DEMENTIA, ANOTHER COMPLICATION OF DIABETES

Naushira Pandya M.D., CMD, FACP
Professor and Chair
Department of Geriatrics
Director, Geriatrics Education Center
Nova Southeastern University College of Osteopathic Medicine

International Conference on Geriatrics & Gerontology
July 8-10, 2014 , Chicago, USA

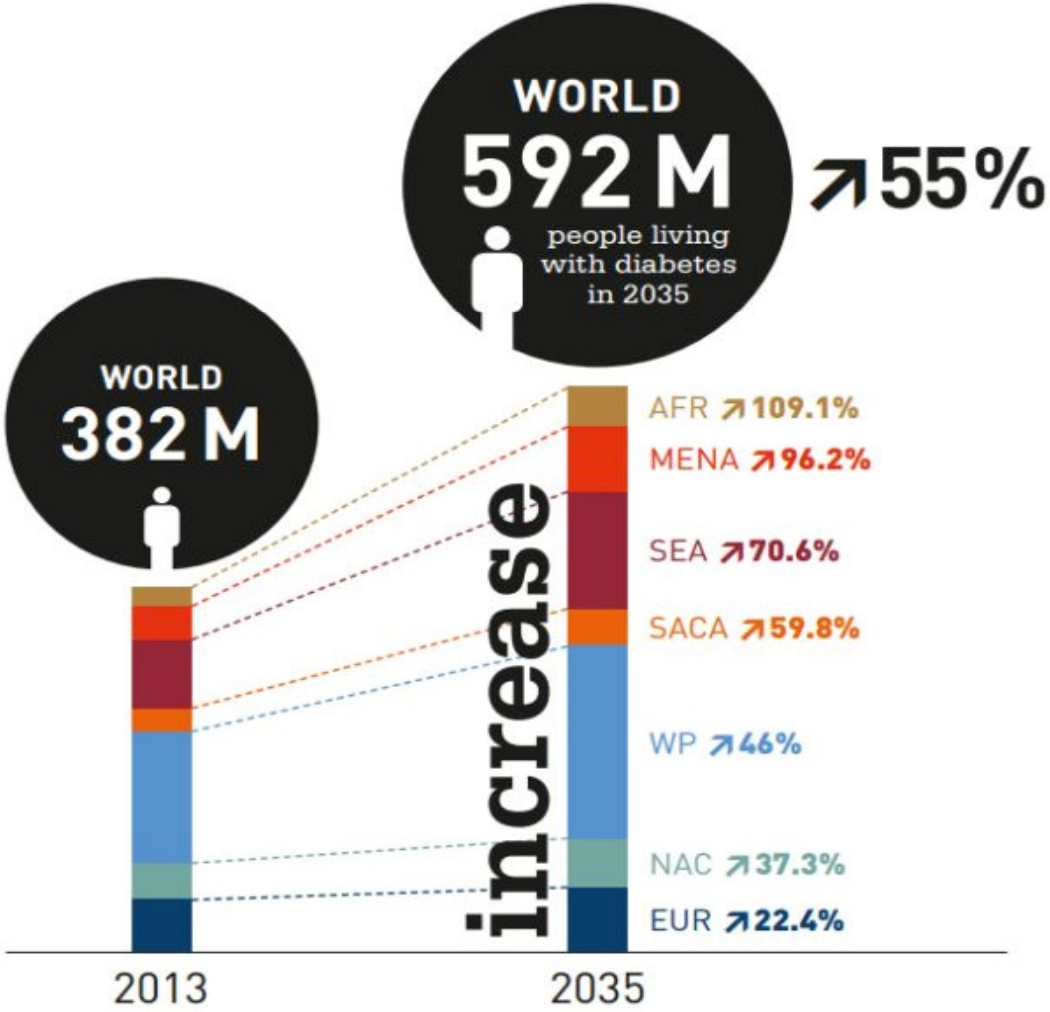
NOVA SOUTHEASTERN UNIVERSITY
College of Osteopathic Medicine

the GREAT GEC

Disclosures

- Dr. Pandya has no relevant disclosures

Diabetes Prevalence Worldwide (IDF 2013)



80% live in low income countries

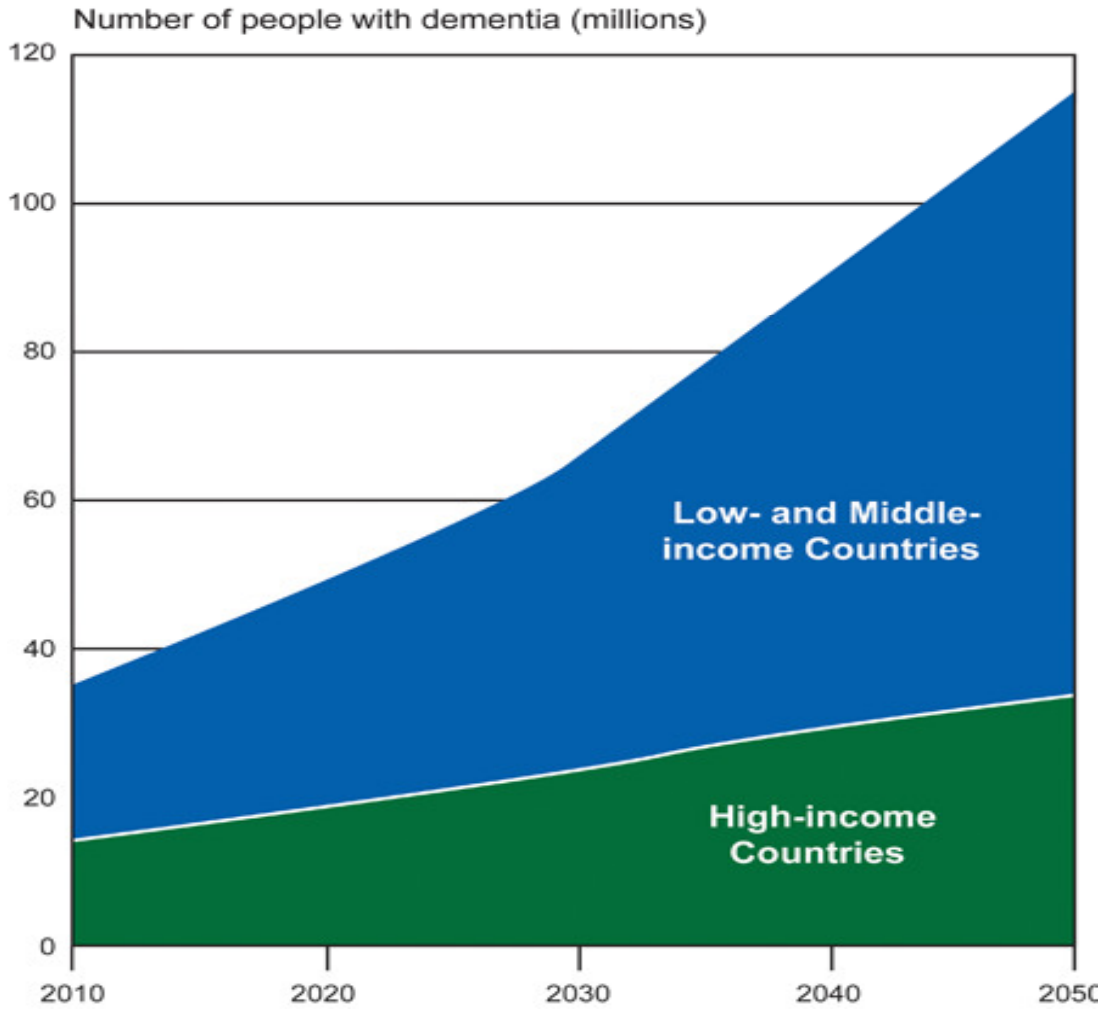
4M deaths yearly

IDF defines mental health to include mental and neurological disorders, including depression, anxiety, dementia and Alzheimer's

Diabetes and mental health; two global tsunamis that fuel each other

Improved coordination between the responses to diabetes, NCDs and mental health

Dementia Prevalence Worldwide is Increasing



Alzheimer's Disease International, *World Alzheimer Report, 2010*. Available at: http://www.alz.co.uk/research/files/WorldAlzheimerReport2010

Emerging complications of diabetes



- Improvement in management of microvascular complications (due to improved glycemic, and blood pressure control) and macrovascular complications (improved lipid control also)
- People with diabetes are living longer
- Emergence of novel complications such as cognitive impairment and dementia
- Mediated by mechanisms not addressed by conventional therapies

Diabetes and Dementia

- Type 1 Diabetes: mild to moderate slowing of mental speed and diminished mental flexibility
- Type 2 Diabetes: cognitive changes affect ***learning, memory,*** mental flexibility and mental speed
- The rate of cognitive decline is accelerated in elderly people with type 2 diabetes
- T2 DM or impaired fasting glucose may be present in 80% of people with Alzheimer's disease

Janson et al, Diabetes 2004;83

Risk of Dementia among Persons with DM

- 1970 Rochester MN study of 1445 cases of DM2 followed for 9981 person years
- Persons with DM2 exhibited increased risk of developing dementia (RR 1.66)
- Risk of Alzheimer's was also increased (RR 2.27 in men and 1.37 in women)

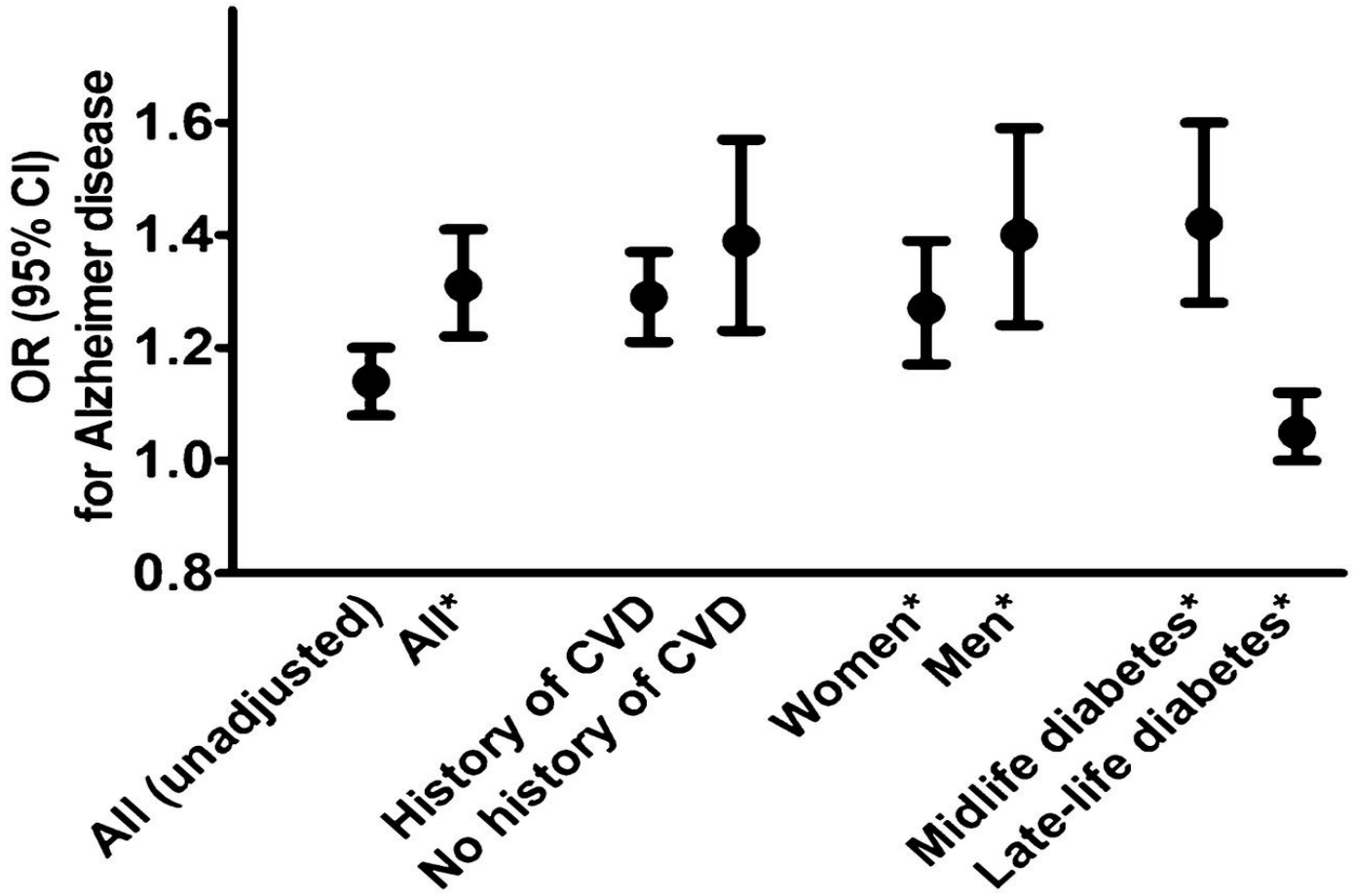
Leibson et al. Am. J. Epidemiol. (1997) 145 (4)

History of Medically Treated Diabetes and Risk of Alzheimer Disease in a Nationwide Case-Control Study

- Information on diabetes medication reimbursement (both type 1 and 2 DM) of all Finnish individuals also reimbursed for AD medication in 2005 (*n* = 28,093) and their AD-free control subjects during 1972–2005 was obtained
- 12.0% of AD subjects had DM compared to 10.7% in controls
- People with AD were more likely to have DM than matched controls subjects (OR 1.14), even after adjusting for CV diseases (OR 1.31)
- ***The associations were stronger with diabetes diagnosed at midlife (OR 1.60) compared to OR 1.25 for late-life***

Tolppanen A et al. Diabetes Care 2013;36:2015-2019

Association between diabetes and incident AD in the whole study population, according to previous cardiovascular disease (CVD), sex, and onset age of diabetes. *Adjusted for cardiovascular diseases.



Tolppanen A et al. Dia Care 2013;36:2015-2019

American Diabetes Association.

Copyright © 2011 American Diabetes Association, Inc.

Assessing the risk of dementia with diabetes

- Metanalysis of 16 studies
- Incidence of ***any dementia*** was increased in people with diabetes in 5 of 7 studies
- Overall, the incidence of dementia was increased by 50-100% relative to people without diabetes (CV factors not controlled in all)
- Increased risk of Alzheimer's disease by 50-100% (7 of 11 studies)
- Increase in risk of vascular dementia of 100-150% (6 of 7 studies)

Biessels et al. Lancet Neurology 5(1); Jan 2006

Link between Diabetes and Dementia in Institutionalized Populations

- Audit of 11 nursing homes in Coventry, UK
  - 16% had diabetes
  - Of those, 56% had some form of dementia

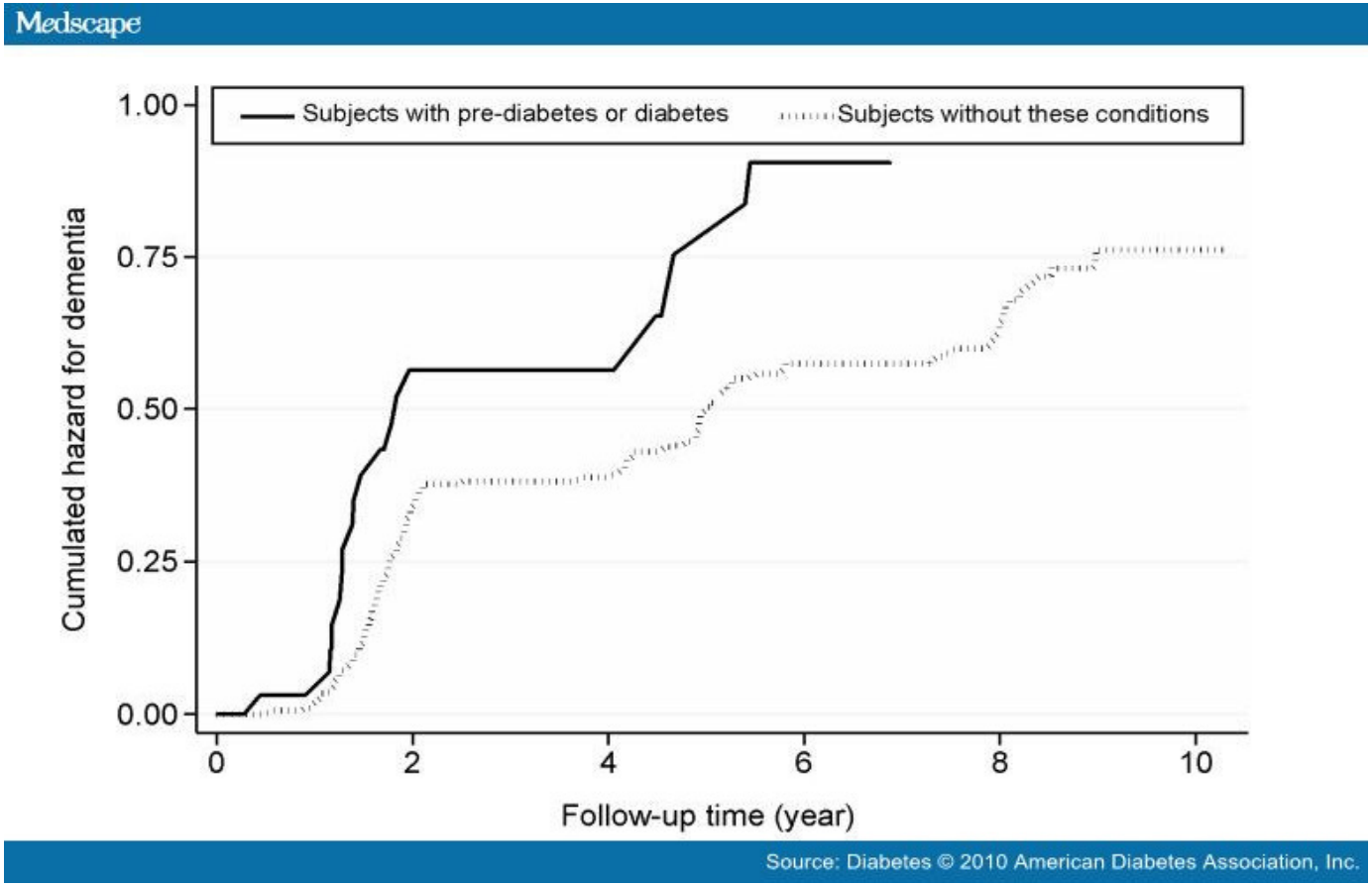
    Velayudhan L et al. Br J Psych 2010

- 8.2 % of patients in British nursing homes had undiagnosed diabetes
  - But in those with dementia, the prevalence rose to 13%

    Aspray JA; Diab Care 2006

Accelerated Progression from Mild Cognitive Impairment to Dementia in People with Diabetes

Weili Xu et al. Diabetes. 2010;59(11):2928-2935



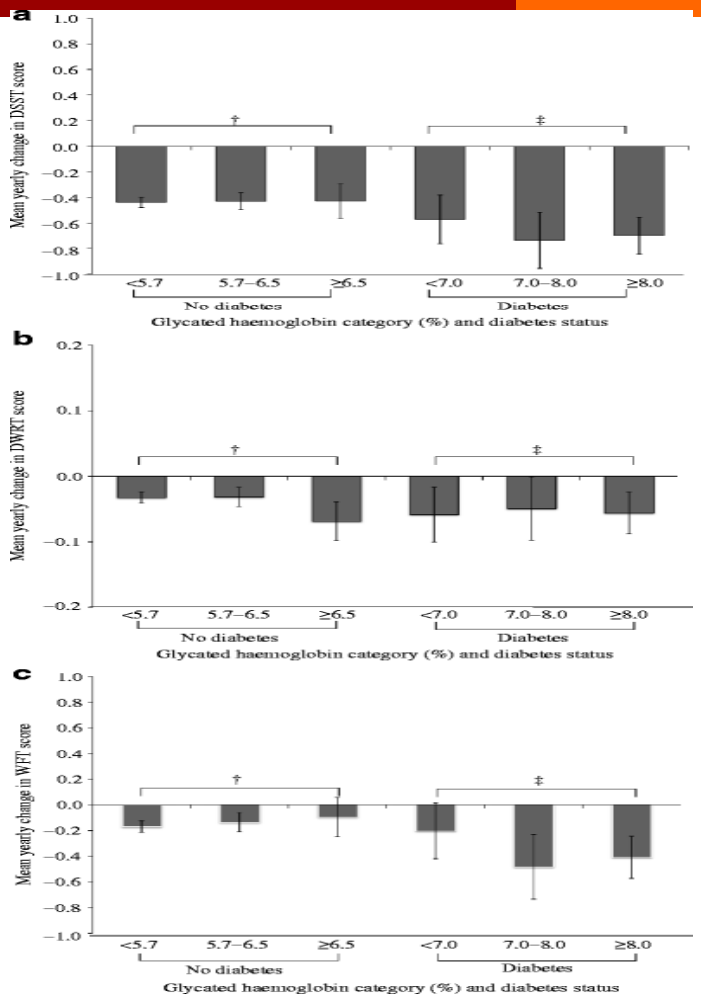
Predictors of cognitive impairment and dementia in older people with diabetes

- Surviving participants of the Fremantle Diabetes Study (FDS), who were aged 70 years
- Of 302 participants, 28 (9.3%) had dementia (16 with probable Alzheimer's disease) and 60 (19.9%) had cognitive impairment without dementia
- The major independent longitudinal predictors of dementia were
  - older age (per decade; odds ratio 4.0)
  - diabetes duration (for each 5 years; odds ratio 1.69)
  - peripheral arterial disease (odds ratio 5.35)
  - exercise (which was protective; odds ratio 0.26)
  - **For Alzheimer's disease, diabetes duration was an independent predictor in addition to age and diastolic blood pressure**

Bruce et al. Diabetologia Feb 2008

Glycated hemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study

Christman et al. Diabetologia 2011; 54

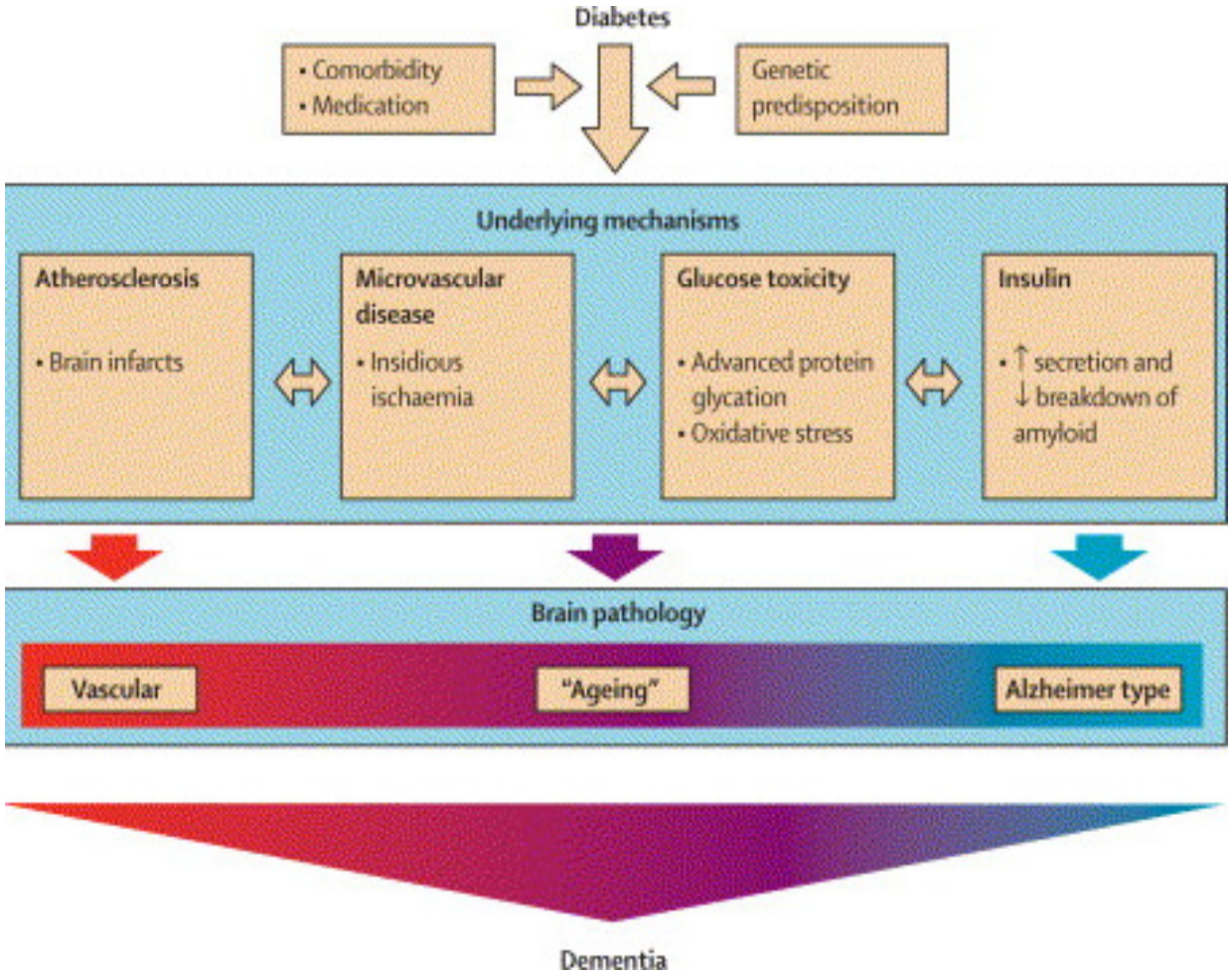


- Mean age 56 years.
- Women 56%, 21% black
- Mean HbA1c 8.5% in DM, and 5.5% controls
- Diagnosed diabetes was associated with cognitive decline on the DSST (OR 1.42, $p = 0.002$),
- But HbA1c was not a significant independent predictor of cognitive decline when stratifying by diabetes diagnosis (diabetes, p trend = 0.320; no diabetes, p trend = 0.566)

DSST=digit symbol substitution test
DWRT= delayed word recall test
WFT=word fluency test

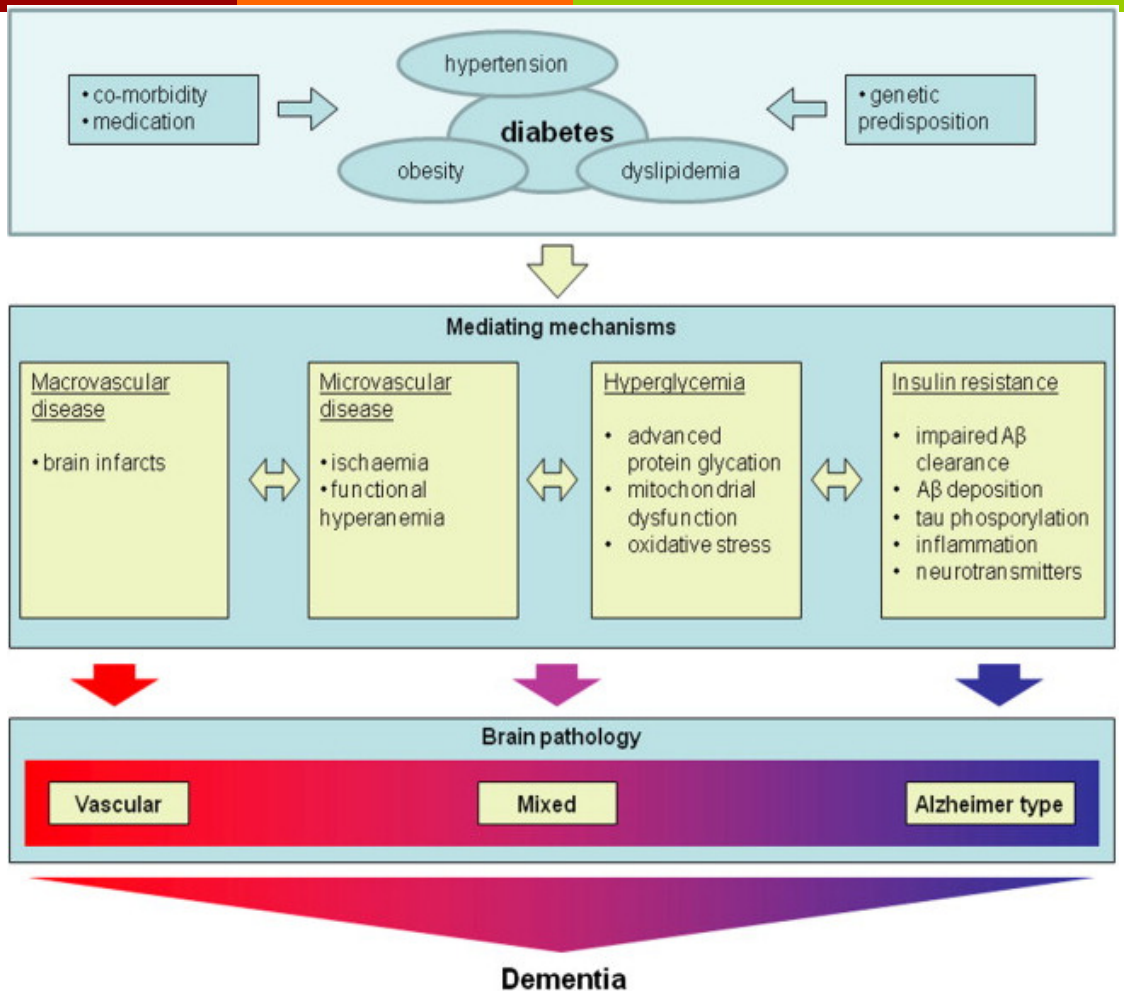
Determinants of the risk of dementia in individuals with diabetes.

Biessels et al. Lancet Neurology 5(1); Jan 2006



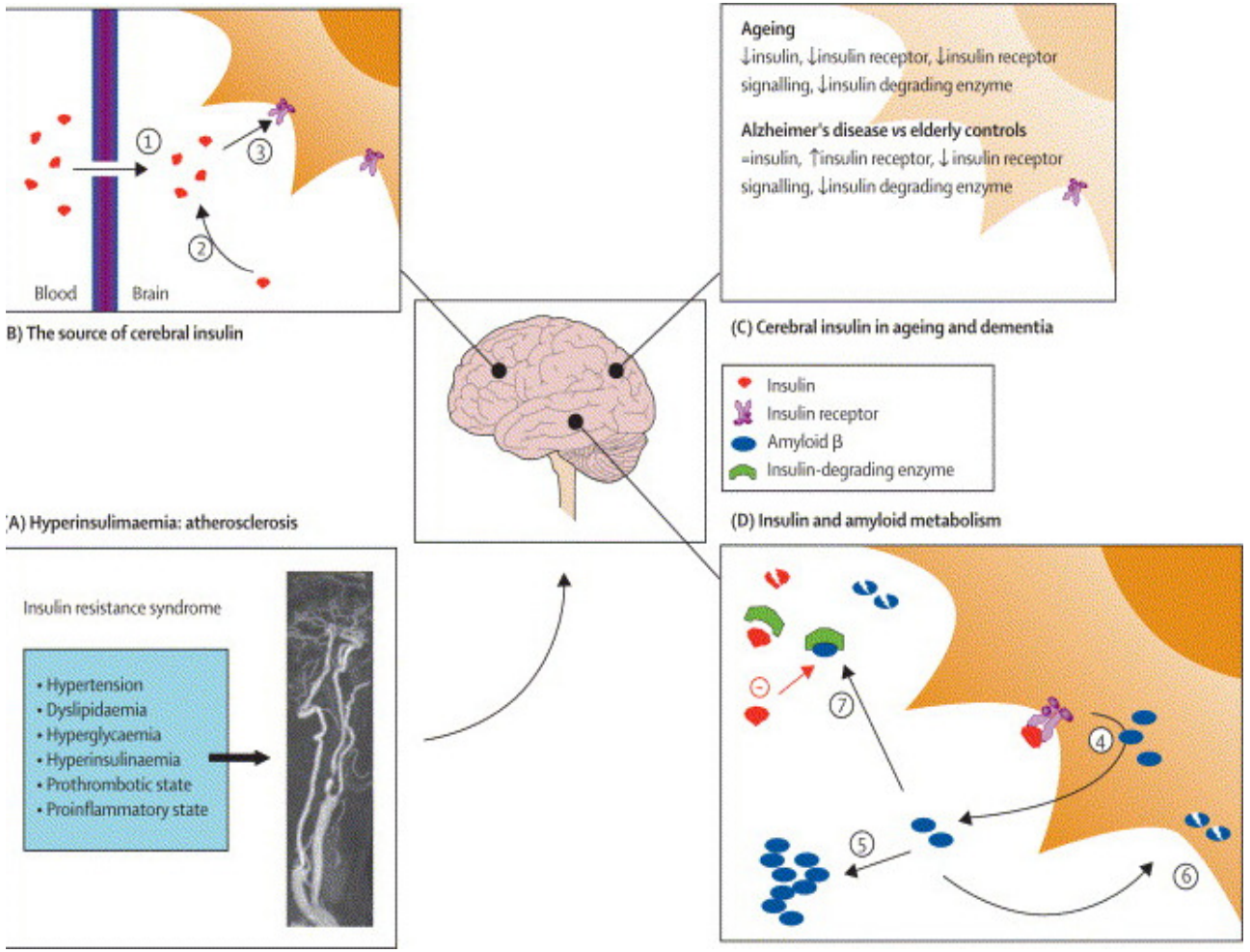
Mechanisms that may link diabetes and dementia

Exalto et al. Exp Gerontol. 47 (11) Nov 2012



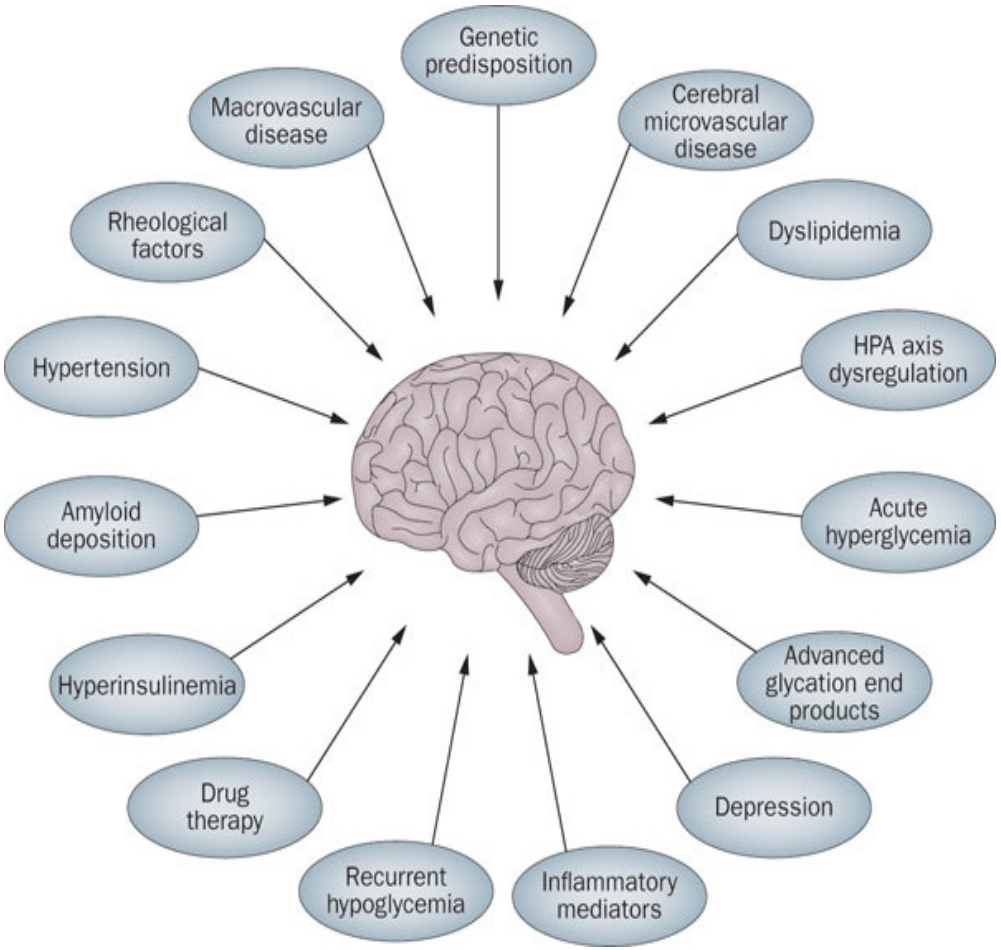
The potential role of insulin in the pathogenesis of dementia

Biessels et al. Lancet Neurology 5(1); Jan 2006



Potential mediators of cognitive impairment in patients with type 2 diabetes mellitus.

Nature Endo Rev 7; Feb 2011

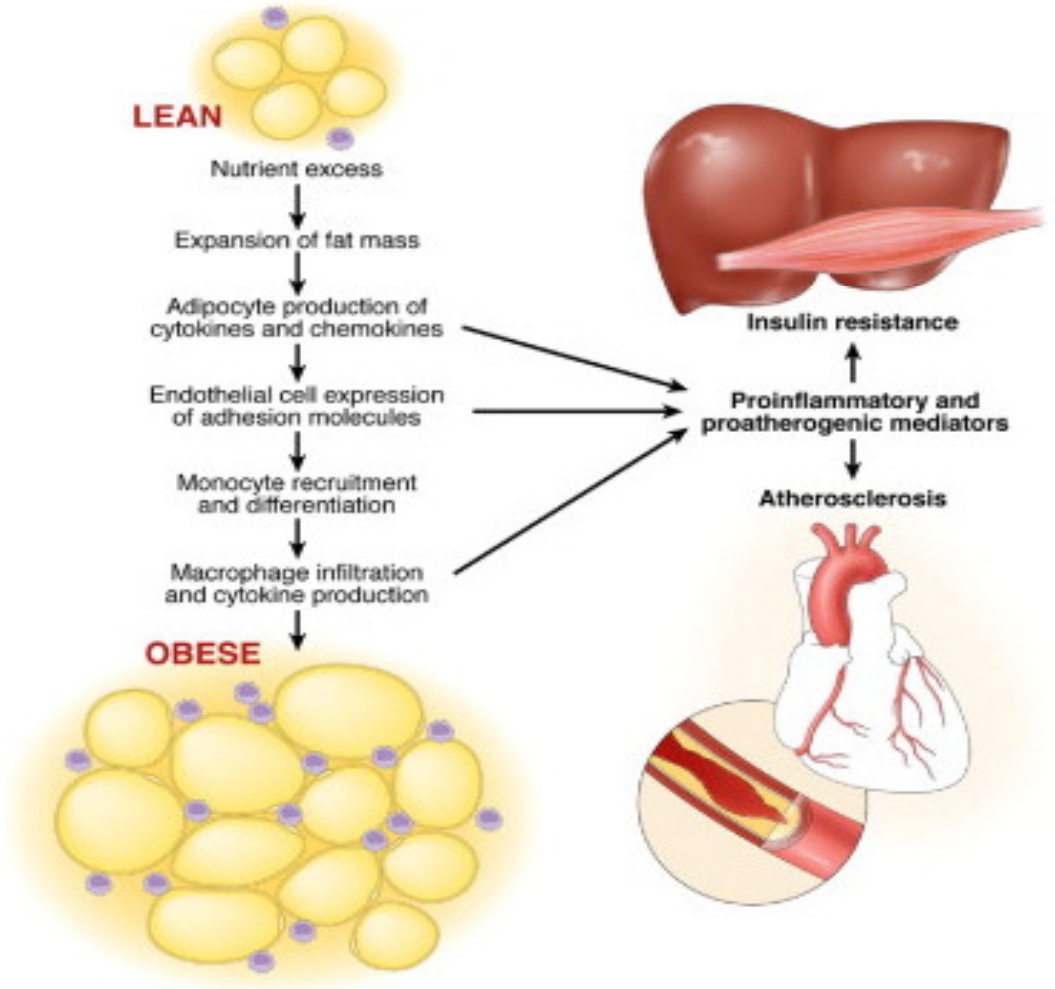


The role of inflammation

- Inflammation is now thought to be involved in insulin resistance and the development of diabetes
- Human studies point towards increased inflammatory biomarkers (IL-6 and TNF) and age-related cognitive impairment
- One cross-sectional study in T2DM suggests association between cognitive ability and Il-6

Potential mechanisms for obesity induced inflammation

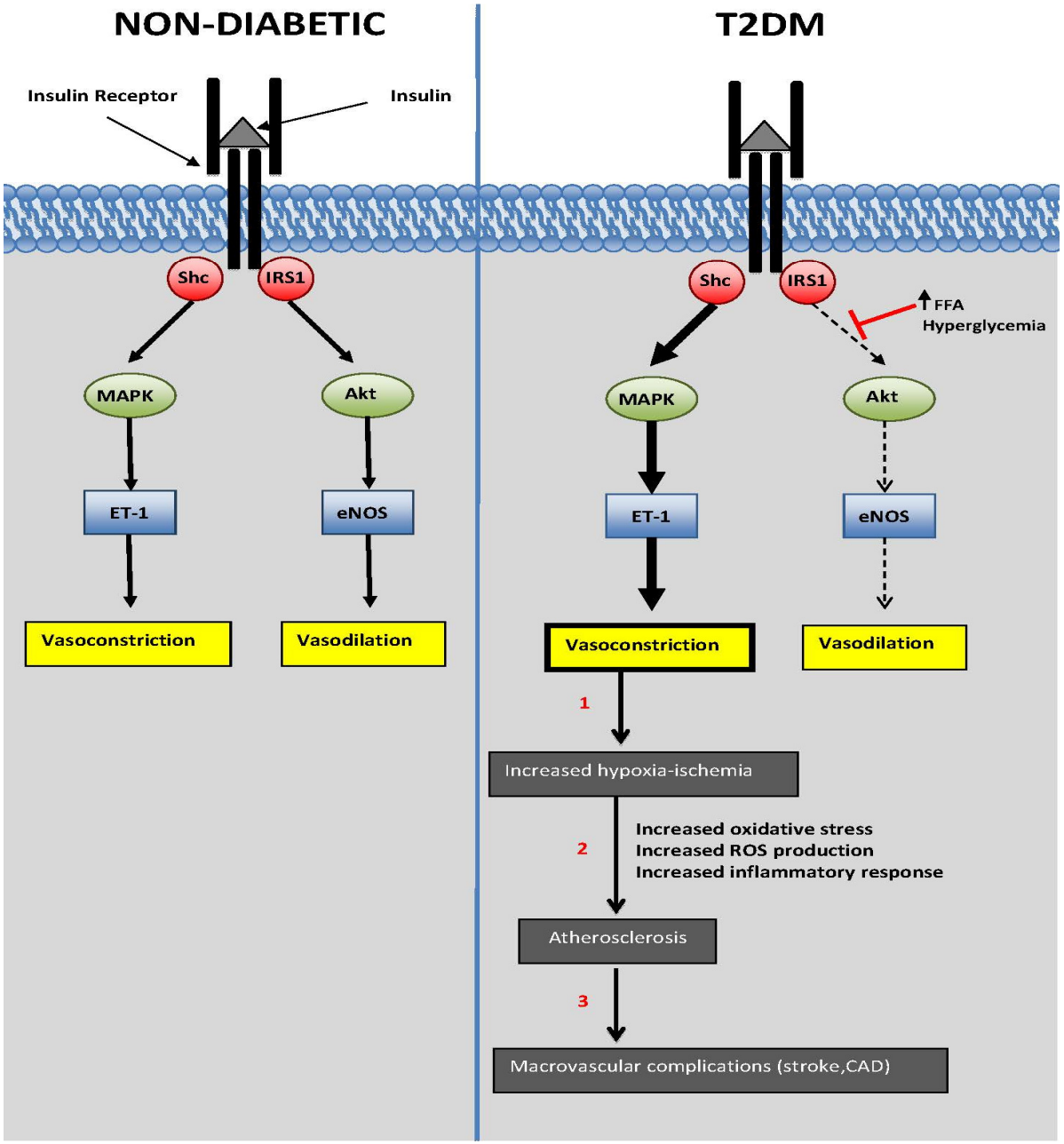
Shoelson et al. Gastroenterol 132(6) May 2007



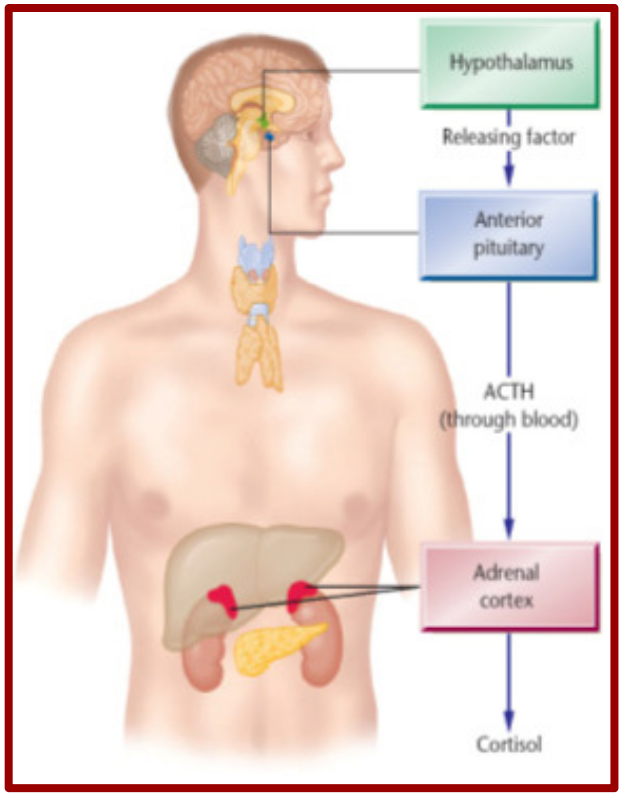
T2DM is associated with the development of vascular dysfunction in the brain.

T2DM is a risk factor for microvascular complications as well as macrovascular defects such as stroke

Chap 16; Mental and Behavioral disorders; Diseases of the Nervous System Feb 2013



Hypothalamic-pituitary-adrenal dysregulation in diabetes



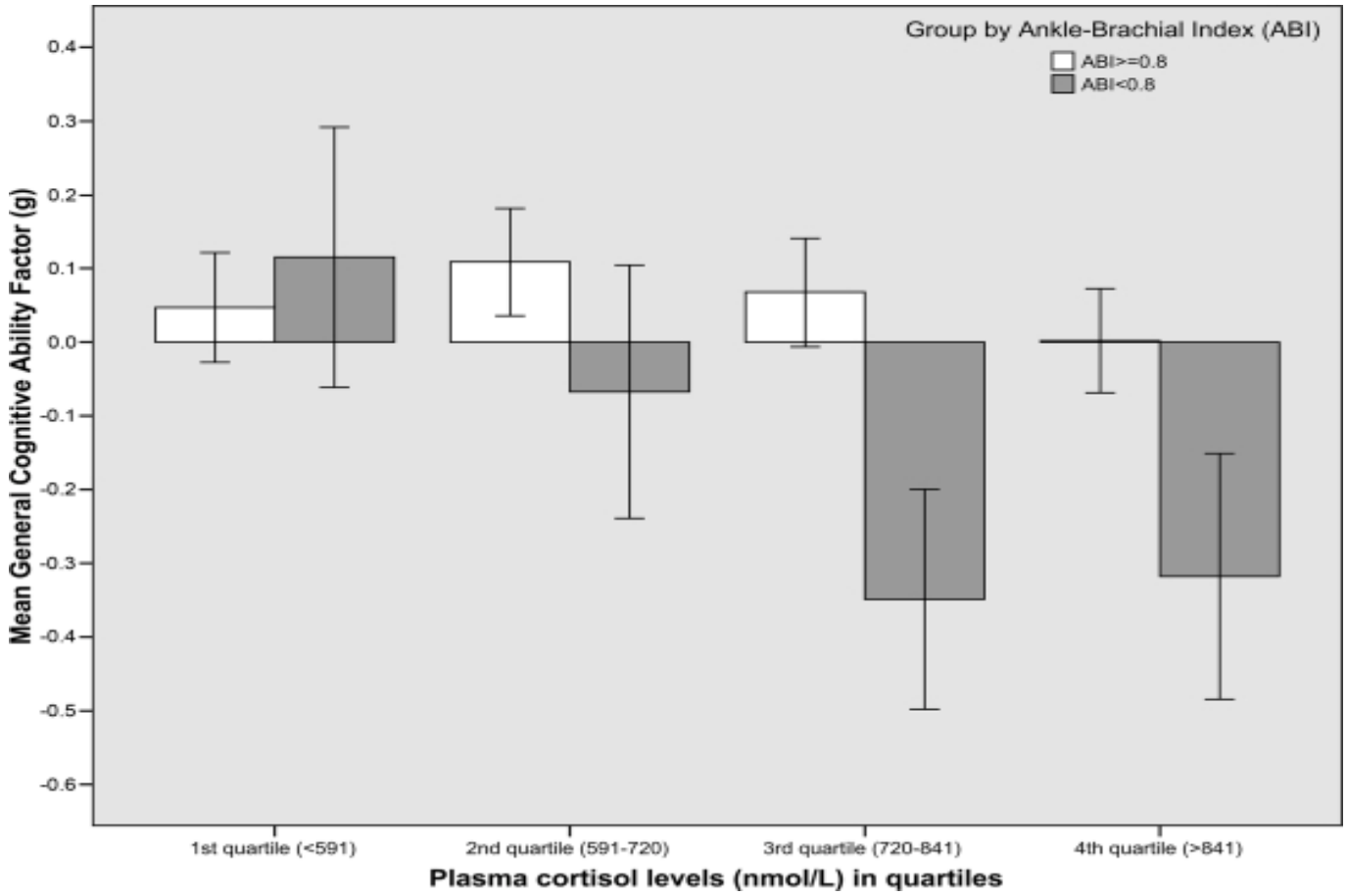
- People with T2DM have activation of the hypothalamic-pituitary-adrenal (HPA) axis
- Raised levels of cortisol and adrenocorticotrophic hormone (ACTH)
- Increased cortisol levels are associated with increased heart disease and diabetic complications
- Dysregulation of the HPA axis may be associated with accelerated cognitive decline and mood disturbances in patients with T2DM

Glucocorticoids and cognitive decline

- Chronic exposure of the hippocampus to high levels of glucocorticoids (cortisol) thought to contribute to age-related cognitive decline
- Also patients with Alzheimer's have high cortisol levels and low hippocampal volumes
- Studies in T2DM suggest high cortisol levels are associated with accelerated cognitive decline, reduced working memory, processing speed, mental flexibility, immediate and delayed memory (Edinburgh Type 2 Diabetes Study)

Morning cortisol levels and cognitive abilities in people with Type 2 diabetes: the Edinburgh Type 2 diabetes study

Diabetes Care 33;714-720. 2010



Glucocorticoids and depression

- Depression is a well-established risk factor for cognitive impairment
- Depression is more common in people with DM
- High cortisol levels and more depressive symptoms were associated with high blood glucose levels in people with DM
- This effect was stronger in African American participants (who have a high incidence of both diabetes and depression) than in white individuals[1]
- Is depression due to neurotransmitter changes from metabolic changes in DM, or due to cerebrovascular disease?
- **Relation between Type 2 DM and depression may be bidirectional; type 2 DM may develop from depression[2]**

1. Boyle, S. H. et al. *Diabetes Care* 30, 2484-2488 (2007)

2. Myint, Aye Aye et al. *Science* 2.3, 114-121(2013)

What can be done to reduce the development of dementia in diabetes?

- Blood pressure control?
- Better control of diabetes?
- Avoidance of hypoglycemia
- Statins?
- Treat depression?

Does treatment of diabetes make a difference?

- **Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years** (Logroscino et al. BMJ 2004, Mar 6)
- Nurses' health study in the US; two cognitive interviews were carried out by telephone during 1995-2003
- Women with type 2 diabetes performed worse on all cognitive tests than women without diabetes at baseline (odds ratios 1.34)
- In contrast, women with diabetes who were on oral hypoglycaemic agents performed similarly to women without diabetes (OR 1.06 and 0.99)
- Women not using any medication had the greatest odds of poor performance (OR 1.74 and 1.45)
- Women with type 2 diabetes have about 30% greater odds of poor cognitive function than those without diabetes, with a 50% increase after 15 years' of diabetes

Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND)

- Participants (aged 55–80 years) with T2DM, high HbA_{1c} concentrations (>7·5%; >58 mmol/mol), and a high risk of cardiovascular events
- The Digit Symbol Substitution Test (DSST) score, at baseline and at 20 and 40 mth and total brain volume (TBV) by MRI, as a primary brain structure outcome
- There was ***no significant treatment difference*** in mean 40-month DSST score (difference in mean 0·32, 95%;p=0·2997)in the intensive and standard BP arms, or the fenofibrate arms
- The intensive-treatment group had a greater mean TBV than the standard-treatment group (4·62, 2·0 to 7·3; p=0·0007)

Lancet Neurology, The, 2011-11-01, Volume 10, Issue 11

Limitations of ACCORD MIND

- Participants were over age 55 with established CV complications or risks; intervention may be too late
- Benefits of hyperglycemia may have been offset by increased incidence of hypoglyemia
- The 40 mth follow up period may be too short
- Suggest trials that utilize agents that do not lead to hypoglycemia

Strachan and Price. *Nat. Rev. Endocrinol.* 10,258–260 (2014)

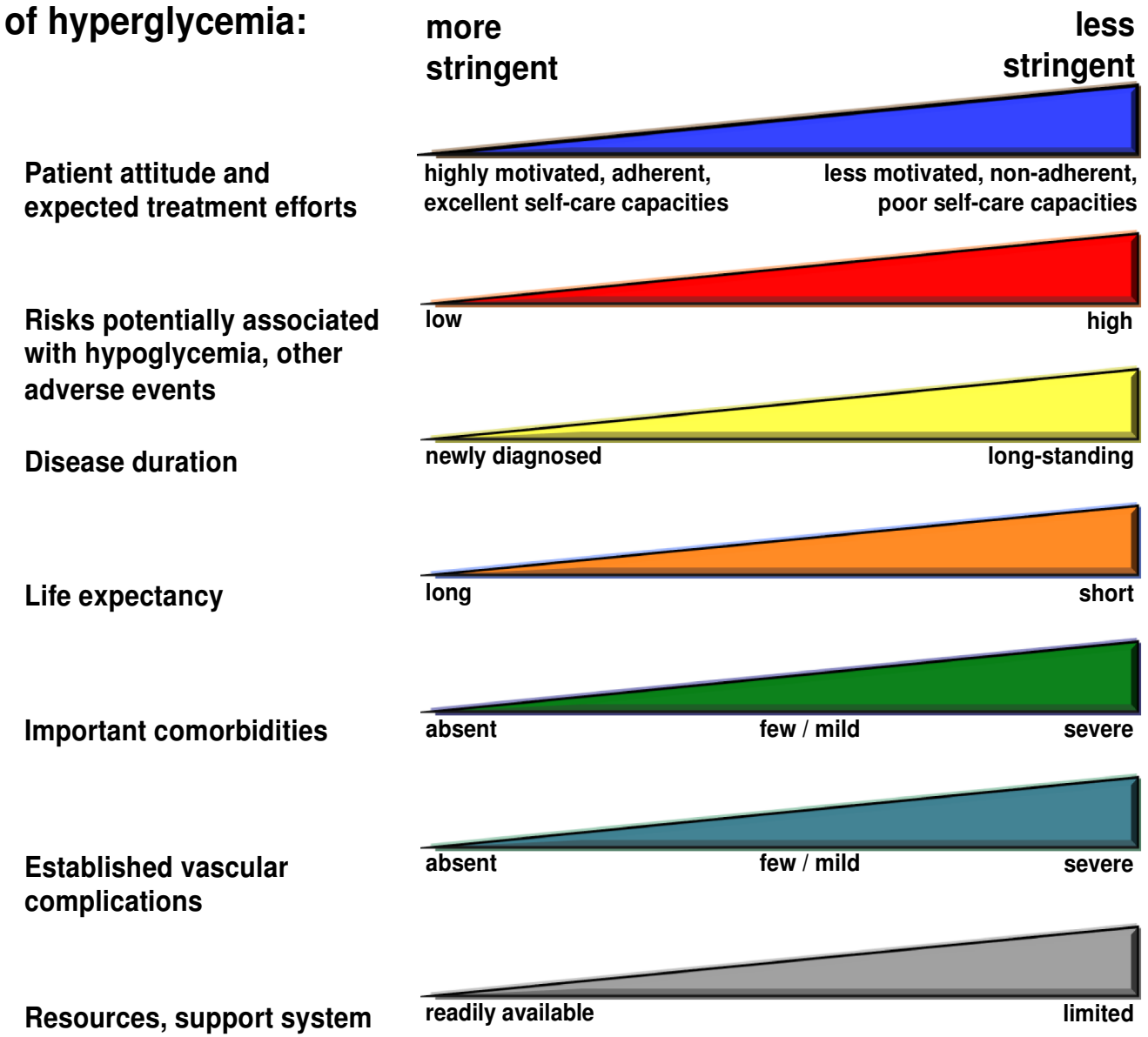


Figure 1

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]
(Adapted with permission from: Ismail-Beigi F, et al. *Ann Intern Med* 2011;154:554)

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

- **Age: Older adults**
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia

✓ Less ambitious targets
✓ HbA1c <7.5–8.0% if tighter targets not easily achieved
✓ Focus on drug safety

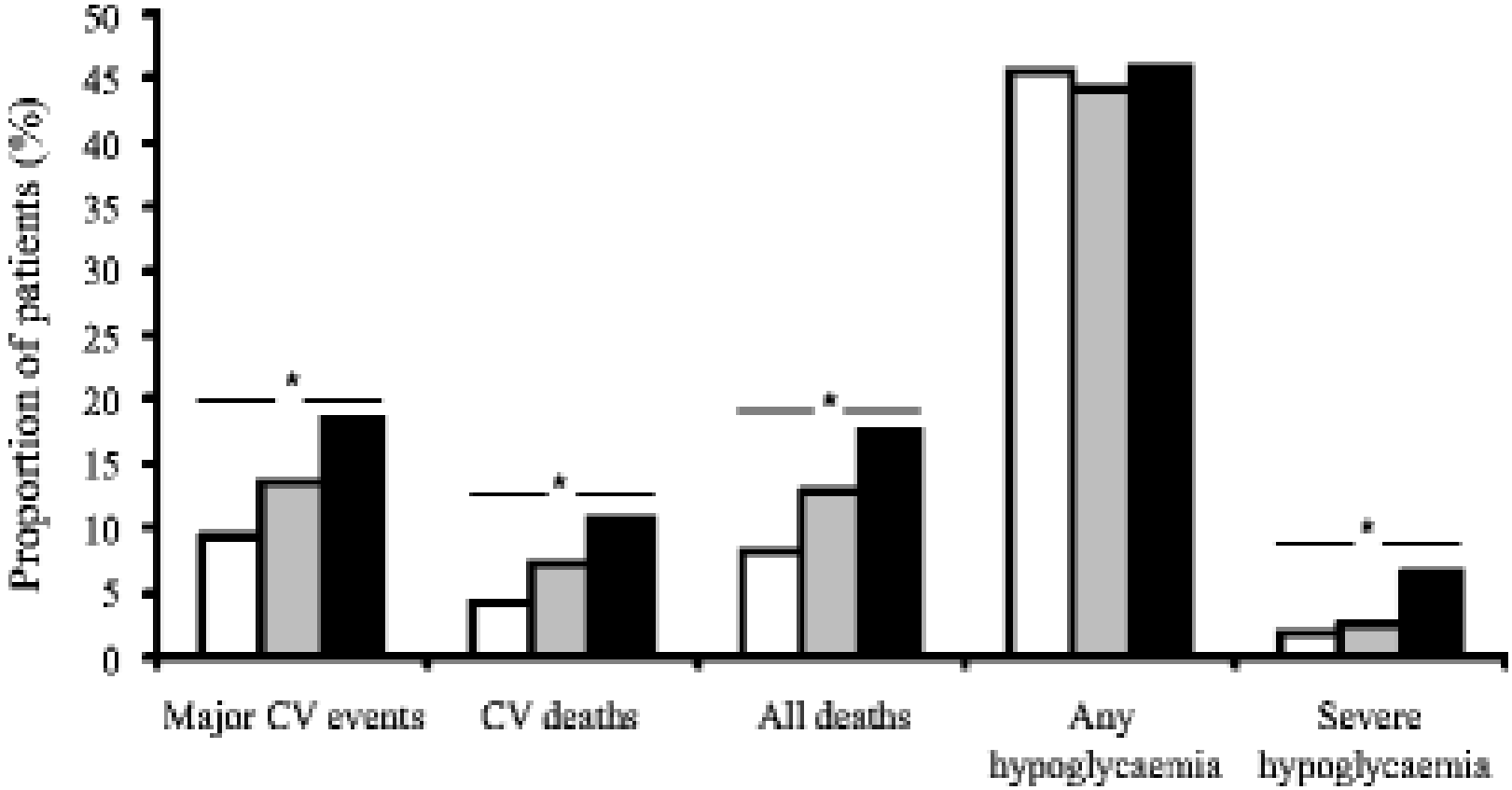
Diabetes Care, Diabetologia. 19 April 2012

Cognitive impairment affects management of diabetes and treatment-related complications

- Less involvement on diabetes self-care and monitoring
- Medication and dosing errors; complex insulin regimens..
- Active management to passive non-management
- Increased likelihood of severe hypoglycemia
- Increased risk of major cardiovascular events and death
- Increased risk of injurious falls
- We need efficient screening tools and to establish whether early detection can improve long-term outcomes

Proportion of patients with clinical outcomes during follow-up according to cognitive function status at baseline.

ADVANCE De Galan et al. Diabetologia Nov 2009 52(11)



Risk Factors For Severe Hypoglycemia

- Age
- Unawareness of, or previous severe hypoglycemia
- High doses of insulin or sulfonylureas
- Recent hospitalization or intercurrent illness
- Polypharmacy (>5 prescribed meds)
- "Tight control" of diabetes
- Poor nutrition or fasting
- Chronic liver, renal or cardiovascular disease
- Vigorous sustained exercise
- Endocrine deficiency (thyroid, adrenal, or pituitary)
- Alcohol use
- Loss of normal counter-regulation

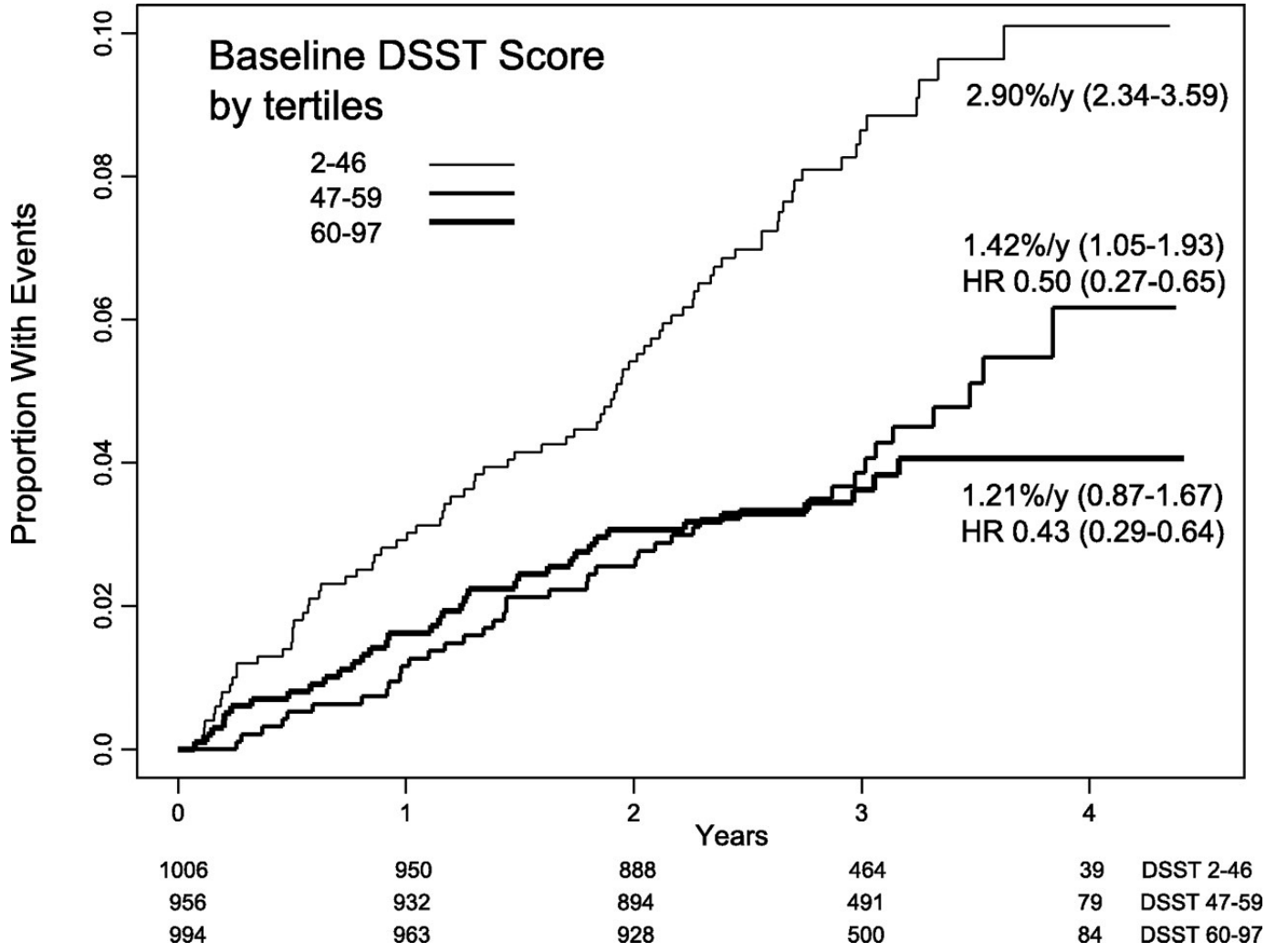
Chelliah. Drugs aging 2004:21

Hypoglycemia and Dementia- Biderectional Association

- Lower cognitive status (lower DSST scores) appear to be associated with more hypoglycemia requiring medical assistance
- Cognitive decline over 20 months increased the risk of subsequent hypoglycemia to a greater extent in those with lower baseline cognitive function **Punthakee Z et al. Dia Care 2012;**
- 783 biracial older adults in Health, Aging and Body Composition study with diabetes
  - In the 12 y follow-up, those experiencing hypoglycemia had a 2-fold risk of developing dementia

***Yaffe. JAMA Intern Med.* 2013**

Kaplan-Meier curves for HMA according to baseline thirds of the DSST score.



Punthakee Z et al. Dia Care 2012;35:787-793

American Diabetes Association.

Copyright © 2011 American Diabetes Association, Inc.

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

JAMA. 2009;301(15):1565-1572. doi:10.1001/jama.2009.460

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

No. of Hypoglycemic Episodes[b]	No. of Dementia Cases	Hazard Ratio (95% Confidence Interval)		
		Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for Comorbidities[c]	Additionally Adjusted for 7-Year Mean HbA_{1c} Level, Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.68 (1.47-1.93)	1.48 (1.29-1.70)	1.44 (1.25-1.66)
1	150	1.45 (1.23-1.72)	1.29 (1.10-1.53)	1.26 (1.10-1.49)
2	57	2.15 (1.64-2.81)	1.86 (1.42-2.43)	1.80 (1.37-2.36)
3 or more	43	2.60 (1.78-3.79)	2.10 (1.48-2.73)	1.94 (1.42-2.64)

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.
[a] Analyses combined using Cox proportional hazard models.
[b] The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.
[c] Adjustment made using a comorbidity composite scale.

Date of download: 5/7/2013

Copyright © 2012 American Medical Association. All rights reserved.

The JAMA Network

From: **Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus**

JAMA Intern Med. 2013;173(14):1300-1306. doi:10.1001/jamainternmed.2013.6176

Table 2. Multivariate-Adjusted Cox Proportional Hazards Regression Estimates for Time to Dementia Associated With a Hypoglycemic Event

Variable	Hazard Ratio (95% CI)
Hypoglycemic event	2.09 (1.00-4.35)
Age	1.15 (1.08-1.22)
Black race/ethnicity	0.77 (0.51-1.16)
Female sex	0.78 (0.54-1.12)
Education	1.30 (0.85-1.96)
APOE ε4 status	2.17 (1.53-3.08)
Prevalent diabetes mellitus	1.70 (1.12-2.58)
Insulin use	1.04 (0.64-1.67)
Glycated hemoglobin level	1.00 (0.85-1.17)
Baseline Mini-Mental State Examination score	0.96 (0.93-0.99)

Abbreviation: APOE, apolipoprotein E.

Figure Legend:

Multivariate-Adjusted Cox Proportional Hazards Regression Estimates for Time to Dementia Associated With a Hypoglycemic Event

Date of download: 6/13/2014

Copyright © 2014 American Medical Association. All rights reserved.

Depression

- Depression is a risk factor for cognitive impairment in person with DM
- Persons with DM have higher rates of depression than those without DM
- Is depression due to neurotransmitter changes from metabolic changes in DM, or due to cerebrovascular disease?
- Relation between Type 2 DM and depression may be bidirectional; type 2 DM may develop from depression

Myint, Aye Aye et al. *Science* 2.3 (2013): 114-121.

Screening

- Persons with diabetes are screened for retinopathy, neuropathy, microalbuminuria
- Screening for peripheral arterial or cardiovascular disease if symptomatic
- Cognitive impairment or dementia is often undiagnosed
- Perceived lack of benefit of early diagnosis
- How does this translate to persons with T2 DM?

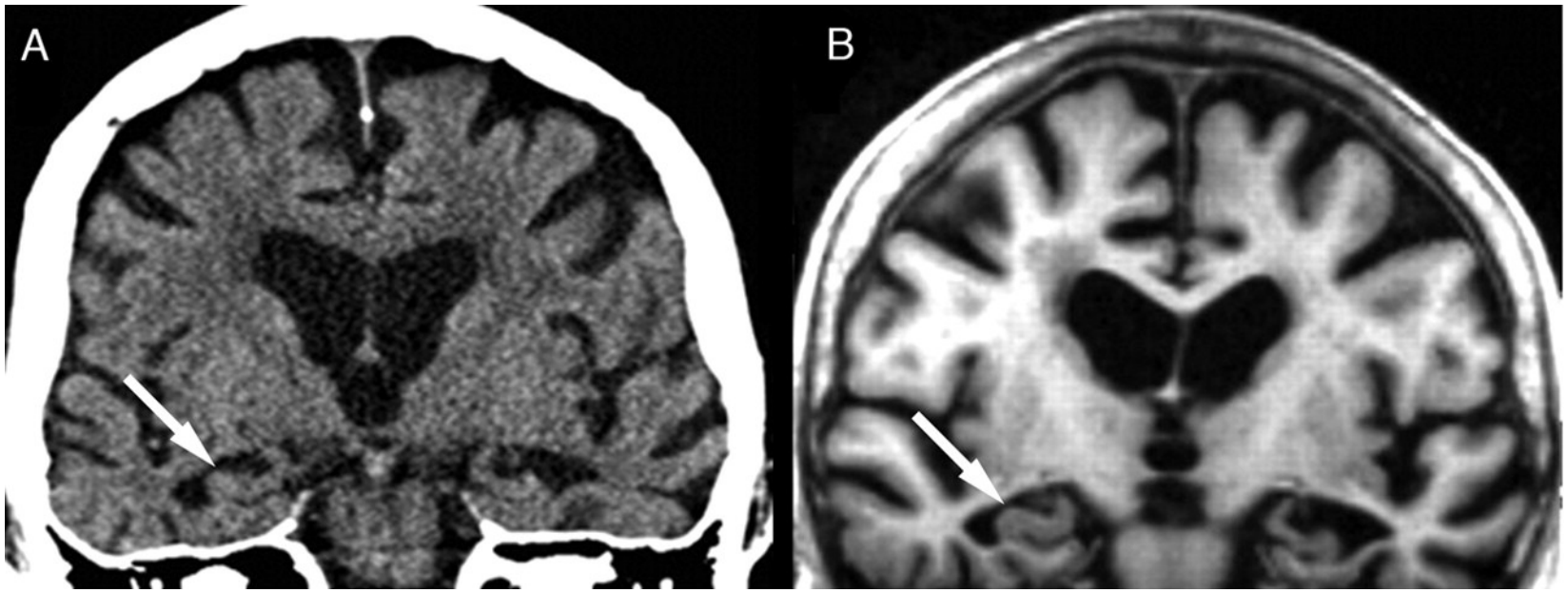
Diagnosis

- Work-up of any patient with T2DM and cognitive dysfunction is the same as any other patient with cognitive complaints
- Behavior, mood and personality changes should be addressed
- Assess diabetes management and support system
- Serum chemistry, thyroid, B12, HIV, RPR as indicated
- Neuroimaging (MRI if possible)

Cognitive trajectories in T2DM

- Modest decline in cognition over time even in people without dementia
- This affects verbal memory, information processing speed, attention and executive function
- Modest decrements affect all age groups and are slowly progressive over time
- These are NOT early manifestations of dementia
- Dementia only affects a subset; possible added effect of Alzheimer's or severe cerebrovascular disease?

Bilateral medial temporal lobe atrophy (right hippocampus illustrated with arrows) in a subject with Alzheimer's disease demonstrated on coronal images acquired with: (A) 64 detector row computed tomography scanning; (B) 1.5 tesla MRI volumetric T1 weighted sequence

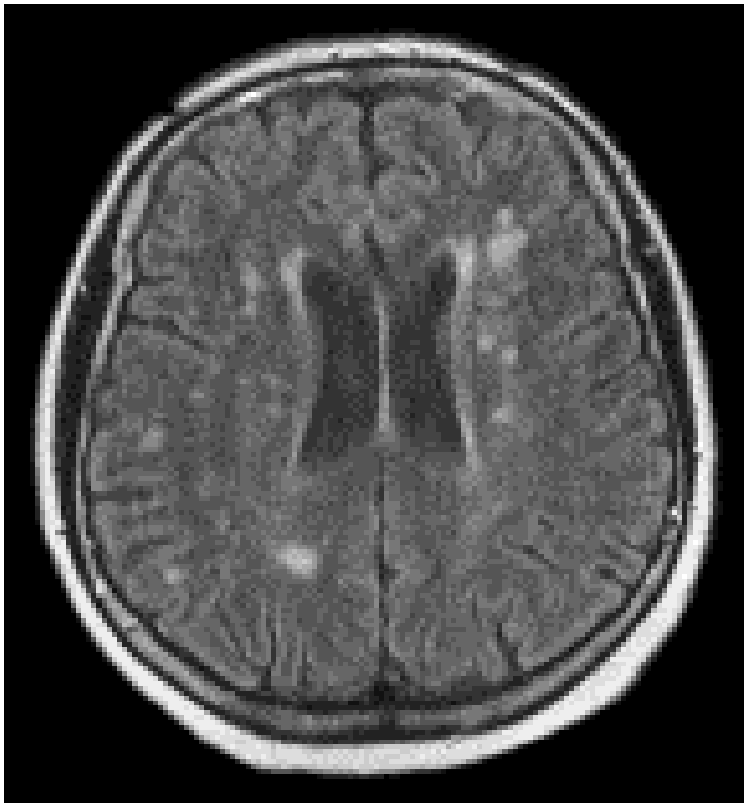


Schott J M et al. BMJ 2011;343:bmj.d5568

BMJ

©2011 by British Medical Journal Publishing Group

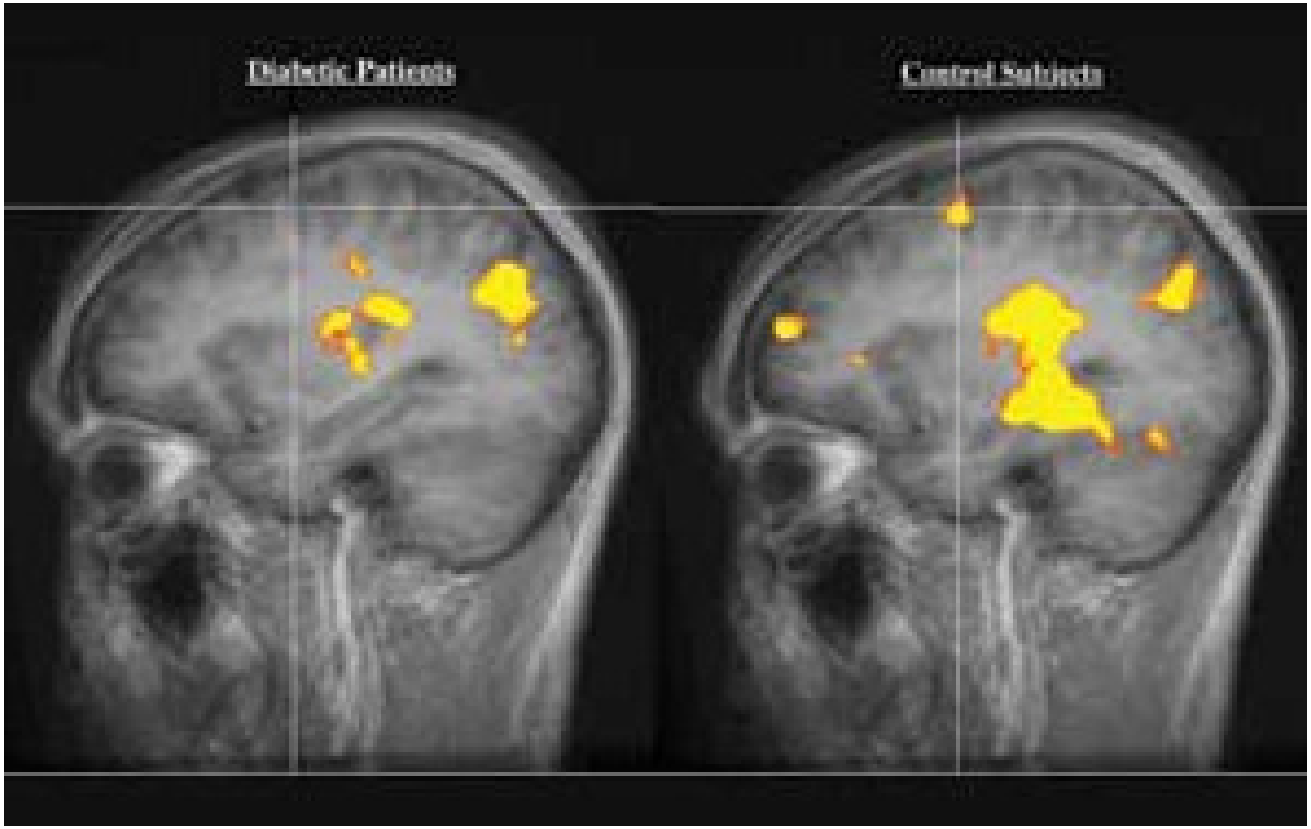
What about MRI?



Multiple white matter areas of ischemia

Functional MRI showing less brain activation in diabetic subject

Gail Munsen PhD. Joslin Diabetes Center 2011



Diabetic subject

Control subject

Treatment

Type 2 DM is a modifiable risk factor for Alzheimer's disease

- As yet there are no diabetes-specific therapies with proven efficacy in preventing or ameliorating cognitive decline
- Cognitive function is being included as an outcome measure in more therapeutic trials
- Glucose lowering does not show consistent benefit on cognition
- The large ACCORD-MIND study showed that intensive glucose lowering treatment over 40 mth in people over 55 with T2DM did not benefit cognitive performance

THANK YOU

TODAY WE HAVE

- ***15 NATIONS***
- ***5 CONTINENTS***
- ***12 PROFESSIONS***

TOGETHER WE CAN MAKE A DIFFERENCE!!

NOVA SOUTHEASTERN UNIVERSITY
College of Osteopathic Medicine

the GREAT GEC