Findings We consecutively enrolled 2977 patients (mean age 62·5 years; SD 5·8) who had been randomly assigned to treatment groups in the ACCORD study. Our primary cognitive analysis was of patients with a 20-month or 40-month DSST score: 1378 assigned to receive intensive treatment and 1416 assigned to receive standard treatment. Of the 614 patients with a baseline MRI, we included 230 assigned to receive intensive treatment and 273 assigned to receive standard treatment in our primary MRI analysis at 40 months. There was no significant treatment difference in mean 40-month DSST score (difference in mean 0·32, 95% CI −0·28 to 0·91; p=0·2957). The intensive-treatment group had a greater mean TBV than the standard-treatment group (4·62, 2·8 to 7·3; p=0·0007).

Interpretation Although significant differences in TBV favoured the intensive treatment, cognitive outcomes were not different. Combined with the non-significant effects on other ACCORD outcomes, and increased mortality in participants in the intensive treatment group, our findings do not support the use of intensive therapy to reduce the adverse effects of diabetes on the brain in patients with similar characteristics to those of our participants.

Funding US National Institute on Aging and US National Heart, Lung, and Blood Institute.

Introduction

People older than 70 years with type 2 diabetes have at least twice the likelihood of developing late-life cognitive impairment or dementia compared with those without type 2 diabetes.[1] The mechanisms underlying these cognitive disorders are increasingly thought to involve mixed pathology, with contributions from vascular, neurodegenerative, and neurovascular processes.[2] Pathophysiological mechanisms that have been implicated include inflammation, oxidative stress, energy imbalance, protein misfolding, glucocorticoid-mediated effects, and differences in genetic susceptibilities.[3] On the basis of extensive published work on the causes, management, and prevention of diabetes, we took as a premise that early intervention with treatment strategies that improve glycaemic control could mitigate the adverse effects of type 2 diabetes on the brain. There are no clinical trials testing the effects of early intervention on brain outcomes in older people with type 2 diabetes. Targeting this risk group, we designed the Memory in Diabetes (MIND) substudy, embedded in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[4,5] to test the primary hypothesis that at 40 months, people randomised to receive an intensive glycaemic treatment strategy targeting glycated haemoglobin A_1 (HbA_1) to less than 6·0% (42 mmol/mol) would have better cognitive function and a

- ACCORD – cognitive function assessed in a subset of 2977 patients.
- Median study duration 39 months.
- Hypoglycaemia more common in intensive arm
- No effect of intensive treatment on cognition
- Poorer cognitive function associated with an increased risk of severe hypoglycaemia

Launer et al Lancet Neurol 2011; 10: 969-977

Problems with RCTs

- Patients with multiple comorbidities often excluded
- Duration of trials relatively short
- Cognition will invariably not be a primary outcome measure
- Usually very limited cognitive testing

Does Recurrent Severe Hypoglycaemia Cause Cumulative Cognitive Impairment?

"Not Proven"

Summary

- Dementia is more common in people with diabetes
- In adults with T2DM, there is a strong association between recurrent severe hypoglycaemia and onset of dementia and cognitive decline
- This association has not been replicated in RCTs
- Reverse association also holds true – dementia and cognitive decline are associated with an increased risk of severe hypoglycaemia

Conclusions

- Cognitive function should be included as an end-point in more RCT's of anti-diabetic agents
- In the absence of any 'benefit' of severe hypoglycaemia in T2DM, should we not be prescribing anti-diabetic agents that do not cause hypoglycaemia in preference to insulin/SU's?