Vascular Factors that modify risk for dementia

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Sunnybrook HEALTH SCIENCES CENTRE

HEART & STROKE FOUNDATION Canadian Partnership for Stroke Recovery

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CME Lecturer:

Novartis, Eisai

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Learning Objectives

1. Appreciate that the brain is a key target organ for vascular health and disease, as revealed by modern neuroimaging techniques
2. Understand the role that vascular disease may play role in development of Alzheimer's disease (AD).
3. Recognize the importance of lifestyle choices (especially exercise) and vascular risk management in protecting brain health

Cost of Dementia in the United States

- New England Journal study in 2013 suggested we are unprepared for the coming surge in the ***cost*** and ***cases*** of **dementia**
- **Estimates:**

  in 2013: 3.8 million people with dementia at annual cost of $157- $215 B

  by 2040: 9.1 million people with dementia-- annual estimated cost will be $379-$611B

Hurd NEJM 2013

Aging trends

- **In 1900**, life expectancy was 47 years; 3 million people in the US (4% of the population) were > 65 and typically were ill.

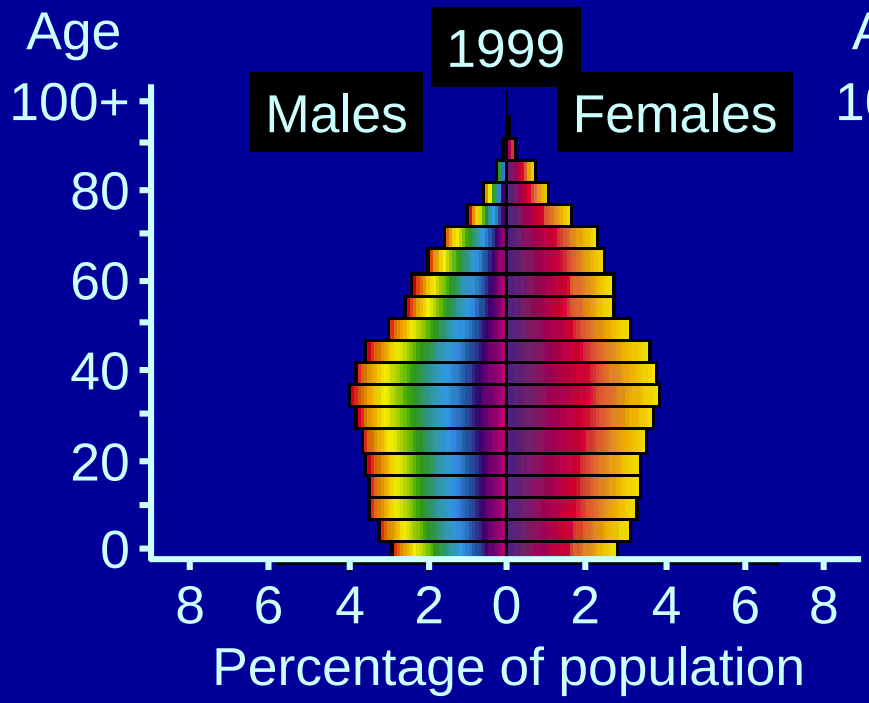
- **By 1990**, life expectancy was >75 years, 30 million people were > 65 (12 % of the population) and many were healthy.

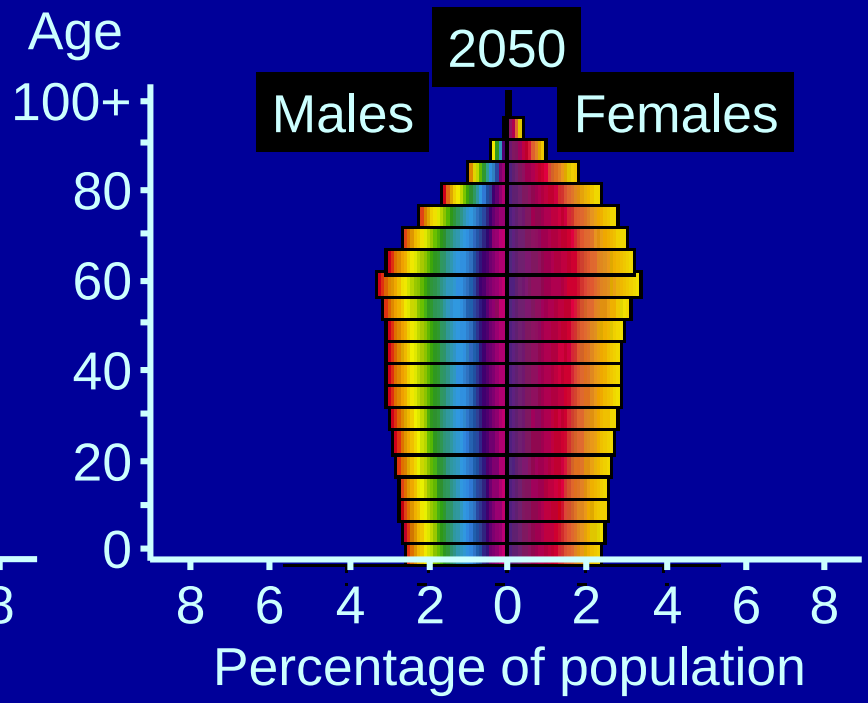
- **As of 2000**, 50% of those born in 2000 may live to be 100 years old *(Christensen et al Lancet 2011)*

- *Aging rivals all other risk factors for the common forms of AD and Stroke*

Aging Trends

(developed countries)





Boomer bulge:10,000 baby boomers are reaching 65 every day in the US

For the first time in history, adults in developed countries have more parents than children

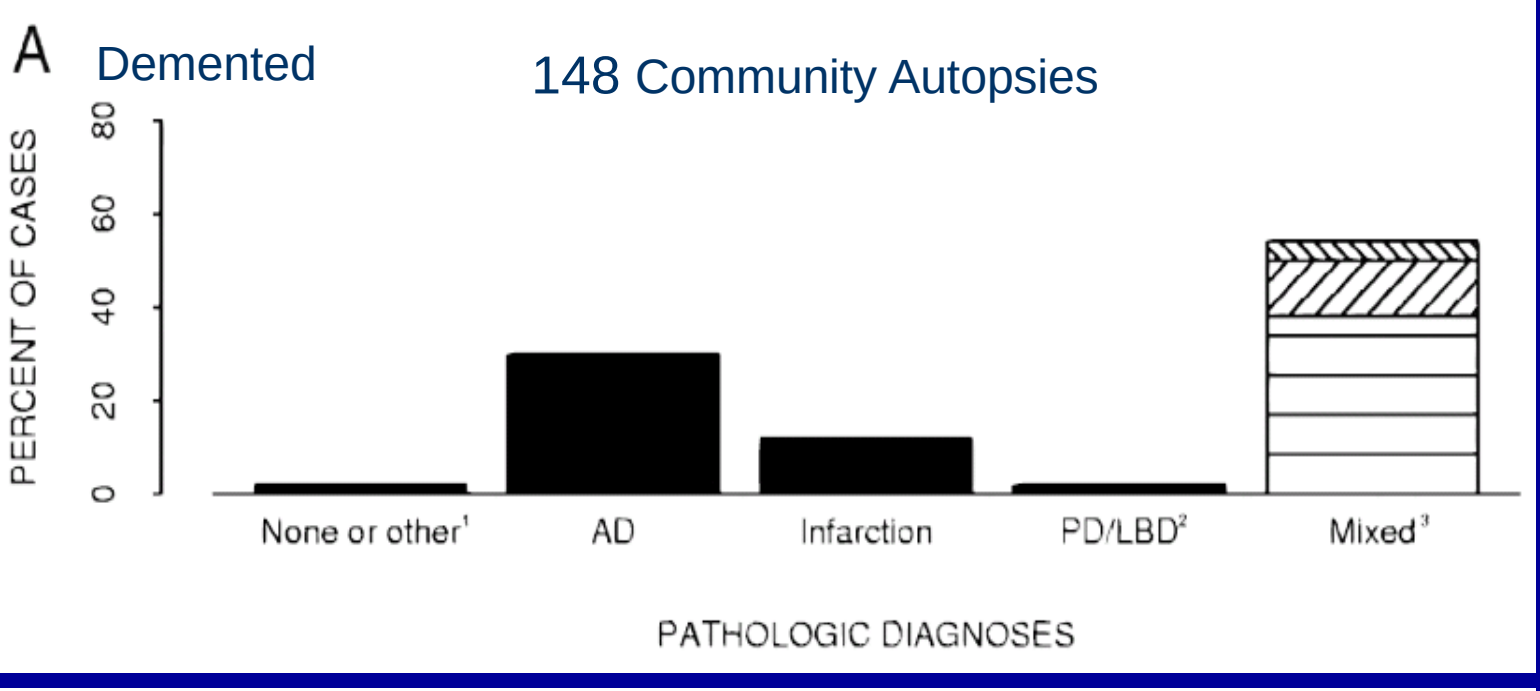
Co-Morbid AD CVD is an increasing reality with our aging demographics

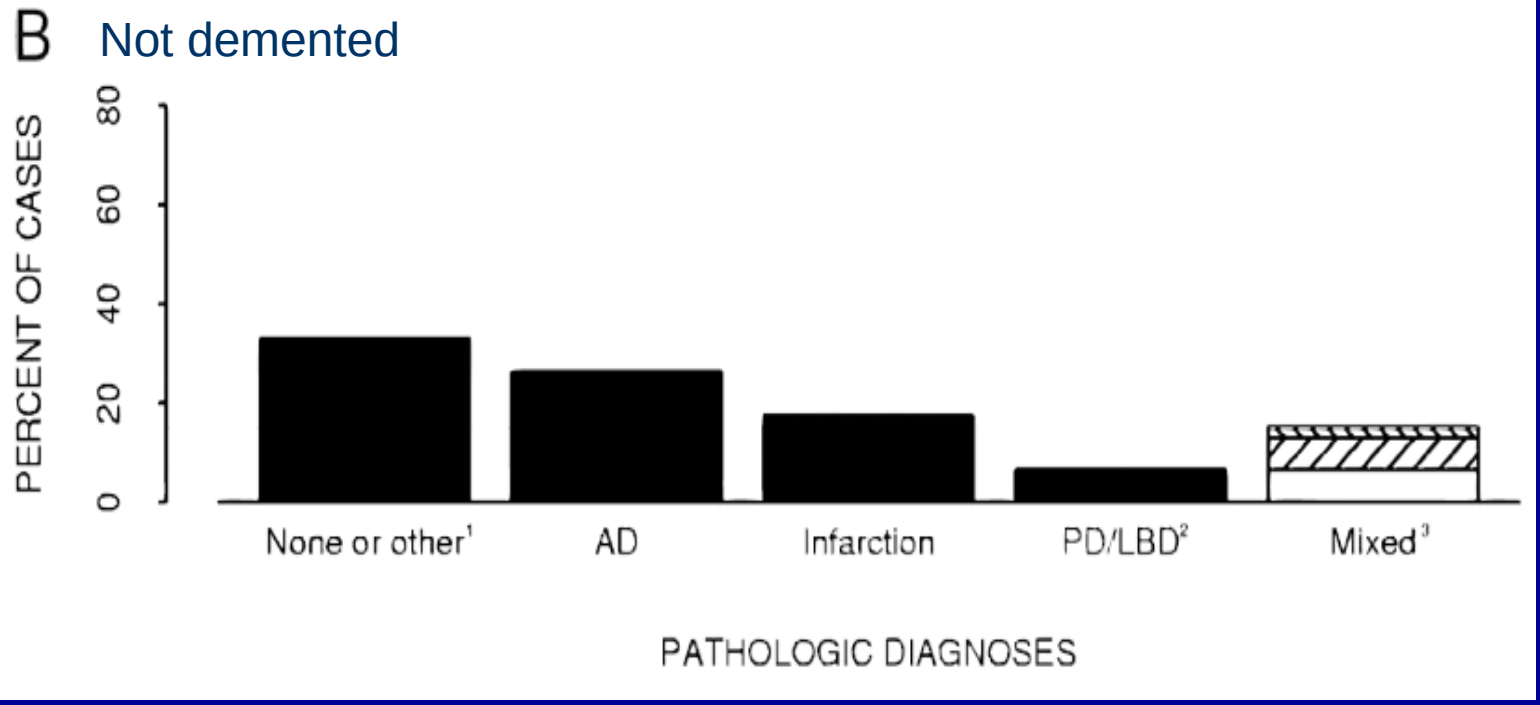
Coexisting AD and Cerebrovascular Disease (CVD) is common

Alone or together they may account for 80% of dementia

- **In US community autopsy series:**
  - **AD: 24-36%**
  - **AD+CVD: 36-45%**
  - **VaD: 3-13%** (Lim et al, JAGS,1999; Snowdon et al, JAMA, 1997)

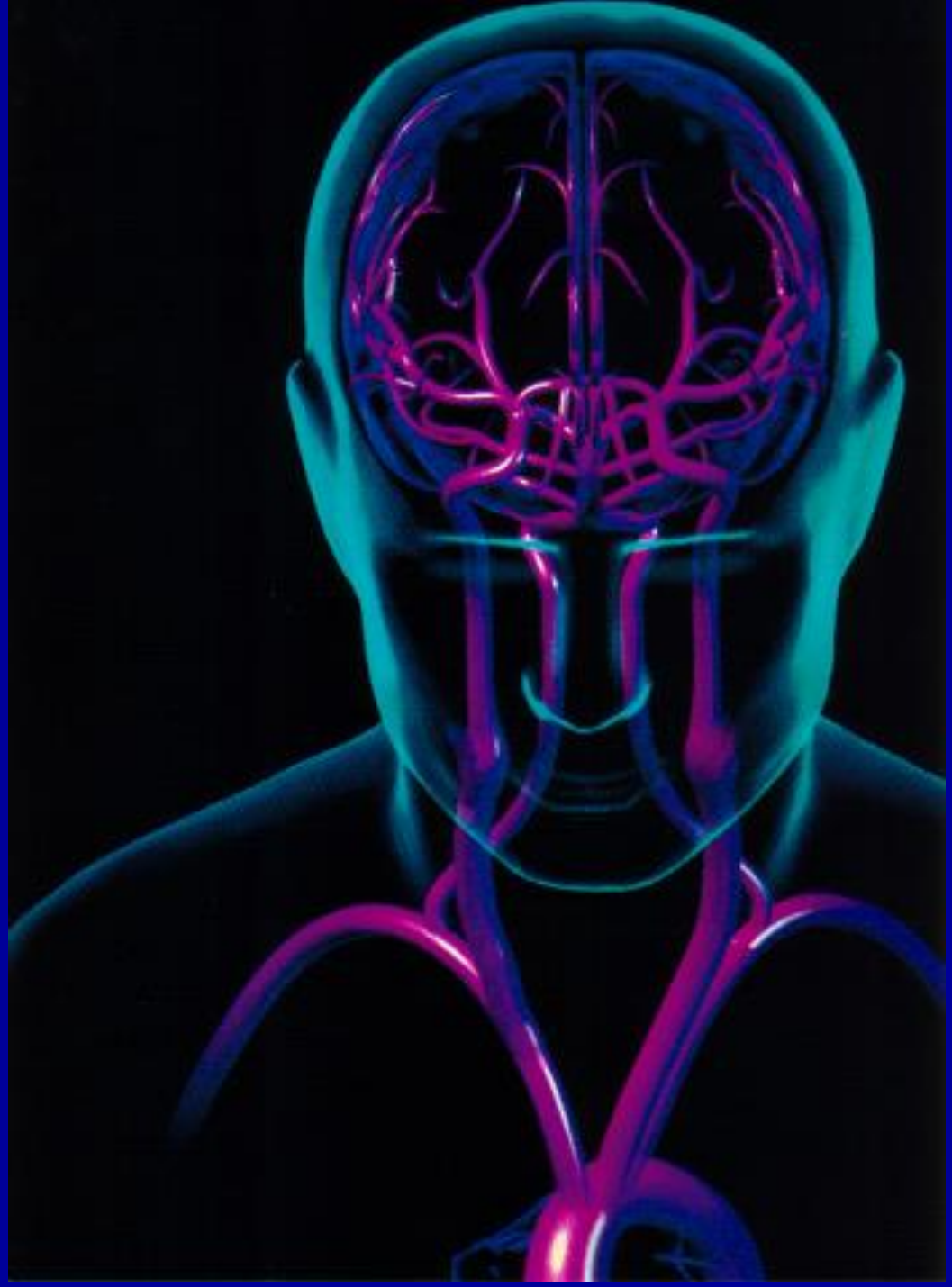
In a British community autopsy study (Lancet, 2001) (median age 85): **70% had AD and 78% had CVD**





Autopsy findings in Chicago Aging Study

(Schneider Neurology 2007)



Blood Pressure is one of the most important risk factors for stroke but also for Alzheimer's

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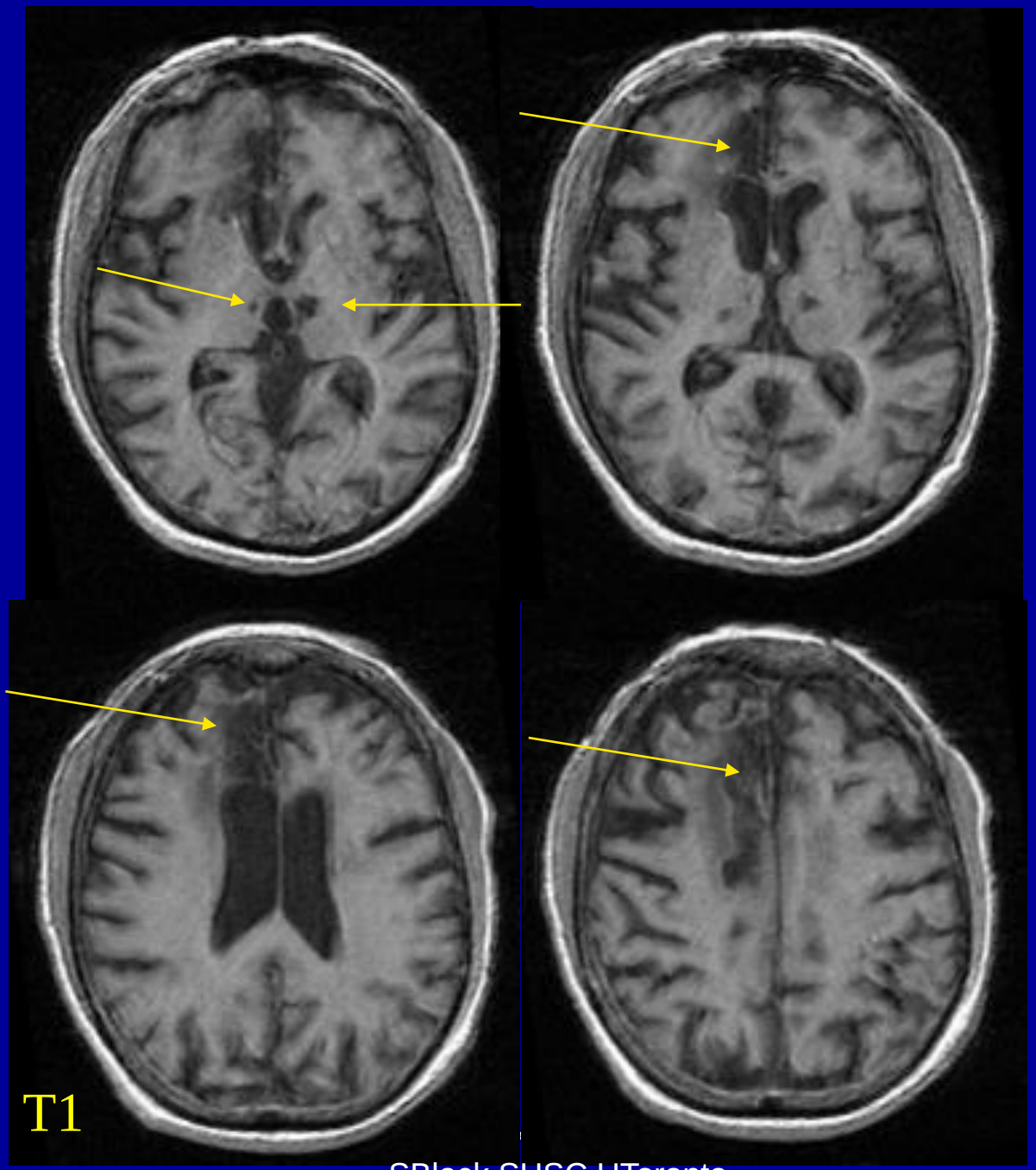
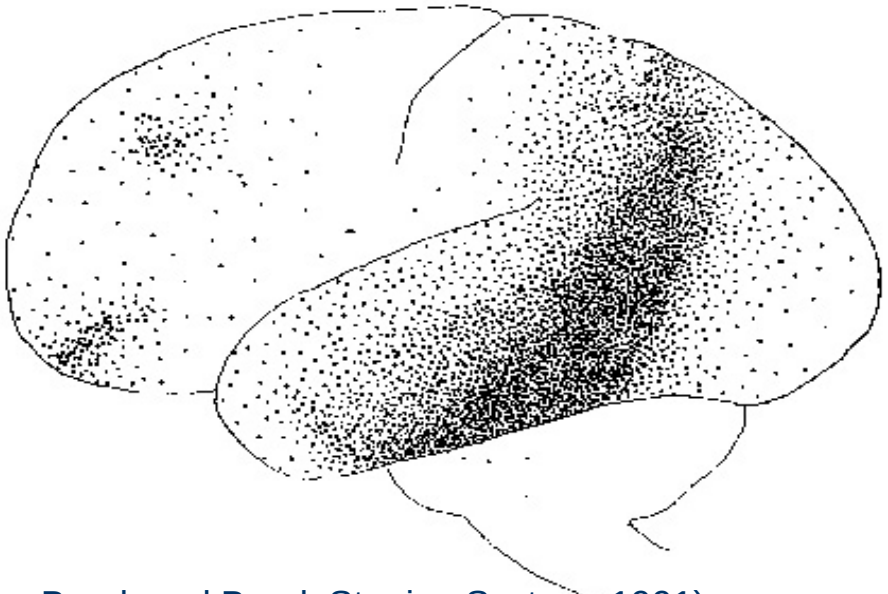
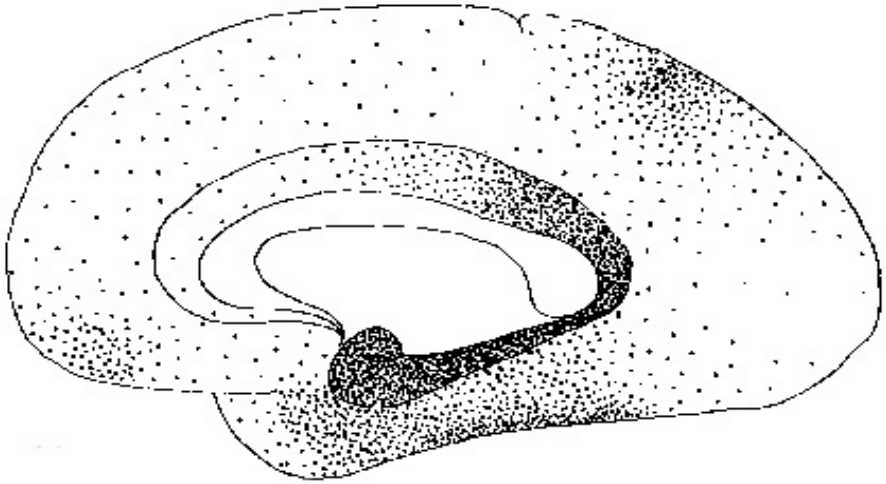
Strokes Strategically Located can Cause dementia

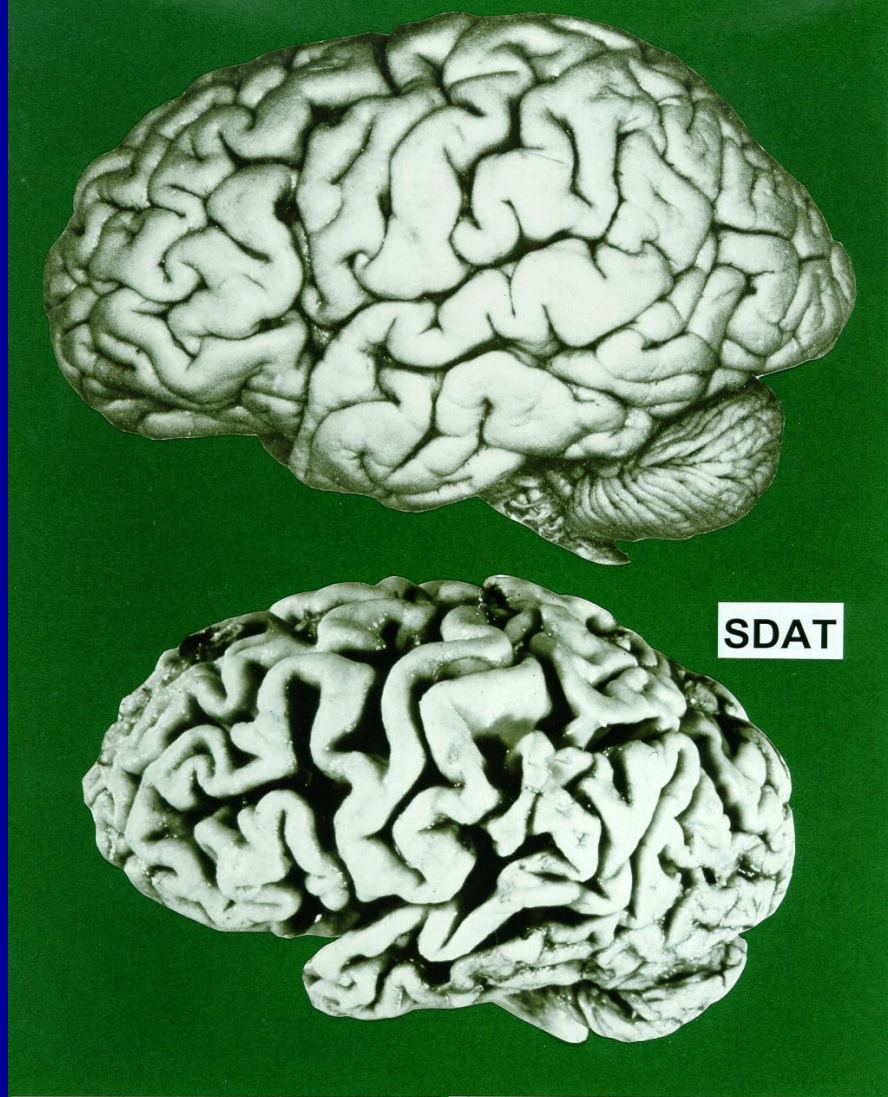


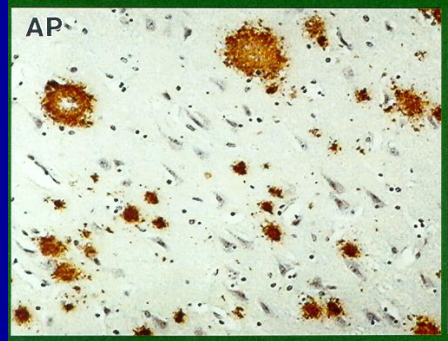
Alzheimer's Disease

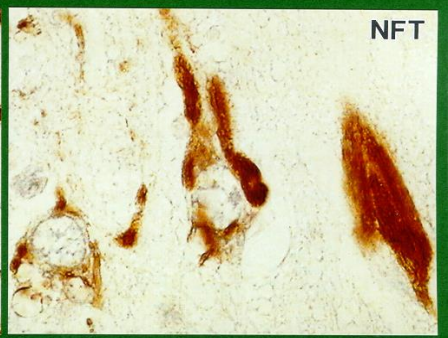


Braak and Braak Staging System, 1991)









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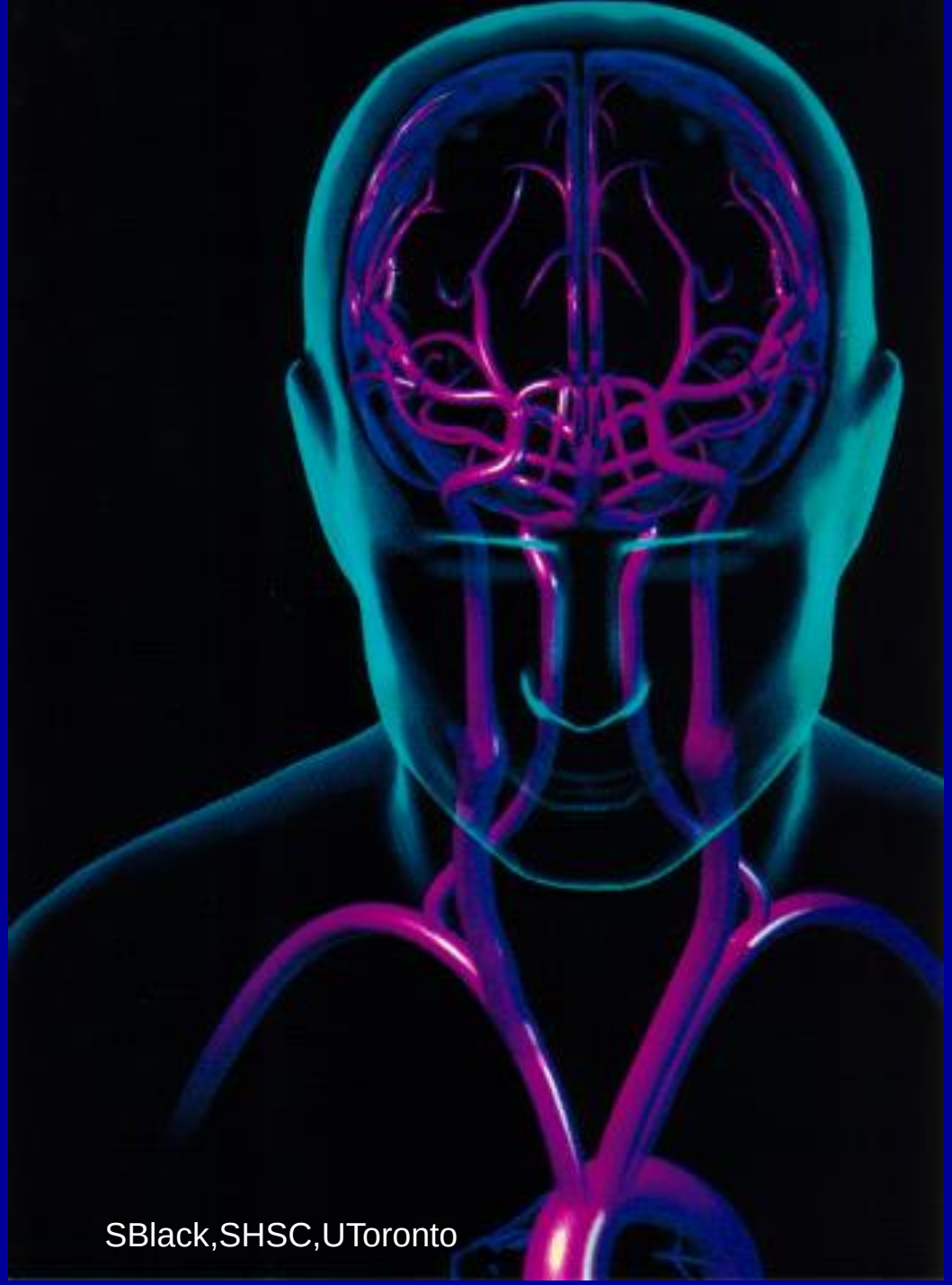
Honolulu-Asia Aging Study

- **3703 Japanese-Americans followed for 36**
- **243 donated their brain for post-mortem study**
  - **those with systolic hypertension had more neuritic plaques**
  - **those with diastolic hypertension→more hippocampal tangles**
- **Untreated mid-life hypertension was associated with later dementia:**
  - **if dbp>90, Odds Ratio was 4 X risk**
  - **if sbp>160, Odds Ratio was 5 X risk**
  - Launer and Petrovitch Neurobiol Aging 2001



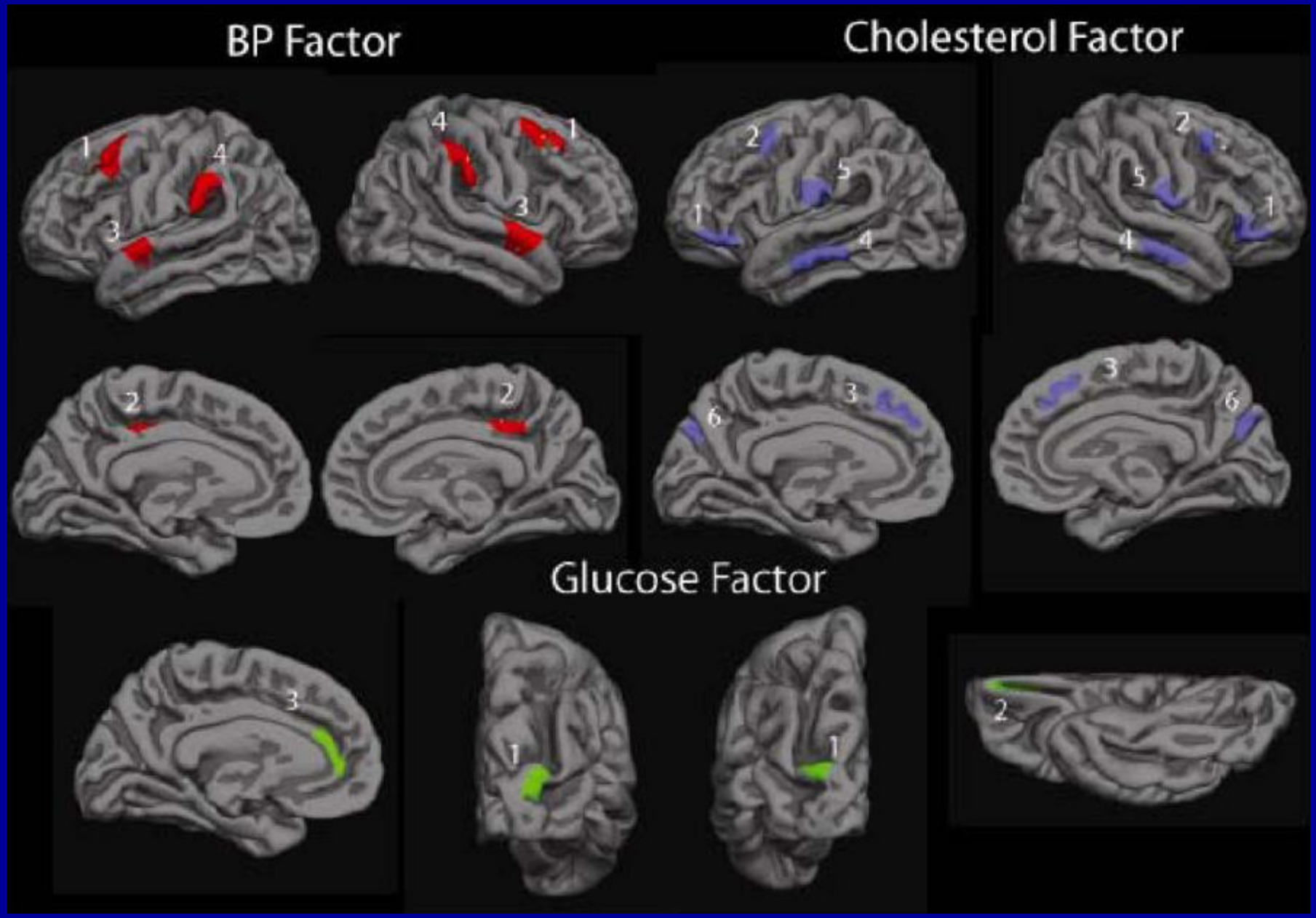
Hypertension not only is a key risk for stroke but it can drive brain shrinkage and cognitive decline

(Tzourio Neur 1999)

Blood pressure, Diabetes and cognitive function

- In 2802 independent seniors (65 to 94) cognitively tested at one year:
  - Hypertension was associated with a faster decline in logical reasoning
  - Diabetes was associated with speed of processing decline
  - Both were associated with faster decline in activities of daily living and physical functioning. (*Kuo JAGS 2005)*

ROI for Blood Pressure, Cholesterol, and Glucose factor scores



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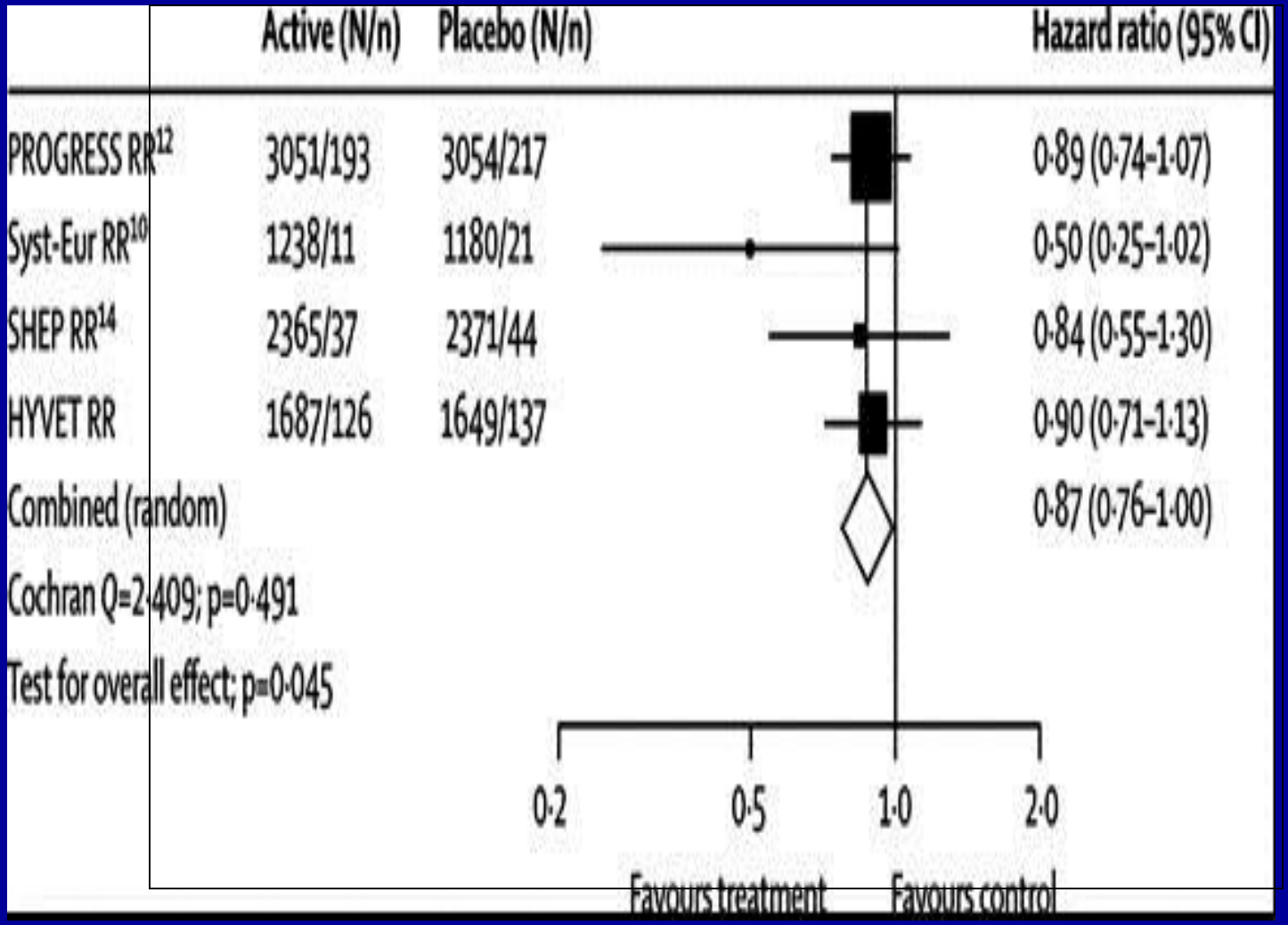
Leritz et al, NeuroImage 2011

Meta-analysis of Antihypertensive Trials and Dementia



PROGRESS
Lancet 2001

Syst-Eur
Forette et al
Lancet 1998

SHEP
JAMA 1991

HYVET
Becket et al
NEJM 2008

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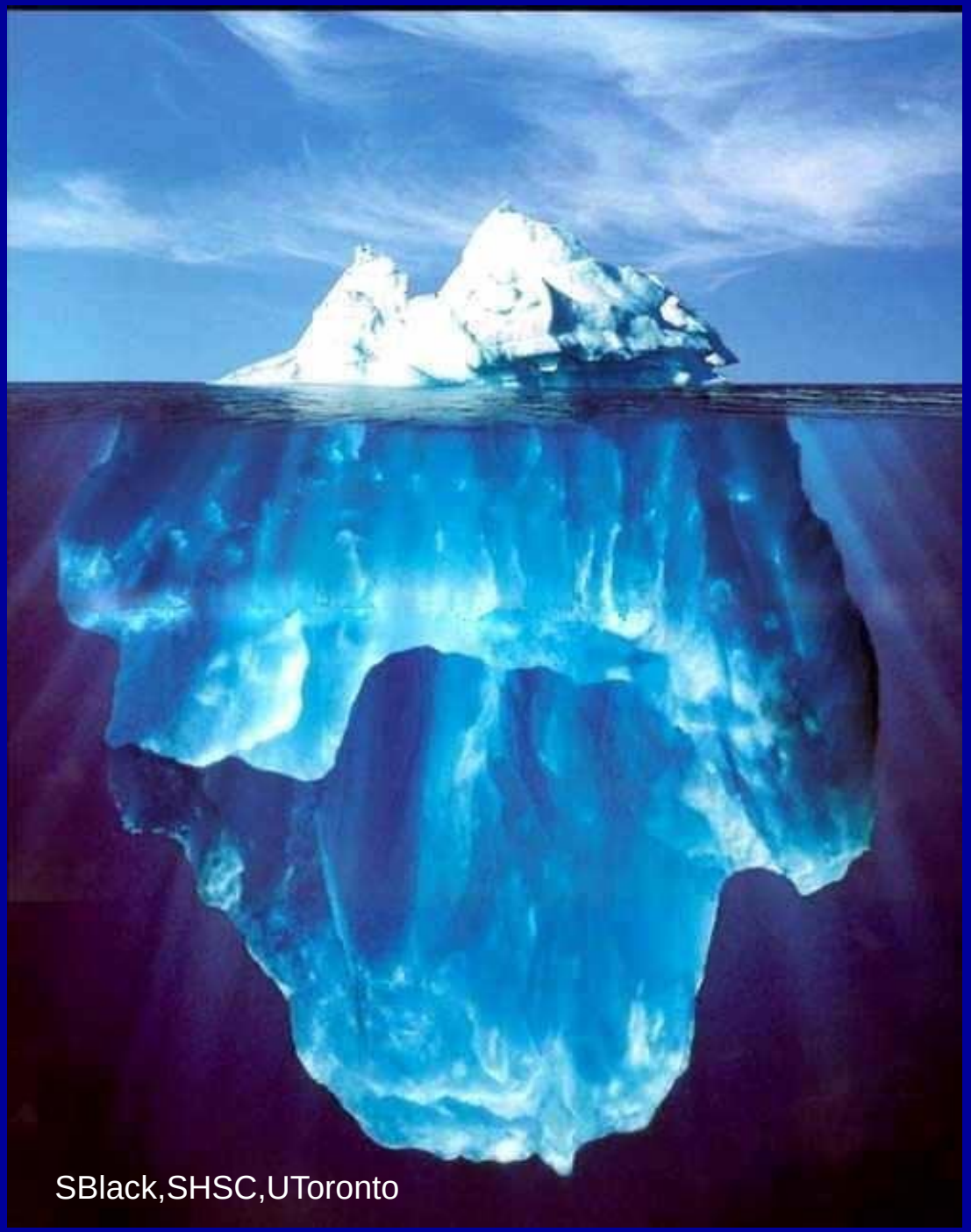
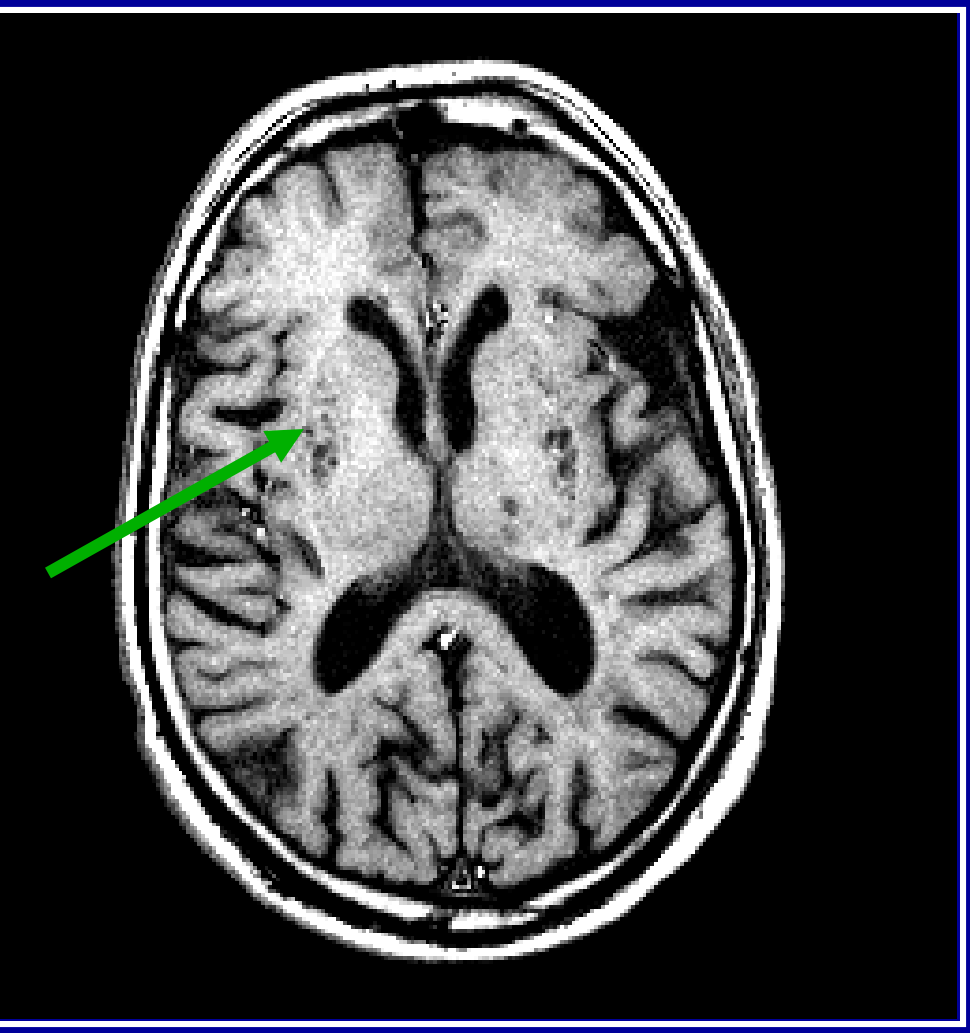
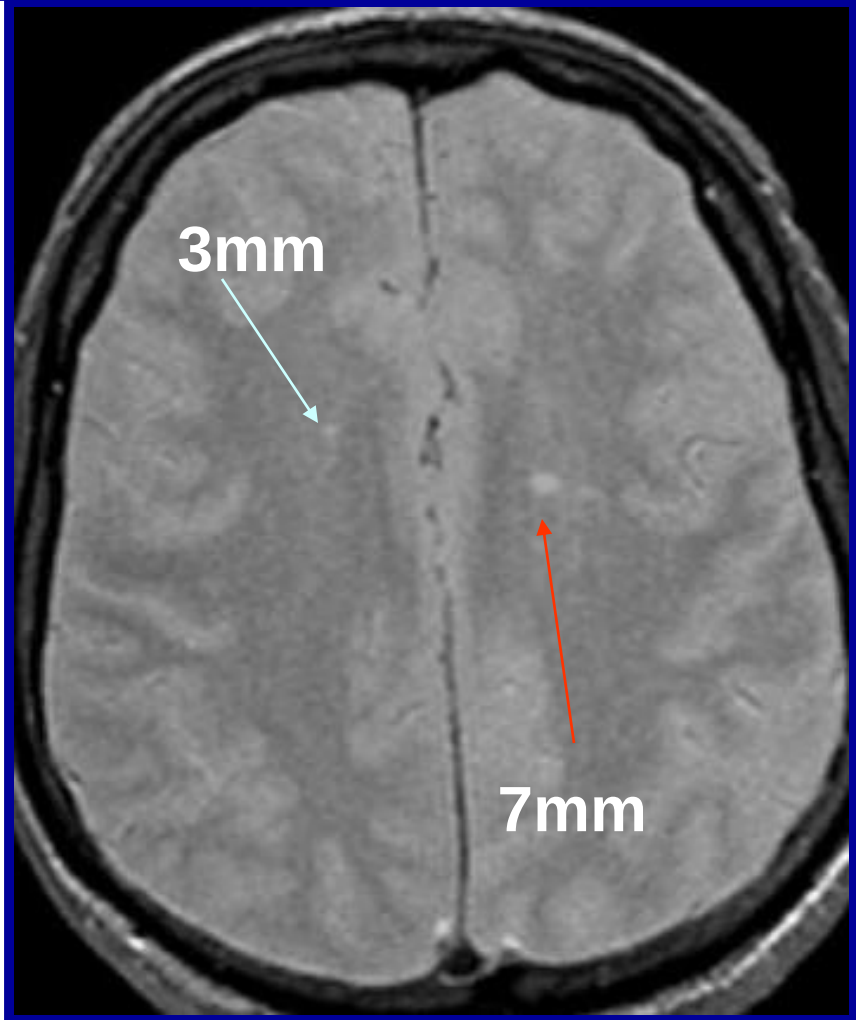
Peters R., et al. Lancet Neurol. 2008

High blood pressure can also drive cerebral small vessel disease

Silent Strokes (Covert Infarcts)







Small strokes on T1 weighted MRI

Appear as white spots on Proton Density MRI

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Silent Strokes are frequent

- 3 mm holes (dark on T1; white on T2) MRI scans are potentially relevant even if “silent”
- Baseline MRI showed silent strokes in 28% of 3660 seniors > 65, (mean age75), in the Cardiovascular Health Survey (Longstreth 1998)
- Frequency depends on age (12% seen in Framingham Study (mean age 62) (DeCarli Neurobiol Aging 2005)
- Silent (covert) strokes are >10X as prevalent as overt strokes

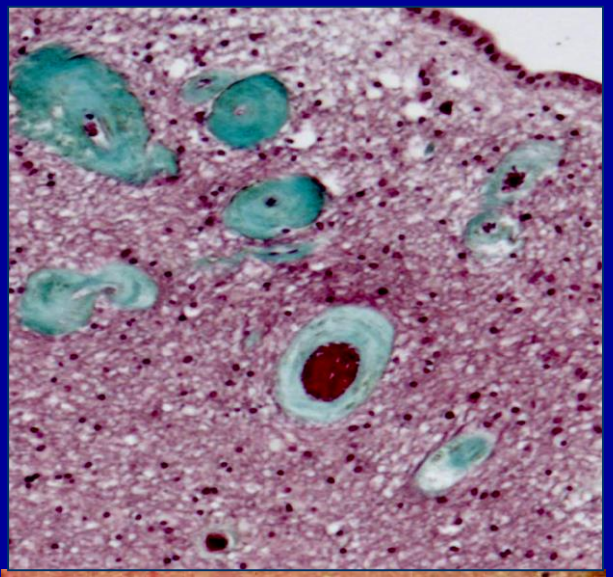
Covert is not benign

- In > 1000 elderly aged 60-90 followed for 4 years in the Rotterdam Study, baseline silent infarcts on MRI meant:
  - more rapid cognitive decline
  - **2X** the risk of emergent dementia
  - **5X** the risk of stroke
  - **3X** stroke risk even after correcting for other vascular risk factors

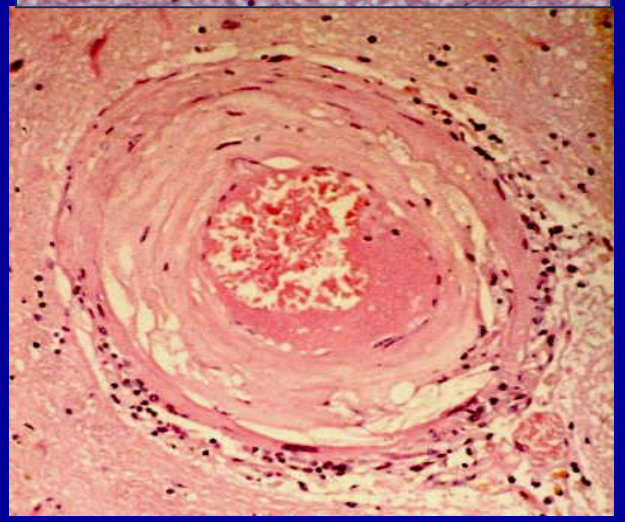
(Vermeer NEJM, 2003 & Stroke, 2003; CHS-Bernick, 2001)

Small Vessel Disease

- Wall thickening leads to blockage
- Tortuosity, coiling
- Increased vessel resistance
- Vessels leak
- Don’t respond as needed to changes in demand

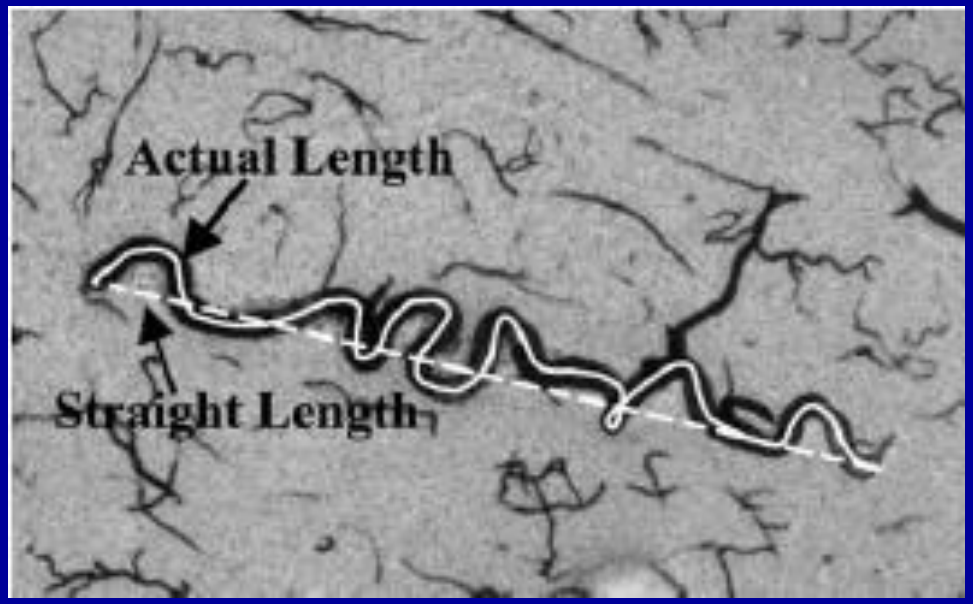


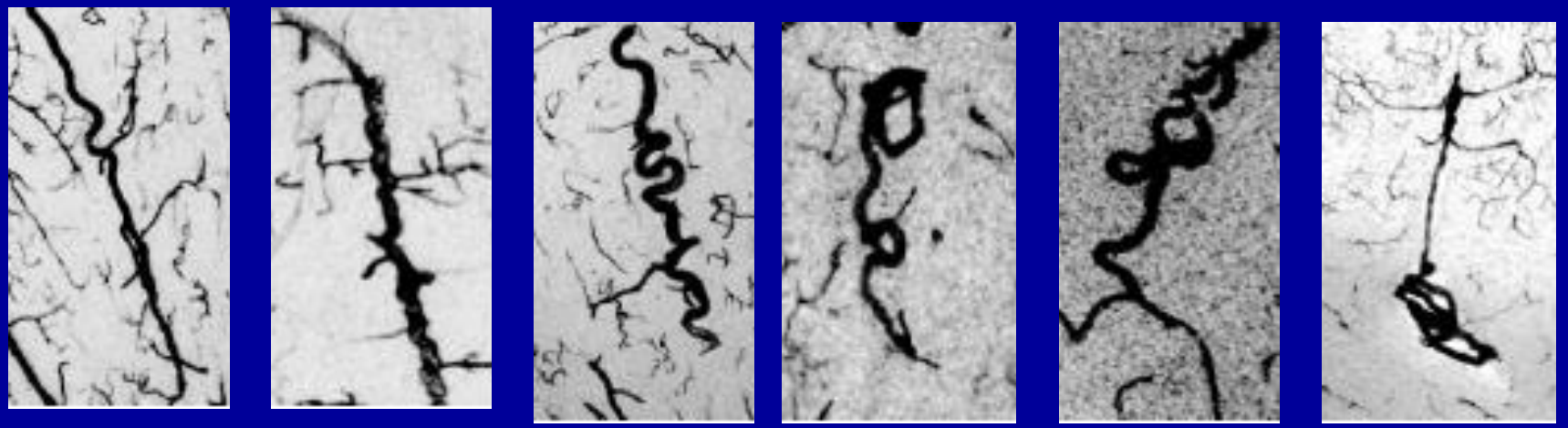
Blocked and thickened venules



Blocked and thickened Arterioles

Arterioles becomeTortuose





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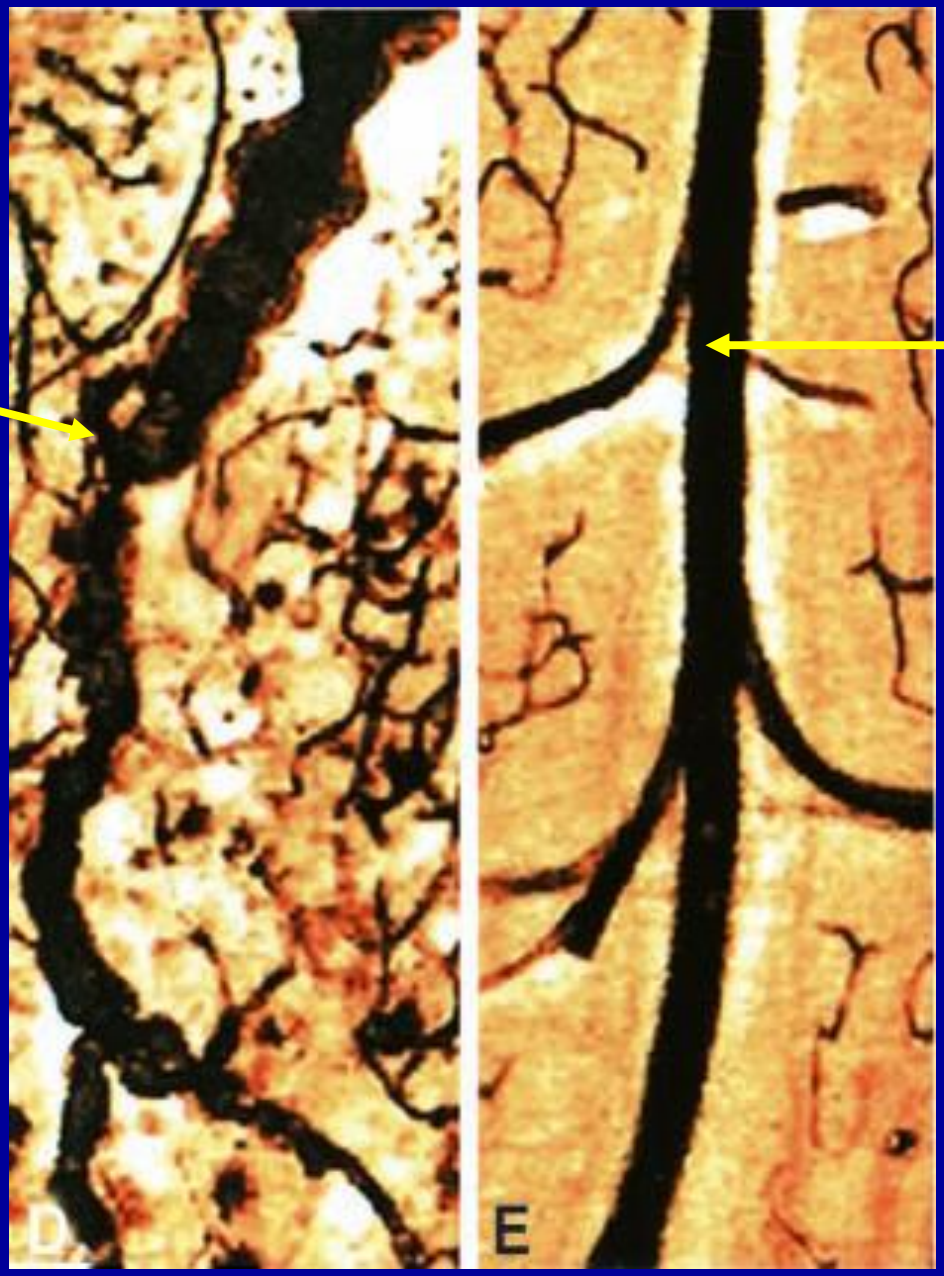
Thore Exp Neuro 2007

Severely disturbed cortical vascular network in AD

Amyloid can also deposit along the vessels



Normal

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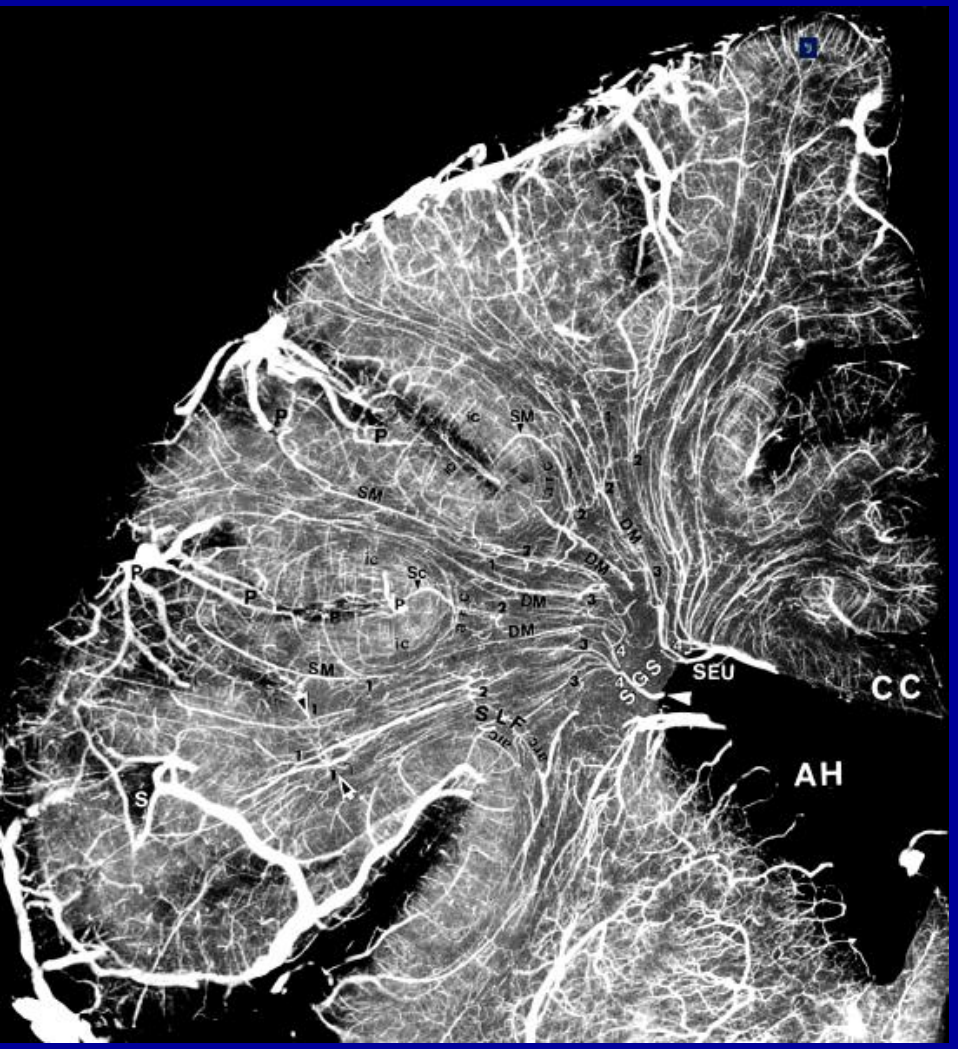
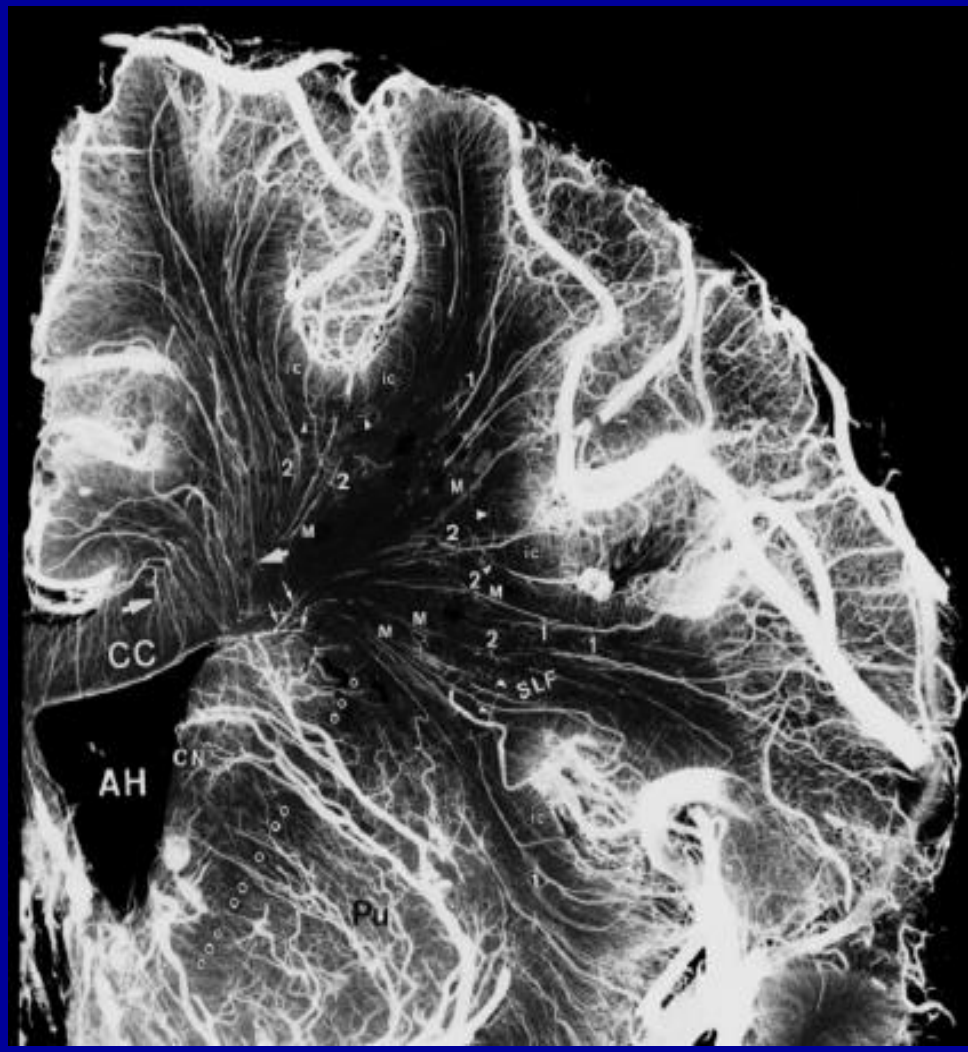
Suter et al Stroke 2002

Medullary veins

Penetrating arteries





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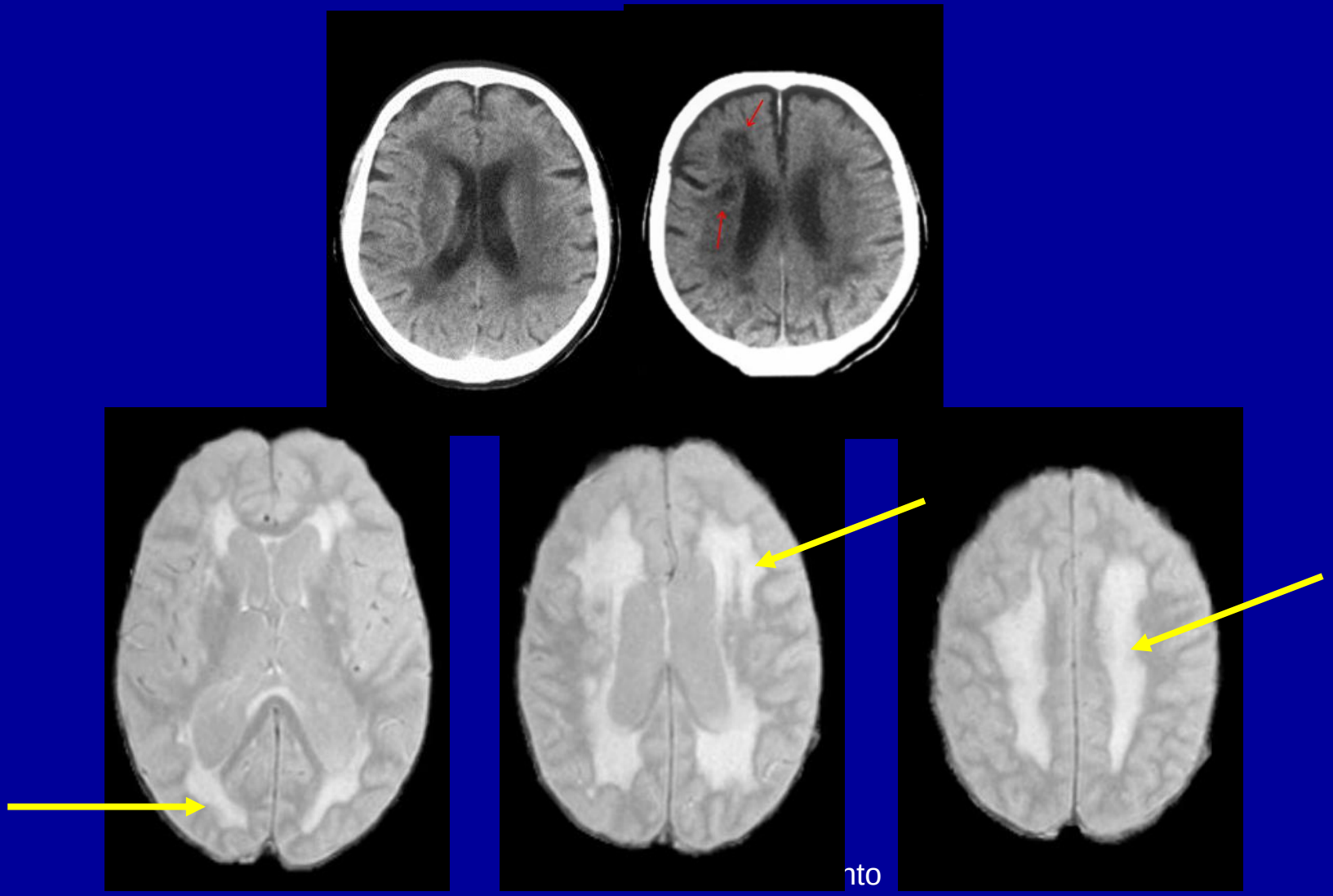
Okudera et al., Neuropathology 1999;.

Periventricular White matter Disease)



White Matter Hyperintensities (WMH) and Cognition in Normal Elderly

- In the Cardiovascular Health Study, only 4.4% had no white matter lesions (N= 3301 >65)
  - 20% with extensive disease had poorer cognition, gait and dexterity (Longstreth 1996)

- Decreased psychomotor speed and global cognitive function seen with severe white matter disease (Rotterdam Study of 1077 normal elderly) (DeGroot 2000)

- **Al**so memory and executive functions affected, but not fine motor or intelligence tests (Gunning Dixon and Raz 2000)

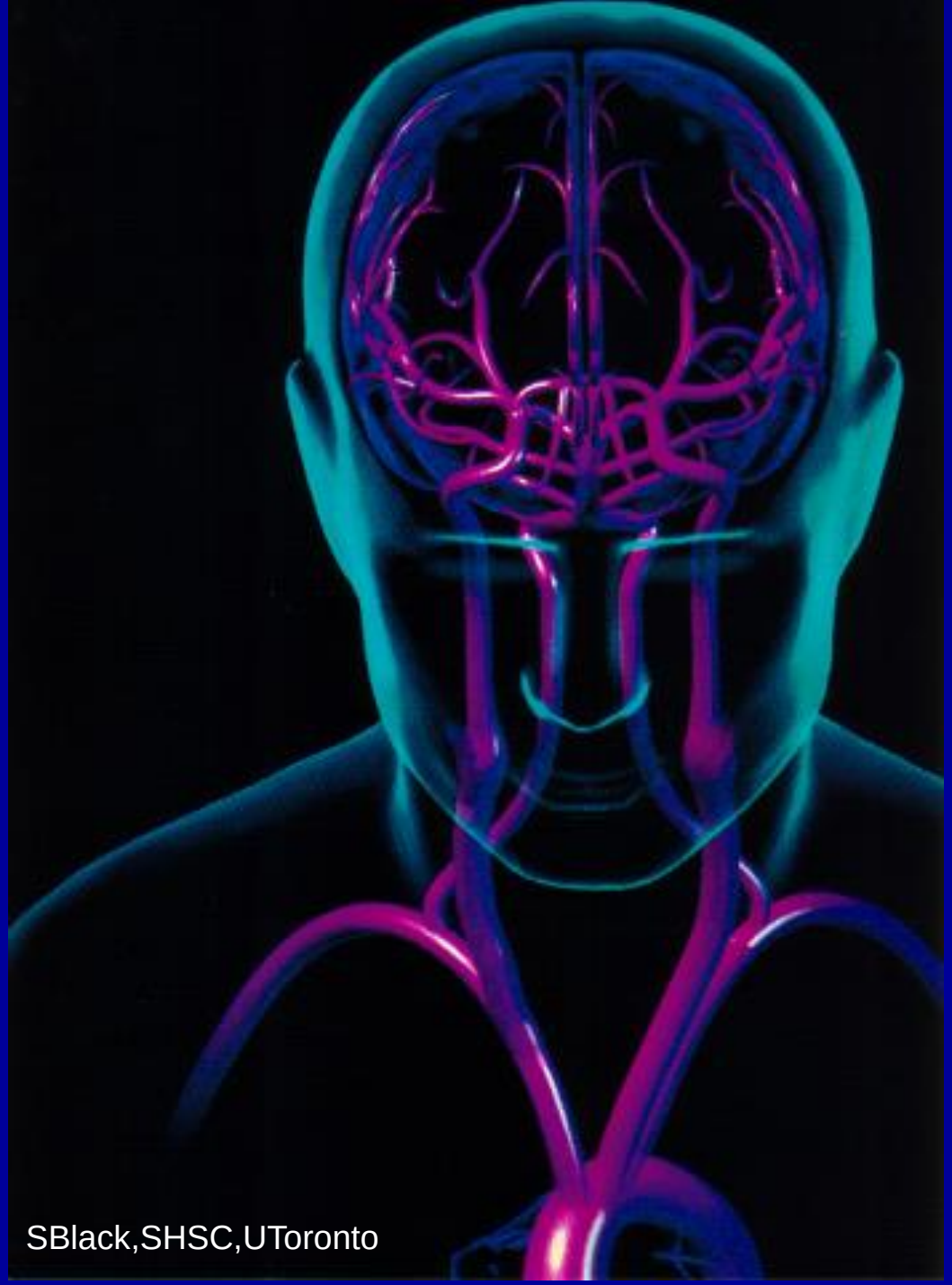
- Threshold of 10cc of periventricular hyperintensity needed to see cognitive effects **(DeCarli et al,1996)**

Clinical Significance of WMH

- 22 longitudinal studies evaluating association of WMH with risk of stroke, cognitive decline, dementia, and death found increased risk of:
  - stroke (3.3 X risk)
  - dementia (1.9 X risk)
  - death (2.0 X risk)

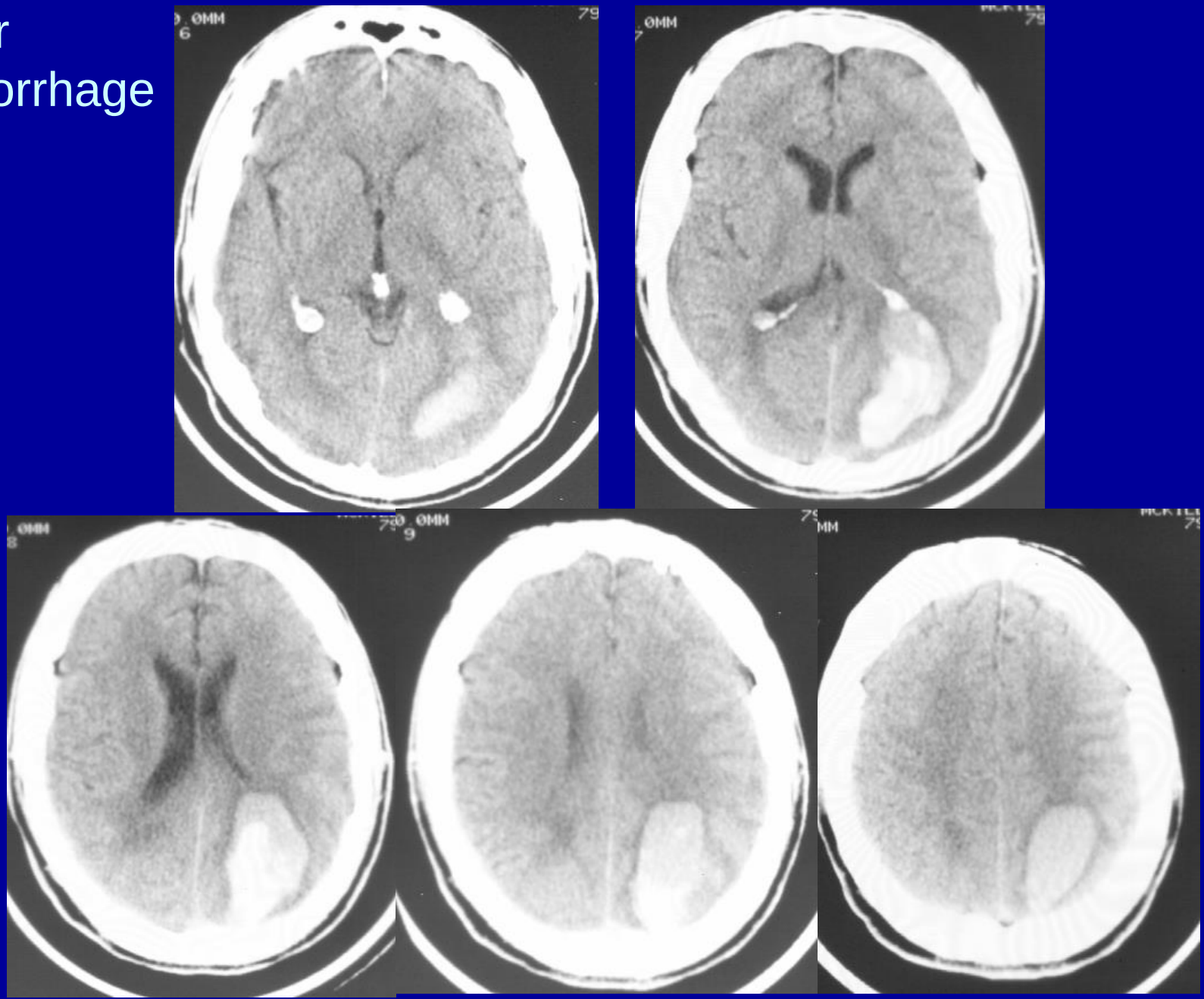
- Also, faster decline in global cognitive performance, executive function, and processing speed was found

Debette&Markus *BMJ* 2010



Alzheimer's Disease can also cause stroke!

Lobar Hemorrhage



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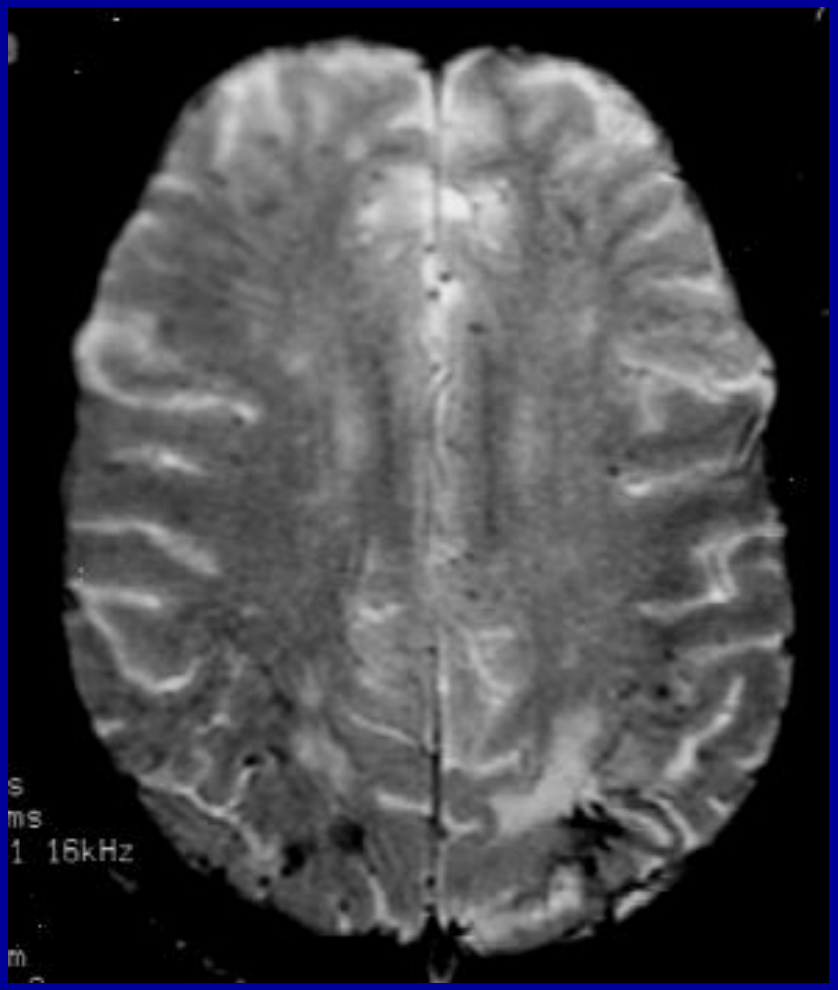
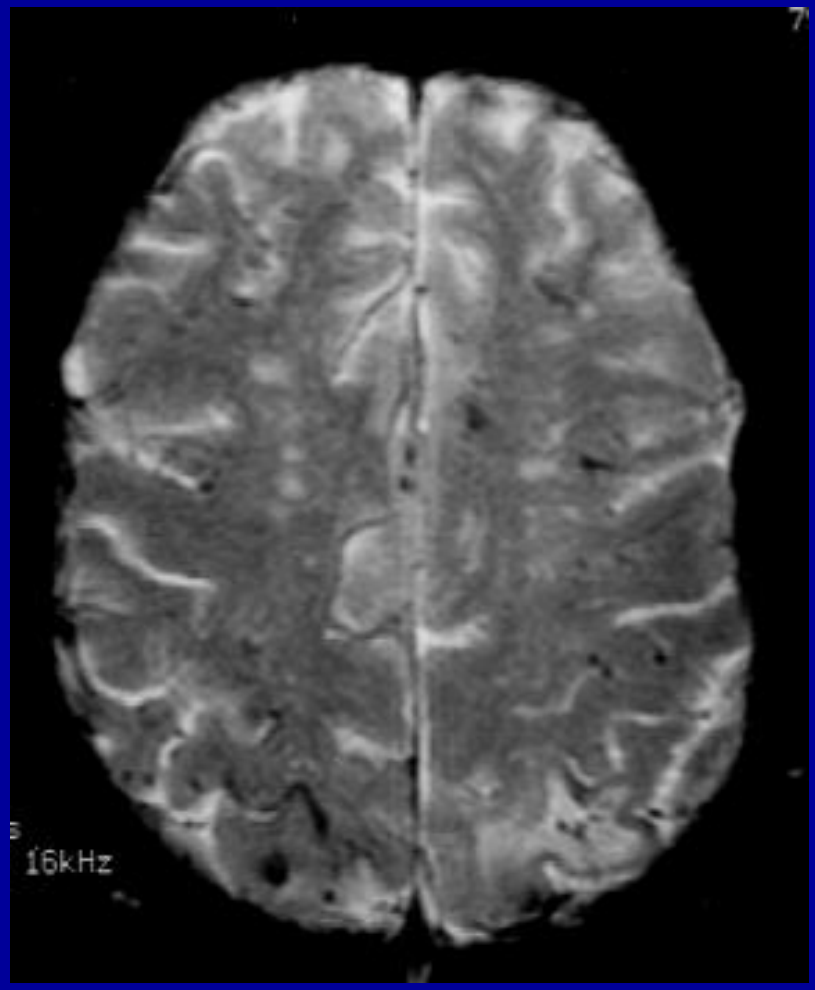
MRI Gradient Echo: Microbleeds





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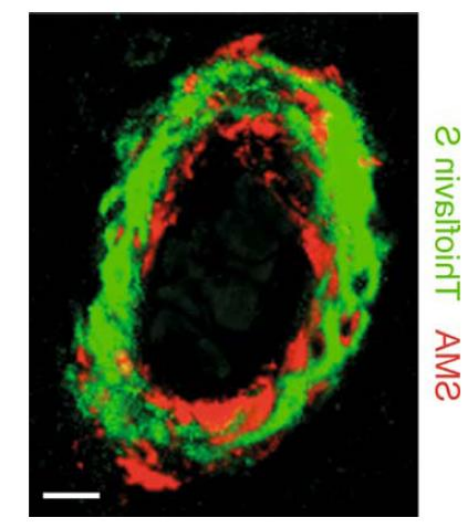
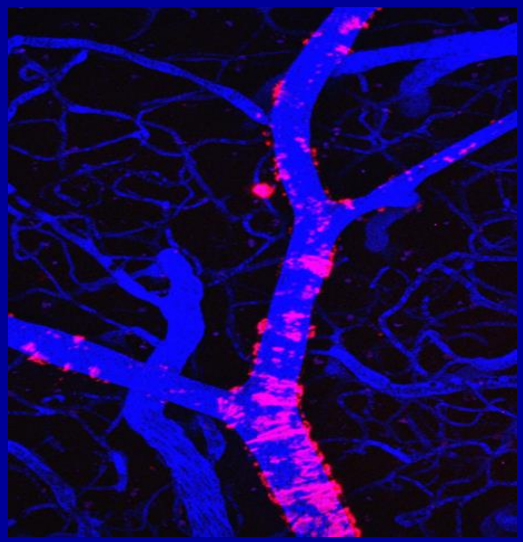
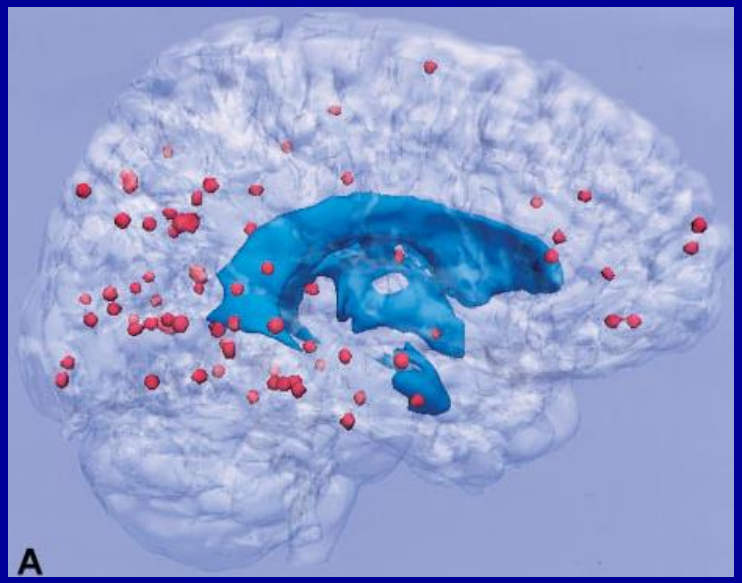
Amyloid Angiopathy



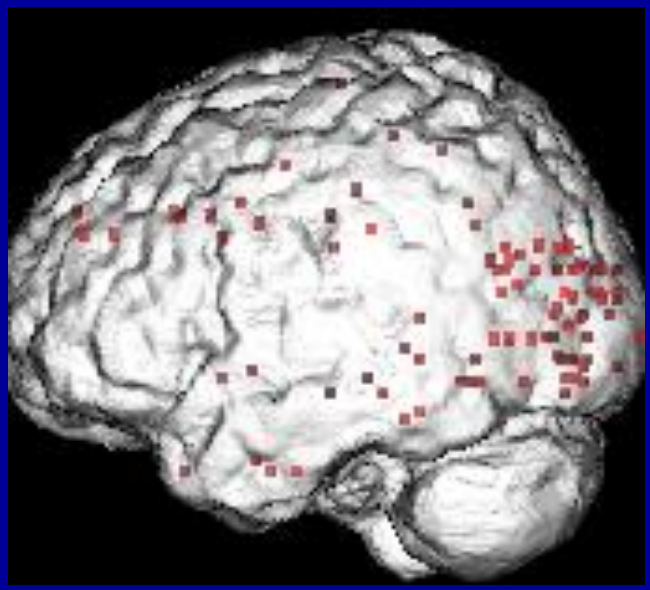
Bell&Zlokovic ActaNeuro2009



Prada 2007



Rosand AnnNeur 2005



Pettersen Arch Neur 2008

Common Vascular Risk Factors for Cognitive Decline related both to Alzheimer's and Vascular Dementia

Age

Alcohol in excess

Apolipoprotein E e4 (Slooter,1998)

Hypertension (**Kivipelto, 2001,2006; Launer, 2001)**

Cholesterolemia **(Kivipelto et al, 2001)**

Diabetes (Arvanitikas et al, 2004)

Homocysteinemia (Seshradi et al, 2002)

Heart Disease (atrial fibrillation)

Obesity

Previous stroke

Smoking; excessive alcohol

Poor dietary habits (fat, sugar, salt)

Physical inactivity

Sleep Apnea

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What can we do to prevent or delay dementia?

1) control vascular risk factors- *blood pressure and cholesterol, diabetes*
2) Eat a heart healthy diet and maintain a safe body weight
3)Treat sleep apnea
4) Quit smoking and use alcohol in moderation
5)EXERCISE

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Physical Inactivity is bad for you!

- Worldwide,~ 13% (~ 4.3 M) of AD cases are potentially attributable to physical inactivity, including 21% (> 1.1M) in the USA
- A 10% reduction in the prevalence of physical inactivity could potentially prevent 380,000 AD cases worldwide (90,000 in the USA)
- A 25% reduction in physical inactivity prevalence could potentially prevent 1 M AD cases worldwide and 23**2**,000 cases in the USA

Barnes & Yaffe *Lancet Neurol* 2011

Physical Activity over the Life Course

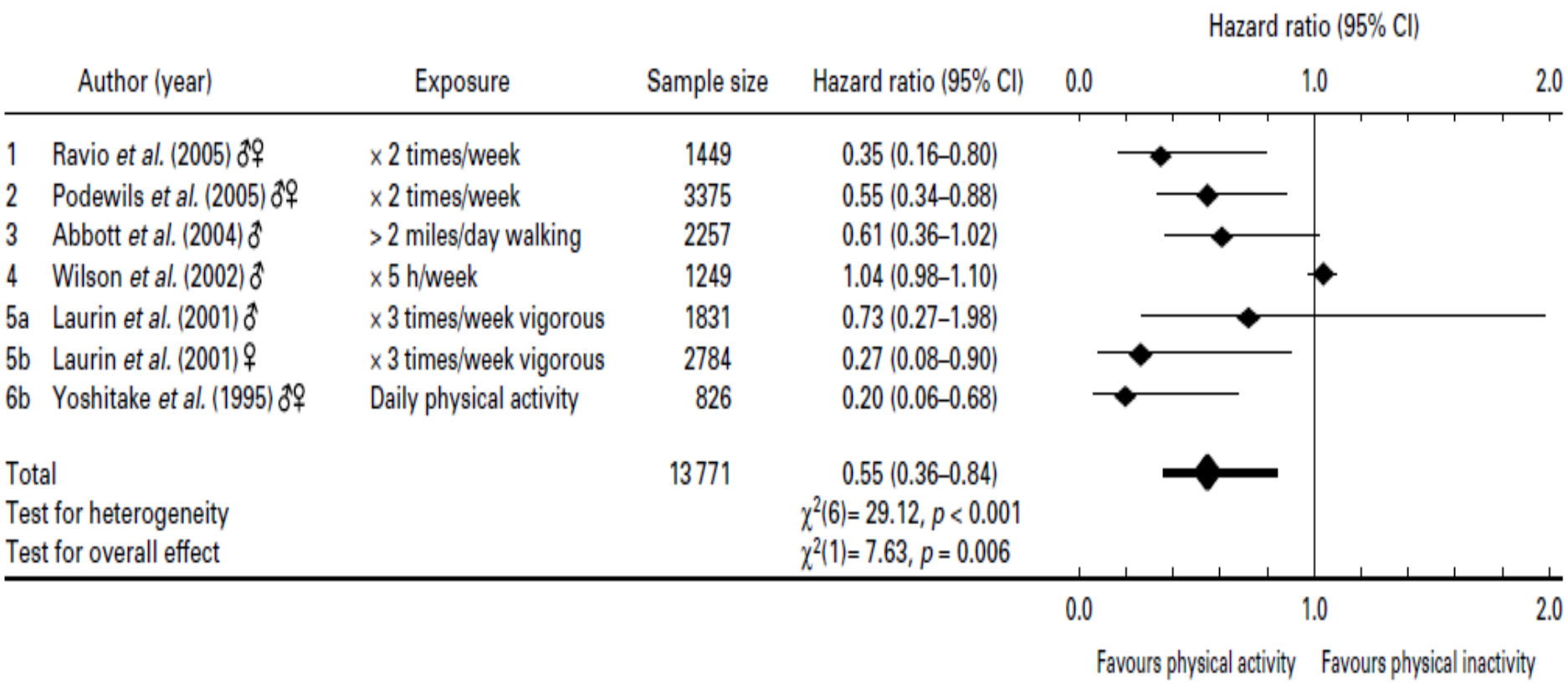
- Subjects: 9344 women (age ≥65, mean 71.6) who self-reported teenage, age 30, age 50, and late-life exercise

- Adjusting for age, and other relevant factors, physically active women had lower frequency of cognitive impairment in late life (MMSE<22) than inactive women:
  - **teenage: 8.5% vs 16.7%**
  - **age 30: 8.9% vs 12.0%**
  - **age 50: 8.5% vs 13.1%**
  - **old age: 8.2% vs 15.9%**

Of all ages, teenage physical activity most strongly associated with lower odds of late-life Cog impairment, but becoming active at any age was still associated with better cognition

Middleton *Am Geriatr Soc* 2010

The association between physical activity and Alzheimer's disease in prospective studies



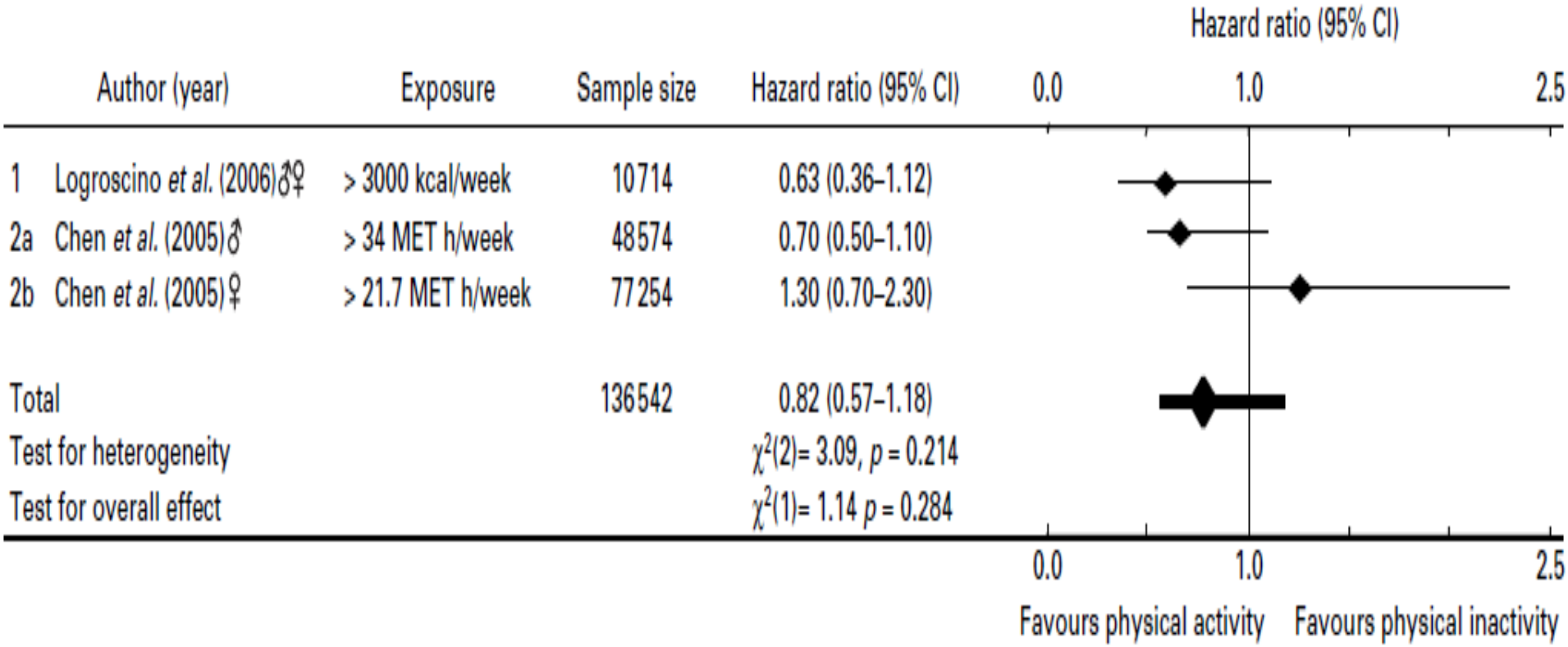
Hamer & Chida *Psychological Medicine* 2009

Physical Activity (PA), Brain Plasticity and Alzheimer's Disease

- Physical activity has a consistent association with brain regions implicated in age-related cognitive decline and AD
- It can increase frontal and hippocampal brain volumes, which are also larger in those physically active earlier in life
- Relatively modest amounts of physical activity suffice to improve cognitive function and increase brain volumes
- Even those at higher risk (apoe E e4 carriers) of developing cognitive impairment show reduced AD risk and symptoms if they engage in greater amounts of physical activity

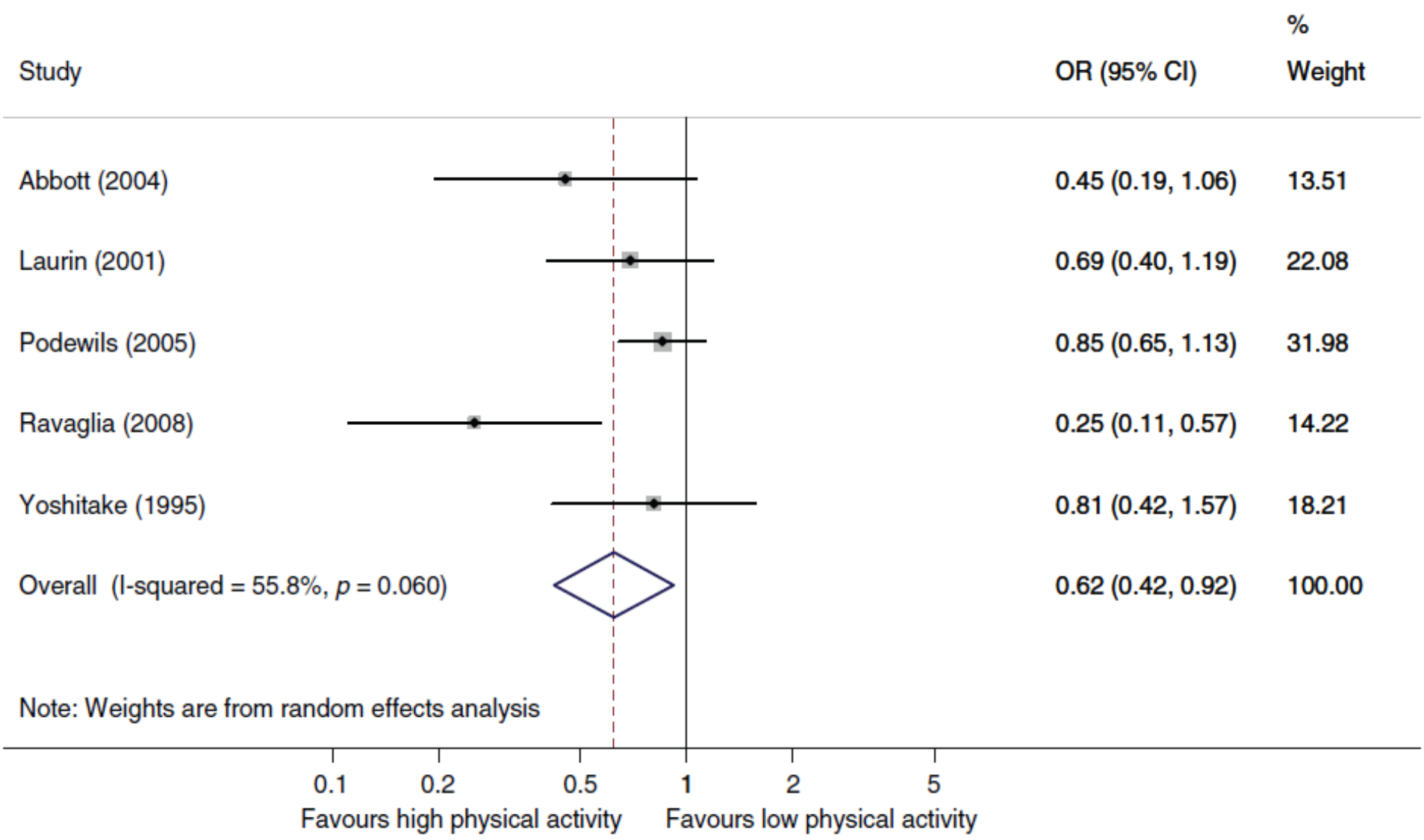
Erickson et al *Arch Med Res* 2012

The association between physical activity and Parkinson's disease in prospective studies



Hamer & Chida *Psychological Medicine* 2009

Association between physical activity and Vascular Dementia



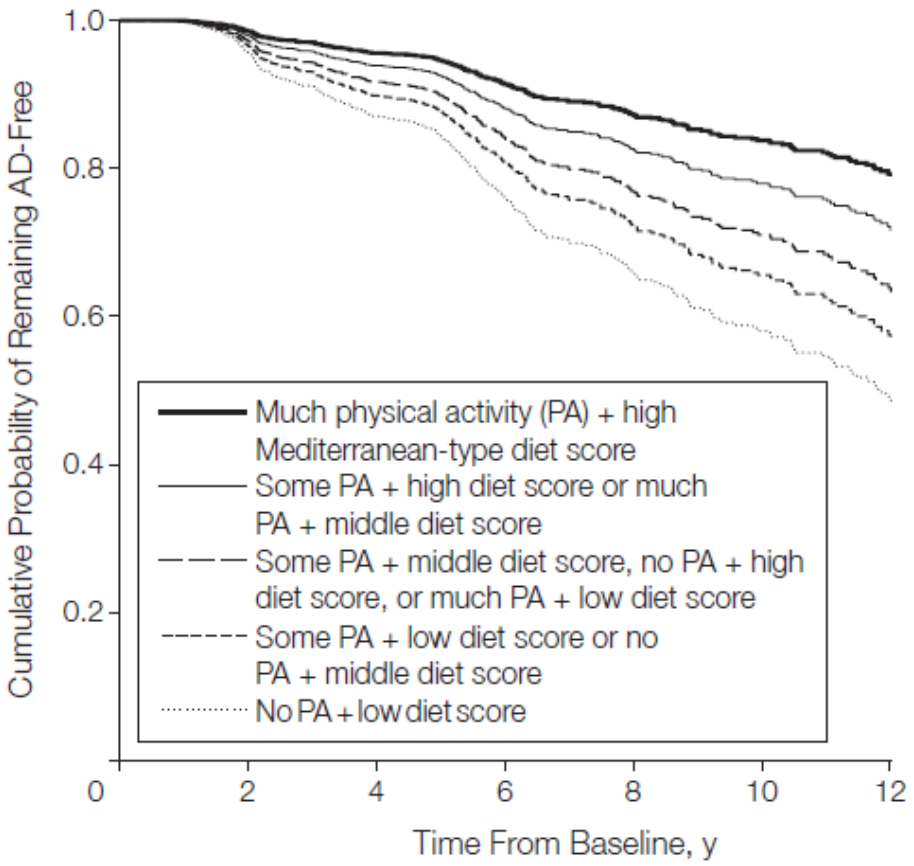
Aarsland *Aging and Mental Health* 2010

Recommendations for Nutraceutical Use in Prevention and Treatment of Dementia

Nutraceutical	Recommendations
B vitamins	• Consider use in B12 deficient patients (1,000 mcg per day) • Oral administration less expensive and equally efficacious to intramuscular administration • Folate and B6 have no role in therapy
Vitamin D	• Supplement in older adults with low levels (25OHD <30 nmol/L) • Cholecalciferol (D3) daily recommended over ergocalciferol (D2) (50,000 IU per month)
Vitamin E	• Caution with recommending given limited evidence of efficacy and risk of toxicity
Omega-3 fatty acids	• Cannot recommend for or against given limited evidence of efficacy and limited toxicity • Example dose: 675 mg DHA, 975 mg EPA
Ginkgo biloba	• No benefit in healthy individuals • EGb 761 has mixed evidence of efficacy in dementia, but risks of bleeding and interactions make use not recommended at this time

Ford, Gerontological Nursing, 2014

AD by amount of Physical Activity and Low, Middle, and High Mediterranean-Type Diet Adherence Scores: high of both do best !



No. at risk							
Much PA + high diet	200	192	141	60	45	35	19
Some PA + high diet or much PA + middle diet	496	470	332	135	106	73	37
Some PA + middle diet, no PA + high diet, or much PA + low diet	573	526	374	168	121	82	35
Some PA + low diet or no PA + middle diet	421	377	241	99	72	48	27
No PA + low diet	190	165	103	39	27	18	9

Scarmeas , JAMA 2009

Conclusions

- Midlife Hypertension shrinks the brain and increases stroke and white matter disease
- Hypertension at any age is not good for executive functioning
- Hypertension is a major driver of atherosclerosis and white matter disease—arteriolar and venular disease and Alzheimer pathology
- Since co-morbid Alzheimer's cerebrovascular disease is the commonest substrate of dementia, hypertension control continues be a major healthcare priority

Conclusions

- Preventing cognitive decline and preserving optimal brain structure and function should be a primary goal of any healthcare strategy

- Modern imaging is revealing that the brain and its vasculature are very sensitive to vascular risks and still responsive to their amelioration and control at any age, lifelong regular daily exercise should be a key societal and personal goal for a healthy lifestyle

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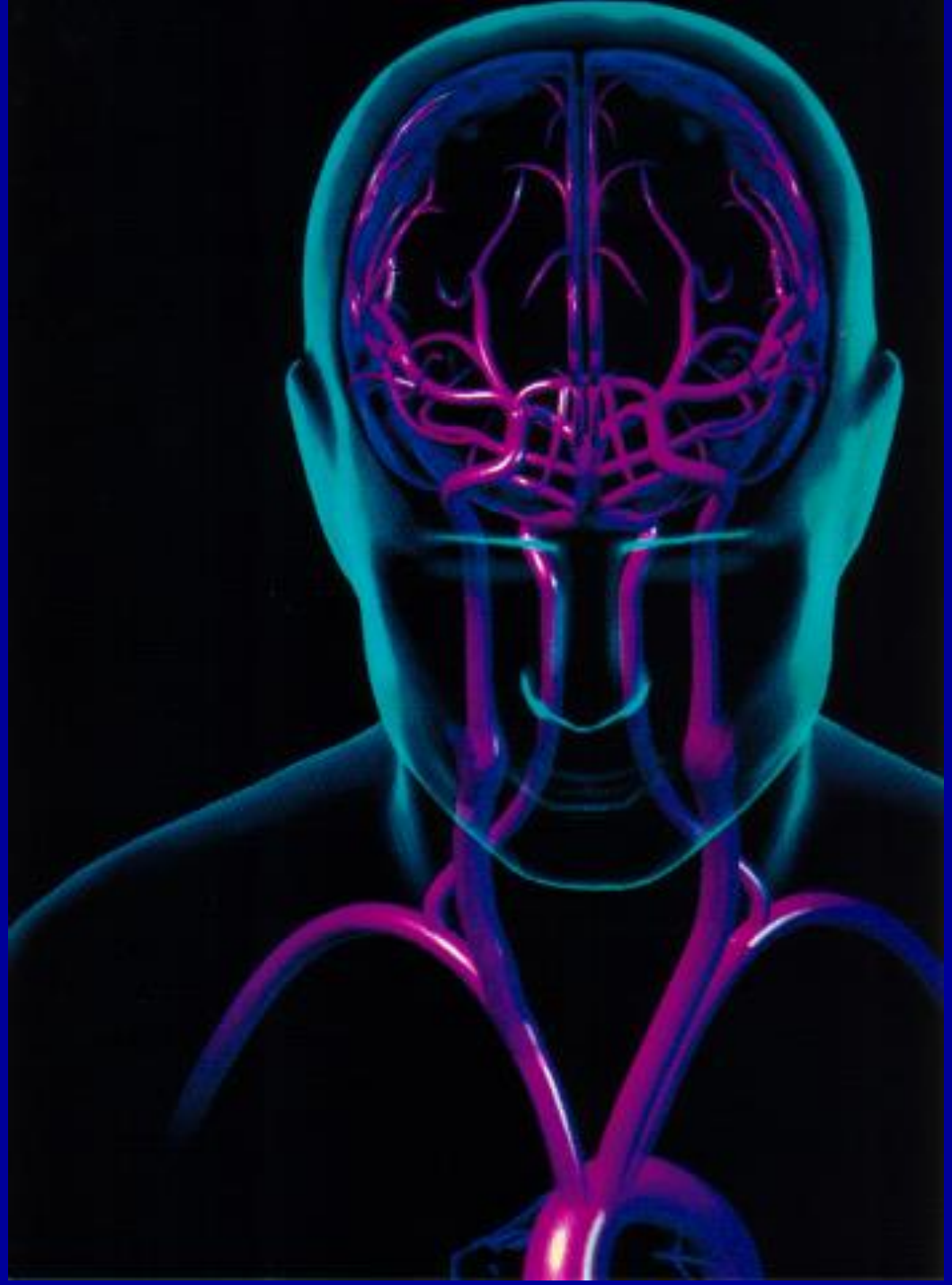


Extra slides

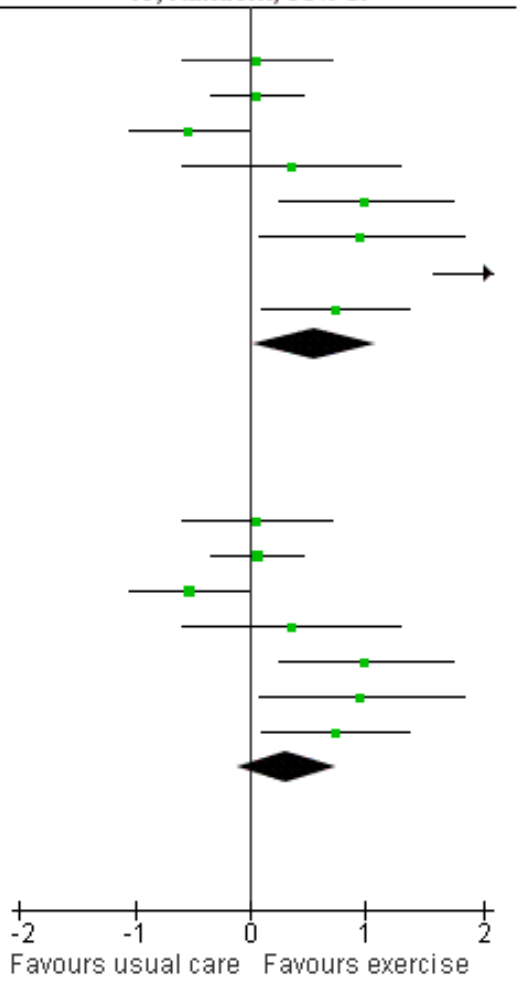
Mechanisms underlying exercise effects

Moderating factors			
Neurogenesis	Neurotrophic factors	Angiogenesis	Depression
Hippocampus	BDNF	↑ Vascularization	Stress
Dentate gyrus	BDNF mRNA	↓ Blood pressure	Hopelessness
Arborization	IGF-1	PIGF	Mood-fluctuation
Remodeling[1]	IGF-1 mRNA	Astroglial cell proliferation	HPA-axis dynamics
Synaptogenesis	BDNF gene	eNOS-dependency[5]	Epigenetic factors
Stem cell efficacy	VEGF[3]	Endothelium efficacy	Institutionalized exercise-regimes[7]
-"- restoration	UmtCK[4]	VEGF	
SynRas mice[2]	AMPK[4]	Vascular volume fraction[6]	
Epigenetic factors	Ghrelin[4]	Cholesterol status	
Type of exercise: treadmill, running wheel, walking, nordic walking, gait, aerobic, moderate intensive			

Archer, *Acta Neurol Scand* 2011

Physical Activity vs. Usual Care: Cognition

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Cognition: all trials								
Christofoletti 2008	14.9	2.2	17	14.8	1.3	20	13.4%	0.06 [-0.59, 0.70]
Eggermont 2009a	0.24	0.78	51	0.2	0.63	46	15.2%	0.06 [-0.34, 0.45]
Eggermont 2009b	0.07	0.37	30	0.47	0.97	31	14.4%	-0.53 [-1.05, -0.02]
Hwang 2010	28.9	11.86	10	24	14.68	8	11.0%	0.35 [-0.58, 1.29]
Kemoun 2010	30.38	7.66	16	22.23	8.37	15	12.5%	0.99 [0.24, 1.74]
Van de Winckel 2004	15.33	4.44	15	11	4.3	9	11.5%	0.95 [0.08, 1.83]
Venturelli 2011	12	2	11	6	2	10	8.5%	2.88 [1.59, 4.17]
Vreugdenhil 2012	23.9	5	20	19	7.7	20	13.4%	0.74 [0.10, 1.38]
Subtotal (95% CI)			**170**			**159**	**100.0%**	**0.55 [0.02, 1.09]**
Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 34.67$, df = 7 (P < 0.0001); $I^2 = 80\%$								
Test for overall effect: Z = 2.03 (P = 0.04)								
1.1.2 Cognition: excluded moderate-severe dementia								
Christofoletti 2008	14.9	2.2	17	14.8	1.3	20	14.7%	0.06 [-0.59, 0.70]
Eggermont 2009a	0.24	0.78	51	0.2	0.63	46	18.6%	0.06 [-0.34, 0.45]
Eggermont 2009b	0.07	0.37	30	0.47	0.97	31	16.8%	-0.53 [-1.05, -0.02]
Hwang 2010	28.9	11.86	10	24	14.68	8	10.7%	0.35 [-0.58, 1.29]
Kemoun 2010	30.38	7.66	16	22.23	8.37	15	13.1%	0.99 [0.24, 1.74]
Van de Winckel 2004	15.33	4.44	15	11	4.3	9	11.4%	0.95 [0.08, 1.83]
Vreugdenhil 2012	23.9	5	20	19	7.7	20	14.7%	0.74 [0.10, 1.38]
Subtotal (95% CI)			**159**			**149**	**100.0%**	**0.31 [-0.11, 0.74]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 18.49$, df = 6 (P = 0.005); $I^2 = 68\%$								
Test for overall effect: Z = 1.45 (P = 0.15)								



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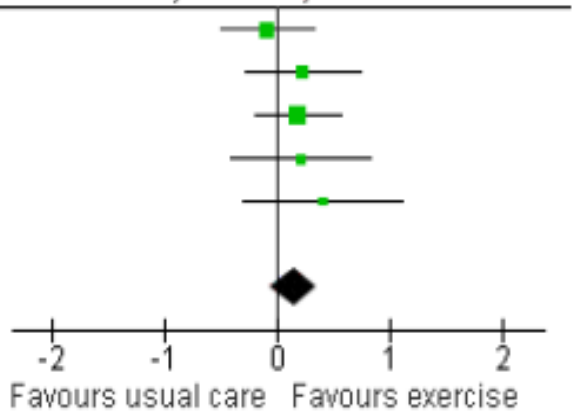
Physical Activity vs. Usual Care: Depression

Study or Subgroup	Usual care Mean	SD	Total	Exercise Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Conradsson 2010	-0.13	1.9	45	0.07	2.6	42	26.6%	-0.09 [-0.51, 0.33]
Eggermont 2009b	7.13	5.1	31	6.03	4.38	30	18.5%	0.23 [-0.28, 0.73]
Rolland 2007	14.8	7.2	54	13.4	8	56	33.5%	0.18 [-0.19, 0.56]
Vreugdenhil 2012	2.3	1.4	20	2	1.5	20	12.2%	0.20 [-0.42, 0.82]
Williams 2008	11.75	8.1	10	9.01	6.11	33	9.2%	0.41 [-0.31, 1.12]
Total (95% CI)			**160**			**181**	**100.0%**	**0.14 [-0.07, 0.36]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.87$, df = 4 (P = 0.76); $I^2 = 0\%$

Test for overall effect: Z = 1.29 (P = 0.20)



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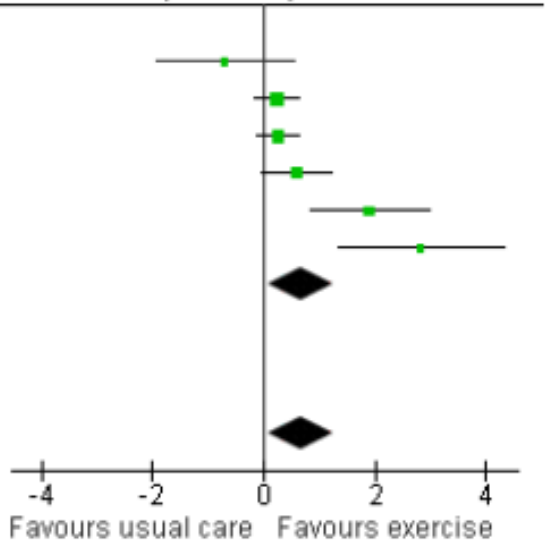
Physical Activity vs. Usual Care: Activities of Daily Living (ADLs)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 ADL: all trials								
Francese 1997	24.67	2.66	6	26.6	2.3	5	12.0%	-0.70 [-1.95, 0.54]
Conradsson 2010	-1	2.72	43	-1.69	3.19	48	22.3%	0.23 [-0.18, 0.64]
Rolland 2007	2.6	1.5	56	2.2	1.5	54	22.7%	0.26 [-0.11, 0.64]
Vreugdenhil 2012	99.6	1.2	20	94.2	12.6	20	19.5%	0.59 [-0.04, 1.23]
Venturelli 2011	42	4	11	32	6	10	13.8%	1.90 [0.83, 2.97]
Santana-Sosa 2008	92.5	8.5	8	70	6.5	8	9.7%	2.81 [1.32, 4.30]
Subtotal (95% CI)			**144**			**145**	**100.0%**	**0.68 [0.08, 1.27]**
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 22.19$, df = 5 (P = 0.0005); $I^2 = 77\%$								
Test for overall effect: Z = 2.24 (P = 0.03)								
Total (95% CI)			**144**			**145**	**100.0%**	**0.68 [0.08, 1.27]**
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 22.19$, df = 5 (P = 0.0005); $I^2 = 77\%$								
Test for overall effect: Z = 2.24 (P = 0.03)								
Test for subgroup differences: Not applicable								



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Amount of Exercise and APOE4 Status

- Population
  - n=347 elderly Dutch men, aged 65-84 yrs,
- Exercise definition
  - Self-administered questionnaire on
    - frequency of walking and bicycling in previous week,
    - time spend on hobbies and gardening weekly
    - time spend on odd jobs and sport monthly
  - Groups included
    - < 30 min/d
    - 31-60 min/d
    - >60 min/d
- **Results**
  - Subjects with only up to 1h/day of physical activity had twice the risk of cognitive decline, and risk was particularly strong in carriers of the APOE*4 allele.
  - Suggests that elderly individuals who are relatively inactive have an increased risk of cognitive decline as compared with active individuals.

Schuit et al. *Med Sci Sports Exerc* (2004)