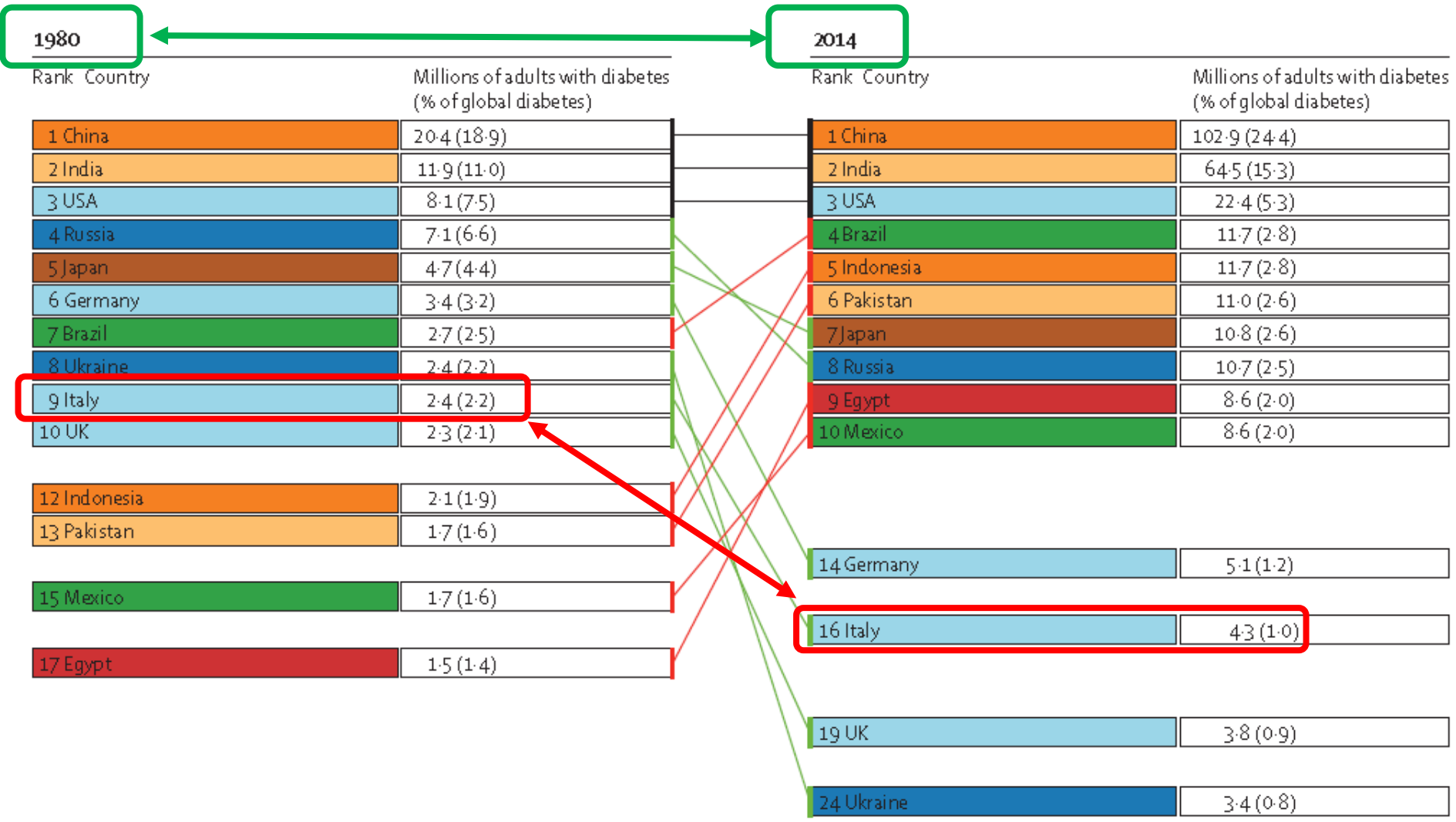
Diabete e demenza

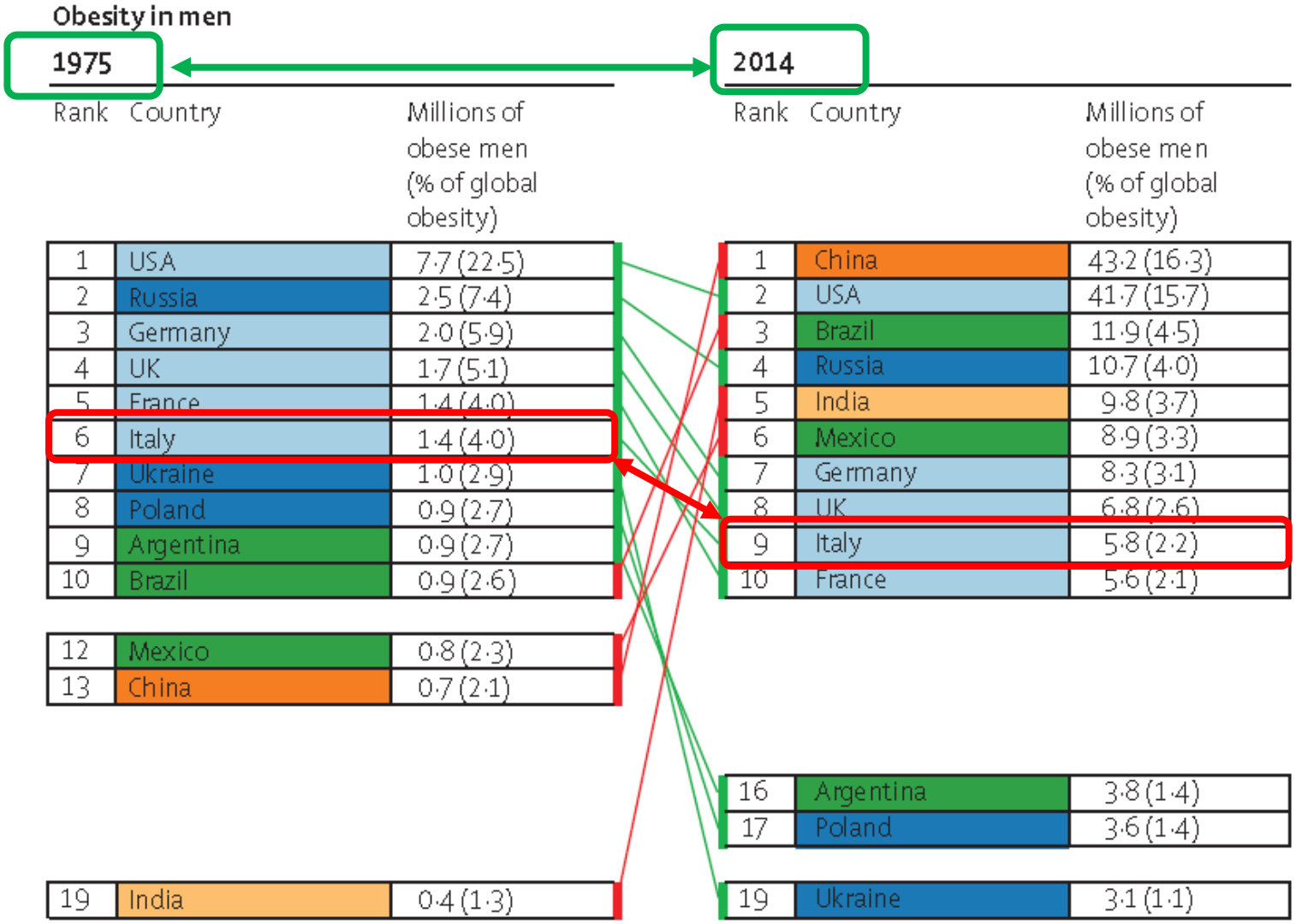
Enzo Manzato

Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants



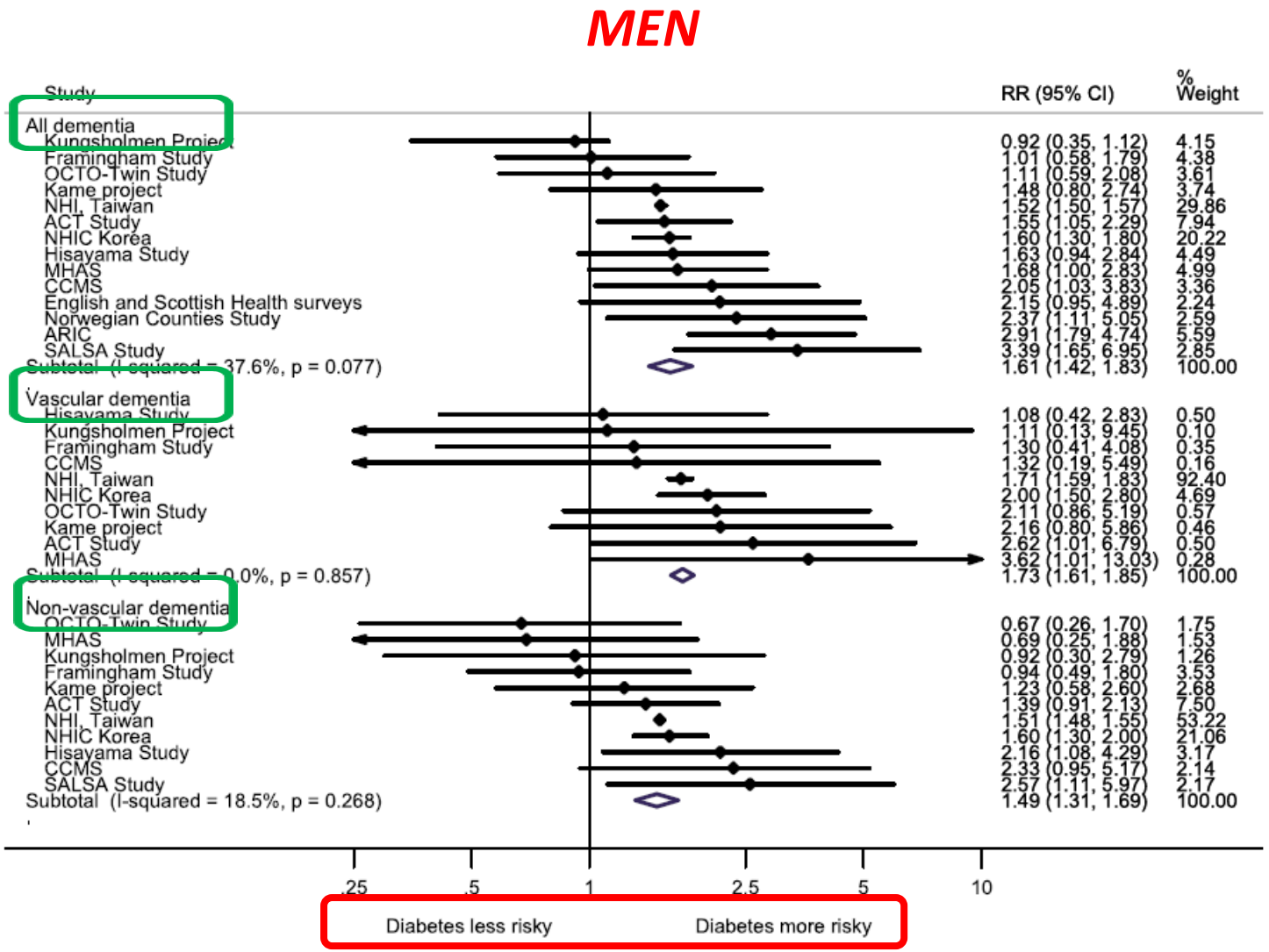
Lancet 2016; 387: 1513

Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants



Lancet 2016; 387: 1377

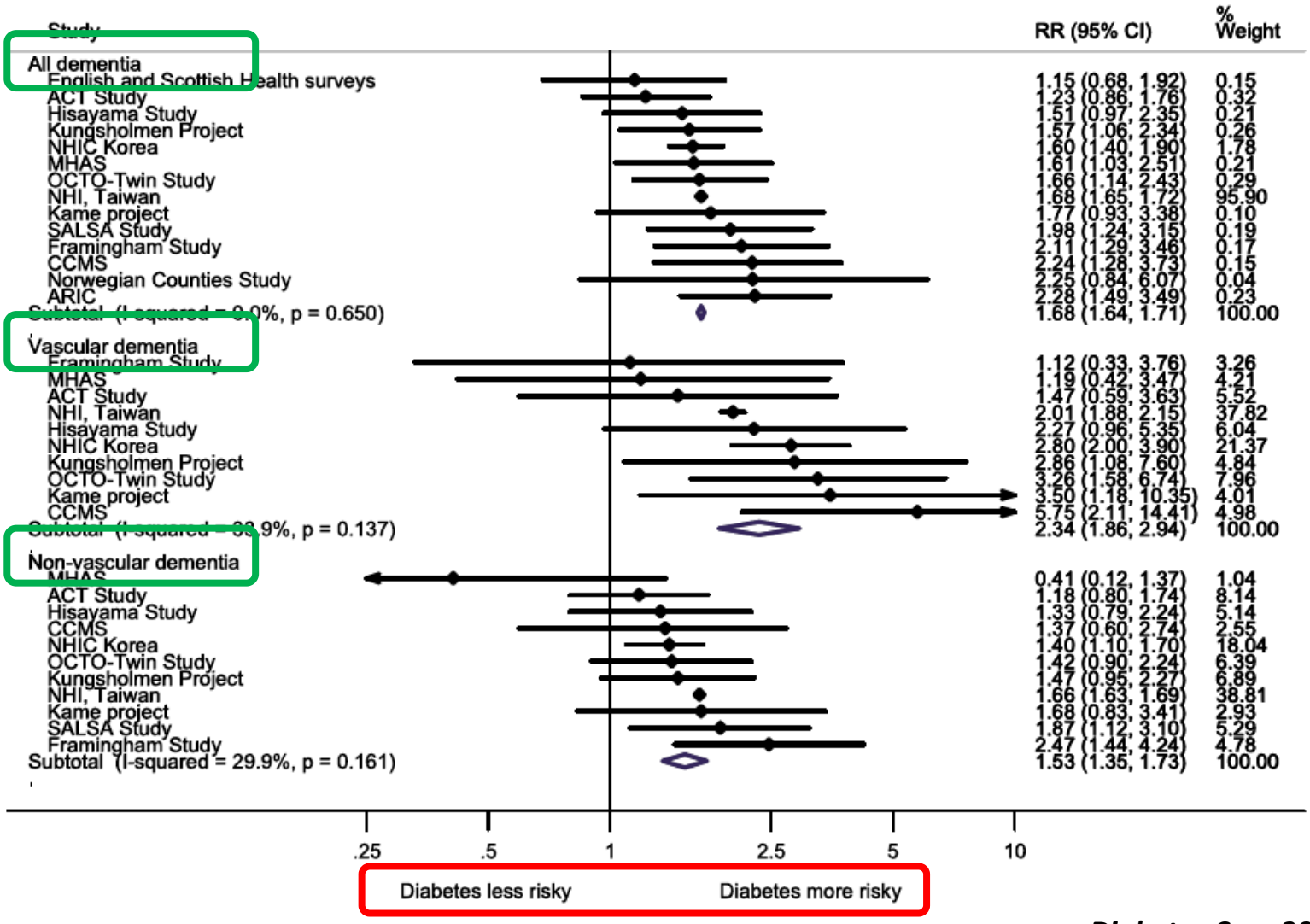
Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia



Diabetes Care 2016;39:300

Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia

WOMEN

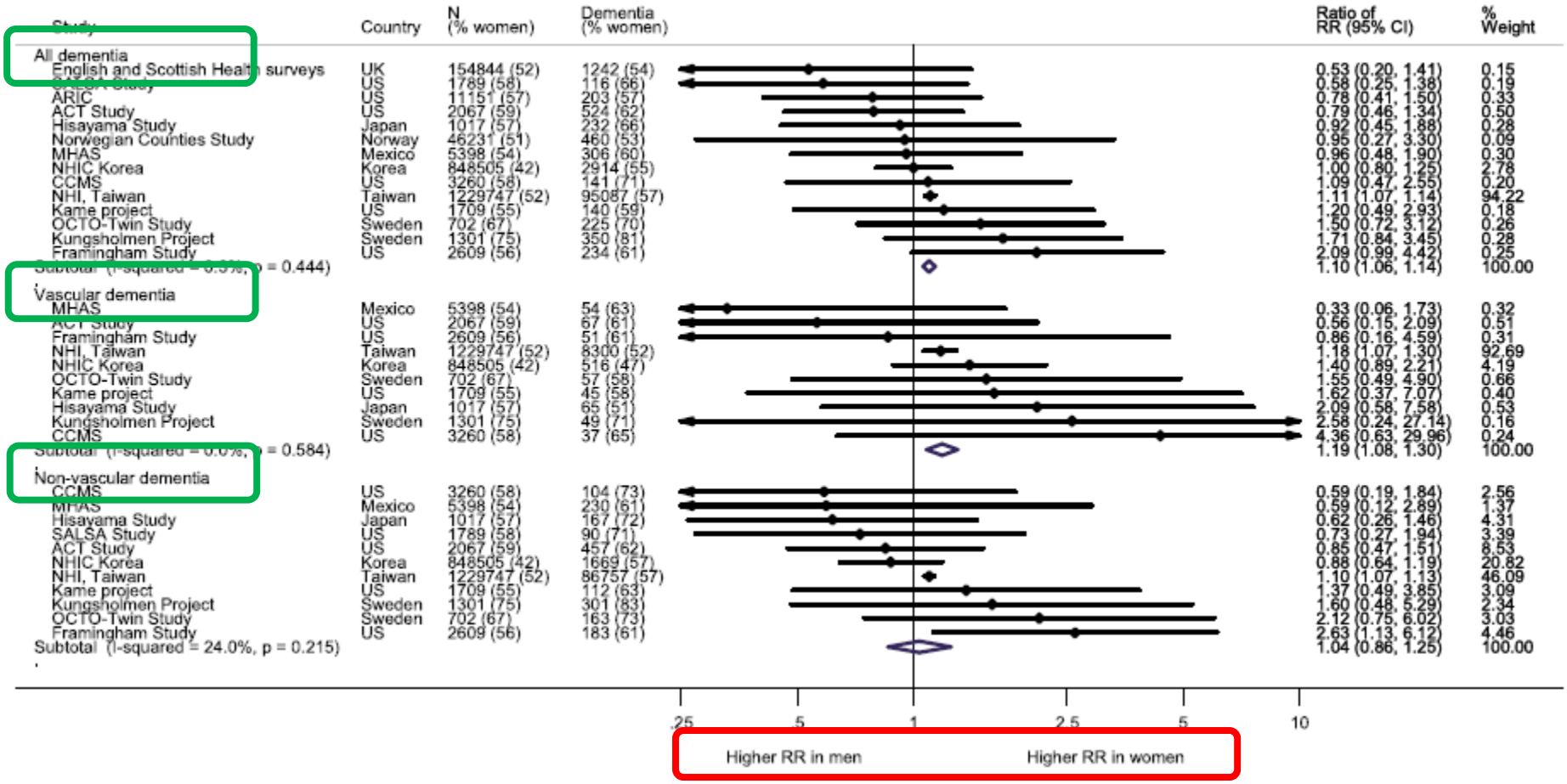


Diabetes Care 2016;39:300

Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia

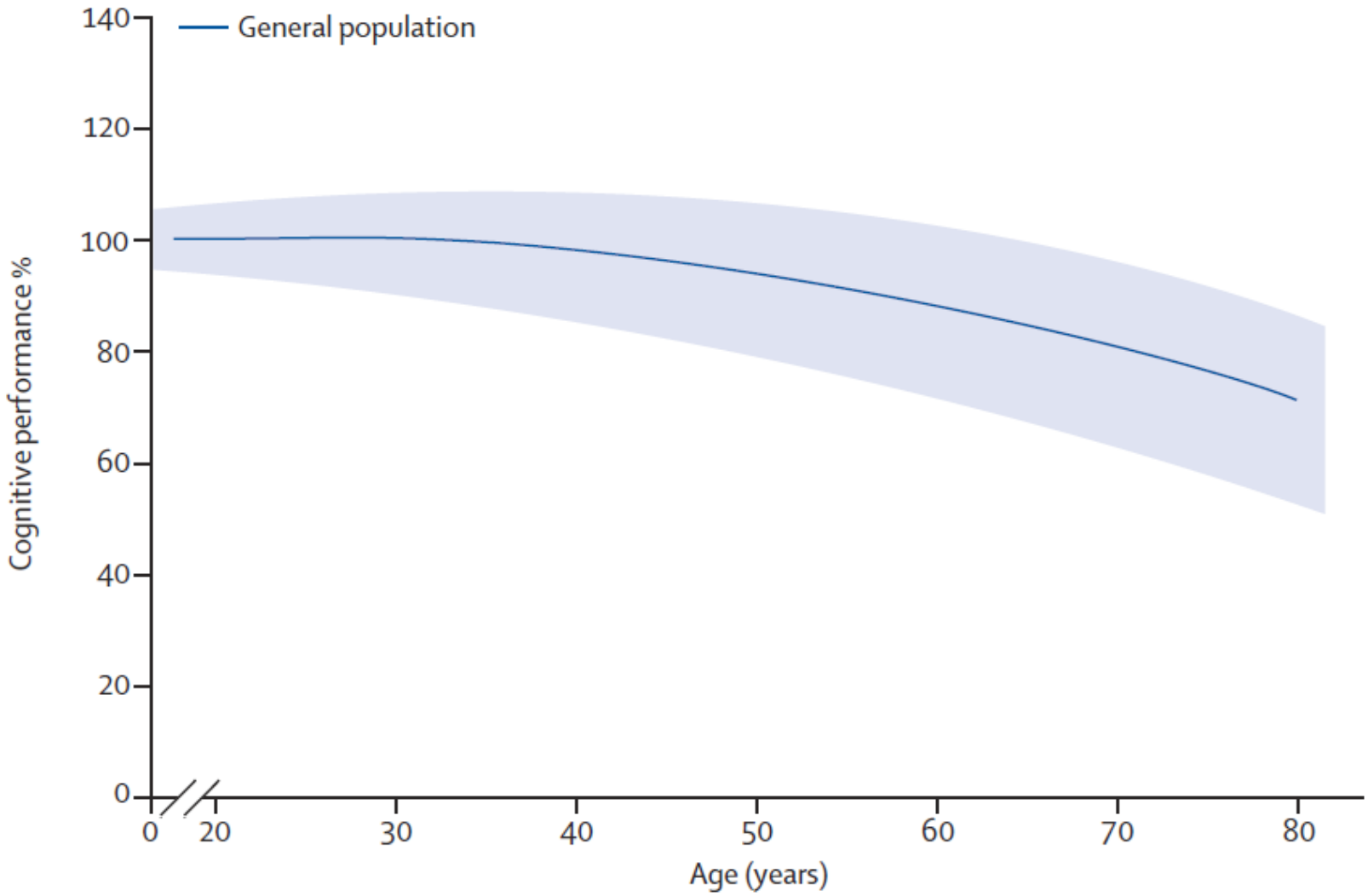
Multiple-adjusted women to men RR for any dementia, vascular dementia, and nonvascular dementia

MEN vs WOMEN



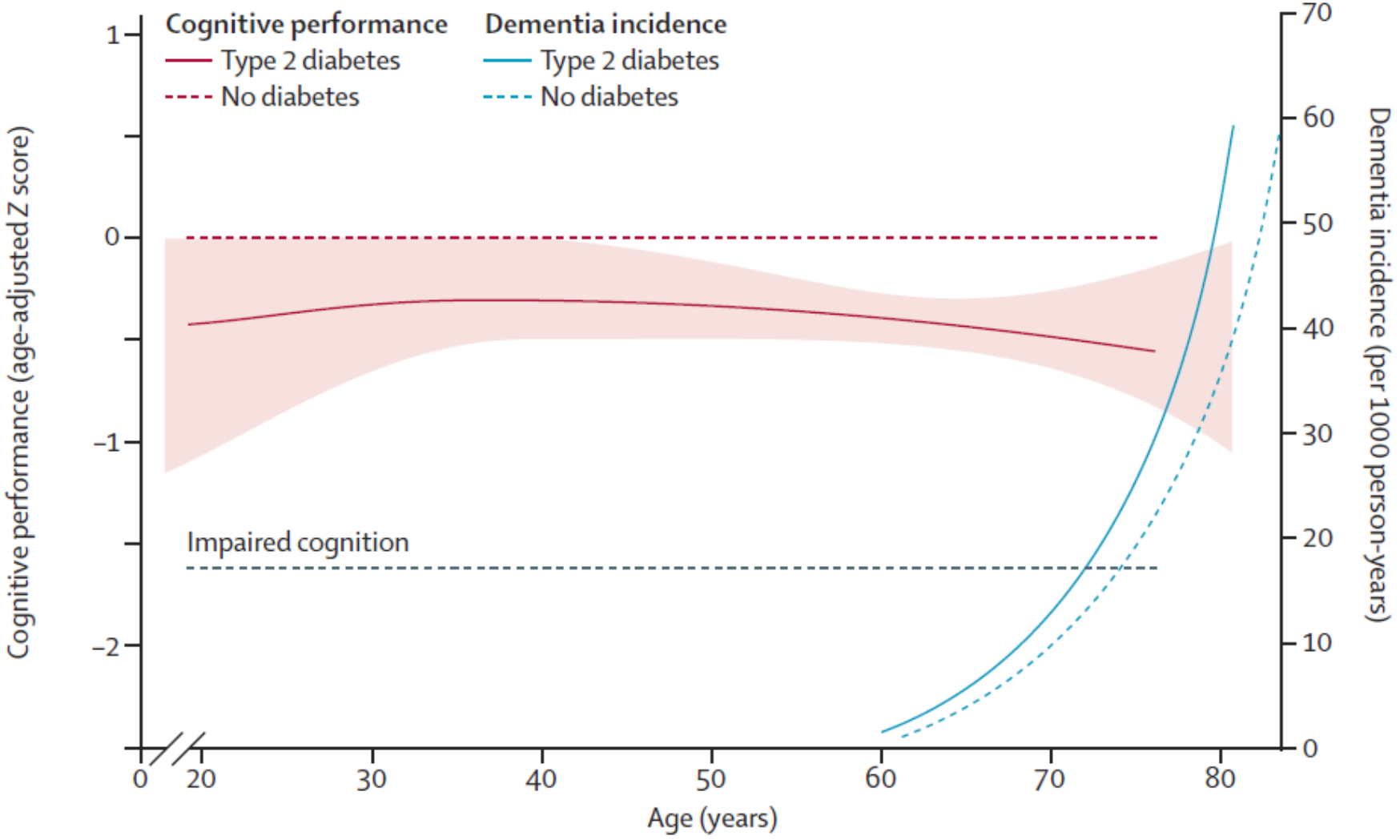
Diabetes Care 2016;39:300

Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions



Lancet Diabetes Endocrinol 2014; 2: 246

Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions



Lancet Diabetes Endocrinol 2014; 2: 246

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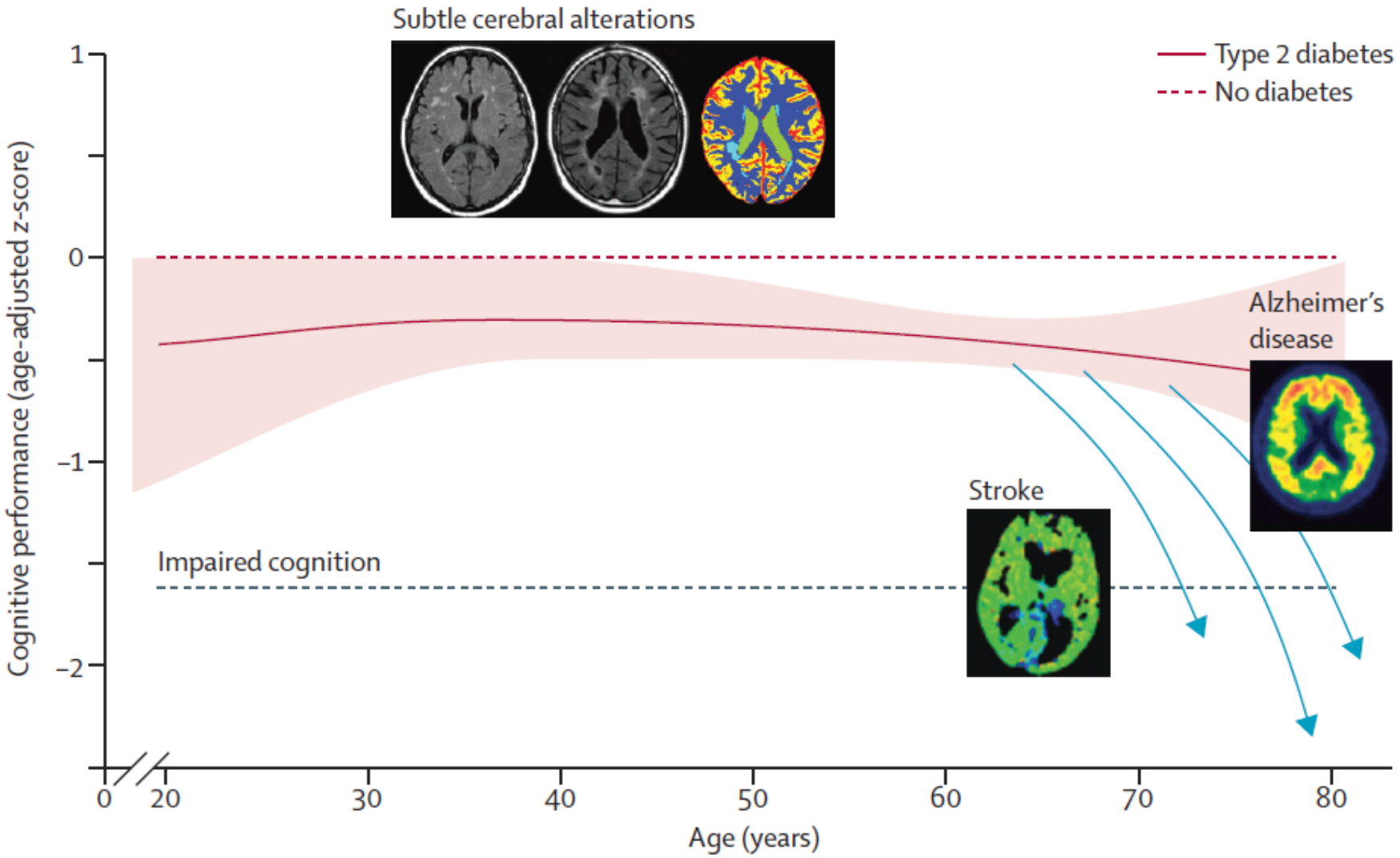
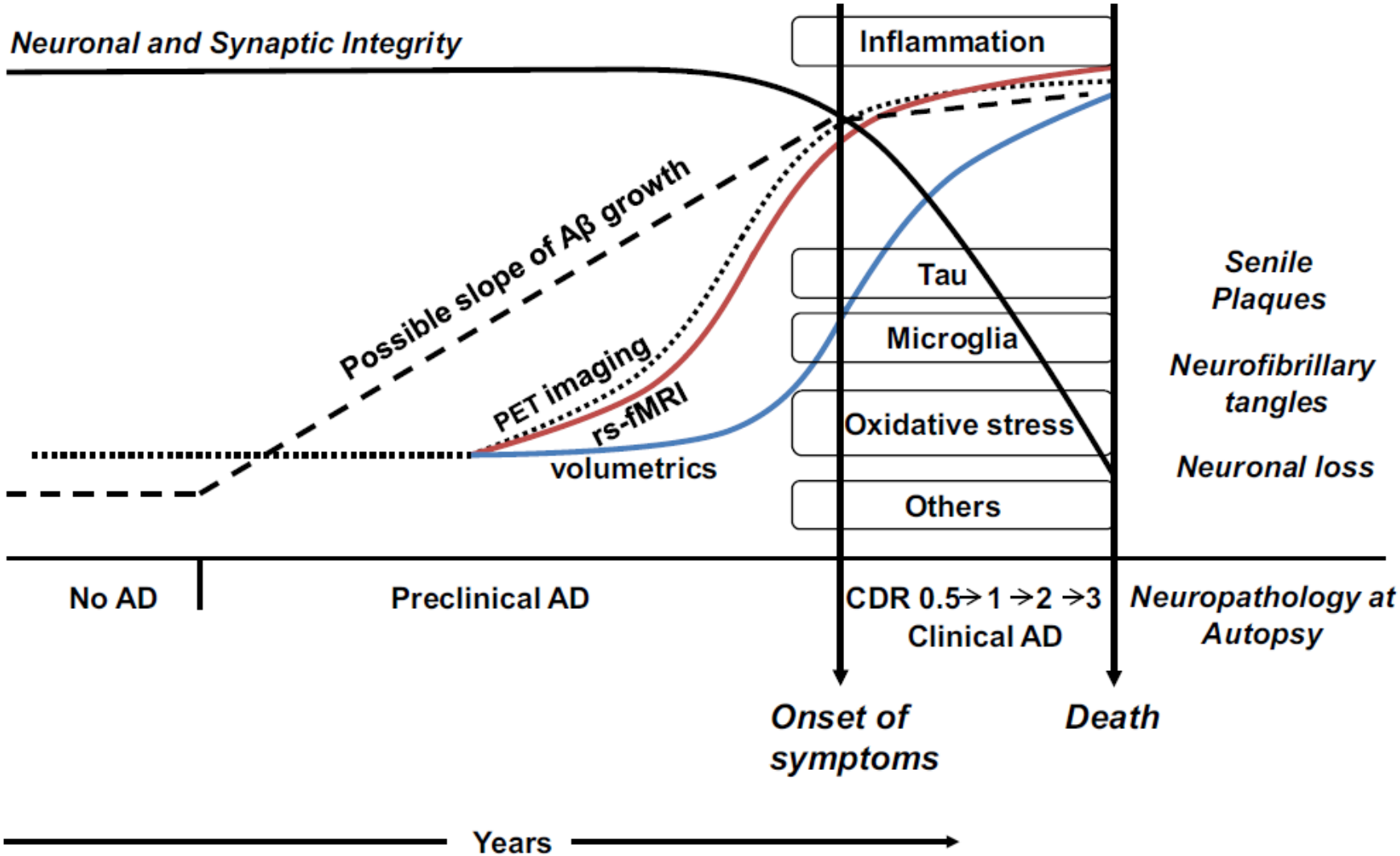


Lancet Diabetes Endocrinol 2014; 2: 246

Resting State Functional Connectivity in Preclinical Alzheimer's Disease

Timecourse from preclinical to clinical Alzheimer's disease



Biol Psychiatry 2013;74:340

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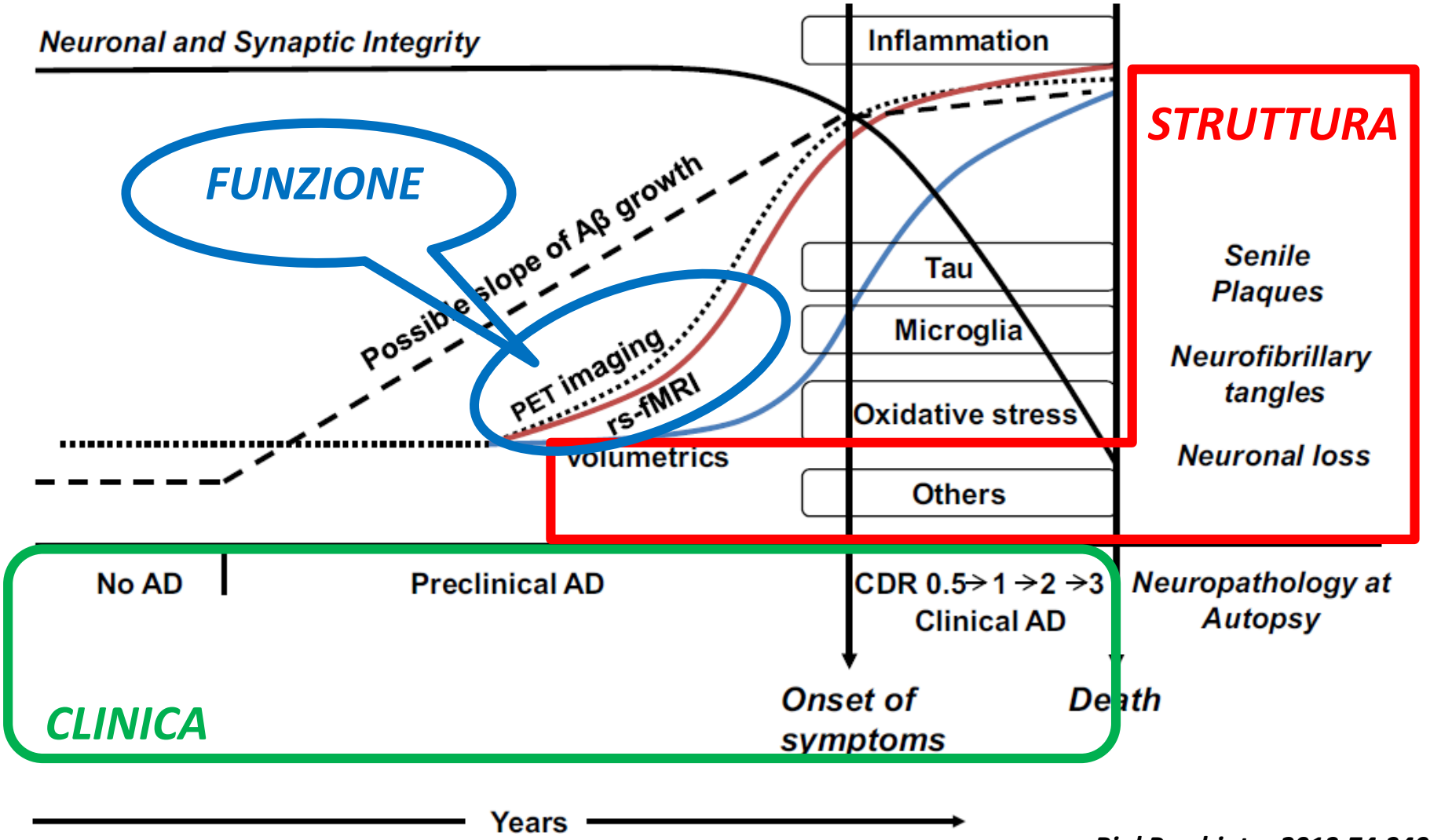
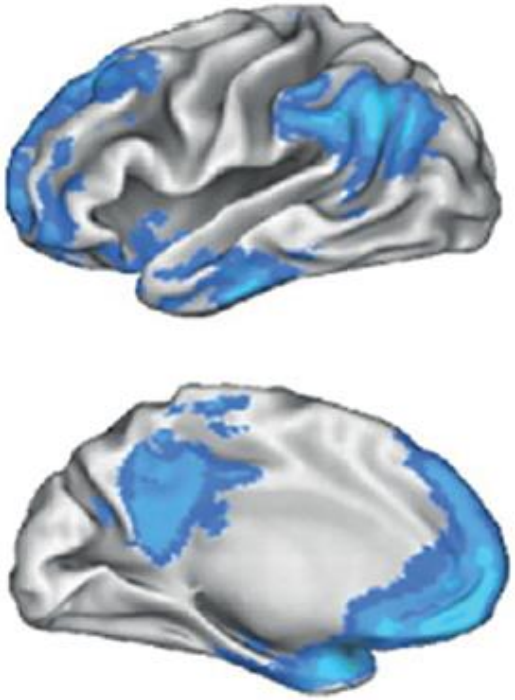


Biol Psychiatry 2013;74:340

Network abnormalities and interneuron dysfunction in Alzheimer disease

Default mode network
(fMRI)

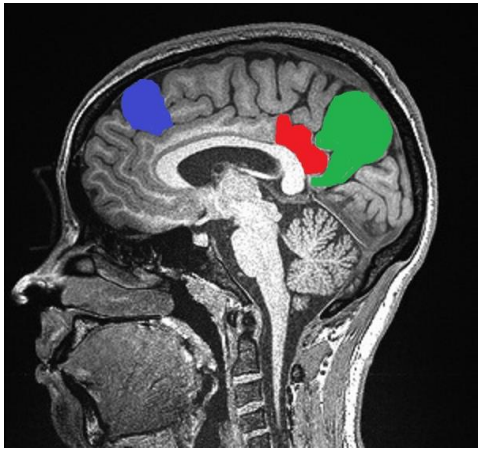


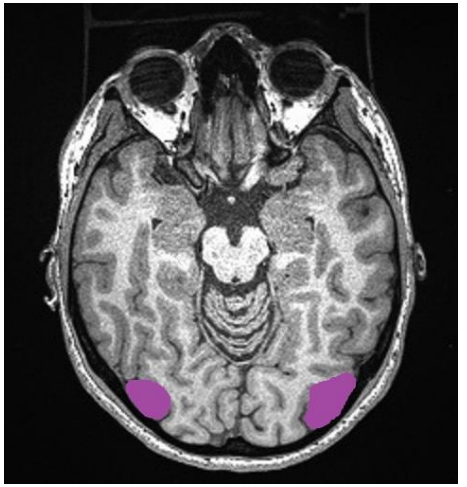
- ***Default mode network: brain regions that show increased functional MRI signals during inwardly oriented mental activity and decreased functional MRI signals during attention demanding tasks.***

Nature Reviews|Neuroscience 17, 777, 2016

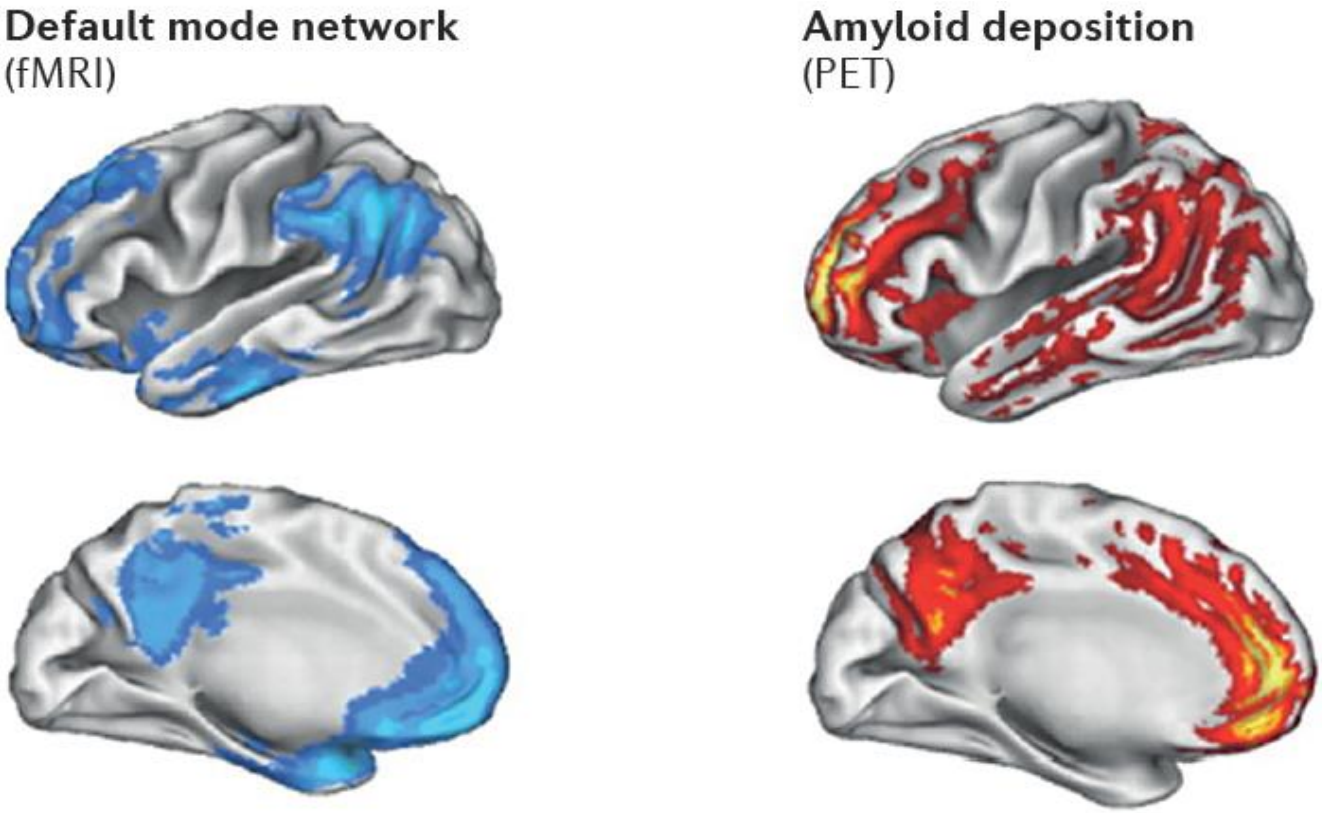
Componenti del Default-Mode Network

- ***Porzione posteriore della corteccia cingolata***
- ***Precuneo***
- ***Porzione mediale della corteccia prefrontale***
- ***Circonvoluzioni angolari***





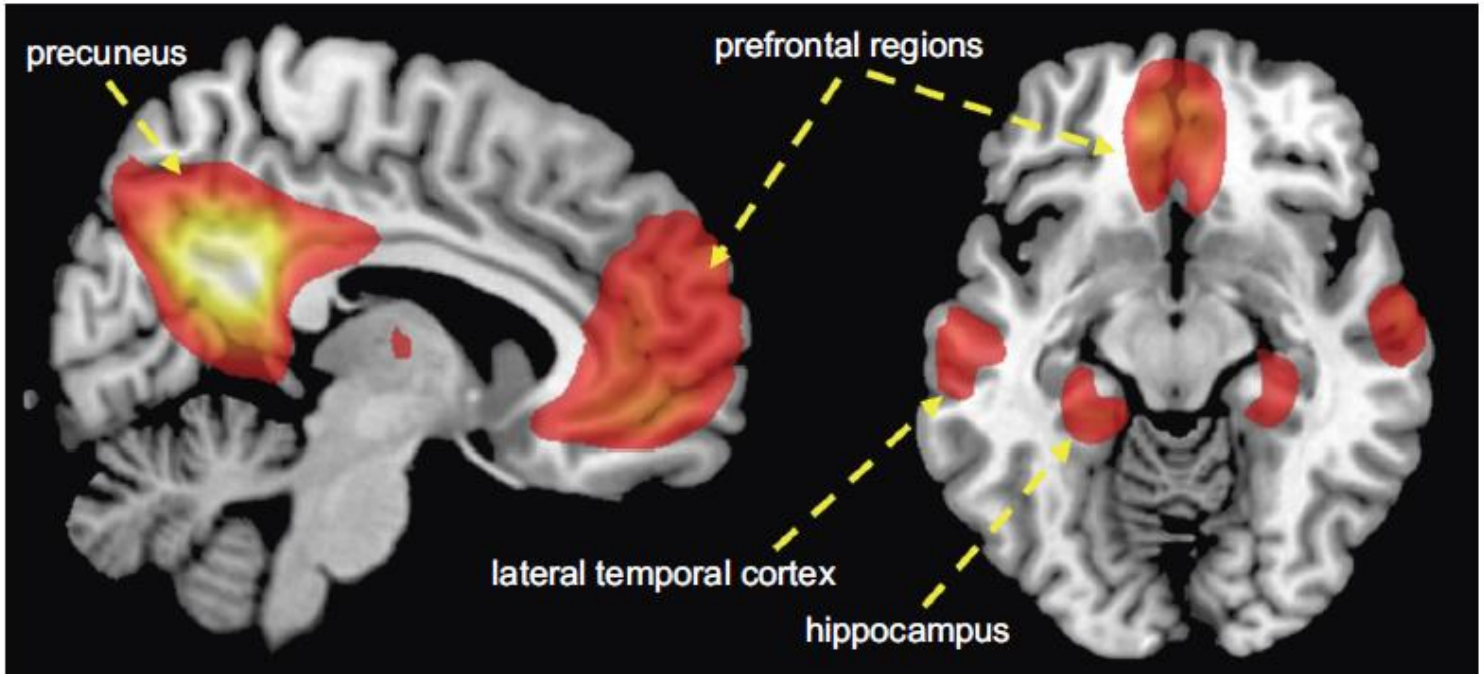
Network abnormalities and interneuron dysfunction in Alzheimer disease



- ***Default mode network: brain regions that show increased functional MRI signals during inwardly oriented mental activity and decreased functional MRI signals during attention demanding tasks.***
- ***Amyloid deposits (red) predominate in brain regions of the default mode network (blue), which shows deactivation deficits in Alzheimer disease.***

Nature Reviews|Neuroscience 17, 777, 2016

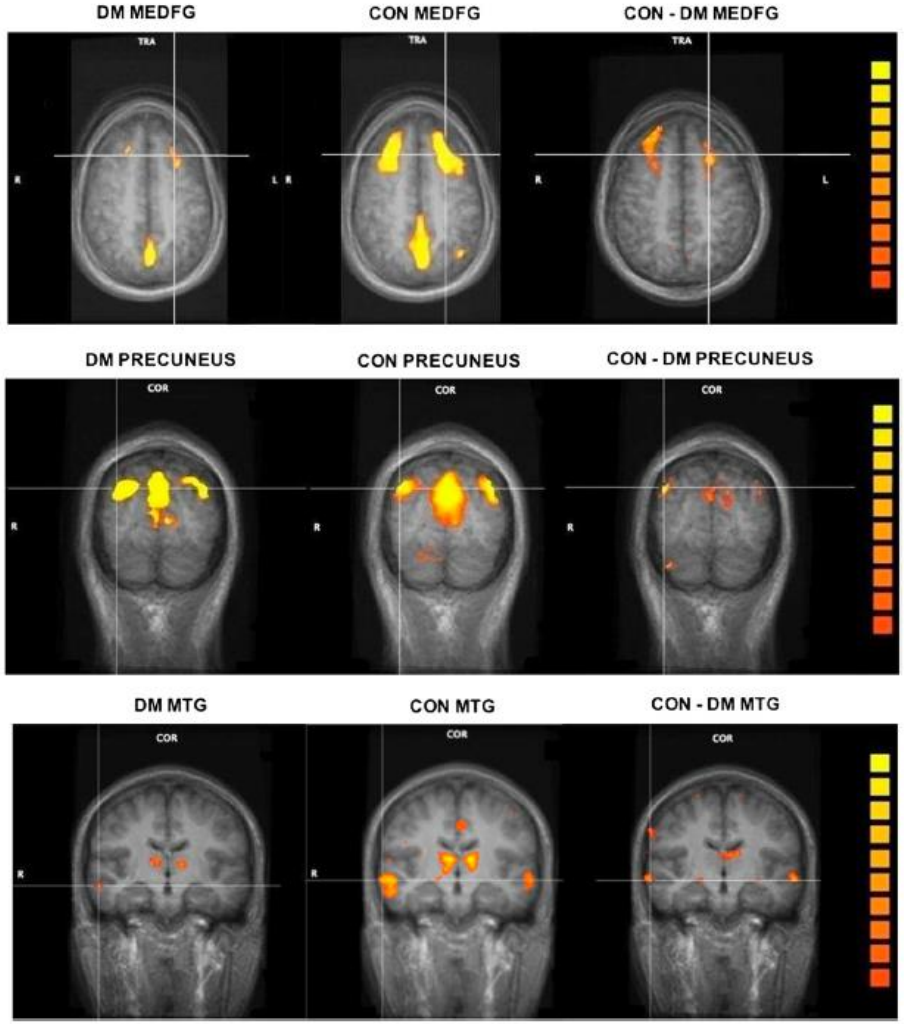
BRAIN INSULIN RESISTANCE AT THE CROSSROADS OF METABOLIC AND COGNITIVE DISORDERS IN HUMANS



- ***Brain regions within the default mode network are particularly vulnerable to aging and dementia.***
- ***They are the first to develop amyloid deposition as well as to show decreased glucose metabolism and a loss in functional connectivity.***
- ***The disruption of functional connectivity and reduced cerebral glucose metabolism in these regions is related to the severity of peripheral insulin resistance and cognitive impairment.***

Physiol Rev 96: 1169, 2016

Resting-State Brain Functional Connectivity Is Altered in Type 2 Diabetes



medial frontal gyrus

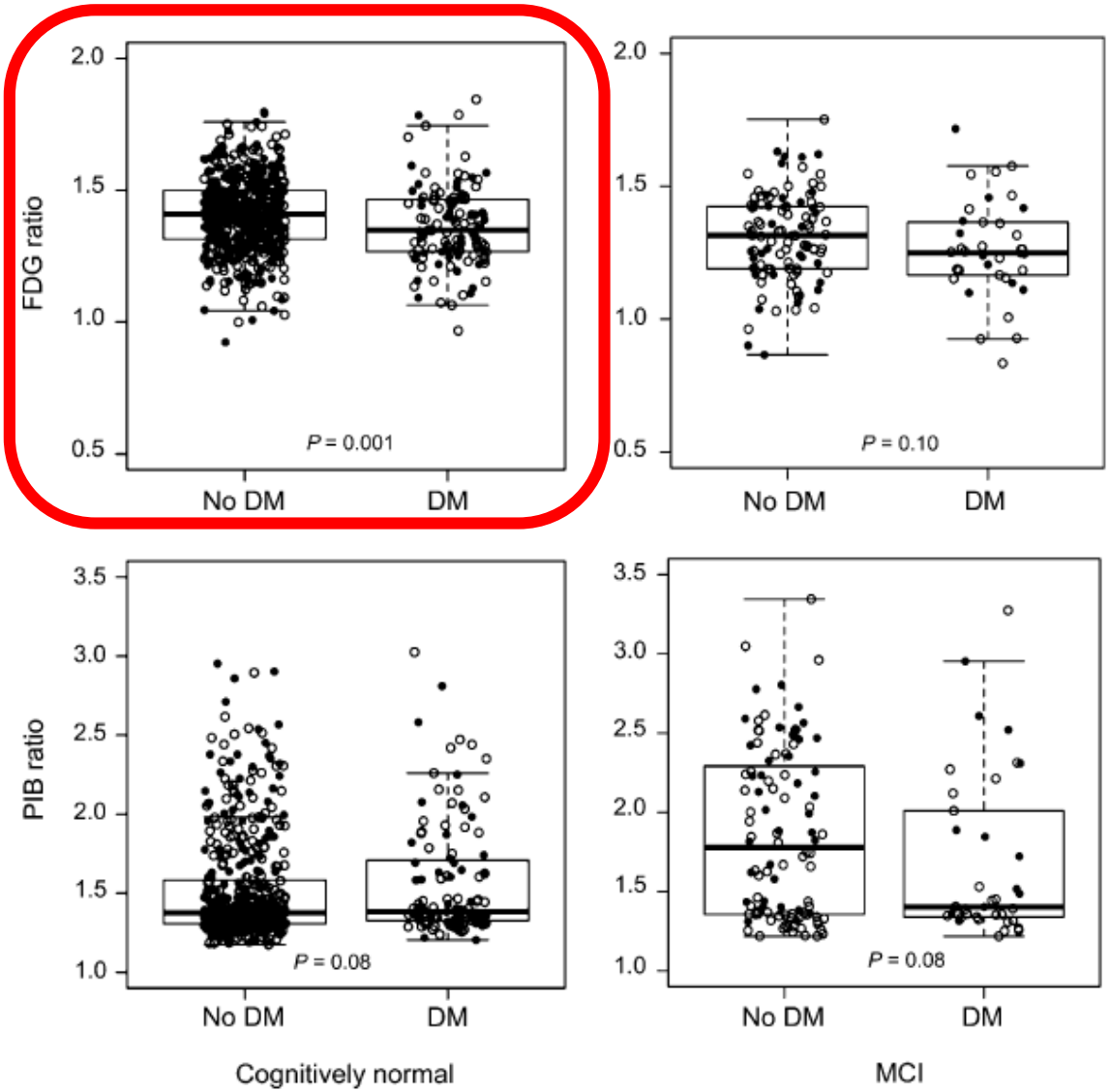
precuneus

middle temporal gyrus

T2DM patients showed reduced functional connectivity in the default mode network compared with control subjects, which was associated with insulin resistance in selected brain regions, but there were no group effects of brain structure or cognition.

Diabetes 61:2375, 2012

Diabetes and Elevated Hemoglobin A1c Levels Are Associated with Brain Hypometabolism but Not Amyloid Accumulation

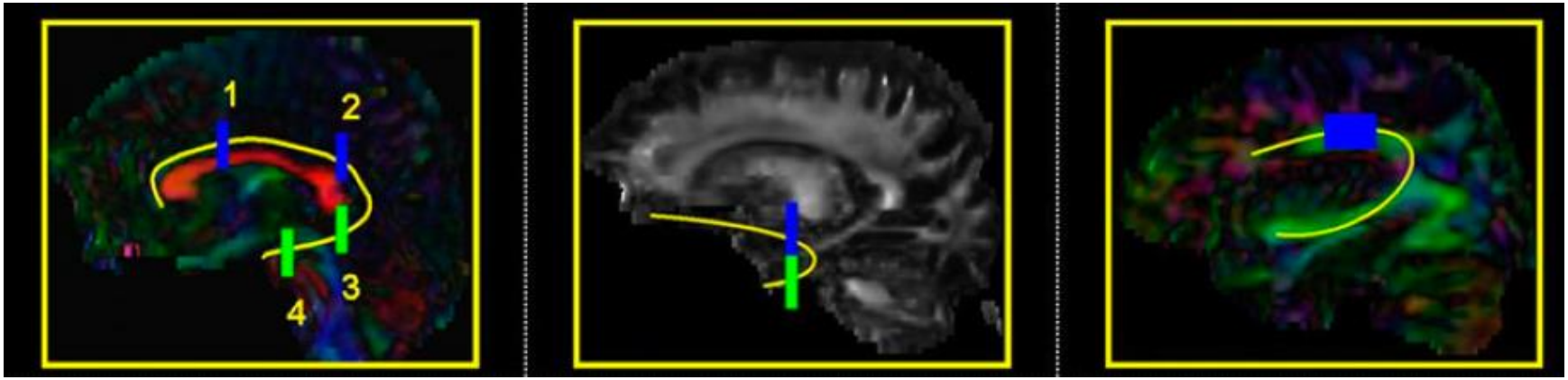


J Nucl Med 2014; 55:759

Cerebral White Matter Integrity and Resting-State Functional Connectivity in Middle-aged Patients With Type 2 Diabetes

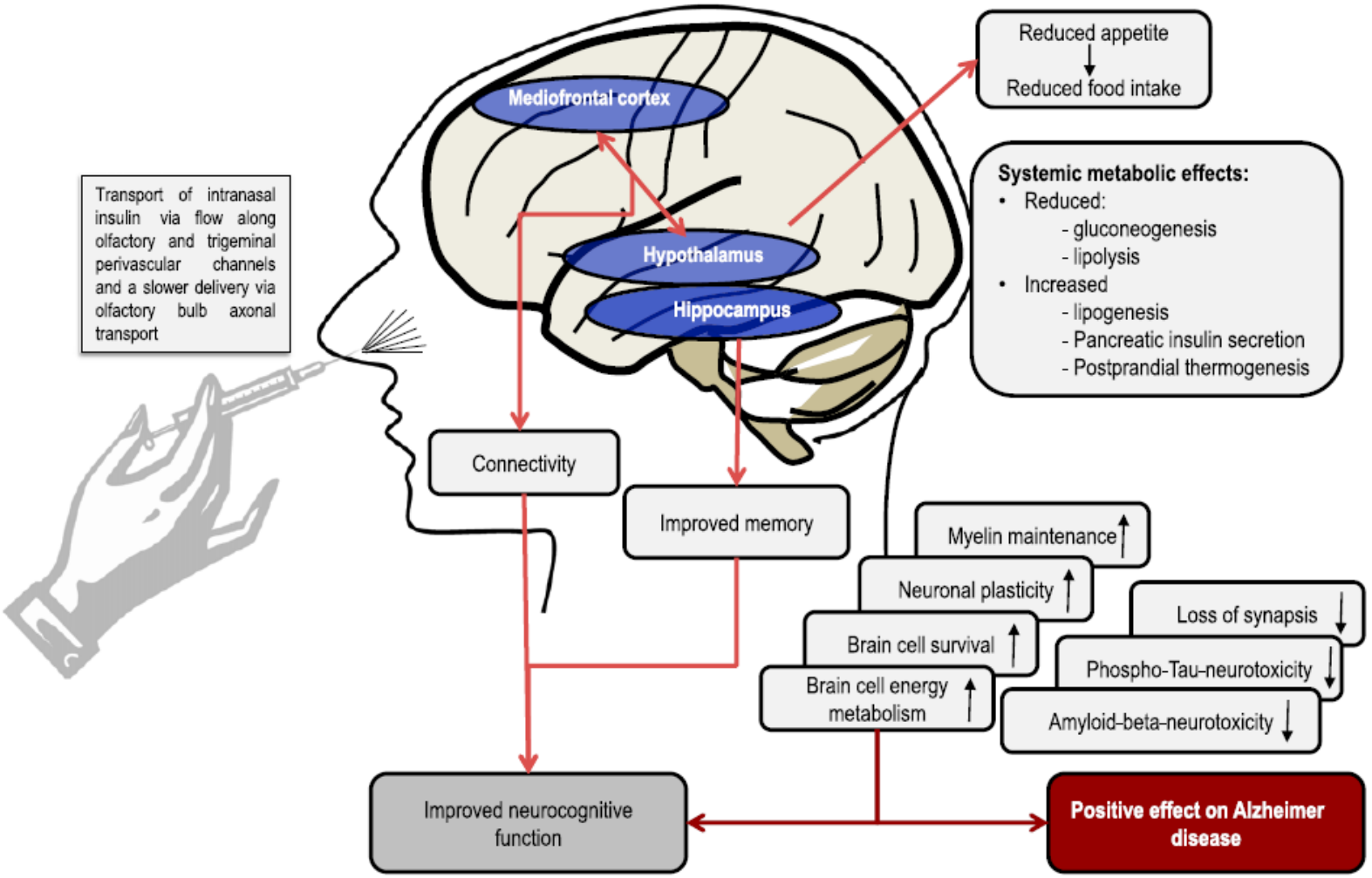
- *diffusion tensor imaging* → *struttura*
- *functional magnetic resonance imaging* → *funzione*
- *cognitive assessment* → *clinica*

CINGULUM BUNDLE | **UNCINATE FASCICULI** | **SUP LONGITUD FASCICULI**



- ➢ *middle-aged patients with type 2 diabetes show white matter abnormalities that correlate with disrupted functional connectivity in the default mode network (a network of brain regions most active during rest)*
- ➢ *common mechanisms may underlie structural and functional connectivity*

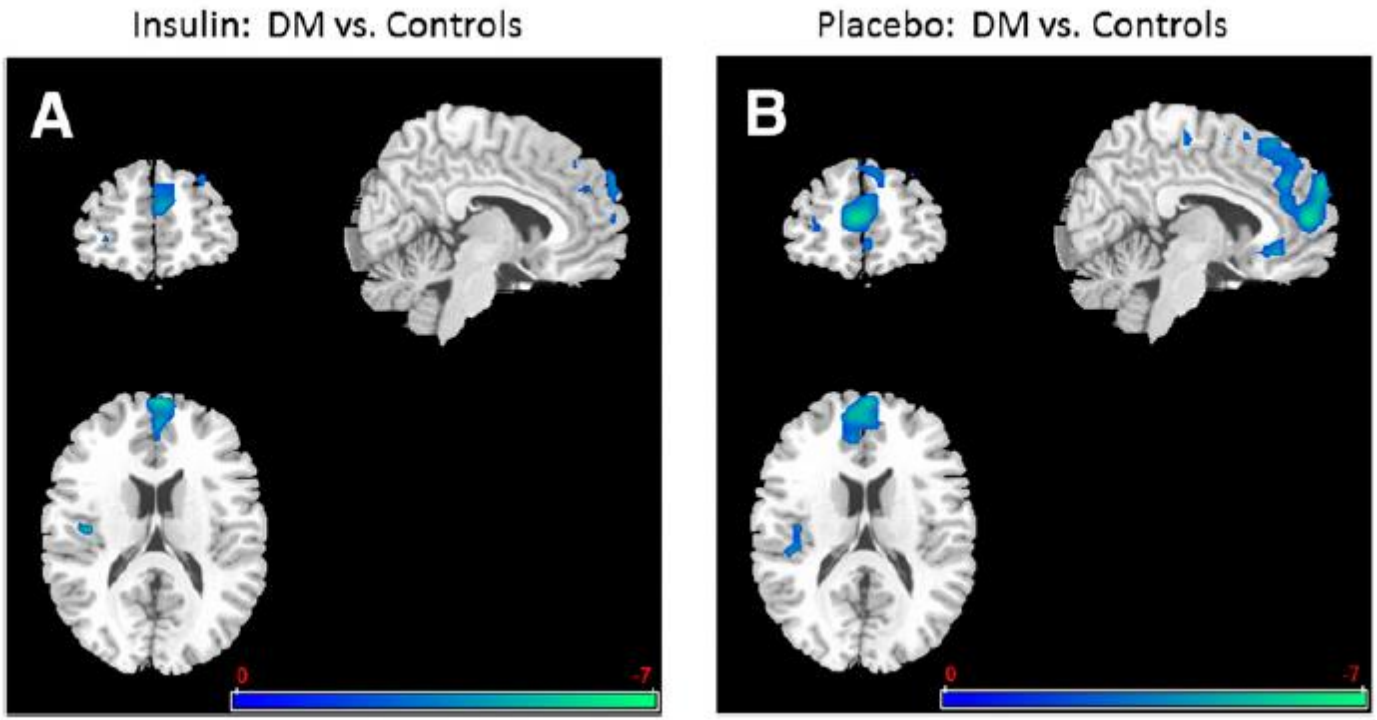
Diabetes 2014;63:728



Diabetes 64, 687, 2015

Intranasal Insulin Enhanced Resting-State Functional Connectivity of Hippocampal Regions in Type 2 Diabetes

Differences in connectivity



A single dose of intranasal insulin increases resting-state functional connectivity between the hippocampal regions and multiple DMN regions in older adults with T2DM.

Diabetes 64, 1025, 2015

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

***intensive glycaemic control** targeting HbA1c to less than 6·0%*

vs

standard strategy targeting HbA1c to 7·0–7·9%

*significant differences in **total brain volume** favoured the intensive treatment*

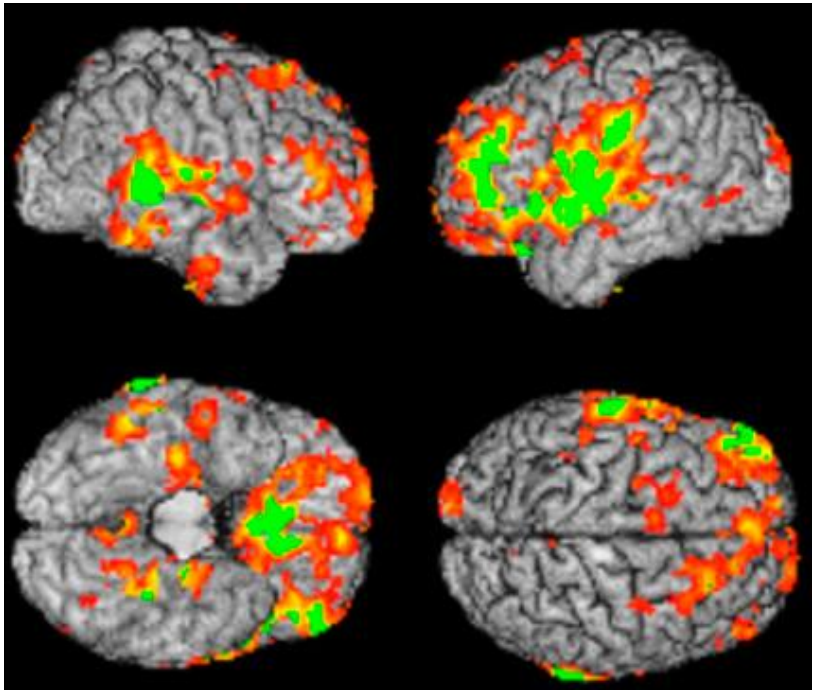
but

***cognitive outcomes** were not different.*

Lancet Neurol 2011; 10: 969

Spatial Patterns of Structural Brain Changes in Type 2 Diabetic Patients and Their Longitudinal Progression With Intensive Control of Blood Glucose

Three-dimensional surface renderings of optimally-discriminative voxel-based analysis results



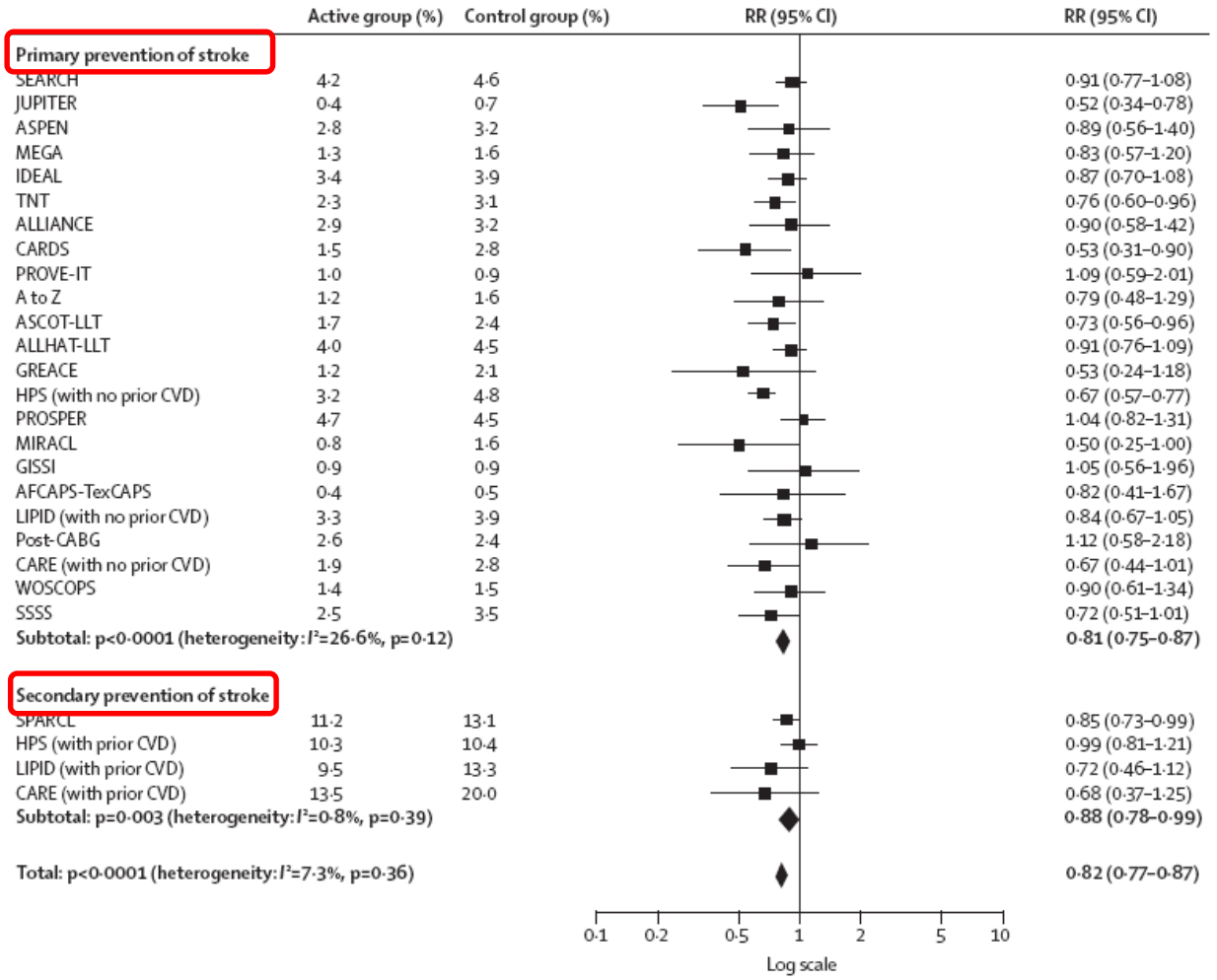
Subjects in the intensive treatment arm (n = 221) had lower longitudinal decrease in gray matter tissue volume in the highlighted areas compared with subjects in the standard treatment arm (n = 267) (regional analysis of volumes examined in normalized space [RAVENS]).

- ***there are spatially specific patterns of brain changes that vary by diabetes characteristics***
- ***the progression of gray matter volume loss is slowed by intensive glycemic treatment, particularly in regions adjacent to areas affected by diabetes.***

Diabetes Care 2015;38:97

Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention

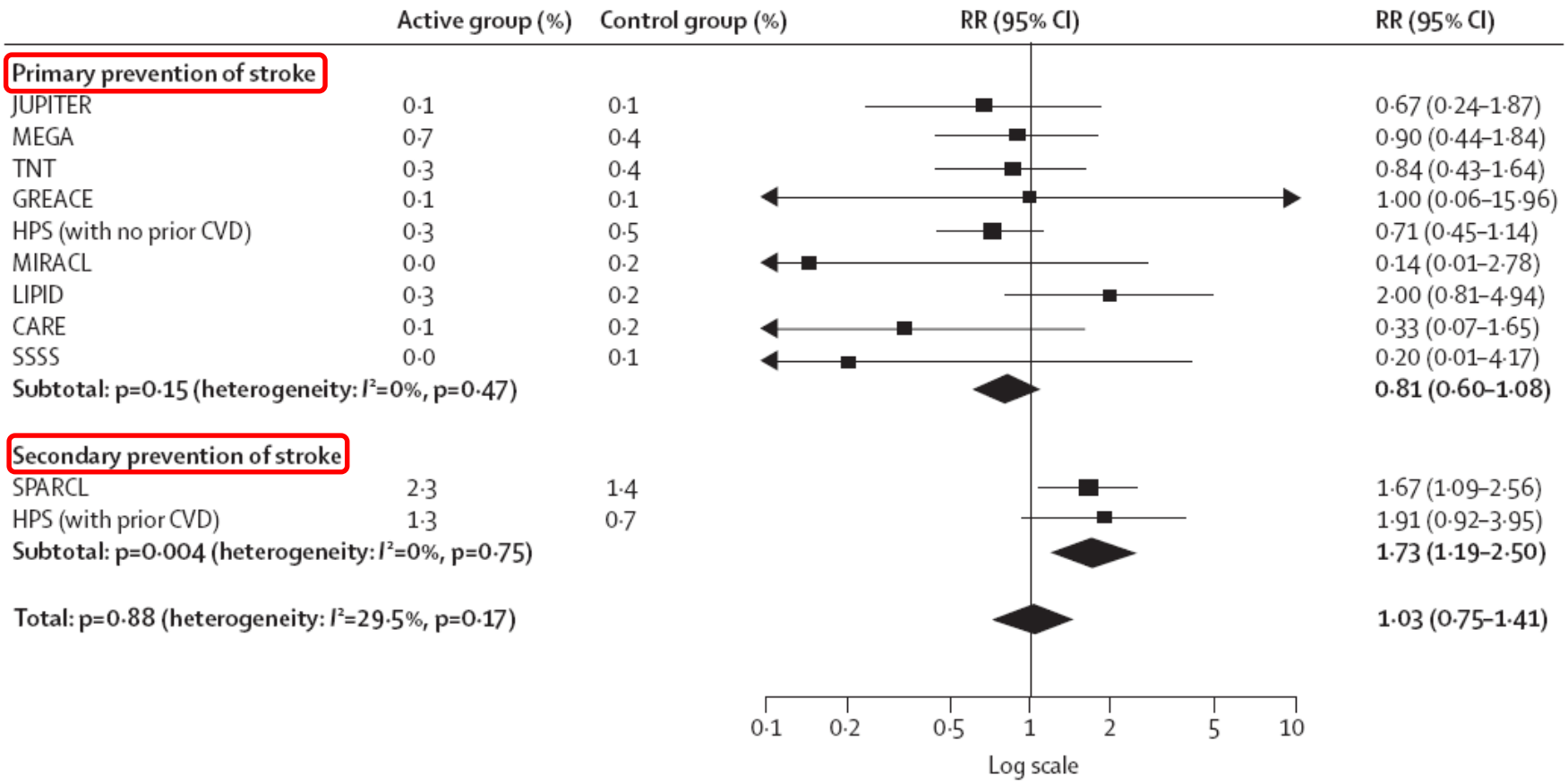
Updated meta-analysis of major statin trials that assessed the effect of statins on fatal and non-fatal stroke



Lancet Neurol 2009; 8: 453

Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention

Updated meta-analysis of major statin trials that assessed the effect of statins on haemorrhagic stroke



Lancet Neurol 2009; 8: 453

Remembering Statins: Do Statins Have Adverse Cognitive Effects?

Table 1—Observational studies of cognitive effect of statins

Ref.	Design	No. of subjects	Age (years)	Follow-up (years)	Diagnosis of dementia	Results (95% CI)
17	Nested case control	1,364	50–89	N/A	Computer-recorded clinical diagnosis	RR 0.29 (0.13–0.63)
18	Case control	655	Mean 78.7	N/A	Clinical diagnosis and MMSE	OR 0.23 (0.1–0.56)
19	Case control	2,305	≥65 (average 70.3)	N/A	Clinical diagnosis and MMSE	OR 0.26 (0.08–0.88)
20	Prospective observational	1,037	Mean 70	4	MMSE	OR 0.67 (0.42–1.05)
21	Retrospective cohort	1,290,071	≥65 (average 74.6)	N/A	ICD-9	HR 0.46 (0.44–0.48)
22	Prospective observational	1,674	≥60 (mean 70)	5	DSM-IV	HR 0.52 (0.34–0.80)
23	Prospective observational	6,992	Mean 69.4	Mean 9	DSM-III-R	HR 0.57 (0.37–0.90)
24	Propensity analysis	57,669	≥65 (mean 72.9)	Median 11.8	ICD-9	HR 0.385–0.829 depending on exposure
25	Prospective cohort	478	80	69	MHT	F = 5.78 for IQ change from childhood
26	Retrospective cohort	13,626	30–85 (mean 61)	7	ICD-9	OR 1.56 (1.19–2.03) in nonpersistent vs. persistent statin users
27	Cross-sectional	24,595	≥45	N/A	SIS	OR 1.03 (0.86–1.24)
28	Case control	548	≥65 (median 72)	N/A	Various tests	OR 0.8–1.5 depending on test, P = NS
29	Retrospective cohort	2,798	≥65 (56.7% >80)	N/A	Various tests	HR 0.57 (0.77–1.52)
30	Prospective observational	3,587	Mean 72.8	3.4	CDR-SOB, MMSE	P = NS for deterioration
31	Observational cohort	756	Mean 74.2	N/A	Trail Making Test Part B	P = NS
32	Retrospective cohort	991,570	Mean 63.8	30 days	Computer-recorded clinical diagnosis	OR 4.40 (3.01–6.41)

Diabetes Care 2016;39(Suppl. 2):S253

Remembering Statins: Do Statins Have Adverse Cognitive Effects?

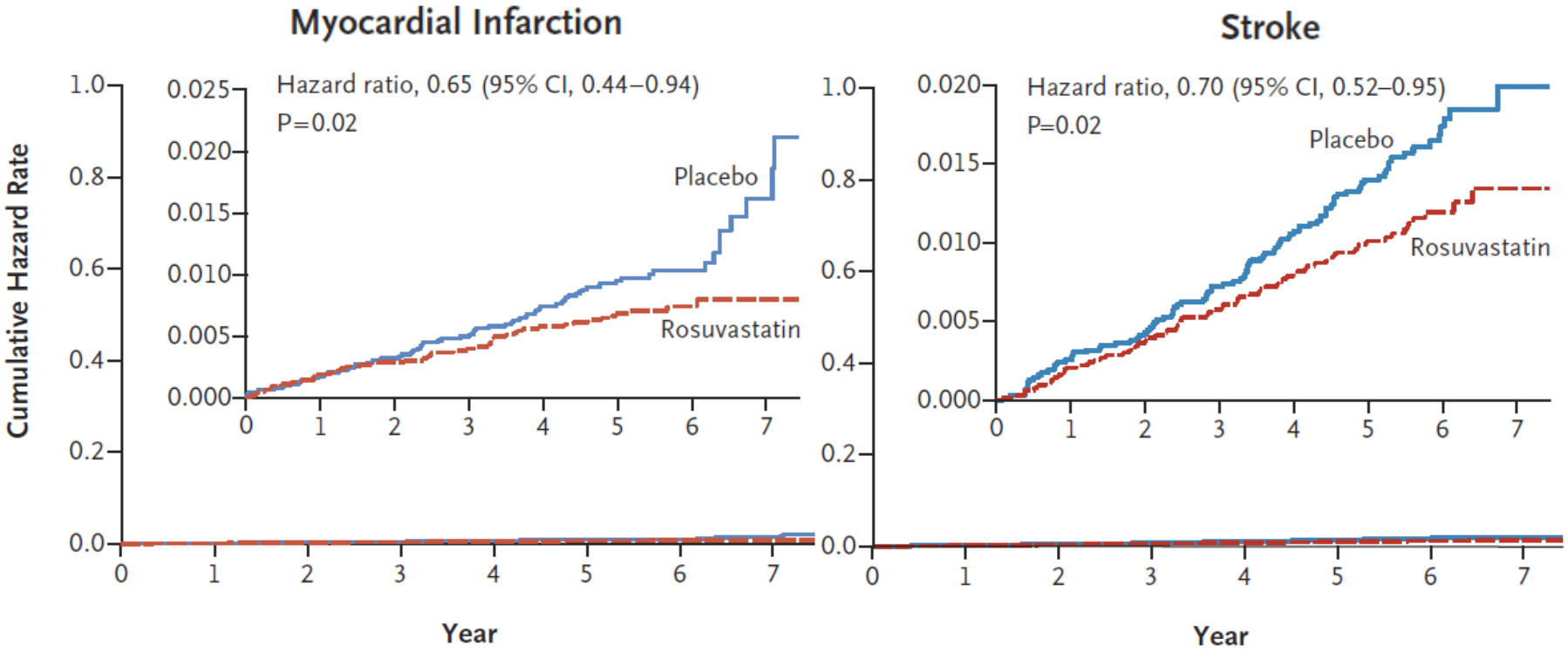
Table 2—Randomized controlled trials with the relationship between statin use and cognitive function as a primary outcome

Ref.	No. of subjects	Age (years)	Follow-up	Diagnosis of cognitive function	Statin tested (mg)	Results (95% CI)
37	25	Average 23.8	4 weeks	Digit symbol substitution test	Simvastatin 40, pravastatin 40	*P* = NS
38	22	36–65	6 weeks	Rey Auditory Learning, Trail Making Test, Embedded Figures, Benton Visual Retention, Verbal fluency	Lovastatin 40, pravastatin 40	*P* = NS
39	36	Mean 51	4 weeks	Digit symbol substitution, auditory vigilance, selective reminding word recall, choice reaction time, finger tapping	Simvastatin 20, pravastatin 40	*P* = NS
40	36	Mean 50	4 weeks	Digit symbol substitution, choice reaction time, auditory vigilance, selective reminding word recall, finger tapping	Lovastatin 40, pravastatin 40	*P* = NS
41	367	Mean 71	6 months	Digit symbol substitution	Lovastatin 20–40	*P* = NS
42	308	Mean 54	6 months	12 neuropsychological tests	Simvastatin 10–40	Detrimental effect on recurrent words, Elithorn maze, and 4-word short-term memory tests
43	209	Mean 46	6 months	10 neuropsychological tests	Lovastatin 20–40	Detrimental effect on attention and psychomotor speed domains, as well as digit vigilance, recurrent words, Elithorn maze, and grooved pegboard tests
44	82	Mean 34	4 weeks	10 neuropsychological tests	Lovastatin 40, pravastatin 40	*P* = NS
45	1,016	>20	6 months	Recurrent words, Elithorn maze, digit vigilance, grooved pegboard tests	Simvastatin 20, pravastatin 40	*P* = NS
46	97	Mean 57	6 months	8 neuropsychological tests	Atorvastatin 10	Beneficial effect on all domains
47	57	Mean 62	73 weeks	Digit Symbol Coding subtest, Trail Making Test, Stroop Color-Word Reading Test	Atorvastatin 10	*P* = NS
48	30	45–75	30 weeks	8 neuropsychological tests	Atorvastatin 10–80	Beneficial effect on verbal memory

Diabetes Care 2016;39(Suppl. 2):S253

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Heart Outcomes Prevention Evaluation (HOPE)–3



N Engl J Med 2016; 374:2021

Heart Outcomes Prevention Evaluation (HOPE)–3

Effect on cognitive function

Assessed in patients ≥70 years (available n = 1,626).
Median age 74 years; 59% female.
Cognitive decline was noted in all patients.

The primary outcome: processing speed
(measured by Digit Symbol Substitution Test at study end):

- ***rosuvastatin vs. placebo: 29.1 vs. 29.4 (p = 0.38)***
- ***BP lowering vs. placebo: 29.1 vs. 29.4 (p = 0.86)***
- ***combination vs. placebo: 29.3 vs. 29.9 (p = 0.63).***

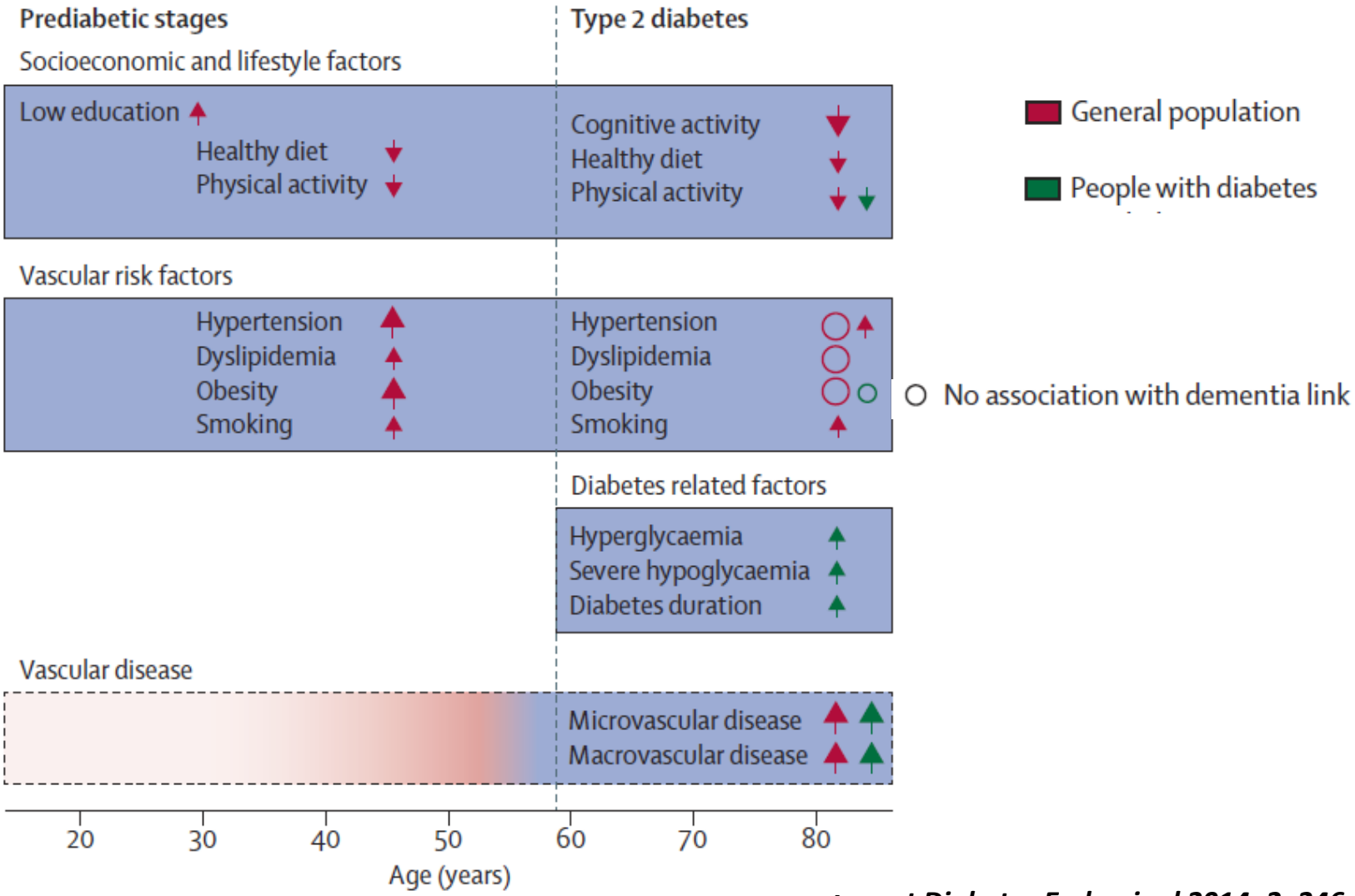
Any functional impairment for rosuvastatin vs. placebo: 57% vs. 59%, p = 0.89; for BP lowering vs. placebo: 59% vs. 56%, p = 0.19.

No signal of differential cognitive decline with all three strategies compared with placebo.

Presented by Dr. Jackie Bosch at the American Heart Association Annual Scientific Sessions
New Orleans, LA, November 13, 2016

Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions

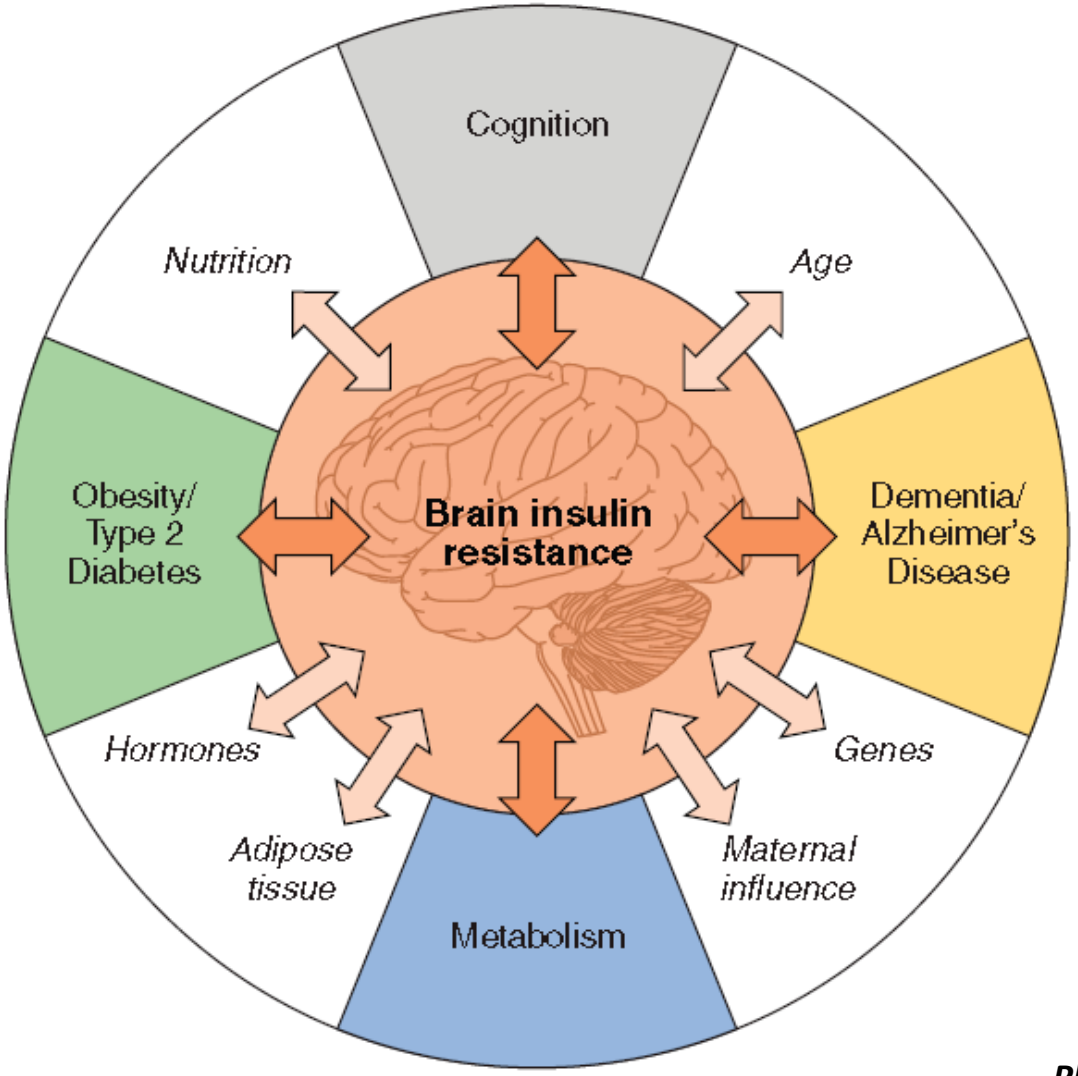
Risk factors for late-life cognitive decline in diabetes



Lancet Diabetes Endocrinol 2014; 2: 246

BRAIN INSULIN RESISTANCE AT THE CROSSROADS OF METABOLIC AND COGNITIVE DISORDERS IN HUMANS

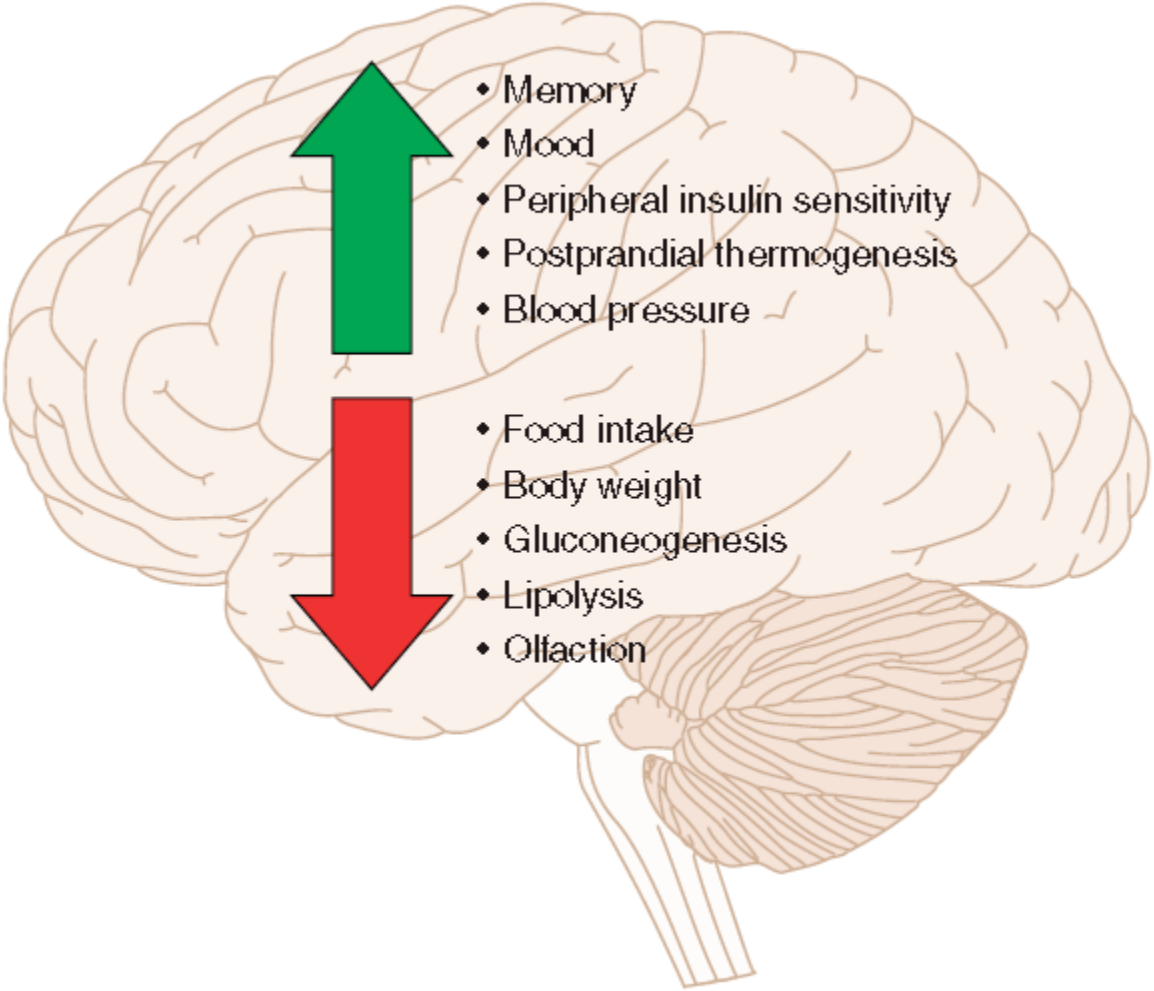
BRAIN INSULIN RESISTANCE IN COGNITIVE AND METABOLIC DISTURBANCES



Physiol Rev 96: 1169, 2016

BRAIN INSULIN RESISTANCE AT THE CROSSROADS OF METABOLIC AND COGNITIVE DISORDERS IN HUMANS

PHYSIOLOGICAL AND BEHAVIORAL EFFECTS OF BRAIN INSULIN ACTION



Physiol Rev 96: 1169, 2016