The search for causes of disease in an ageing world

Albert Hofman

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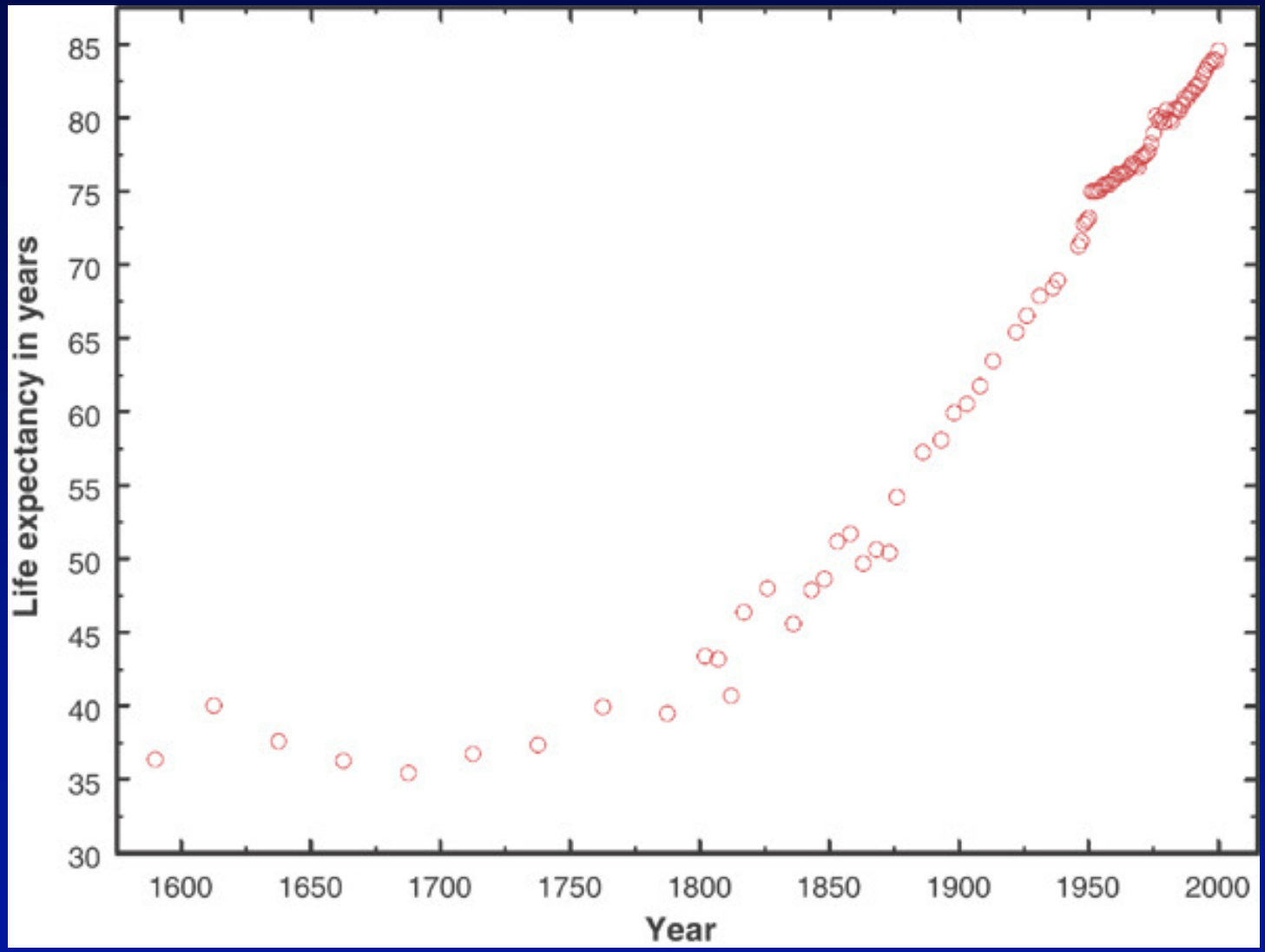
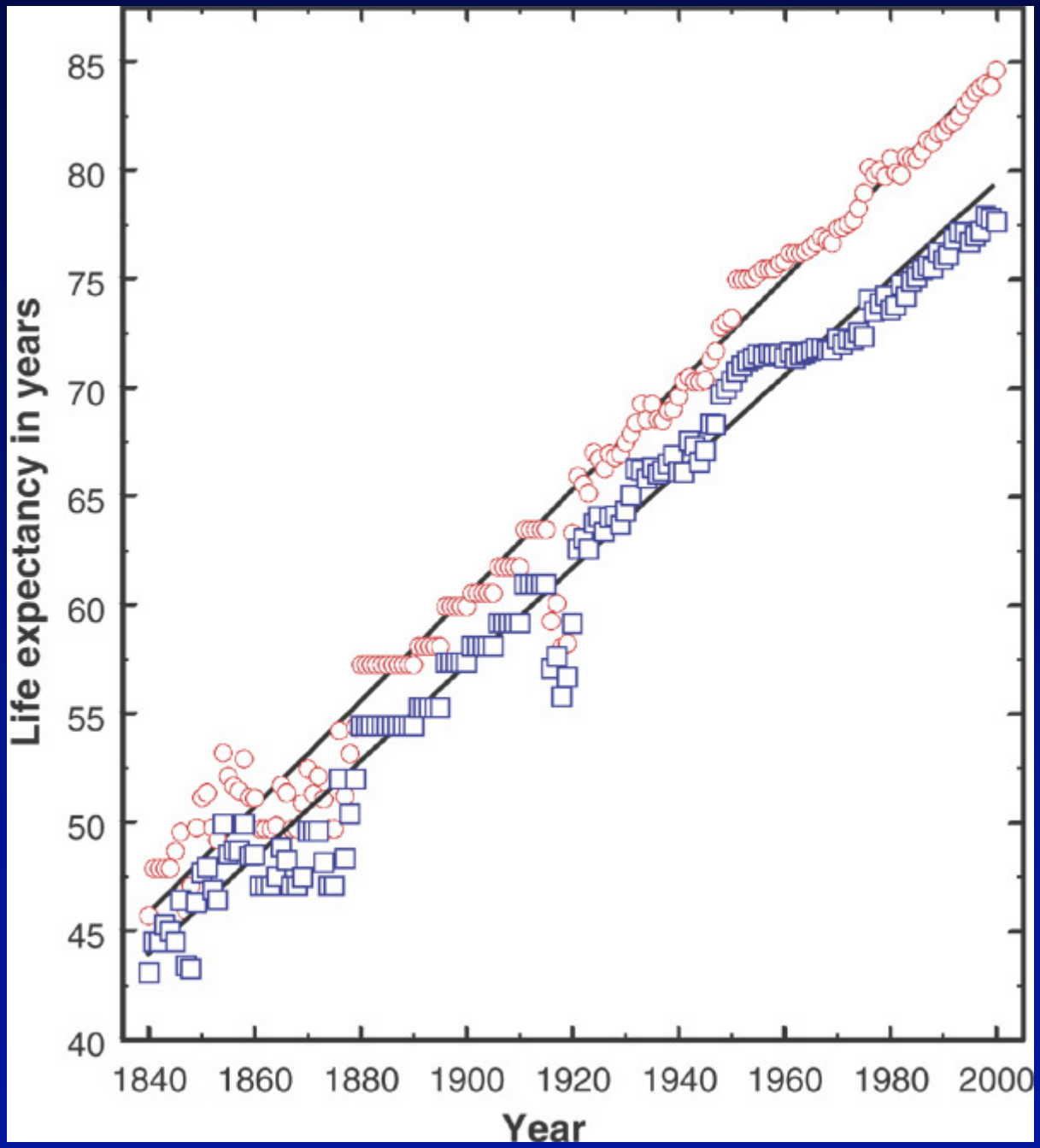


Vaupel, Science, 2002


Life expectancy in years
85
80
75
70
65
60
55
50
45
40
1840
1860
1880
1900
1920
1940
1960
1980
2000
Year

Epidemiology and causes of disease

Three big health problems

- Catastrophic global diseases
- Poverty-related diseases
- Aging-related diseases

The Rotterdam Study

- 15,000 participants
- Since 1990
- 45 years or over
- One district of Rotterdam

The Rotterdam Study

- 800 coronary heart disease
- 650 stroke
- 500 heart failure
- 700 dementia
- 300 Parkinson disease
- 700 maculopathy (250 macular degeneration)
- 450 glaucoma
- 1200 non-vertebral fractures
- 850 diabetes mellitus

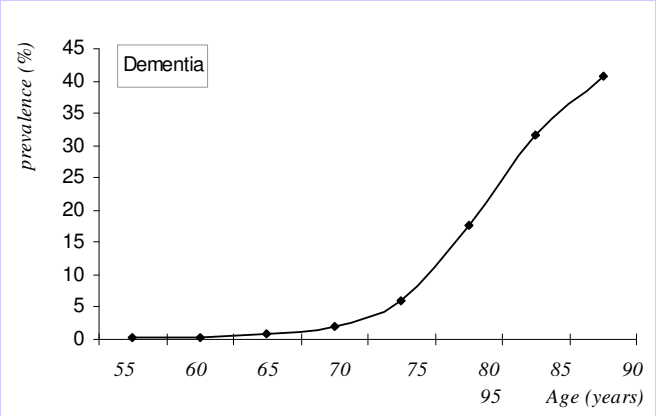
The Rotterdam Study

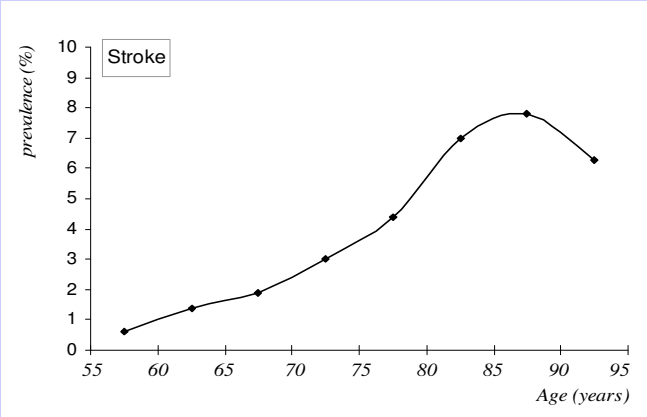
- Food frequency questionnaire
- Imaging brain, circulation, bone (1.5 T MRI machine)
- Genome wide analysis (Illumina 550k SNPs) in total cohort

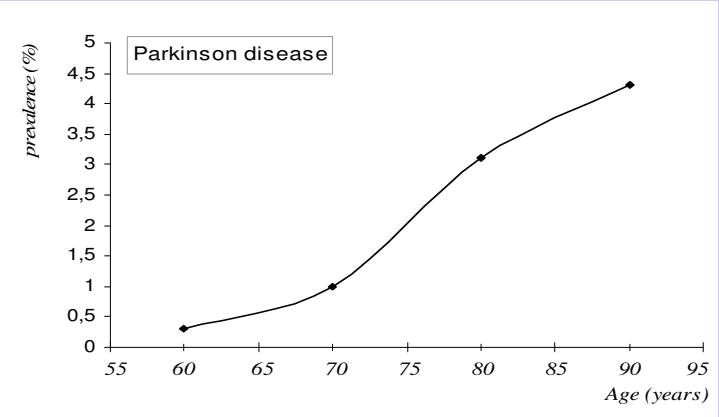
Frequency of neurologic disorders

Rotterdam Study

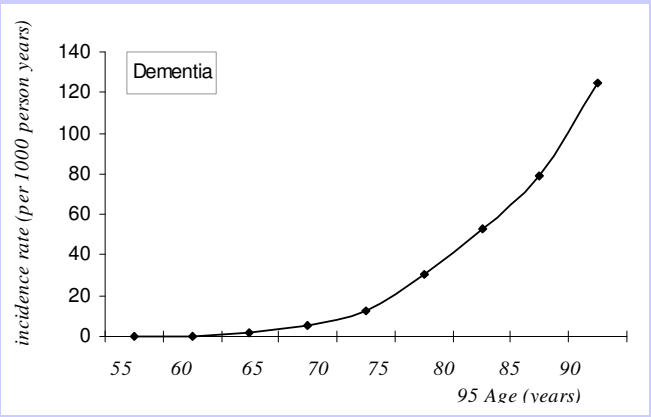
Prevalence

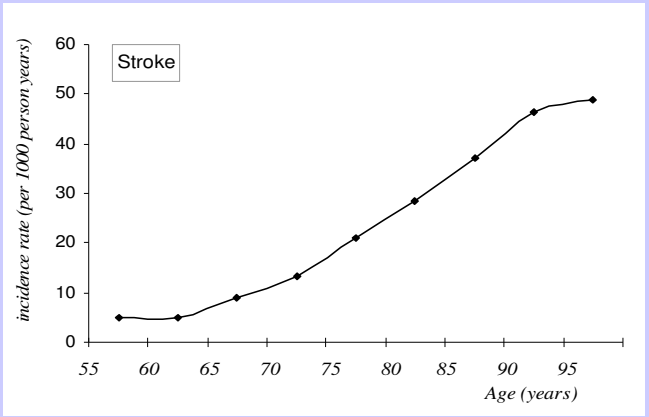


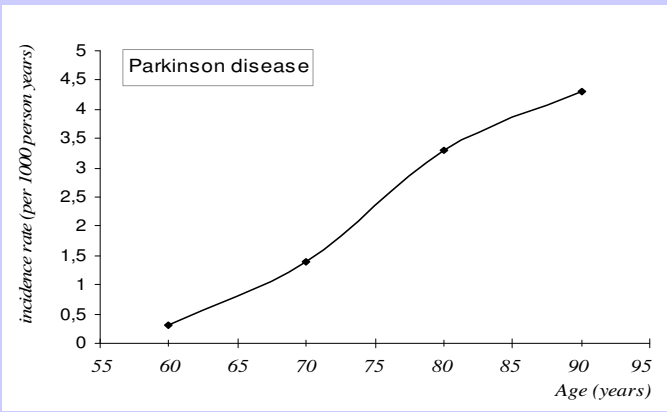


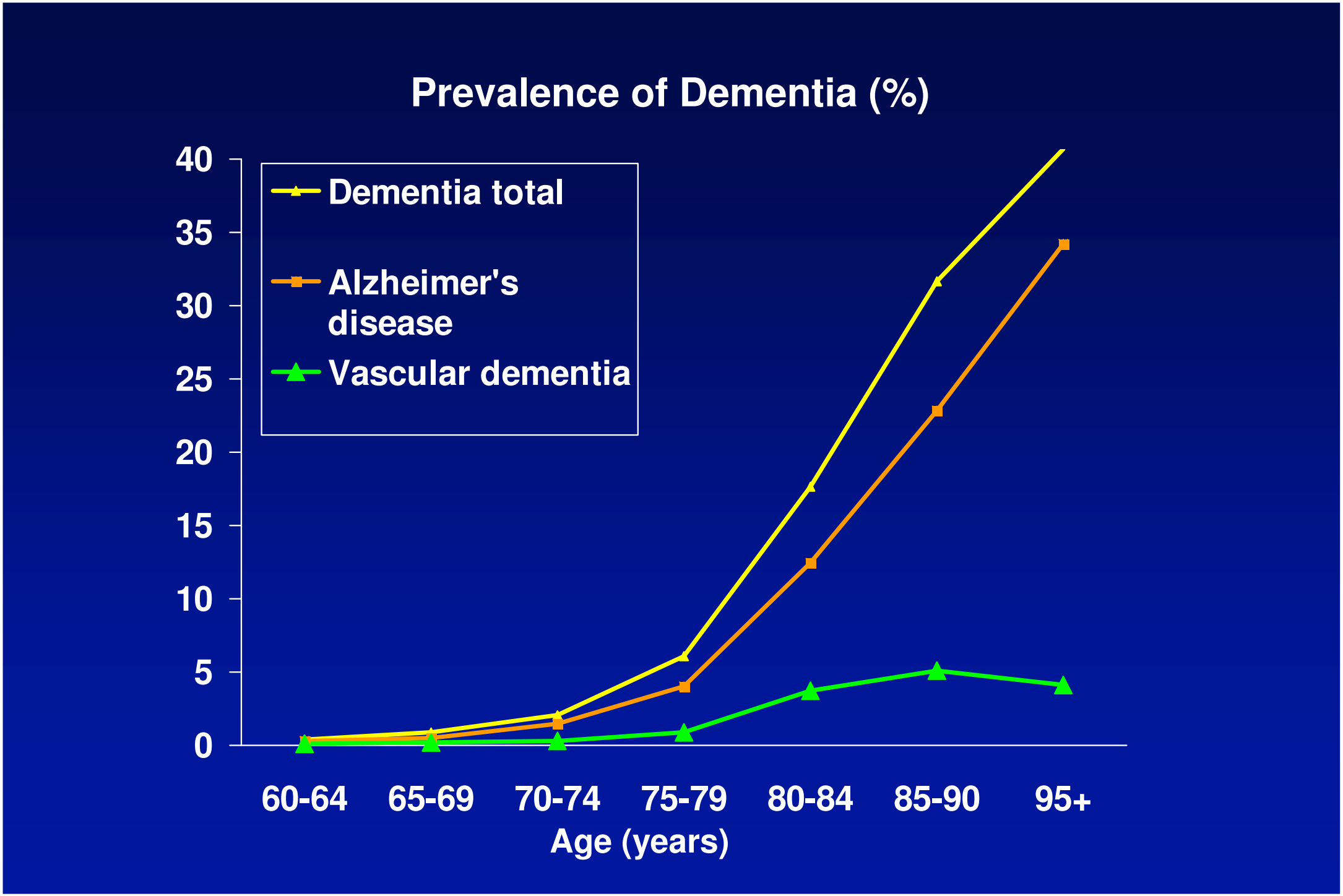


Incidence

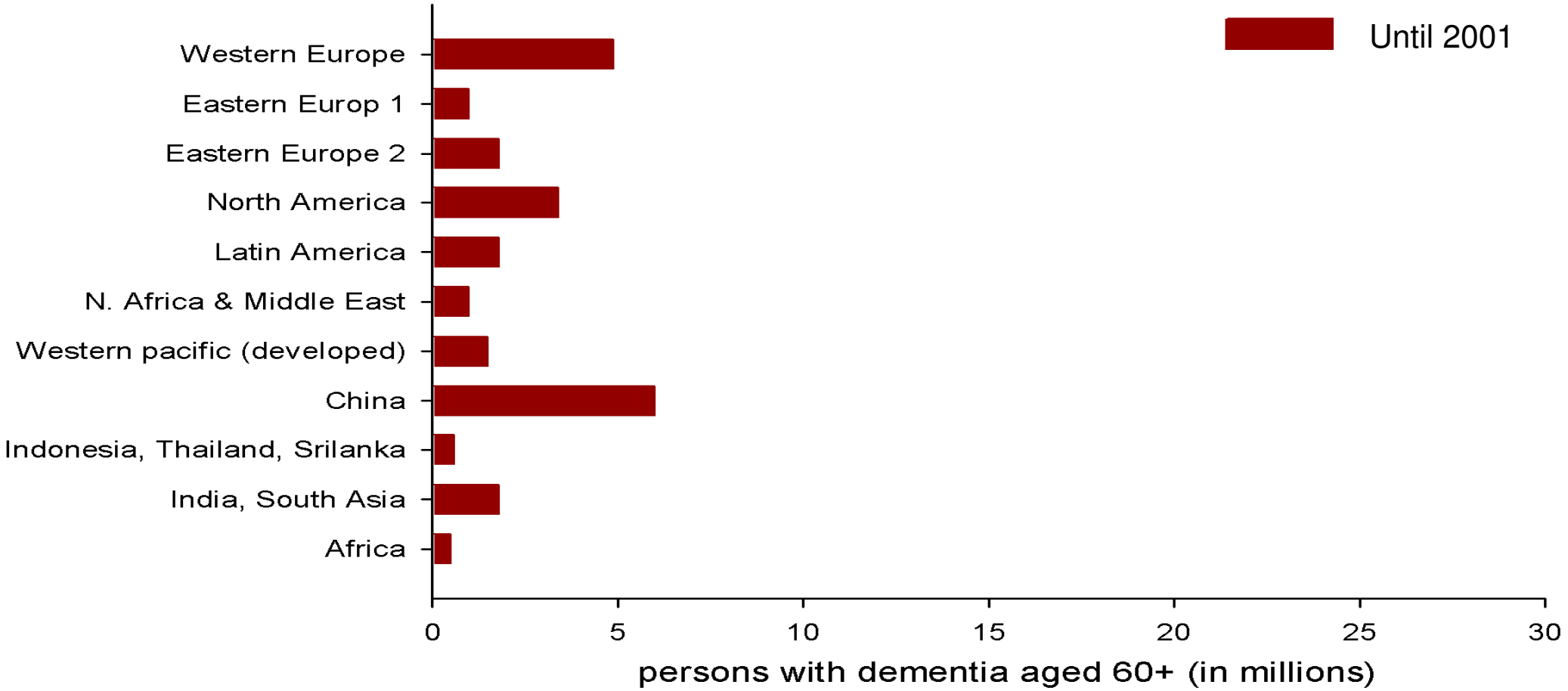






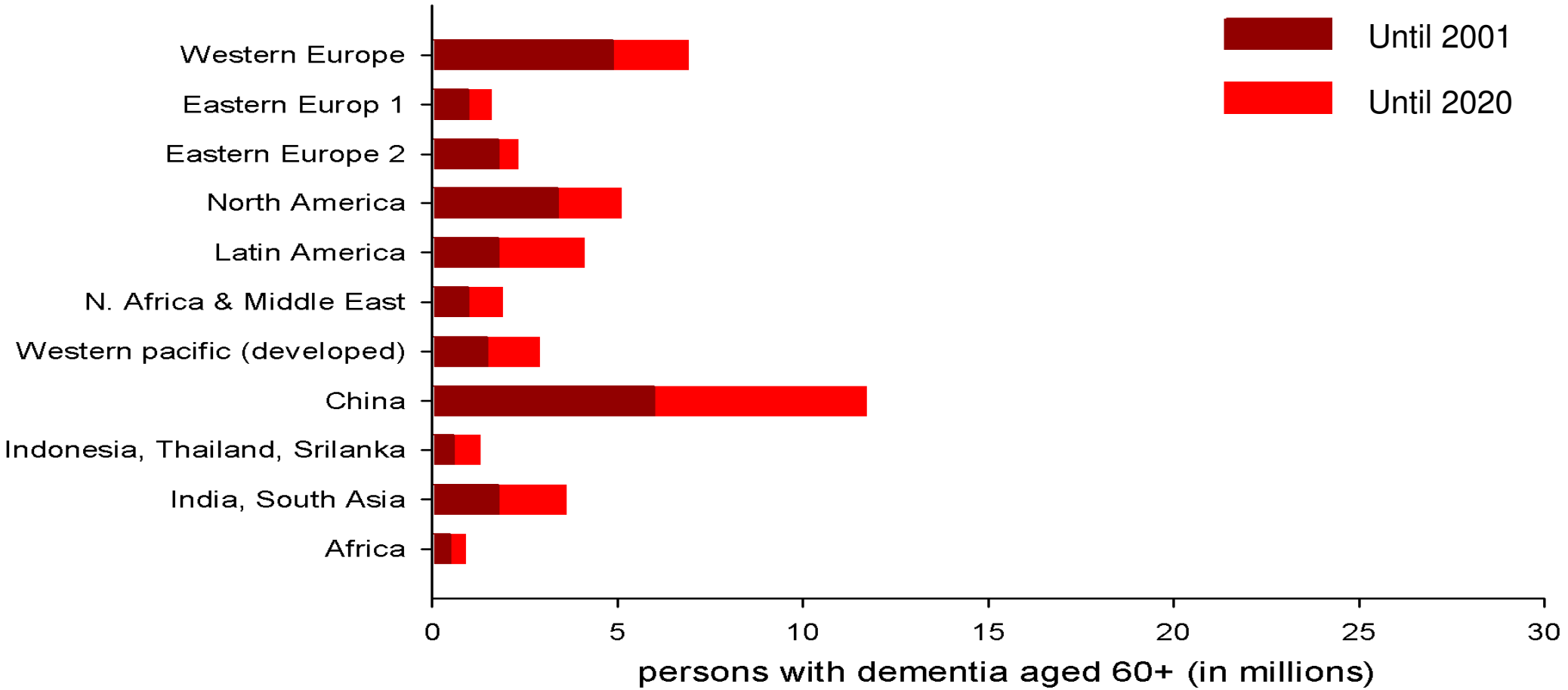

Prevalence of Dementia (%)
40
35
30
25
20
15
10
5
0
Dementia total
Alzheimer's disease
Vascular dementia
60-64
65-69
70-74
75-79
80-84
85-90
95+
Age (years)

Global burden of dementia
Estimated number of people with dementia



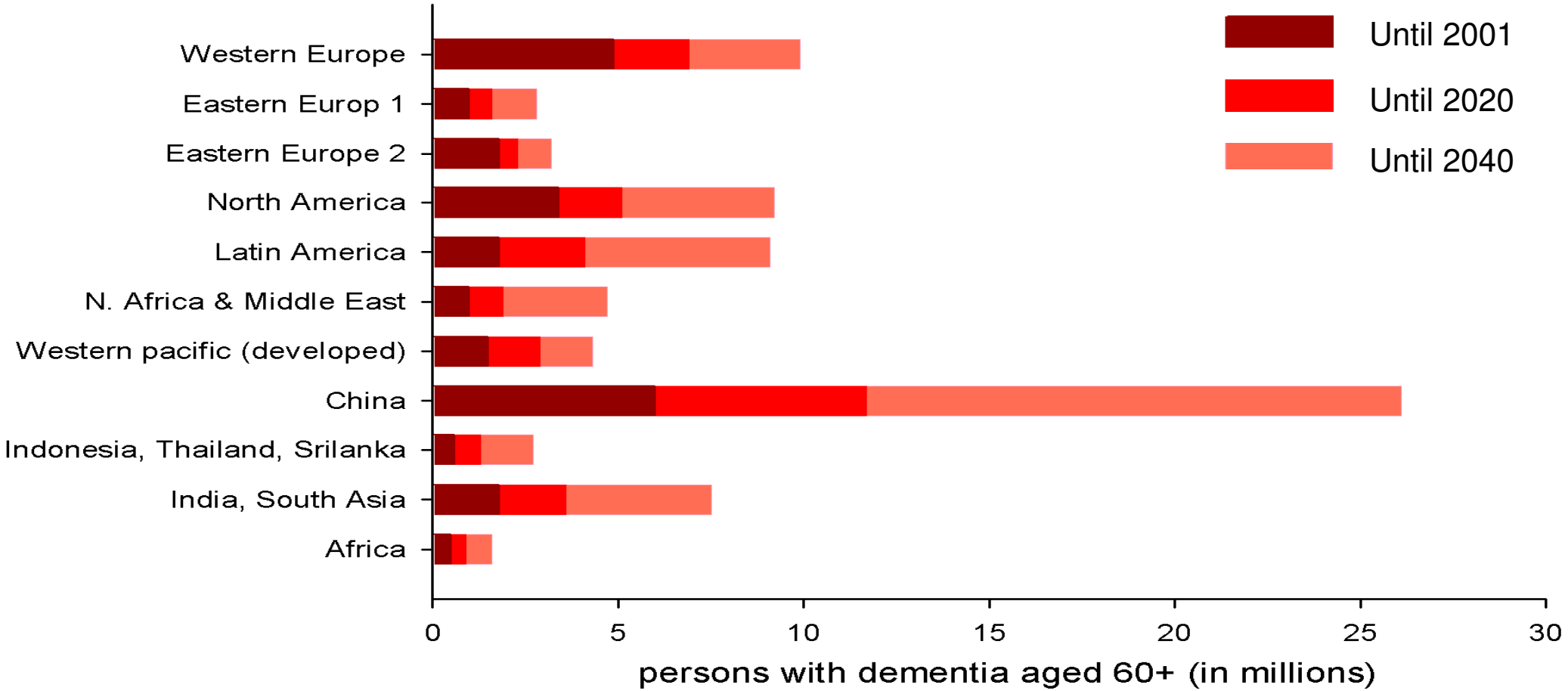
Lancet 2005;366:2112-17

Global burden of dementia
Estimated number of people with dementia



Lancet 2005;366:2112-17

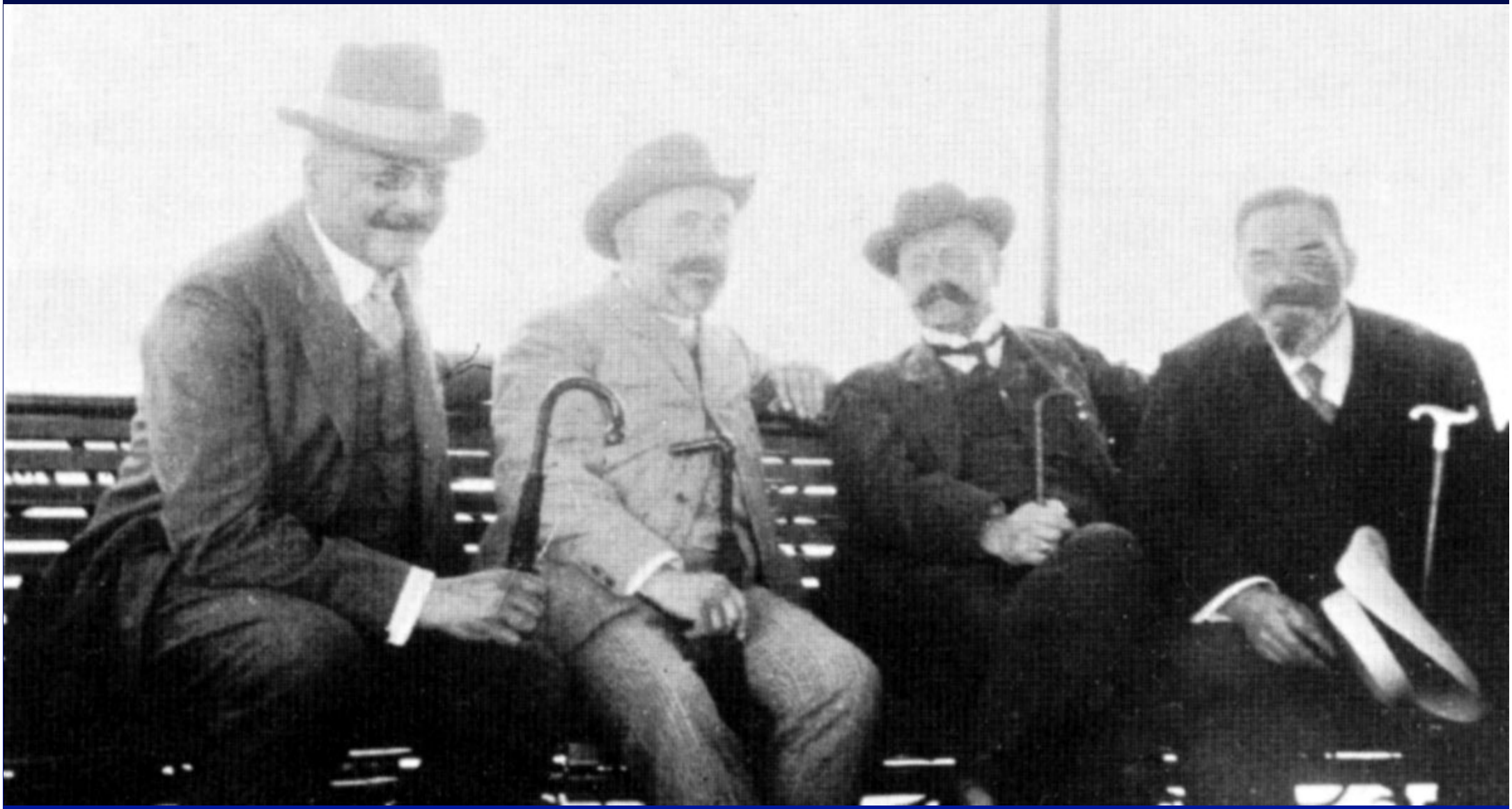
Global burden of dementia
Estimated number of people with dementia



Lancet 2005;366:2112-17

Determinants

- Genetic factors
- Environmental factors
- Gene-environment interaction



Genes in Alzheimer's disease

- Major genes
- Susceptibility genes

Major genes

- APP (Chromosome 21)
- Presenilin 1 (Chromosome 14)
- Presenilin 2 (Chromosome 1)

Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease

Alison Goate*, Marie-Christine Chartier-Harlin*, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Giuffra†, Andrew Haynes‡, Nick Irving*, Louise James‡, Rebecca Mant||, Phillippa Newton*, Karen Rooke*, Penelope Roques*, Chris Talbot*, Margaret Pericak-Vance§, Allen Roses§, Robert Williamson*, Martin Rossor*, Mike Owen|| & John Hardy*¶

Nature 1991;349:704–6

Major genes in Alzheimer's disease

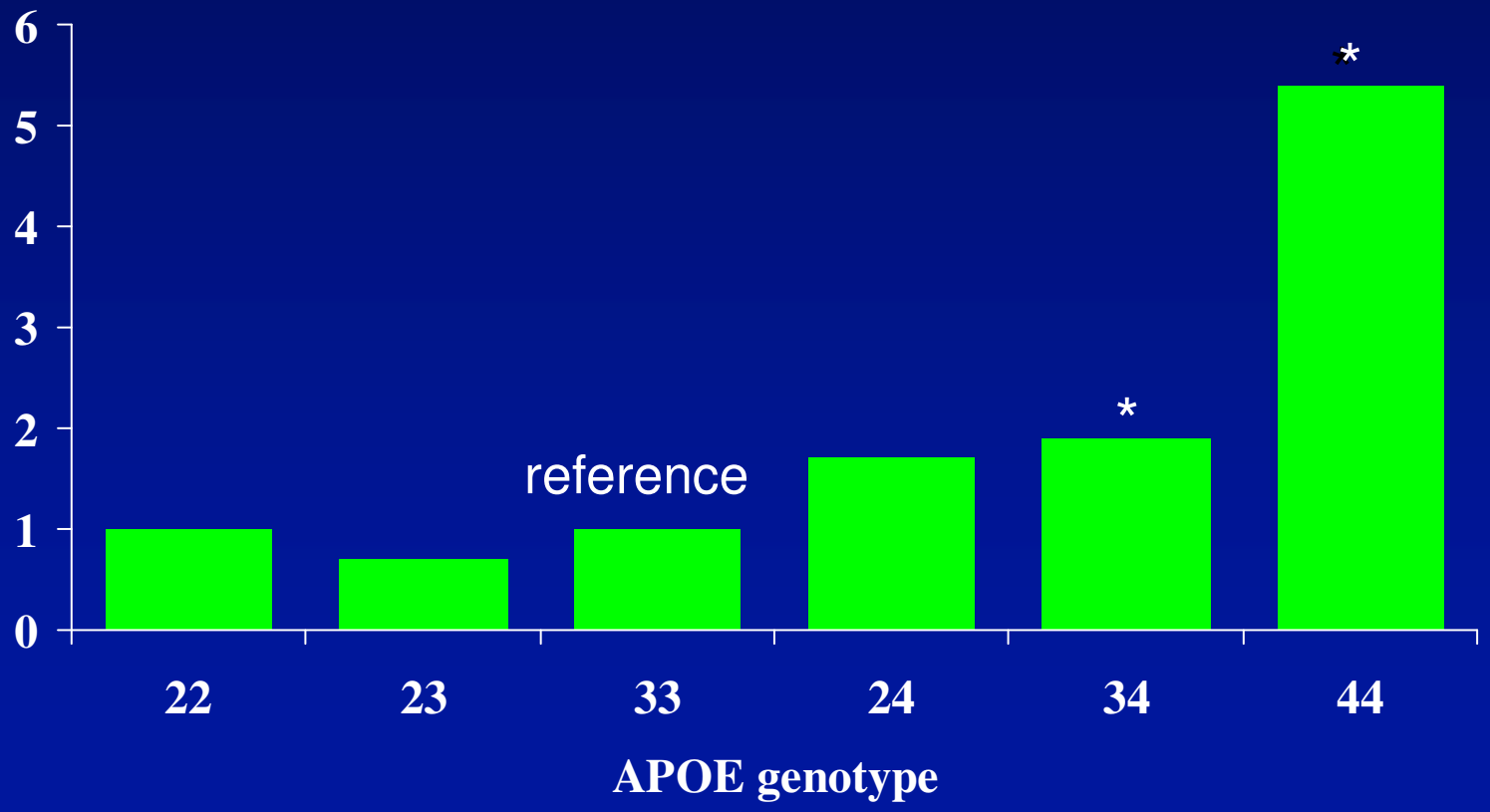
	Risk Carriers	Contribution Population
APP Gene	100+	<0.02%
Presenilin 1	100+	<0.24%
Presenilin 2	100+	<0.04%

Susceptibility Genes

APOE
AACT
VLDL-Receptor
LRP
α2-Macroglobulin
Presenilin
Tau

NACP
Ubiquitin
HLA
Interleukin-1
Butyrylcholinesterase-K
Bleomycin hydrolase
ACE

Relative Risk of Dementia by APOE Genotype



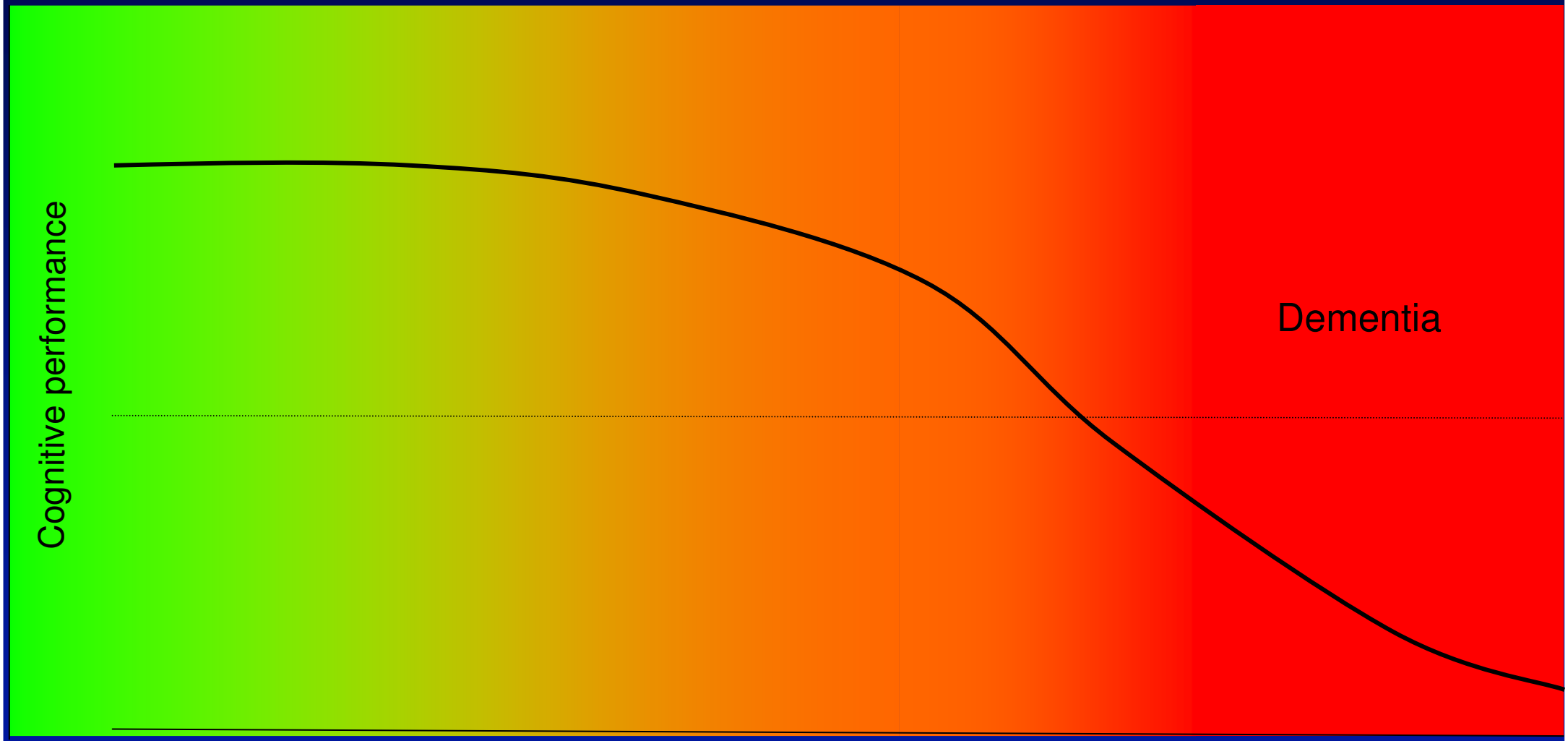
Determinants

- Genetic factors
- Environmental factors
- Gene-environment interaction

Limitations of disease focus

- Clinical symptoms become manifest late in disease course
- Dichotomous outcomes are relatively infrequent and do not reflect underlying spectrum of disease
- Clinical syndromes are etiologically heterogeneous

Dementia



Rotterdam Scan Study

- in core protocol Rotterdam Study
- repeated scanning
- dedicated 1.5 T GE scanner
- 6 series scanned
- 40 minute examination
- 1780 images per participant (0.5 Gb)

Structural Imaging

Diffuse brain changes

Volume and shape of:

- total grey matter
- total white matter
- ventricles
- hippocampus
- entorhinal cortex
- corpus callosum
- anterior cingulate
- cortical thickness

Focal structural abnormalities

- brain infarcts
- lacunes
- white matter lesions
- microbleeds
- iron deposition
- Virchow robin spaces
- calcifications

The NEW ENGLAND JOURNAL of MEDICINE

November 1, 2007 Volume 357:1821-1828

Incidental Findings on Brain MRI in the General Population

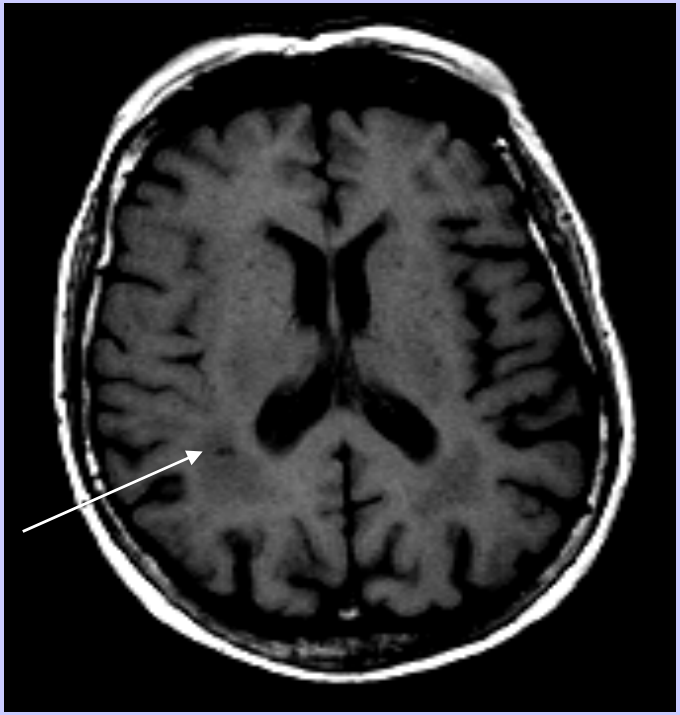
Meike W. Vernooij, M.D., M. Arfan Ikram, M.D., Hervé L. Tanghe, M.D., Arnaud J.P.E. Vincent, M.D., Albert Hofman, M.D., Gabriel P. Krestin, M.D., Wiro J. Niessen, Ph.D., Monique M.B. Breteler, M.D., and Aad van der Lugt, M.D.

Table 1. Incidental Findings on 2000 MRI Scans.*

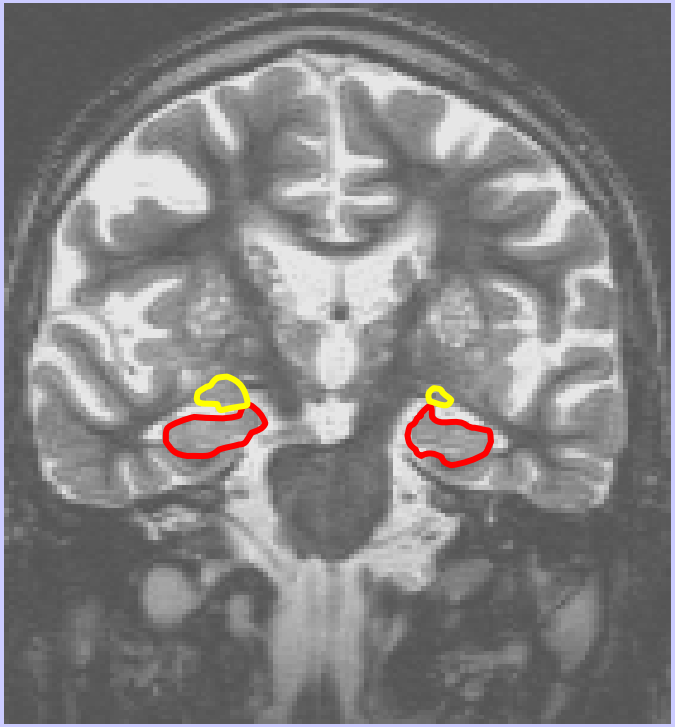
Finding	No. (%)		No. (%)
Asymptomatic brain infarct†	145 (7.2)	Other findings	
Lacunar infarct	112 (5.6)	Aneurysm	35 (1.8)
Cortical infarct	41 (2.0)	Cavernous angioma	7 (0.4)
Primary tumors, benign	31 (1.6)	Metastases	1 (<0.1)
Meningioma	18 (0.9)	Subdural hematoma	1 (<0.1)
Vestibular schwannoma	4 (0.2)	Arachnoid cyst¶	22 (1.1)
Intracranial lipoma‡	2 (0.1)	Type I Chiari malformation‖	18 (0.9)
Trigeminal schwannoma	1 (<0.1)	Major-vessel stenosis**	9 (0.5)
Pituitary adenoma	6 (0.3)	Dermoid cyst of lateral orbital rim	1 (<0.1)
Primary tumors, malignant§	1 (<0.1)	Fibrous dysplasia	1 (<0.1)

Magnetic resonance imaging the Rotterdam Scan Study

White matter lesions



Silent brain infarcts

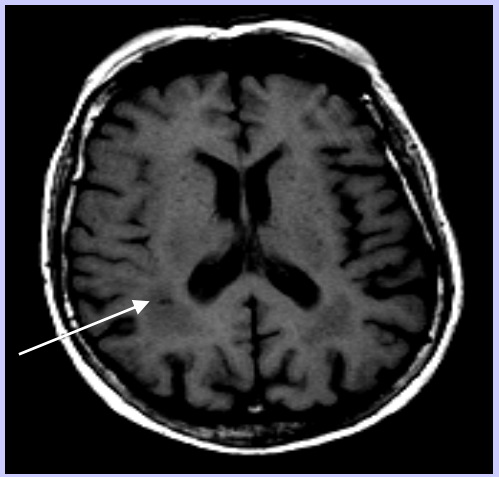


Hippocampal and amygdalar atrophy

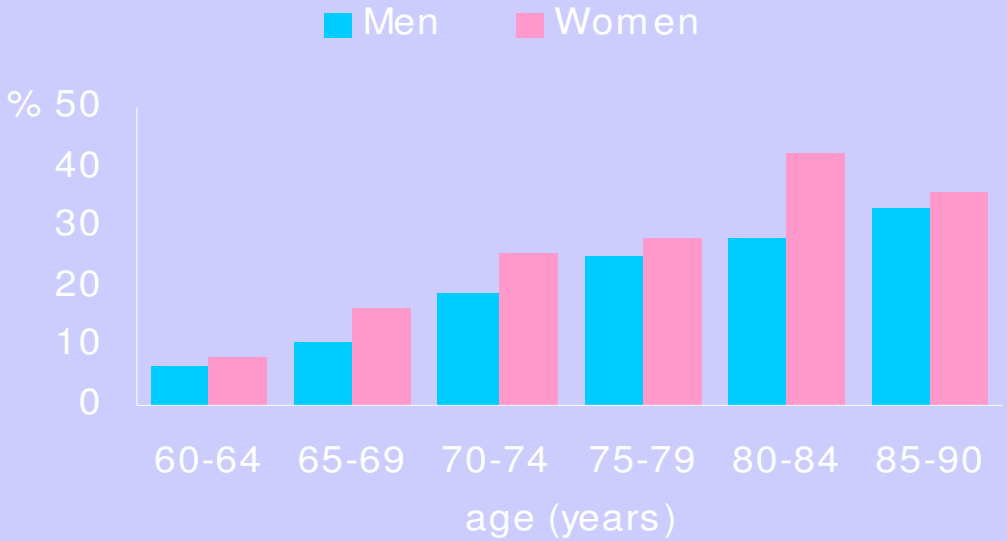
White Matter Lesions

- Highly prevalent
- Associated with worse performance on cognitive test
- Associated with increased rate of cognitive decline
- Associated with increased risk of dementia

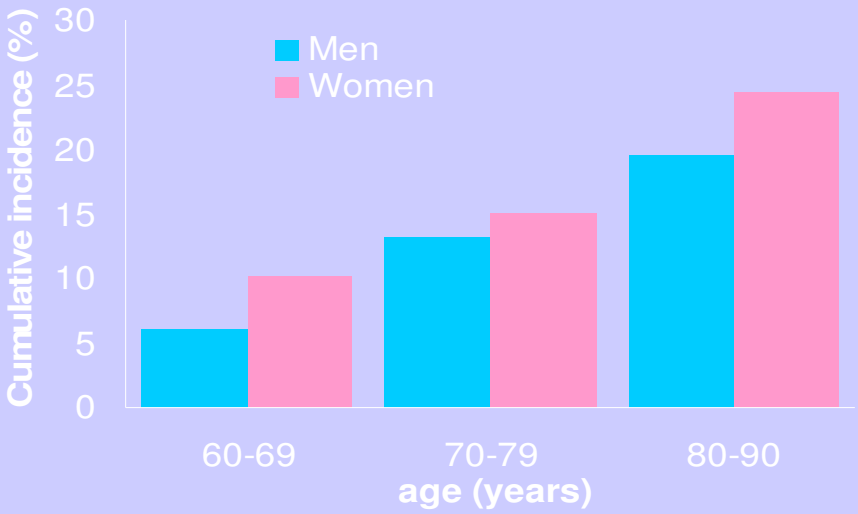
Silent brain infarcts



prevalence



incidence



Stroke 2002;33:21-25; Stroke 2003;34:392-6

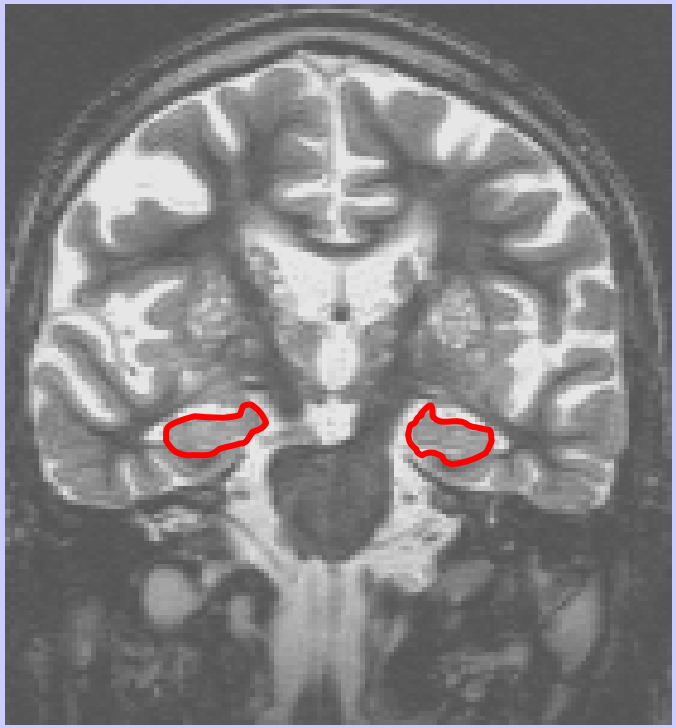
Silent brain infarcts and dementia

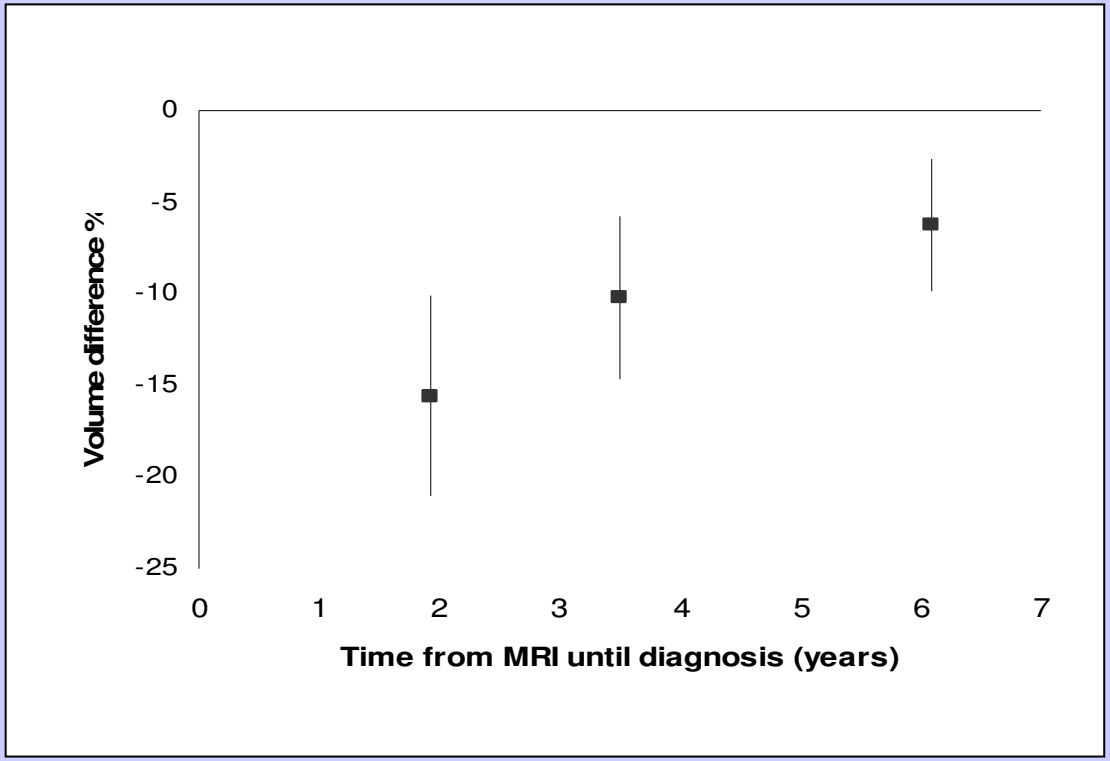
	Risk of dementia HR (95% CI)	Risk of Alzheimer's disease HR (95% CI)
Silent brain infarct†	2.3 (1.1-4.7)	2.6 (1.2-5.7)
Silent brain infarct‡	2.0 (0.9-4.4)	2.6 (1.1-6.0)

†Adjusted for age, sex, and education.
‡Additionally adjusted for subcortical atrophy, and periventricular white matter lesions.

Vermeer S et al. NEJM 2003;348:1215-22

Magnetic resonance imaging hippocampus atrophy





Arch Gen Psych 2006;63:57-62

Environmental factors

- Traumatic factors
- Endocrine factors
- Inflammatory factors
- Vascular factors

Vascular factors

- Stroke
- Atrial fibrillation
- Diabetes mellitus
- Atherosclerosis

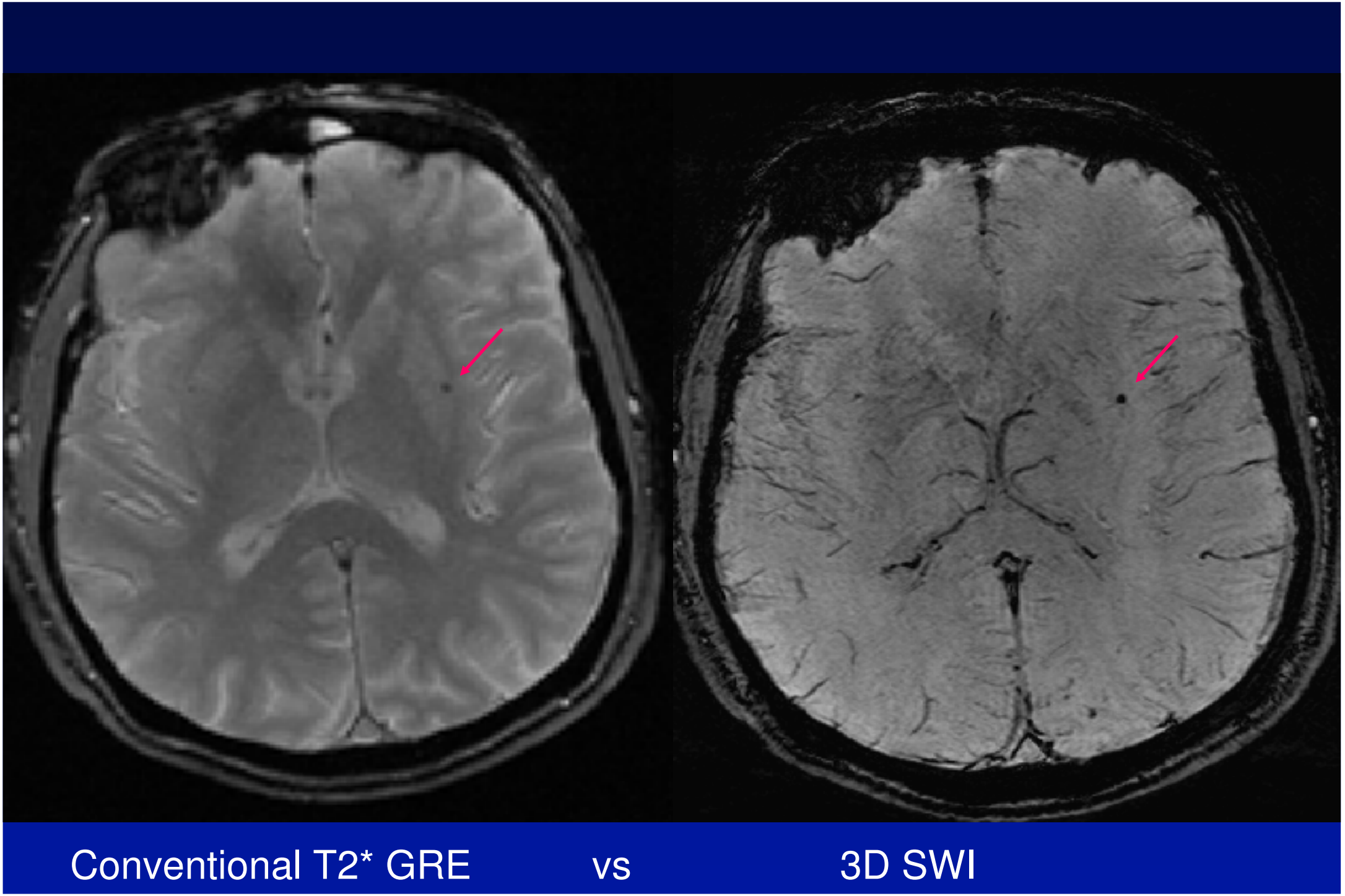
Outcomes of silent brain infarcts

	RR
Dementia	2.3 (1.1 - 4.7)
Depression	2.5 (1.3 - 4.9)
Stroke	3.6 (2.1 - 6.1)

NEJM 2003;348:1215-22

Cerebral microbleeds

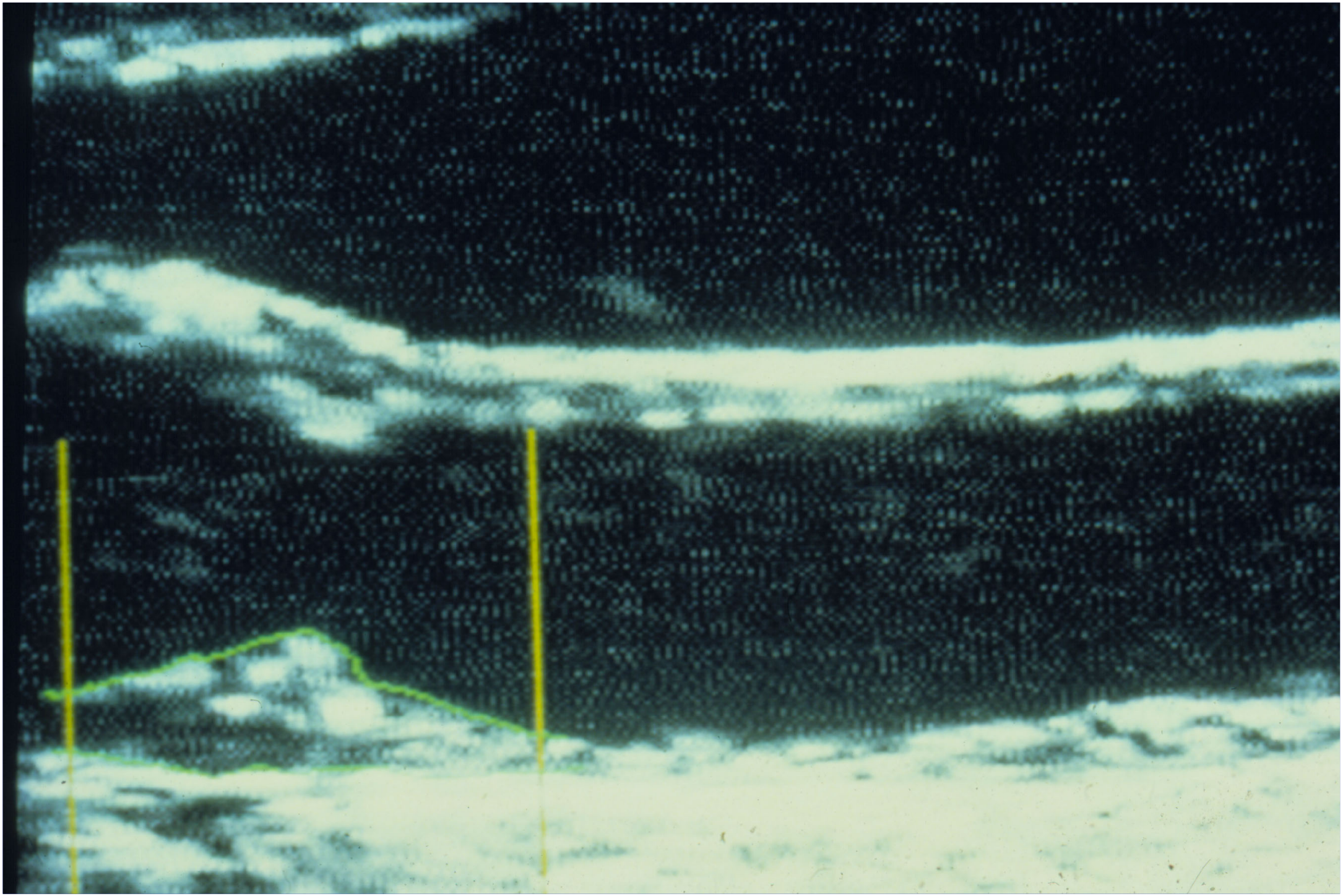
- Hemosiderin deposits in brain
- Leakage of red blood cells through vessel walls
- Possibly new marker of cerebral small vessel disease
- Visible on MRI using T2* GRE imaging


Conventional T2* GRE
vs
3D SWI

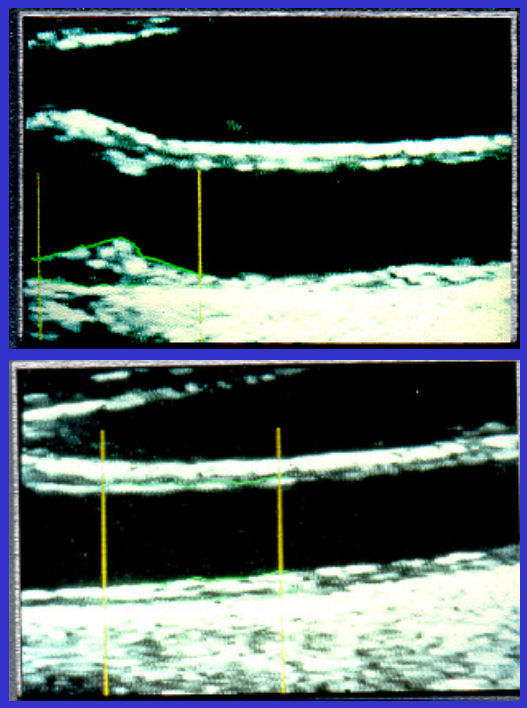
Prevalence of cerebral microbleeds

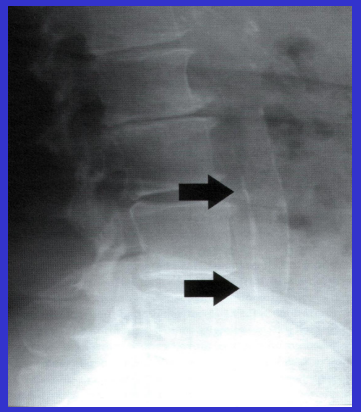
Age	%
60-69	17.8
70-79	31.3
80-97	38.3

Vernooij, Neurology, in press



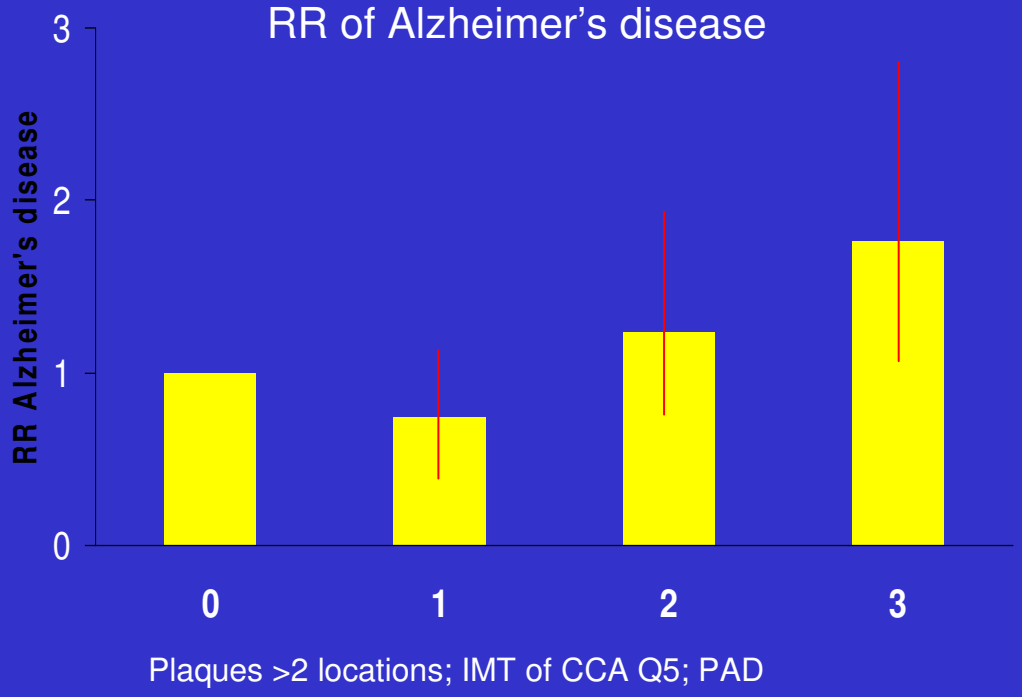
Atherosclerosis and risk of AD the Rotterdam Study





Peripheral arterial disease:

Ankle to brachial blood pressure ratio <0.9



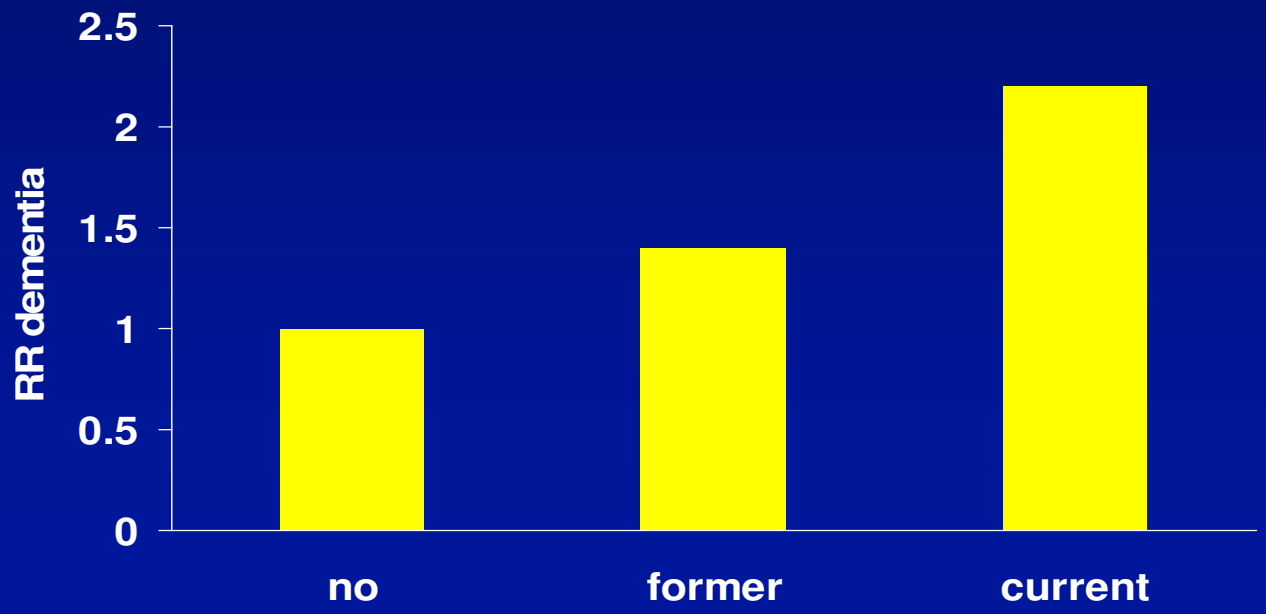
Hofman et al. Lancet 1997; van Oijen et al. Ann Neurol 2007

ARTICLES

Lancet 1998;351:1840-3

Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study

A Ott, A J C Slooter, A Hofman, F van Harskamp, J C M Witteman, C Van Broeckhoven, C M van Duijn, M M B Breteler



ORIGINAL CONTRIBUTION

Dietary Intake of Antioxidants and Risk of Alzheimer Disease

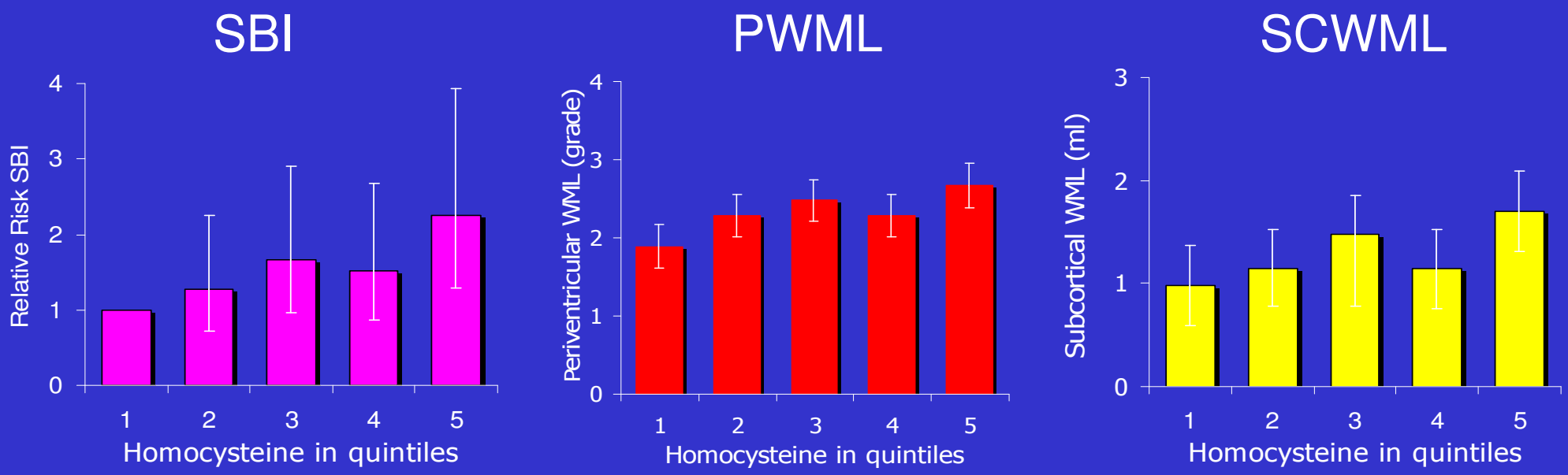
JAMA. 2002;287:3223-3229

Marianne J. Engelhart, MD, MSc
Mirjam I. Geerlings, PhD
Annemieke Ruitenberg, MD, PhD
John C. van Swieten, MD, PhD
Albert Hofman, MD, PhD
Jacqueline C. M. Witteman, PhD
Monique M. B. Breteler, MD, PhD

- 5395 subjects
- 6 year follow-up
- 197 dementia cases (146 AD)

	RR of AD per sd
vit E	0.81 (0.66-0.99)
vit C	0.82 (0.68-0.98)
vegetables	0.82 (0.67-1.00)

Homocysteine and small vessel disease



Vermeer et al. Ann Neurol 2002

Diabetes 53:687–692, 2004

Magnetic Resonance Imaging of the Brain in Diabetes

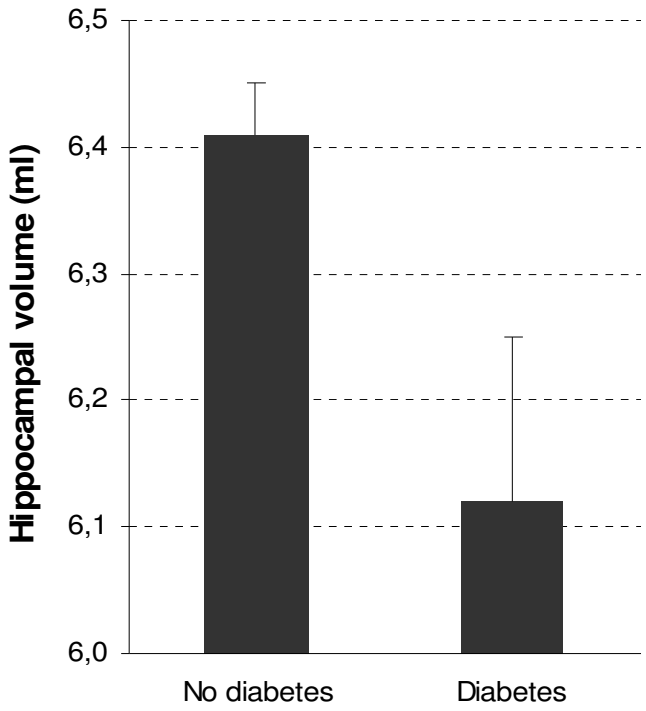
The Cardiovascular Determinants of Dementia (CASCADE) Study

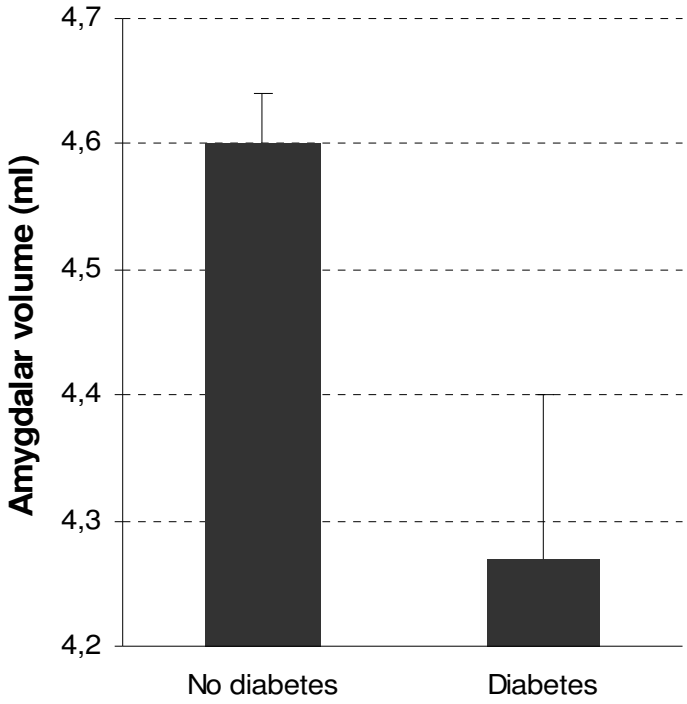
Reinhold Schmidt,[1] Lenore J. Launer,[2,3] Lars-Göran Nilsson,[4] Andrzej Pajak,[5] Susanna Sans,[6] Klaus Berger,[7] Monique M. Breteler,[3] Maria de Ridder,[3] Carole Dufouil,[8] Rebecca Fuhrer,[9] Simona Giampaoli,[10] and Albert Hofman,[3] for the CASCADE Consortium

- No association between DM and markers of cerebrovascular small vessel disease
- Significant relation between DM and markers of brain atrophy (cortical atrophy, subcortical atrophy)

Diabetes and hippocampal volume

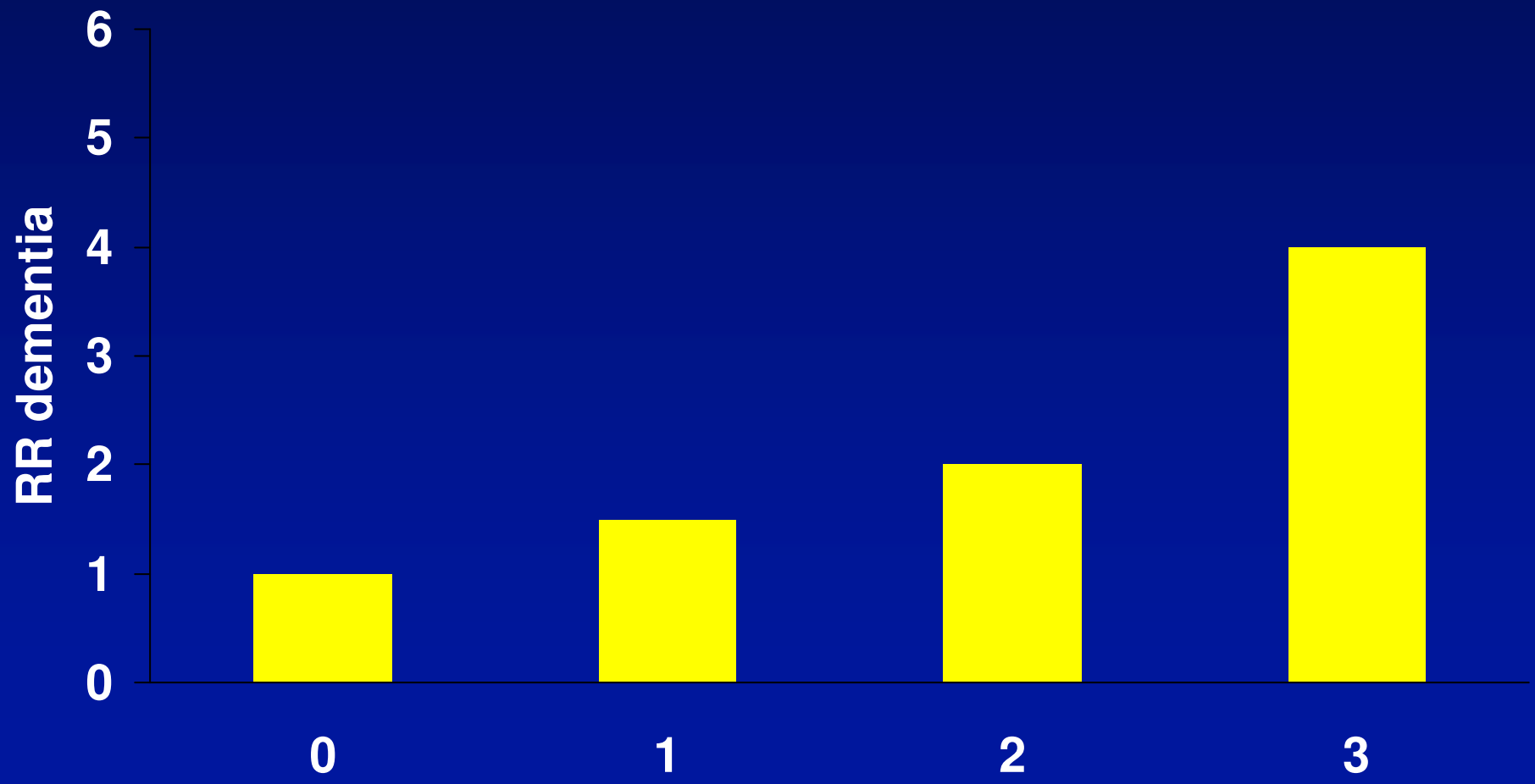
the Rotterdam Scan Study





Den Heijer et al. Diabetologia 2003;46:1604-10

Vascular score

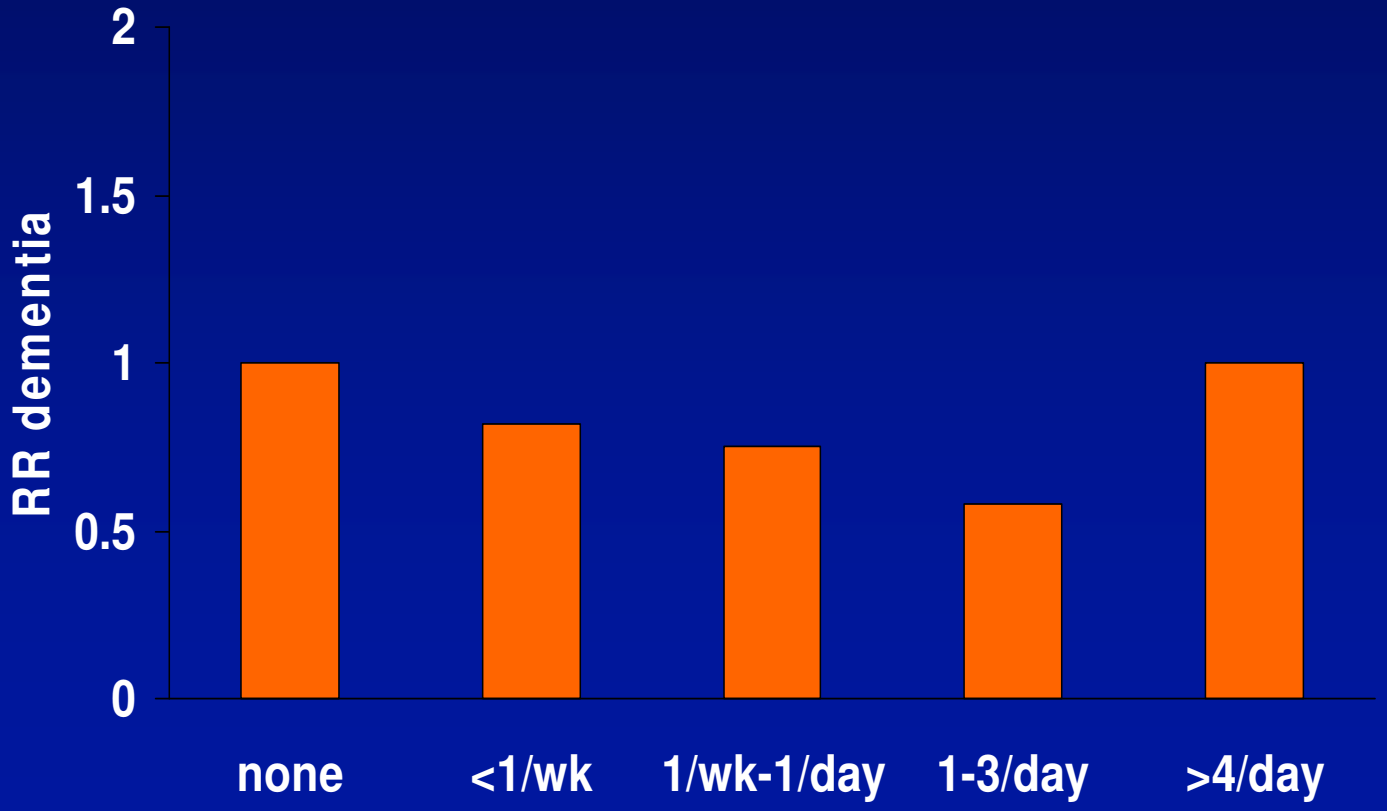


Articles

Alcohol consumption and risk of dementia: the Rotterdam Study

Annemieke Ruitenberg, John C van Swieten, Jacqueline C M Witteman, Kala M Mehta, Cornelia M van Duijn, Albert Hofman, Monique M B Breteler

Lancet 2002; 359: 281–86



Principal investigators Rotterdam Study

Monique Breteler

Albert Hofman

Paulus de Jong

Huib Pols

Bruno Stricker

Henning Tiemeier

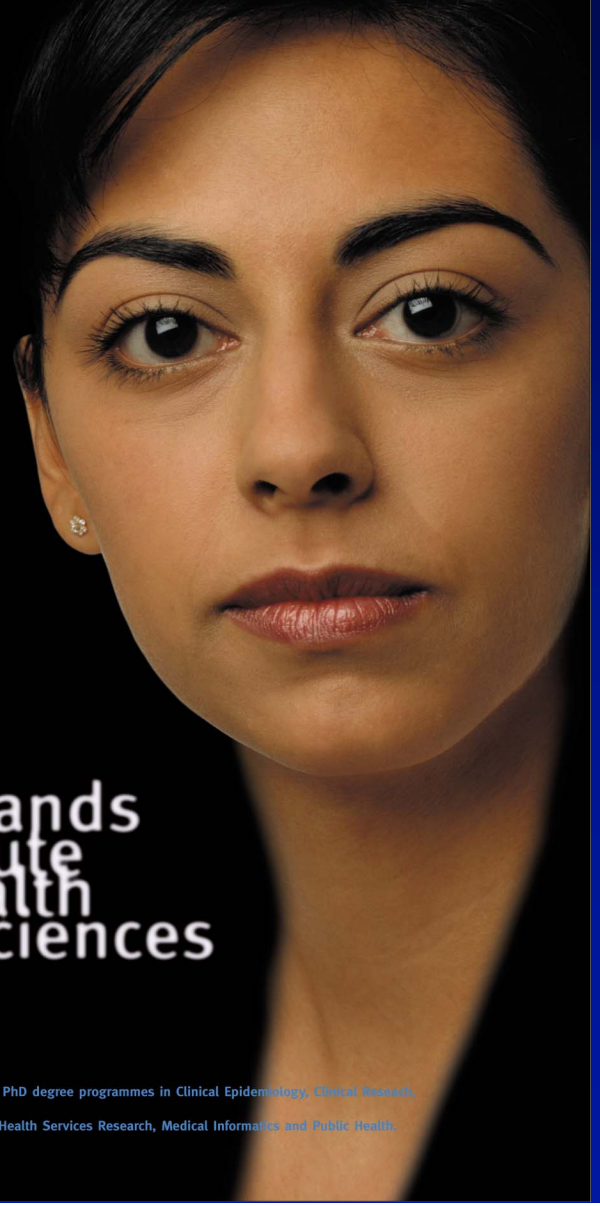
Cornelia van Duijn

Jacqueline Witteman

nihes

Dare to be outstanding

Research Training in Medicine and the Health Sciences



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N i h e s offers MSc, MPH, DSc and PhD degree programmes in Clinical Epidemiology, Clinical Research, Epidemiology, Genetic Epidemiology, Health Services Research, Medical Informatics and Public Health.

Conclusions

- Alzheimer's disease is a frequent disorder with a high absolute risk
- Autosomal-dominant mutations are an important but infrequent cause of Alzheimer's disease
- Susceptibility genes are important in interaction with environmental factors
- Vascular factors play an important part in the etiology of Alzheimer's disease