World Alzheimer's Month
September 2016

REMEMBER ME

Angelo Bianchetti

- World Alzheimer's Day was launched at the opening of ADI's annual conference in Edinburgh on 21 September 1994 to celebrate our 10th anniversary.
- World Alzheimer's Month is observed in September every year. World Alzheimer's Month was launched in September 2012. The decision to introduce the full month, to contain the existing World Alzheimer's Day, was made to enable national and local Alzheimer associations worldwide to extend the reach of their awareness programmes over a longer period of time.

September
Remember Me

World Alzheimer's Month

To find out more visit:

www.worldalzmonth.org

@AlzDisInt #WAM2016

Alzheimer's Disease International

The global voice on dementia

World Alzheimer's Month

September
Remember Me

The theme for this year's World Alzheimer's Month campaign is Remember Me. We're encouraging people all around the world to learn to spot the signs of dementia, but also not to forget about loved ones who are living with dementia, or who may have passed away. The impact of September's campaign is growing, but the stigmatisation and misinformation that surrounds dementia remains a global problem.

If you are living with dementia:

Remember that you are not alone. It is possible to live well with dementia by seeking help and support from your family, friends, doctor, health and social workers and from the Alzheimer association in your country. You have a right to feel empowered and listened to, and to be treated as an individual.

If you are a caregiver:

Remember that caring for someone with dementia is a challenging task. However, it is easier to cope if you make sure you look after yourself too, taking care of your own physical and mental health needs. This will make a big difference to the wellbeing for both you and the person you are caring for.

As a society:

Remember that people living with dementia and their caregivers can often feel isolated, so we need to do more to tackle this stigma. Dementia Friendly Communities are being established all over the world to educate people about dementia and to provide stronger, community-based support networks for people living with dementia, caregivers and families.

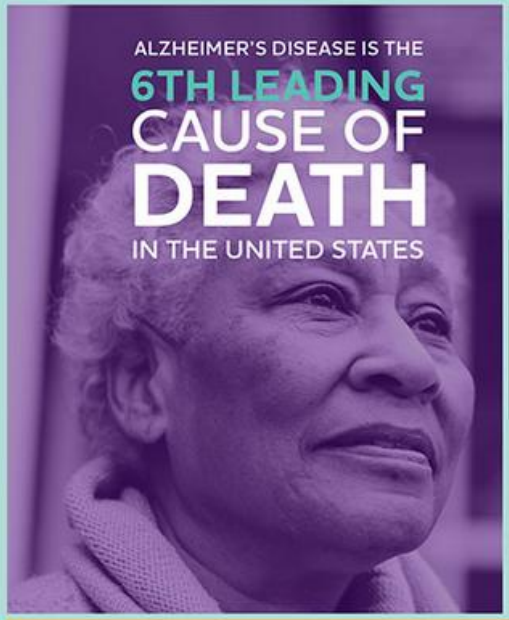
As an individual:

Remember that leading a healthy lifestyle may help to reduce your risk of developing dementia later in life. The general rule is what's good for the heart is good for the brain, so both should be well looked after with a balanced diet and regular physical and mental exercise. Much of what's needed are simple activities you can do in your day to day life.

As a government:

Remember that developing a national dementia plan will help your country to deal with the growing impact of dementia's rising prevalence and cost. These plans help to increase national awareness and education about dementia and can improve access to diagnosis, treatment and care, promoting a better quality of life for people living with dementia.

2016 ALZHEIMER'S DISEASE FACTS AND FIGURES



MORE THAN
5 MILLION
AMERICANS ARE LIVING WITH ALZHEIMER'S

1 IN 3 SENIORS
DIES WITH ALZHEIMER'S
OR ANOTHER DEMENTIA

IN 2015, MORE THAN 15 MILLION CAREGIVERS PROVIDED AN ESTIMATED
18.1 BILLION HOURS OF UNPAID CARE

ALZHEIMER'S COSTS CAREGIVERS MORE THAN THEIR TIME

FAMILY CAREGIVERS SPEND MORE THAN
$5,000 A YEAR
CARING FOR SOMEONE WITH ALZHEIMER'S

FOR SOME FAMILIES THIS MEANS
MISSING A VACATION

BUT FOR OTHERS, IT MAY MEAN
GOING HUNGRY

EVERY
66 SECONDS
SOMEONE IN THE UNITED STATES DEVELOPS THE DISEASE

IN 2016, ALZHEIMER'S AND OTHER DEMENTIAS WILL COST THE NATION
$236 BILLION

IT KILLS MORE THAN
BREAST AND PROSTATE CANCER COMBINED

alz.org® | alzheimer's association®

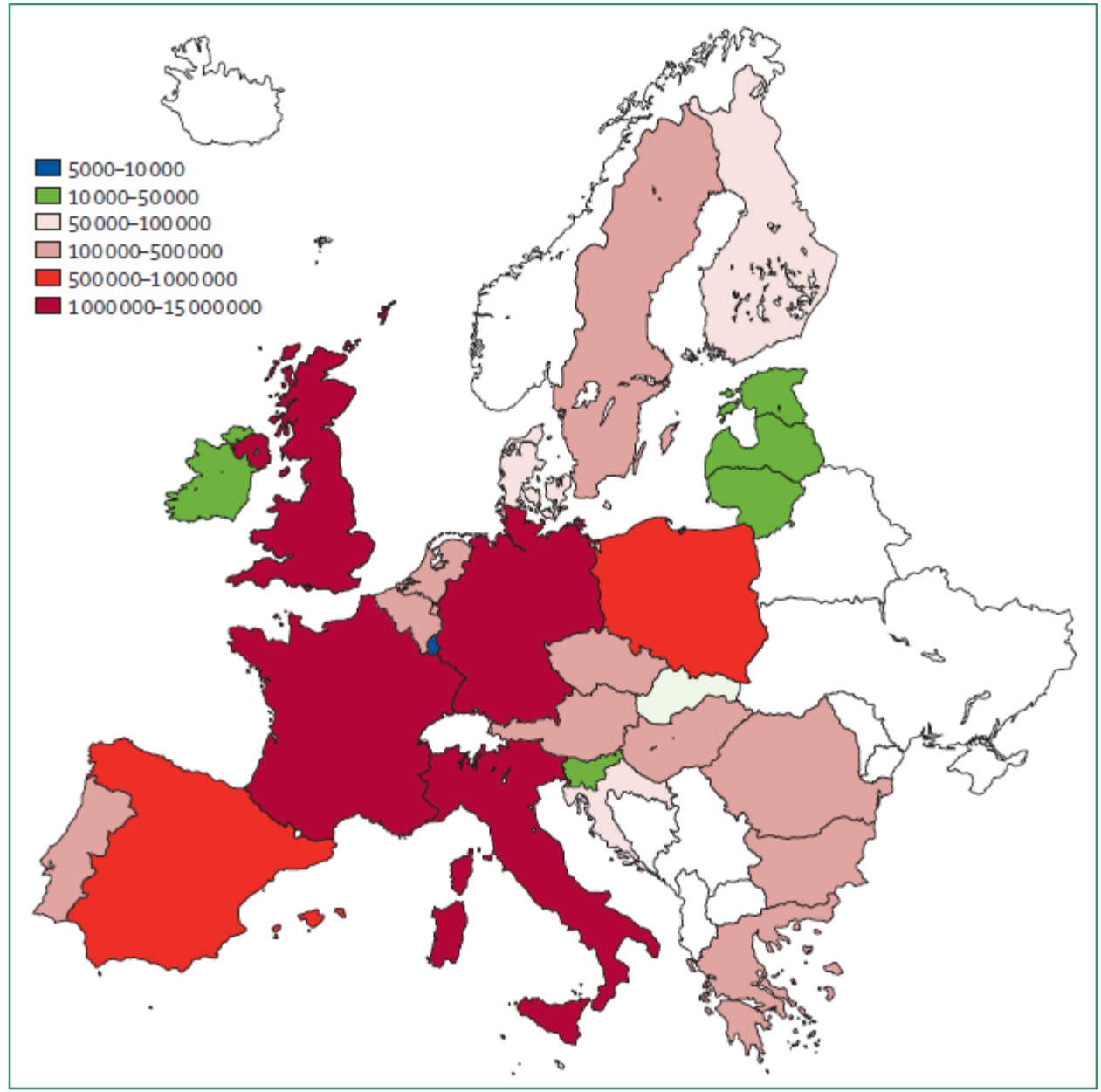


Figure 1: **Number of people with dementia in 28 European countries in 2013**
Estimates of the total number of people with dementia in each of 28 European countries were obtained from Alzheimer Europe.[26]

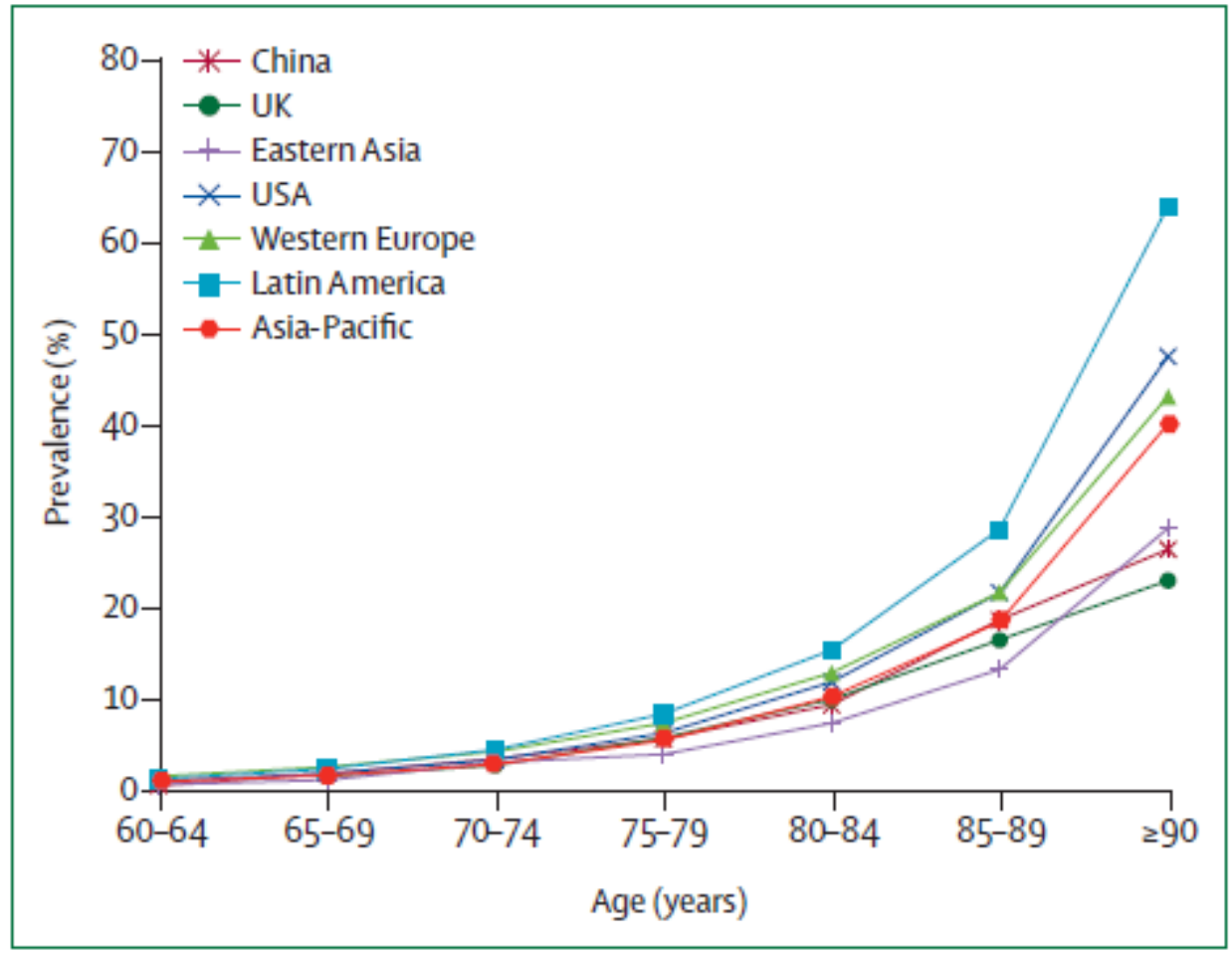
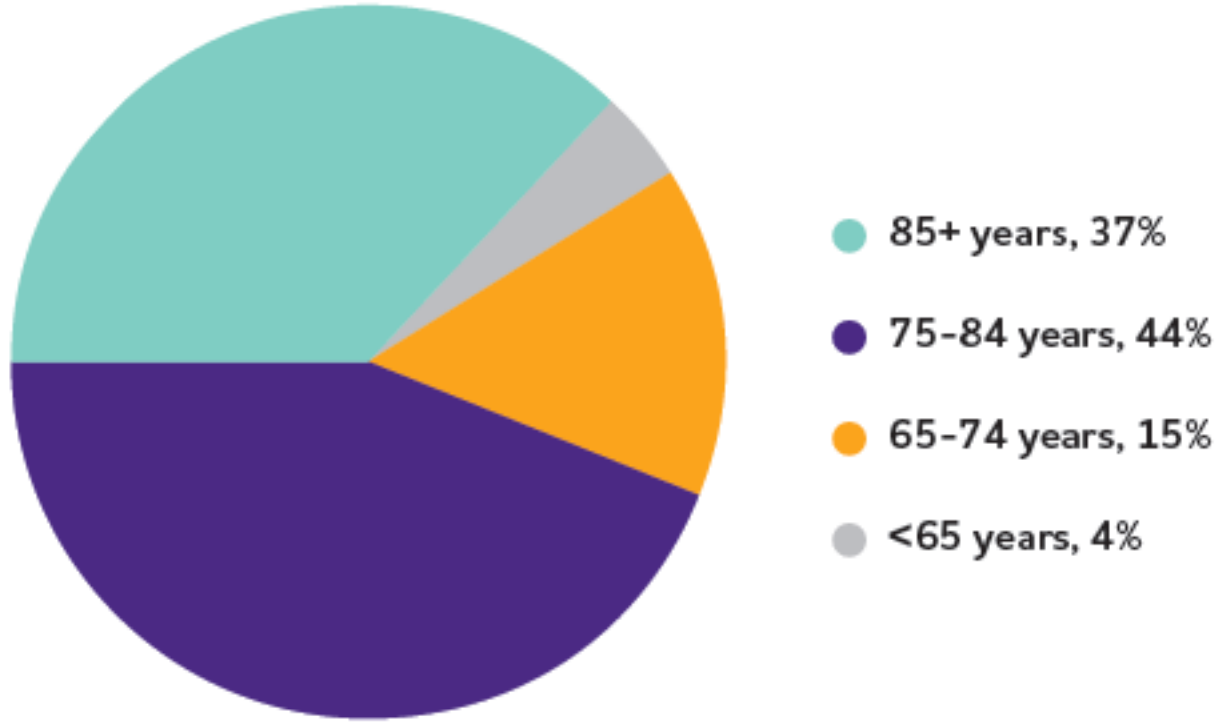


Figure 3: **Age-specific prevalence of dementia by world region and in major countries**

Patterns of age-specific prevalence of dementia are similar across worldwide regions, but vary substantially among the oldest old (age ≥90 years).[72–75]

FIGURE 1 | Ages of People with Alzheimer's Disease in the United States, 2016



Created from data from Hebert et al.[33,A4]

FIGURE 3 | Estimated Lifetime Risk for Alzheimer's, by Age and Sex, from the Framingham Study

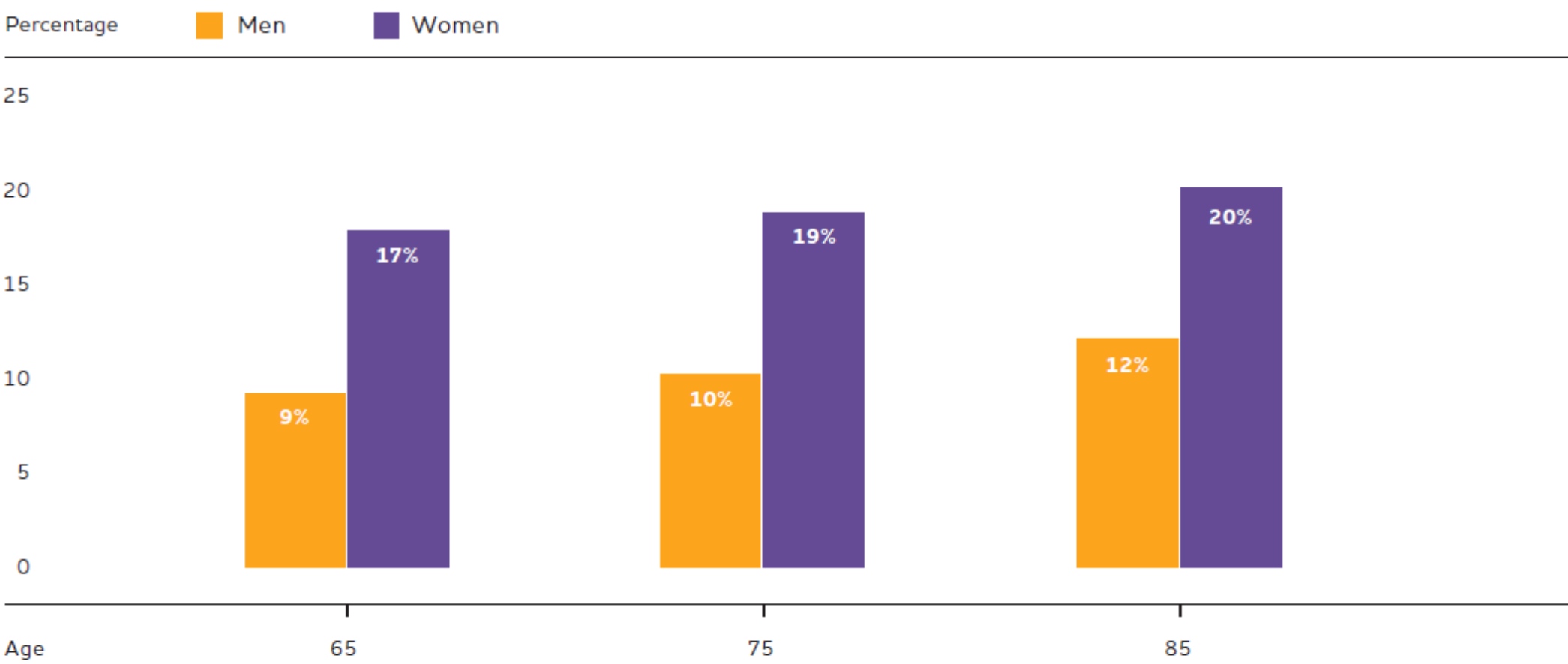
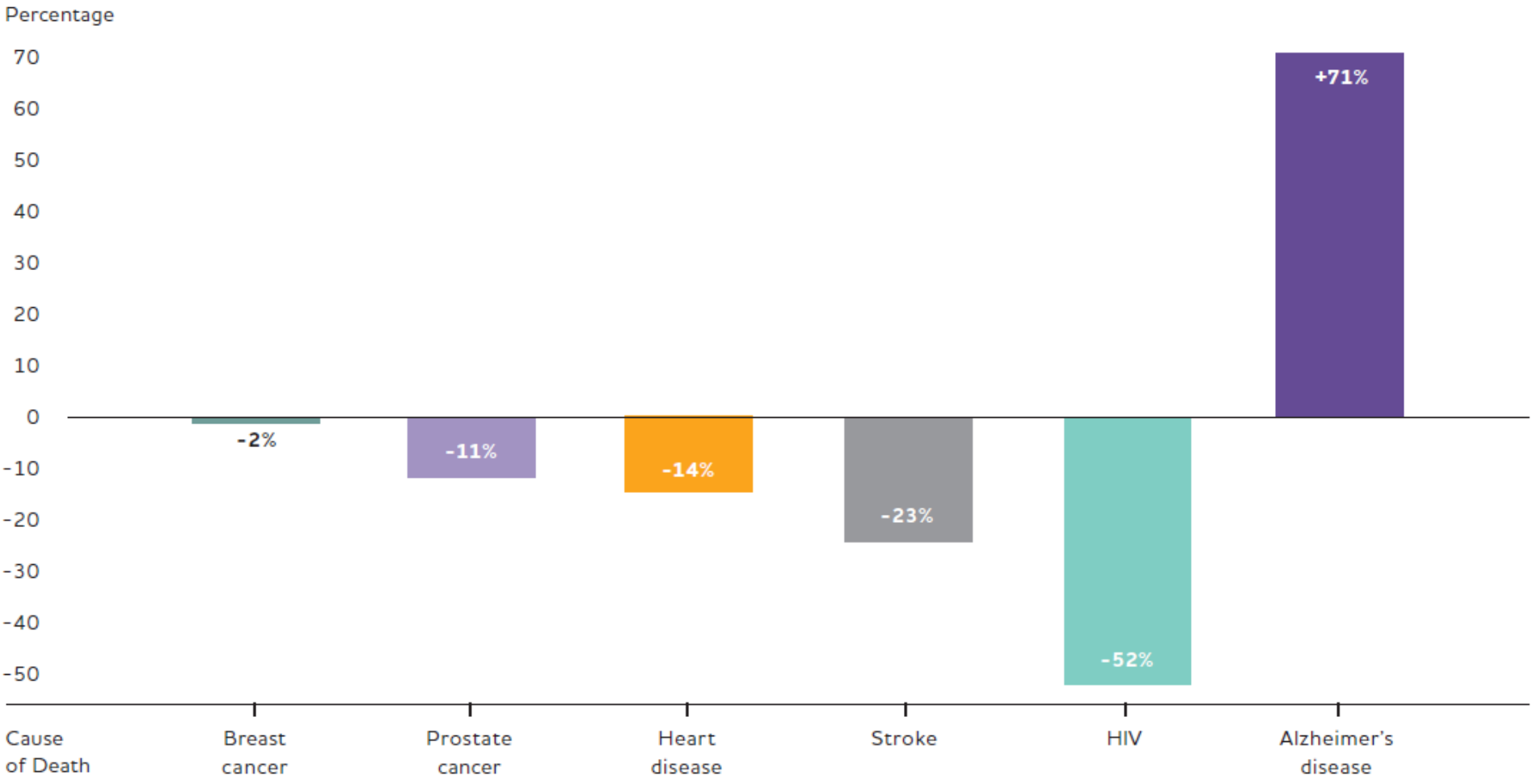


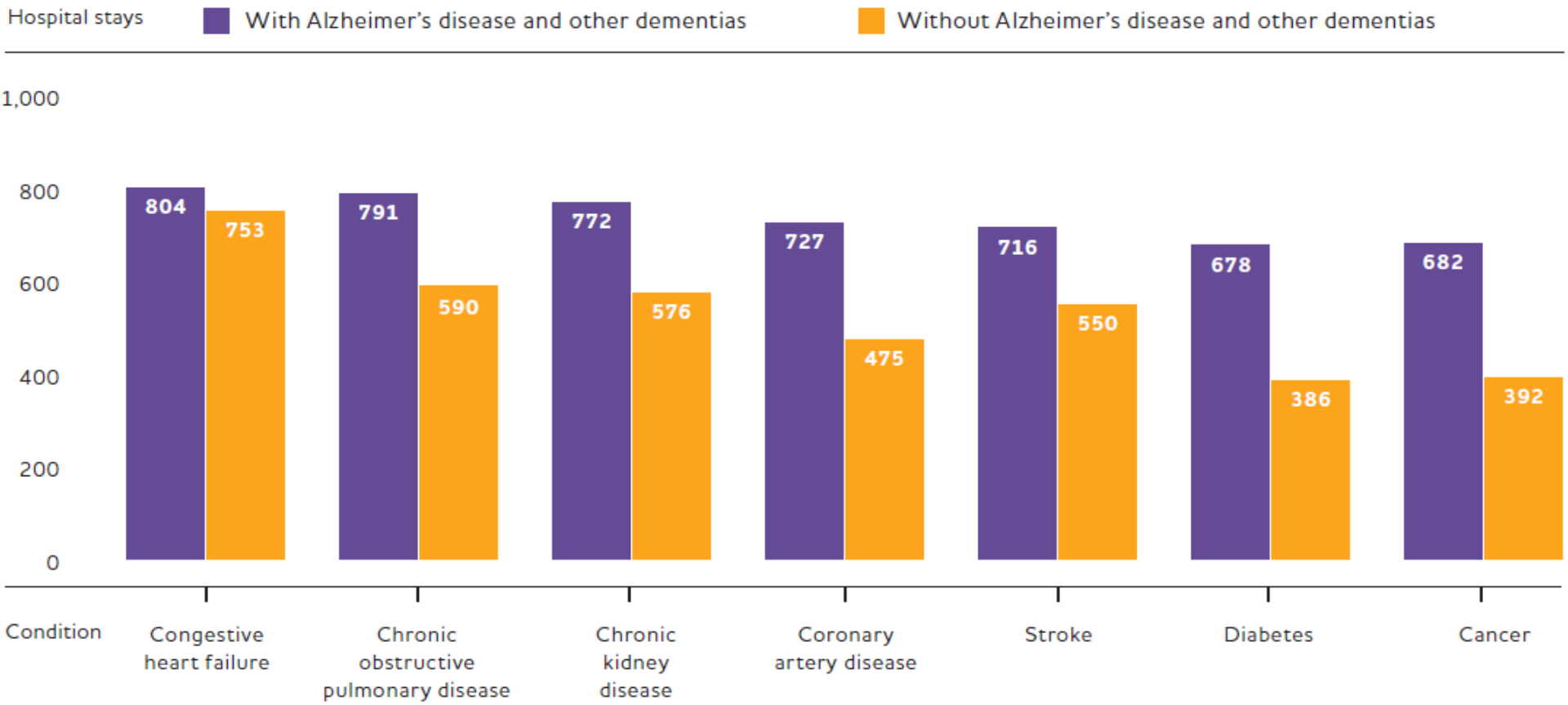
FIGURE 5 | Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2013



Created from data from the National Center for Health Statistics.[180]

FIGURE 12

Hospital Stays per 1,000 Beneficiaries Age 65 and Older with Specified Coexisting Medical Conditions, with and without Alzheimer's Disease and Other Dementias, 2014



Created from unpublished data from the National 5% Sample Medicare Fee-for-Service Beneficiaries for 2014.[165]

The Lancet Neurology Commission

Defeating Alzheimer's disease and other dementias: a priority for European science and society

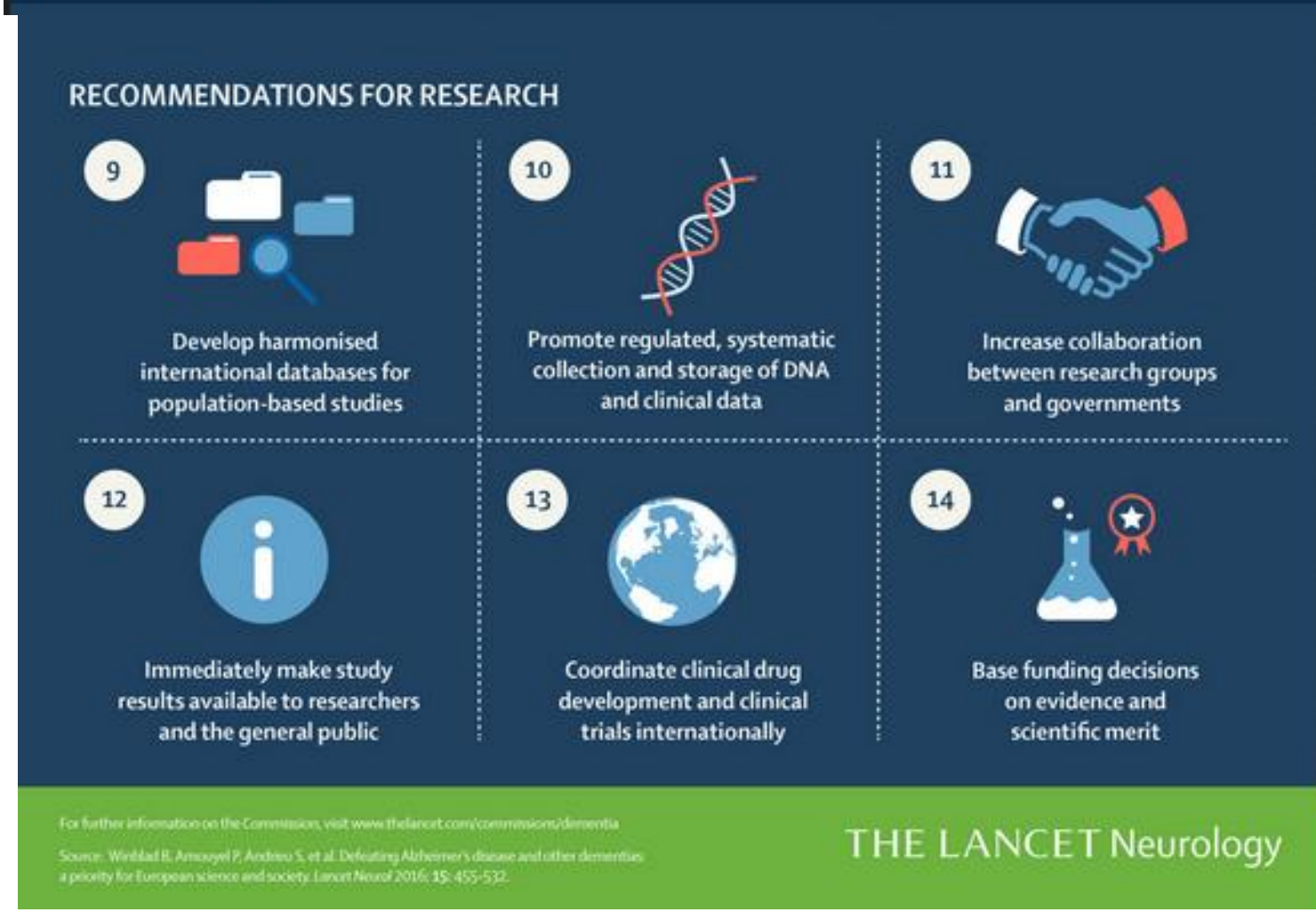
Bengt Winblad, Philippe Amouyel, Sandrine Andrieu, Clive Ballard, Carol Brayne, Henry Brodaty, Angel Cedazo-Minguez, Bruno Dubois, David Edvardsson, Howard Feldman, Laura Fratiglioni, Giovanni B Frisoni, Serge Gauthier, Jean Georges, Caroline Graff, Khalid Iqbal, Frank Jessen, Gunilla Johansson, Linus Jönsson, Miia Kivipelto, Martin Knapp, Francesca Mangialasche, René Melis, Agneta Nordberg, Marcel Olde Rikkert, Chengxuan Qiu, Thomas P Sakmar, Philip Scheltens, Lon S Schneider, Reisa Sperling, Lars O Tjernberg, Gunhild Waldemar, Anders Wimo, Henrik Zetterberg

The Lancet Neurology Commission:
Defeating Alzheimer's disease and other dementias

RECOMMENDATIONS FOR PREVENTION, TREATMENT, AND CARE

Lancet Neurol 2016; 15: 455–532

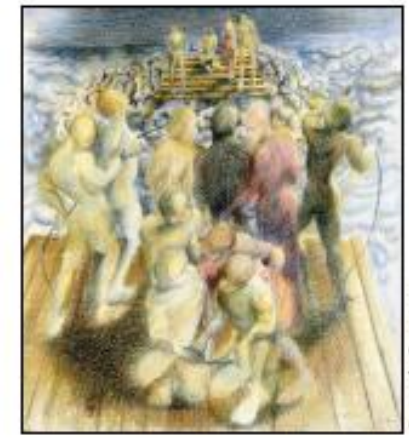
The Lancet Neurology Commission:
Defeating Alzheimer's disease and other dementias



Lancet Neurol 2016; 15: 455-532

Finding a cure for Alzheimer's disease starts with prevention

The most recent Alzheimer's Association report affirms that there are more than 5 million patients with dementia in the USA, and that the disease kills more people than do prostate and breast cancers combined. According to *The Lancet Neurology* Commission on Alzheimer's disease and other dementias, "an effective therapy is perhaps the greatest unmet need facing modern medicine". It is therefore imperative that research funders set the right priorities to find a cure, and thereby align the goals of the research community with those of society. Yet, the focus of much current research is on the preclinical states of neurodegeneration and on developing interventions to prevent clinical symptoms, rather than on addressing unmet clinical needs. This emphasis on prevention, which might seem paradoxical at best or unethical at worst, is however a judicious decision.



Carmelo Serrano

See Commission *Lancet Neurol* 2016; **15:** 455–532

For the **Alzheimer's Association report** see http://www.alz.org/facts/

Panel 4: Putative risk and protective factors for late-onset dementia and Alzheimer's disease

Risk factors

Older age

Genetic factors

- Familial aggregation (two or more family members with the disease)
- *APOE* ε4 allele
- Other susceptibility genes (eg, *CR1*, *PICALM*, *CLU*, *TREM2*, *TOMM40*)

Vascular risk and metabolic factors

- Atherosclerosis
- Cerebral macrovascular and microvascular lesions
- Cardiovascular diseases
- Diabetes mellitus and pre-diabetes
- Midlife hypertension
- Midlife overweight and obesity
- Midlife high serum cholesterol

Lifestyle factors

- Sedentary lifestyle
- Smoking
- Heavy alcohol consumption

Diet and nutritional factors

- Saturated fats
- Hyperhomocysteinaemia
- Deficiencies in vitamin B6, B12, and folate

Other factors

- Depression
- Traumatic brain injury
- Occupational exposure (eg, heavy metals, extremely-low-frequency electromagnetic fields)
- Infectious agents (eg, herpes simplex virus type I, *Chlamydophila pneumoniae*, spirochetes)

Protective factors

Genetic factors

- Some genes proposed (eg, *APP*, *APOE* ε2 allele)

Psychosocial factors

- High education and socioeconomic status
- High work complexity
- Rich social network and social engagement
- Mentally stimulating activity

Lifestyle factors

- Physical activity
- Light-to-moderate alcohol intake

Diet and nutritional factors

- Mediterranean diet
- Polyunsaturated fatty acid and fish-related fats
- Vitamin B6, vitamin B12, and folate
- Antioxidant vitamins (A, C, E)
- Vitamin D

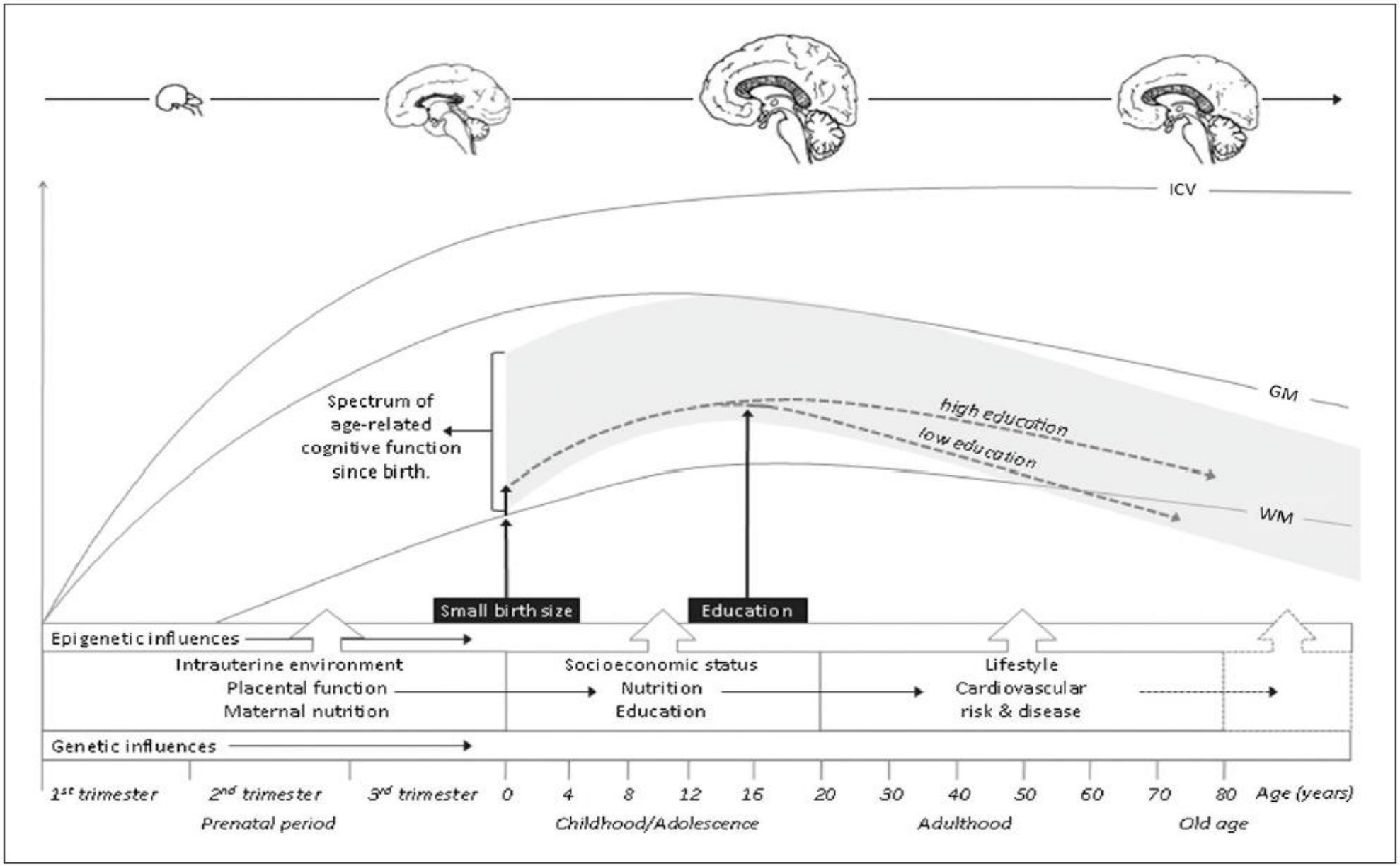
Drugs

- Antihypertensive drugs
- Statins
- Hormone replacement therapy
- Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer's disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two *APOE* ε4 alleles.

APOE=apolipoprotein E. *CR1*=complement component receptor 1. *PICALM*=phosphatidylinositol-binding clathrin assembly protein. *CLU*=clusterin. *TREM2*=triggering receptor expressed on myeloid cells 2. *TOMM40*=translocase of outer mitochondrial membrane 40 homologue. *APP*=amyloid precursor protein.

Hypothesized model of the origins and life course of brain aging – From Muller M et al. 2014



	Study design	Study population and period	Outcome (diagnostic criteria)	Findings
North America				
Langa et al, 2008 (USA)[77]	Repeated surveys in the Health and Retirement Study	Age ≥70 years for both waves: wave 1 (1993; n=7406), wave 2 (2002; n=7104)	Prevalence of cognitive impairment (≤10 on 35-point cognitive scale)	Prevalence decreased from 12·2% to 8·7%
Hall et al, 2009 (Indiana, USA)[78]	Repeated cross-sectional surveys	African Americans ≥70 years: wave 1 (1992; n=1500), wave 2 (2001; n=1892)	Prevalence of dementia and AD (ICD-10)	Prevalence stable for dementia (6·75% to 7·45%) and AD (5·47% to 6·77%)
Hebert et al, 2010 (Chicago, USA)[79]	Repeated cross-sectional surveys every 3 years	Age ≥65 years for all cycles (1997–2008; n>10 000): cycle 1 (n=6158)	Incidence of AD (NINCDS–ADRDA)	Risk of AD stable over time (OR for trend variable 0·97, 95% CI 0·90–1·04)
Rocca et al, 2011 (USA)[80]	Review	1993–2002	Prevalence or incidence of dementia and AD (DSM-III-R, DSM-IV, NINCDS–ADRDA, ICD-10, others)	Prevalence and incidence stable
Gao et al, 2015 (Indiana, USA)[81]	Repeated surveys in the Indianapolis-Ibadan Dementia Project	African Americans ≥70 years: 1992 cohort (n=1440), 2001 cohort (n=1835)	Incidence of dementia (DSM-III-R) and AD (NINCDS–ADRDA)	Age-standardised annual incidence rate declined from 1992 to 2001 for dementia (3·6% [95% CI 3·2–4·1%] *vs* 1·4% [1·2–1·7%]) and AD (2·5% [2·1–2·9%] *vs* 1·3% [1·0–1·5%])
Satizabal et al, 2016 (Boston, USA)[82]	Repeated surveys in the Framingham Heart Study	Age ≥60 years: epoch 1 (1977–83; n=2457), epoch 2 (1986–91; n=2135), epoch 3 (1992–98; n=2333), epoch 4 (2004–08; n=2090)	Incidence of dementia (DSM-IV), AD (NINCDS–ADRDA), and vascular dementia (NINDS–AIREN)	Decline in incidence rate per decade of 20% (95% CI 10–28%) for dementia, 12% (0–23%; p=0·052) for AD, and 29% (10–44%) for vascular dementia
Europe				
Lobo et al, 2007 (Spain)[83]	Repeated cross-sectional surveys	Age ≥65 years for both waves: wave 1 (1988–89; n=1080), wave 2 (1994–96; n=3715)	Prevalence of dementia (DSM-IV)	Prevalence stable overall (5·2% to 3·9%) and decreased in men (5·8% to 2·3%)
Schrijvers et al, 2012 (Rotterdam, Netherlands)[84]	Repeated cross-sectional surveys	Age ≥60 years for both waves: wave 1 (1990; n=5727), wave 2 (2000; n=8384)	Incidence of dementia (DSM-III-R)	Incidence decreased, but not significantly (age-adjusted IRR 0·75, 95% CI 0·56–1·02; p=0·06)
Qiu et al, 2013 (Stockholm, Sweden)[68]	Repeated cross-sectional surveys	Age ≥75 years for both waves: wave 1 (1987–89; n=1700), wave 2 (2001–04; n=1575)	Prevalence and survival of dementia (DSM-III-R)	Prevalence stable (17·5% to 17·9%); evidence suggests decline in incidence
Wiberg et al, 2013 (Gothenburg, Sweden)[85]	Repeated cross-sectional surveys	Wave 1 (1976–77; age=70 years, n=404; age=75 years, n=303), wave 2 (2000–01; age=70 years, n=579; age=75 years, n=753)	Prevalence of dementia (historical criteria in wave 1; DSM-III-R in wave 2)	Prevalence stable (70 years, 2·0% to 2·4%; 75 years, 5·0% to 6·0%)
Matthews et al, 2013 (England)[86]	Repeated cross-sectional surveys	Age ≥65 years for both waves: wave 1 (1989–94; n=7635), wave 2 (2008–11; n=7796)	Prevalence of dementia (Geriatric Mental State scale)	Prevalence decreased (8·3% to 6·5%)
Asia				
Li et al, 2007 (Beijing, China)[87]	Repeated cross-sectional surveys	Age ≥60 years for both waves: wave 1 (1986–89; n=1090), wave 2 (1997–99; n=1593)	Prevalence and incidence of dementia (ICD-10, DSM-IV)	Prevalence increased (1·7% to 2·5%); incidence increased (0·6% to 0·9%)
Yu et al, 2012 (Hong Kong, China)[88]	Review	Age ≥70 years (1995–2006)	Prevalence of dementia (ICD-9, ICD-10)	Prevalence increased from 4·5% to 9·3%
Chan et al, 2013 (China)[89]	Systematic review of 75 cross-sectional surveys	Age ≥55 years (1990–2010; n=340 247)	Prevalence of dementia and AD (DSM-III, DSM-III-R, DSM-IV, NINCDS–ADRDA, ICD-9, ICD-10)	Prevalence increased in all age groups
Wu et al, 2014 (China, including Hong Kong and Taiwan)[90]	Systematic review of 70 prevalence studies	Age ≥60 years (1990–2012)	Prevalence of dementia by survey years, age groups, and birth cohorts (DSM-III, DSM-III-R, DSM-IV, ICD-10, others)	Controlling for methodological factors, prevalence increased slightly from 1995 to 2012; a birth cohort effect was reported (ie, a more recent cohort of the same age had higher dementia prevalence)
Sekita et al, 2010 (Hisayama, Japan)[91]	Repeated cross-sectional surveys	Age ≥65 years for all waves: wave 1 (1985; n=887), wave 2 (1992; n=1189), wave 3 (1998; n=1437), wave 4 (2005; n=1566)	Prevalence of all-cause dementia and AD (DSM-III, DSM-III-R)	Prevalence increased from 1985 to 2005 for all-cause dementia (6·0% to 8·3%) and for AD (1·1% to 3·8%)
Dodge et al, 2012 (Japan)[92]	Systematic review of eight cross-sectional surveys	Age ≥65 years (1985–2008; n=13 396)	Prevalence of dementia (DSM-III, DSM-III-R, DSM-IV)	Prevalence increased (6·7% to 11·3%)

Population-based surveys and systematic reviews of population surveys about the temporal trends of dementia occurrence. AD=Alzheimer's disease. ICD=*International Classification of Diseases* criteria. NINCDS–ADRDA=National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. OR=odds ratio. DSM=*Diagnostic and Statistical Manual of Mental Disorders* criteria. NINDS–AIREN=National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria. IRR=incidence rate ratio.

Table 3: **Temporal trends of dementia occurrence according to continent**

N ENGL J MED 374;6 NEJM.ORG FEBRUARY 11, 2016

HISTORY OF MEDICINE

Is Dementia in Decline? Historical Trends and Future Trajectories

David S. Jones, M.D., Ph.D., and Jeremy A. Greene, M.D., Ph.D.

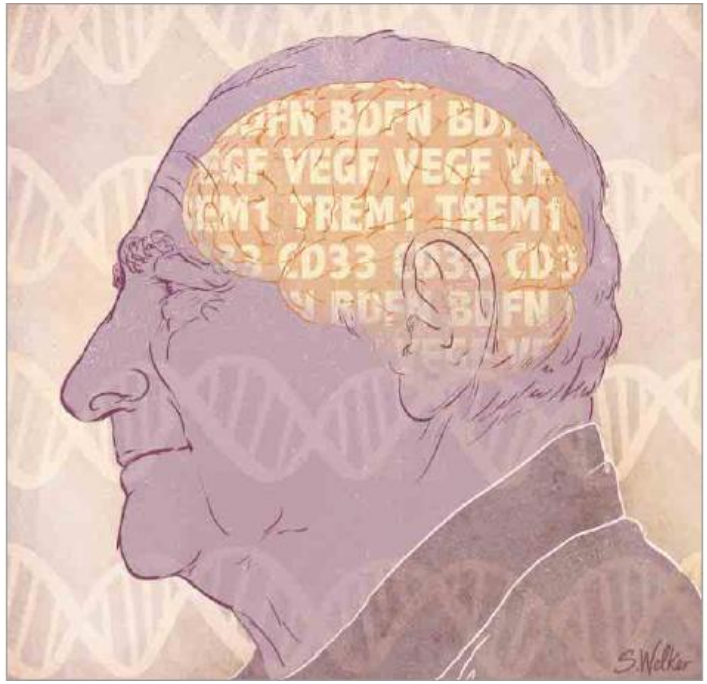
History offers reasons for hope. Evidence of dementia's decline shows once again that our burden of disease is malleable.

News & Analysis

Medical News & Perspectives

The Brain Fights Back: New Approaches to Mitigating Cognitive Decline

Bridget M. Kuehn, MSJ



- pathology is not destiny
- certain behavioral factors appeared to modify the association between cellular pathologies and cognitive declines
- we need to better understand factors involved in cognition resilience

JAMA Published online November 25, 2015

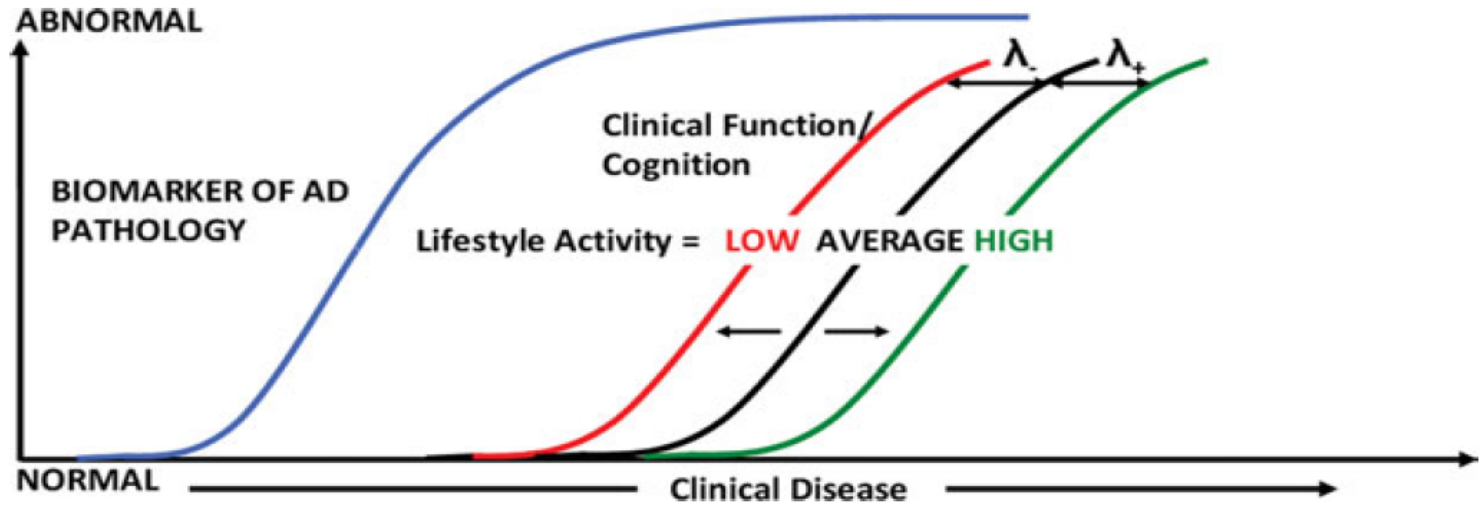


FIGURE 2: Model illustrating the effect of lifestyle activities on Alzheimer disease (AD) biomarkers and cognition or clinical function in subjects. Clinical disease stage is indicated on the horizontal axis and the magnitude of biomarker abnormalities and cognition (from normal to maximally abnormal) on the vertical axis. The cognition or clinical function curve is moved left or right based on the individual's lifestyle activity. The variable λ for lifetime intellectual activity is greater than that for current intellectual activity, and the variable λ for physical activity is close to zero.

ANN NEUROL 2012;72:730–738

THE LANCET Neurology

Panel 2: Interventions tested in completed Alzheimer's disease prevention trials

Lancet Neurol 2015; 14: 926–44

Alzheimer's disease-specific pharmacological interventions

- Donepezil (5 mg/day, 10 mg/day, or 5 mg/day for 42 days followed by forced dose escalation to 10 mg/day)[28,31,40]
- Rivastigmine (3–12 mg/day)[29]
- Galantamine (16 mg/day or 16–24 mg/day)[33,67]
- Galantamine (16 mg/day) + memantine (20 mg/day)[67]

Non-specific pharmacological interventions

Non-steroidal anti-inflammatory drugs

- Naproxen (400 mg/day)[35]
- Celecoxib (440 mg/day)[35]
- Rofecoxib (25 mg/day)[37]
- Triflusal (900 mg/day)[66]

Antihypertensive treatment

- Lisinopril (10–40 mg/day)[58]
- Candesartan (8–32 mg/day)[58]
- Slow-release indapamide (1·5 mg/day) with optional perindopril (2–4 mg/day)[36]
- Nitrendipine (10–40 mg/day) with optional enalapril (5–20 mg/day), hydrochlorothiazide (12·5–25 mg/day), or both[21]
- Perinopril (4 mg/day) with optional indapamide (2·5 mg/day [or 2 mg/day in Japan])[22]

Hormone replacement therapy

- 17β-oestradiol (1 mg/day) and norethindrone (0·35 mg on 3 days per week)[34]
- Conjugated equine oestrogen (0·625 mg/day)[23]
- Conjugated equine oestrogen (0·625 mg/day) + medroxyprogesterone acetate (2·5 mg/day)[24]

Other

- Intensive glycaemic control targeting HbA_{1c} to less than 6·0% (42 mmol/mol) using various antidiabetic treatments[41]
- Ginkgo biloba (240 mg/day)[33,38]

Nutritional interventions

Nutritional supplements

Homocysteine-lowering vitamins:

- Vitamin B12 (1000 µg/day)[42]
- Vitamin B12 (1000 µg/day) + folic acid (400 µg/day)[42]
- Vitamin B12 (400–500 µg/day) + folic acid (2–2·5 mg/day) or folate (800–1000 µg/day) + vitamin B6 (10–25 mg/day)[25,32,39,45]

Fish oil or omega-3 fatty acids:

- Docosahexaenoic acid (DHA; 900 mg/day)[47]
- DHA (500 mg) + eicosapentaenoic acid (EPA; 200 mg/day)[48]
- Fish oil (1800 or 400 mg/day EPA–DHA)[46]

Other:

- High-dose (990 mg/day), medium-dose (520 mg/day), or low-dose (45 mg/day) flavanol supplement[52,53]
- Vitamin E (2000 IU/day)[28]

Advice or counselling

- Regular group dietary counselling and menu changes[51]

Multidomain interventions

- Intensive computer intervention and aerobic intervention[59]
- Multidomain lifestyle counselling (nutritional guidance, physical activity, cognitive training, increased social activity, and intensive monitoring of vascular and metabolic risk factors)[62]
- Bimonthly or monthly telephonic care management (targeting physical activity, smoking cessation, social activity, cognitive activity, moderate alcohol consumption, lean body mass, and healthy diet) alone or with educational materials, health-worker-initiated visits and counselling, or rewards for adherence to the programme[60]
- Intensive multifactorial vascular risk factor management (targeting blood pressure, cholesterol, homocysteine, and body-mass index via diet, medication, smoking cessation, and physical activity)[55]

Cognitive activity or training

Global (or unspecified) cognitive training

- Active Mind cognitive training program (including attention, verbal fluency, and memory training)[64]
- Healthy Brain Ageing Cognitive Training Program (involving psychoeducation and computer-based cognitive training)[61]
- Discussion of age-associated changes in cognition and activities employing strategies to enhance attention capacity, memory functions, and executive processes[56]
- General or unspecified cognitive activity or training programme[50]

Specific cognitive training

- Memory training[26]
- Reasoning training[26]
- Speed of processing training[26,63]
- Auditory information processing-targeted brain plasticity-based training[49]
- Intensive computer visual and auditory processing training[59]

Physical exercise

Non-specific physical intervention

- Physical activity intervention (weekly goal: 150 min exercise)[44]

Specific exercise

- Aerobic exercise or endurance training[43,59]
- Resistance training[54]
- Cybercycling[57]
- Yoga[30]
- Walking[30]

Multicomponent exercise programme

- Aerobic exercise, muscle strength training, postural balance retraining and dual-task training, and focus on promoting exercise and behaviour change[65]
- Aerobic endurance, strength, flexibility, balance, and coordination[50]
- Aerobic exercise, muscle strength training, and postural balance training[68]

	FINGER[185]	MAPT[186]	PreDIVA[187]	HATICE[188]
Sample size	1260 community dwellers from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia CAIDE risk score >6 and cognitive performance at the mean level or slightly lower than expected for age	Frail elderly individuals (subjective memory complaint, slow walking speed, IADL limitations)	All elderly patients without dementia in general practices	Older adults without dementia with increased risk of cardiovascular disorders and dementia
Age at enrolment	60–77 years	≥70 years	70–78 years	≥65 years
Study design	Multicentre, randomised parallel-group controlled trial	Multicentre, randomised controlled trial	Multisite, cluster-randomised parallel-group controlled trial	Multinational, multicentre, randomised parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity, management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training with or without 800 mg docosahexaenoic acid per day	Multidomain: nurse-led vascular care, including medical treatment of risk factors, nutritional advice, exercise advice	Multidomain e-health: interactive internet platform with nurse-led support to optimise management of vascular and lifestyle-related risk factors
Duration	2 years plus 5 years' follow-up	3 years plus 2 years' follow-up	6 years	1·5 years
Outcomes	Primary: change in cognitive function Secondary: dementia, depression, disability, cardiovascular events, quality of life, health-resource use, change in AD biomarkers	Primary: change in cognitive function Secondary: cognition, functional status, depression, health-resource use, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimisation of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospital admission, depression, disability, cost-effectiveness
Status	Completed in 2014	Completed in 2014	Completed in 2015	Due to finish in 2017

FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. MAPT=Multidomain Alzheimer Prevention Study. PreDIVA=Prevention of Dementia by Intensive Vascular Care. HATICE=Healthy Ageing Through Internet Counselling in the Elderly. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. IADL=instrumental activities of daily living. AD=Alzheimer's disease.

Table 4: **Randomised controlled trials of multidomain interventions for prevention of cognitive impairment, dementia, or Alzheimer's disease**

ELSEVIER

CrossMark

Alzheimer's & Dementia 12 (2016) 292-323

Alzheimer's & Dementia

Perspective

Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria

Abstract

During the past decade, a conceptual shift occurred in the field of Alzheimer's disease (AD) considering the disease as a continuum. Thanks to evolving biomarker research and substantial discoveries, it is now possible to identify the disease even at the preclinical stage before the occurrence of the first clinical symptoms. This preclinical stage of AD has become a major research focus as the field postulates that early intervention may offer the best chance of therapeutic success. To date, very little evidence is established on this "silent" stage of the disease. A clarification is needed about the definitions and lexicon, the limits, the natural history, the markers of progression, and the ethical consequence of detecting the disease at this asymptomatic stage. This article is aimed at addressing all the different issues by providing for each of them an updated review of the literature and evidence, with practical recommendations.

GLOSSARY

Lexicon used in the article.

State versus stage

"State" refers to a given pathophysiological framework (state of asymptomatic at-risk versus state of Alzheimer's disease), whereas "stage" refers to a degree of disease progression within a given state (preclinical, prodromal, and dementia for AD).

Alzheimer's disease

AD is defined by the positivity of biomarkers of both amyloidopathy (A+) and tauopathy (T+) in line with the pathologic definition of the disease. Therefore, two phases of the disease can be distinguished in the continuum:

- A clinical stage ("clinical AD") defined by the occurrence of the clinical phenotype of AD (either typical or atypical) and which encompasses both the prodromal and the dementia stages;
- A preclinical stage ("preclinical AD") before the onset of the clinical phenotype. The development of biomarkers of Alzheimer pathology makes possible to recognize AD before the onset of the specific clinical phenotype.

Asymptomatic at risk for AD

This state consists of cognitively normal individuals for whom the biomarker pattern is insufficient to reach the above definition of AD. They can be characterized by the positivity of the pathophysiological biomarker (i.e. either "Asymptomatic A+" or "Asymptomatic T+").

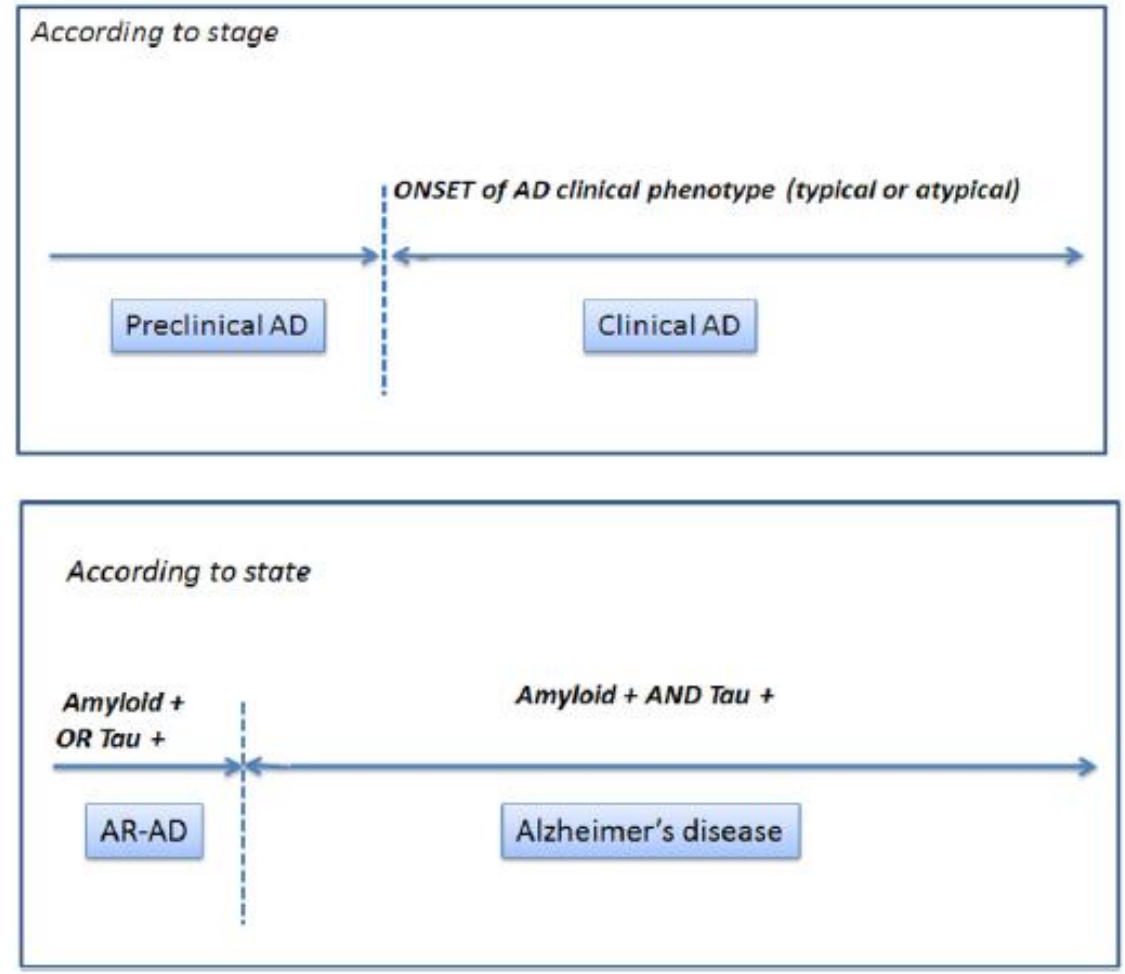


Fig. 1. Proposal for a unified lexicon for preclinical AD. Abbreviation: AD, Alzheimer's disease.

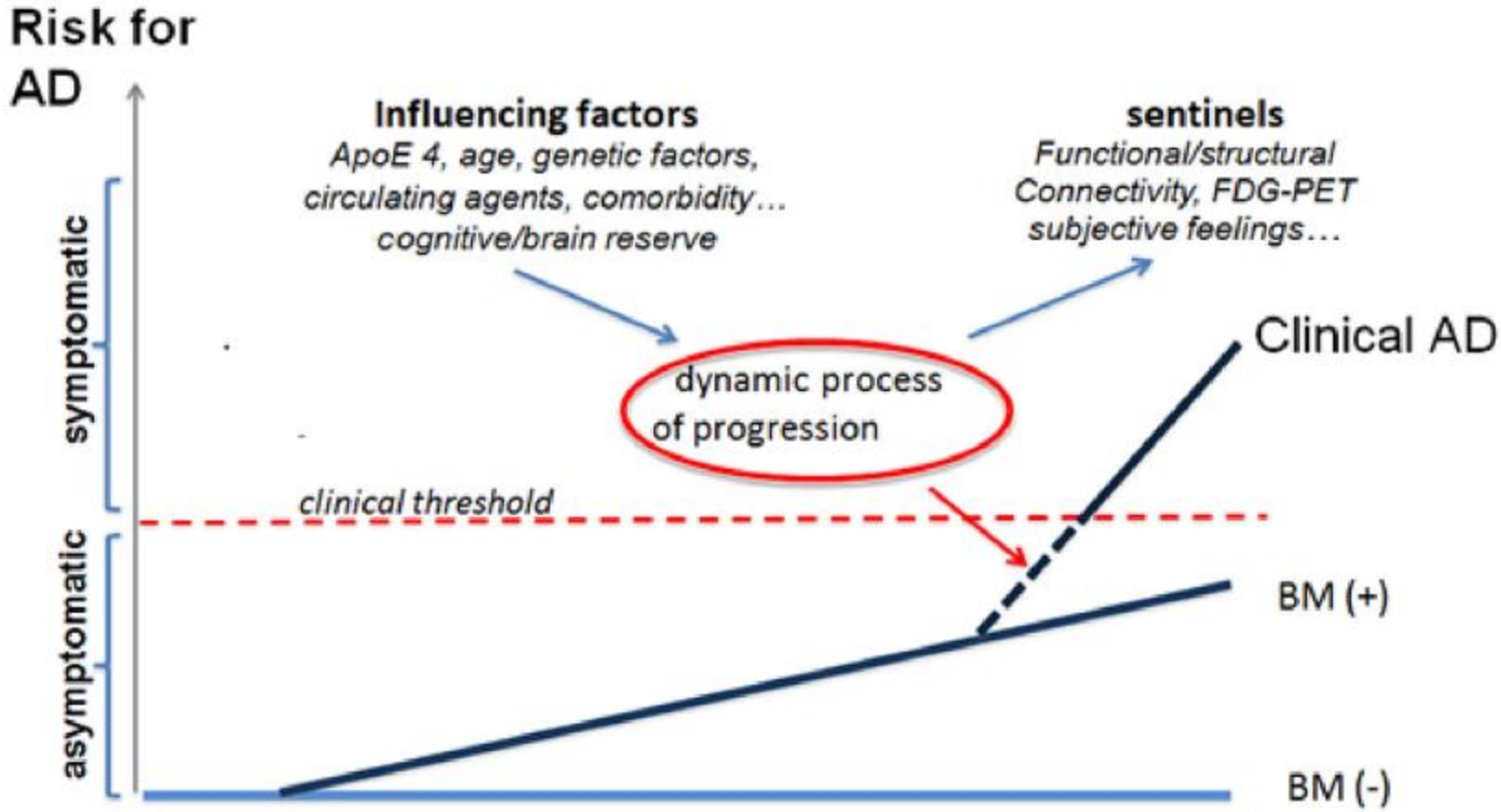


Fig. 2. The risk of clinical AD–hypothetical model. Abbreviation: AD, Alzheimer's disease; BM, pathophysiological biomarkers.

Table 1
Toward a unified conception of preclinical AD

Proposed definition	NIA-AA, 2011	IWG-2, 2014	Proposed criteria, 2016
AD starts			
With the first brain lesion	+		
With the first symptom of AD		+	
When there is evidence of Aß and Tau pathology			+
Preclinical AD can be detected in asymptomatic individuals			
When there is evidence of Aß pathology	+ (stage 1)	+ (PET)	
When there is evidence of Aß and Tau pathology	+ (stage 2)*	+ (CSF)	+
Asymptomatic at risk for AD can be detected in cognitively normal individuals			
When there is evidence of Aß pathology ("Asymptomatic A+") OR evidence of Tau pathology ("Asymptomatic T+")			+

Abbreviations: AD, Alzheimer's disease; NIA-AA, National Institute on Aging/Alzheimer Association; IWG, international working group.

NOTE. The criteria now stipulate that the Aß+ group (A+) is asymptomatic at risk for AD, whereas the Aß+/Tau+ group (A+, T+) is considered as having preclinical AD.

*In the NIA-AA criteria, markers on neurodegeneration (i.e., brain atrophy on MRI or hypo-metabolism on FDG PET) were also considered instead of tau markers to diagnose preclinical AD.

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

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Summary

Background Alzheimer's disease biomarkers are important for early diagnosis in routine clinical practice and research. Three core CSF biomarkers for the diagnosis of Alzheimer's disease (Aβ42, T-tau, and P-tau) have been assessed in numerous studies, and several other Alzheimer's disease markers are emerging in the literature. However, there have been no comprehensive meta-analyses of their diagnostic performance. We systematically reviewed the literature for 15 biomarkers in both CSF and blood to assess which of these were most altered in Alzheimer's disease.

Methods In this systematic review and meta-analysis, we screened PubMed and Web of Science for articles published between July 1, 1984, and June 30, 2014, about CSF and blood biomarkers reflecting neurodegeneration (T-tau, NFL, NSE, VLP-1, and HFABP), APP metabolism (Aβ42, Aβ40, Aβ38, sAPPα, and sAPPβ), tangle pathology (P-tau), blood–brain-barrier function (albumin ratio), and glial activation (YKL-40, MCP-1, and GFAP). Data were taken from cross-sectional cohort studies as well as from baseline measurements in longitudinal studies with clinical follow-up. Articles were excluded if they did not contain a cohort with Alzheimer's disease and a control cohort, or a cohort with mild cognitive impairment due to Alzheimer's disease and a stable mild cognitive impairment cohort. Data were extracted by ten authors and checked by two for accuracy. For quality assessment, modified QUADAS criteria were used. Biomarker performance was rated by random-effects meta-analysis based on the ratio between biomarker concentration in patients with Alzheimer's disease and controls (fold change) or the ratio between biomarker concentration in those with mild cognitive impariment due to Alzheimer's disease and those with stable mild cognitive impairment who had a follow-up time of at least 2 years and no further cognitive decline.

Findings Of 4521 records identified from PubMed and 624 from Web of Science, 231 articles comprising 15 699 patients with Alzheimer's disease and 13 018 controls were included in this analysis. The core biomarkers differentiated Alzheimer's disease from controls with good performance: CSF T-tau (average ratio 2·54, 95% CI 2·44–2·64, p<0·0001), P-tau (1·88, 1·79–1·97, p<0·0001), and Aβ42 (0·56, 0·55–0·58, p<0·0001). Differentiation between cohorts with mild cognitive impairment due to Alzheimer's disease and those with stable mild cognitive impairment was also strong (average ratio 0·67 for CSF Aβ42, 1·72 for P-tau, and 1·76 for T-tau). Furthermore, CSF NFL (2·35, 1·90–2·91, p<0·0001) and plasma T-tau (1·95, 1·12–3·38, p=0·02) had large effect sizes when differentiating between controls and patients with Alzheimer's disease, whereas those of CSF NSE, VLP-1, HFABP, and YKL-40 were moderate (average ratios 1·28–1·47). Other assessed biomarkers had only marginal effect sizes or did not differentiate between control and patient samples.

Interpretation The core CSF biomarkers of neurodegeneration (T-tau, P-tau, and Aβ42), CSF NFL, and plasma T-tau were strongly associated with Alzheimer's disease and the core biomarkers were strongly associated with mild cognitive impairment due to Alzheimer's disease. Emerging CSF biomarkers NSE, VLP-1, HFABP, and YKL-40 were moderately associated with Alzheimer's disease, whereas plasma Aβ42 and Aβ40 were not. Due to their consistency, T-tau, P-tau, Aβ42, and NFL in CSF should be used in clinical practice and clinical research.

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A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

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ABSTRACT

Biomarkers have become an essential component of Alzheimer disease (AD) research and because of the pervasiveness of AD pathology in the elderly, the same biomarkers are used in cognitive aging research. A number of current issues suggest that an unbiased descriptive classification scheme for these biomarkers would be useful. We propose the "A/T/N" system in which 7 major AD biomarkers are divided into 3 binary categories based on the nature of the pathophysiology that each measures. "A" refers to the value of a β-amyloid biomarker (amyloid PET or CSF $A\beta_{42}$); "T," the value of a tau biomarker (CSF phospho tau, or tau PET); and "N," biomarkers of neurodegeneration or neuronal injury ([^{18}F]-fluorodeoxyglucose–PET, structural MRI, or CSF total tau). Each biomarker category is rated as positive or negative. An individual score might appear as A+/T+/N−, or A+/T−/N−, etc. The A/T/N system includes the new modality tau PET. It is agnostic to the temporal ordering of mechanisms underlying AD pathogenesis. It includes all individuals in any population regardless of the mix of biomarker findings and therefore is suited to population studies of cognitive aging. It does not specify disease labels and thus is not a diagnostic classification system. It is a descriptive system for categorizing multidomain biomarker findings at the individual person level in a format that is easy to understand and use. Given the present lack of consensus among AD specialists on terminology across the clinically normal to dementia spectrum, a biomarker classification scheme will have broadest acceptance if it is independent from any one clinically defined diagnostic scheme. *Neurology*® 2016;87:539–547

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Table 1 Clinically normal individuals

A/T/N classification	NIA-AA classification preclinical AD	2014 IWG classification
A−/T−/N−	Not defined	Not defined
A+/T−/N−	Stage 1	Asymptomatic at risk of AD (if A+ established by amyloid PET)
A+/T+/N−	Stage 2/3	Asymptomatic at risk of AD
A+/T−/N+	—[a]	Asymptomatic at risk of AD (if A+ established by amyloid PET)
A+/T+/N+	Stage 2/3	Asymptomatic at risk of AD
A−/T+/N−[b]	Not defined	Not defined
A−/T−/N+[b]	Not defined	Not defined
A−/T+/N+[b]	Not defined	Not defined

Abbreviations: AD = Alzheimer disease; FDG = [^{18}F]-fluorodeoxyglucose; IWG = International Working Group; NIA-AA = National Institute on Aging-Alzheimer's Association.

[a] This combination was not addressed in NIA-AA preclinical AD criteria on the assumption that neurodegeneration on MRI and FDG-PET that is specifically attributable to AD was tau-related.

[b] Described as SNAP (suspected non-Alzheimer pathophysiology) in several publications.

Table 2 Individuals who meet clinical criteria for MCI

A/T/N score	NIA-AA classification	2014 IWG classification
A−/T−/N−	MCI, unlikely due to AD	Not defined
A+/T−/N−	MCI, core clinical criteria[a]	Typical AD (if A+ established by amyloid PET)
A+/T+/N−	MCI, core clinical criteria[a]	Typical AD
A+/T−/N+	MCI, core clinical criteria[a]	Typical AD (if A+ established by amyloid PET)
A+/T+/N+	MCI due to AD, high likelihood	Typical AD
A−/T+/N−[b]	Not defined	Not defined
A−/T−/N+[b]	Not defined	Not defined
A−/T+/N+[b]	Not defined	Not defined

Abbreviations: AD = Alzheimer disease; IWG = International Working Group; MCI = mild cognitive impairment; NIA-AA = National Institute on Aging–Alzheimer's Association.
[a] In the event of conflicting results, biomarkers are regarded as "uninformative" and therefore do not alter the individual's diagnostic classification based on clinical assessment alone.
[b] Described as MCI-SNAP (suspected non-Alzheimer pathophysiology) in several publications.

Table 3 Individuals who meet clinical criteria for probable AD dementia

A/T/N score	NIA-AA classification	2014 IWG classification
A−/T−/N−	Dementia, unlikely due to AD	Not defined
A+/T−/N−	Intermediate likelihood; probable AD dementia; based on clinical criteria[a]	Typical AD (if A+ established by amyloid PET)
A+/T+/N−	High likelihood probable AD dementia; based on clinical criteria[a]	Typical AD
A+/T−/N+	High likelihood; probable AD dementia; based on clinical criteria[a]	Typical AD (if A+ established by amyloid PET)
A+/T+/N+	High likelihood AD pathophysiology	Typical AD
A−/T+/N−	Probable AD dementia; based on clinical criteria[a]	Not defined
A−/T−/N+	Intermediate likelihood; probable AD dementia; based on clinical criteria[a]	Not defined
A−/T+/N+	Intermediate likelihood; probable AD dementia; based on clinical criteria[a]	Not defined

Abbreviations: AD = Alzheimer disease; IWG = International Working Group; NIA-AA = National Institute on Aging–Alzheimer's Association.

[a] In the event of conflicting results, biomarkers are regarded as "uninformative" and therefore do not alter the individual's diagnostic classification based on clinical assessment alone.

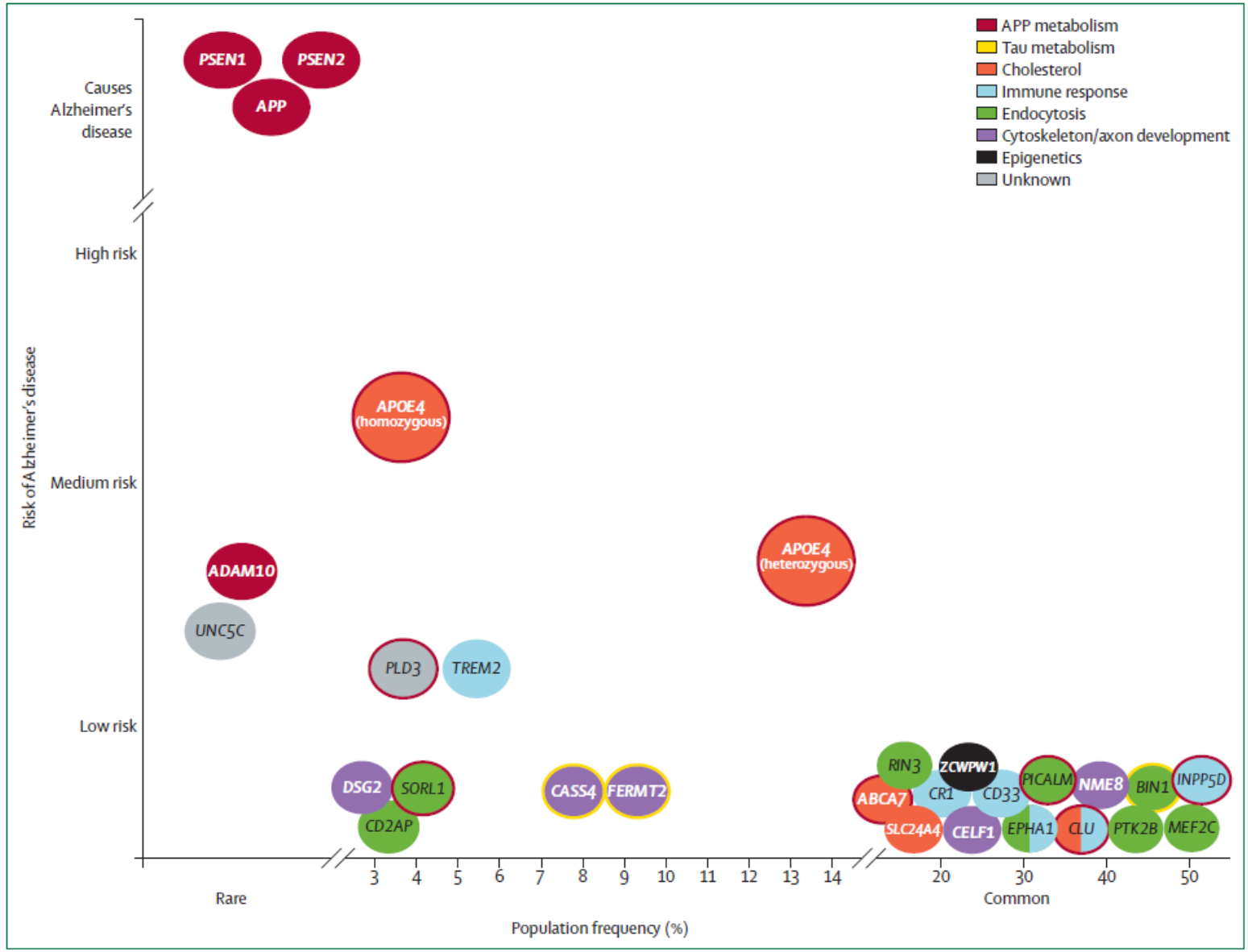

Figure: **Schematic overview of genes linked to Alzheimer's disease**

The colours in the key show the pathways in which these genes are implicated. Genes that are known to affect APP metabolism are circled in red, whereas those that affect the tau pathway are circled in yellow. The interior colours provide further information on what functions the genes have. When there are two colours, the gene might have functional roles in two different biological pathways. Many of the genes have been related to APP processing or trafficking (red or red border), suggesting the central importance of APP metabolism in Alzheimer's disease. The figure was adapted with permission from Karch et al, 2015.[39]

Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study

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Summary

Background Few data on the pathology of cerebral vessel disease, dementia, and cognition are available. We examined the association of cerebral atherosclerosis and arteriolosclerosis neuropathology with probable and possible Alzheimer's disease dementia and cognitive function.

Methods This cross-sectional study included men and women aged 65 years or older who had yearly clinical assessments and had agreed to brain autopsy at the time of death, as part of one of two cohort studies of ageing (The Religious Orders Study and the Rush Memory and Aging Project). Individuals without dementia or with Alzheimer's disease dementia, and with complete neuropathological data, are included in our analyses. We used neuropsychological data proximate to death to create summary measures of global cognition and cognitive domains. Clinical data recorded between 1994 and 2015 were used to determine presence of Alzheimer's disease dementia. Systematic neuropathological assessments documented the severity of cerebral large vessel (atherosclerosis) and small vessel (arteriolosclerosis) disease. By use of regression analyses adjusted for demographics, gross and microscopic infarcts, and Alzheimer's disease pathology, we examined associations of vessel disease severity (mild, moderate, and severe) with odds of probable and possible Alzheimer's disease dementia and cognitive function.

Findings Study enrolment began in January, 1994, and two cohort studies are ongoing. 1143 individuals were included in our analyses (median age at death 88·8 years; 478 [42%] with Alzheimer's disease dementia). Moderate-to-severe atherosclerosis was present in 445 (39%) individuals, and arteriolosclerosis in 401 (35%) individuals. Each level increase in the severity of atherosclerosis or arteriolosclerosis was associated with significantly higher odds of Alzheimer's disease dementia (odds ratio [OR] for atherosclerosis 1·33, 95% CI 1·11–1·58; OR for arteriolosclerosis 1·20, 1·04–1·40). Atherosclerosis was associated with lower scores for global cognition (estimate –0·10 [SE 0·04], p=0·0096) and four cognitive domains (episodic memory –0·10 [0·04], p=0·017; semantic memory –0·11 [0·05], p=0·018; perceptual speed –0·14 [0·04], p=0·00080; and visuospatial abilities –0·13 [0·04], p=0·0080), but not working memory (–0·05 [0·04], p=0·21). Arteriolosclerosis was associated with lower scores for global cognition (estimate –0·10 [0·03], p=0·0015) and four domains (episodic memory –0·12 [0·04], p=0·00090; semantic memory –0·10 [0·04], p=0·013; working memory –0·07 [0·03], p=0·045; perceptual speed –0·12 [0·04], p=0·0012), and a non-significant association was noted for visuospatial abilities (–0·07 [0·03], p=0·052). Findings were unchanged in analyses controlling for the presence of *APOE* ε4 allele or vascular risk factors.

Interpretation Cerebral atherosclerosis and arteriolosclerosis are associated with Alzheimer's disease dementia, and are also associated with low scores in most cognitive domains. Cerebral vessel pathology might be an under-recognised risk factor for Alzheimer's disease dementia.

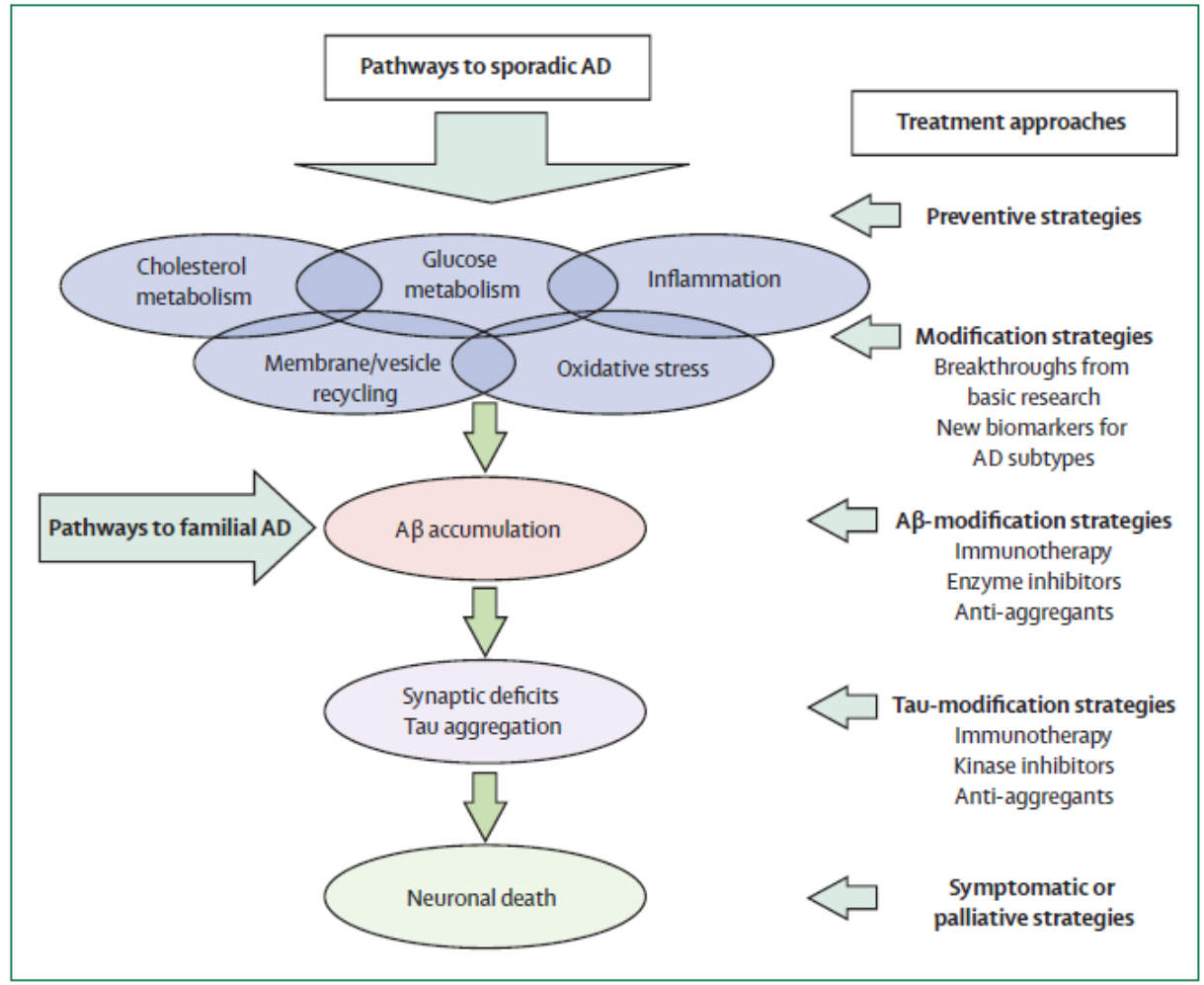

Figure 5: **Pathways to Alzheimer's disease**
Epidemiological and genetic studies of people with non-genetically determined (ie, sporadic) AD have identified mechanisms that might underlie brain Aβ accumulation, neuronal tau hyperphosphorylation, and synaptic deficits, ultimately leading to cognitive impairment and dementia. In familial AD, the disease begins with Aβ pathology. It seems likely that different causative pathways result in distinct disease subtypes, which should be treated differently. The identification of subtypes of patients, with homogeneous pathogenesis and prognosis, will facilitate research and result in more accurate and personalised treatments for sporadic and familial AD. AD=Alzheimer's disease. Aβ=amyloid β.

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for Aβ production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for Aβ production	APECS (NCT01953601; phase 3)	1500 people aged 50–85 years with prodromal AD	2 years (completion in 2018)
JNJ-54861911	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02260674 (phase 2)	100 people aged 50–85 years with early (pre-dementia) AD; an extension study of 100 people with early AD (50–85 years) who participated in previous phase 1 and phase 2 RCTs with the drug is ongoing (NCT02406027; phase 2)	10 months (completion in 2016); extension study 2 years (completion in 2024)
Reduced aggregation or oligomerisation of amyloid				
PQ912	Glutaminyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified Aβ peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)
Increased clearance of amyloid				
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01224106 (phase 3)	799 people aged 50–85 years with prodromal AD	2 years (completion in 2015)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIIB037)	Anti-amyloid monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	2700 people (1350 per trial) aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Intravenous immunoglobulin derived from healthy donors	Passive immunotherapy (contains naturally occurring polyclonal anti-Aβ antibodies)	NCT01300728 (phase 2)	50 people aged 50–84 years with MCI	2 years (completion in 2017)
Reduced production of P-tau or reduced fibrillation or deposition of tau				
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged ≥60 years with MCI or mild AD dementia	About 18 months (completion in 2016)

(Table 12 continues on next page)

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Modulation of neurotransmission				
Atomoxetine	Noradrenaline reuptake inhibitor (licensed): increases brain concentrations of noradrenaline	ATX-001 (NCT01522404; phase 2)	40 people aged 50–90 years with MCI	6 months (completion in 2017)
Ladostigil (TV-3326)	Acetylcholinesterase inhibitor and MAO inhibitor: increases cholinergic neurotransmission and transmission mediated by monoamines; a derivative of rasagiline and rivastigmine, it also has antioxidant properties and can modulate APP processing and cellular signalling pathways	NCT01429623 (phase 2)	200 people aged 55–85 years with MCI	3 years (completion in 2015/2016)
DAOIB	NMDA receptor regulator: enhances NMDA-receptor-mediated glutamatergic neurotransmission	NCT02239003 (phase 2)	50 people aged 50–90 years with MCI	6 months (completion in 2016)
PXT00864*	Regulates GABAergic neurotransmission (depending on the receptor, it can have antagonistic or agonistic effects)	PLEODIAL-I (NCT02361424; phase 2)	45 people aged ≥60 years with mild AD dementia; an open-label extension study, PLEODIAL-II, is ongoing (NCT02361242; phase 2)	12 weeks (completion in 2015); extension study 24 weeks
Other mechanisms of action				
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥65 years with MCI or mild AD dementia	1 year (completion in 2018)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can reduce amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
Cilostazol	PDE3 inhibitor (licensed antiplatelet drug): can reduce amyloid toxicity	COMCID (NCT02491268; phase 2)	200 people aged 55–84 years with MCI	About 2 years (completion in 2018)
BI 409306 (SUB 166499)	PDE9 inhibitor: enhances synaptic plasticity and reduces amyloid toxicity	NCT02240693 (phase 2) and NCT02337907 (phase 2)	624 people aged ≥55 years with MCI due to AD	12 weeks (completion in 2016)
Simvastatin	Cholesterol-lowering drug (licensed) with antioxidant and anti-inflammatory properties: can lower brain Aβ production and reduce Aβ-mediated neurotoxicity	SIMaMCI (NCT00842920; phase 4)	520 people aged 55–90 years with amnestic MCI	2 years (completion in 2018)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)

Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. APECS=β Amyloid Production and Effects on Cognition Study. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. MAO=monoamine oxidase. APP=amyloid precursor protein. NMDA=*N*-methyl-D-aspartate. GABA=γ-aminobutyric acid. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. PDE=phosphodiesterase. SIMaMCI=Simvastatin in Amnestic Mild Cognitive Impairment. *A combination of acamprosate and baclofen (both licensed drugs).

Table 12: **Drugs in late-stage clinical development for Alzheimer's disease in people at symptomatic, pre-dementia stages**

	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial	Amyloid biomarker inclusion criteria in trials	Trials planned or in progress	Rate of amyloid-related imaging abnormalities
Solanezumab (NCT0760005, NCT01900665)	Eli Lilly	Mid-domain	Humanised	IgG1	Soluble, monomeric, non-fibrillar Aβ	Sequestration of soluble monomeric Aβ	Negative clinical outcomes in two phase 3 trials in mild-to-moderate Alzheimer's disease; possible slowing of cognitive decline in mild disease	None	Phase 3 trials underway in mild, preclinical, and autosomal-dominant Alzheimer's disease	Low
Bapineuzumab (NCT00575055, NCT00574132)	Pfizer/Johnson & Johnson	N-terminus	Humanised	IgG1	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in two phase 3 trials despite significant decrease in amyloid PET and phosphorylated tau concentrations in cerebrospinal fluid	None	..	Related to dose and *APOE* ε4 carrier status
Crenezumab (NCT 01397378, NCT01723826, NCT01998891)	Roche/ Genentech	Mid-domain	Humanised	IgG4	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in phase 2 trials in mild-to-moderate Alzheimer's disease; possible cognitive slowing in mild disease in patients given high doses	None in ABBY trial; amyloid PET in BLAZE trial	Phase 3 trial in autosomal-dominant Alzheimer's disease underway	Low
BAN2401 (NCT01767311)	Eisai/Biogen	N-terminus	Humanised	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	No phase 2 trials yet completed	Amyloid PET	Phase 2 trial underway in mild cognitive impairment	..
Gantenerumab (NCT01224106, NCT02051608)	Roche/ Genentech	N-terminus and mid-domain	Human (phage display library and affinity maturation)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Negative clinical outcomes in phase 3 trial for prodromal Alzheimer's disease	Cerebrospinal fluid Aβ	New phase 3 trial in planning phase	Related to dose and *APOE* ε4 carrier status
Aducanumab (NCT02484547, NCT02477800)	Biogen/ Neurimmune	N-terminus	Human (RTM)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Dose-dependent decrease in amyloid PET and cognitive decline in early Alzheimer's disease (mild cognitive impairment and mild disease) in interim analysis of phase 1b trial	Amyloid PET	Phase 1 trial in prodromal or mild Alzheimer's disease and phase 3 trial of early disease underway	Related to dose and *APOE* ε4 carrier status

Aβ=amyloid β. ..=not applicable. RTM=reverse translational medicine.

***Table*: Anti-amyloid monoclonal antibodies in clinical development**

Gruppo di ricerca geriatrica

Cosa ci ha insegnato il Mese dell'Alzheimer nella presa in carico della fragilità