57° Congresso Nazionale
Società Italiana di Gerontologia e Geriatria

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MiCo – Milano Convention Centeri

LA SINDROME METABOLICA (SM) NEL SOGGETTO ANZIANO: ASPETTI EPIDEMIOLOGICI ED IMPLICAZIONI TERAPEUTICHE

SINDROME METABOLICA, DISABILITÀ E DEFICIT COGNITIVO

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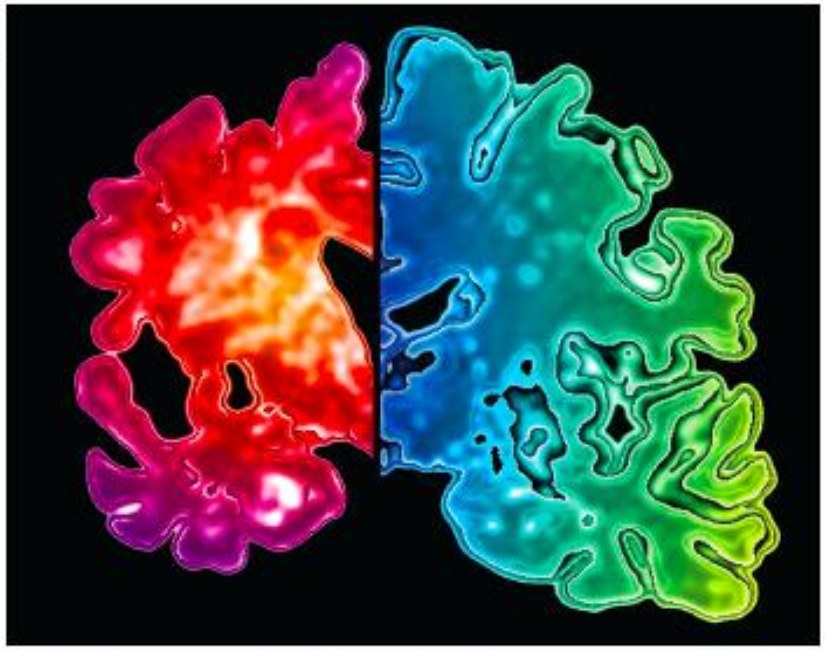
Centro per lo Studio dell'Invecchiamento Cerebrale

NATURE.COM
Read *Nature*'s Outlook on Alzheimer's disease:
go.nature.com/hdiuds

CALLAWAY E.

Nature
06/09/2012
VOL. 489/ pag 13

NEWS IN FOCUS



PASIEKA/SPL

Amyloid plaques accumulate in the brains of Alzheimer's patients (left), but not in unaffected brains (right).

MEDICAL RESEARCH

Alzheimer's drugs take a new tack

Hopes pinned on pre-emptive clinical trials after latest setbacks.

by the hundreds of millions of dollars spent on failed trials will be reluctant to support a continuing search for effective treatments for Alzheimer's and other dementias, which affect an estimated 36 million people worldwide. "Money is tight," says Husseini Manji, global therapeutic area head in neuroscience at Johnson & Johnson in New Brunswick, New Jersey. But "we're still very committed. We think this is a major societal problem that needs tackling."

Amyloid-β plaques are thought to cause Alzheimer's disease by killing neurons and severing their connections to their neighbours. But the evidence is circumstantial. Autopsies of patients show that larger numbers of plaques occur in more severe cases of the disease. Also, mutations in the gene responsible for amyloid-β seem to have either a risk-enhancing or a protective effect. Yet despite all the money invested in amyloid-targeting drugs, "we need to confirm or refute the amyloid hypothesis", says Paul Aisen, a neuroscientist at the University of California, San Diego.

The first results for solanezumab, released by Eli Lilly, which is headquartered in Indianapolis, Indiana, seem to support the hypothesis. The drug is meant to recognize and block amyloid-β before it forms plaques. In patients with mild and moderate forms of disease, however, solanezumab failed to meet its main goals of slowing the decline in memory and other cognitive measures, or in the ability to perform tasks such as eating and maintaining personal care. But other analyses suggest that the drug slowed cognitive decline in patients with milder forms of Alzheimer's. No data have been released on the magnitude of these improvements, though, so it is unclear whether they are enough to make a difference to patients' lives.

"From a purely scientific standpoint, we're

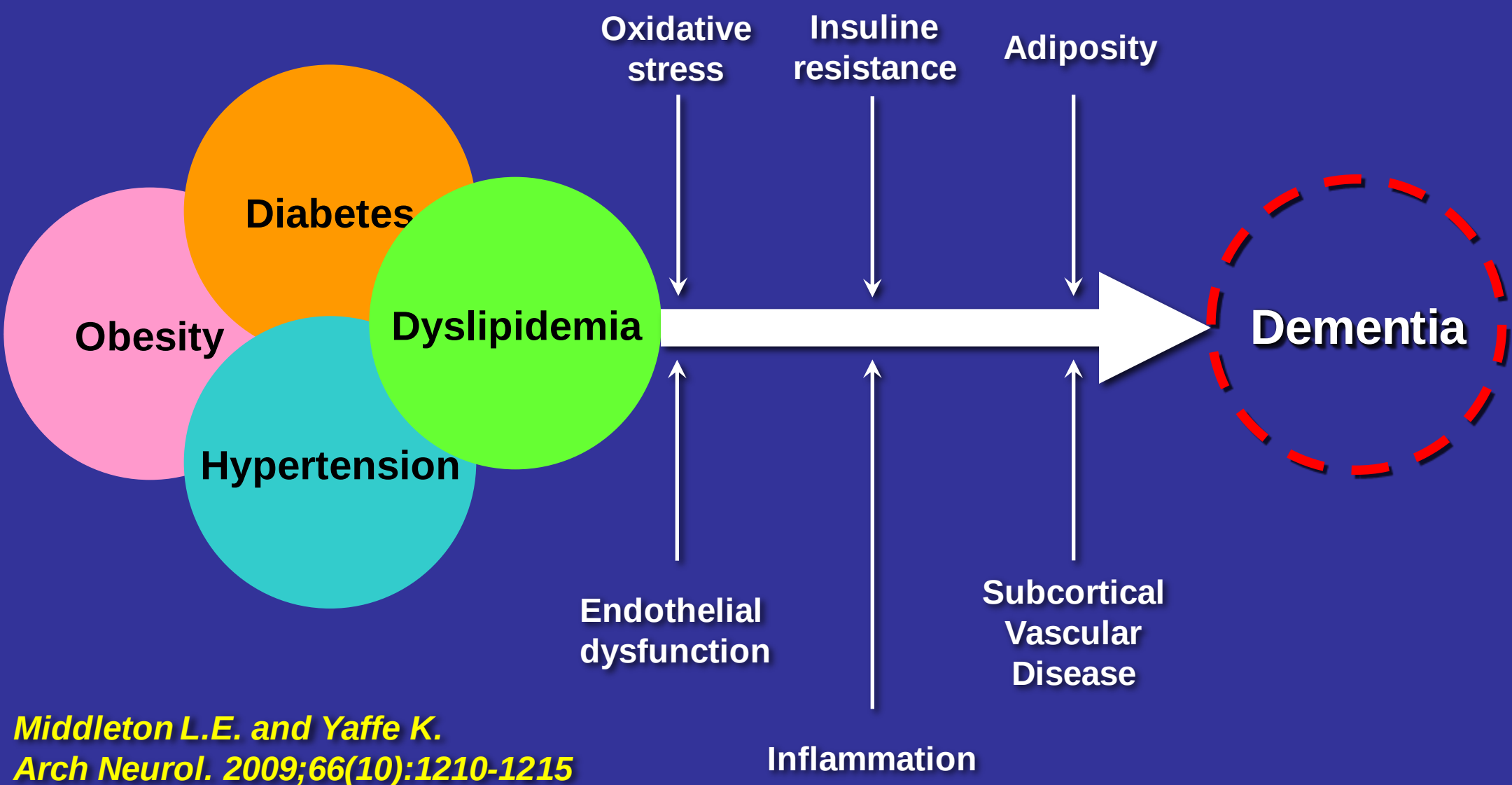
NEUROLOGICAL REVIEW

Promising Strategies for the Prevention of Dementia

Laura E. Middleton, PhD; Kristine Yaffe, MD

Middleton L.E. and Yaffe K. Arch Neurol. 2009;66(10):1210-1215

POSSIBLE MECHANISMS THAT MAY EXPLAIN THE ASSOCIATION BETWEEN VASCULAR RISK FACTORS AND AN INCREASED RISK OF DEVELOPING DEMENTIA



Middleton L.E. and Yaffe K.
Arch Neurol. 2009;66(10):1210-1215

CRITERIA FOR CLINICAL DIAGNOSIS OF THE METABOLIC SYNDROME

Joint Scientific Statement among International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute.

Measure*	Categorical Cut Points
WAIST CIRCUMFERENCE	Population and country specific definitions
TRIGLYCERIDES (or drug treatment for elevated triglycerides)	≥ 150 mg/dL (1.7 mmol/L)
HDL-C (drug treatment for reduced HDL-C)	< 40 mg/dL (1.0 mmol/L) in men < 50 mg/dL (1.0 mmol/L) in women
BLOOD PRESSURE (or antihypertensive drug treatment)	Systolic ≥ 130 and/or diastolic ≥ 85 Hg
FASTING GLUCOSE (or drug treatment for elevated glucose)	≥ 100 mg/dL

*At least three or more of these factors involved

Circulation. 2009;120:1640-1645

ELSEVIER

Neurobiology of Aging 32 (2011) 1932–1941

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian Longitudinal Study on Aging

Vincenzo Solfrizzi[a,*], Emanuele Scafato[b], Cristiano Capurso[c], Alessia D'Introno[a], Anna Maria Colacicco[a], Vincenza Frisardi[a], Gianluigi Vendemiale[c,d], Marzia Baldereschi[e], Gaetano Crepaldi[f], Antonio Di Carlo[e], Lucia Galluzzo[b], Claudia Gandin[b], Domenico Inzitari[g], Stefania Maggi[f], Antonio Capurso[a], Francesco Panza[h], for the Italian Longitudinal Study on Aging Working Group[1]

Solfrizzi V et al Neurobiology of Aging32(2011)1932–1941

HAZARD RATIOS DI PROGRESSIONE VERSO LA DEMENZA NEL CAMPIONE DI SOGGETTI CON MILD COGNITIVE IMPAIRMENT AFFETTI DA SINDROME METABOLICA

		HR Parzialmente corretto (95% CI)	HR Totalmente corretto (95% CI)
Progressione verso la demenza	Intero campione	3.89 (1.09 – 13.86)	8.15 (1.16 – 57.51)

Parzialmente corretto: età e sesso

Totalmente corretto: età, sesso, scolarità, GDS, drink per day, pacchetti di sigarette-anno, fibrinogeno, colesterolo non-HDL, rapporto ApoB/Apo A-I, CAD, stroke

Research paper

Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing

Vincenzo Solfrizzi,[1] Emanuele Scafato,[2] Cristiano Capurso,[3] Alessia D'Introno,[1] Anna Maria Colacicco,[1] Vincenza Frisardi,[1] Gianluigi Vendemiale,[3,4] Marzia Baldereschi,[5] Gaetano Crepaldi,[6] Antonio Di Carlo,[5] Lucia Galluzzo,[2] Claudia Gandin,[2] Domenico Inzitari,[7] Stefania Maggi,[6] Antonio Capurso,[1] Francesco Panza;[1] for the Italian Longitudinal Study on Ageing Working Group*

Solfrizzi V et al J Neurol Neurosurg Psychiatry 2010;81:433e440

HAZARD RATIOS (HRS) OF DEMENTIA IN WHOLE SAMPLE, IN PARTICIPANTS EXCLUDING UNDERNUTRITION AND IN PARTICIPANTS WITH HIGH INFLAMMATION STATUS EXCLUDING UNDERNUTRITION AT BASELINE (ITALIAN LONGITUDINAL STUDY ON AGEING (FIRST AND SECOND SURVEYS, 1992-1996))

	Whole sample	Participants excluding undernutrition at baseline	Participants with high inflammation status excluding undernutrition at baseline¶
	No 2,097	No 1,759	No 938
	HR adjusted* (95% CI)	HR adjusted* (95% CI)	HR adjusted† (95% CI)
Dementia	1.00 (0.61 to 1.65)	1.34 (0.78 to 2.33)	1.24 (0.56 to 2.73)
Alzheimer disease	0.83 (0.42 to 1.63)	1.07 (0.51 to 2.26)	0.84 (0.30 to 2.39)
Vascular dementia	3.71 (1.40 to 9.83)	5.49 ‡ (1.62 to 18.55)	9.55§ (1.17 to 78.17)
Other dementias	0.23 (0.06 to 1.08)	0.26 (0.02 to 1.36)	0.30 (0.03 to 3.43)

Solfrizzi V et al J Neurol Neurosurg Psychiatry 2010;81:433e440

SYNERGISTIC EFFECT OF OVERALL METABOLIC SYNDROME (METS) (≥3 METS COMPONENTS) VERSUS INDIVIDUAL METS COMPONENT EFFECTS ON THE RISK OF DEMENTIA (ALL CAUSES), ALZHEIMER DISEASE, VASCULAR DEMENTIA AND OTHER DEMENTIAS IN THE WHOLE SAMPLE (ITALIAN LONGITUDINAL STUDY ON AGEING (FIRST AND SECOND SURVEYS, 1992 - 1996))

Statistics	Dementia HR (95% CI)	Alzheimer disease HR (95% CI)	Vascular dementia HR (95% CI)	Other dementias HR (95% CI)
Likelihood ratio test	χ^2= 5.13, df=1, p<0.05	χ^2= 0.38, df=1, p<0.60	χ^2= 19.82, df=1, p<0.01	χ^2= 1.65, df=1, p<0.20
Rothman synergy index	0.66 (0.20 to 2.25)	-	4.66 (1.05 to 28.76)	-

Solfrizzi V et al J Neurol Neurosurg Psychiatry 2010;81:433e440

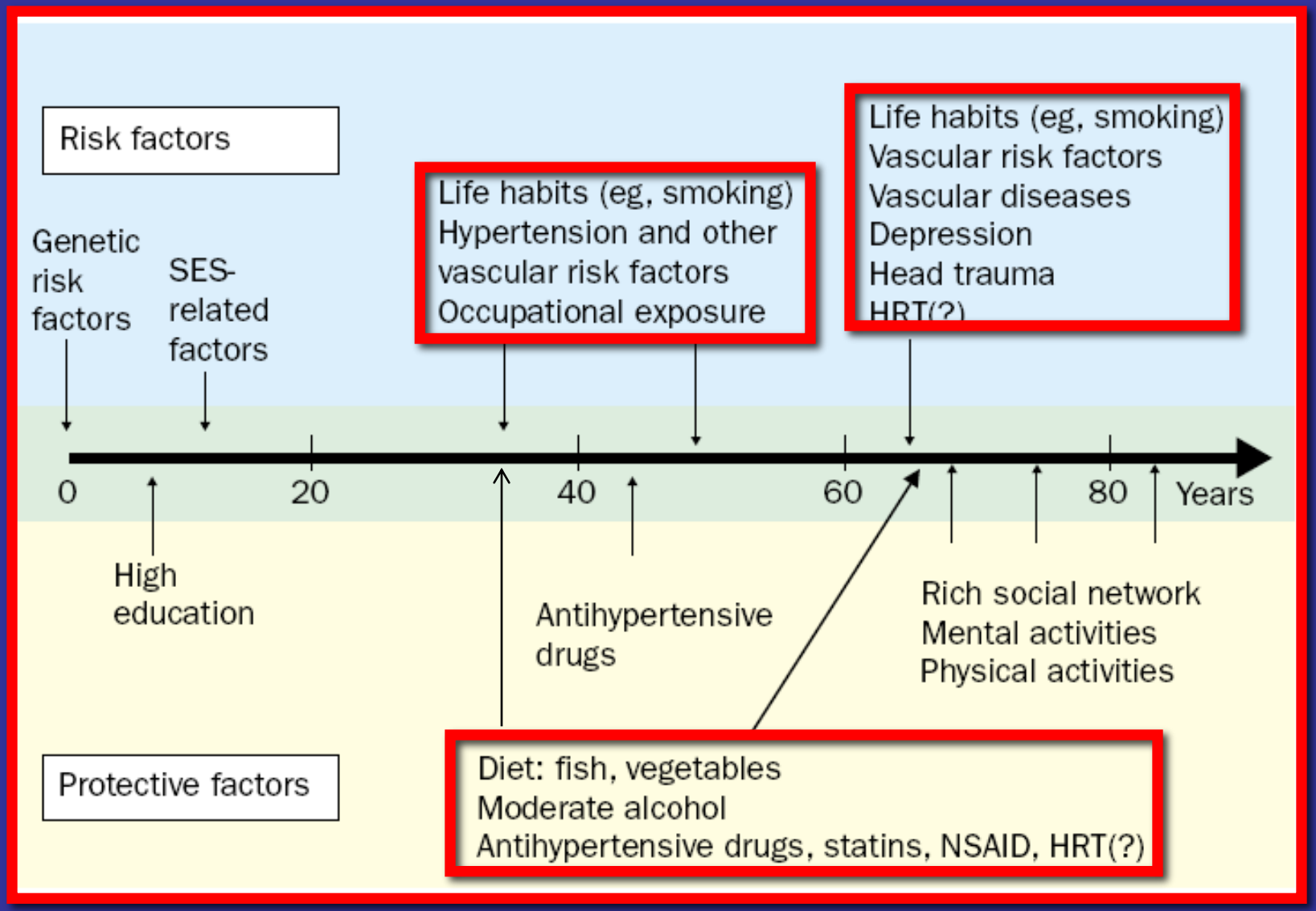
Can the Treatment of Vascular Risk Factor Slow Cognitive Decline in Alzheimer's Disease Patients?

AVAILABLE EVIDENCE THAT TREATMENT OF VASCULAR RISK FACTORS CAN PREVENT COGNITIVE DECLINE OR DEMENTIA

Risk Factos	No.of RCTs	Meta-analysis	Categorical Cut Points
Hypertension	6	Yes	Decreased incidence of dementia, slowing cognitive decline
Diabetes	2	No	No effect on cognition. Trend toward increased dementia risk
Hyper-cholesterolemia	2	Yes	No effect on cognitive decline
Obesity	0	No	n.a.
Multy-component	2	No	No effect on cognitive decline in early AD (n=1) or vascular disease (n=1)

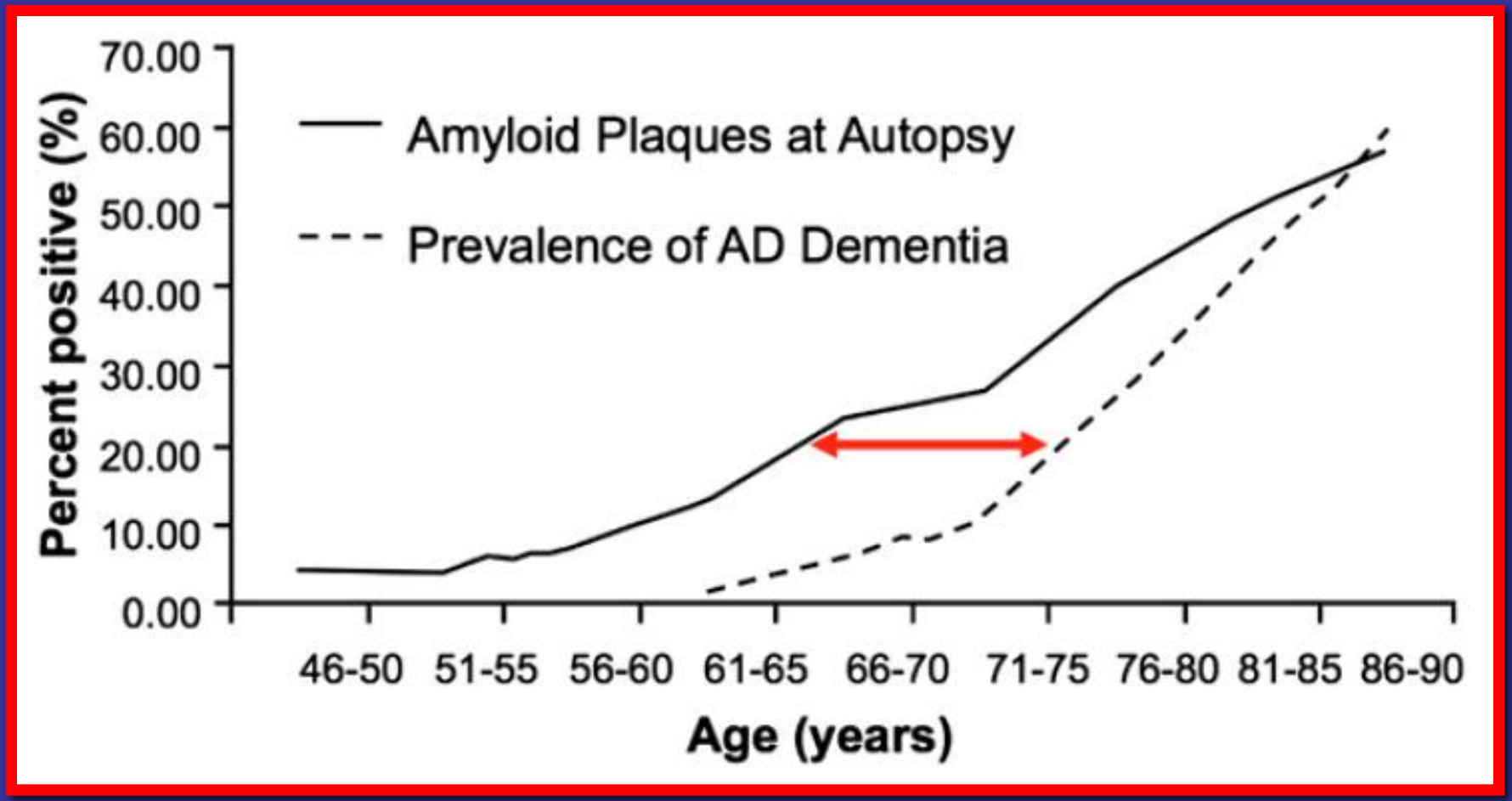
Richard F et al Journal of Alzheimer's Disease 32 (2012) 733–740

THE TIMELINE OF RISK FACTORS AND PROTECTIVE FACTORS FOR DEMENTIA



Fratiglioni L et al Lancet Neurol 2004; 3: 343–53

APPEARANCES OF PLAQUES vs DEMENTIA



R.A. Sperling et al. / Alzheimer's & Dementia- (2011) 1–13

ASSOCIATIONS BETWEEN VASCULAR RISK FACTORS AND ALZHEIMER'S DISEASE IN META-ANALYSES

Risk factor	Study design	Estimate	Reference
Obesity			
Low BMI in midlife	Cohort studies	1.96, 1.32–2.92	[1]
Overweight in midlife	Cohort studies	1.35 (1.19–1.54)	[1]
High BMI in midlife	Cohort studies	2.04, 1.59–2.62	[1]
Blood pressure			
Hypertension*	Cohort studies	1.01, 0.87–1.18	[2]
Antihypertensive medication*	Cohort studies	0.90, 0.79–1.03	[2]
Late-life diastolic blood pressure**	Cohort studies	0.95, 0.91–1.00	[3]
Late-life antihypertensive medication	Randomized controlled trials	0.89, 0.74–1.07	[4]
Diabetes in midlife	Cohort studies	1.54 (1.33–1.79)	[5]

*Mainly based on studies in older individuals; **midlife studies could not be pooled together.

1. *Anstey KJ, et al. (2011) Obes Rev 12, e426-e437*
2. *Guan JW, et al (2011) J Alzheimers Dis 27, 799-807.*
3. *Power MC,et al (2011) Epidemiology 22, 646-659*
4. *McGuinness B et al (2009) Cochrane Database Syst Rev (4), CD004034.*
5. *Profenno LA et al Biol Psychiatry 67, 505-512.*

Duration of antihypertensive drug use and risk of dementia

A prospective cohort study

Study design:
Followed up from baseline (1990–1993) until 2005 for incident dementia

Study population:
6,249 participants (60% women) of a prospective population-based cohort

Objective:
association between the duration of antihypertensive use and risk of dementia.

Haag M.D.M. et al Neurology 2009;72:1727–1734

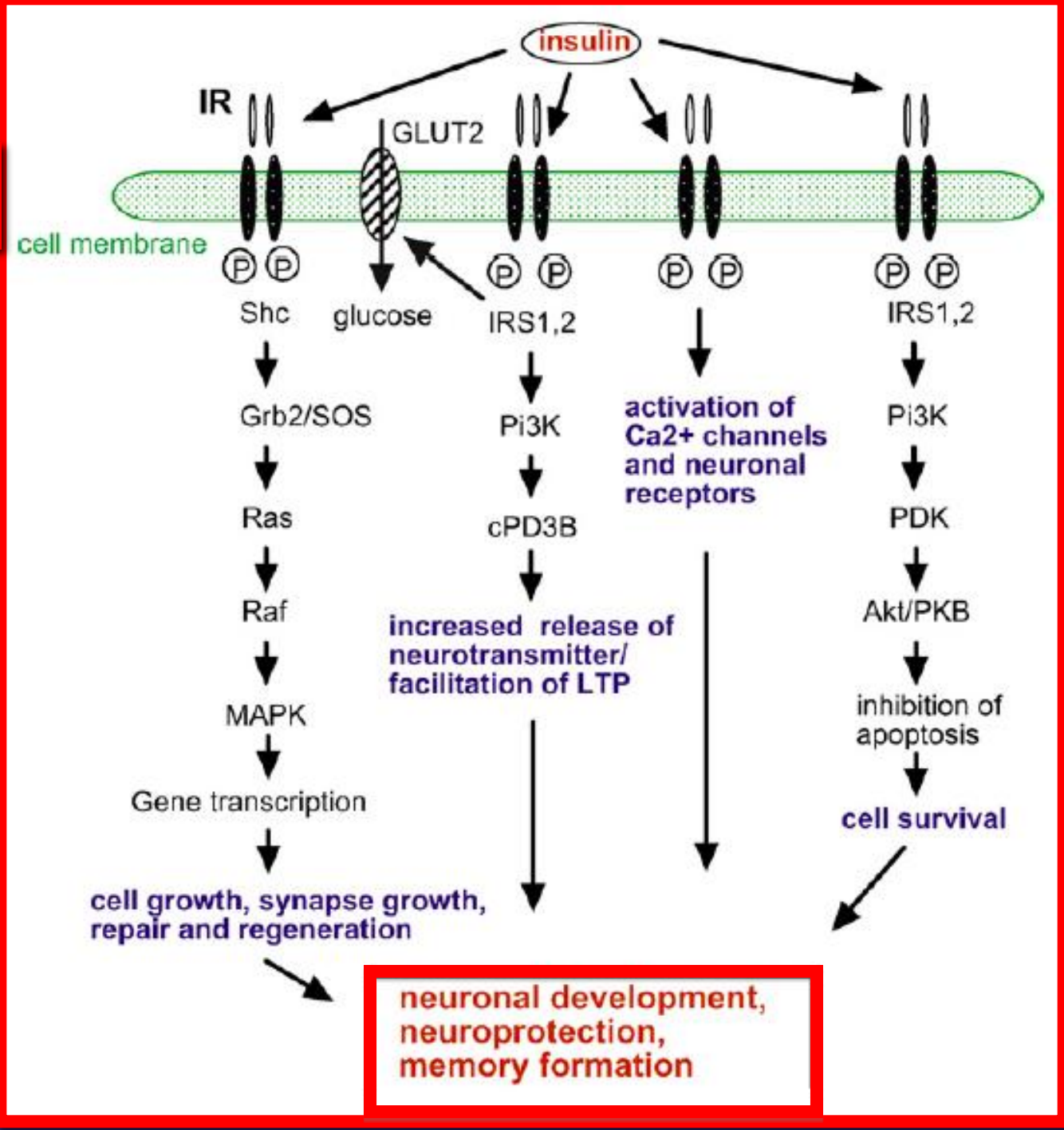
HAZARD RATIOS (HR) OF ALL DEMENTIA AND ALZHEIMER DISEASE WITH USE OF ANTIHYPERTENSIVE DRUGS ACROSS STRATA OF AGE

	All dementia			Alzheimer disease		
		HR (95% CI)			HR (95% CI)	
	Cases	Model I*	Model II†	Cases	Model I*	Model II†
≤75 years of age						
Never use	139	1.00 (ref)		110	1.00 (ref)	
Antihypertensive use						
<1.6 y	60	1.08 (0.80-1.47)	1.03 (0.75-1.41)	48	1.11 (0.78-1.57)	1.11 (0.78-1.56)
1.6-5.3 y	42	0.72 (0.50-1.03)	0.68 (0.47-0.99)	32	0.66 (0.44-1.00)	0.67 (0.55-1.02)
>5.3 y	19	0.59 (0.36-0.99)	0.56 (0.33-0.95)	14	0.56 (0.31-1.01)	0.57 (0.41-1.04)
Per year treatment	121	0.93 (0.87-0.99)	0.92 (0.86-0.98)	94	0.91 (0.85-0.98)	0.92 (0.85-0.99)
>75 years of age						
Never use	124	1.00 (ref)		104	1.00 (ref)	
Antihypertensive use						
<1.6 y	66	0.81 (0.60-1.10)	0.76 (0.56-1.04)	54	0.79 (0.56-1.10)	0.75 (0.53-1.06)
1.6-5.3 y	56	0.75 (0.53-1.05)	0.68 (0.48-0.96)	51	0.76 (0.53-1.09)	0.70 (0.48-1.02)
>5.3 y	21	0.89 (0.52-1.52)	0.83 (0.48-1.43)	19	0.90 (0.51-1.59)	0.85 (0.48-1.51)
Per year treatment	143	0.98 (0.91-1.04)	0.97 (0.90-1.04)	124	0.97 (0.90-1.04)	0.96 (0.89-1.04)

VASCULAR RISK FACTORS AS TREATMENT TARGET TO PREVENT COGNITIVE DECLINE

Biological plausibility

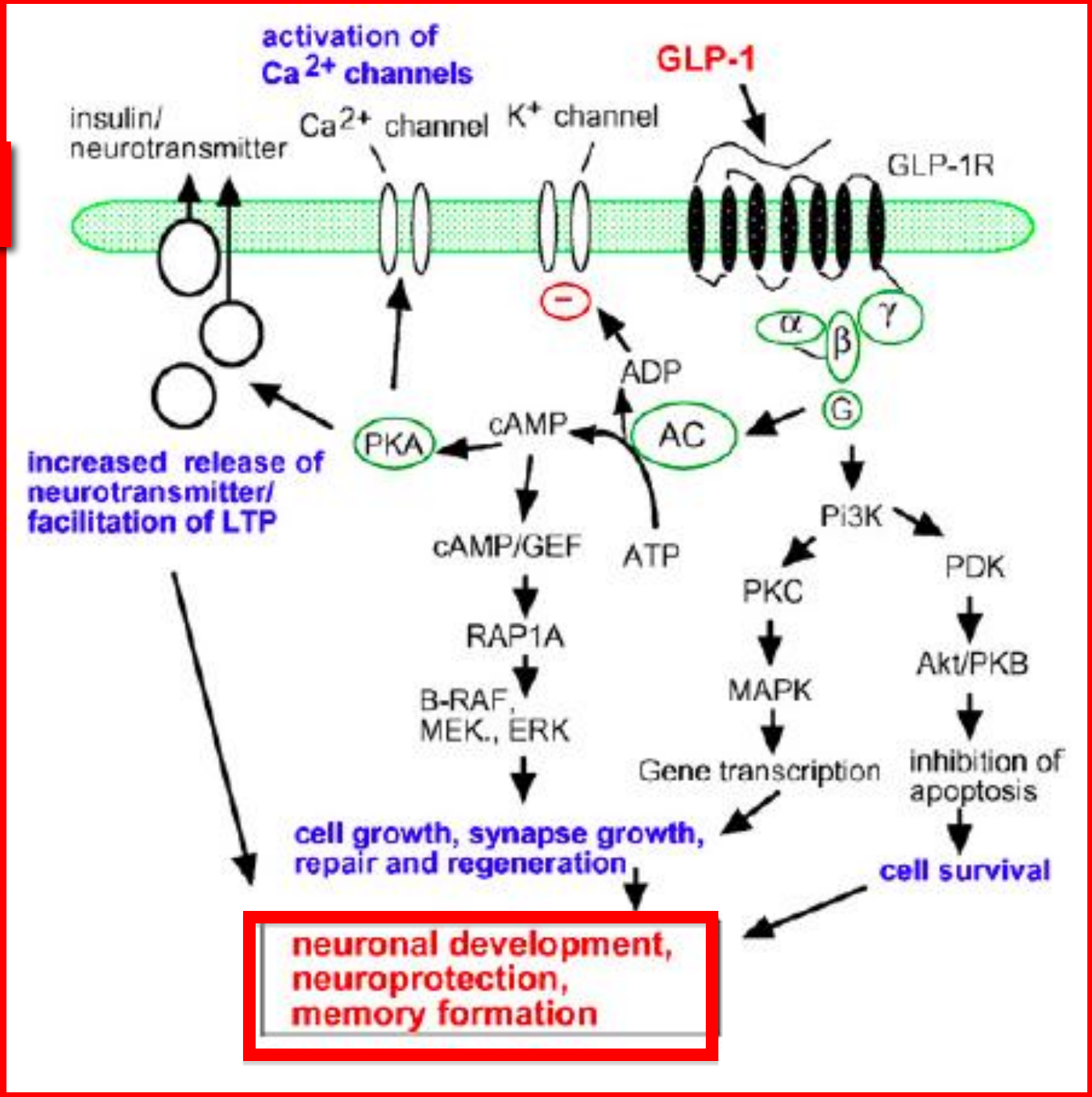
PATHWAY AND FUNCTION OF INSULIN RECEPTOR ACTIVATION



C. Hölscher, L. Li

Neurobiology of Aging 31 (2010) 1495–1502

PATHWAY AND FUNCTION OF GLP-1 RECEPTOR ACTIVATION

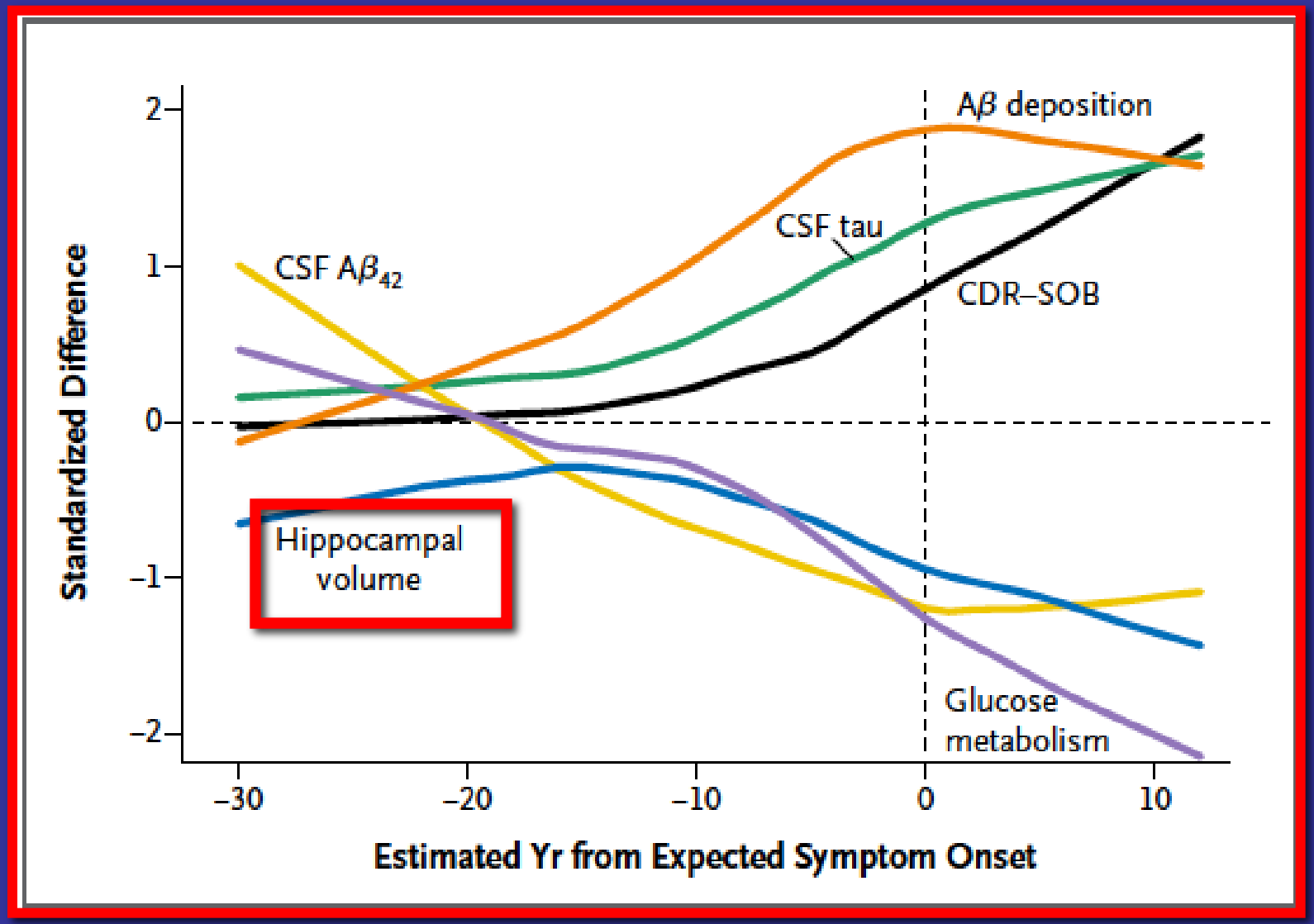


C. Hölscher, L. Li

Neurobiology of Aging
31 (2010) 1495–1502

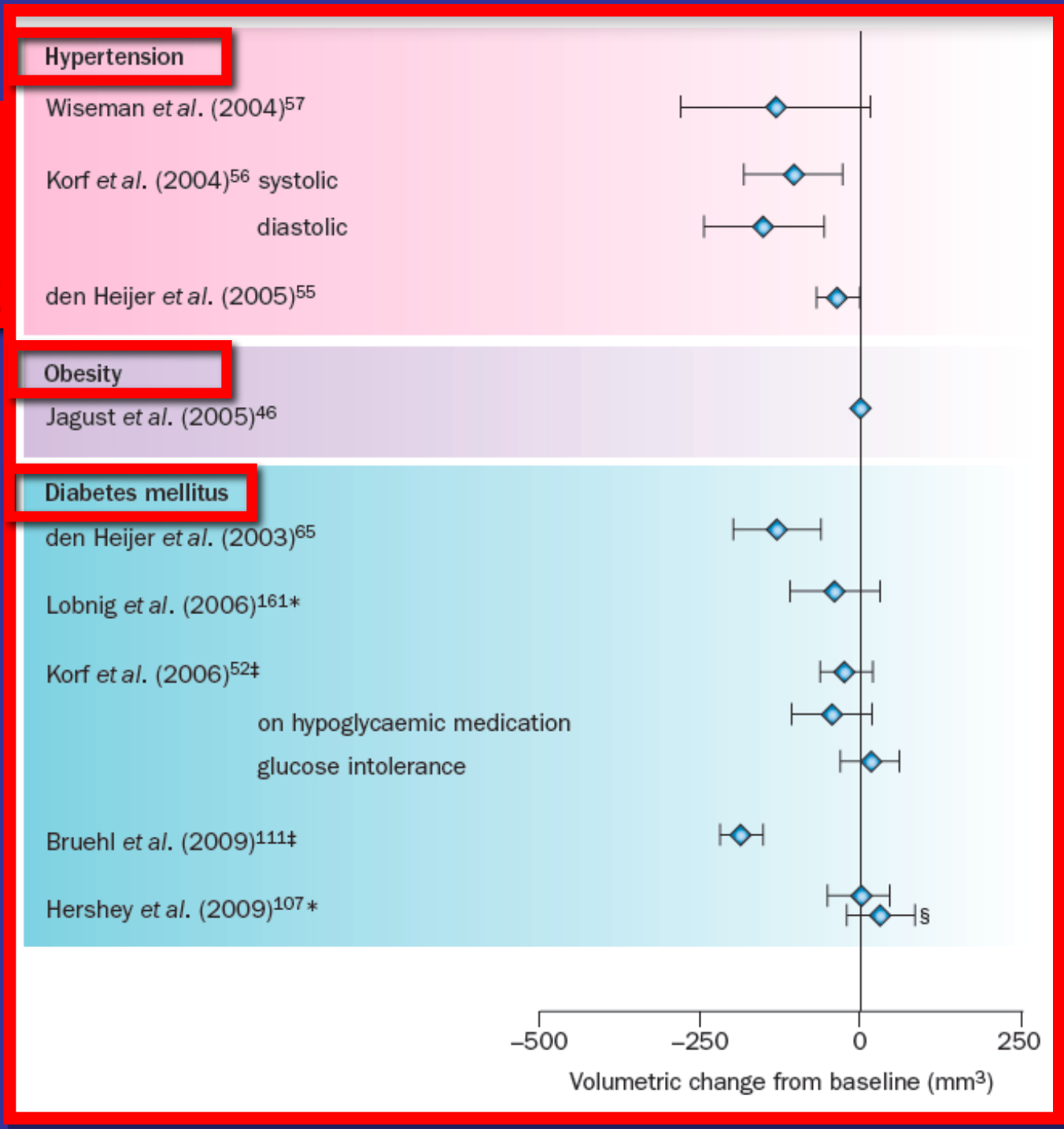
GLP-1: Glucagon-like peptide-1

COMPARISON OF CLINICAL, COGNITIVE, STRUCTURAL, METABOLIC, AND BIOCHEMICAL CHANGES AS A FUNCTION OF ESTIMATED YEARS FROM EXPECTED SYMPTOM ONSET.



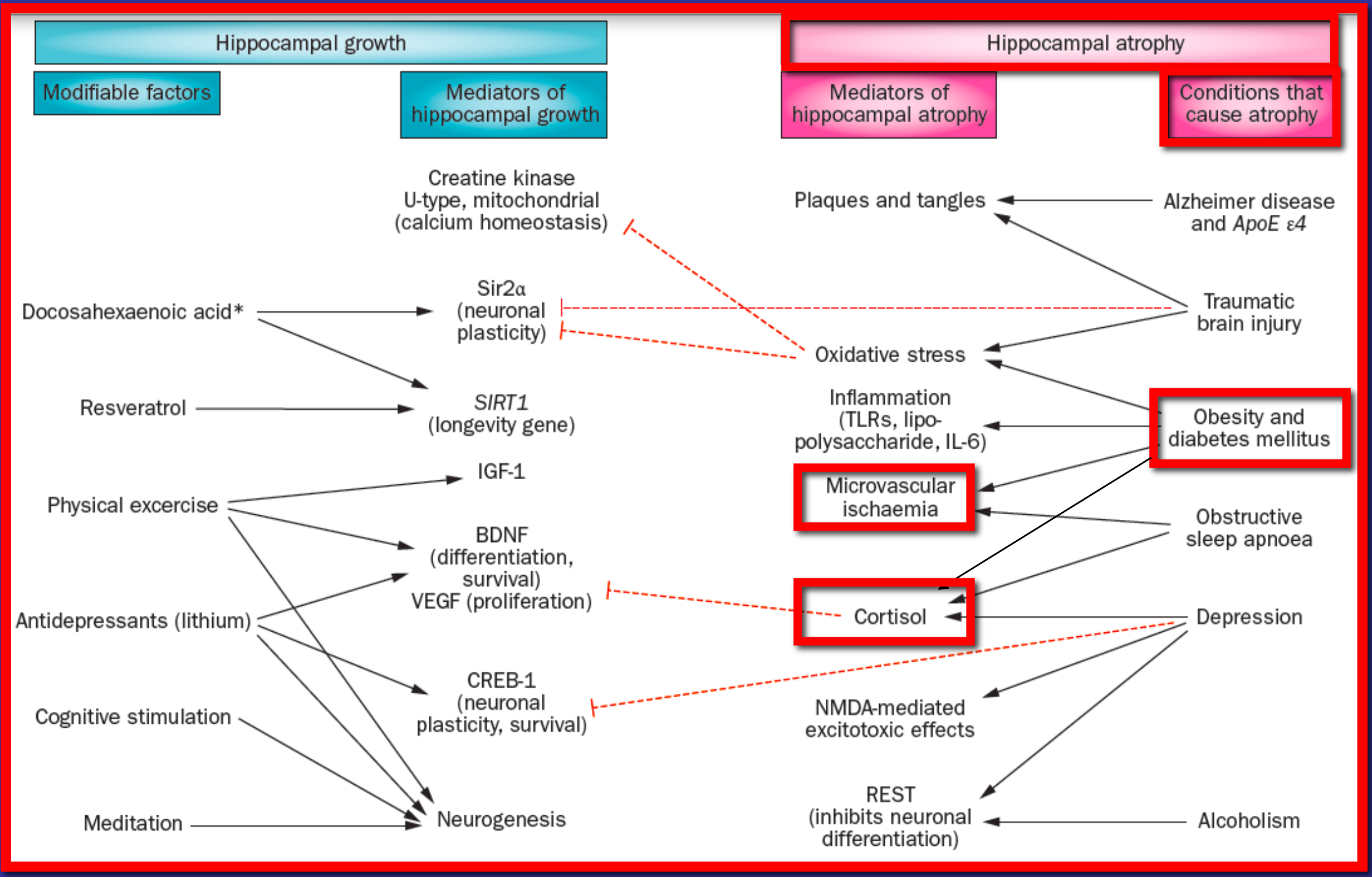
Bateman RJ et al NEJM 2012;367;9

COMPARISON OF STUDIES OF HIPPOCAMPAL VOLUME IN PATIENTS WITH CARDIOVASCULAR DISEASE



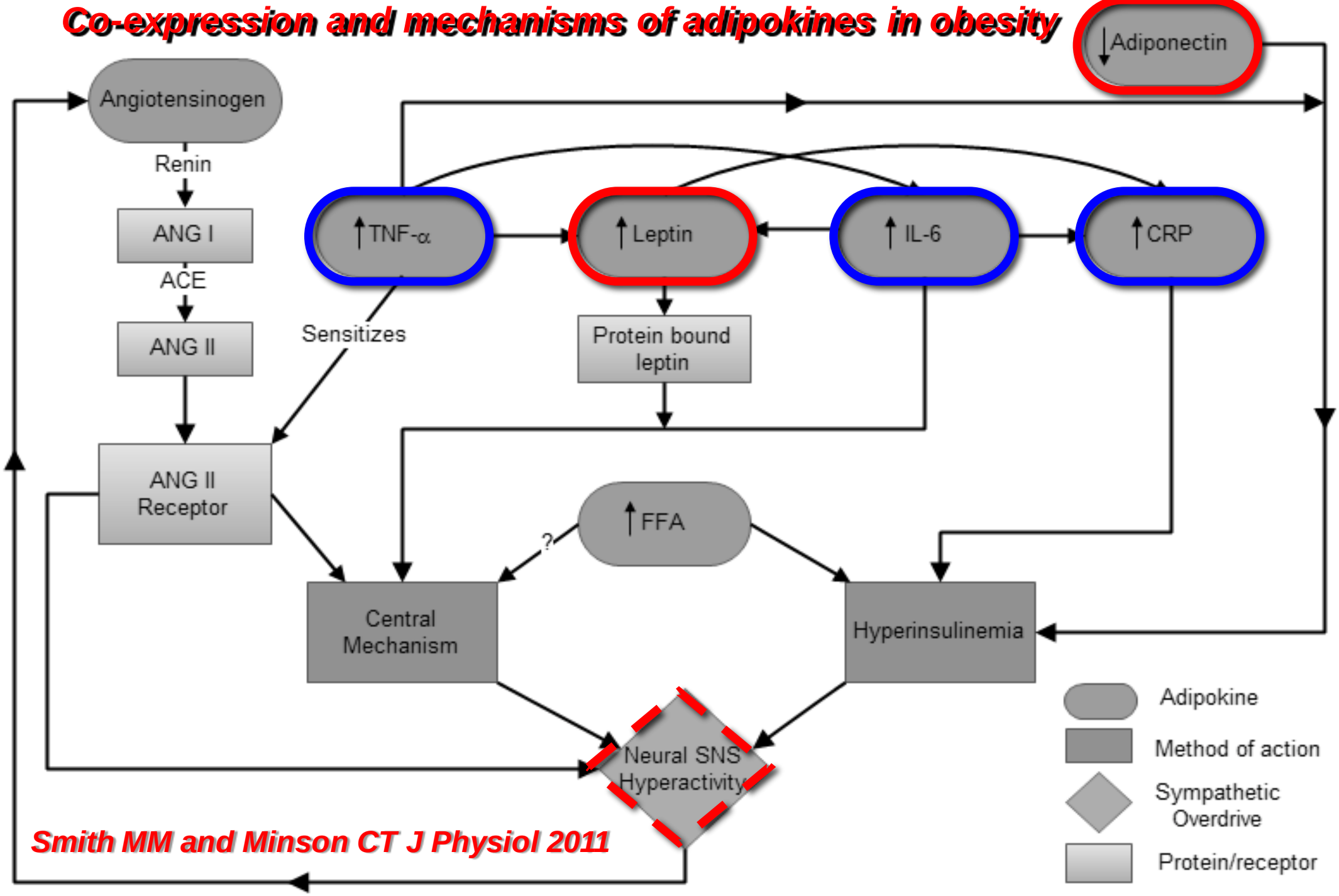
Fotuhi, M. et al. (2012)

Nat. Rev. Neurol.
doi:10.1038/nrneurol.2012.27



Fotuhi, M. et al. Nat. Rev. Neurol 2012

Co-expression and mechanisms of adipokines in obesity



Smith MM and Minson CT J Physiol 2011

METABOLIC SYNDROME, COGNITIVE DECLINE AND DEMENTIA

Public health interventions

In Context

Locked up and at risk of dementia

Factors such as inactivity, poor nutrition, smoking, and depression could contribute to an increased risk of dementia in prisoners. But limited prison resources mean that even simple measures to reduce these risks might not be implemented. Mario Christodoulou reports.

Christodoulou M Lancet 2012;379: 1975–82

"The prison regime provides an environment in which modifiable risk factors can be easily controlled, but limited resources could hinder the delivery of such strategies."

Christodoulou M Lancet 2012;379: 1975–82

Review

The projected effect of risk factor reduction on Alzheimer's disease prevalence

Deborah E Barnes, Kristine Yaffe

The aim of this Review was to summarise the evidence regarding seven potentially modifiable risk factors for AD: diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity.

Additionally, the Authors projected the effect of risk factor reduction on AD prevalence by calculating population attributable risks (the percent of cases attributable to a given factor) and the number of AD cases that might be prevented by risk factor reductions of 10% and 25% worldwide and in the USA.

Yaffe K et al Lancet Neurol 2011; 10: 819–28

ALZHEIMER'S DISEASE CASES ATTRIBUTABLE TO POTENTIALLY MODIFIABLE RISK FACTORS WORLDWIDE AND IN THE USA

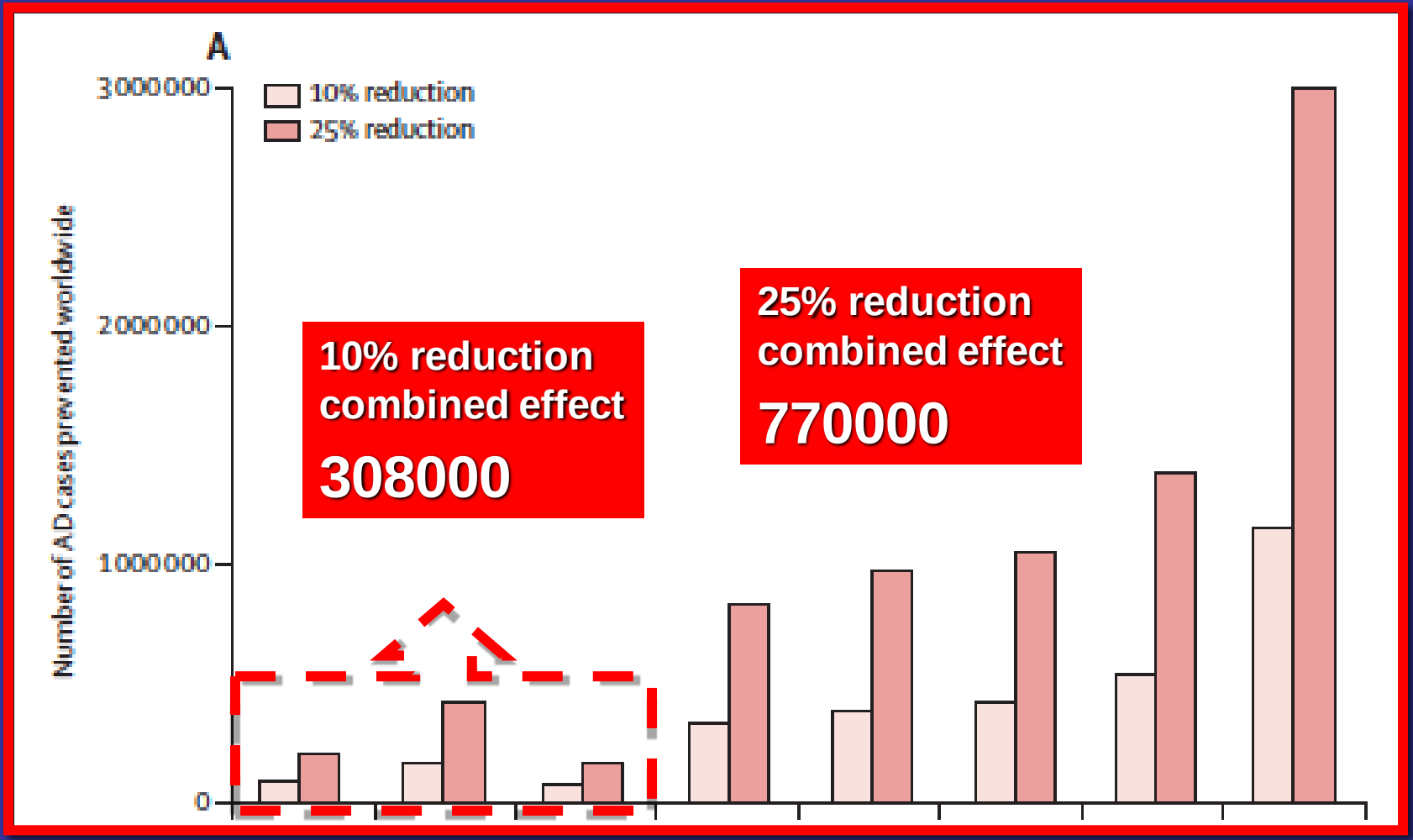
	Population prevalence	Relative risk (95% CI)	PAR (confidence range)	Number of cases attributable (thousands; confidence range)
Worldwide				
Diabetes mellitus	6·4%	1·39 (1·17–1·66)	2·4% (1·1–4·1)	826 (365–1374)
Midlife hypertension	8·9%	1·61 (1·16–2·24)	[illegible]	[illegible] (476–3369)
Midlife obesity	3·4%	1·60 (1·34–1·92)	[illegible]	[illegible] (387–1028)
Depression	13·2%	1·90 (1·55–2·33)	10·6% (6·8–14·9)	3600 (2295–5063)
Physical inactivity	17·7%	1·82 (1·19–2·78)	12·7% (3·3–24·0)	4297 (1103–8122)
Smoking	27·4%	1·59 (1·15–2·20)	13·9% (3·9–24·7)	4718 (1338–8388)
Low education	40·0%	1·59 (1·35–1·86)	19·1% (12·3–25·6)	6473 (4163–8677)
Combined (maximum)	..	..	50·7%	17 187 028*

9,2%

3.131.733

Yaffe K et al Lancet Neurol 2011; 10: 819–28

POTENTIAL NUMBER OF AD CASES THAT COULD BE PREVENTED THROUGH RISK FACTOR REDUCTION



Yaffe K et al Lancet Neurol 2011; 10: 819–28

Prevention of cognitive decline in ageing: dementia as the target, delayed onset as the goal

. . . . the choice of endpoint is crucial, although with present knowledge the delay of dementia onset seems to be the only realistic endpoint.[9] Because age is the strongest determinant of dementia, an intervention should be regarded as effective if disease onset can be postponed.

Fratiglioni L et al Lancet Neurol. 2011 Sep;10(9):778-9

MEAN AGE OF ONSET OF CHF BETWEEN 1948 AND 1988

57.3±7.6 years in the 1950s,

65.9±7.9 years in the 1960s,

71.6±9.4 years in the 1970s, and

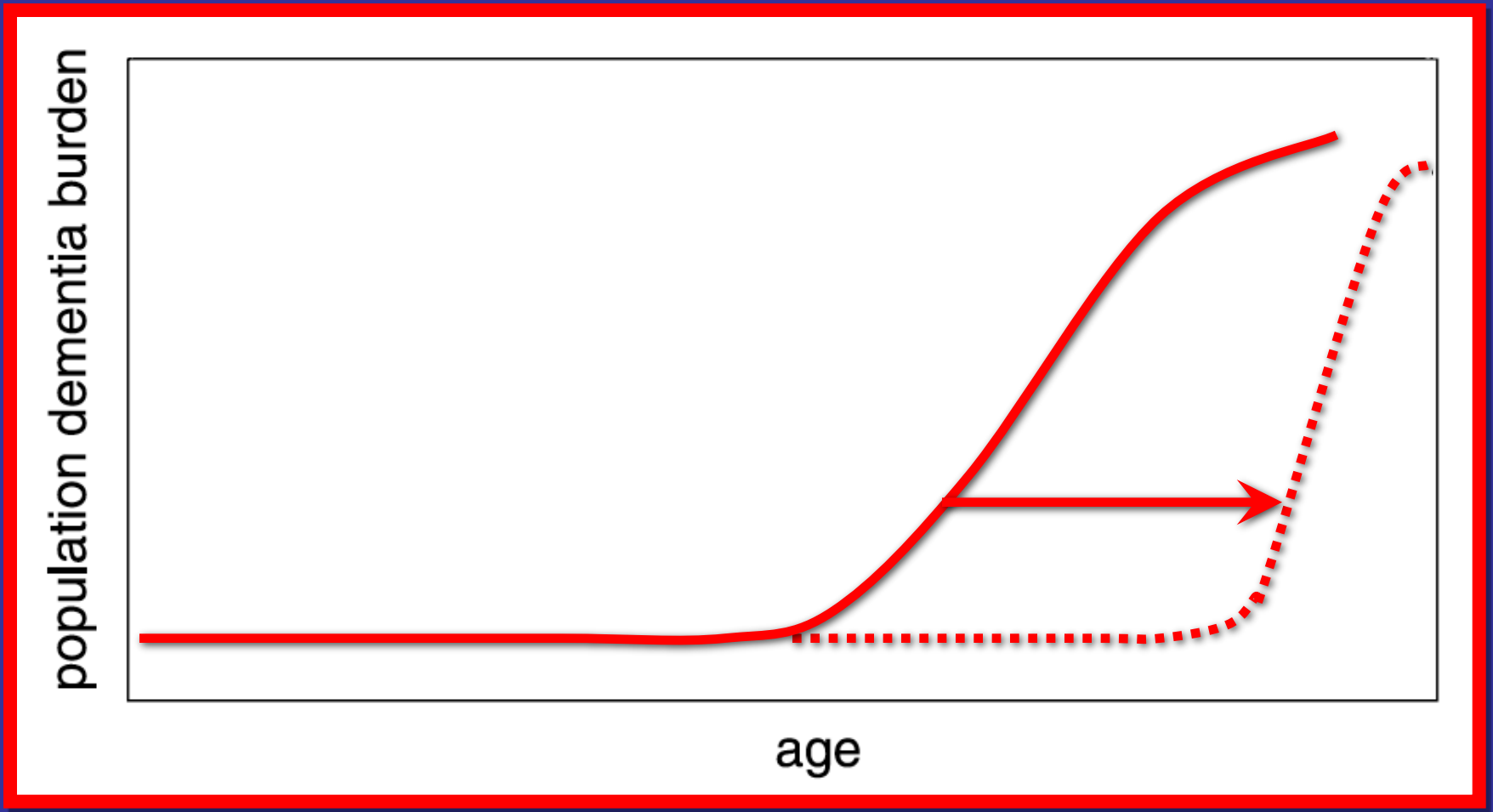
76.4±10.0 years in the 1980s

Trend

$p<0.001$

KK Ho, et al Circulation 1993;88;107-115

AGE, THE EFFECT OF PREVENTIVE INTERVENTIONS AND COMPRESSION OF MORBIDITY



Richard et al Journal of Alzheimer's Disease 32 (2012) 733–740