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Is Alzheimer's Disease Risk Modifiable?

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Abstract

Population-based clinic-pathological studies have established that the most common pathological substrate of dementia in community-dwelling elderly people is mixed, especially Alzheimer's disease (AD) and cerebrovascular ischemic disease (CVID), rather than pure AD. While these could be just two frequent unrelated comorbidities in the elderly, epidemiological research has reinforced the idea that mid-life (age < 65 years) vascular risk factors increase the risk of late-onset (age ≥65 years) dementia, and specifically AD. By contrast, healthy lifestyle choices such as leisure activities, physical exercise, and Mediterranean diet are considered protective against AD. Remarkably, several large population-based longitudinal epidemiological studies have recently indicated that the incidence and prevalence of dementia might be decreasing in Western countries. Although it remains unclear whether these positive trends are attributable to neuropathologically definite AD versus CVID, based on these epidemiological data it has been estimated that a sizable proportion of AD cases could be preventable. In this review, we discuss the current evidence about modifiable risk factors for AD derived from epidemiological, preclinical, and interventional studies, and analyze the opportunities for therapeutic and preventative interventions.

Keywords

Alcohol drinking; Alzheimer's disease; dementia; diet; diabetes mellitus; education; exercise; hypertension; hyperlipidemia; smoking

PATHOLOGICAL HETEROGENEITY UNDERLYING DEMENTIA

Dementia is a health care problem with an enormous economic and societal impact. Alzheimer's disease (AD) is considered the most common cause of dementia, the most common neurodegenerative disease, and one of the most common neurological disorders [1,2]. AD affects 5.4 million Americans and is the fifth leading cause of death among Americans aged 65 years or older [3]. While we have witnessed considerable advances in our understanding of its molecular and cellular underpinnings in the last four decades [4], AD remains incurable.

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Although AD is pathologically defined by the presence of amyloid plaques and neurofibrillary tangles (NFTs) in sufficient number and distribution to cause dementia [5], population-based clinic-pathological studies have established that the most common pathological substrate of dementia in community-dwelling elderly people is not pure AD, but mixed pathologies, especially some proportion of AD and cerebrovascular ischemic disease (CVID), but also Lewy body disease and hippocampal sclerosis with Tar DNA binding protein 43 KDa (TDP-43) pathology [6–9]. CVID is a heterogeneous clinic-pathological entity that encompasses both large vessel infarcts and small vessel disease. Attempts to operationalize CVID as a cause of cognitive impairment and a clinic-pathological entity distinct from AD have evolved from the first vascular dementia criteria [10,11] to the more recent and broader vascular cognitive impairment construct [12,13] . Within this CVID spectrum, it is small vessel disease due to lipohyalinosis of small size arteries that frequently coexists with some degree of AD neuropathological changes. Of note, CVID contributes to the severity of cognitive decline even in a convenience sample selected to represent the AD clinic-pathological continuum and devoid of cases with vascular dementia as the primary neuropathological diagnosis [14]. Up to 30% of subjects clinically diagnosed with probable AD dementia in the United States Alzheimer Disease Centers database actually do not meet neuropathological criteria for AD, mainly due to insufficient AD neuropathological changes and the co-occurrence of CVID and other neuropathologic findings [15,16].

The expansion of brain imaging and cerebrospinal fluid (CSF) AD biomarkers in clinical practice is enabling clinicians to appreciate this clinic-pathological heterogeneity when diagnosing and treating patients with dementia and mild cognitive impairment (MCI) [17–19]. Brain magnetic resonance imaging (MRI) has become the gold-standard imaging diagnostic method to evaluate both the CVID burden and the severity and regional pattern of brain atrophy in patients with dementia. A bilateral temporo-parietal hypometabolism in [^{18}F]-fluoro-deoxy-glucose positron emission tomography ([^{18}F]-FDG-PET) is typical of AD dementia and can often be already seen in patients with MCI due to AD. Similarly, amyloid PET and CSF AD biomarkers (amyloid-β (Aβ) and phospho-tau) can demonstrate the presence of AD pathology already at the MCI stage and predict conversion from MCI to AD dementia with high accuracy. Tau PET radiotracers are being developed and may soon be added to our clinical practice.

Although AD and CVID could just be frequent brain comorbidities in the elderly, the realization of this clinic-pathological complexity and heterogeneity has led researchers to inquire about a pathophysiological link between both entities. If this link exists, controlling the modifiable vascular risk factors and promoting cardio- and cerebrovascular health could help prevent AD dementia, as well as vascular dementia.

In this review, we discuss the current evidence about modifiable risk and protective factors for AD derived from epidemiological, preclinical, and interventional studies, and analyze the opportunities for therapeutic and preventative interventions. While multiple other risk factors have been postulated, we selected only those for which there are sufficient data within these three domains. Whenever the distinction was available, we will discern between all-cause

dementia, vascular dementia, and AD, and between autopsy-proven, biomarker-supported, and clinically-based diagnosis.

AGE-ADJUSTED INCIDENCE AND PREVALENCE OF DEMENTIA MIGHT BE DECREASING

Remarkably, although the expansion of human lifespan is leading to an increase in the total number of patients with dementia in developed and many developing countries, many recent longitudinal epidemiological studies have revealed that the age-adjusted estimates of incidence and prevalence of dementia might be decreasing, especially in Western countries (Figs. 1 and 2) [20–35].

It should be noted that, in order to obtain comparable measures of incidence and prevalence of dementia across decades in the same population, the methods of ascertainment of incident and prevalent cases must be kept constant in spite of the remarkable advances achieved in diagnostic biomarkers. Moreover, implementation of imaging and CSF diagnostic biomarkers in population scale epidemiological studies is logistically and financially challenging. Thus, most of these epidemiological studies ascertained dementia using either old sets of clinical diagnostic criteria or algorithms based on predetermined cut-off scores in brief cognitive screening tests, which might not be sensitive or specific for the detection of very mild dementia, and do not discern between different etiologies of dementia such as CVID and AD. Hence, it is not possible to accurately know what proportion of the observed decrease in dementia incidence and prevalence is attributable to AD versus CVID. For example, stroke incidence is decreasing among people aged 65 years and older in the United States [36], which predicts a decrease in vascular dementia incidence.

Also of note, dementia prevalence studies were overall less positive than dementia incidence studies (Figs. 1 and 2). One possible explanation is that prevalence measures can be strongly influenced by changes in survival trends. While no disease-modifying drugs are yet available for AD, currently approved drugs and specialized care might be prolonging AD survival [37], and therefore increasing its age-adjusted prevalence. Stroke care has improved enormously in the last two decades with the expansion of cardiovascular secondary prevention, in-hospital acute interventions, and rehabilitation programs, which could be contributing to decrease stroke mortality [36,38] but, secondarily, increasing the prevalence of vascular dementia [38].

Notwithstanding these potential caveats, the findings of these epidemiological studies have reinforced the role of modifiable environmental factors in AD pathophysiology and fueled optimism in preventative strategies. Indeed, it has been estimated that between a third to half of AD cases could be attributable to modifiable risk factors and, therefore, preventable [39–41]. However, it should be noted that many of these “AD cases” likely bear mixed pathologies in the brain and that the preventable component could just be the concurrent CVID burden. In any case, whether this decreasing incidence and prevalence of dementia is due to a *resistance* to accumulate AD neuropathological changes and/or CVID, or to *resilience* mechanisms that enable elderly people to better cope with their AD

neuropathological and CVID burdens ("cognitive reserve" and "brain reserve" hypotheses) [42], remains to be elucidated.

GENETIC RISK FOR ALZHEIMER'S DISEASE

Besides aging itself, the main other unmodifiable risk factor for sporadic AD is a genetic polymorphism in the *APOE* gene encoding for apolipoprotein E: the ϵ4 allele. Compared to ϵ3/ ϵ3 individuals—the most common genotype in the general population—, carrying one *APOE* ϵ4 allele increases the risk of developing AD ≈3 fold, whereas carrying two *APOE* ϵ4 alleles increases the risk up to 12 times. In addition, the *APOE* ϵ4 allele anticipates the clinical onset of AD in a dose-dependent fashion, with individuals who are homozygous often presenting before age 65. By contrast, carrying the *APOE* e2 allele reduces the risk of developing AD by half, delays its clinical onset, and reduces the age-related burden of AD neuropathological changes [43,44]. Among other mechanisms, it has been proposed that the apolipoprotein E4 isoform encoded by the *APOE* ϵ4 allele leads to Aβ accumulation in amyloid plaques and cerebral amyloid angiopathy (CAA) [43] by both reducing its clearance and promoting its aggregation [45]. Of note, clinic-pathological studies have also linked the *APOE* ϵ4 allele to an increased risk of CVID [46] and TDP-43 pathology [47] in the context of AD.

While *APOE* ϵ4 is the strongest known genetic factor for sporadic AD, it is not necessary nor sufficient to cause AD, and it is by no means the only genetic risk factor. Genome-wide association studies have discovered multiple susceptibility loci in as many genes, which correspond to common variants of small effect size [48]. These genetic variants have been used to devise polygenic hazard scores that improve the estimation of the genetic risk for AD beyond the *APOE* genotype [49]. However, as with many common diseases, the development of AD is thought to be ultimately determined by the combination of the individual's genetic make-up and his/her exposure to certain (modifiable) environmental factors. In fact, *APOE* and many of the recently discovered susceptibility gene polymorphisms are related to the innate immune system, thus highlighting the crucial role of microglia—the macrophage of the brain—in AD pathophysiology, and linking the individual's genome with his/her response to environmental exposures.

MODIFIABLE RISK AND PROTECTIVE FACTORS FOR ALZHEIMER'S DISEASE

Given the premises above, we sought to review the literature on the main modifiable risk and protective factors for the development of AD, which include the classic vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, and smoking), alcohol drinking, physical exercise, diet, educational attainment, and leisure and social activities. We will analyze the findings of epidemiological studies, the discoveries of preclinical research in AD mouse models, and the results of randomized clinical trials (RCTs) conducted in human subjects. We will highlight the opportunities for therapeutic and preventative interventions, as well as the remaining areas of uncertainty and knowledge gaps.

Hypertension

Epidemiological studies—Midlife hypertension has been associated with an increased risk of all cause and AD dementia in multiple longitudinal studies [50–53]. In a clinic-pathological study, hypertension was associated with increasing numbers of amyloid plaques and NFTs, as well as lower brain weight (indicating greater atrophy) [54]. However, the relationship between blood pressure and dementia is probably complex; a "goldilocks" phenomenon, whereby not only midlife hypertension but also late-life hypotension (hypoperfusion), have deleterious effects on brain health and cognition has been suggested. Both low blood pressure in late-life and a steeper decline in blood pressure between mid and late life have been associated with an increased risk of dementia and AD [53,55–58]. It has been recently reported that the association of blood pressure with AD dementia is U-shaped, with the lowest risk of AD dementia near the center of the systolic and diastolic blood pressure ranges [59]. Along the same lines, the age of onset of hypertension might be relevant to the risk of developing dementia and AD because, in fact, onset of hypertension in octogenarians and nonagenarians has been associated with a lower risk of dementia [60]. Notwithstanding this finding, an alternative possible explanation to this phenomenon is that incident AD dementia is associated with a reduction in body mass index (BMI), which would lead to a reduction in blood pressure.

Preclinical studies—Numerous experimental animal studies have linked hypertension and AD pathophysiology. Chronically induced hypertension in transgenic AD mice via administration of high salt diet plus deoxycorticosterone (DOCA), angiotensin II or hypertensive drugs [i.e., Nω-Nitro-l-arginine methyl ester hydrochloride (L-NAME)] increases brain Aβ accumulation in the form of amyloid plaques and CAA—leading to disruption of the blood-brain barrier (BBB)—, accelerates neuron loss, and worsens cognitive decline [61–63]. Conversely, a high salt diet alone induced an increase in cerebral blood flow without hypertension, and led to a reduction of amyloid plaque burden in transgenic AD mice [64]. Angiotensin II has been shown to increase Aβ levels through favoring the amyloidogenic processing of AβPP [63]. Multiple classes of anti-hypertensive drugs have shown to improve pathological and/or behavioral/cognitive phenotypes in transgenic AD mice, including beta-blockers [65,66], calcium-channel blockers [67], ACE inhibitors [68], and angiotensin receptor blockers [69]. Proposed mechanisms are unrelated to blood pressure control and include: decreased Aβ production [67], increased Aβ degradation by insulin degrading enzyme (IDE) [66,69], increased clearance of Aβ through the BBB [67], inhibition of Aβ oligomerization into high molecular weight neurotoxic species [69], and reduction of inflammation [65,68] and oxidative stress [68]. Of note, blood pressure may be less responsive to anti-hypertensive drugs in hypertensive transgenic AD mice than in wild-type mice [70].

Interventional studies—The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a secondary prevention RCT conducted in elderly people with history of prior stroke or transient ischemic attack who were randomized to either the ACE inhibitor perindopril/indapamide (n = 3,051) or placebo (n = 3,054). Cognitive impairment, as indicated by a new diagnosis of dementia [based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria] or a decline in Mini-Mental State Examination

(MMSE) score of 3 or more, was a primary outcome. Compared to placebo, the perindopril/indapamide combination was associated with a statistically significant reduction in the risk of dementia and cognitive decline [71]. However, this risk reduction was only significant for the subgroups of "dementia/cognitive decline with recurrent stroke", not for the "other dementia/cognitive decline" subgroup, indicating that vascular cognitive impairment rather than AD was driving the beneficial effects of perindopril/indapamide on cognition.

Diabetes mellitus

Epidemiological studies—Longitudinal epidemiological studies have yielded conflicting results regarding whether diabetes mellitus (DM) in midlife increases the risk of developing late onset dementia and AD. Some studies have shown such association [72–75], but others have failed to detect it [76]. A recent meta-analysis of 17 longitudinal cohort studies amounting ≈1.7 million people concluded that DM increases the risk of developing AD with a relative risk (RR) of ≈1.5 [77]. However, clinic-pathological studies have reported either no association between a DM diagnosis and the extent of AD neuropathological changes, or exacerbated AD neuropathology only in *APOE ϵ*4 carriers [78–80].

Preclinical studies—Experimental studies in AD mouse models have supported a contribution of DM to AD pathology and cognitive impairment. Although multiple links between Aβ and DM have already been unveiled, the mechanism(s) by which DM promotes AD remains an area of active research. As mentioned above, IDE is one of the major Aβ-degrading enzymes [81]. The receptor for advanced glycation end-products (RAGE) is a receptor for Aβ present in neurons, microglia, and endothelial cells [82]. RAGE mediates the influx of Aβ from the plasma to the brain interstitial fluid (ISF) through the BBB [83]. Plasma insulin growth factor I (IGF-I) reduces brain Aβ levels and amyloid plaque burden in transgenic AD mice [84]. Plasma hyperinsulinemia in the setting of normoglycemia leads to an increase in brain ISF Aβ levels without altering brain insulin levels or brain insulin signaling, whereas direct delivery of insulin to the brain does not affect Aβ levels, despite stimulating the insulin signaling pathway [85]. Acute hyperglycemia can increase ISF Aβ levels by augmenting neuronal activity, which is known to enhance Aβ generation, in a K-ATP channel dependent fashion [86]. Peritoneal administration of streptozotocin leading to hypoinsulinemia (a model of type 1 DM) reduces amyloid plaque deposition but increases the levels of soluble Aβ species and the severity of CAA, accelerates neurodegeneration, and worsens cognition in transgenic AD mice [87]. A similar phenotype can be seen in transgenic AD mice fed with high fat diet to develop insulin resistance and hyperinsulinemia, or crossed with the leptin receptor null mice (db/db), the most widely used mouse model of insulin resistance and type 2 DM [88].

Interventional studies—Small pilot randomized placebo-controlled clinical trials have suggested that metformin [89,90], intranasal regular insulin [91,92], and intranasal long-acting insulin (detemir) [92,93] may have a beneficial effect on cognition in patients with amnestic MCI or mild AD dementia. In addition, a positive effect on AD biomarkers has been suggested in these pilot trials, including a slower rate of brain atrophy by MRI, an improved cerebral hypometabolism by [^{18}F]-FDG-PET scan, an improved profile of CSF

AD biomarkers (Aβ/phospho-tau) with intranasal regular insulin [91,92], and an improved cerebral perfusion with metformin by resting-state arterial spin labeling MRI [90]. Larger phase III RCTs are needed to confirm these promising results. Conversely, rosiglitazone did not impact cognition compared to placebo in subjects mild to moderate AD dementia [94].

Hypercholesterolemia

Epidemiological studies—The relationship between hypercholesterolemia and AD risk remains unclear and is probably complex. For example, two studies assessing the effects of mid-life serum cholesterol on late-life risk of dementia and AD have yielded conflicting results. One showed a positive association between serum cholesterol level in midlife and development of AD 21 years later [95], whereas the other did not find any significant association between midlife serum cholesterol level and risk of AD 32 years later [96]. However, both studies concurred in finding that a decrease in serum cholesterol levels between mid and late life is associated with a higher risk of developing AD. Survival and competing risk biases associated with death from cardiovascular causes could explain these apparently contradictory results. In addition, late life hypercholesterolemia has been reported to both reduce [97] and not change [98] dementia risk. Similarly, while early cross-sectional revealed an up to 70% reduction in dementia risk in statin users [99,100], longitudinal prospective studies subsequently rendered mixed results [101–105]. Moreover, mild hypercholesterolemia has been associated with increased early amyloid plaque deposition in the brain independently of the *APOE* genotype [106], but no association between late life cholesterol and AD neuropathological changes was found in the Adult Changes in Thought (ACT) population-based study [107]. Last, statin use has been associated with reduced AD neuropathological changes, specifically NFTs, in the autopsy cohort of the ACT study [108], but not in the Religious Orders Study [104].

Preclinical studies—Diet-induced hypercholesterolemia enhances Aβ plaque deposition in transgenic AD mice [109,110]. Atorvastatin and pitavastain therapy can reduce Aβ plaque burden and microglial inflammation in transgenic AD mice [111], whereas simvastatin has been reported to improve the cognitive deficits in these mice without altering amyloid plaque burden [112,113]. Simvastatin, atorvastatin, and ezetimibe have been shown to reduce NFTs in a mouse model of tauopathy [114].

Interventional studies—Two large RCTs investigated the effects of statins on cognition in non-demented elderly people with high cardiovascular risk and both concluded that statins have no significant protective effect on cognition. The Heart Protection Study (HPS) compared the effects of simvastatin versus placebo at reducing cardiovascular risk in a large sample of elderly individuals at high risk of suffering cardiovascular disease. Cognitive impairment was assessed at baseline and at the trial completion by means of the modified Telephone Interview for Cognitive Status (TICS-m), which was administered either in person or by telephone, and considered a tertiary endpoint. No significant differences were found in TICS-m scores or the proportion of TICS-m impaired versus non-impaired subjects between the simvastatin (n=10,269) and the placebo (n=10,267) groups [115]. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial enrolled high cardiovascular risk elderly subjects to test the effects of pravastatin (n=2,891) versus placebo

(n=2,913) in cardiovascular morbidity and mortality. Cognitive function was evaluated at baseline and 5 more times over a 42-month follow-up with the MMSE and a brief battery of executive and memory tests (Stroop-Color-Word test, Letter-Digit Coding test, and Picture Learning test immediate and delayed recall), and included as a tertiary endpoint. No significant differences in cognitive scores between pravastatin and placebo were observed at any follow-up visit [116,117].

RCTs of statins in patients at the stage of mild-to-moderate AD dementia have also rendered disappointing results. A positive signal in cognitive, functional, and behavioral outcome measures was observed in the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial, which compared atorvastatin (80 mg/day, n = 32) with placebo (n = 31) in a small sample (n = 63) of mild to moderate AD dementia patients [118]. However, longer and larger clinical trials failed to reproduce these promising results. The Lipitor's Effect in Alzheimer's Dementia (LEADe) study randomized 640 patients with mild to moderate AD dementia to atorvastatin (80 mg/day, n = 297) or placebo (n = 317). After 72 weeks, no differences were observed in the primary endpoints: a measure of global cognition and a measure of global level of functioning [119]. Similarly, simvastatin (40 mg/day) also failed to impact rate of cognitive decline in another clinical trial conducted in 406 patients with mild-to-moderate AD dementia and normal lipid profile [120].

Smoking

Epidemiological studies—Several large population-based cohort studies have reported a 2–4-fold increased risk of being diagnosed with AD among current smokers, but only within *APOE* ϵ4 non-carriers [121–123]. A more recent meta-analysis of 37 prospective cohort studies has confirmed that smoking increases the risk of all-cause dementia and vascular dementia, whereas AD risk is significantly increased only among *APOE* ϵ4 non-carriers [124]. Of note, the analysis of the Honolulu-Asia Aging Study (HAAS) autopsy cohort revealed an association between mid-life smoking and higher numbers of cortical neuritic amyloid plaques at autopsy independently of age of death, presence of the *APOE* ϵ4 allele, systolic blood pressure, and neuropathological evidence of stroke [125]. Environmental tobacco exposure, colloquially called passive or second-hand smoking, has also been associated with an increased risk of dementia and AD [126,127]. Importantly, ex-smokers have a similar risk of dementia as never smokers, suggesting that smoking cessation alone could prevent many dementia cases 124].

Preclinical studies—Exposure of transgenic AD mice to high dose cigarette smoke in a smoking chamber leads to an increased amyloid plaque deposition, microglial and astrocyte responses, and hyperphosphorylated tau in plaque-associated neuritic dystrophies, but not neuron loss [128]. Studies investigating the effects of nicotine have yielded conflicting results. Chronic nicotine administration has been reported to reduce amyloid deposition in one mouse model of β-amyloidosis [129], but not in another more aggressive model [130], and to worsen tau aggregation in a triple transgenic mouse which develops both plaques and tangles [131]. Cotinine, the main metabolite of nicotine, reduced Aβ deposition and ameliorated cognitive deficits in AD transgenic mice [132].

Interventional studies—A smoking cessation program in the elderly led to significantly slower rates of cognitive decline over the following 2 years in successful quitters compared with unsuccessful quitters [133]. Smoke-free laws banning smoking in workspaces and designated public areas have been implemented in many developed countries. In some of these countries, the anti-tobacco legislation is more comprehensive and encompasses also restrictions to tobacco advertising in mass media, as well as the addition of a "healthcare" tax on tobacco purchase. Smoke-free legislation has been shown to reduce the number of hospitalizations for acute coronary syndrome [134] and the rates of preterm birth and hospital attendances for childhood asthma [135]. Thus, although research evidence is awaiting, it is conceivable that anti-tobacco public health policies could be contributing to reduce the incidence of vascular dementia and possibly AD.

Alcohol drinking

Epidemiological studies—Although epidemiological studies based on self-reported measurements such as alcohol intake should be taken with caution, light to moderate alcohol consumption in late life has been associated with a reduced risk of AD dementia [136–138]. A meta-analysis of 15 longitudinal prospective studies confirmed that moderate alcohol drinkers have a significantly reduced risk of AD and vascular dementia compared to non-drinkers [139]. With regards to the alcohol beverage type, the Rotterdam study [137] found no difference between wine, beer, or liquor, whereas the Washington Heights Inwood-Columbia Aging Project [138] found that only wine was protective. Somewhat surprisingly, late life heavy drinking has been shown to have no effect on the risk of dementia compared to non-drinkers [137,139]. However, the HUNT study, a large population-based study from Norway, found that, relative to infrequent alcohol intake (1–4 times in last 14 days), frequent alcohol intake (≥5 times in last 14 days) is associated with an increased risk of both AD and vascular dementia up to 27 years later [140].

Despite this epidemiological evidence, the relationship between alcohol and dementia may not be straightforward; confounding factors such as socioeconomic status, education, and healthy lifestyle choices (such as diet and exercise), which are frequently associated with light to moderate alcohol consumption, could be influencing or even driving the above results.

Preclinical studies—Multiple studies have shown that resveratrol, a sirtuin 1 (SIRT1) activator, and other polyphenols present in the grapes of red wine reduce Aβ plaque burden and improve cognitive phenotype, through specific mechanisms depending on the polyphenol: promoting the non-amyloidogenic pathway of AβPP processing [141], interfering with Aβ oligomerization [142,143], favoring Aβ degradation through the proteasome [144], and reducing oxidative stress [145].

Interventional studies—A phase II double-blind, placebo-controlled RCT of resveratrol in mild-to-moderate AD patients showed that resveratrol is detectable in CSF and is safe and well tolerated. Of note, resveratrol reduced CSF $A\beta_{40}$ and $A\beta_{42}$ levels but accelerated brain atrophy [146]. A larger phase III RCT is needed to confirm these promising results.

Obesity and diet

Epidemiological studies—Numerous epidemiological studies have agreed that midlife obesity, measured with anthropometric parameters such as BMI and/or the waist-to-hip ratio, is associated with an increased risk of late-life dementia independently of other vascular or socioeconomic risk factors [147–153]. However, most of these studies have also concurred in that there is a reverse causality effect whereby the BMI declines in the years prior to the onset of dementia. It has been proposed that this "obesity paradox" or weight loss immediately prior to and during the clinical phase of dementia is related to an increase in energy expenditure and a hypothalamic dysregulation. Whether the significant association between mid-life obesity and late-life dementia is driven by AD, vascular dementia, or mixed AD/vascular dementia remains controversial [147,150]. However, obesity (higher BMI) has been linked with greater cortical atrophy in 700 AD and MCI patients in a large study combining the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Cardiovascular Health Study-Cognition Study (CHS-CS) datasets [154], and midlife obesity was associated with an earlier age of AD clinical onset, greater amyloid burden by PET imaging, and greater Braak NFT stage at autopsy, but not higher CERAD neuritic plaque score, in the Baltimore Longitudinal Study of Aging (BLSA) [155].

Mediterranean diet, that is, a diet rich in fruits, vegetables, whole-grain cereals, fish and olive oil, has been associated with cognitive health and a lower risk of developing MCI and AD dementia, and of converting from MCI to AD dementia [156–159]. Furthermore, adherence to Mediterranean diet might be associated with a lower mortality risk in AD patients [160]. While it is clear that adherence to Mediterranean diet is associated with cardiovascular health and protects against cerebrovascular disease [161–165], the protective association between Mediterranean diet and AD dementia does not seem to be mediated by its effects on the incidence of stroke and/or vascular risk factors [166]. In fact, of particular relevance to AD prevention, a 3-year serial amyloid and FDG-PET imaging study has recently reported that adherence to a Mediterranean-style diet by middle-aged cognitively healthy adults slowed down both amyloid plaque deposition and cerebral hypometabolism independently of *APOE* genotype and vascular risk factors [167]. This finding strongly supports a preventative or protective effect of Mediterranean diet against AD.

Perhaps because of the cumulative beneficial effects of its many components, the evidence in favor of the Mediterranean diet as a whole is more solid that the evidence on individual nutrients or food groups [168]. Attempts to dissect which components of the Mediterranean diet are beneficial for cognition have supported a role of nutrients and bioactive compounds contained in fish [169,170], and cruciferous and green leafy vegetables, but not fruits [171–173]. Conversely, a diet rich in saturated fat has generally been associated with an increased risk of dementia [174–176] (but see also [177]). Low vitamin E and D levels have been associated with a higher risk of developing dementia [178–180], whereas studies investigating the association between vitamin B12 and folic acid levels and dementia have yielded conflicting results [181,182]. It should be noted, however, that patients with AD can exhibit an impaired nutritional status already at the stage of mild dementia and that this aspect of the disease could be a confounder of many of the above cross-sectional epidemiological studies [183,184].

Preclinical studies—As mentioned above, a high fat diet promotes amyloid plaque deposition and cognitive deficits in transgenic AD mice [88,185,186]. Of note, these effects can be effectively reverted by environmental enrichment and exercise, despite continuation of high fat diet [185,186]. It is unclear whether high fat diet-induced obesity can also accelerate tau pathology independently of its effects on Aβ [187,188]. The components of Mediterranean diet have been extensively studied in AD mouse models. Oleuropein aglycone, the main polyphenol present in extra virgin olive oil, reduced Aβ plaque burden in transgenic AD mice through enhancing autophagy [189]. Oleocanthal, another phenolic component of extra virgin olive oil, reduced Aβ plaque burden in transgenic AD mice by facilitating Aβ clearance through the BBB [190]. A diet deficient in folate, and vitamins B6 and B12 can accelerate Aβ plaque deposition in transgenic AD mice [191]. Vitamin E supplementation can prevent Aβ plaque deposition in young, but not aged, transgenic AD mice [192]. Genetic depletion of vitamin E in transgenic AD mice increases Aβ plaque deposition through a reduction in plaque clearance, a phenotype than can be reverted with vitamin E supplementation [193,194]. Studies investigating the effects of supplementation with ω3-poly-unsaturated fatty acids (ω3-PUFA) such as docosahexaenoic acid (DHA) in the brain Aβ levels and cognition of transgenic AD mice have rendered contradictory results [195,196].

Interventional studies—Despite all this epidemiological and preclinical evidence, all diet-based clinical trials have essentially failed to slow down the progression of cognitive decline in AD. Vitamin E supplementation failed to prevent the progression from MCI to AD dementia [197]. A combination of the antioxidants vitamin C, vitamin E, and lipoic acid in a small sample of mild to moderate AD patients failed to impact AD biomarker levels in CSF and, actually, accelerated cognitive decline compared to placebo [198]. Supplementation with ω3-PUFA failed to delay cognitive decline in a small RCT enrolling 174 patients with mild to moderate AD dementia [199]. Moreover, ω3-PUFA, with or without a multi-domain intervention consisting of a physical exercise program, cognitive training and dietary advice, failed to prevent cognitive decline in a 3-year RCT conducted in elderly people with memory complaints but not demented [200]. Souvenaid®, containing Fortasyn Connect®, a micronutrient combination including DHA, eicosapentaenoic acid (EPA), uridine monophosphate, choline, vitamins B12, B6, C, E, and folic acid, phospholipids and selenium, improved cognition in a 12-week proof-of-concept RCT in drug-naïve patients with mild AD [201]. A subsequent 24-week RCT in drug-naïve mild AD patients also revealed a trend towards cognitive improvement in the experimental group [202]. However, another 24-week RCT of Souvenaid® as add-on therapy in patients treated for mild-to-moderate AD dementia [203] and a 24-month RCT targeting the earliest stage of AD (prodromal or pre-symptomatic AD) [204] failed to show improvement of the cognitive primary outcome. Of note, Souvenaid® corrected the micronutrient deficits in the plasma of mild and mild-to-moderate AD patients [205], preserved a quantitative electroencephalogram measure representing brain network integrity in mild AD patients [206], and improved both a cognitive/functional secondary outcome and an MRI-based hippocampal volume measurement in prodromal AD patients [204]. If these findings are confirmed in larger samples of cognitively intact individuals, it would support its value as a protective, rather than therapeutic, intervention. The FINGER trial is a 2-year RCT that

compared a multi-modal intervention with diet, exercise, cognitive and social stimulation against just counseling in a large cohort (n = 1260) of at risk but non-demented elderly subjects. A significant beneficial effect of the intervention on the cognitive outcome measure (Neuropsychological Test Battery or NBT), especially on the executive functioning and processing speed scores, was reported. While the contribution of each of the components of this multi-domain intervention to this favorable result is unclear, the recommended diet was very similar to a Mediterranean-style diet [207].

Exercise

Epidemiological studies—A vast majority of epidemiological longitudinal prospective studies have established that a lower level of physical activity is associated with a higher risk of developing AD dementia and, conversely, a higher level of physical activity protects against AD dementia [208–213]. While elderly people who exercise are more likely to follow a healthy diet, the beneficial effect of exercise is independent of the protective effects of Mediterranean diet [214]. According to a recent meta-analysis of prospective studies, the protective association between leisure time physical activity and AD risk is dose-dependent [215].

Preclinical studies—Numerous studies have established that aerobic physical exercise can ameliorate neuropathology and cognition in multiple Aβ [216,217] and tau [218,219] mouse models of AD. Exercise can promote neuronal plasticity and the non-amyloidogenic processing of AβPP through enhancing brain-derived neurotrophic factor (BDNF) signaling [220]. Another protective mechanism invoked is a change in microglia phenotype towards inhibition of neuroinflammation [217].

Intervention studies—A number of clinical trials have indicated that a program of regular aerobic exercise has beneficial effects on cognition and level of functioning in patients with subjective cognitive complaints [221], MCI [221–224], and very mild AD dementia [225], but not in patients with mild to moderate dementia [226]. In the successful FINGER trial described above, the exercise program consisted of 1 to 3 weekly sessions of progressive muscle strength exercises for the eight main muscle groups plus 2 to 5 weekly sessions of aerobic individual and group activities [207]. Of note, in its new guidelines for the assessment and management of MCI, the American Academy of Neurology has recently issued a Level B (moderate confidence) recommendation for regular (twice per week) exercise in MCI patients [227], based on the promising results of two 6-month-long RCTs [223,224].

Education attainment, leisure, and social activities

Epidemiological studies—Epidemiological research has established that the level of education is inversely correlated with the risk of developing dementia due to both CVID and AD [228–232]. Leisure cognitive and physical activities have also been associated with a reduced risk of developing dementia [233–235]. Conversely, loneliness and single or widow/widower marital status have been associated with a higher risk of developing dementia [236,237]. It should be noted that education and leisure and social activities are intimately related to other lifestyle factors (i.e., level of physical exercise, diet quality, alcohol/tobacco

use, adherence to pharmacological treatment of vascular risk factors), which could be driving or contributing to these effects and may not have been fully accounted for in the above studies.

Nonetheless, this epidemiological evidence has lent support to the "cognitive reserve" hypothesis, which posits that some highly educated individuals can exhibit either *resistance* to the development of AD neuropathology, or a special *resilience* that allows them to remain asymptomatic despite high burdens of amyloid plaques and NFTs thanks to their "brain reserve" (so called "mismatch AD", "high pathology control", or "asymptomatic AD" individuals) [238–243]. Recent imaging studies in cognitively healthy subjects support the existence of both resistance and resilience pathways linking education and intellectual enrichment with risk of AD dementia [244–249]. Specifically, some studies have reported that a higher education attainment and intellectual enrichment during midlife predict greater cortical thickness in brain MRI, even after adjusting for early life intelligence [249], lower amyloid burden in amyloid PET scan [246,248], and greater cortical metabolism in FDG-PET [246] in late life, whereas other studies have found an association between a higher education and intellectual activity levels and better cognitive performance in late life independently of cerebral amyloid burden, metabolism, and atrophy [244,247].

Multiple mechanisms have been proposed to explain the resilience of some individuals to high AD neuropathological burden, including a higher or preserved number of neurons and synapses [241], a compensatory hypertrophy of the neuronal somas and nuclei [239,240], lower levels of toxic Aβ and tau oligomers at the synapses [241,242], limited microglial and astrocyte inflammatory responses [238,241], and a greater expression of the glutamate transporter GLT-1 in astrocytes to palliate glutamate-mediated neuronal excitotoxicity [243].

Preclinical studies—Social isolation by housing individual mice in separate cages can exacerbate AD-like pathology and cognitive deficits in mouse models of AD [250–252]. Conversely, environmental enrichment by introduction of novel objects in their cages as a method of cognitive stimulation has been reported to reduce the AD-like pathology and alleviate or prevent cognitive impairment in multiple mouse models of amyloid plaque [253–259] as well as NFT deposition [257,260] (but see [261]).

Intervention studies—A meta-analysis of 17 RCTs of computerized cognitive training in patients with MCI rendered small to moderate but significant benefits in cognition, whereas the beneficial effects for dementia patients were weaker. Unfortunately, most studies are short-lasting and have not assessed long term effects on cognition [262]. A recent 2-year RCT testing a behavioral activation paradigm designed to increase the level of cognitive, physical and/or social activity versus supportive (counseling) therapy in a sample of 221 black patients with MCI revealed a significant slowing in memory and functional decline in the behavioral activation group [263]. The recent American Academy of Neurology guidelines for the assessment and management of MCI assign a Level C (low confidence) recommendation for cognitive stimulation interventions at this early stage [227].

OPPORTUNITIES FOR THERAPEUTIC AND PREVENTATIVE INTERVENTIONS

We have shown that there is a substantial body of epidemiological evidence consistent with the idea that mid-life vascular risk and metabolic factors increase the risk of late-onset dementia and AD, whereas education attainment, leisure and social activities, physical exercise, and Mediterranean diet protect against AD dementia (Fig. 3). Importantly, although the most widely used AD mouse models only recapitulate some aspects of the disease (i.e., either plaques or NFTs), the results of preclinical mechanistic research are largely in agreement with these epidemiological findings, adding support to the pursuit of preventative and therapeutic interventions that target these factors. Moreover, it is tempting to speculate that the recently reported trends of reduction of all-cause dementia and AD incidence and prevalence are related to a higher prevalence of modifiable protective factors and/or a lower prevalence of modifiable risk factors [264]. Indeed, a more widespread and stricter control of vascular risk factors through the popularization of antiplatelet, antihypertensive and statin drugs [265], the smoke-free policies resulting in lower numbers of tobacco users and second-hand smokers [266], and the expansion of college level education [267] could all be contributing to some extent to this positive trend. Noteworthy, while antiplatelet drugs have proven to be beneficial in secondary prevention of cardiovascular events, recent large primary prevention RCTs with aspirin have failed to prevent cardiovascular events and dementia in healthy elderly subjects [268,269]. Conversely, the rapidly propagating vicious cycle of sedentary life, high fat diet, obesity, and type 2 diabetes mellitus could threaten this positive trend in the near future [270].

Despite this epidemiological and preclinical evidence, virtually all attempts of clinical translation have failed to date, casting doubts about the validity of these modifiable factors as therapeutic targets. Rather than attributing the failure of these interventions to the selection of wrong targets, one alternative plausible explanation could be that most interventional studies have been designed with a therapeutic rather than preventative goal. For example, many of the RCTs have targeted MCI or mild-to-moderate AD dementia patients, when the AD neurodegenerative cascade has already begun and seems unstoppable. In addition, in most cases the diagnosis of MCI or AD dementia at enrollment was based on clinical criteria without biomarker support, but the clinical constructs of MCI and AD dementia are pathologically heterogeneous due to the high frequency of pathological comorbidities and to clinical misdiagnosis [8,15,16].

Whereas efforts to reduce cardiovascular and metabolic and increase healthy lifestyle factors have weak therapeutic impact in patients with established AD dementia, they may play much larger roles in lowering the risk of AD in cognitively normal individuals. It is now clear that both amyloid plaques and NFTs start to accumulate one to two decades before the first cognitive symptoms arise, and that this preclinical phase is a window of opportunity for preventative interventions [271]. The challenge, therefore, is to identify and then treat individuals at heightened risk for AD before cognitive symptoms and signs develop. To address this opportunity for preventative therapy, a recent consensus research framework has redefined the concept of AD based on CSF and imaging biomarkers of the AD

pathophysiological process, rather than on the presence of clinical symptoms. A biomarker-based staging system termed AT(N) has been proposed, where A^+ indicates evidence of Aβ accumulation (either by amyloid PET or low CSF Aβ levels), T^+ indicates evidence of hyperphosphorylated tau pathology (either by tau PET or elevated CSF phospho-tau levels), and $(N)^+$ refers to evidence of neurodegeneration (either by a typical atrophy pattern in brain MRI, hypometabolism in FDG-PET, or elevated CSF total tau levels) [272]. While this staging system is a working research model that remains to be fully validated [273], biomarker-based staging may enable the design of primary prevention RCTs in cognitively intact individuals with negative AD biomarkers [$A^-T^-(N)^-$] and secondary prevention RCTs in cognitively normal subjects who have positive AD biomarkers [i.e., those with $A^+T^-(N)^-$ (termed "preclinical Alzheimer pathologic change"), and those with $A^+T^+(N)^-$ or $A^+T^+(N)^+$ (categorized as "preclinical AD")]. By identifying different groups of subjects with different pathologies, it will be possible to determine the target populations in which interventions to modify risk factors for AD are most likely to prevent or delay onset of dementia. The observation that nutritional [167,202,206] and educational factors [244–249] can alter some of these biomarkers emphasizes the potential these modifiable risk and lifestyle factors have for reducing the risk of developing AD in healthy populations.

Last, future research should clarify the effects of other potential environmental risk factors, such as mild traumatic brain injury [274,275], air pollution [276,277], and other toxic exposures [278]. If confirmed as risk factors, appropriate public health policies against them could also have a huge beneficial impact on AD incidence and prevalence. Moreover, although methodologically challenging, a lifespan approach to evaluate whether and how the above genetic and acquired risk and protective factors influence brain development and/or vulnerability to injury in early life [279–282] could decisively inform public health policies aimed at preventing AD in late-life.

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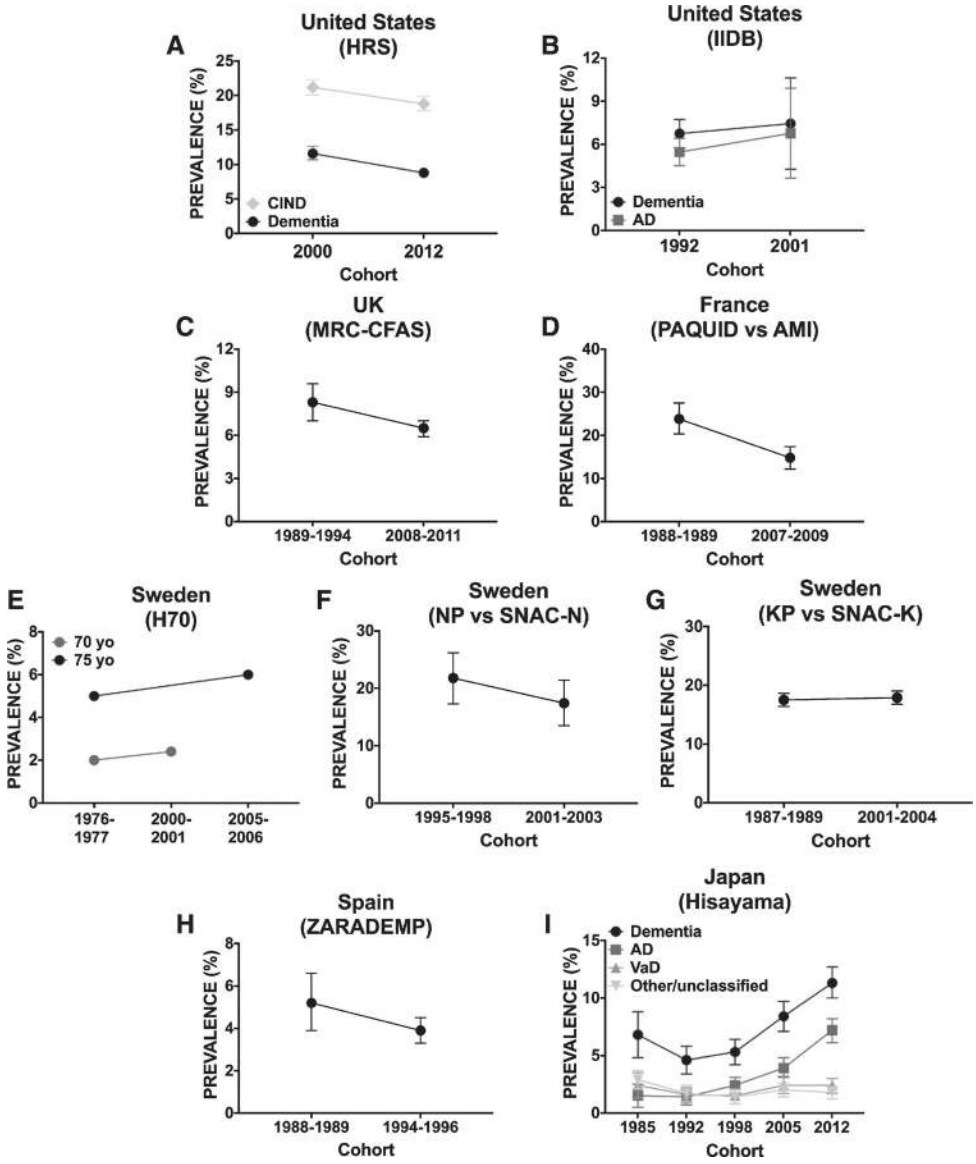

Fig. 1. Trends in dementia prevalence.

Dementia prevalence appears to be decreasing in the United States and Western Europe, but not in Japan or Sweden. Graphs depicting the changing prevalence of cognitive impairment not dementia (CIND, light grey diamonds), all-cause dementia (black circles), Alzheimer's disease (AD, steel grey squares), vascular dementia (VaD, aluminum grey triangles), and other/unclassified dementias (inverted silver-grey triangles). Error bars represent 95% confidence intervals (95%CI). A) Prevalence results for all-cause dementia and CIND from the 2000 and 2012 waves of the Health and Retirement Study (HRS) [34], conducted among people ≥65 years across the United States. B) Prevalence results for all-cause dementia and AD from the 1992 and 2001 waves of the Indianapolis-Ibadan Dementia Project (IIDB) [25], conducted among ≥70 years old African-Americans in Indianapolis, Indiana (USA). C) Prevalence results for all-cause dementia from the waves I (1989–1994) and II (2008–2011) of the Medical Research Council Cognitive and Function Aging Study (MRC-CFAS) [27],

conducted among people ≥65 years old in three geographically defined areas of England (UK). D) Prevalence rates for the algorithmic diagnosis of dementia ("cognitive impairment with disability" or CIWD) from the Persones Agées Quid (PAQUID, 1988–1989) and the Aging Multidisciplinary Investigation (AMI, 2007–2009) studies [31], conducted among farmers aged 65 and older in the area of Bourdeaux, France. E) Crude prevalence rates for all-cause dementia in the 1976–1977, 2000–2001, and 2005–2006 waves of the H70 study [22], conducted among 70- and 75-year-old residents of Gothenburg, Sweden (95%CI not available). F) Crude prevalence rates for all-cause dementia from the Nordanstig Project (NP, 1995–1998) and the Swedish National study on Aging and Care in Nordanstig (SNAC-N, 2001–2003), derived from residents aged 78 and older in the municipality of Nordanstig, Sweden [33]. G) Prevalence rates for all-cause dementia from the Kungsholmen Project (KP, 1987–1989) and the Swedish National study on Aging and Care in Kungsholmen (SNAC-K, 2001–2004) [23], conducted among people ≥75 years old in central Stockholm, Sweden. H) Prevalence rates for all-cause dementia from the waves 0 (1988–89) and I (1994–1996) of the Zaragoza Dementia Depression Project (ZARADEMP) [21], conducted among people ≥ 65 years old in the city of Zaragoza, Spain. I) Prevalence rates for all-cause dementia, AD, VaD, and other/unclassified dementia from the 1985, 1992, 1998, 2005, and 2012 waves of the Hisayama Study [32], conducted among people ≥65 years old in Hisayama, Japan.

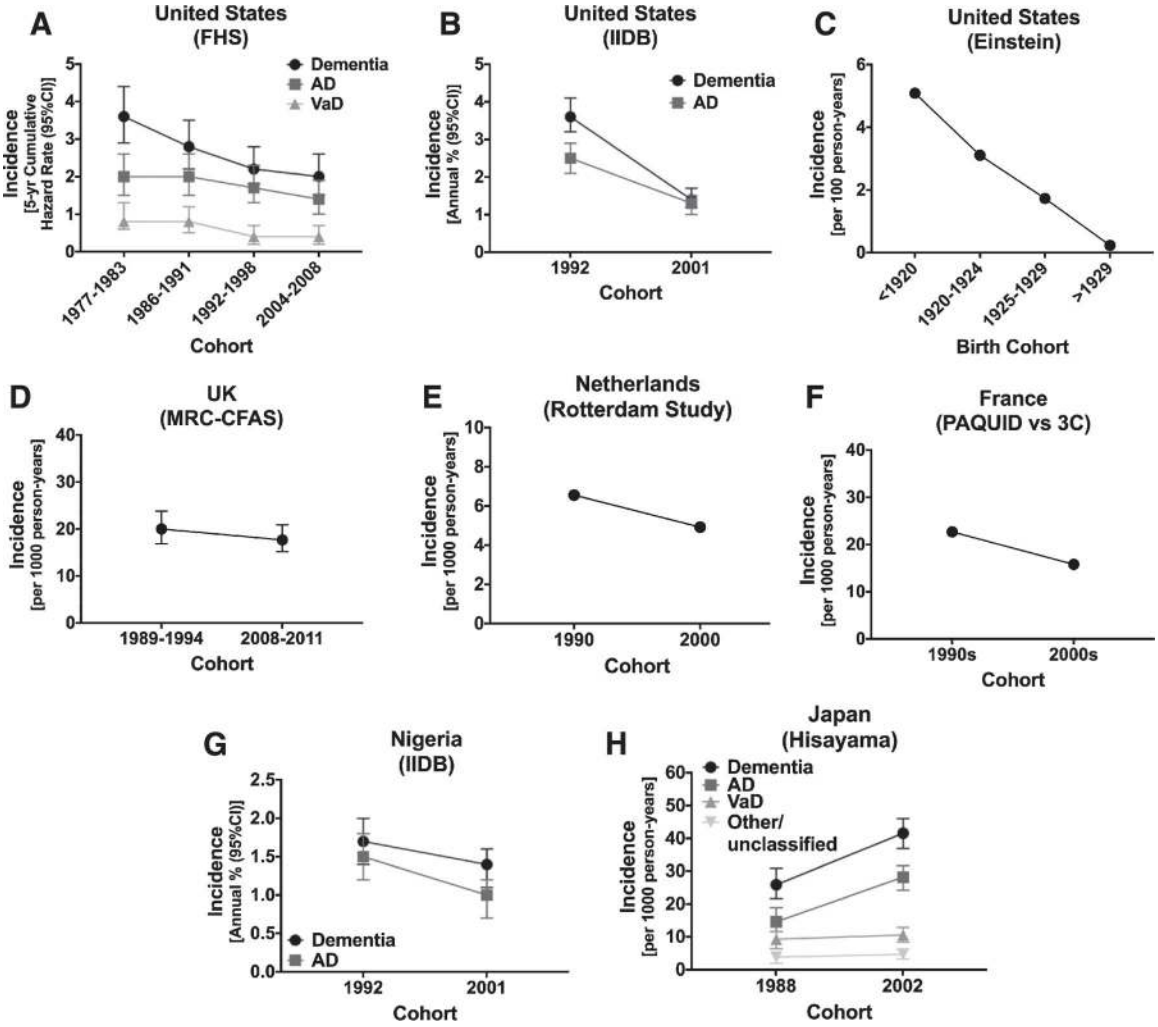

Fig. 2. Trends in dementia incidence.

Dementia incidence appears to be decreasing in the United States and Western Europe, but not in Japan. Graphs depicting the changing incidence of all-cause dementia (black circles), Alzheimer's disease (AD, steel-grey squares), vascular dementia (VaD, aluminum-grey triangles), and other/unclassified dementias (inverted silver-grey triangles). Error bars represent 95 confidence intervals (95%CI). A) Age- and sex-adjusted 5-year cumulative hazard rate (cumulative incidence per 100 persons over a period of 5 years) for all-cause dementia, AD, and VaD from the Framingham Heart Study (FHS) [29], conducted among people ≥65 years old in Framingham, Massachusetts (USA). B) Age-standardized annual incidence rate (%) for all cause dementia and AD from the 1992 and 2001 waves of the Indianapolis-Ibadan Dementia Project (IIDB) [26], conducted among ≥70 years old African-Americans in Indianapolis, Indiana (USA). C) Crude dementia incidence (expressed as rate per 100 person-years) of the serial birth cohorts from the Einstein Aging Study [35], conducted among people ≥70 years old in the Bronx County, New York (USA) (95%CI not available). D) Incidence rates per 1000 person-years from the Medical Research Council Cognitive and Function Aging Study (MRC-CFAS) I and II [28], conducted among people ≥ 65 years in three geographically defined areas from England (UK). E) Age-adjusted

incidence per 1000 person-years from the 1990 and 2000 waves of the Rotterdam Study [20], conducted among people aged 60 to 90 in Rotterdam, Netherlands. The 95%CI are not available, but the incidence rate ratio of the 2000 cohort relative to the 1990 cohort was 0.75 (0.56–1.02). F) Crude dementia incidence per 1000 person-years based on the algorithmic diagnosis from the Three-City Study (3C, 2000s cohort) compared with the Personnes Agées Quid study (PAQUID, 1990s cohort) [30], both conducted among people ≥65 years old in the Bourdeaux area of France. The 95%CI are not available, but the fully adjusted (for age, education, vascular risk factors and depression) hazard ratio of the 3C versus the PAQUID cohorts was 0.77 (0.61–0.97). G) Age-standardized annual incidence rate (%) for all cause dementia and AD in the 1992 and 2001 waves of the Indianapolis-Ibadan Dementia Project (IIDB) [26], conducted among ≥70 years old Yoruba in Indaba, Nigeria. H) Age- and sex-adjusted incidence per 1000 person-years for all-cause dementia, AD, VaD, and other/unclassified dementia from the 1988 and 2002 cohorts of the Hisayama Study [32], conducted among people ≥65 years old in Hisayama, Japan.

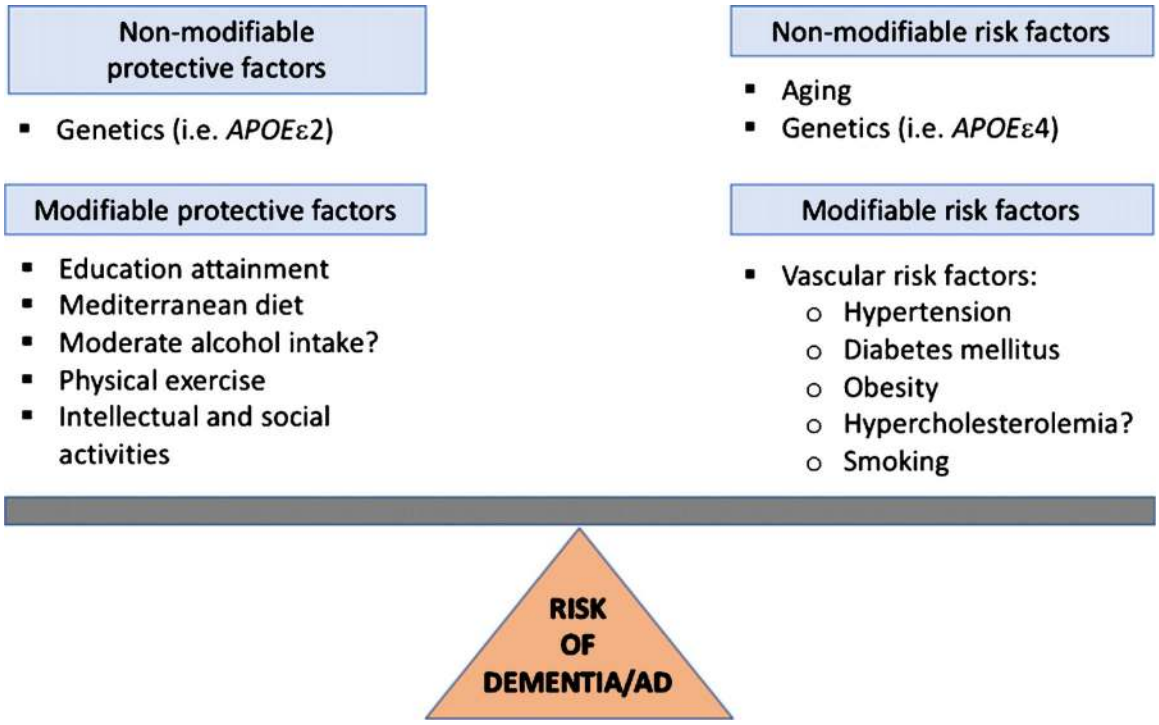

Fig. 3.
Schematic representing the risk of dementia and Alzheimer's disease as a balance between modifiable and unmodifiable protective and risk factors.