

lacunes, leukoencephalopathy, cerebral atherosclerosis, arteriolar and capillary angiopathies, and microvascular changes resulting in blood-brain barrier dysfunctions. The spectrum of neurodegenerative and cerebrovascular changes in the brains of persons dying with ageing-related dementia and in those with normal cognition at the time of death has been investigated in several major studies.

The Medical Research Council Cognitive Function and Ageing (MRC-CFAS) Study: The epidemiology and neuropathology of 456 brain donations from an elderly population were studied comprehensively [7]. Both AD and CVD type changes were common and there was a high prevalence of mixed pathology. A significant proportion of the donors had more limited pathology than traditionally associated with dementia and a proportion of the donors with significant pathology remained cognitively intact until death. The dissociation between clinical dementia and the pathology of AD and CVD increased with increasing age of the subjects at the time of death.

Vienna Trans -Danube Aging Study: A community-based autopsy study of the brains of 233 elderly individuals, with and without dementia, found a wide spectrum of lesions and proteinopathies [8]. Virtually all the cases showed some degree of neurofibrillary degeneration but amyloid- β deposits were only present in 68.7%. Other pathologies included vascular lesions (48.9%), α -synucleinopathies (24.9%), non-Alzheimer tauopathies (23.2%), TDP-43 proteinopathies (13.3%) and others including inflammation and tumours (15.1%). The authors concluded that (a) pure AD pathology with dementia was infrequent (b) a number of non-AD neurodegenerative pathologies may result in dementia and that their prevalence has been underestimated. The commonest of the other underestimated pathologies were vascular lesions which were most probably due to CVD.

Religious Orders Study and Rush Memory and Aging Project: In 483 consecutive autopsies of elderly participants followed for several years with a battery of neuropsychological tests, the clinical diagnosis according to NINDCDS/AARDA 1984 criteria was probable AD in 179, mild cognitive impairment (MCI) in 134, and no cognitive impairment in 170 [9]. Of those diagnosed as probable AD, 87.7% had pathologically-confirmed AD, 45.8% had mixed pathologies most commonly AD combined with macroscopic infarcts. Of those diagnosed as MCI, 54.4% had pathologically confirmed AD, and 19.4% had mixed pathologies. Of those with no cognitive impairment 45.3% had AD pathology, 9.4% had mixed pathology. Major neuropathological lesions only accounted for 25% - 30% of the variance in cognition measured using a global measure of cognitive function assessed proximate to death [10]. Many individuals suffered varying degrees of cognitive and neurological deterioration whilst others maintained normal cognitive

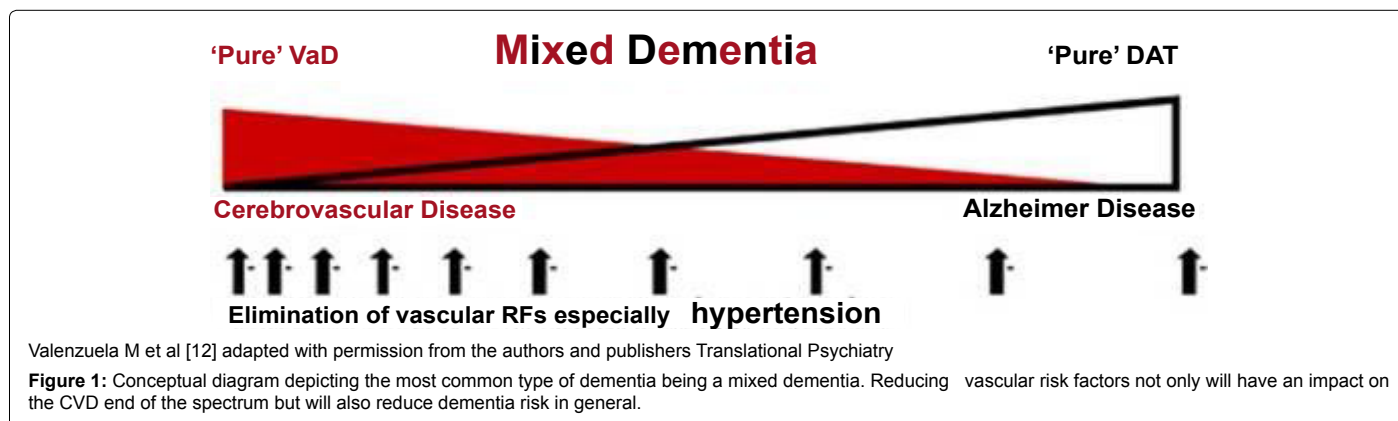
functioning in spite of significant brain pathology and the authors advanced the concept of cognitive resilience and resilient aging. The macroscopic infarcts were most likely the result of CVD and the author's state "Infarcts are the most common unrecognized contributing pathology in clinical AD, prevention of infarcts is likely to be most important in delaying onset and slowing cognitive decline in persons with AD pathology. From a public health perspective, measures that can improve vascular health, such as life-style changes and prevention and treatment of hypertension and diabetes, could decrease both the incidence and severity of clinical AD in the population."

The National Alzheimer's Coordinating Centre USA Study: In an analysis of 4,629 cases in with autopsy-confirmed neurodegenerative diseases, 79.9% were classified as also having CVD [11]. Concurrent CVD was a common finding in aged subjects with dementia and was more common with AD than in other neurodegenerative diseases. The occurrence of CVD changed the threshold for dementia due to AD and α -synucleinopathies. CVD accelerated β amyloid production, aggregation and deposition. CVD changes act both additively and synergistically with AD to cause dementia and cognitive impairment. The prevalence of cardiovascular risk factors was hypertension 56.2%, hypercholesterolemia 47.4%, coronary heart disease 18.0%, atrial fibrillation 13.7%, and diabetes 12.2%. AD and CVD pathologies appeared to have additive and synergistic effects on ageing-related cognitive decline and dementia. In persons with ageing-related cognitive impairment and dementia AD, LBD, and CVD changes frequently co-exist and the neurodegenerative and cerebrovascular changes form a spectrum from the extremes of "pure AD" to "pure CVD". A combination of changes is the most common and results in "mixed dementia" (Figure 1).

The separation of AD and "vascular dementia" has been claimed to be a false dichotomy [12]. The changes of AD and CVD overlap and both pathologies have both additive and synergistic effects on cognitive decline [13]. The interaction between the cerebrovascular and neurodegenerative changes is important in the pathogenesis of ageing-related cognitive impairment and dementia [14-16]. Both cerebrovascular and neurodegenerative brain changes are frequently found in persons with normal cognition at the time of death and protective factors are important in the prevention of ageing-related cognitive impairment and dementia.

Cognitive reserve, cognitive resilience and cognitive health

The maintenance of normal cognition in a significant proportion of persons with the pathological changes of AD, LBD or CVD is prima facie evidence of the importance of cognitive reserve and cognitive



resilience [17]. Cognitive reserve refers to high cognitive ability from an early age and the maintenance of high cognitive ability in mid-life and a consequent prevention or delay of ageing-related impaired cognition or dementia [18]. Cognitive resilience or resilient aging refers to retention of normal cognition and delay of the onset of impaired cognition or dementia in spite of the development of neuropathological changes of AD, LBD or CVD10. Cognitive health means the achievement and maintenance of high cognitive reserve, the promotion of protective factors throughout life and the avoidance and preventive treatment of modifiable risk factors that affect the development of impaired cognition and dementia.

Risk factors for cognitive impairment and dementia

Age is the most important factor determining the incidence and prevalence of cognitive impairment and dementia. In a prospective cohort study in the USA the age specific rates of all-cause dementia increase from 4.85 per 1,000 person-years in the 65-69 age groups to 84.19 per 1,000 person-years in the 90+ age group [19]. These figures are consistent with other US and European studies. Both neurodegenerative and cardiovascular changes have a long preclinical phase, commonly starting in mid-life. With increasing age converging genetic, environmental, and lifestyle factors trigger a pathophysiological cascade that over decades results in the neurodegenerative and cerebrovascular changes that may manifest in cognitive impairment and dementia. It is

estimated that seven potentially modifiable factors are present in about 50% of persons with AD [20] (Table 2). These estimates do not take into account the non-independence of risk factors and the combined population-attributable risks factors have been estimated to be about 30% for Europe, UK and USA [21]. A meta-analysis of 31 studies of incident AD found that low education, high homocysteinemia and smoking were significant risk factors and that higher physical activity and n-3 fatty acids were significant protective factors [22]. Because current therapies are of limited value and do not appear to significantly prevent the progression of ageing-related cognitive impairment and dementia, increasing attention is being focused on modifiable risk factors, protective factors and measures that may prevent, delay the onset or modify ageing-related cognitive impairment and dementia [23].

Measures to prevent delay or modify ageing -Related cognitive impairment and dementia

There have been few long-term, randomized, control investigations but a large number of observational studies suggest that various measures may prevent, delay the onset or minimize the severity of ageing related cognitive impairment and dementia [24] (Table 3). Many of these measures are similar, if not identical, to those shown to prevent or reduce the incidence of cardiovascular disease. The measures can be divided into (a) those aimed at preventing and reducing CVD and

RISK FACTOR	POPULATION PREVALENCE	RELATIVE RISK (95% CI)	PAR% (confidence range)	NO. OF CASES ATTRIBUTABLE (thousands; confidence range)
Worldwide				
Diabetes mellitus	6.4%	1.39 (1.17-1.66)	2.4% (1.1-4.1)	826 (365-1374)
Midlife hypertension	8.9%	1.61 (1.16-2.24)	5.1% (1.4-9.9)	1746 (476-3369)
Midlife obesity	3.4%	1.60 (1.34-1.92)	2.0% (1.1-3.0)	678 (387-1028)
Depression	13.2%	1.90 (1.55-2.33)	10.6% (6.8-14.9)	3600 (2295-5063)
Physical inactivity	17.7%	1.82 (1.19-2.78)	12.7% (3.3-24.0)	4297 (1103-8122)
Smoking	27.4%	1.59 (1.15-2.20)	13.9% (3.9-24.7)	4718 (1338-8388)
Low education	40.0%	1.59 (1.35-1.86)	19.1% (12.3-25.6)	6473 (4163-8677)
Combined (maximum)	50.7%	17 187 028*
USA				
Diabetes mellitus	8.7%	1.39 (1.17-1.66)	3.3% (1.5-5.4)	174 (77-288)
Midlife hypertension	14.3%	1.61 (1.16-2.24)	8.0% (2.2-15.1)	425 (119-798)
Midlife obesity	13.1%	1.60 (1.34-1.92)	7.3% (4.3-10.8)	386 (226-570)
Depression	19.2%	1.90 (1.55-2.33)	14.7% (9.6-20.3)	781 (506-1078)
Physical inactivity	32.5%	1.82 (1.19-2.78)	21.0% (5.8-36.6)	1115 (308-1942)
Smoking	20.6%	1.59 (1.15-2.20)	10.8% (3.0-19.8)	574 (159-1050)
Low education	13.3%	1.59 (1.35-1.86)	7.3% (4.4-10.3)	386 (236-544)
Combined (maximum)	54.1%	2 866 951*

PAR = population attributable risk

Table 2 Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA.

Measures that may Prevent, Delay or Minimize Ageing-related cognitive impairment or dementia	
Related to cardiovascular and cerebrovascular health	Mediterranean diet and specific nutrients
	Exercise, maintenance of cardiovascular fitness and healthy life-style
	Prevention of obesity and diabetes
	Early and active treatment of hypertension
	Early and active treatment of hyperlipidaemia
	Aspirin and non-steroidal anti-inflammatory drugs
Related to cognition reserve and cognitive health	Improved level of education
	Maintenance of cognitive activity
	Social interventions
	Depression management
	Correction of sleep disorders
Specific cognitive interventions	

Table 3 Severity of ageing related cognitive impairment and dementia.

(b) those aimed at improving and maintaining functional cognition irrespective of whether or not there are associated neuropathologies.

Measures aimed at prevention CVD: The measures aimed to prevent or protect against CVD have been well documented and include exercise, Mediterranean diet and omega-3-fatty acids and the aggressive treatment of hypertension, hyperlipidaemia and diabetes from early and mid-life onwards [24].

Measures aimed at the improvement and maintenance of cognition: These measures include education, maintenance of cognitive and social activity throughout life and the treatment of depression and sleep disorders. These measures can modify the relation between the degree of neuropathology and the level of cognition and the occurrence of dementia [17].

Education: The level of education is an important factor in relation to the later development of impaired cognition and dementia irrespective of the presence, amount or type of brain pathology. Education appears to delay the onset of cognitive decline but is associated with a more rapid progression once decline commences [25].

Cognitive activity: A systematic review of 22 cohort studies including 29,000 individuals concluded that complex patterns of mental activity in early, mid- life was associated with a significant reduction in dementia incidence in late life (RR 0.54 95% CI 0.49-0.59) [18]. In the Rush Studies cognitive stimulating activities over the life span, including games and puzzles, was associated with slower late-life cognitive decline and was independent of the development of common neuropathological conditions [26]. More frequent participation in cognitive activity was associated with reduced incidence of AD (HR 0.58 95%CI 0.44-0.77). Frequent cognitive activity was associated with reduced incidence of mild cognitive impairment and less rapid decline in cognitive function.

Social factors: Social isolation and loneliness appear to increase cognitive decline irrespective of AD pathology, and the deleterious effects of AD pathology are minimized by social engagement [27,28]. Conscientiousness in particular was associated with a slower rate of cognitive decline and a lower incidence of dementia [29]. In the MRC-CFAS Study a combined Cognitive Lifestyle score (CLS) based on educational attainment, occupational complexity and social engagement was calculated. Those who maintained a high CLS throughout their lives had a 40% reduced risk of developing dementia [30].

Progress and future perspective: In the last 10-15 years the age-specific prevalence of dementia in older adults in England, Denmark, Sweden, The Netherlands and USA appears to be decreasing [31-35]. The estimates of the national prevalence of dementia in England in 2011 were revised downwards by 24% from those predicted earlier from the findings two decades earlier in the Cognitive Function and Ageing Study I and II [31]. The decreases in the age-specific prevalence of dementia in these countries were attributed to higher educational levels, lower cardiovascular risk factors and a healthier life-style in more recent generations.

In early 2012 President Obama in the USA declared a "War on Alzheimer's disease" and in March 2012 the Prime Minister David Cameron in the UK issued a challenge to "go further and faster" making life better for people with dementia and their carers. The government authorities in both countries have voted considerable funds and advocated screening and testing for MCI and dementia of all at-risk individuals. Reservations however have been expressed about possible harms of population testing, including false-positive and false

negative tests and the stigma associated with a diagnosis of dementia [36]. In January 2014 a conference of 59 experts in dementia and non-communicable diseases (The Blackfriars Consensus on promoting brain health and reducing the risks for dementia) concluded that (a) "the evidence is now sufficient to justify policy action across the life course and for further research to reduce the modifiable risk factors and improve the populations profile for recognized protective fact, (b) these gains are likely to be greater if combined with action to protect brain health throughout life (c) the best strategy would be to work throughout the life course to bring people to the threshold of older age in good health [37,38]. These strategies may help to combat the predicted increase in the prevalence of dementia due to the increasing incidence of obesity and diabetes in many countries and to the increasing longevity and numbers of the elderly throughout the world [3]. In 2010 a seminal review on delaying the rising tide of world-wide late-life dementias concluded that delaying dementia appears feasible and that "if people can delay the onset of dementias they can lead more fulfilling lives for longer, spend less time suffering from the disease and letting their families spend less time in coping with the disease" [39]. Compression of cognitive morbidity well into old age is achievable and ageing-related cognitive impairment and dementia is not necessarily inevitable and inexorable and can be prevented, delayed or modified.

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