Impact of diabetes and hypoglycemia on brain structure and function across the life span

Pacific Northwest Neuropsychological Society
32nd annual conference
March 2, 2019

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Disclosure Information

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.

Overview

- Patterns of cognitive impairment in type 1 and type 2 diabetes
- Potential risk factors associated with cognitive dysfunction in diabetes
- Brain structural changes that may underlie cognitive dysfunction in people with diabetes
- Clinical implications of cognitive dysfunction in diabetes

Primary types of diabetes

Type 1

- Autoimmune destruction of pancreatic islet beta cells
- Often diagnosed in childhood
- Insulin deficiency
- Seldom overweight

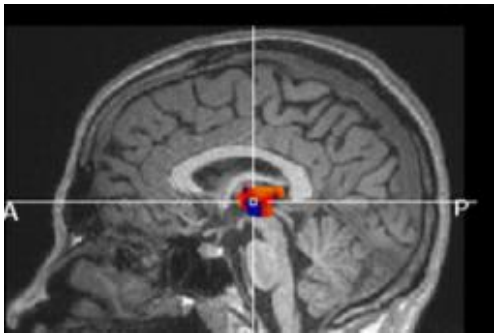
Type 2

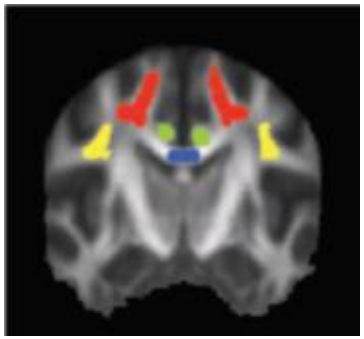
- Decreased beta cell mass and dysfunction of islets
- Usually diagnosed in adults
- Insulin resistance
- Often obese
- More likely to have comorbidities like HTN and dyslipidemia

Diabetes

Brain structural changes

Cognitive impairment





- What is the magnitude and patterns of cognitive impairment in people with diabetes?

PSYCHOLOGIC TESTS APPLIED TO DIABETIC PATIENTS *

W. R. MILES, PH.D., AND H. F. ROOT, M.D.

BOSTON

Archives of Internal Medicine 1922

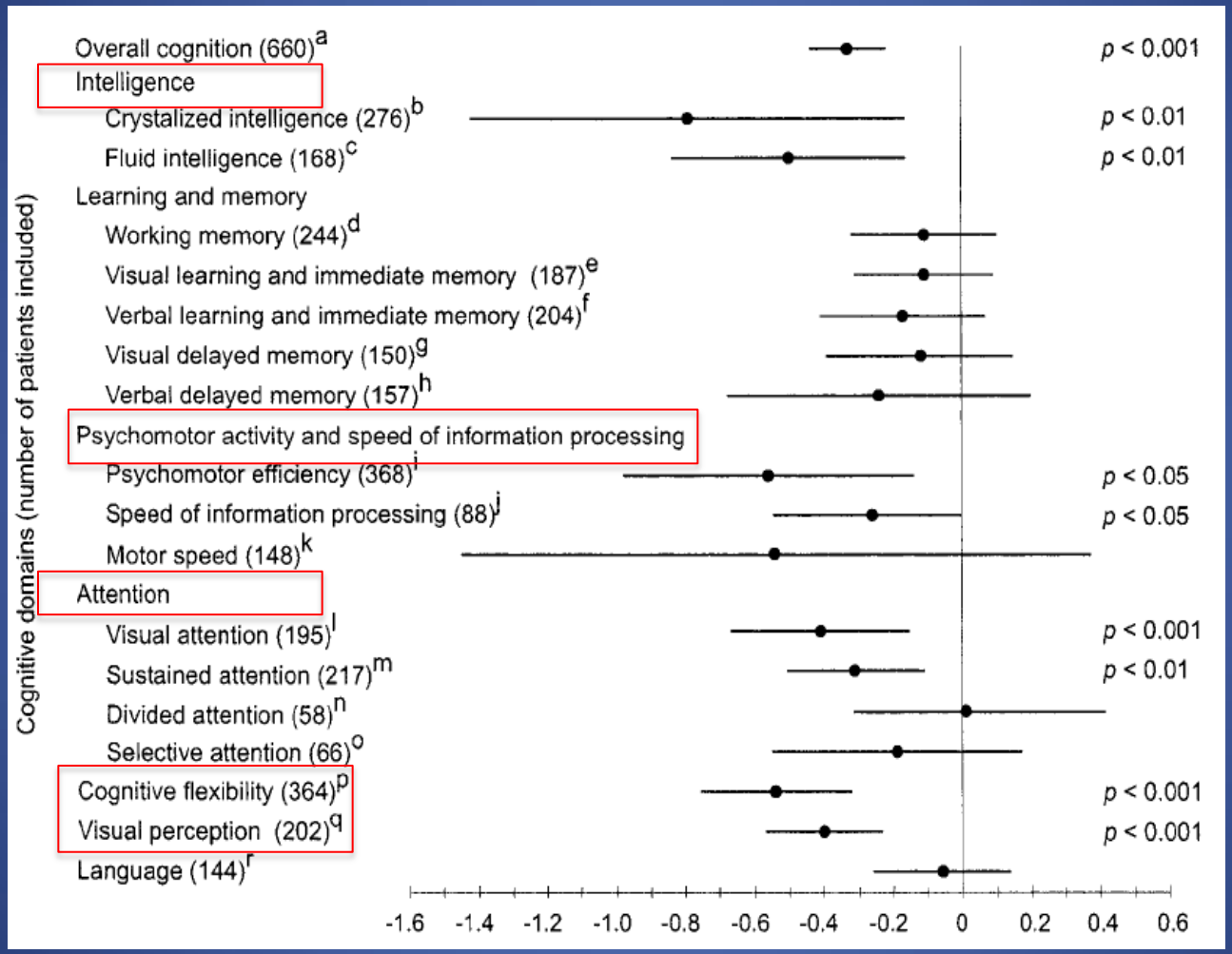
- In the early 20th century, researchers and clinicians recognized that people with diabetes complained of impairment in cognitive function.
- In 1922, Miles et al. showed that people with diabetes (n=40) performed poorly on cognitive tasks examining memory and attention.

Cognitive function in children with type 1 diabetes

- Longitudinal study of children with type 1 diabetes
- Children with newly diagnosed type 1 diabetes and healthy controls underwent neurocognitive testing at enrollment and after 12 years.
- At baseline no difference in IQ between groups
- After 12 years, lower verbal and full scale IQs found in children with type 1 diabetes (n=106) compared with control (n=75).
- Early –onset diabetes and hypoglycemia associated with lower IQ.

Northam et all. 2009 diabetes care

Cognitive dysfunction in type 1 diabetes: meta analyses



included 33 studies with participants who were mostly less 50 years of age

Brands et al, diabetes care 2005

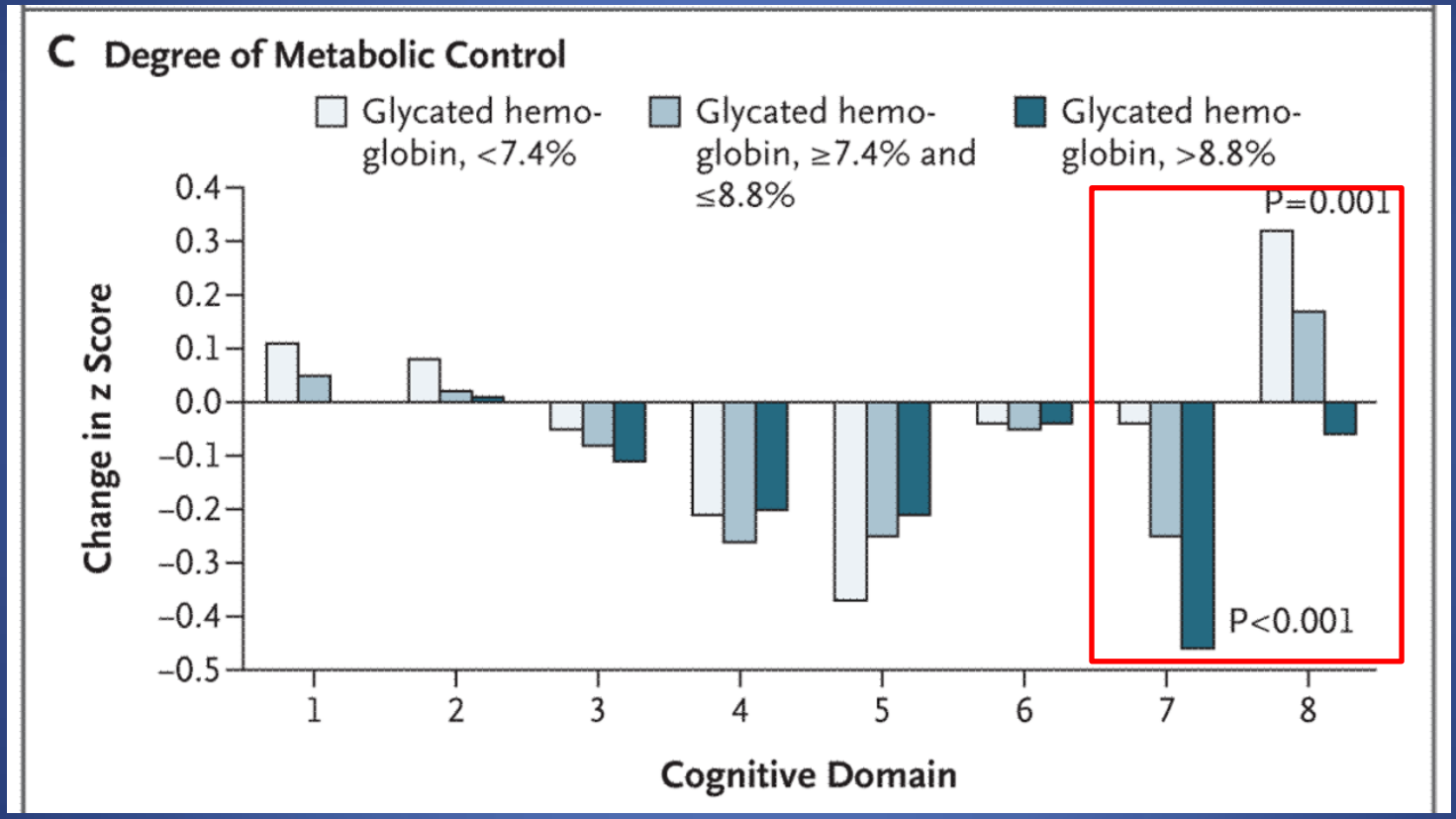
Cognitive dysfunction in type 1 diabetes DCCT-EDIC

- The Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, patients with type 1 diabetes underwent comprehensive battery of cognitive tests at study enrollment (at mean age of 27 years) and 18 years later.
- Eight cognitive domains evaluated.
- EDIC Study: 1059 participants of the DCCT (75% of original cohort) followed for average of 18 years.
- 537 from intensive group and 522 from conventional group

DCCT/EDIC study research group-NEJM 2007

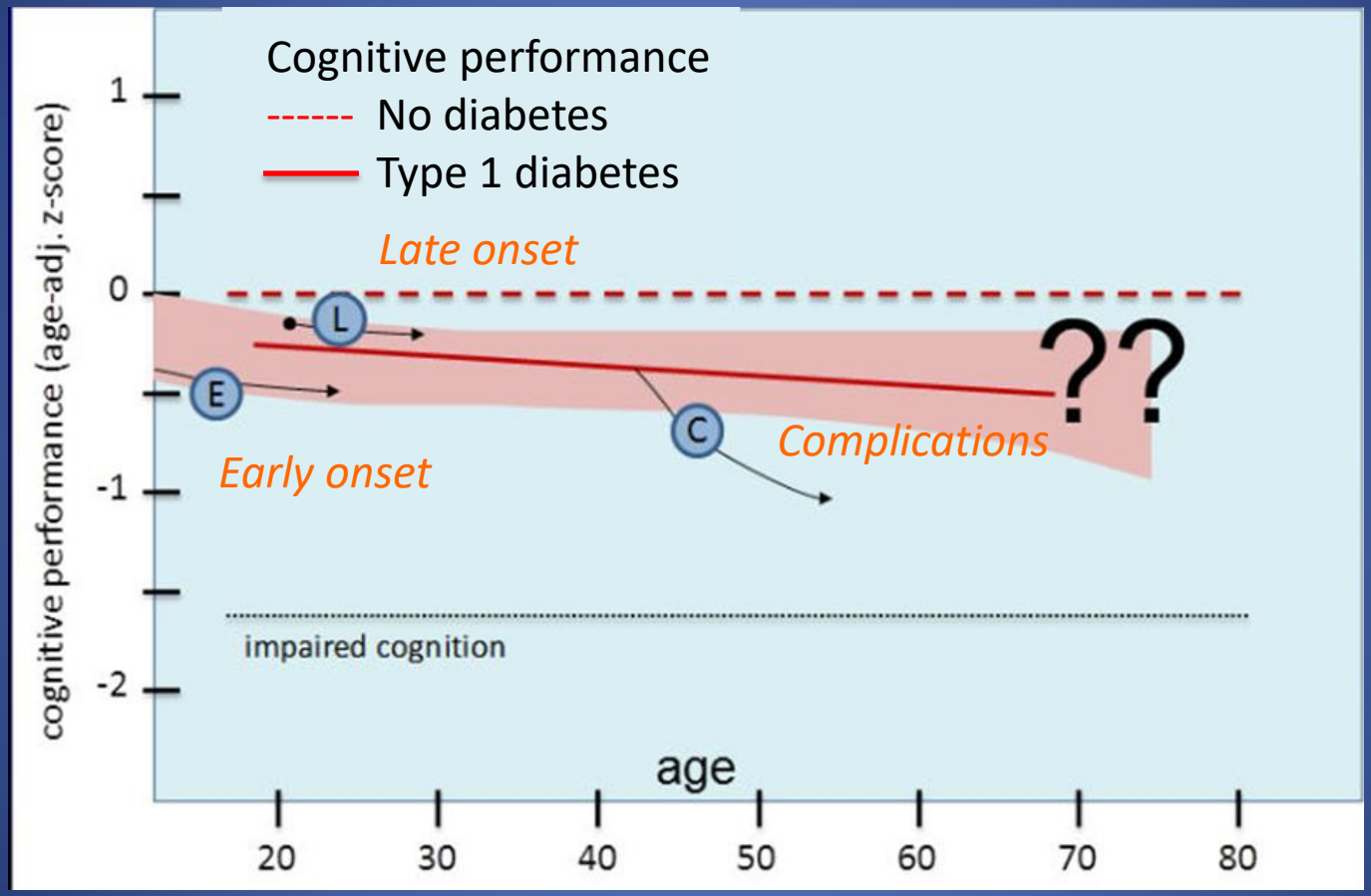
Cognitive dysfunction in type 1 diabetes

DCCT-EDIC Study



Cognitive domains are numbered as follows: 1, problem solving; 2, learning; 3, immediate memory; 4, delayed recall; 5, spatial information; 6, attention; 7, psychomotor efficiency; and 8, motor speed.

Trajectories of cognitive decline in type 1 diabetes



Biessels et al. Lancet Diabetes & Endo 2014

Clinically Relevant Cognitive Impairment in Middle-Aged Adults With Childhood-Onset Type 1 Diabetes

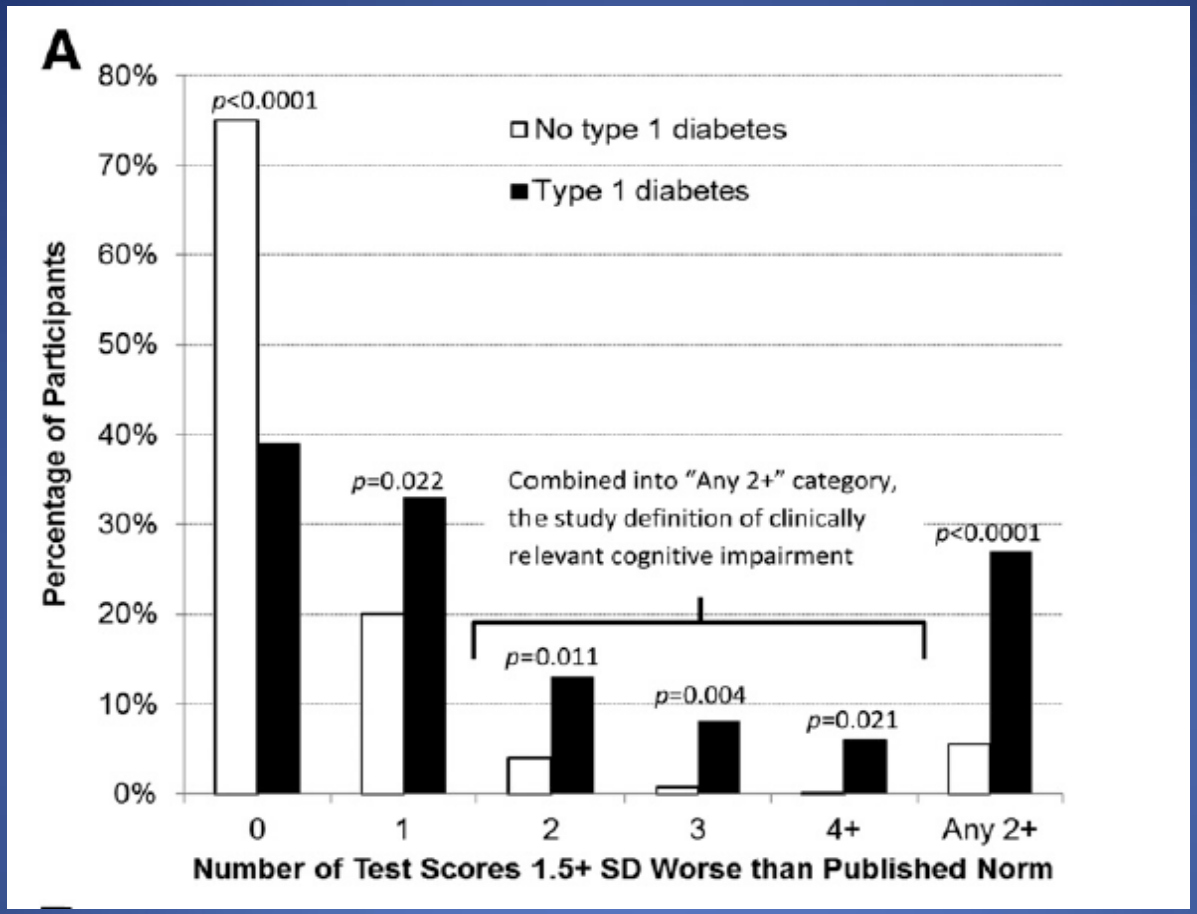
Karen A. Nunley,[1] Caterina Rosano,[1] Christopher M. Ryan,[2] J. Richard Jennings,[2] Howard J. Aizenstein,[2] Janice C. Zgibor,[1] Tina Costacou,[1] Robert M. Boudreau,[1] Rachel Miller,[1] Trevor J. Orchard,[1] and Judith A. Saxton[3]

Diabetes Care 2015;38:1768–1776 | DOI: 10.2337/dc15-0041

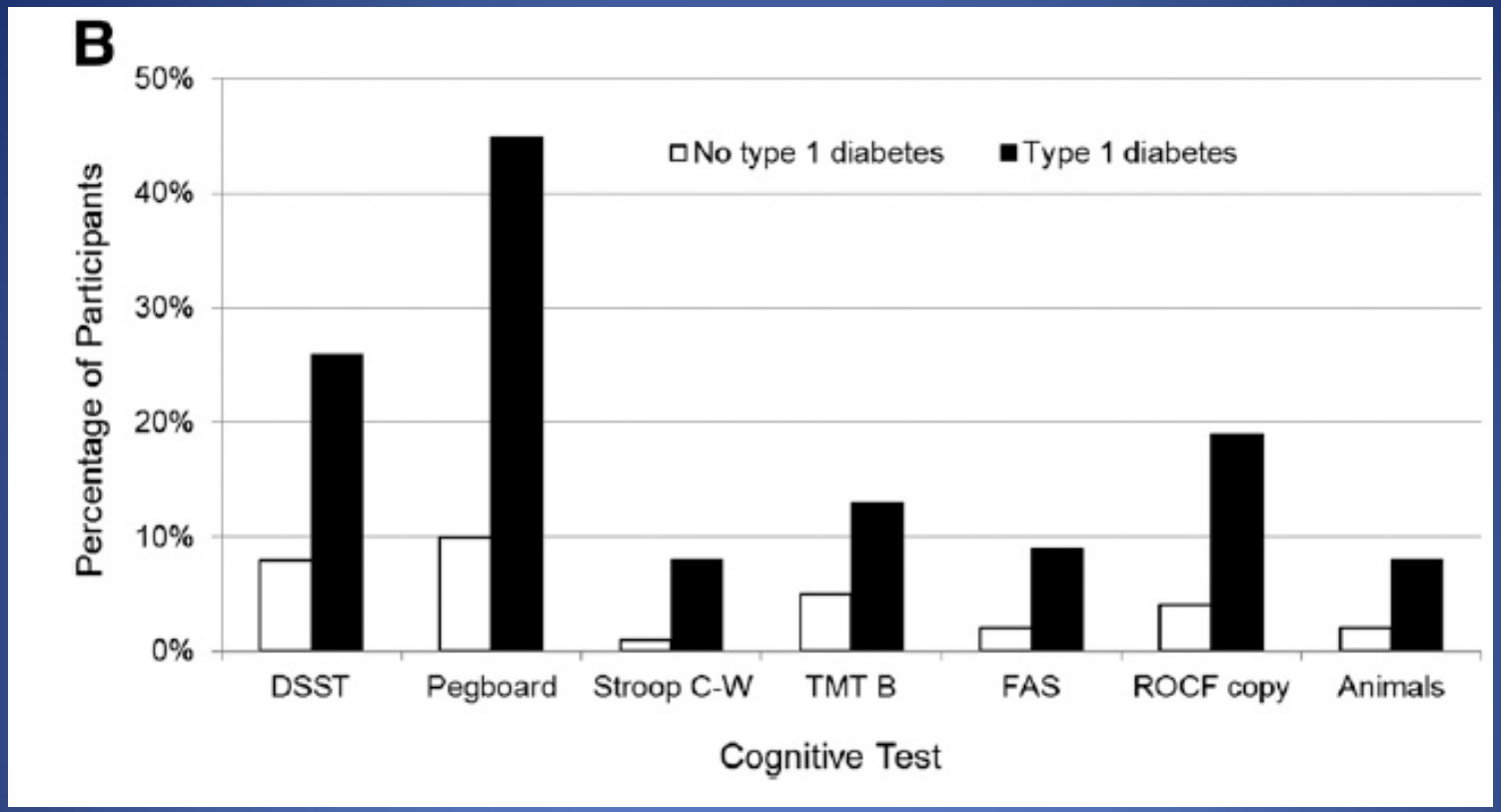
- It is not clear whether aging individuals with T1D have an increased risk of manifesting “clinically relevant cognitive impairment”.
- This study tests the hypothesis that childhood-onset T1D is associated with an increased risk of developing clinically relevant cognitive impairment detectable by middle age.
- Study compared cognitive test results between adults with and without T1D
- Cognitive impairment status was based on the number of test scores $\geq$1.5 SD worse than demographically appropriate published norms: none, mild (only one test), or clinically relevant (two or more tests).

	No T1D (n = 138)	T1D (n = 97)
Demographic factors		
Age (years)	48.7 ± 7.2	49.1 ± 6.6
Female sex	76 (55)	49 (51)
Education (years)	16 ± 3	15 ± 3
Diabetes factors		
T1D duration (years)	–	41.0 ± 6.2
Age at T1D diagnosis (years)	–	8.0 ± 4.2

Nunley KA et al Diabetes Care 2015



- Percentage of participants scoring ≥1.5 SD worse than published normative data in no, one, two, three, or four or more tests.
- White bars indicate participants without T1D; black bars represent participants with T1D.
- "Any 2+" indicates the percentage of participants scoring ≥1.5 SD worse than published normative data on two or more tests, thereby meeting the study definition of clinically relevant cognitive impairment.



Percentage of participants with T1D (black bars) and without T1D (white bars) scoring ≥1.5 SD worse than published normative data, by test. C-W, Color-Word.

Nunley KA et al Diabetes Care 2015

Large % of middle-aged adults with childhood-onset T1D have clinically relevant cognitive impairment

- In this study clinically relevant cognitive impairment was seen in 28% of middle-aged participants with T1D.
- This prevalence rate of mild cognitive impairment in this T1D cohort is comparable to prevalence typically reported among community-dwelling adults aged 85 years and older (29%).
- In a previous study 12.8% of the pediatric participants with T1D met this early study's definition of clinically relevant cognitive impairment.

Long-term Glycemic Control and Dementia Risk in Type 1 Diabetes

Mary E. Lacy,[1,2] Paola Gilsanz,[1,2] Andrew J. Karter,[2] Charles P. Quesenberry,[2] Mark J. Pletcher,[1] and Rachel A. Whitmer[1,2,3]

Diabetes Care 2018;41:2339–2345 | https://doi.org/10.2337/dc18-0073

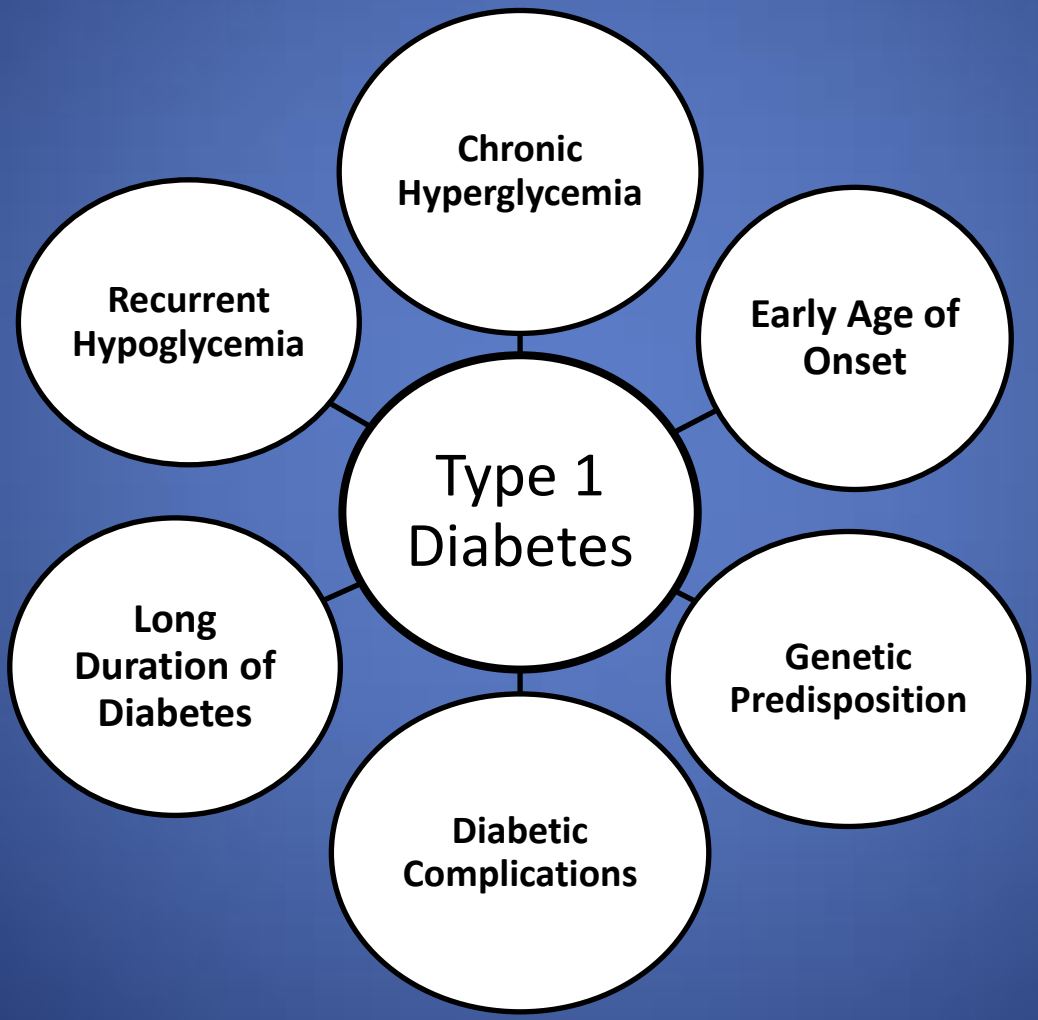
- Investigators examined the association of long-term glycemic control with dementia in older individuals with T1D.
- Followed 3,433 subjects with T1D aged ≥50, who were part of a health care system from 1996 to 2015 . Subjects did not have diagnosis of dementia at baseline.
- Repeated measurements of hemoglobin A1c (HbA1c), dementia diagnoses, and comorbidities were ascertained from health records.
- Cox proportional hazards models were fit to evaluate the association of time-varying glycemic exposure with dementia, with adjustment for age, sex, race/ethnicity, baseline health conditions.

Glycemic control and risk of dementia in T1D

>50% of HbA_{1c} measurements	HR (95% CI) adjusted for race, sex, and baseline health conditions*
<6%	1.44 (0.75, 2.77)
6–6.9%	0.54 (0.34, 0.87)
7–7.9%	0.55 (0.37, 0.82)
8–8.9%	1.64 (1.05, 2.57)
≥9%	1.80 (1.11, 2.90)

Lacy ME et al Diabetes care 2018

Factors associated with increased risk of cognitive dysfunction in type 1 diabetes



Summary
Cognitive dysfunction in type 1 diabetes

- Domains of intelligence, processing speed, and attention are commonly affected.
- On these domains, the magnitude of the decrements is 0.3 to 0.7 SD units relative to people without diabetes.
- Early age of onset and presence of microvascular complications are important risk factors.
- More studies are needed to examine link to dementia.

Cognition in type 2 diabetes: meta analyses

- Data from 24 studies (mostly cross-sectional)
- Type 2 diabetes relative to controls:
- Subtle decrements in

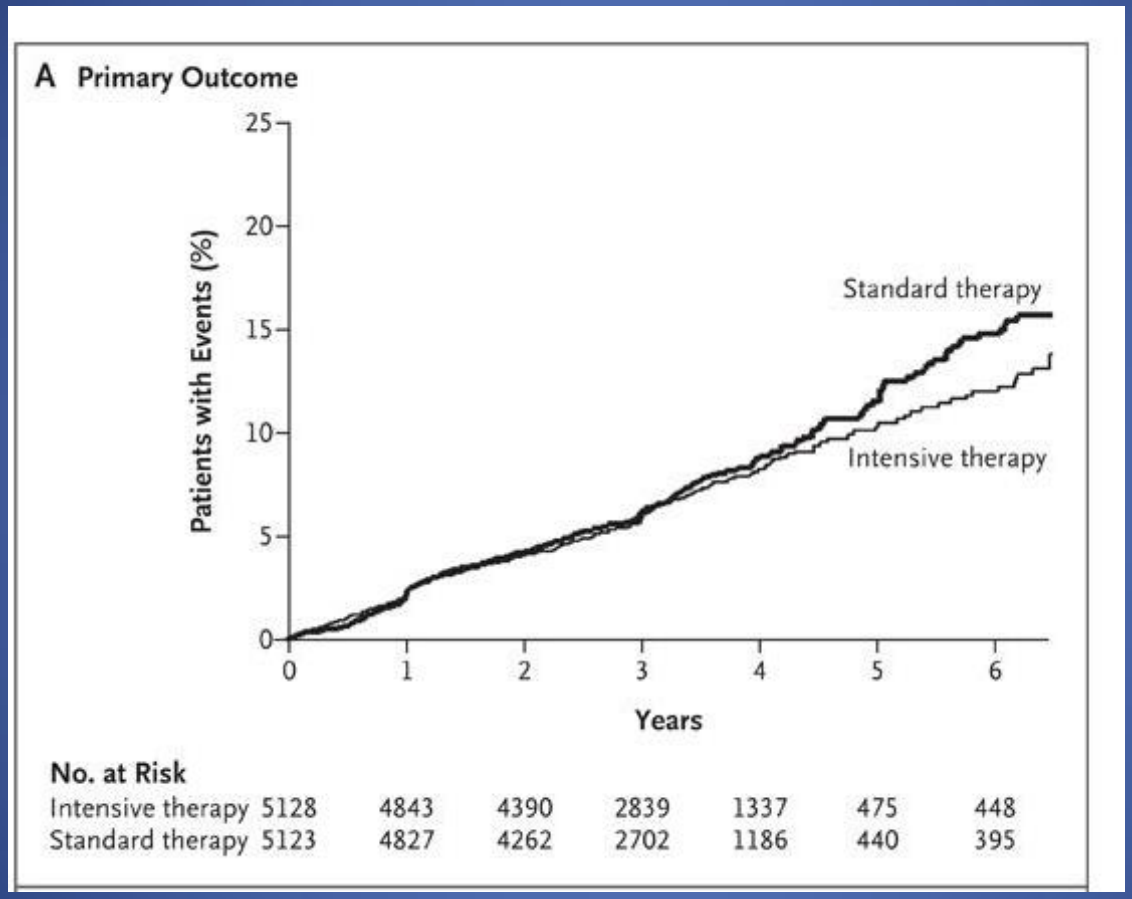
Executive function

Information processing speed

Memory

Palta, et al, JINS 2014; 20: 278-91

Type 2 diabetes : The ACCORD Study



Patients with type 2 diabetes (n=10251) with cardiovascular disease or risk factor for CVD
Assigned to intensive (A1C < 6%) or Standard therapy (A1C 7-7.9%)

ACCROD Study group NEJM 2008

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**

Lancet Neurology 2011

- The ACCORD (MIND) Study sought to directly determine if the level of glycemic control impacts cognitive performance over time in nearly 3000 subjects with type 2 diabetes.
- Cognitive function assessed at baseline, 20 and 40 months.
- Primary outcome-test of psychomotor speed (Digit Symbol Substitution test)
- Secondary outcome- memory (Rey Auditory verbal learning test); executive function (stroop test)

ACCORD Memory in Diabetes (MIND) Study

- At baseline, there was an inverse relationship between cognitive function and glycemic control as measures by A1C.
- However, after 40 months of follow up there was no significant difference in the cognitive function between the intensive and standard treatment arms.
- Study did not provide evidence that intensive treatment strategy was of benefit to cognitive function in type 2 diabetes.

Cukierman-Yaffe T et al Idab care 2009
Launer L et al Lancet Neurology 2011

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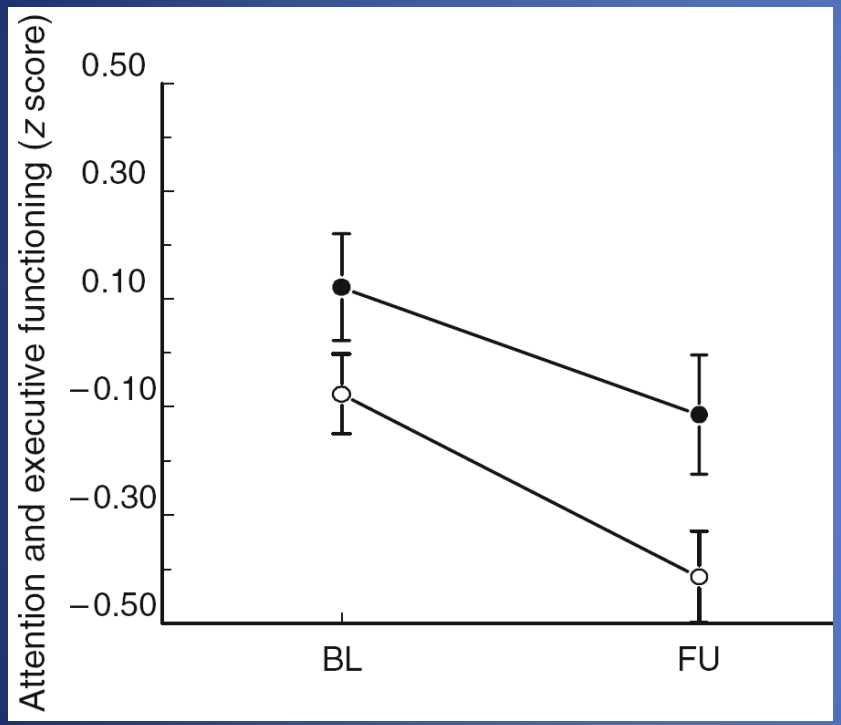
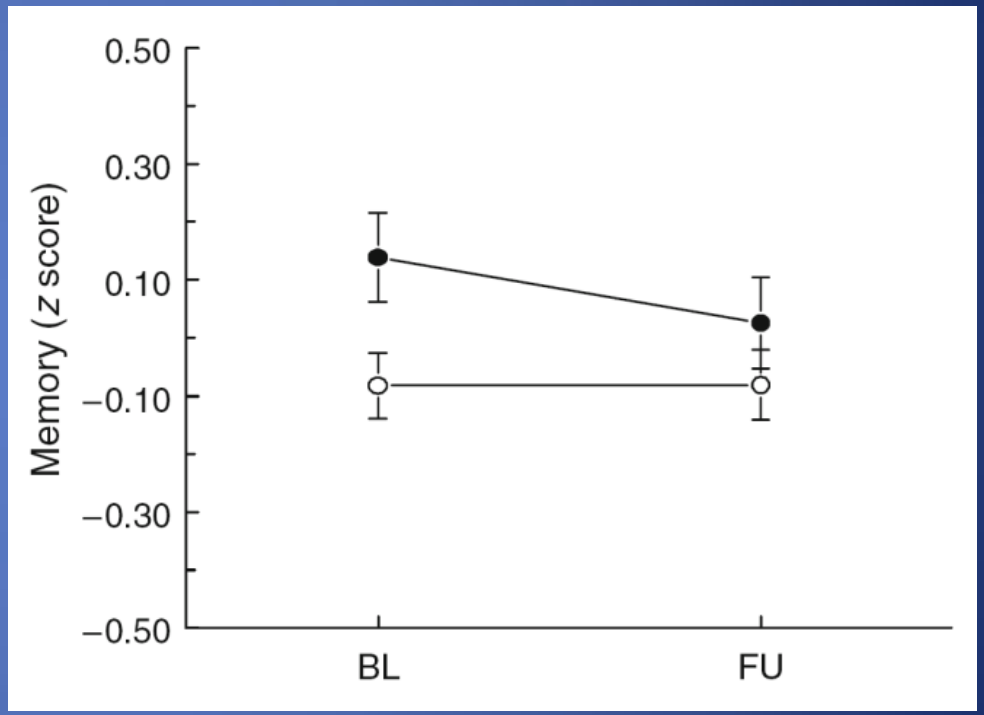
Cognition in subjects with type 2 diabetes

Utrecht Diabetic Encephalopathy Study





●Control n=38 , ○type 2 diabetes, n=68, mean age 65

van den Berg E, et al. *Diabetologia* 2010;53(1):58–65.

Hyperglycemia and cognitive function

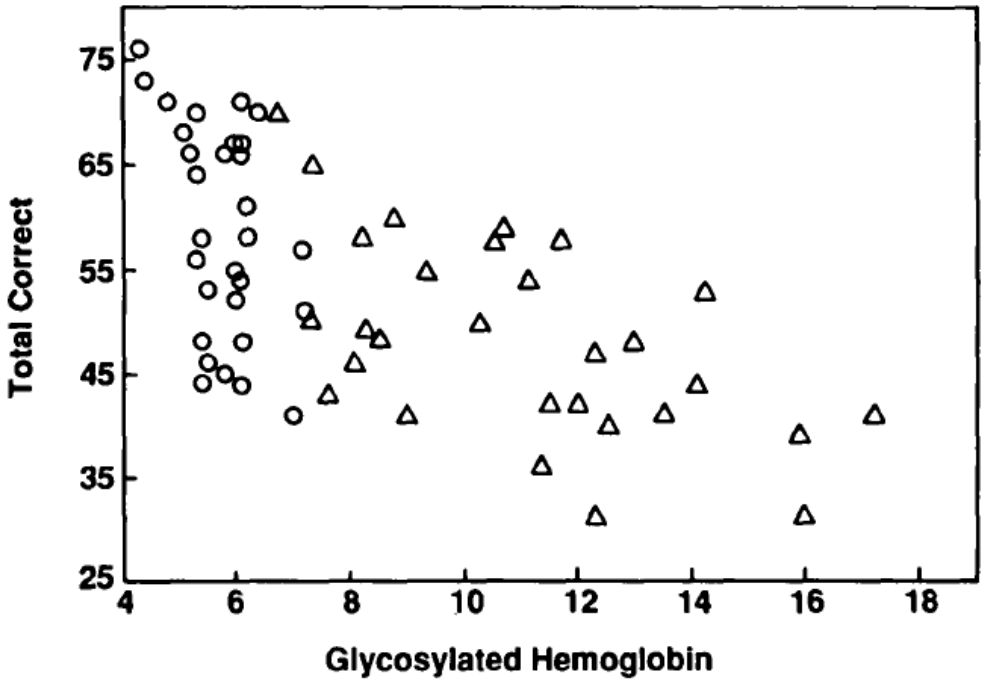


FIG. 1. Relationship between glycosylated hemoglobin concentration and number of correct responses on California Verbal Learning Test. △, Diabetic (n = 29); ○, control (n = 30).

Reaven et al, Diabetes care 1990

Youth onset type 2 diabetes and cognition

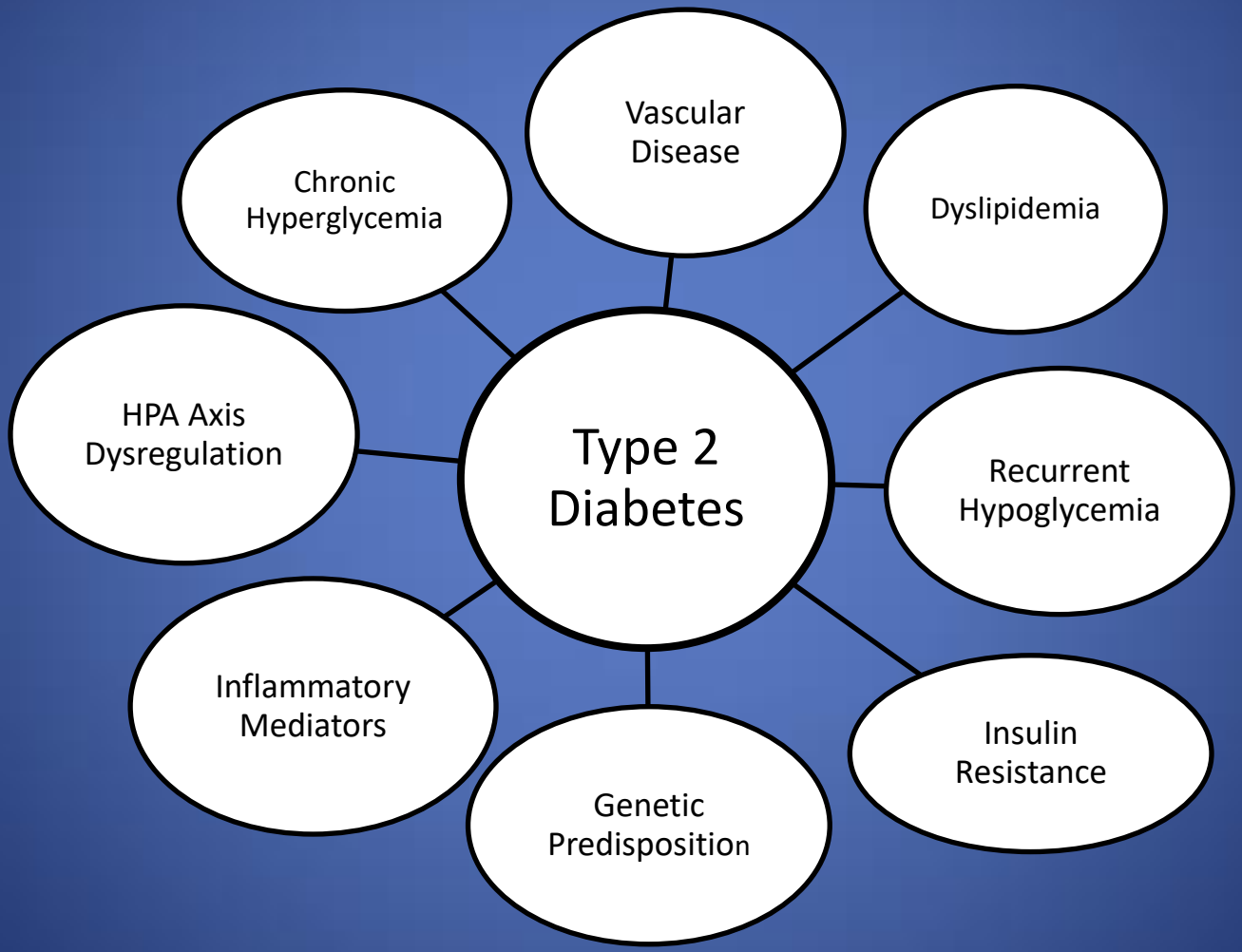
Table 1 Cognitive function literature summary: significantly poorer cognitive domains in type 2 diabetes

Author, year, (T2D group *n* value)	Control group	Executive function and IQ	Memory	Attention
Yau et al., 2010, ($n = 18$)	Obese only ($n = 18$)	Full scale IQ	WRAML verbal memory	DSST
Brady et al., 2017, ($n = 20$)	HWC only ($n = 20$)	WISC/WAIS Processing Speed	WISC/WAIS working memory and WRAML verbal memory	n/a

IQ intelligence quotient, *HWC* healthy weight controls

Redel JM et al Current diabetes reports 2019

Factors associated with increased risk of cognitive dysfunction in type 2 diabetes



Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies

Kapil Gudala[1], Dipika Bansal[1]*, Fabrizio Schifano[2], Anil Bhansali[3]

Journal of Diabetes Investigation Volume 4 Issue 6 November 2013

Meta-analysis of prospective observational studies in people with diabetes compared with individuals without diabetes

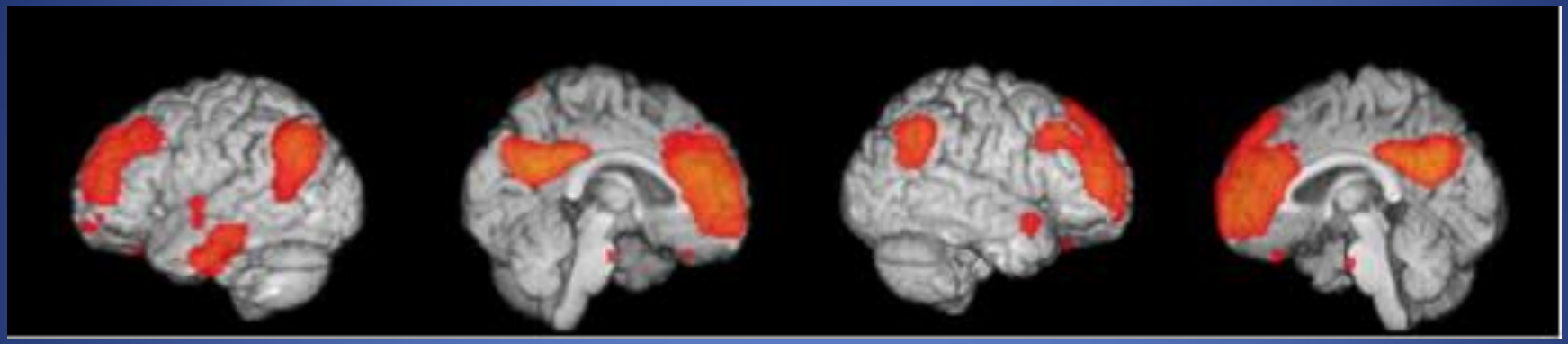
- 73% increased risk of all types of dementia
- 56% increased risk of Alzheimer dementia
- 127% increased risk of vascular dementia

Insulin resistance and diabetes increases risk of Alzheimer's disease

- In epidemiologic studies insulin resistance, impaired glucose tolerance and type 2 diabetes have been associated with increased risk of Alzheimer's disease. (Ott et al 99; Peola et al 02)
- Possible mechanism of increased risk include
- *Impaired cerebral glucose metabolism*
- *Disrupted regulation of B-amyloid trafficking and clearance*
- *Increased inflammation*
- *Impaired vascular function*
- *Reduced brain insulin uptake/signaling*

Cholerton B et al 2013

Brain glucose metabolism and Alzheimer's disease

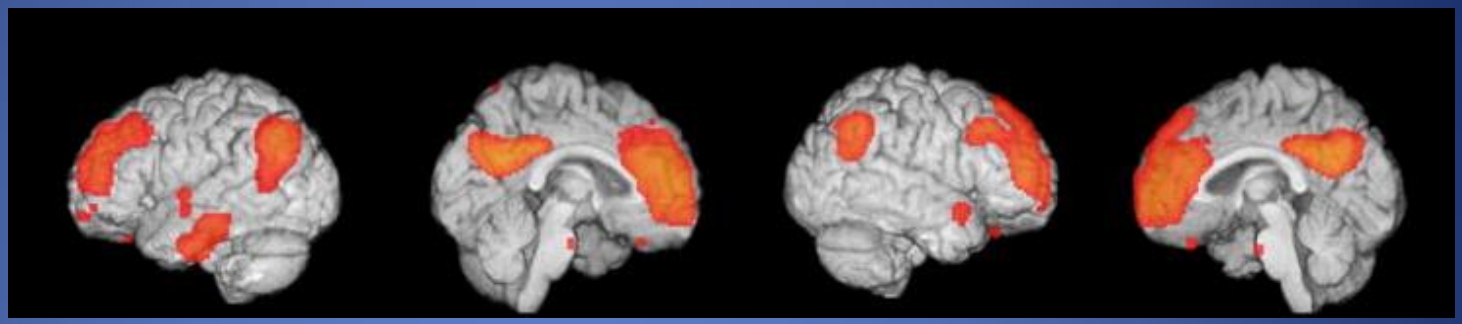


Pattern of resting hypometabolism in frontal, cingulate and temporal-parietal regions associated with AD and is apparent years before clinical onset.

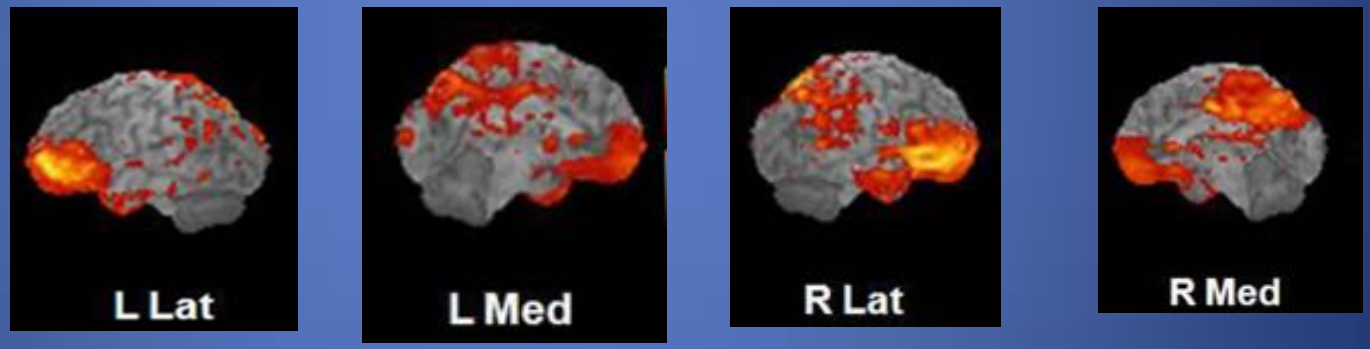
Langbaum et al. 2009

Insulin resistance and diabetes increases risk of Alzheimer's disease

Alzheimer's disease pattern
Langbaum et al. 2009



IGT/Type 2 diabetes pattern
Baker et al. 2010

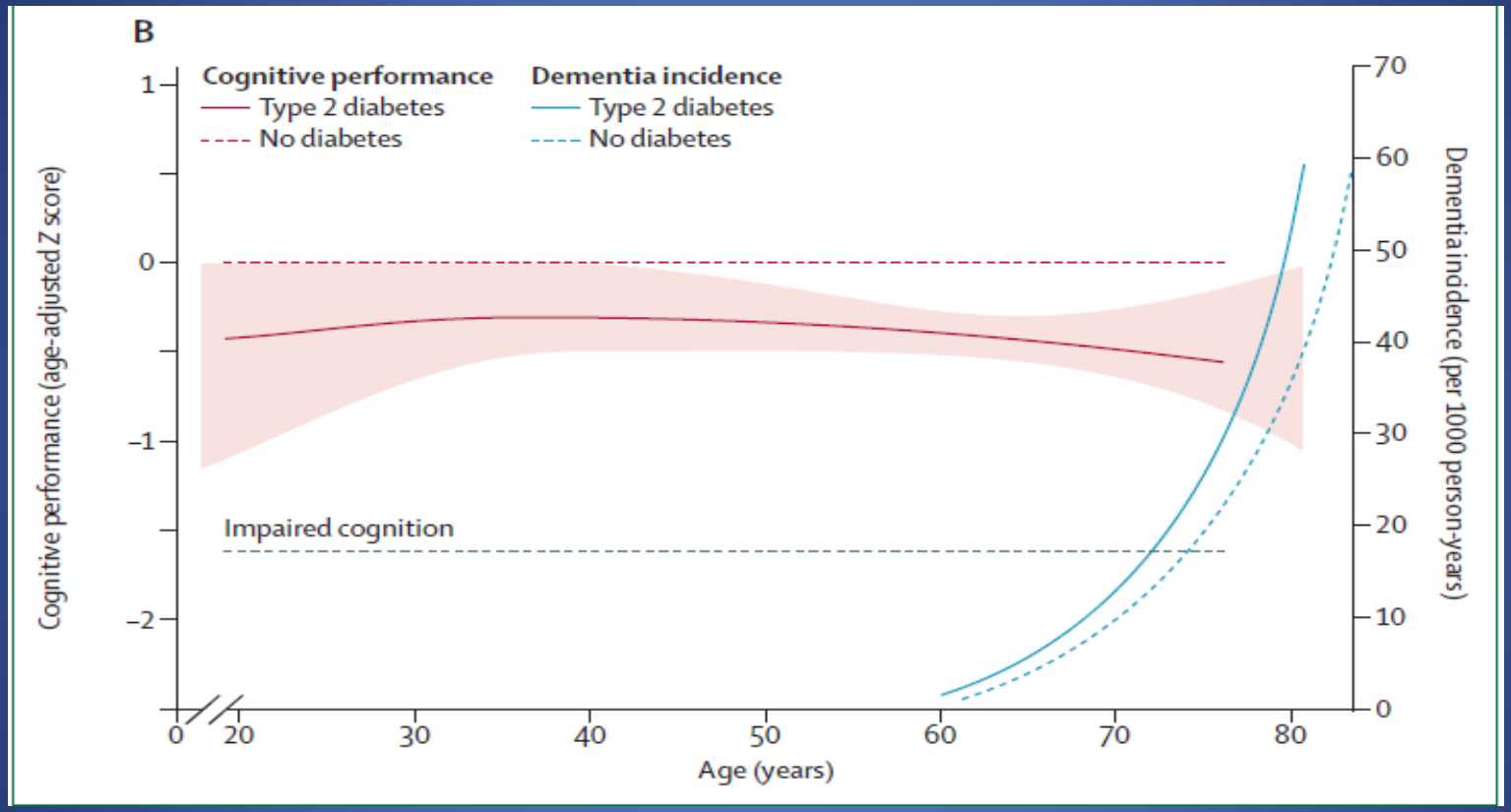


Greater insulin resistance was associated with Alzheimer's disease like pattern of resting hypometabolism in non demented older adults.

Intranasal insulin improves cognitive function and brain connectivity

- Intranasal insulin improves performance on cognitive testing in healthy adults (Benedict c et al 2007), as well as in patients with cognitive impairment (Craft S et al 2012).
- Intranasal insulin acutely increase functional connectivity between the hippocampal regions and the default mode network in older adults with type 2 diabetes (Zhang Diabetes 2015).

Trajectories of cognitive decline in type 2 diabetes



compiled results of >30 cross-sectional & longitudinal studies

Biessels, et al. Lancet Diabetes & Endo 2014

Summary
Cognitive dysfunction in type 2 diabetes

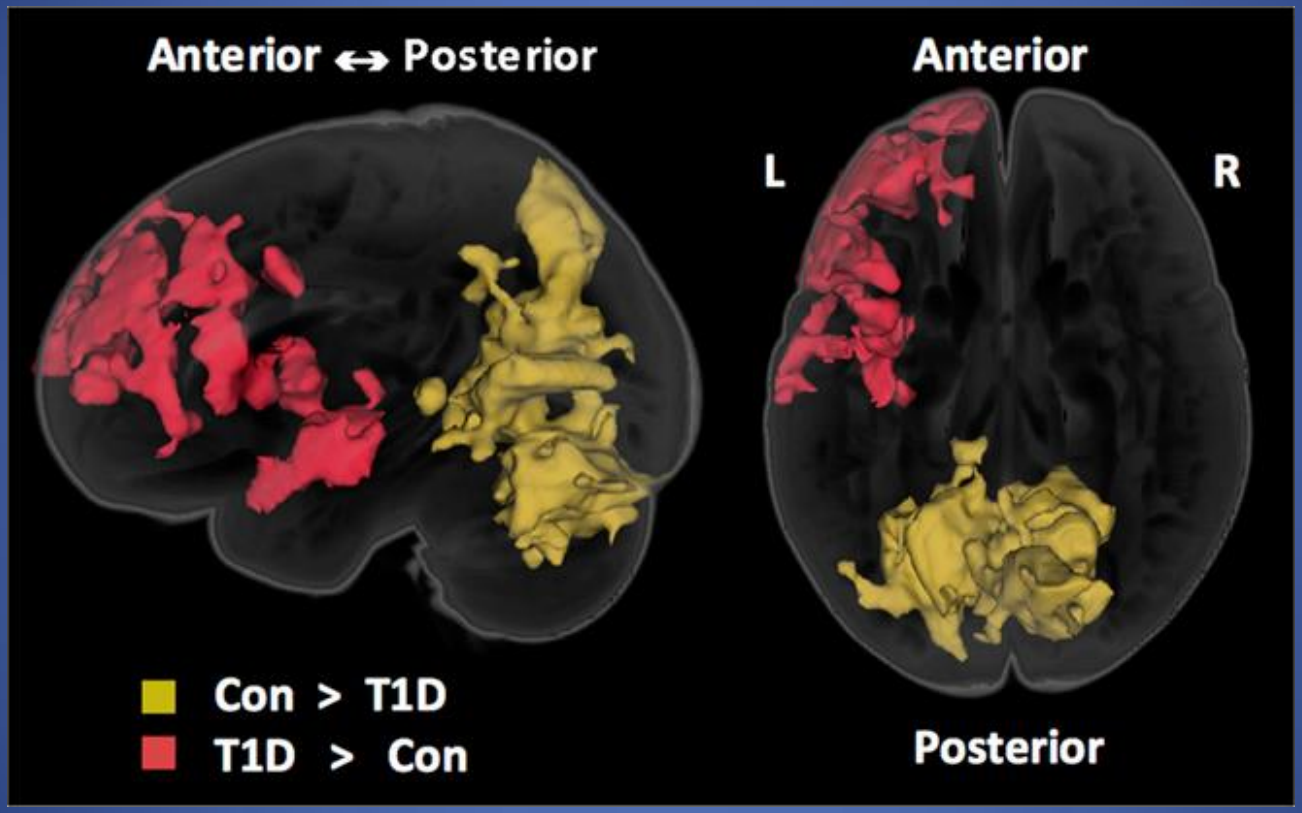
- Type 2 diabetes is associated with mild to moderate cognitive deficits mostly in the domains of memory, psychomotor speed, and executive function.
- Changes in cognitive function compared to non-diabetic controls can be seen early in the course of type 2 diabetes.
- Duration of diabetes, glycemic control and presence of microvascular complications are important risk factors.
- In the elderly population, type 2 diabetes increases the risk of dementia.

Does diabetes associated cognitive decrements have structural brain correlates detectable with brain MRI?

Brain structural changes seen in diabetes

- Total and regional brain volumes
- Markers of small-vessel disease
  - White matter hyperintensities
  - Microbleeds
  - Infarcts
- Microstructural abnormalities in white matter tracts

Brain MRI in type 1 diabetes: volumtery

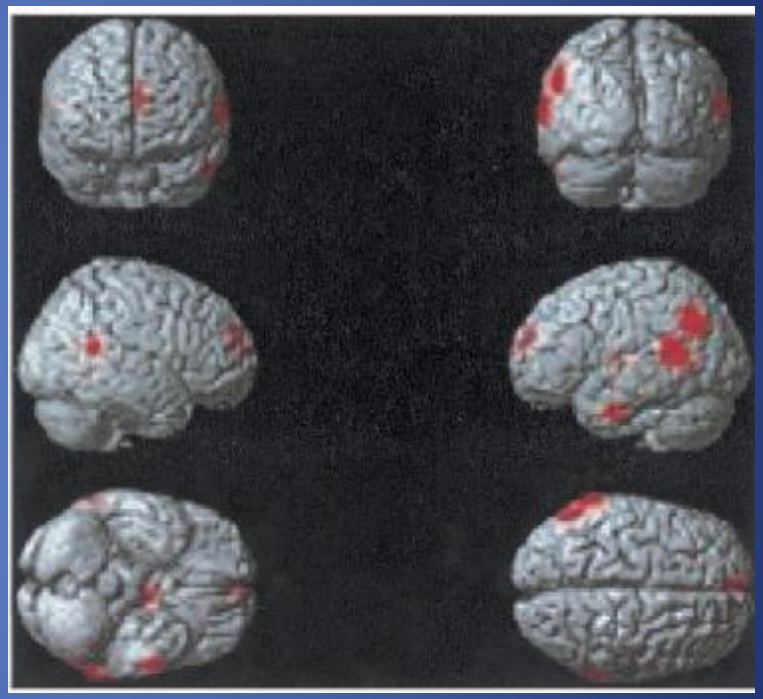


Type 1 diabetes, n=142
Control, n=68
Mean age 7

Marzelli et al , diabetes, 2014

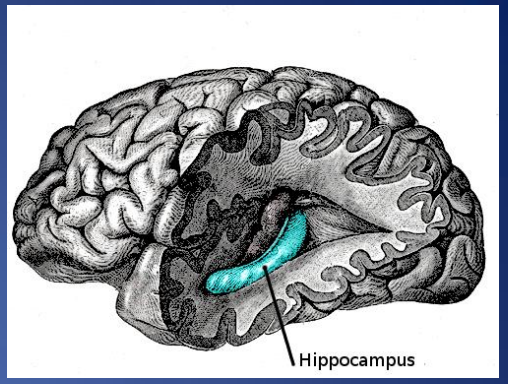
Brain MRI in type 1 diabetes: volumtery

- Type 1 diabetes, n=82; Control, n=36; Mean age 32
- Compared to non-diabetic control, subjects with diabetes had lower gray matter density primarily in the posterior, temporal, and cerebellar regions.
- Lower gray matter density was associated with poor glycemic control, higher frequency of severe hypoglycemic events, age of onset and duration of diabetes.



Musen et al , diabetes, 2006

Effects of diabetes on hippocampal structure



- The hippocampus, plays an essential role in learning and memory processing.
- It expresses both insulin receptors and insulin sensitive glucose transporters.
- The hippocampus is thought to be particularly vulnerable to effects of extremes of glycemia.

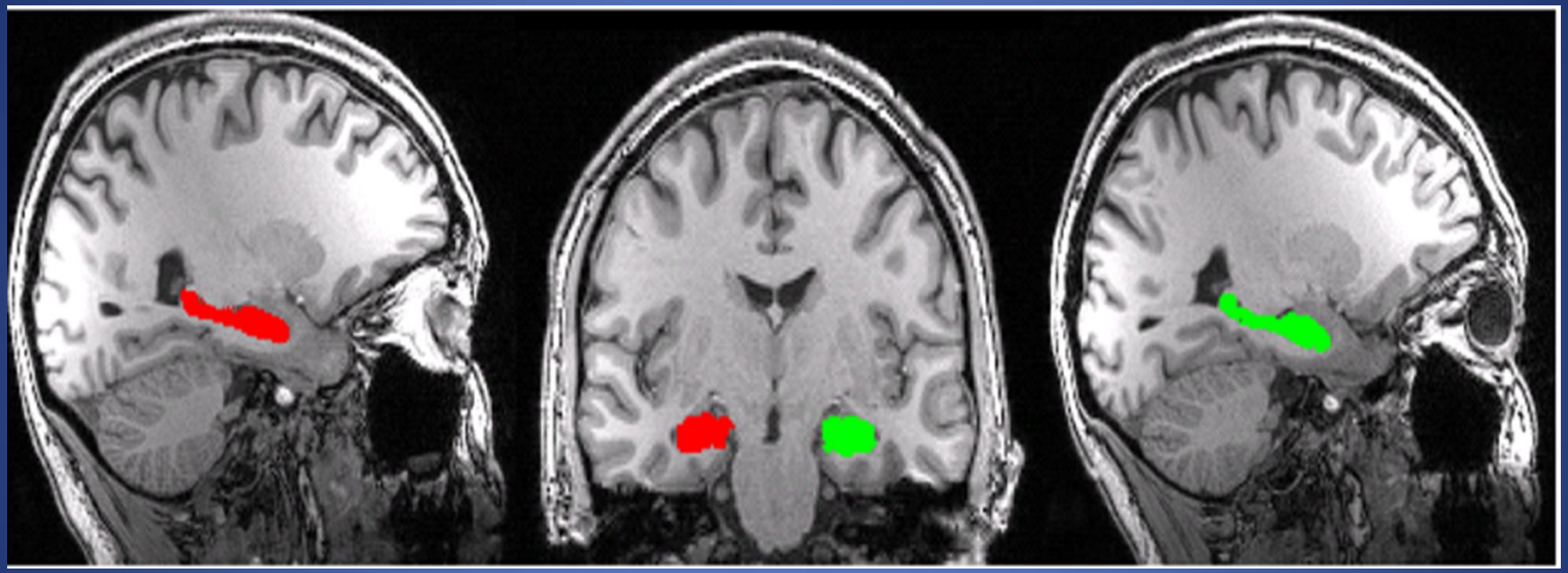
McEwen B.S. et al. Journal of Psychosomatic Research 2002
Craft S. et al Lancet Neurology 2004

Hippocampal volume in adults with type 1 Diabetes

	Type 1 diabetes n=35	Healthy Control n=34
Female/male	16/19	18/16
Age (years)	38±12	36±14
BMI (kg/m^2)	25±4	26±4
HbA1c (%)	7.1 ±0.9	
Duration of diabetes (years)	23±12	

Moheet et al, unpublished data

Hippocampal volume in patients with type 1 Diabetes



No differences found in hippocampal volumes between subjects with type 1 diabetes compared to non-diabetic controls

Moheet et al, unpublished data

Brain structural changes seen in T1D

Structural MRI techniques are most commonly used to examine the impact of diabetes on total and regional brain volumes.

Compared to non-diabetic controls; T1D in adults is associated with

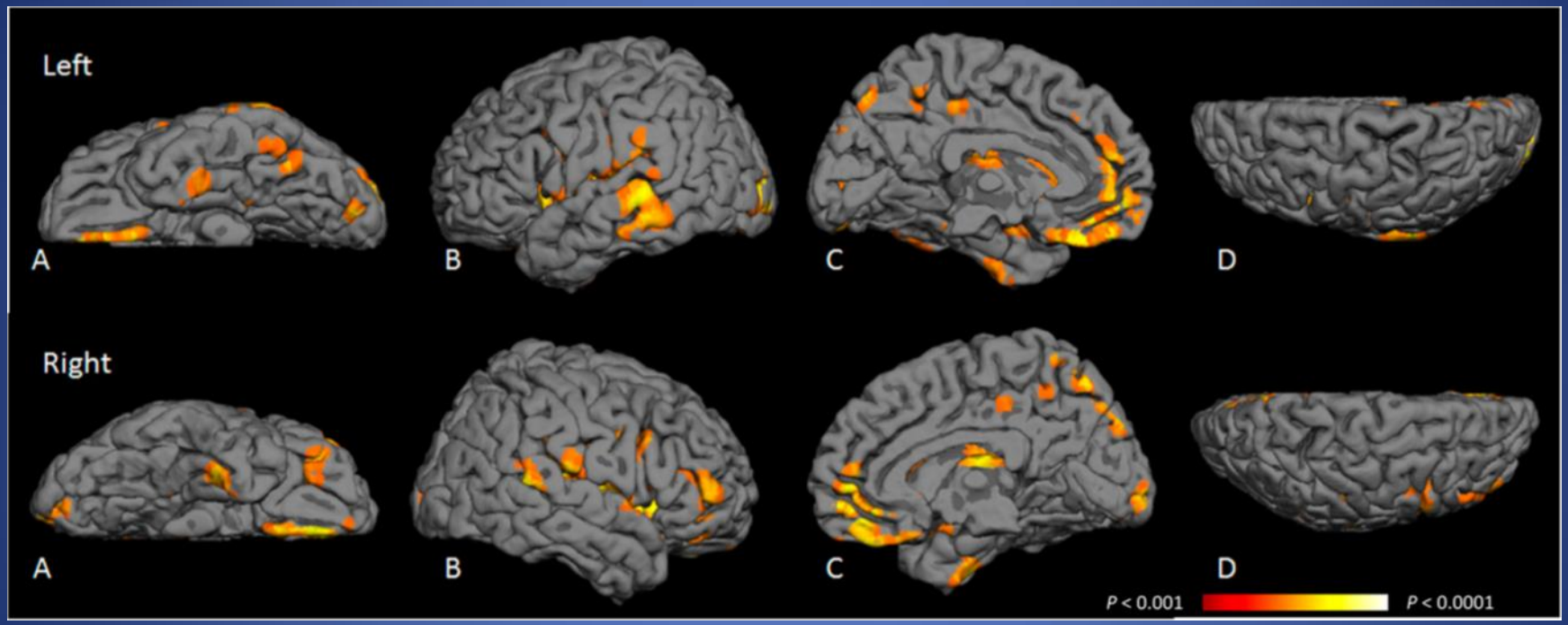
- Reduction in gray and white matter brain volume
- Distribution across brain is variable
- Changes in brain structure has been associated with decline in cognitive performance

Reduced brain volume in T1D is associated with

- Poor glycemic control
- Diabetic retinopathy
- Severe hypoglycemic events
- Disease duration
- Age of onset

Wessels et al., 2006;
Moheet A et al. 2015;
Musen G et al 2006

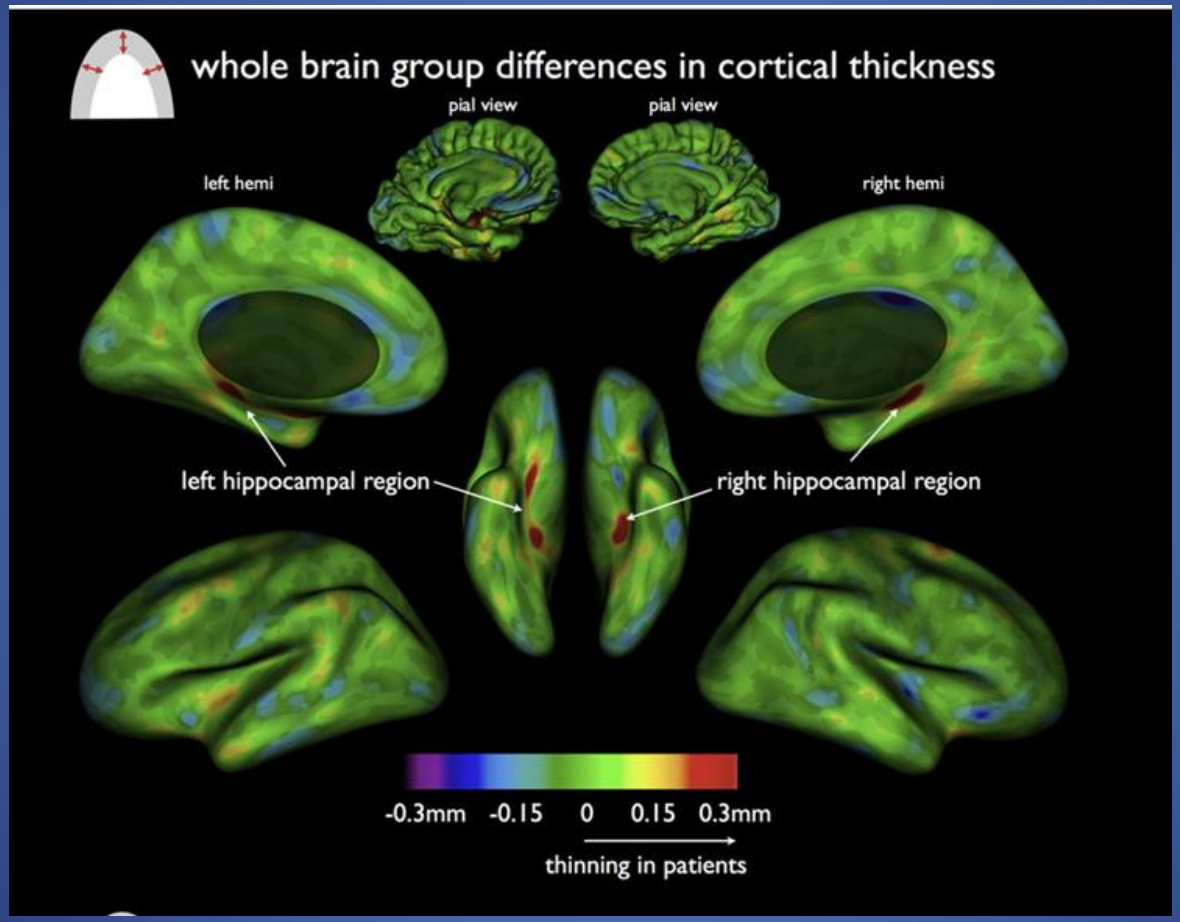
Brain MRI in type 2 diabetes: volumetery



- Type 2 diabetes, n=350; Control, n=363 Ave age 68
- Regions with loss of gray matter include the medial temporal, anterior cingulate, and medial frontal lobes.
- Brain volume loss was associated with poor performance in cognitive testing.

Moran et al. Diabetes care 2013

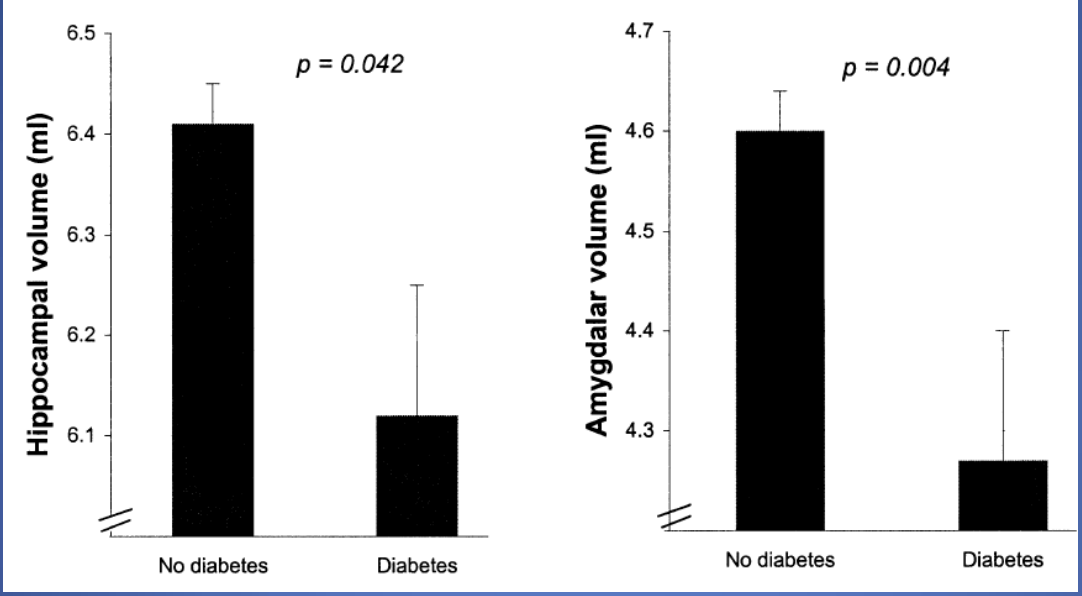
Brain MRI in type 2 diabetes: volumetery



Type 2 diabetes, n=56; Control, n=30 Ave age 70

Brundel et al 2010

Hippocampal volume in patients with type 2 Diabetes



Diabetes n=41 and without diabetes n=465

- Subjects with type 2 diabetes had more hippocampal and amygdalar atrophy on MRI compared to subjects without diabetes mellitus.

T. den Heijer et al, Diabetologia 2003

Youth onset type 2 diabetes and brain structural changes

Table 2 Brain imaging literature summary of structural data

Author, year, (T2D group *n* value)	Control group(s) (*n* value)	Global GMV	Global WMV	Regional volume
Yau et al., 2010, ($n = 18$)	Obese only ($n = 18$)	No difference	Lower	Lower frontal lobe
Bruehl et al., 2011, ($n = 18$)	Obese only ($n = 18$)	n/a	n/a	Lower hippocampus and prefrontal area
Rofey et al., 2015 ($n = 5$)	Obese ($n = 5$), HWC ($n = 5$)	n/a	n/a	Lower caudate, thalamus
Nouwen et al., 2017, ($n = 15$)	Obese ($n = 21$), HWC ($n = 22$)	n/a	n/a	Lower caudate and putamen vs HWC only
Redel et al., 2018, ($n = 20$)	HWC only ($n = 20$)	Lower	No difference	14 lower gray matter clusters, 6 higher gray matter clusters

HWC healthy weight controls, *GMV* gray matter volume, *WMV* white matter volume, *NS* not significant

Redel JM et al Current diabetes reports 2019

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Yau et al., 2010, ($n = 18$)	Obese only ($n = 18$)	No difference	Lower	Lower frontal lobe
Bruehl et al., 2011, ($n = 18$)	Obese only ($n = 18$)	n/a	n/a	Lower hippocampus and prefrontal area
Rofey et al., 2015 ($n = 5$)	Obese ($n = 5$), HWC ($n = 5$)	n/a	n/a	Lower caudate, thalamus
Nouwen et al., 2017, ($n = 15$)	Obese ($n = 21$), HWC ($n = 22$)	n/a	n/a	Lower caudate and putamen vs HWC only
Redel et al., 2018, ($n = 20$)	HWC only ($n = 20$)	Lower	No difference	14 lower gray matter clusters, 6 higher gray matter clusters

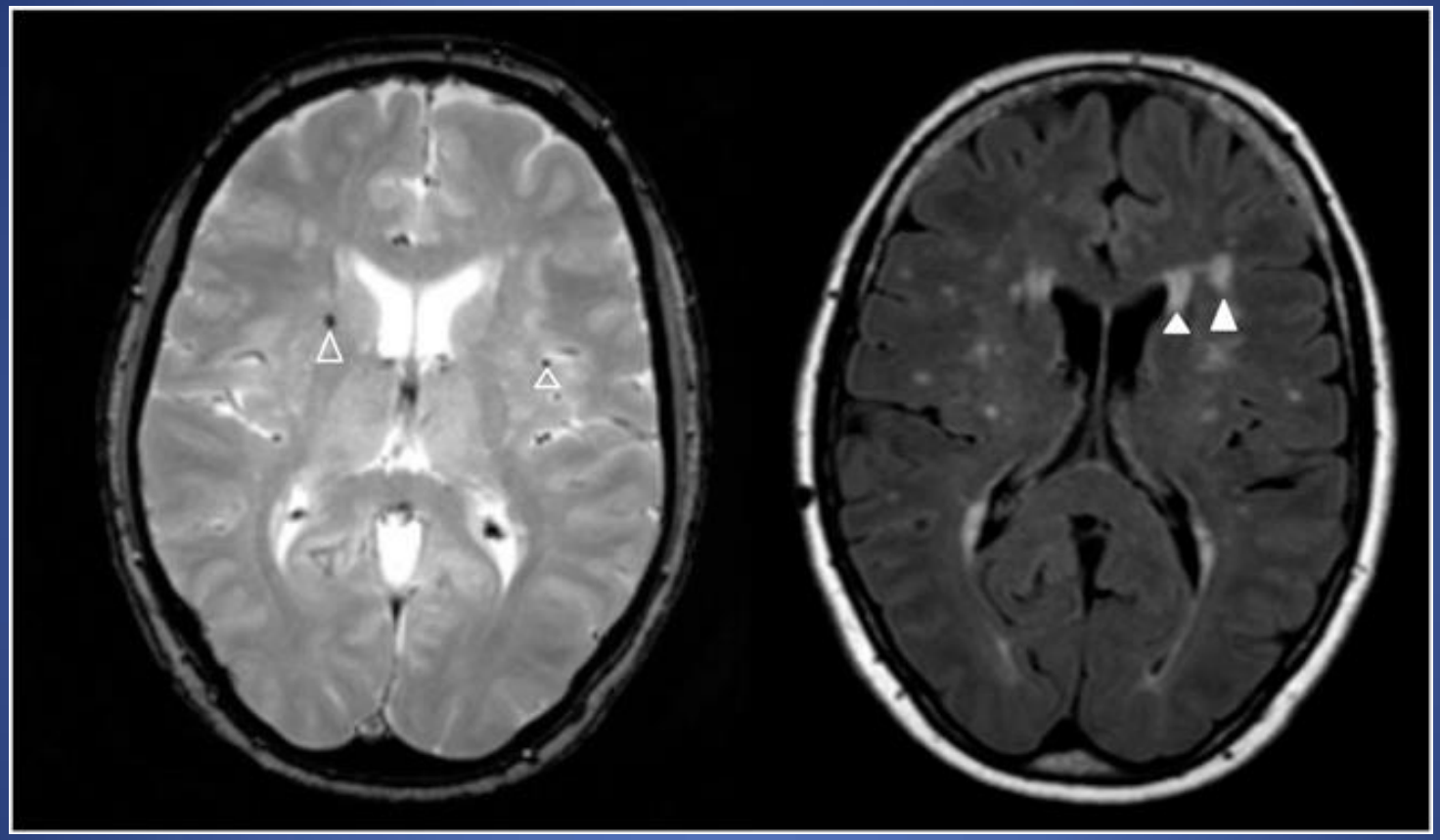
HWC healthy weight controls, *GMV* gray matter volume, *WMV* white matter volume, *NS* not significant

Table 2 Brain imaging literature summary of structural data

Author, year, (T2D group *n* value)	Control group(s) (*n* value)	Microstructural integrity
Yau et al., 2010, ($n = 18$)	Obese only ($n = 18$)	Lower gray and white region integrity
Bruehl et al., 2011, ($n = 18$)	Obese only ($n = 18$)	n/a
Rofey et al., 2015 ($n = 5$)	Obese ($n = 5$), HWC ($n = 5$)	NS
Nouwen et al., 2017, ($n = 15$)	Obese ($n = 21$), HWC ($n = 22$)	Lower white matter tract integrity
Redel et al., 2018, ($n = 20$)	HWC only ($n = 20$)	n/a

Redel JM et al Current diabetes reports 2019

Small vessel disease on brain MRI



lacunes

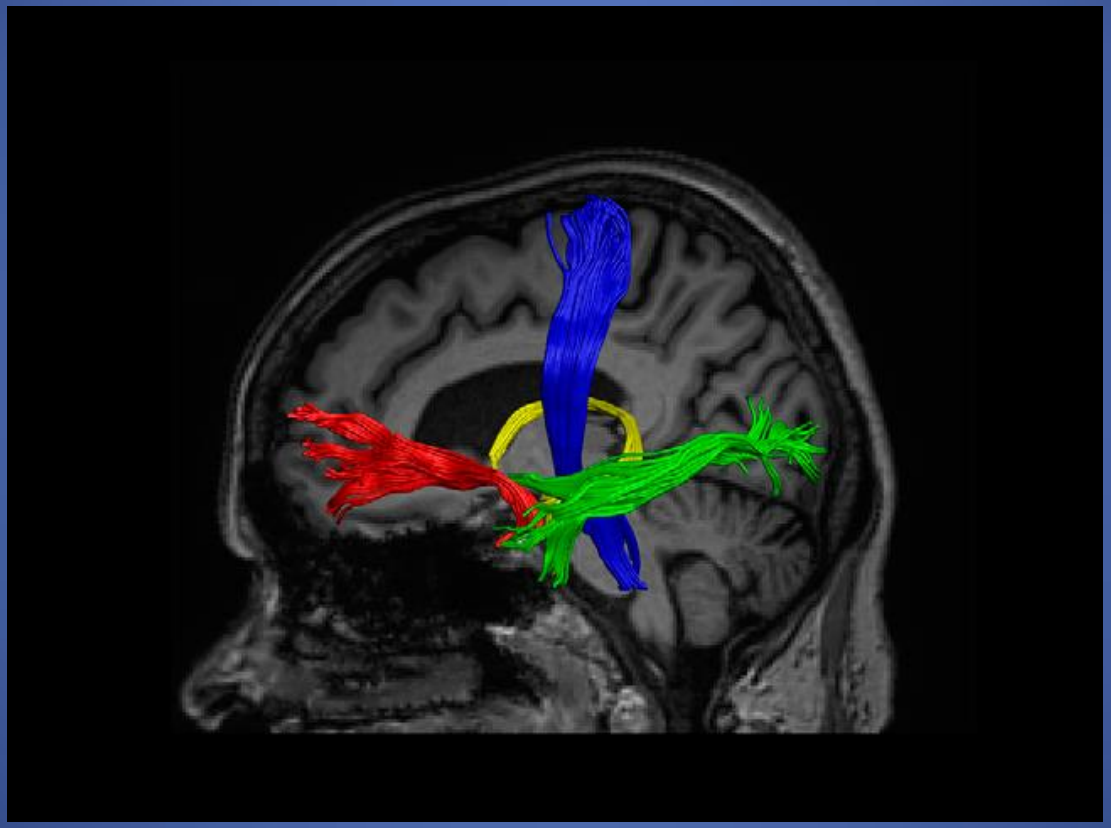
White matter hyperintensities

Biessel et al, diabetes 2014

Small vessel disease on brain MRI
White matter hyperintensities

- Increase severity of white matter hyperintensities seen in T2D then controls and associated with cognitive decline.
- Inconsistent finding across studies

Diffusion tensor imaging (DTI)



Diffusion tensor imaging in type 1 diabetes

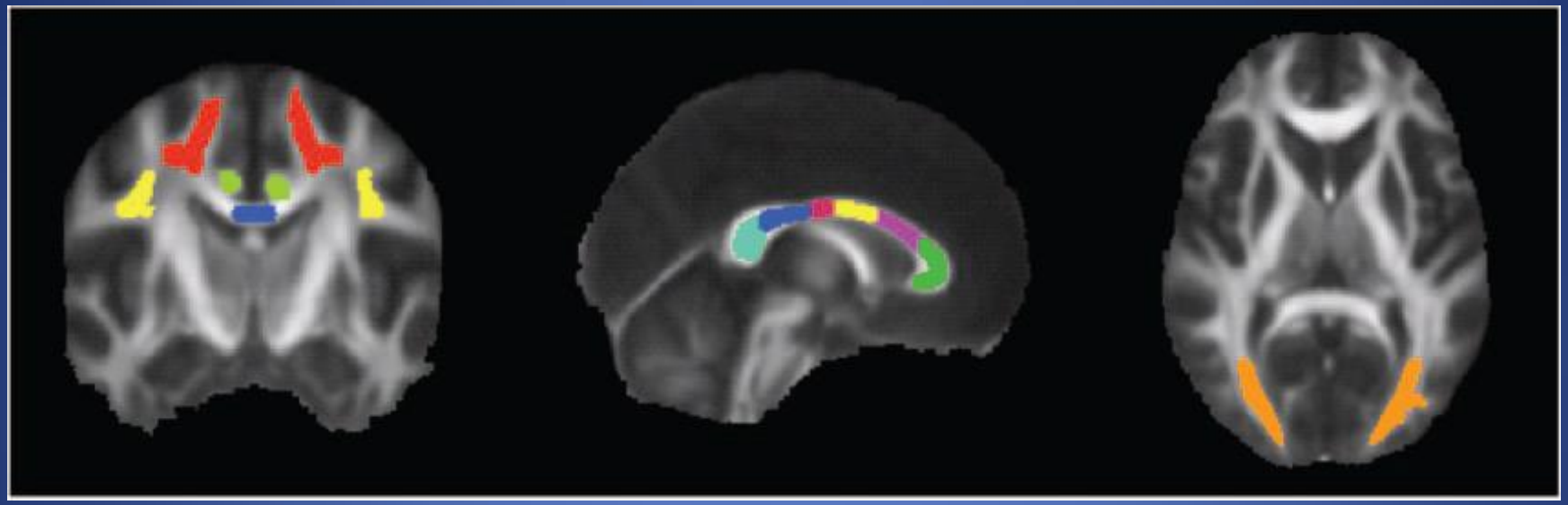
TABLE 1
Characteristics of subjects

	Subjects with type 1 diabetes	Control subjects
n	25	25
Age	45.1 ± 10.5	45.6 ± 10.8
Sex (F/M)	17/8	17/8
Education (years)	16.7 ± 1.9	16.1 ± 2.3
Duration of diabetes (years)	30.3 ± 10.8	NA
A1C (%)	7.4 ± 1.0	NA
Blood glucose before MRI (mmol/l [mg/dl])	9.3 ± 3.6 (168 ± 64)	NA
Blood glucose before neurocognitive testing (mmol/l [mg/dl])	8.4 ± 2.7 (152 ± 49)	NA

Data are means ± SD. NA, not applicable.

Kodl et al, Diabetes 2008

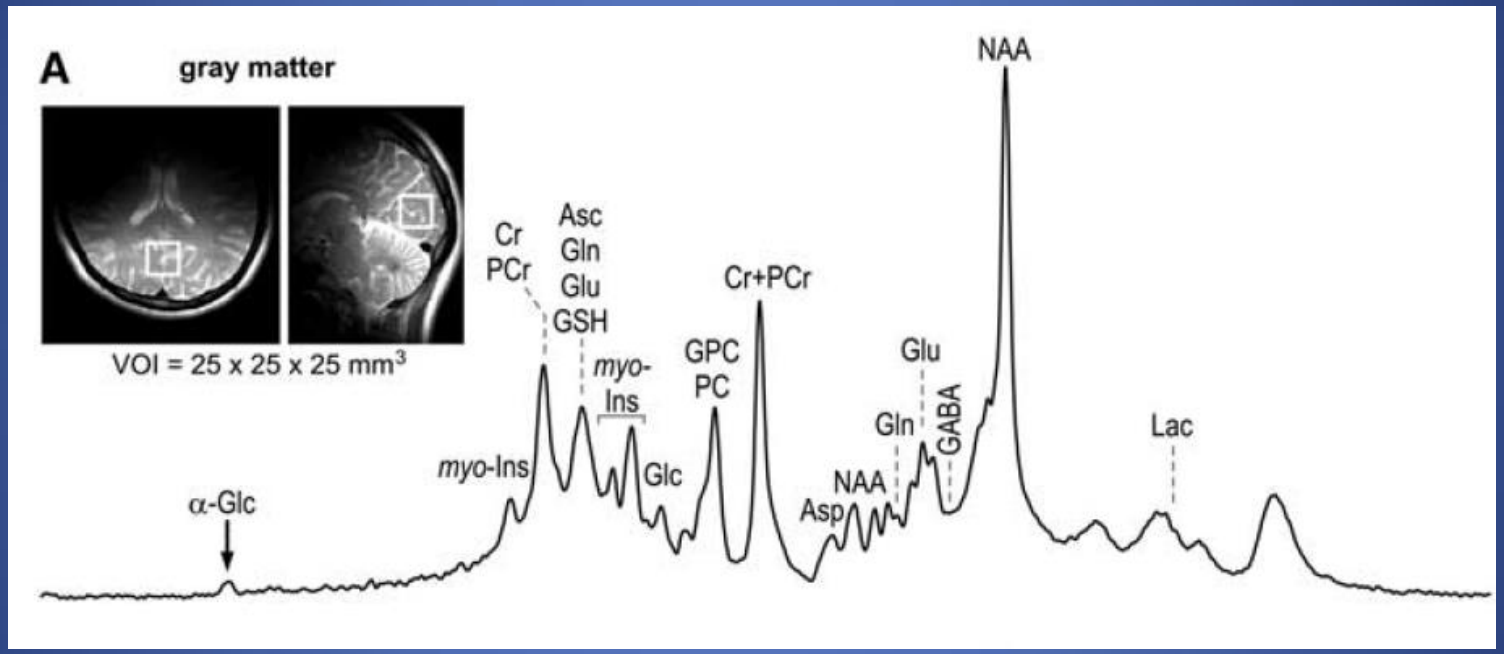
Diffusion tensor imaging in type 1 diabetes



- white matter microstructural deficits in the posterior corona radiata and the optic radiation .
- correlated with lower performance in cognitive tests thought to be associated with white matter function.

Kodl et al, Diabetes 2008

Magnetic resonance spectroscopy (MRS)



Mangia et al, Journal of Cerebral Blood Flow & Metabolism 2013

Impact of type 1 diabetes on neurochemical profile of the human brain measured by ^{1}H-MRS

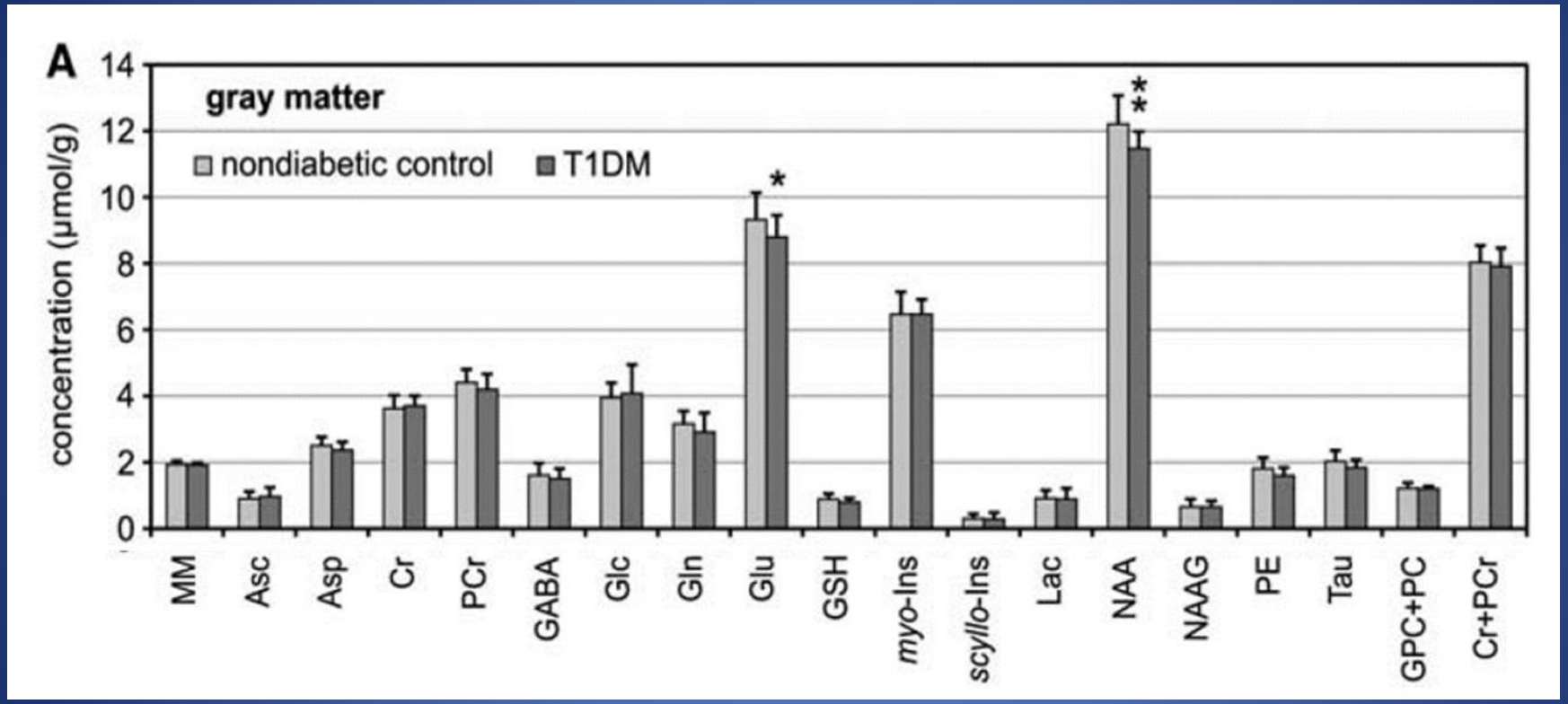
Table 1. Characteristics of subjects with type 1 diabetes mellitus (T1DM) and nondiabetic controls included in this study

	T1DM N = *13 (4 F/9 M)*		*Control* N = *32 (14F/18M)*		*P values*
	N available	*Mean ± s.d.*	*N available*	*Mean ± s.d.*	
Age (years)	13	41 ± 11	32	36 ± 10	0.160
$[Glc]_{plasma}$ (mg/dL)	13	302 ± 13	32	297 ± 9	0.159
BMI	13	26 ± 3	32	27 ± 6	0.497
A1C	12	7.5 ± 2.0	NA	NA	NA
Diabetes duration (years)	12	22 ± 12	NA	NA	NA

A1C, hemoglobin A1C test; BMI, body mass index; $[Glc]_{plasma}$, average level of plasma glucose during ^{1}H-MRS data collection.

Mangia et al, Journal of Cerebral Blood Flow & Metabolism 2013

Impact of Type 1 diabetes on neurochemical profile of the human brain measured by ^{1}H-MRS



Lower levels of **N**-acetylaspartate (NAA) by 6% (**P.**0.007) and glutamate (GLU) by 6%, (**P.**0.045) were observed in the gray matter of type 1 diabetes as compared with controls, which might indicate a partial neuronal loss or dysfunction as a consequence of long-term type 1 diabetes.

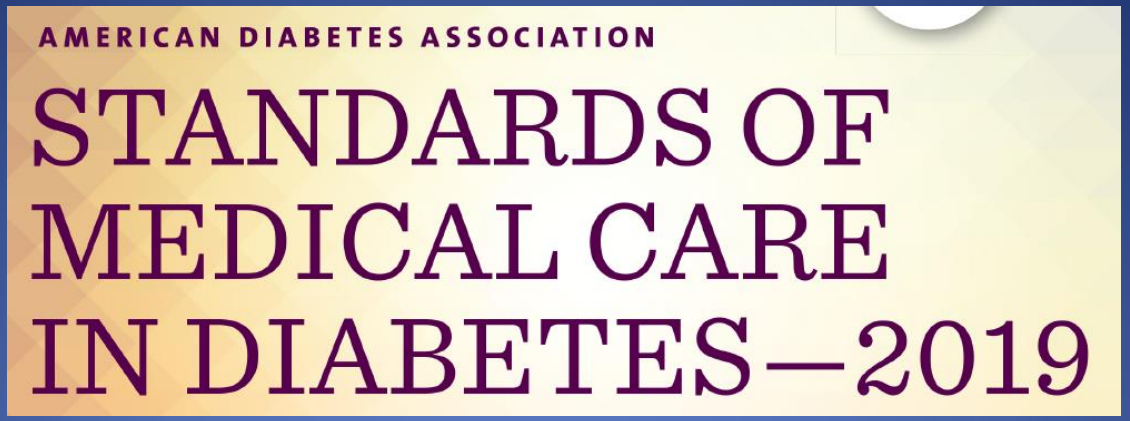
Cognitive dysfunction in diabetes: Clinical relevance

- Mild to moderate degree of cognitive impairment likely does not cause clinically significant problems in the day to day activities of most people with diabetes.
- More studies are needed to understand the impact of mild to moderate decrements in cognitive function in the daily lives people with diabetes.
- People at the extremes of age are more likely to be at increased risk of developing clinically significant decline in cognitive function.

Cognitive dysfunction in diabetes: Clinical relevance

- Cognitive impairment in children with early onset type 1 diabetes appears to negatively affect their academic performance (Ryan C et al. 1985).
- In elderly people with type 2 diabetes cognitive dysfunction is associated with poor diabetes self-management, increased medication errors, requiring more assistance with personal care and increased risk of hospitalization (Sinclair AJ et al. 2000).

- Should we routinely screen for cognitive impairment in patients with diabetes, just like other diabetic complications?



Cognitive Impairment/Dementia

- Screening for early detection of mild cognitive impairment or dementia and depression is indicated or adults 65 years of age or older at the initial visit and annually as appropriate.

- In people with a history of cognitive impairment/dementia, intensive glucose control cannot be expected to remediate deficits. Treatment should be tailored to avoid significant hypoglycemia.

Conclusions

- Both type 1 and type 2 diabetes are associated with mild to moderate decrement in cognitive function.
- These diabetes-associated cognitive decrements have structural brain correlates detectable with brain MRI.
- Glycemic control, age of onset, duration of diabetes, presence of microvascular complications and other vascular comorbidities like dyslipidemia and hypertension are associated with cognitive decline and brain structural changes in people with diabetes.
- Type 2 diabetes is associated with increased risk of dementia.

Conclusions

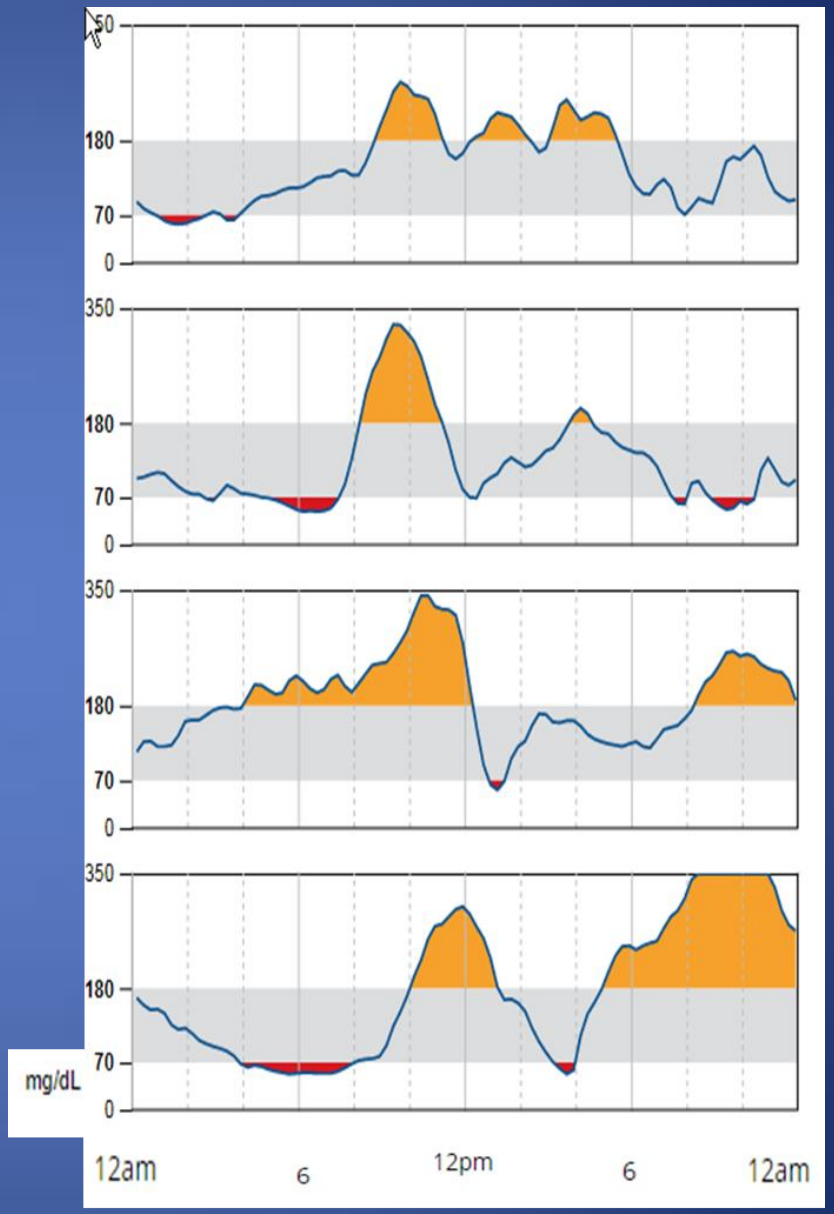
- The underlying mechanism and the risk factors that may lead to the development of more severe cognitive dysfunction like dementia in some but not all people with type 2 diabetes are not well understood.
- Large longitudinal studies, in especially in older people with diabetes, are needed to better understand the impact, progression and risk factors that drive the development of diabetes related cognitive dysfunction.
- With the growing epidemic of diabetes and the increasing number of people who live to old age, diabetes related cognitive dysfunction could have challenging future public health implications.

Impact of hypoglycemia on cognitive function and brain structure

Overview

- How common is hypoglycemia in diabetes?
- Does hypoglycemia affect the brain structure and function in patients with diabetes?
- Which patients are at greatest risk for hypoglycemia?
- How can the risk of hypoglycemia be minimized?

- 62 year old female with long standing type 2 diabetes
- Basal bolus regimen with glargine and aspart insulin, recent A1C 8.3 %
- Complains of memory and concentration issues, frequently misses insulin doses.
- Usually does not feel typical symptoms of low blood glucose until glucose is below 50 mg/dl.
- History of one episode of severe hypoglycemia in the last 1 year.



Hypoglycemia in diabetes

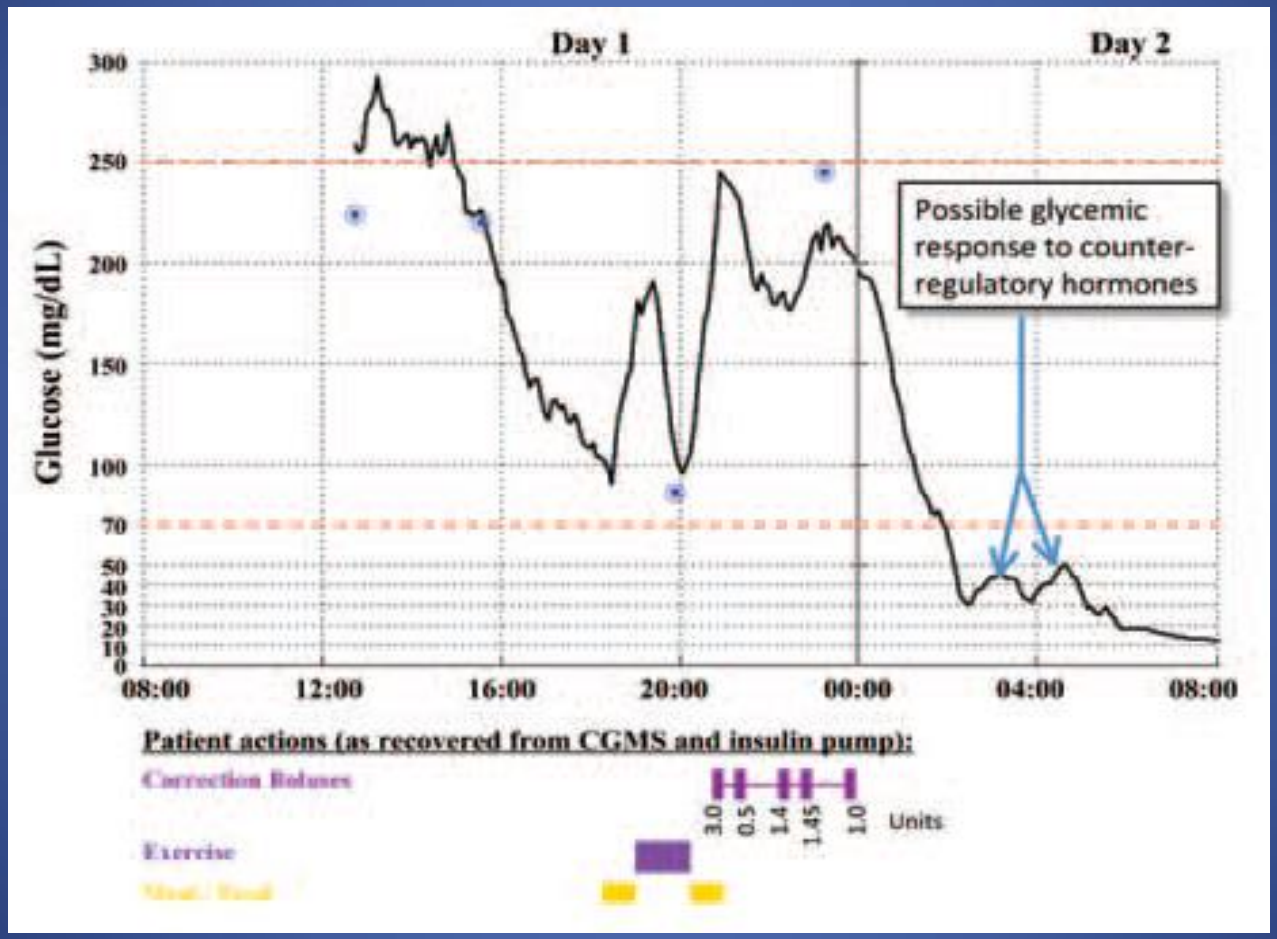
- Hypoglycemia is a common side effect of insulin therapy in patients with diabetes and is considered a limiting factor in the successful glycemic control.

- In a recent international study, 83% of all enrolled patients with T1D and 46.5% with T2D had at least one episode of hypoglycemia each month.

- Hypoglycemia causes recurrent morbidity in most people with T1D and many with advanced T2D, and is sometimes fatal.

Cryer PE. N Engl J Med 2004.
Khunti K et al. Diabetes, Obesity and Metabolism 2016

23-year-old man with a type 1 diabetes , history of severe hypoglycemia, started on continuous subcutaneous glucose monitoring system (CGMS)



Tanenberg RJ et al Endocrine Practice 2010

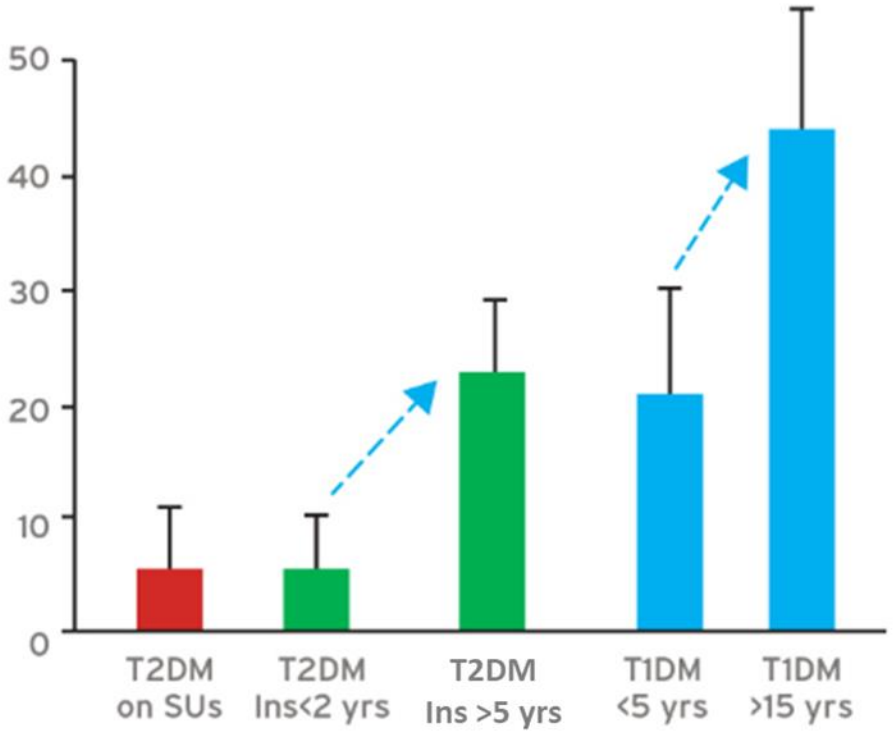
Classification of Hypoglycemia in Diabetes

Table 6.3—Classification of hypoglycemia (44)

Level	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

ADA Standards of medical care in diabetes 2019

Annual prevalence of severe hypoglycaemia
By diabetes type and medication status[1]



Adapted from Diabetologia 2007;50:1140.

IHSG International HYPOGLYCAEMIA Study Group

Clinical manifestations of hypoglycemia

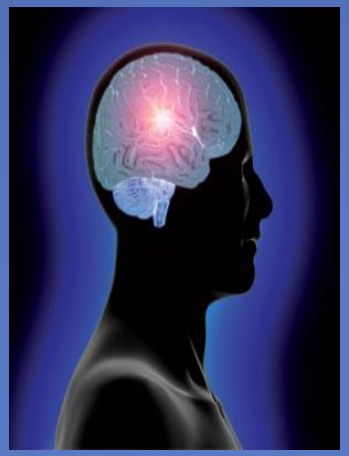
Symptoms	
Neurogenic	Neuroglycopenic
Shakiness	Warmth
Tremulousness	Weakness
Palpitations	Difficulty in thinking
Nervousness/anxiety	Difficulty speaking
Sweating	Confusion
Hunger	Tiredness
Tingling	Drowsiness
	Stupor
	Seizures
	Coma
	Death

Tesfaye & Seaquist Ann. N.Y. Acad. Sci. 2010

How does hypoglycemia affect the brain in patients with diabetes?

Acute hypoglycemia

- Acute symptoms
- Cognitive impairment
- Risk of cardiac arrhythmias
- Poor sleep quality due to nocturnal hypoglycemia
- Neurological manifestations include coma, convulsions
- Rarely fatal



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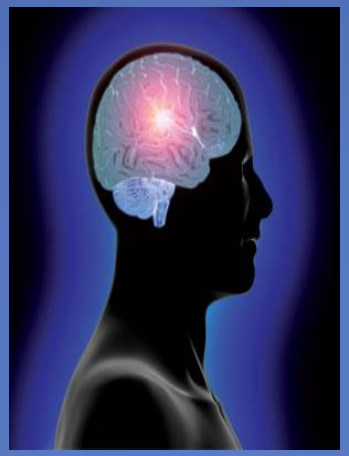
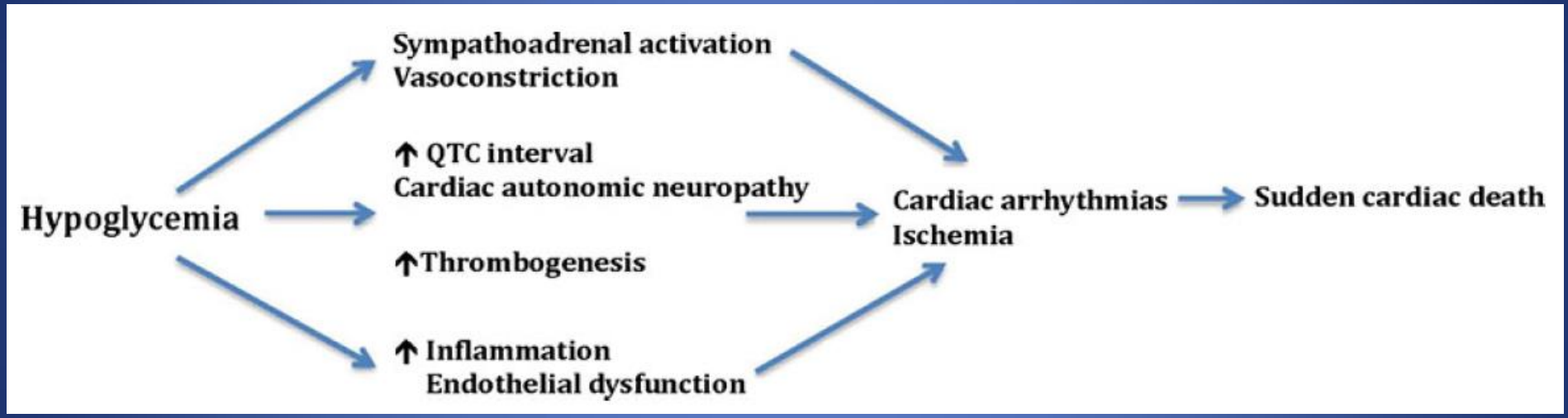


Recurrent hypoglycemia

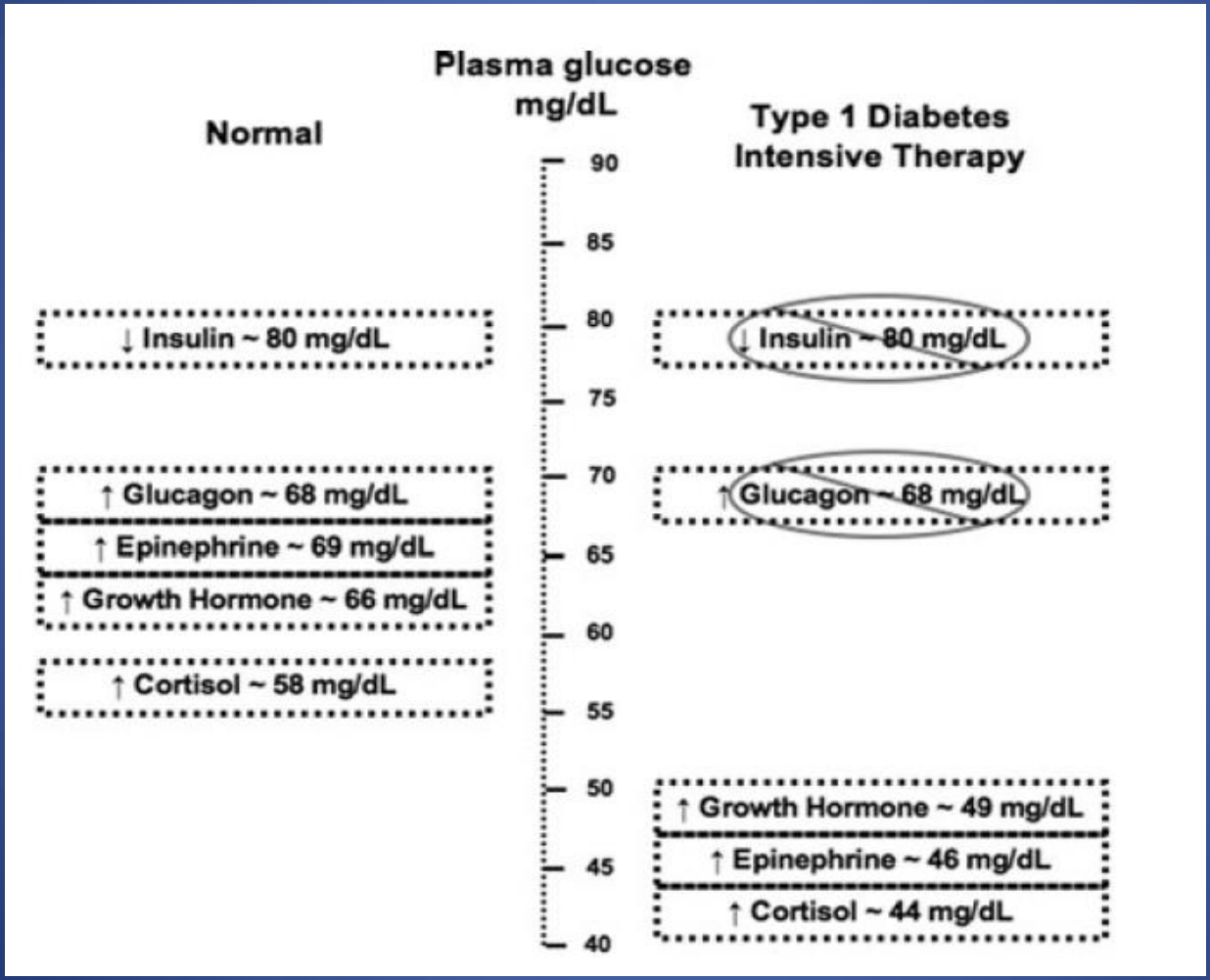
- Reduced quality of life
- Fear of hypoglycemia
- Impaired awareness of hypoglycemia
- Affects employment, driving licensing etc.
- Brian structural changes
- Cognitive decline

Possible mechanisms of increased mortality in hypoglycemia



Moheet & Seaquist. Curr Atheroscler Rep 2013

Counterregulatory factors and glucose threshold for their secretion in the normal setting and in type 1 diabetes



Tesfaye & Seaquist Ann. N.Y. Acad. Sci. 2010

Clinical impact of impaired awareness of hypoglycemia

- Impaired awareness of hypoglycemia occurs in approximately 25% of adults with type 1 diabetes.
- It is associated with a six fold higher risk of having severe hypoglycemia.
- Strict avoidance of hypoglycemia has been shown to partially restore awareness of hypoglycemia; however it is very difficult to achieve and maintain over the long term.

Fanelli CG, et al. Diabetes 42:1683, 1993.
Dagogo-Jack S, et al. Diabetes 43:1426, 1994.

Impaired awareness of hypoglycemia (IAH) is associated with cognitive deficits in type 1 diabetes

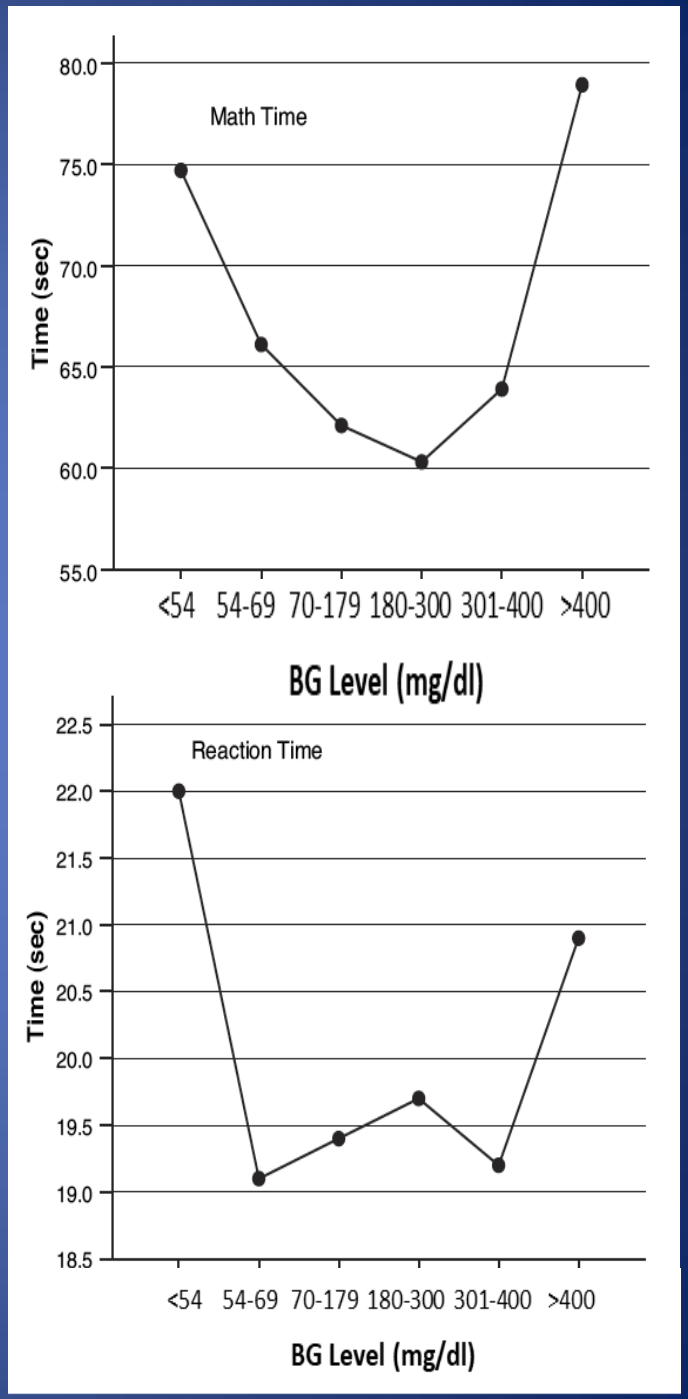
- In a study of 201 older adults (≥60 years) with longstanding TID: IAH, two or more severe hypoglycemic events in the past year, any microvascular complication, higher HbA1c were all associated with increased odds of clinically significant cognitive impairment (Chaytor NS et al Journal of Diabetes and Its Complications 2018).

- Another study, found that subjects with T1D and IAH had reduce performance in domains of learning and memory compared to age, sex and diabetes duration matched T1D with normal awareness of hypoglycemia (Hansen TI et al Diabetologia 2017).

Effects of glycemia on cognition in school age children

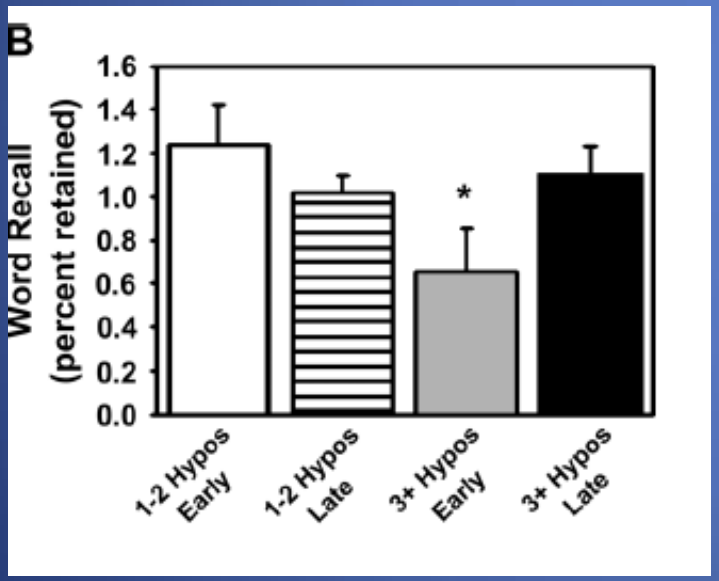
- Examined 61 children with T1D, mean age of 9 years
- Children did tests on PDA just prior to pre-meal glucose testing for 4-6 weeks

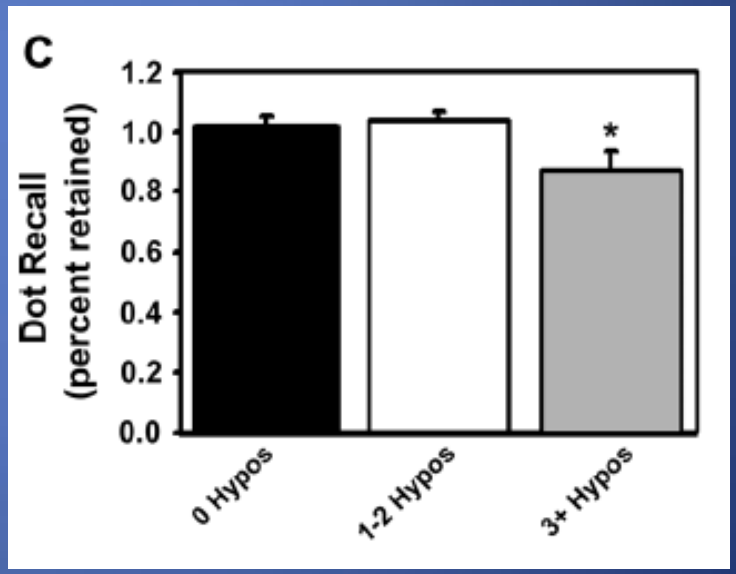
Gonder-Frederick et al. Diabetes Care 2009



Effects of prior hypoglycemia on cognition in children T1D

- 5–16 yr, T1D n = 117; non-diabetic sibling controls n = 58
- T1D participants were categorized as having experienced 0, 1–2, or 3 or more 3+ Hypo episodes
- Hypo episodes further characterized to be before (early)or after (late) 5 yr of age





Perantie et al. Pediatric Diabetes 2008

The Effect of Recurrent Severe Hypoglycemia on Cognitive Performance in Children With Type 1 Diabetes: A Meta-analysis

Annalisa Blasetti, PhD, MD[1], Rosa Maria Chiuri, MD[1], Anna Maria Tocco, MD[1], Concetta Di Giulio, MD[1], Peter A. Mattei, MD[2], Enzo Ballone, PhD, MD[2], Francesco Chiarelli, PhD, MD[1], and Alberto Verrotti, PhD, MD[1]

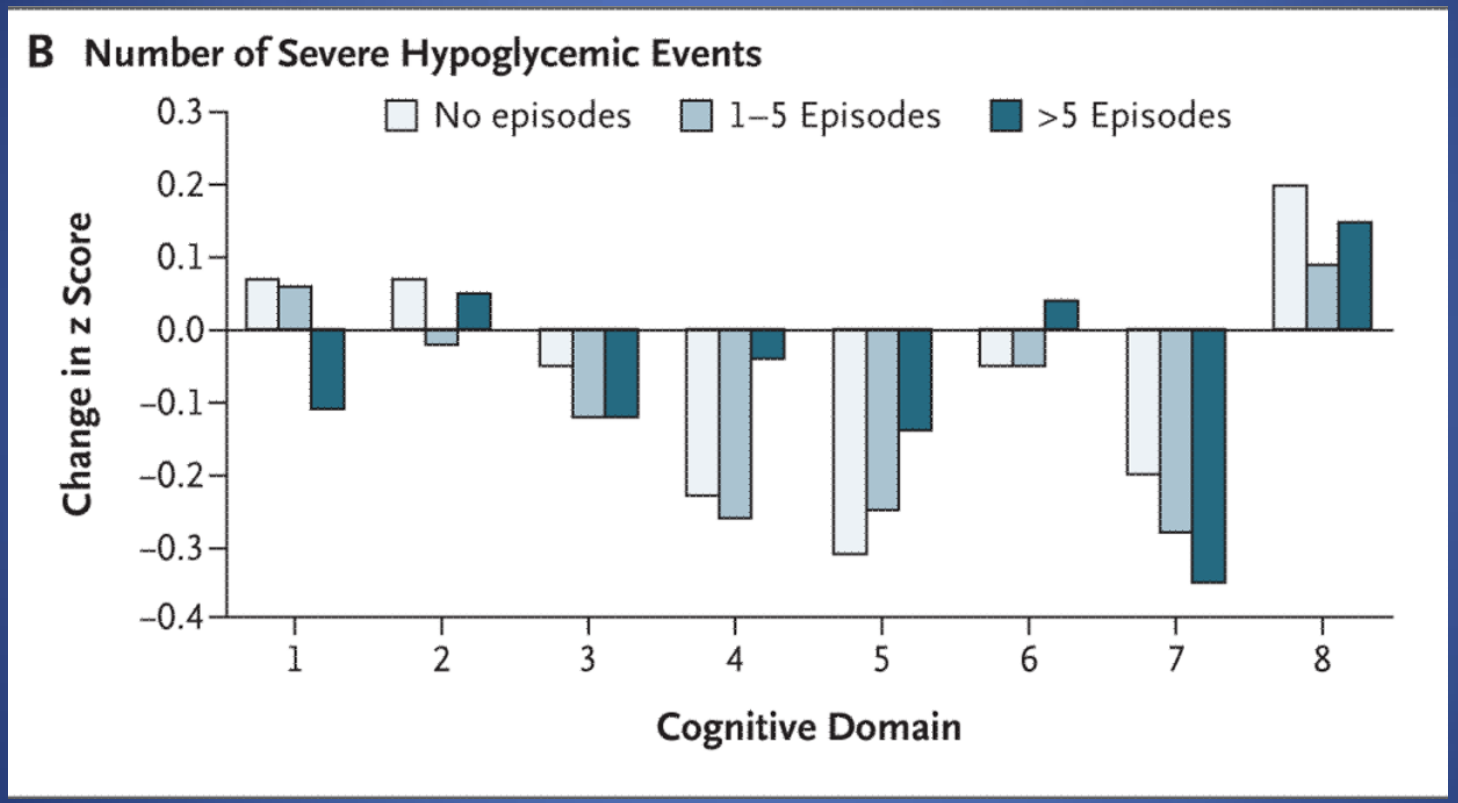
Journal of Child Neurology
26(11) 1383-1391

DOI: 10.1177/0883073811406730
http://jcn.sagepub.com
SAGE

- Meta-analysis included studies with children and/or adolescents under 18 years of age.
- Included 1390 children, 441 with T1D and recurrent severe hypoglycemia, 560 children with T1D and without recurrent severe hypoglycemia, and 389 nondiabetic children.
- Children with T1D with recurrent severe hypoglycemia performed lower in domains of intelligence, learning, memory, and verbal fluency/language, when compared to children with T1D without recurrent severe hypoglycemia.

Cognitive dysfunction in type 1 diabetes: Effect of recurrent severe hypoglycemia

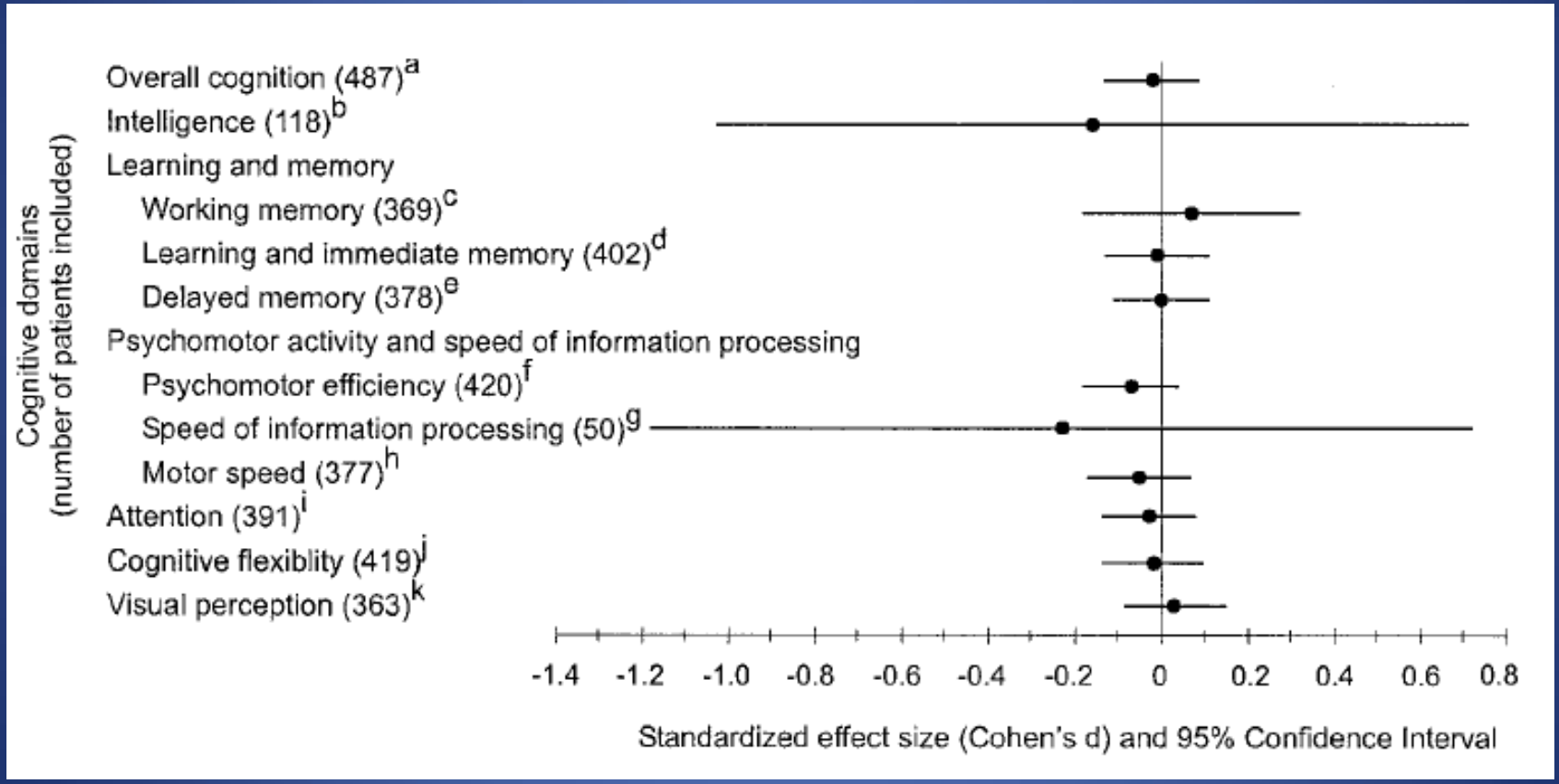
DCCT-EDIC Study



Frequency of severe hypoglycemia was not associated with decline in any cognitive domain in this population

Cognitive dysfunction in type 1 diabetes: Effect of recurrent hypoglycemia

Meta analyses



Brands et al, diabetes care 2005

Hypoglycemic Episodes and Risk of Dementia in Older Patients with Type 2 Diabetes Mellitus

Rachel A. Whitmer[1], Andrew J. Karter[1], Kristine Yaffe[2], Charles P. Quesenberry Jr.[1], and Joseph V. Selby[1]

JAMA 2009

- A longitudinal cohort study of 16,667 patients with type 2 diabetes who were > 55 years of age on 1/1/2003 and had no diagnosis of dementia or mild cognitive impairment.
- Examined relationship between hypoglycemia episodes requiring hospitalization or ED visit between 1/1/1980-12/31/2002 and 1822 incident cases of dementia identified after 1/1/2003

Severe hypoglycemia is associated with increased risk of dementia in older people with type 2 diabetes

Table 3. Hypoglycemia and Risk of Incident Dementia[a]

No. of Hypoglycemic Episodes[b]	No. of Dementia Cases	Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes
1 or more	250	1.68 (1.47-1.93)
1	150	1.45 (1.23-1.72)
2	57	2.15 (1.64-2.81)
3 or more	43	2.60 (1.78-3.79)

- In this study severe hypoglycemic episodes were associated with increased risk of dementia, particularly for patients who have a history of multiple episodes.

Whitmer R et al, JAMA 2009

Type 1 Diabetes and Impaired Awareness of Hypoglycemia Are Associated with Reduced Brain Gray Matter Volumes

Petr Bednarik[1†], Amir A. Moheet[2†], Heidi Grohn[1], Anjali F. Kumar[2], Lynn E. Eberly[3], Elizabeth R. Seaquist[2] and Silvia Mangia[1]*

- Cross-sectional morphometric MRI study examined the association of T1D with gray matter (GM) volumes
- Retrospectively analyzed anatomical MRI data acquired in our laboratory from subjects with long-standing T1D and non-diabetic subjects.
- The T1D group was further sub-divided in two groups based on whether subjects had normal (NAH) or impaired awareness of hypoglycemia (IAH)

Frontiers in Neuroscience 2017

Methods

- **Subjects**

- 18 to 65 years of age
- Long standing (≥10 years) T1D (A1C < 8.5%) and healthy controls
- Healthy control group matched to T1D based on age, sex, and BMI
- Patients were categorized as having IAH based on scoring on a standardized (Clark) questionnaire.

- **Exclusion**

- history of seizure, cardiac disease, stroke, head injury, or other chronic CNS disease
- drug or alcohol abuse
- history of renal insufficiency (creatinine >1.5 mg/dL)
- pregnancy or breastfeeding
- presence of any characteristics that would preclude placement in the magnet (weight > 300 lbs, presence of metallic implants, etc.)

. Clarke W et al. Diabetes care 1995

Brain structural changes in T1D and IAH

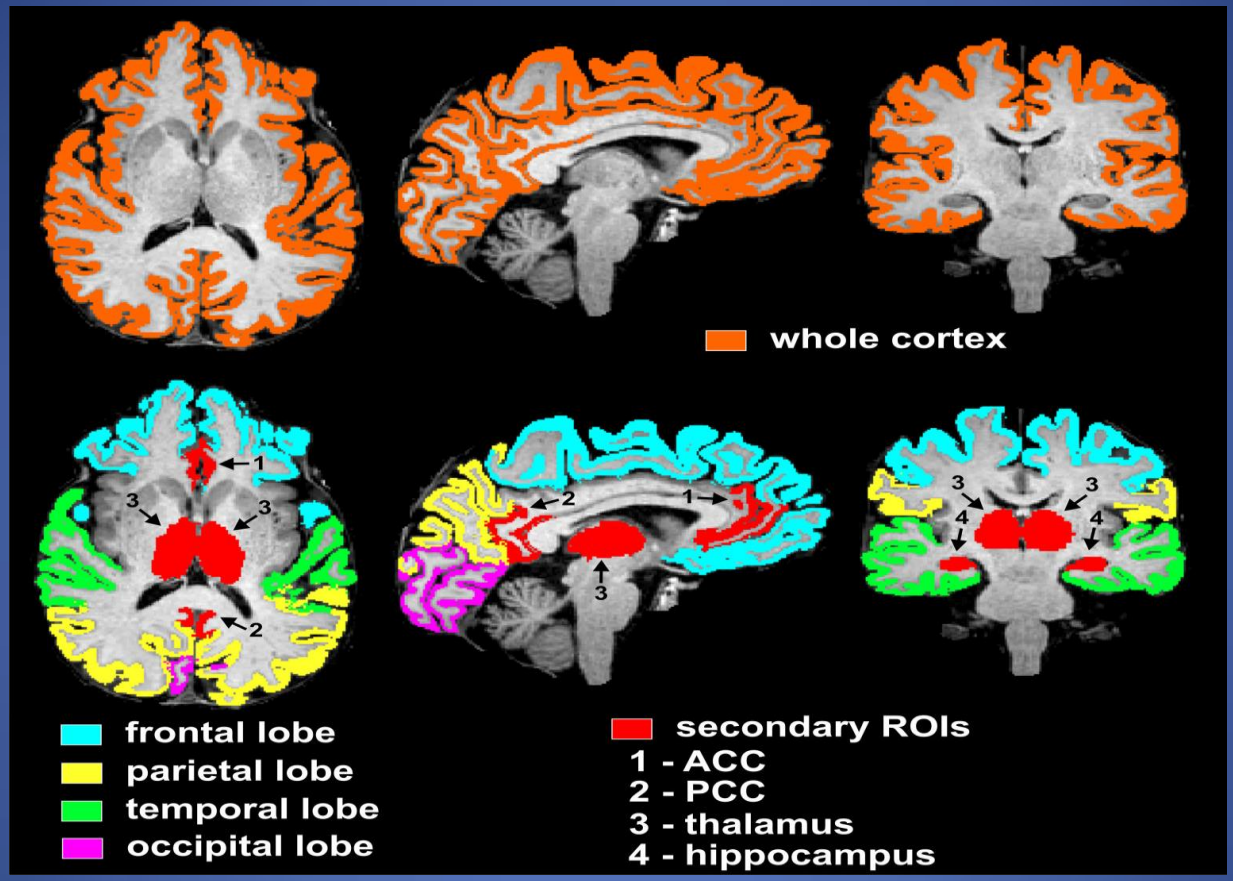
Group	n	Age (years)	Sex (M/F)	BMI (kg/m²)	T1D duration (years)	A1C (%)
Control	50	36±14	25/25	25±4	-	-
T1D	52	36±11	26/26	26±4	20±11	7.2±0.9
p-values*		0.86	0.99	0.25	-	-
T1D – NAH	31	32±10	18/13	26±4	17±10	7.4±0.8
T1D – IAH	20	43±10	8/12	27±5	25±11	6.9±0.8
p-values§		0.0005	0.26	0.45	0.008	0.042

*** Comparisons between control and T1D subjects**

§ Comparisons between T1D-NAH (normal awareness of hypoglycemia) and T1D-IAH subjects

Bednarik, Moheet et al. Front Neurosci 2017

Regions of interest



Visualization of regions of interest subjected to volumetry analyses from one representative non-diabetic subject

T1D is associated with reduced brain gray matter volumes

Volumetry comparisons between T1D subjects and controls

Region	Group values (mean ± *SD*)		Group-comparisons		
	Control (*n* = 50)	T1D (*n* = 52)	Diff* (%)	unadj_p	fdr_p
Whole cortex	0.33 ± 0.02	0.32 ± 0.02	**−2.7**	0.016	0.016
Frontal lobe	0.119 ± 0.010	0.115 ± 0.009	**−3.6**	0.006	0.024
Occipital lobe	0.031 ± 0.003	0.030 ± 0.002	−3.4	0.084	0.112
Parietal lobe	0.079 ± 0.006	0.077 ± 0.006	−2.9	0.040	0.081
Temporal lobe	0.073 ± 0.005	0.072 ± 0.005	−1.3	0.345	0.345

Impaired awareness of hypoglycemia is associated with reduced brain gray matter volumes

Volumetry comparisons of controls with T1D-NAH and T1D-IAH subjects

Region	Group-comparisons					
	T1D-NAH vs. Controls			T1D-IAH vs. Controls		
	Diff* (%)	unadj_p	fdr_p	Diff* (%)	unadj_p	fdr_p
Whole cortex	0.4	0.632	0.632	**−7.6**	0.0001	0.0002
Frontal lobe	0.0	0.435	0.569	**−9.1**	0.00004	0.0003
Occipital lobe	−2.0	0.207	0.331	−5.7	0.118	0.237
Parietal lobe	−0.1	0.719	0.719	**−7.8**	0.0006	0.002
Temporal lobe	1.9	0.498	0.569	**−6.4**	0.007	0.019

Impaired awareness of hypoglycemia is associated with reduced brain gray matter volumes

Volumetry comparisons for T1D subjects those with NAH and IAH

Region	Group values (mean ± *SD*)			With adjustment for T1D duration and A1C	
	T1D with NAH (*n* = 31)	T1D with IAH (*n* = 20)	Diff* (%)	unadj_p	fdr_p
Whole cortex	0.33 ± 0.01	0.30 ± 0.02	**–7.9**	0.0009	0.0009
Frontal lobe	0.120 ± 0.007	0.108 ± 0.008	**–9.1**	0.002	0.006
Occipital lobe	0.031 ± 0.002	0.029 ± 0.003	–3.8	0.342	0.342
Parietal lobe	0.079 ± 0.005	0.073 ± 0.006	**–8.0**	0.011	0.015
Temporal lobe	0.074 ± 0.004	0.069 ± 0.005	**–8.2**	0.005	0.009

Impaired awareness of hypoglycemia is associated with reduced brain gray matter volumes

Age-matched comparisons

Group	n	Age (years)	Sex (M/F)	BMI (kg/m²)	T1D duration	A1c
T1D – IAH	18	41±8	7/11	27±6	25±12	6.8±0.8
T1D – NAH	18	36±11	7/11	26±5	19±11	7.4±0.8
p-					0.09	0.04

Region	Diff* (%)	unadj_p
Whole cortex	**-5.2**	0.002
Frontal lobe	**-5.7**	0.002
Occipital lobe	-1.8	0.452
Parietal lobe	**-5.5**	0.013
Temporal lobe	**-6.0**	0.007

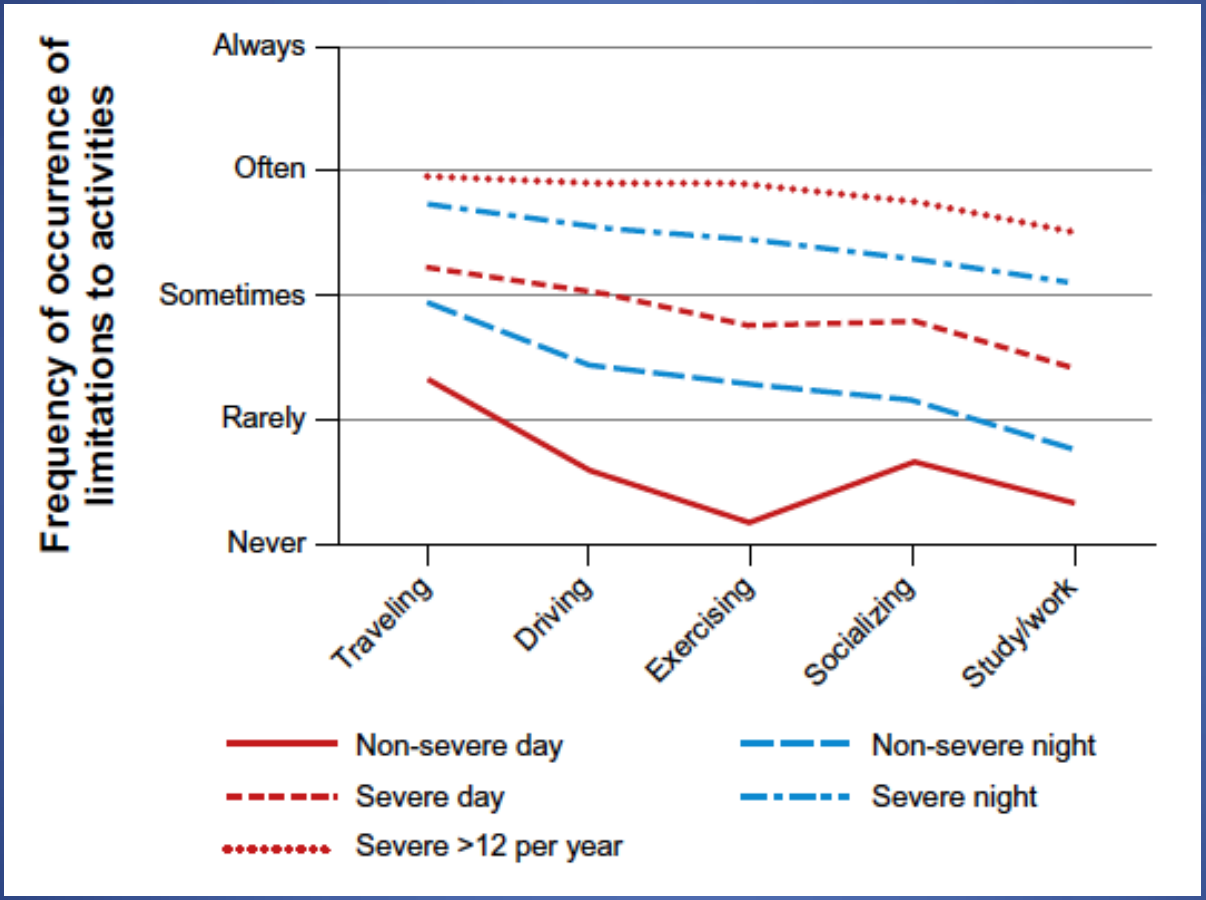
Group	n	Age (years)	Sex (M/F)	BMI (kg/m²)
T1D – IAH	20	43±10	8/12	27±5
Control	20	44±12	8/12	26±4
p-values		0.83	-	0.43

Region	Diff* (%)	unadj_p
Whole cortex	**-5.0**	0.023
Frontal lobe	**-5.2**	0.030
Occipital lobe	-2.9	0.396
Parietal lobe	**-6.6**	0.004
Temporal lobe	-4.2	0.075

Summary

- Subjects with long standing T1D had smaller whole cortex and frontal lobe GM volumes compared to non-diabetic controls of similar age, sex and BMI.
- Structural effects of larger magnitude were present in T1D patients with IAH as compared to patients with NAH, as well as compared to controls.
- Interestingly, patients with NAH did not show volume reductions as compared to controls.
- IAH are generally those who experience episodes of hypoglycemia more frequently, one can speculate that the long-term exposure to recurrent hypoglycemia may be associated with reduced brain volumes.

Impact of hypoglycemia on activities of daily living

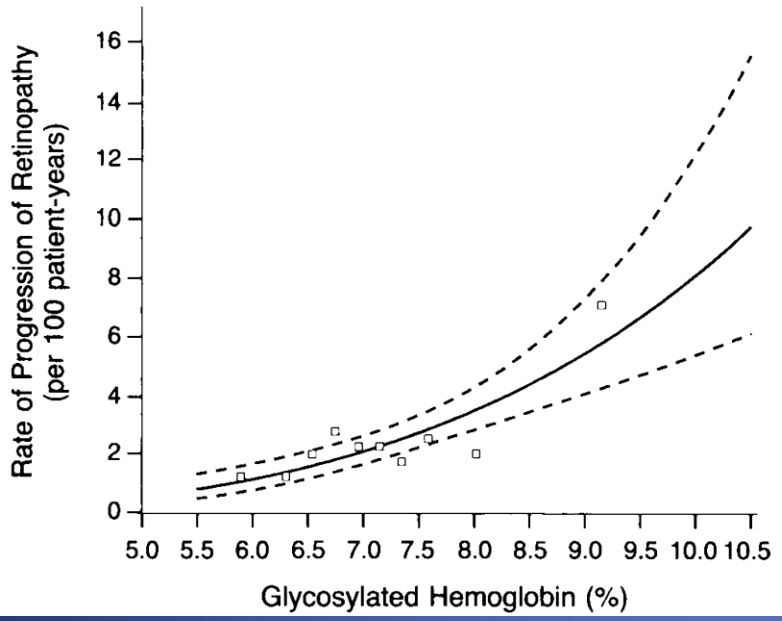


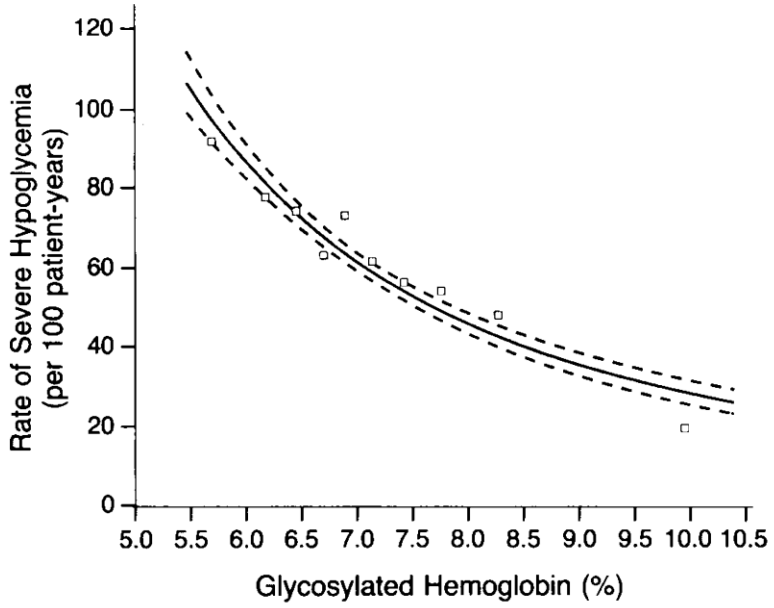
Effect of hypoglycemia on aspects of daily life for 247 people with diabetes (type 1 = 85, type 2 = 162)

Harris et al. Patient Preference and Adherence 2013

Which patients are at greatest risk for hypoglycemia?

Improving glycemic control reduces microvascular complications but increases risk of hypoglycemia





DCCT. NEJM 1993

Severe hypoglycemia was significantly higher in the intensive glucose-lowering arms of ACCORD, ADVANCE and VADT trials

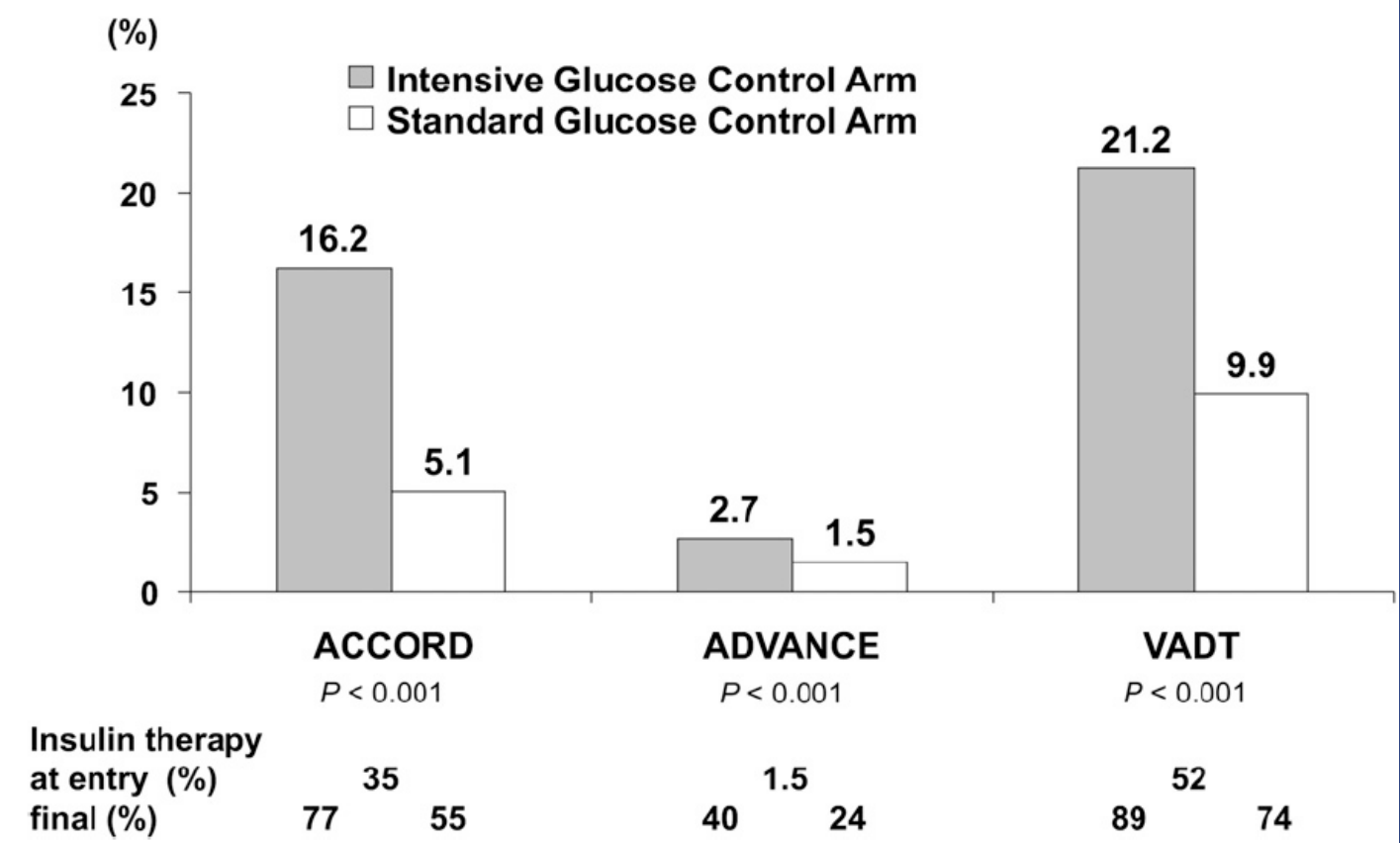
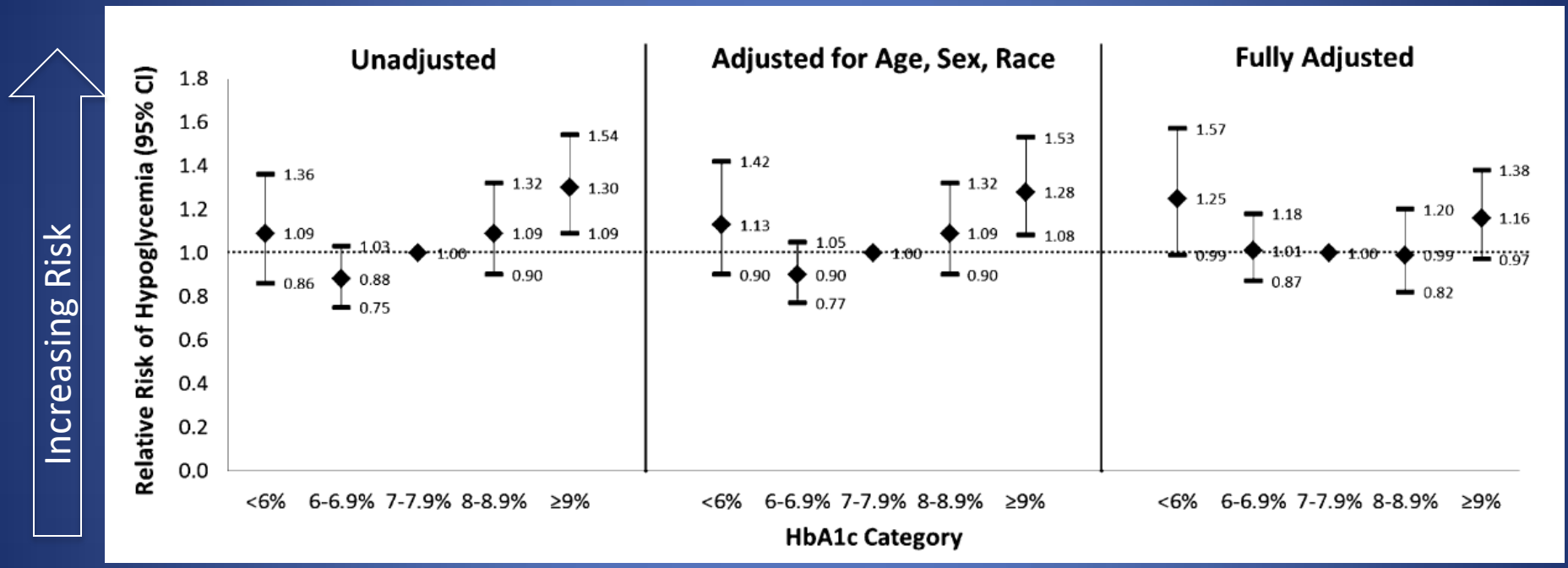


Figure 2—*Percentage of severe hypoglycemic events in ACCORD, ADVANCE, and VADT.*

Frier et al, Diabetes care 2011

Risk of severe hypoglycemia in type 2 diabetes varies with baseline HbA1c



Association between HbA1c level and self-reported severe hypoglycemia in patients with type 2 diabetes (n=9094)

Lipska et al Diab care 2013

Risk factors for hypoglycemia in diabetes

Physiological/Therapeutic
• Duration of diabetes • Old age • Negative C-peptide • Presence of comorbidities • Strict glycemic control • Impaired awareness of hypoglycemia • Previous severe hypoglycemia

UK Hypoglycemia Study Group, Diabetologia 2007
Cryer P et al. JCEM 2009
Seaquist ER Diabetes care 2013

Risk factors for hypoglycemia in diabetes

Physiological/Therapeutic	Behavioral
• Duration of diabetes • Old age • Negative C-peptide • Presence of comorbidities • Strict glycemic control • Impaired awareness of hypoglycemia • Previous severe hypoglycemia	• Dietary mistakes • Alcohol consumption • Exercise • Weight loss

UK Hypoglycemia Study Group, Diabetologia 2007
Cryer P et al. JCEM 2009
Seaquist ER Diabetes care 2013

Hypoglycemia in Elderly

- Hospital admission rates for hypoglycemia now exceed those for hyperglycemia among older adults among Medicare beneficiaries (Lipska et al JAMA intern Med 2014).

- In patients taking insulin, those ≥80 years were more than twice as likely as those aged 45–64 years to visit the emergency department and nearly five times more likely to then be hospitalized as a result of a hypoglycemic episode (Geller et al JAMA Intern Med 2014).

SPECIAL ARTICLE

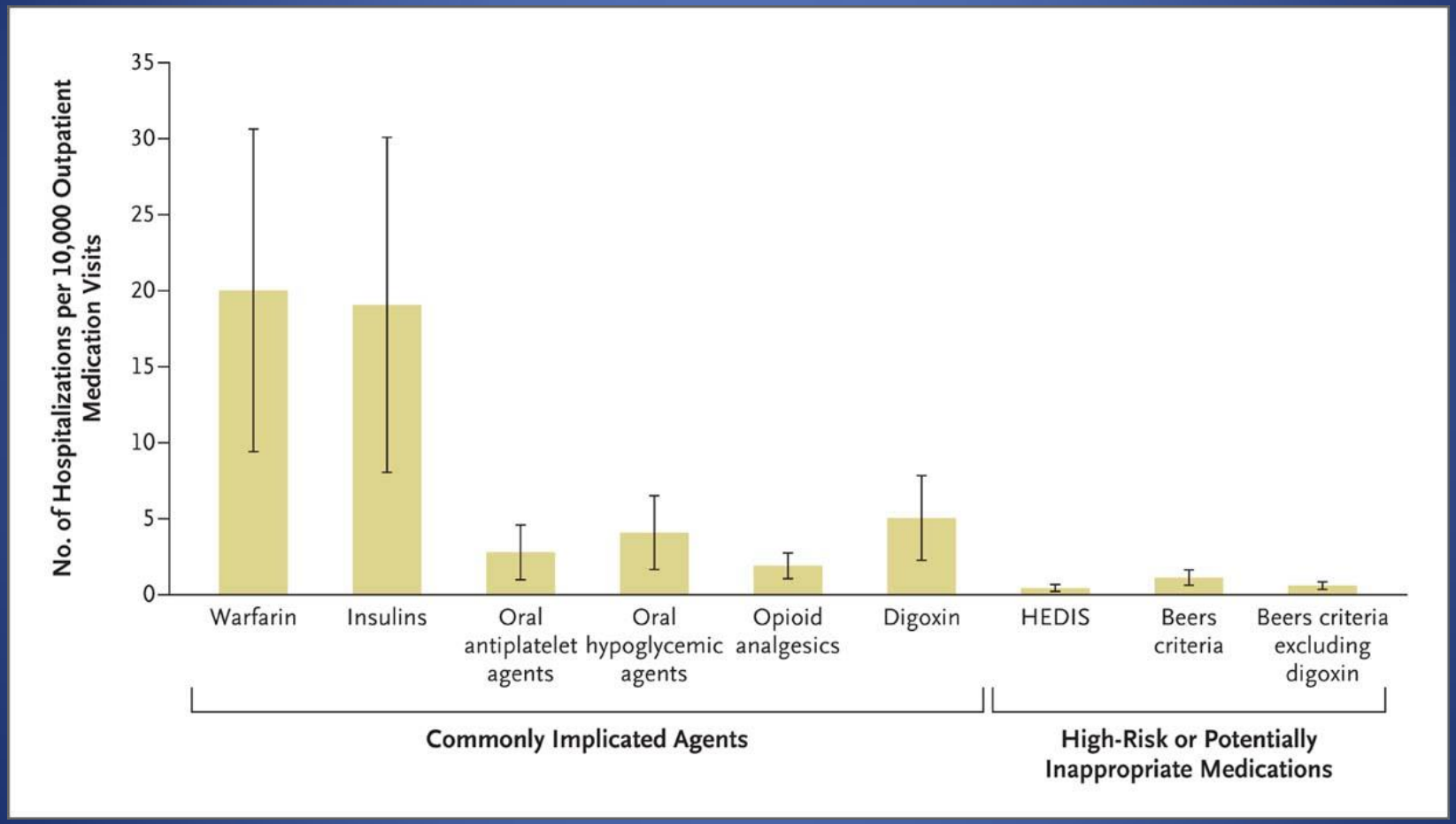
Emergency Hospitalizations for Adverse Drug Events in Older Americans

Daniel S. Budnitz, M.D., M.P.H., Maribeth C. Lovegrove, M.P.H., Nadine Shehab, Pharm.D., M.P.H., and Chesley L. Richards, M.D., M.P.H.

- This national study estimated that nearly 100,000 elderly patients were hospitalized for adverse drug events annually from 2007 through 2009.
- Most resulted from use of common medications such as warfarin and insulin.

Budnitz DS et al, NEJM 2011

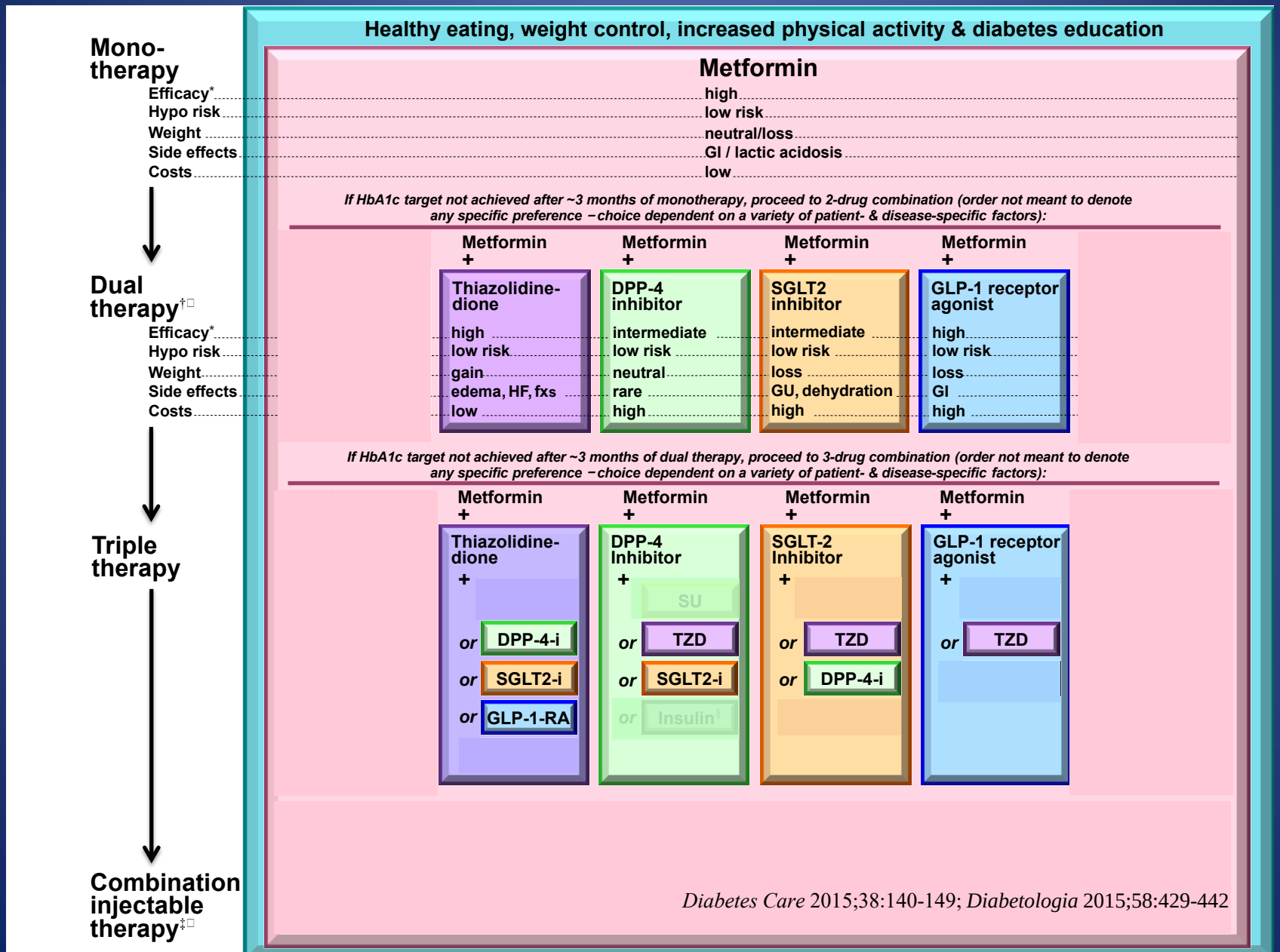
Hypoglycemia in Elderly



Budnitz DS et al, NEJM 2011

How can the risk of hypoglycemia be minimized?

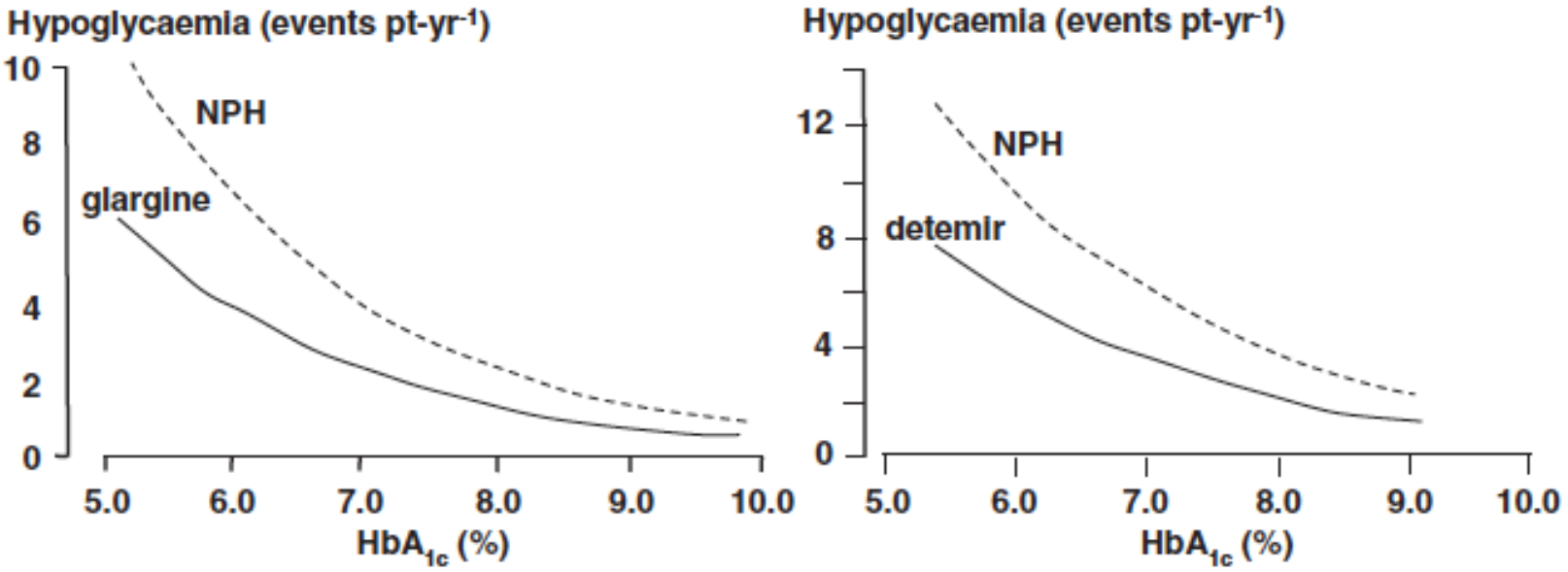
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM When Goal is to Avoid Hypoglycemia



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

Hypoglycemia and basal insulins

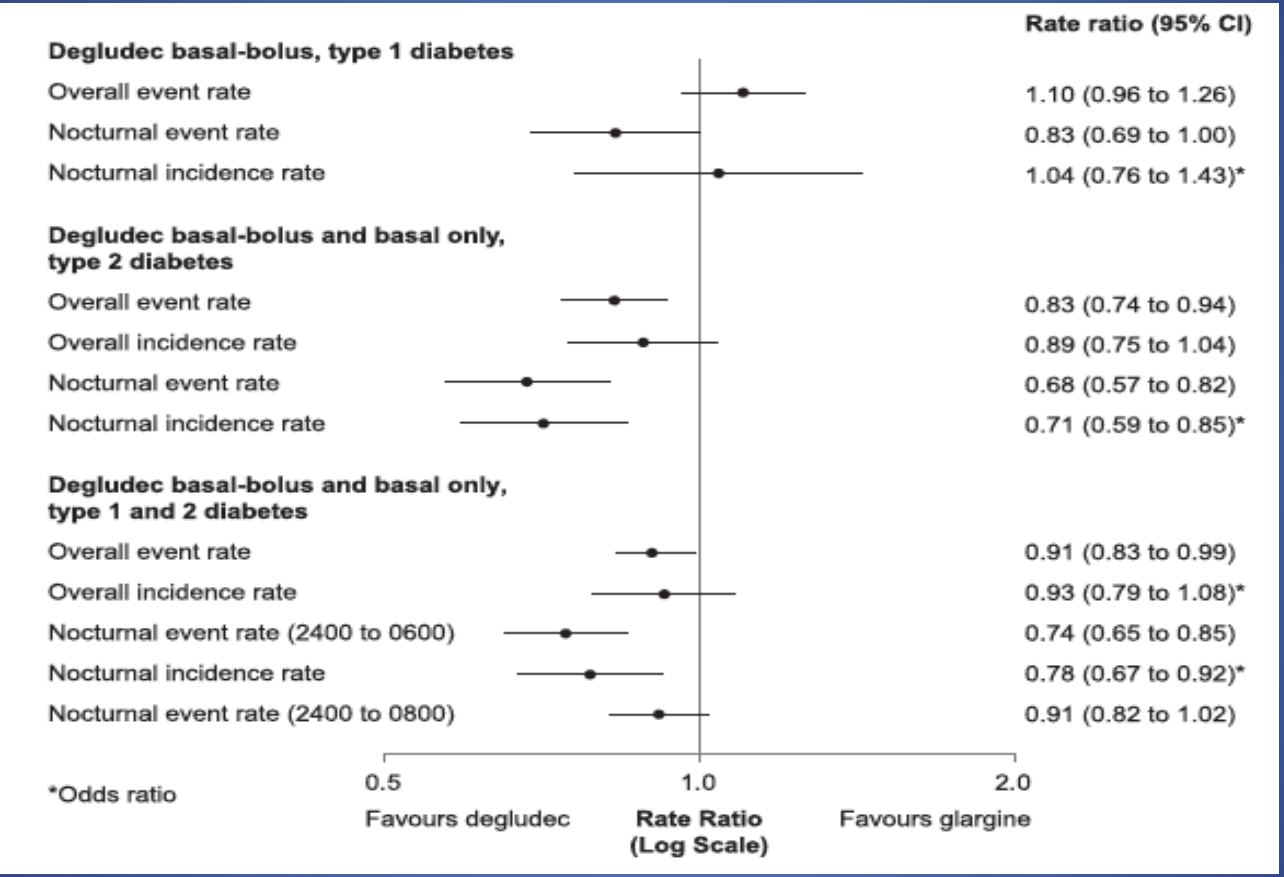
Insulin glargine and detemir cause less hypoglycemia compared to NPH



Modeled regression of hypoglycemia against HbA1c from the insulin glargine and insulin detemir type 2 diabetes treat-to-target studies.

Little S et al Diabetes Technology & Therapeutics 2011
Hermansen K et al, Diabetes Care 2006

Hypoglycemia (≤56 mg/dL) with degludec



Pooled estimates of hypoglycemia risk (degludec/glargine) and 95% confidence intervals for overall confirmed hypoglycemic episodes and nocturnal confirmed hypoglycemic episodes in phase III trials as reported in meta-analyses

Owens DR et al. Diabetes Metab Res Rev 2014

Lower rate of hypoglycemia with glargine U-300 vs U-100

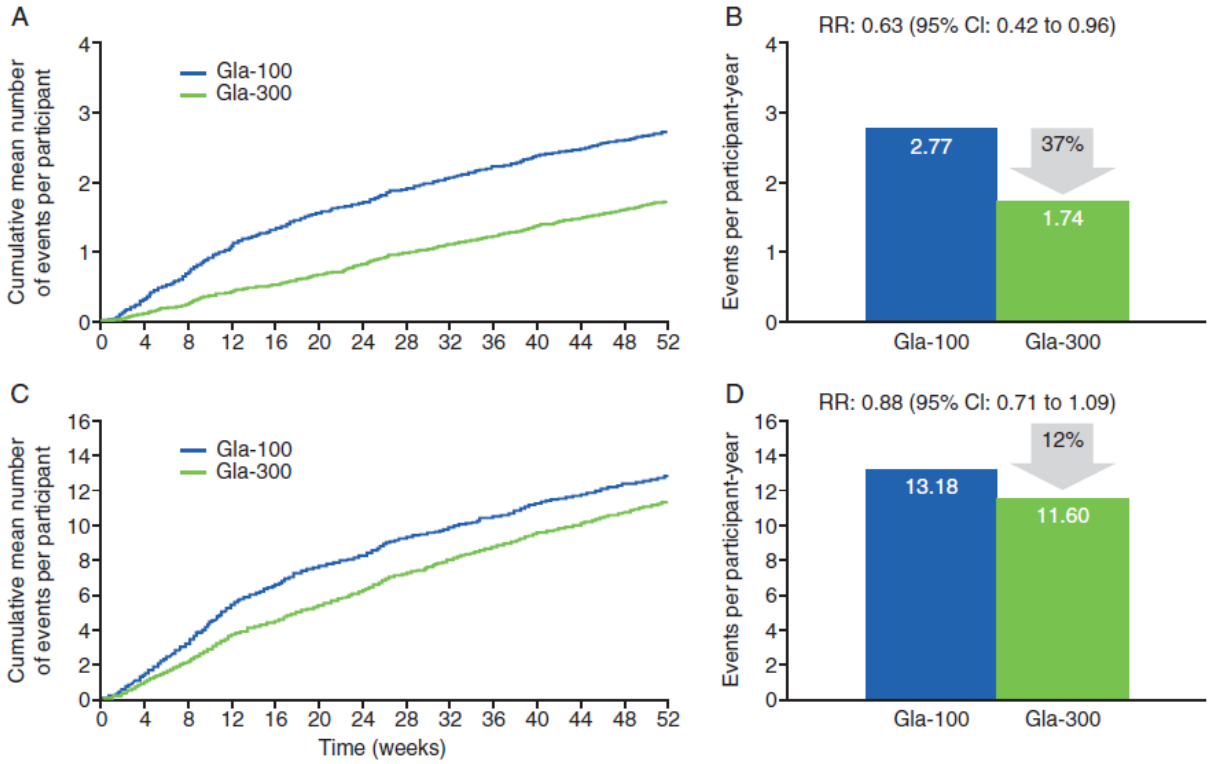
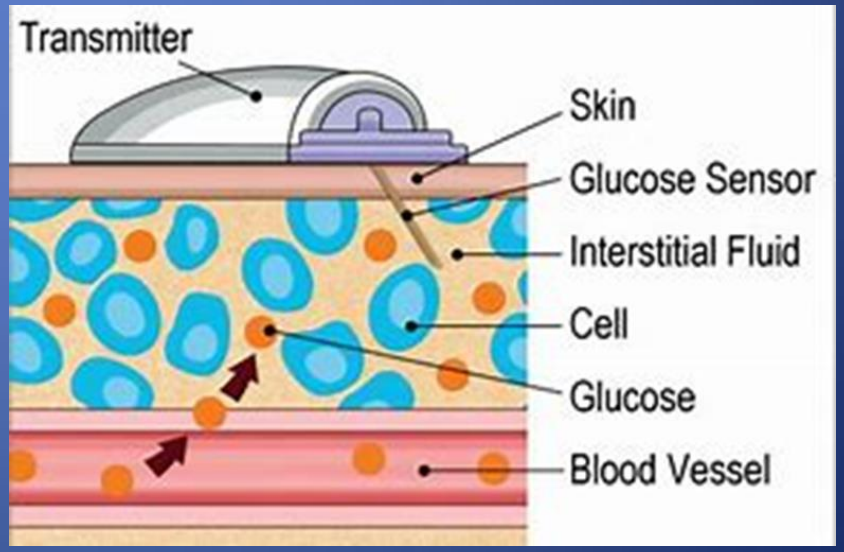


Figure 3. Confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemia. (A) Cumulative mean number of nocturnal (00:00–05:59 hours) events per participant. (B) Nocturnal events per participant-year. (C) Cumulative mean number of events per participant at any time (24 h). (D) Events per participant-year at any time (24 h; safety population). CI, confidence interval; Gla-100, insulin glargine 100 U/ml; Gla-300, insulin glargine 300 U/ml; RR, rate ratio.

Yki-Jarvinen et al 2015

Use of technology to reduce risk of hypoglycemia



Decreased hypoglycemia with continuous glucose monitor use

- 120 subjects:45% children, 55% adults
- A1C <
- Doing

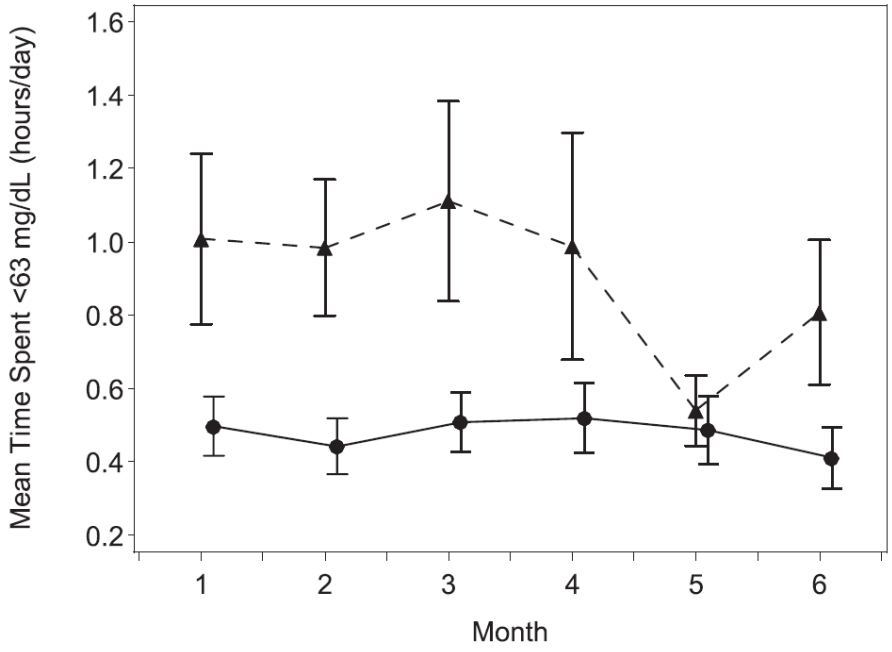


Figure 1—*Time spent below 63 mg/dL by month. Mean values ± SEs for hours per day spent <63 mg/dL over the 6-month study period in all patients. ●, continuous monitoring group; ▲, control group.*

Battelino et al. Diabetes care 2011

Real time CGM in adults with hypoglycemia unawareness on multi daily insulin injections

- 149 participants
  - 74 assigned to control group
  - 75 to rtCGM
- 26 week study

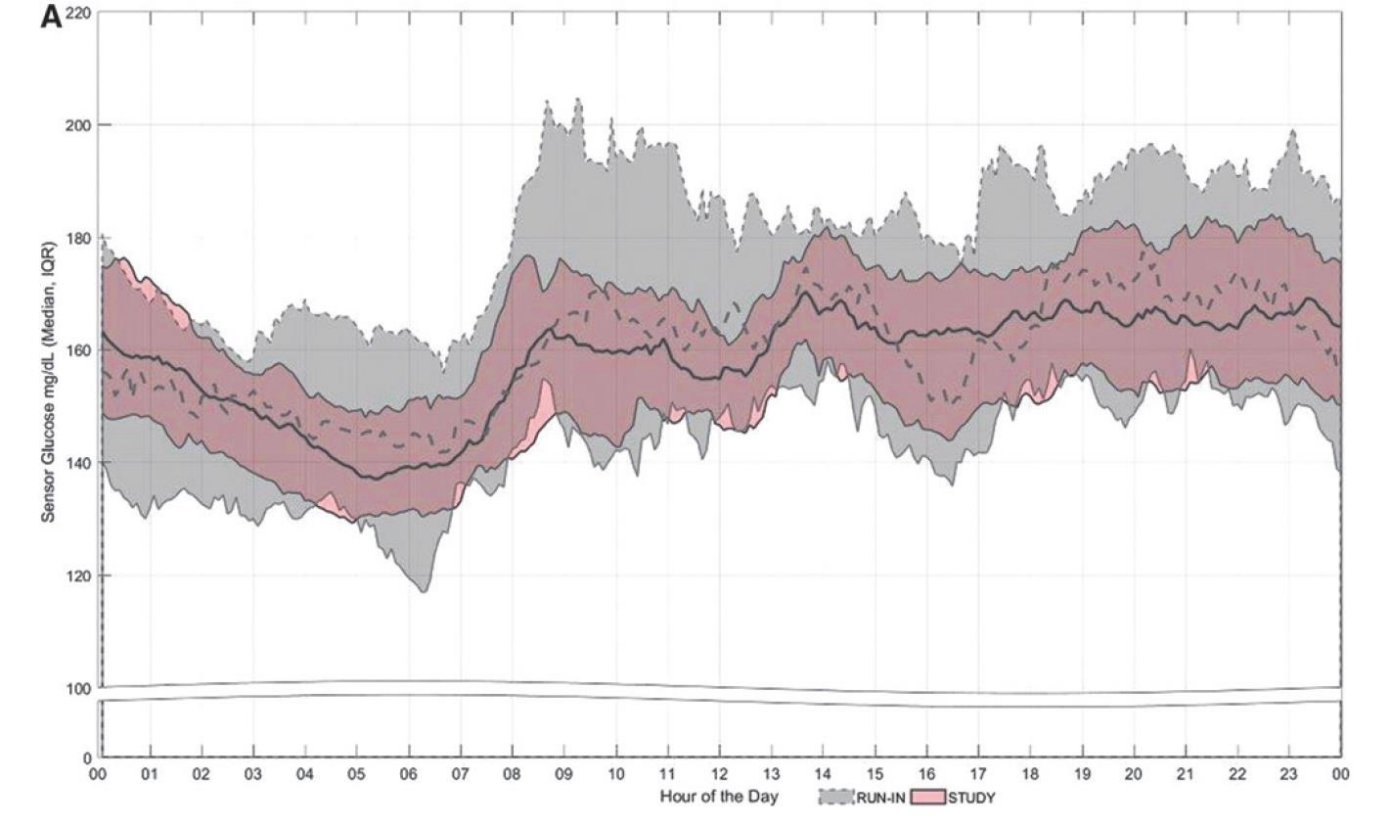
	Baseline		26 week follow up		P value
	Control	rtCGM	Control	rtCGM	
<70 mg/dl	6.9%	5.0%	6.4%	1.6%	<0.0001
CV	40.5%	39.3%	41.4%	34.1%	<0.0001

Heinemann et al Lancet 2018

Hybrid Closed Loop System

- Self-adjusting basal rate based on sensor glucose readings
- Low-threshold suspend technology to help avoid lows

Hybrid Closed Loop System



Garg et al Diab Tech Ther 2017

Hybrid Closed Loop System (670 G)

		Daytime < 70 mg/dl			Nighttime <70 mg /dl		
n	age	Control	Closed loop	p	Control	Closed loop	p
94	45±13	6.4%	3.4%	<0.001	6.6%	3.2%	<0.001
30	16±2	4.3%	2.8%	<0.001	5.8%	2.9%	0.002

Garg et al Diab Tech Ther 2017

Conclusions

- In both type 1 and type 2 diabetes, hypoglycemia is associated with decrement in cognitive function.
- People at the extremes of age appear to be at higher risk of hypoglycemia related cognitive decline.
- Providers should routinely evaluate patients regarding the risk and history of hypoglycemia.
- Clinical judgment must be used in selecting glucose target and therapeutic regimen to reduce risk of hypoglycemia.