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Dementia and Alzheimer's disease: A new direction. The 2010 Jay L. Foster Memorial Lecture

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Abstract

Background—The modern era of Alzheimer's disease (AD) research began in the early 1980s with the establishment of AD research centers and expanded research programs at the National Institute on Aging.

Methods—Over the past 30 years, there has been success in defining criteria for AD and dementia, association of important genetic disorders related to premature dementia in families, the association of apolipoprotein-E₄, and measurement of incidence and prevalence and selected risk factors. However, prevention and treatment have been elusive.

Results—The development of new technologies, especially magnetic resonance imaging, positron emission tomography to measure amyloid in vivo in the brain and glucose metabolism, cerebrospinal fluid examination, better genetic markers, large-scale longitudinal epidemiology studies, and preventive clinical trials has rapidly begun a new era of research that offers opportunities to better understand etiology, that is, determinants of amyloid biology in the brain, neurofibrillary tangles, synaptic loss, and dementia.

Conclusions—There are three major hypotheses related to dementia: amyloid deposition and secondary synaptic loss as a unique disease, vascular injury, and “aging.” New research must be hypothesis-driven and lead to testable approaches for treatment and prevention.

Keywords

Epidemiology; Dementia; Amyloid; Hypertension; Aging

1. Background

The modern era of dementia, Alzheimer's disease (AD) research in the United States began in the early 1980s when Dr. Zaven Khachaturian at the National Institute on Aging successfully convinced the United States Congress that special funding for AD research centers was required to move the focus of dementia from primarily a social service–long-term care problem to a medical disease that could be prevented or treated. The second key was his success of recruiting some of the best scientists and university research facilities to transfer their focus to dementia and AD research. Similarly, coordinate efforts for research started to develop in Asian and European countries, especially in 1990s (e.g., European Community Concerted Action Epidemiology of Dementia [EURODEM]) [1].

There have been great strides over the past 25 years in describing the pathology, standardized clinical criteria, and the incidence, prevalence, and natural history of dementia across many populations. Major advances over these years included the identification and the recognition of apolipoprotein $\epsilon 4$ (*APOE* $\epsilon 4$) as an important genetic risk factor [2]. Although the initial cause of AD is unknown, the deposition of amyloid has a central role in the pathological process, and significant efforts have been devoted to understand metabolism [3–6]. The identification of the structure of the amyloid precursor protein (APP) and the “amyloid cascade” and major genetic disorders of APP and amyloid β ($A\beta$) in high-risk, early-age, familial AD was a very important observation [7–9]. Studies of dynamic metabolism of $A\beta$ and variables related to both increased production and decreased clearance were reported [10, 11]. There was an apparent long incubation period from normal to clinical AD [12, 13].

More recent advances in magnetic resonance imaging (MRI) of the brain in the 1980s opened the door to evaluation of brain morphological abnormalities, vascular disease, and subsequently functional changes (functional MRI) [14–17]. Epidemiological studies described the incidence and prevalence pathology of dementia, substantial increase with age, and the association with education and cognitive measures years before clinical diagnosis of AD [18–22]. More recent longitudinal epidemiological studies have clearly documented that the incidence of dementia increases, even after the age of 90 years [23]. The strong association of atrophy of the mesial temporal lobe regions and global brain atrophy measured by increased size of ventricles was shown in both case–control and longitudinal studies to be a strong predictor of both risk of dementia and death [24,25]. Positron emission tomography (PET) studies reported decreased glucose metabolism in these regions of interest in the brain [26]. Neuroimaging studies have pointed out the importance of the posterior cingulate gyrus and ventral striatum as critical areas in the pathology of AD; however, these regions were not studied in depth in early neuropathological studies [27,28]. Many clinical and epidemiological studies subsequently reported that dementia patients >80 years of age have a combination of both vascular and AD pathology [29–31].

Standardization of classifications of the type of dementia provided an opportunity to compare rates of disease across populations and over time [1,32–35]. Most studies showed that dementia and probable AD are prevalent in most population studies of older individuals [36,37]. Reported large differences in prevalence could be related to variation in cognitive measurements, especially with specific cut-points on initial screening being followed by more detailed evaluation as compared with detailed cognitive testing of the whole cohort [38–40]. Similarly, prevalence could be greatly impacted by different case-fatality rates after dementia diagnosis.

Very high-risk individuals were identified as having mild cognitive impairment based on changes in cognitive tests, especially in memory, without the mild disability that led over time to clinical dementia. Furthermore, measures of MRI, especially smaller size of hippocampus and other brain regions, and vascular changes measured years before were independent predictors of risk of dementia [41,42].

There was a substantial negative to these advances. Specific lifestyle and environmental agents that substantially increased or decreased incidence or prevalence of dementia or AD have not been identified. Unique populations with low incidence and prevalence of dementia, with the exception of possibly two examples in India [43] and Nigeria [44], have not been reported.

There was little evidence to suggest “common source” environmental or lifestyle variables, nutrition, toxic chemicals, infectious agents, trace minerals, vitamin deficiencies, and others

that increased or decreased risk of dementia [45–47]. The major breakthrough in identifying the important genetic associations in amyloid metabolism and *APOE* ϵ 4 has not been followed up with any new important genetic risk with similar magnitude of effect as *APOE* ϵ 4. Newer genetic markers were related to cholesterol metabolism and inflammation in the brain [48].

Clinical and observational epidemiological studies have failed to identify specific risk factors or interventions that have a consistent effect on either the incidence or natural history of dementia. Midlife elevated blood pressure (BP) [49] and cigarette smoking [50] and, in some studies, diabetes mellitus (DM) [51] have been associated with increased risk of dementia and possibly AD. After severe head trauma, there was substantial risk of dementia in some studies [52]. Many studies report that cognitive activity and exercise, especially walking, may lower risk of dementia [53,54].

Clinical trials of disease-modifying therapies and/or lifestyles, that is, nonpharmacological interventions, to prevent or slow progression of AD have been unsuccessful [55]. Treatment of hypertension (HTN) in a few studies has been associated with decreased risk of dementia, but whether treatment of HTN prevents AD is not substantiated by past clinical trials [56].

The conclusion of these first 25 or so years of research is that we can describe the pathology and natural history of AD and other dementias, measure cognition and structural brain abnormalities, document major single gene effects on amyloid cascade, the importance of apolipoprotein E (*APOE*), and have a few symptomatic drug therapies for moderating cognition. We have not identified determinants of increase or decrease in amyloid plaques or soluble amyloid in the brain, except age. The decline in brain size likely due to loss of synapses with age has been shown in mostly cross-sectional and longitudinal studies but, except for age, external factors that increase or decrease brain synapses loss have not been identified [57].

The absence of well-defined risk factors and lack of therapies has led some critics to suggest that dementia among older individuals >80 years of age, the majority of incident dementia, is part of the normal or accelerated aging process and should not be labeled as a unique disease, such as AD [58]. It is possible that the dementia at younger ages, <80 or so, is a unique disease, whereas the syndrome seen among older individuals is primarily because of loss of synapses in the brain during aging. The high prevalence of amyloid deposition in the brain in older individuals could be part of the normal aging process. This dichotomization of disease may have profound implications for the treatment of AD, anti-amyloid therapies, that is, prevention of deposition of amyloid, could have better effects on younger individuals, whereas in older patients, only treatment of symptoms, disability management, or preventing “aging” will be useful [59].

2. New era in research

Fortunately, AD and dementia research is now at an exciting and new crossroads due, in large part, to: (1) improved imaging of the brain with MRI that can now be applied to large populations to predict dementia [60]; (2) measurement of markers in the cerebrospinal fluid (CSF) that may predict the risk of dementia similar to the measurement of lipoproteins in blood and the prediction of coronary heart disease (CHD) [61–64]; (3) improved genetic methodologies [65,66]; (4) PET imaging with specific ligands that can measure amyloid distribution in the brain in vivo and better methods of measuring metabolism in the brain [67–69]; and (5) successful implementation of both large epidemiological longitudinal studies and clinical trials of primary prevention.

These new technologies have several major advantages. First, they likely will provide better characterization of larger numbers of individuals at very high risk of dementia, especially in the short term. Second, in unique populations, it is now possible to study both the distribution of amyloid in the brain in vivo and relationship to risk of clinical dementia over time. Furthermore, pharmacological and nonpharmacological therapies could be directly tested both to prevent and to delay the progression of amyloid in the brain and effects on brain morphology and cognitive decline [70,71].

First, pharmacological therapies that could delay the onset of dementia for several years could result in a substantial reduction in the prevalence of AD because the patients will die of another cause before they develop AD (not a very happy thought). A second and far more important approach will be the application of these new technologies to understand the etiology of AD, that is, to determine whether there are specific lifestyle and environmental factors that interact with host susceptibility, for example, genetics, to modify the incidence of AD and dementia. Specific drug therapy or even lifestyle changes might reduce incidence of dementia.

3. Can we prevent AD?

There are relatively few diseases that have been successfully prevented or even controlled without an understanding of specific etiology. It is possible that by just being able to measure the extent of disease, for example, amyloid plaques and neurofibrillary tangles, a drug therapy could be developed without identification of any specific etiological risk factors that lead to the development of amyloid deposition and/or tangles or structural changes in the brain, or loss of synapses. Would drugs that decrease the amount of A β reduce risk of dementia irrespective of the determinants of the increased A β and secondary changes in brain structure? Is A β deposition in the brain similar to coronary atherosclerosis? Drugs that reduce blood apolipoprotein-B lipoproteins prevent the development and progression of atherosclerosis, for example, statins [71], and reduce the risk of coronary artery disease [72].

Is the amyloid deposition in brain a secondary phenomenon, such as calcium measured in atherosclerotic plaques? Calcium is a marker of atherosclerosis [73]. Higher calcium scores are a powerful predictor of the risk of heart attack and total mortality [74]. Individuals at high genetic risk of atherosclerosis have more calcium in the arterial wall, that is, higher calcium scores. There is no evidence that reducing the amount of calcium in plaque, independent of reducing extent of atherosclerosis, will decrease incidence of cardiovascular disease (CVD) [75].

The identification of specific etiological factors is much more likely in the long term to have a major impact on the incidence, prevalence, and disability because of AD and dementia. This approach, however, assumes that there are only a few lifestyle and environmental variables that contribute along with genetic host susceptibility to the amyloid cascade, that is, attributable risk, of AD and dementia. To date, as noted previously, this approach has been an abysmal failure, perhaps because of the lack of specific objective measures of the extent of amyloid disease in the brain in vivo and measurement of brain morphological changes and, even more important, the inability to adequately measure in vivo the key biological risk factors, including CSF versus blood analysis, brain lipid metabolism, inflammation, and oxidative stress [76].

The long incubation period to the risk of AD may be a major stumbling block in the attempt to identify the key risk factors. Lifestyle and environmental variables that lead to the development of and regression of amyloid in the brain may have been identifiable 10 or 20

or more years before the clinical onset of AD and dementia but not at time of clinical diagnosis of dementia.

4. Etiological hypotheses

At present, there are several major hypotheses not mutually exclusive that are related to the etiology of late-onset AD, which are discussed in the following text.

4.1. Environment-polygenic risk disorder

AD is a unique disorder owing to specific host–environmental agents in “high genetic risk individuals.” This hypothesis also suggests that younger and older age dementias with AD pathology may have similar etiologies but dementia at older age is a function of a longer incubation period, lower exposure to causal risk factors, lesser genetic or host susceptibility, and “better brain reserve” that slows cognitive decline to diagnosis of dementia in the presence of amyloid disease and neurodegeneration. This hypothesis is also consistent with the recent suggestion of a dynamic metabolism of A β in the brain with earlier age dementia associated with increased production of A β -42 as a primary defect and failure of clearance of A β -42 at older ages [77]. The very striking association of *APOE* ϵ 4 with amyloid deposition in the brain in vivo using PET in older asymptomatic individuals documents the very strong evidence for the critical role of *APOE* in amyloid metabolism [78,79].

The observation of increased amyloid levels, especially soluble A β -42, in the brain of young individuals, predominantly *APOE* ϵ 4 carriers, with excised brain tissue within a short period after severe traumatic brain injury suggests that injury to the brain possibly from a variety of sources may be the primary environmental stimuli for increased A β production and deposition leading to dementia [80,81]. For example, it is possible that small artery vascular injury secondary to elevated BP, ischemic lesions, small infarcts, and white matter abnormalities may be the injury stimulus for A β -42 production [82]. The very high prevalence of vascular stiffness, elevated systolic BP and vascular lesions in the brain, white matter lesions, and infarcts in most populations [83] could be the reason for the apparent very high prevalence of AD in most studies.

4.2. Cerebrovascular disease

The second hypothesis therefore is that vascular disease, presumably small vessel ischemic damage and secondary inflammation, oxidative stress, is the primary cause of vascular dementia and AD by increasing the production of A β -42 in response to injury. The angiogenesis hypothesis proposes that injury to blood–brain vessels primarily because of elevated BP leads to localized small vessel thrombosis, injury and inflammation, increased APP and A β -40 and A β -42 plaque formation, neuronal dysfunction, brain atrophy, and dementia [82,84–88]. Pathology studies have found a high prevalence of small brain infarcts and white matter abnormalities at autopsy among individuals who had premorbid AD and dementia [89–91]. The higher prevalence of vascular disease in the brain may result in an increased premorbid diagnosis of AD, dementia with lesser amyloid plaques and neurofibrillary tangles [92]. There is a substantial increased risk of dementia after a stroke [93].

Higher BP has major effects on smaller blood vessels, especially in the brain and kidneys. White matter abnormalities in the brain and infarcts are very strongly associated with BP levels and with the incidence and prevalence of dementia in many studies [94–96].

Trials of antihypertensive drug therapies to lower BP have not consistently demonstrated a reduction in the risk of dementia [56]. The basic problems with these trials have been as follows: First, their limits to older individuals in whom the increase in amyloid secondary to

the vascular injury may have already occurred. Second, the lack of high-quality measures of cognitive change and dementia diagnosis in the clinical trials. Third, competing risks can very substantially affect outcome of clinical trials and longitudinal observational studies, especially among older and higher risk individuals. For example, assume a trial of BP therapy results in a lower incidence of stroke and other CVD in the intervention as compared with the control group. Individuals at higher risk of stroke as well as dementia have greater extent of brain vascular disease at baseline in the trial, that is, number of infarcts and white matter disease. In the intervention group, treatment of BP reduced the risk of stroke and CVD. Survivors in the intervention group are therefore at higher risk of dementia, that is, they have brain vascular disease leading to more amyloid plaques. In contrast, in the control group, individuals are more likely to have a stroke, congestive heart failure, renal failure and/or die, or be lost to follow-up endpoints because of the adverse effects of less treatment of their HTN. The study results would therefore suggest that the antihypertensive drug therapy might increase the risk of dementia or at least have no benefit while substantially reducing stroke, renal failure, and congestive heart failure.

A small percentage of older individuals, perhaps 20%, will have persistent low systolic BP, no chronic diseases, and adrenal insufficiency, to account for the low BP. Do such individuals in these populations have a lower prevalence of amyloid deposition on PET, MRI vascular changes and brain morphological abnormalities, as well as better cognitive functioning and risk of dementia?

How can we determine whether elevated BP alone or in combination with DM or cigarette smoking, or other factors related to ischemic brain injury are major determinants of secondary amyloid deposition and dementia? First, the modern tools of PET, MRI, and CSF examination in unique populations may provide important answers. Do populations in which systolic BP does not increase with age and which have low prevalence of elevated systolic BP have a very low age-specific incidence or prevalence of dementia and lesser amounts of amyloid on PET and absence of brain vascular disease? We would hypothesize that populations in which systolic BP and vascular stiffness do not increase with age will have a low prevalence of amyloid deposition and vascular disease in the brain, morphological brain changes such as increase in ventricular size (i.e., brain atrophy or specific posterior temporal lobe atrophy, even in older age groups), and a lower incidence of dementia.

Do the very low dementia prevalence populations in Nigeria and India who likely have lower BP have an extremely low prevalence of amyloid deposition in comparison with other populations? The identification of a well-defined large population in which amyloid plaques do not occur even to advanced age would probably be the single biggest breakthrough in AD clinical epidemiology research, especially if there was also low prevalence in relationship to *APOE* ϵ 4 genotypes or other genetic markers.

Populations in Japan that have very high intake of omega-3 fatty acids, especially docosahexaenoic acid, might have a lower prevalence of amyloid plaques or brain morphological changes on MRI and lower incidence or prevalence of AD. A few epidemiological studies suggest similar incidence of dementia in Japan and in the United States [97,98]. Vascular disease may account for a higher prevalence of dementia in Japan [99].

We have previously shown that the post-World War II populations in Japan have low prevalence of atherosclerosis and rates of CHD as compared with populations in the United States or Japanese migrants to Hawaii, likely related to their high omega-3 consumption [100]. If the elevated BP and vascular disease in the brain are important precipitants of amyloid deposition, then we would find a similar prevalence of amyloid in the Japanese

population associated with high vascular burden. Conversely, if the very high omega-3 dietary intake prevents amyloid deposition, then we would find a much lower prevalence of amyloid in well-defined population samples of older individuals in Japan [101–103].

We can now do much better trials of antihypertensive drug therapies, including baseline measures of brain structure, PET, amyloid, and CSF examinations. We could then determine the effects of antihypertensive drug therapy on changes in the brain structure, in the deposition of amyloid, and in cognition. Such studies will obviously be expensive but will have tremendous potential because drugs are already available, are safe, are available at low cost, and are widely used in the population. Furthermore, it is probably much more worthwhile to do one or two more expensive studies, which provide a higher probability of a true result, than many less expensive studies that may lead to the wrong conclusions, that is, not effective therapies for dementia prevention.

The hypothesis that brain injury secondary to ischemia leads to amyloid deposition and AD, especially in genetic-susceptible hosts, is probably the most important question related to treatment and prevention of elevated BP. It remains on the backburner of most major HTN clinical trials.

A major determinant of elevated BP in many populations is high salt intake [104]. Is higher salt intake beginning early in life a major nutritional risk factor for AD at age 70 or 80? Higher potassium intake has also been reported to reduce brain vascular disease [105].

4.3. Atrial fibrillation

Atrial fibrillation (AF) has become more prevalent in populations with increasing age. Individuals with AF are known to live longer. There is an increased risk of dementia among patients with AF and stroke, but whether silent brain infarcts in patients with AF increase amyloid pathology and dementia can now be determined with the advent of new technologies and better follow-up studies [106].

4.4. Abnormal glucose metabolism

Another important issue is whether abnormal glucose metabolism, either hyperinsulinemia or DM, is an independent risk factor for dementia or, more likely, contributes to the risk of dementia secondary to the high prevalence of HTN and vascular disease associated with both DM and insulin resistance [107,108].

4.5. Cholesterol metabolism

The brain contains probably 25% of the total body cholesterol, most of which is produced and metabolized in the brain [109,110]. It is also likely that cholesterol metabolism in the brain plays a critical role in both the transport and metabolism of A β . Elevated intercellular cholesterol in neurons probably increases synthesis of A β -42 [111]. Measurement of cholesterol metabolism in the brain in vivo is extremely difficult. Measurement of peripheral metabolism, that is, blood cholesterol metabolism, provides little knowledge of brain cholesterol metabolism. Ischemic injury in the brain and inflammation could possibly result in elevated brain cholesterol and secondary amyloid production [112,113].

There is also little evidence in humans that the powerful statin drugs, including those that are lipophilic and cross the blood–brain barrier (BBB), reduce the incidence of dementia [114,115]. The studies have been done primarily in older individuals who may not benefit from this drug therapy, especially if they already have AD or extensive amyloid plaque in the brain. Furthermore, most of the studies are short term and not specifically focused on prevention of dementia.

Lipoprotein-related receptor proteins play an important role in transport of amyloid out of the brain, across BBB. *APOE* and apolipoprotein J, clusterin, also play critical roles in both cholesterol and A β transport. Factors including variation in lipoprotein-related receptor protein and clusterin levels may be important determinants of AD [11,116–118]. A β is also a ligand for the soluble form of the receptor for advanced glycation endproducts (sRAGE), resulting in transport of A β from peripheral circulation through BBB to the brain [119]. Higher levels of sRAGE have been linked to lower risk of both CVD and dementia [109,120]. Will agents that increase sRAGE reduce A β in the brain? Is there a need for a trial to determine whether specific statin therapy prevents deposition of amyloid and possibly dementia in the longer term? Would younger individuals identified as high genetic risk *APOE* $\epsilon 4/\epsilon 4$ have reduced amyloid deposition after being given lipophilic statins that cross BBB versus statins that do not as compared with no statin therapy?

4.6. Inflammation

Injury to the brain secondary to head trauma or vascular lesions could stimulate a secondary inflammatory response. The amyloid hypothesis presumes an inflammatory response to the amyloid deposition, the primary determinant of neuronal injury. This is very similar to the importance of inflammation and progression of atherosclerotic plaques in the arteries. Human studies of inflammation and dementia have been unrewarding. There is relatively little evidence that elevated inflammatory markers or unique genetic polymorphisms of cytokines or other inflammatory markers are risk factors for dementia or amyloid deposition [121,122]. There is little evidence that any of the major systemic and inflammatory diseases, such as rheumatoid arthritis, lupus, and inflammatory bowel disease, are associated with increased risk of amyloid pathology, AD, or dementia. They may be associated with cognitive decline. All of these inflammatory diseases are associated with increased risk of CHD. None of these populations have been studied with the new technologies available for measuring the brain changes, especially deposition of amyloid, brain morphology, and cognitive decline. Thus, a potentially productive research effort may be to determine whether there is increased amyloid deposition as well as brain morphological changes in dementia among older individuals with these systemic inflammatory diseases.

Traditional anti-inflammatory drugs have not generally resulted in substantial decrease in incidence or disability, at least among patients with AD or mild cognitive impairment [123]. However, some of the newer more potent drugs, for example, cytokine inhibitors, may, if they cross the BBB, have a direct effect on reducing either the extent of amyloid or the effects of amyloid on the risk of dementia, especially if tried early in the evolution of amyloid disease [124]. For example, it might be interesting to evaluate effects of methotrexate on brain amyloid deposition on risk of dementia in proposed new trials of CVD prevention.

5. AD and normal aging

The third and default hypothesis for AD is that it is a part of a “normal aging process.” AD-type dementia is of two types: (1) premature dementia, that is, a genetic disorder; and (2) dementia because of aging. The aging hypothesis can be further subdivided, such that amyloid plaques and neurofibrillary tangles are secondary to the aging process, or that the primary aging effect is on neurons, synapses, and brain structure independent of the plaques and neurofibrillary tangles. A further important aspect of the “normal aging hypothesis” is that early age factors, including intelligence, childhood education, occupation, and activities such as cognitive skills and social interactions, lead to an expanded brain reserve [125,126]. The aging process that results in loss of synapses and possible neurons will be far more detrimental for those with little brain reserve as compared with those with high brain reserve [127]. Support for the aging hypothesis is based first on the striking increase in incidence

and prevalence of dementia and AD with aging; second, the absence of identification of any other risk factors except possibly education and socioeconomic status; third, the absence of any substantial geographic variation in both AD pathology and incidence across most populations that have been studied, suggesting the absence of a unique lifestyle or environmental determinant; and fourth, the high prevalence of amyloid plaques in the brain among older individuals even without clinical diagnosis of AD.

An interesting comparison might be amyloidosis in the heart, genetic mutation in transthyretin (TTR) is an autosomal dominant fatal disorder related to increased amyloid derived from a mixture of mutant and normal TTR [128]. In contrast, senile systemic amyloidosis is caused by amyloid deposition of the wild-type or “normal” TTR. Familial amyloid heart disease is a progressive fatal disorder that affects both the heart and the nervous system, whereas senile systemic amyloidosis in elderly individuals results in slowly progressive symptomatology [128,129]. Premature AD could be caused by overproduction of abnormal folded proteins and the inability of the chaperones to clear the proteins [130]. The cause of the disease in older individuals could be the inability to clear the proteins from the brain because of aging, despite normal production of A β -40 and -42 [77].

Amyloid disease in the brain could be similar to atherosclerosis. The prevalence increases with age in many populations, not necessarily because of aging but because of the level of key risk factors and the long incubation period of the disease.

If the amyloid brain disease in older individuals is “part of the aging process,” then the next question is whether aging in brain and systemic nonbrain aging are parallel within an individual or group of individuals. If so, then the key to prevention and treatment of amyloid brain disease should focus on better understanding and prevention or treatment of the aging processes. For example, a therapy aimed only at the amyloid disease in the brain of older individuals would probably have a relatively small benefit. Such individuals would likely have substantial disability related to systemic aging, sarcopenia, and frailty [131,132].

In the Cardiovascular Health Study, we attempted to determine dementia in older (aged ≥ 80) and younger individuals (< 80) at years of onset in relationship to various risk factors and characteristics. The risk factors for dementia at < 80 and > 80 years of age were similar, but the risk factors were much more powerful predictors, that is, *APOE* $\epsilon 4$, ventricular size, cognitive test scores, in the younger as opposed to the older age groups [133].

This issue of whether dementia in the older versus the younger age groups is a different disease has huge implications with regard to therapeutic approaches, for example, clinical trials. Such studies need to include older participants likely to develop disease outcome within a relatively short period to have a reasonable sample size and cost of the study. However, if the key risk factors and pathophysiology in the younger age groups are different than in the older age groups, then a clinical trial in older individuals > 75 years may produce a negative result, whereas a similar therapeutic or preventive agent in the younger population may prevent or delay the onset of dementia. For example, a drug that prevents the deposition of amyloid, that is, slows the production of amyloid plaques in the brain, may be a potentially highly efficacious agent in younger age groups. In older individuals, a drug may have little or no effect where amyloid plaques may already be prevalent or where the primary problem is the inability to clear the amyloid. Similarly, a drug that modifies the effect of the amyloid plaque (i.e., the inflammation, oxidative stress) on neurons and synapses may be effective for individuals who already have substantial disease in the brain but may be of little to no effect, at least in the short term, in preventing the development of amyloid plaques.

6. “Brain reserve”

A very important question related to aging is the concept of “brain reserve,” defined as the brain’s capacity to buffer the effects of multiple insults, for example, amyloid deposition and vascular disease. An alternative hypothesis that combines both the aging and specific amyloid disease hypotheses is that the deposition of A β -42 remains the basic pathology of the disease but the subsequent cognitive changes in relationship to the extent of amyloid are a function of the initial brain reserve, that is, age, intelligence, education, and subsequent learning experiences, which gradually decline with aging of brain structure, that is, loss of brain synapses. This, over time, ultimately results in a clinical diagnosis of dementia. One of the keys to the prevention of late-age dementia may be childhood and life-course skills. However, such a hypothesis is unlikely to have much utility in preventing dementia among current cohorts of individuals of age 70 to 80 and 80 to 90 years [134,135]. Is dementia similar to osteoporosis in which peak bone mass at 35 years of age and decline over time predict risk of osteoporotic fracture?

7. Risk factors for AD and normal aging

A problem in studying the aging hypothesis is how to separate the effects of aging from disease. Variables that are affected only by aging should change in almost all populations with increasing age and have a similar frequency across populations. Many of the early-age risk factors for brain reserve are also associated with longevity. Individuals identified within the populations by the prevalence of genetic determinants of aging, major genetic disorders of premature aging, should have a higher prevalence of early age dementia and brain abnormalities. The number of such studies is very small and difficult to interpret. The new available technologies may make it possible to do collaborative projects across major centers to evaluate amyloid plaques, brain morphologies, and CSF changes among families or individuals with premature aging syndromes [136].

There are few markers of possible brain aging that could be compared within and across populations in relationship to both dementia and, most importantly, to brain pathology, MRI, and PET. This might include measures such as telomere length change over time, lens opacities, especially in younger individuals, modifications of insulin-like growth factors and its binding proteins, mitochondrial functional changes, immune marker characteristics, and specific genetic markers of aging [127,137–141].

It is possible, although unlikely, that deficiency of an important nutrient, for example, nicotinic acid (i.e., pellagra) could increase the rate of synaptic loss in the brain. Loss of receptors with aging could lead to an increased unmet requirement for a specific nutrient with increasing age, especially in combination with genetic host-susceptibility results in a more rapid decline in synapses in the brain. The identification of a specific nutritional or toxic environmental agent will be very difficult and may depend on both good animal models and studies in unique human populations, such as families with a high risk of dementia.

Another interesting approach is to study individuals >90 years of age who have survived without development of dementia or severe disability. In the Cardiovascular Health Cognition Study, only about 6% of individuals who survived to >90 years were considered to be cognitively normal based on longitudinal analysis, without significant physical disability. Longitudinal studies can determine whether the individuals with asymptomatic in vivo brain amyloid over the short term have increased risk of dementia with or without brain morphological abnormalities, and whether such individuals with amyloid as compared with those without amyloid have shorter lifespans (aging), even independent of development of clinical dementia. A key question is what factors protected this unique group of healthy

older individuals from the larger cohort who developed dementia or died from other causes. It is probable that no large single study can identify a large enough group of individuals with longitudinal data, especially key risk factors, cognitive measurements, and MRI.

Caloric restriction and increase in nutritional response-signaling molecules have been shown to increase longevity in monkeys. The small Japanese women now in their 90s represent the best model of human caloric restriction and successful aging. If they have the same prevalence of AD or amyloid plaque as other populations, drugs aimed at these signaling molecules, as in caloric restriction, are unlikely to be very effective in preventing AD [142].

8. Discussion and conclusions

We have entered a new era of dementia and AD research. The driving force for this new era is the development of advanced technologies, MRI imaging of the brain, PET imaging for the in vivo measurement of amyloid plaques in the brain, and CSF measurements that identify important risk markers for AD and dementia. These new technologies have led to proposed changes in diagnostic criteria that separate the brain changes on PET and MRI from cognition and disability. These new technological advances can be rapidly built into successful longitudinal epidemiological studies, genetic analyses, and clinical trials [143].

The recognition that amyloid deposition in the brain is a dynamic process related to increased production, metabolism, and removal of amyloid in the brain may provide leads for new therapeutic approaches. The new era will be built on the substantial successes of the AD research program that began in the 1980s that led to the development of AD research centers, community-based epidemiological studies, longitudinal studies of risk factors for dementia and AD, improvement in measurements of cognition, and standardization of the diagnosis of the specific types of dementia and the companion ongoing basic science programs, including the development of better animal models.

The challenge is to test new hypotheses and not just continue descriptive studies using better and better tools, better and better MRI technology, more CSF analysis, and more and more descriptions of the amount of amyloid in the brain.

Therefore, we must begin to ask good specific questions and test hypotheses that will lead, in a reasonable amount of time, to effective preventive and therapeutic trials. Very few diseases have been successfully controlled, that is, reduced morbidity and mortality, except by prevention. What are the determinants of amyloid deposition and AD? Are the risk factors for amyloid deposition in the brain similar to other protein folding disorders, such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis? What factors increase production or decrease clearance of amyloid in the genetically susceptible host? Is head trauma or concussion, even minor events, a more important determinant of amyloid deposition and dementia than we suspect in genetically predisposed subjects? If so, when, or at what age, are these episodes of head trauma critical for the development of the disease? Is vascular disease in the brain an important determinant of "injury" and increased A β production, as some have suggested? If the median population BP throughout life remains at <120 mm Hg, would the epidemic of AD be substantially reduced? Are there populations of older individuals who have both low incidence and prevalence of dementia and absence of amyloid deposition and absence of consistent brain MRI changes of dementia? Are there unique risk factors and determinants for the brain morphological changes, that is, loss of synapses, especially in the post-temporal lobe, for example, independent of the risk factors that determine the deposition of amyloid? Are there important genetic determinants, perhaps, that interact with specific environmental exposures?

Successful clinical trials could be based on a better understanding of the risk factors, whether they be lifestyle/environmental, primary genetic, or related to the aging process.

A major challenge in AD and dementia research will clearly be the success or lack of success in merging the new technologies to epidemiological and genetic studies and clinical trials.

The price, availability, and improved quality of technologies and their application to studies may prevent the potential for impacting on the growing problem of dementia in an aging population. Quality measurements of dementia and brain morphological changes, and amyloid, should be an integral component of studies of aging and dementia, especially large longitudinal studies and clinical trials of new therapies.

There is an increasing emergency in finding a prevention or treatment for AD and dementia because of the aging of the populations [144]. It would be nice to believe that just being able to quantify the amount of amyloid in the brain in vivo or the specific brain changes, CSF abnormalities, and better cognitive testing will somehow produce effective therapies. History suggests this is unlikely but possible. Usually, better understanding of etiology only results in successful prevention and treatment. Somewhere out there, there may be “statins” or lifestyle factors for amyloid metabolism and loss of brain synapses that will dramatically change the incidence of dementia. The big question is whether we can use these new technologies, clinical skills, and resources (money) to find them.

References

1. Jorm AF, Jolly D. The incidence of dementia: a meta-analysis. *Neurology*. 1998; 51:728–733. [PubMed: 9748017]
2. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer’s disease in late onset families. *Science*. 1993; 261:921–923. [PubMed: 8346443]
3. Herrup K. Re-imagining Alzheimer’s disease: an age-based hypothesis. *J Neurosci*. 2010; 30:16755–16762. [PubMed: 21159946]
4. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer’s disease. *Lancet*. 2011; 377:1019–1031. [PubMed: 21371747]
5. Querfurth HW, LaFerla FM. Alzheimer’s disease. *N Engl J Med*. 2010; 362:329–344. [PubMed: 20107219]
6. Walsh DM, Selkoe DJ. A beta oligomers: a decade of discovery. *J Neurochem*. 2007; 101:1172–1184. [PubMed: 17286590]
7. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer’s disease. *Nature*. 1991; 349:704–706. [PubMed: 1671712]
8. Selkoe DJ. Alzheimer’s disease: genes, proteins, and therapy. *Physiol Rev*. 2001; 81:741–766. [PubMed: 11274343]
9. Tanzi RE, Bertram L. Twenty years of the Alzheimer’s disease amyloid hypothesis: a genetic perspective. *Cell*. 2005; 120:545–555. [PubMed: 15734686]
10. Holtzman DM. In vivo effects of ApoE and clusterin on amyloid- β metabolism and neuropathology. *J Mol Neurosci*. 2004; 23:247–254. [PubMed: 15181253]
11. Sagare A, Deane R, Bell RD, Jonson B, Hamm K, Pendu R, et al. Clearance of amyloid- β by circulating lipoprotein receptors. *Nat Med*. 2007; 13:1029–1031. [PubMed: 17694066]
12. Saxton J, Lopez OL, Ratcliff GR, Dulberg C, Fried LP, Carlson MC, et al. Preclinical Alzheimer disease. Neuropsychological test performance 1.5 to 8 years prior to onset. *Neurology*. 2004; 63:2341–2347. [PubMed: 15623697]
13. Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Arch Neurol*. 2011; 68:351–356. [PubMed: 21403020]

14. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the Framingham heart study: establishing what is normal. *Neurobiol Aging*. 2005; 26:491–510. [PubMed: 15653178]
15. Breteler MM, van Sweiten JC, Bots ML, Grobee DE, Claus JJ, van den Hout JH, et al. Cerebral white matter lesions, vascular risk factors and cognitive function in a population-based study: the Rotterdam Study. *Neurology*. 1994; 44:1246–1252. [PubMed: 8035924]
16. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Risk factors for dementia in the Cardiovascular Health Cognition Study. *Neuroepidemiology*. 2003; 22:13–22. [PubMed: 12566949]
17. Alsop DC, Detre JA. Multisection cerebral blood flow MR imaging with continuous arterial spin labeling. *Radiology*. 1998; 208:410–416. [PubMed: 9680569]
18. Gao S, Hendrie HC, Hall KS, Hui S. The relationship between age, sex and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry*. 1998; 55:809–815. [PubMed: 9736007]
19. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartiques JF, et al. Neurologic Diseases in the Elderly Research Group. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. *Neurology*. 2000; 54:S10–S15. [PubMed: 10854355]
20. Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ*. 2010; 341:c3885. [PubMed: 20688841]
21. Purnell C, Gao S, Callahan CM, Hendrie HC. Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. *Alzheimer Dis Assoc Disord*. 2009; 23:1–10. [PubMed: 18703981]
22. Zaccai J, Ince P, Brayne C. Population-based neuropathological studies of dementia: design, methods and areas of investigation—a systematic review. *BMC Neurol*. 2006; 6:2. [PubMed: 16401346]
23. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: the 90+ Study. *Ann Neurol*. 2010; 67:114–121. [PubMed: 20186856]
24. Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lu A, et al. Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia. *Alzheimer Dis Assoc Disord*. 2007; 21:14–24. [PubMed: 17334268]
25. Kuller LH, Arnold AM, Longstreth WT Jr, Manolio TA, O'Leary DH, Burke GL, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the Cardiovascular Health Study. *Neurobiol Aging*. 2007; 28:1307–1315. [PubMed: 16857296]
26. Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment. Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology*. 2003; 60:1374–1377. [PubMed: 12707450]
27. Convit A, de Sasis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. *Neurobiol Aging*. 2000; 21:19–26. [PubMed: 10794844]
28. Holland D, Brewer JB, Hagler DJ, Fennema-Notestine C, Dale AM. Alzheimer's Disease Neuroimaging Initiative. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci USA*. 2009; 106:20954–20959. [PubMed: 19996185]
29. Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, et al. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. *Neurology*. 2005; 64:1548–1552. [PubMed: 15883315]
30. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007; 69:2197–2204. [PubMed: 17568013]
31. Polvikoski T, Sulkava R, Myllykangas L, Notkola IL, Niinisto L, Verkkoniemi A, et al. Prevalence of Alzheimer's disease in very elderly people: a prospective neuropathological study. *Neurology*. 2001; 56:1690–1696. [PubMed: 11425935]

32. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
33. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989; 39:1159–1165. [PubMed: 2771064]
34. Khachaturian ZS. Diagnosis of Alzheimer's disease: two decades of progress. *Alzheimer Dement*. 2005; 1:93–98.
35. Prince M, Ferri CP, Acosta D, Albanese E, Arizaga R, Dewey M, Gavrilova SI, et al. The protocols for the 10/66 dementia research group population-based research programme. *BMC Public Health*. 2007; 7:165. [PubMed: 17659078]
36. Rodriguez LJ, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob KS, et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *Lancet*. 2008; 372:464–474. [PubMed: 18657855]
37. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M. for the 10/66 Dementia Research Group. Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet*. 2003; 361:909–917. [PubMed: 12648969]
38. Storandt M, Morris JC. Ascertainment bias in the clinical diagnosis of Alzheimer disease. *Arch Neurol*. 2010; 67:1364–1369. [PubMed: 21060013]
39. Wilson RS, Weir DR, Leurgans SE, Evans DA, Hebert LE, Langa KM, Plassman BL, Small BJ, Bennett DA. Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement*. 2011; 7:74–79. [PubMed: 21255745]
40. Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement*. 2011; 7:80–93. [PubMed: 21255746]
41. Jack CR, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999; 52:1397–1403. [PubMed: 10227624]
42. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2006; 256:183–194. [PubMed: 15324362]
43. Chandra V, Ganguli M, Pandav R, Johnston J, Belle S, DeKosky ST. Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. *Neurology*. 1998; 51:1000–1008. [PubMed: 9781520]
44. Hendrie HC, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Gureje O, et al. Incidence of dementia and Alzheimer disease in 2 communities. Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA*. 2001; 285:739–747. [PubMed: 11176911]
45. Plassman BL, Williams JW Jr, Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*. 2010; 153:182–193. [PubMed: 20547887]
46. Chen J, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology*. 2009; 30:231–239. [PubMed: 19150462]
47. Hall P, Adami HO, Trichopoulos D, Pedersen NL, Laggiou P, Ekblom A, et al. Effect of low doses of ionizing radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. *BMJ*. 2004; 328:19. [PubMed: 14703539]
48. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet*. 2011; 43:429–435. [PubMed: 21460840]
49. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging*. 2000; 21:49–55. [PubMed: 10794848]
50. Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA. Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. *Arch Intern Med*. 2011; 171:333–339. [PubMed: 20975015]

51. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. *Diabetes*. 2002; 51:1256–1262. [PubMed: 11916953]
52. Magnoni S, Brody DL. New perspectives on amyloid- β dynamics after acute brain injury. *Arch Neurol*. 2010; 67:1068–1073. [PubMed: 20837849]
53. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *Am J Geriatr Psychiatry*. 2009; 17:179–187. [PubMed: 19225276]
54. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev*. 2008; 9:58–65.
55. Alzheimer's disease prevention: a reality check. *Lancet Neurol*. 2010; 9:643. [PubMed: 20610334]
56. Mackey RH, Kuller LH. Blood pressure and cognitive outcome. *Curr Cardiovasc Risk Rep*. 2010; 4:369–375.
57. Arendt T. Synaptic degeneration in Alzheimer's disease. *Acta Neuropathol*. 2009; 118:167–179. [PubMed: 19390859]
58. George DR. Overcoming the social death of dementia through language. *Lancet*. 2010; 376:586–587. [PubMed: 20734467]
59. Golde TE, Schneider LS, Koo EH. Anti-A β therapeutics in Alzheimer's disease: the need for a paradigm shift. *Neuron*. 2011; 69:203–213. [PubMed: 21262461]
60. Whitwell JL. Longitudinal imaging: change and causality. *Curr Opin Neurol*. 2008; 21:410–416. [PubMed: 18607200]
61. Weiner MW. Commentary on “Diagnosis of Alzheimer's disease: two decades of progress.” Central role of technology in the treatment and prevention of Alzheimer's disease. *Alzheimers Dement*. 2005; 1:112–113. [PubMed: 17356683]
62. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9:119–128. [PubMed: 20083042]
63. Forman MS, Trojanowski JQ, Lee VM. Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs. *Nat Med*. 2004; 10:1055–1063. [PubMed: 15459709]
64. Okonkwo OC, Mielke MM, Griffith R, Moghekar AR, O'Brien RJ, Shaw LM, et al. Cerebrospinal fluid profiles and prospective course and outcome in patients with amnesic mild cognitive impairment. *Arch Neurol*. 2011; 68:113–119. [PubMed: 21220682]
65. Bertram L, McQueen BM, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007; 39:17–23. [PubMed: 17192785]
66. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA*. 2010; 303:1832–1840. [PubMed: 20460622]
67. Rowe CC, Ng S, Ackermann U, Pike K, Savage G, Cowie TF, et al. Imaging beta-amyloid burden in aging and dementia. *Neurology*. 2007; 68:1718–1725. [PubMed: 17502554]
68. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol*. 2004; 55:306–319. [PubMed: 14991808]
69. Edison P, Archer HA, Hinz R, Hammers A, Pavese N, Tai YF, et al. Amyloid, hypometabolism, and cognition in Alzheimer disease: an [11C]PIB and [18F]FDG PET study. *Neurology*. 2007; 68:501–508. [PubMed: 17065593]
70. Blennow K. Biomarkers in Alzheimer's disease drug development. *Nat Med*. 2010; 16:1218–1222. [PubMed: 21052077]
71. Kuller LH. Dementia: is it time for a change in focus? *Alzheimers Dement*. 2008; 4:S77–S84. [PubMed: 18632006]
72. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010; 376:1670–1681. [PubMed: 21067804]

73. Ardehali R, Nasir K, Kolandaivelu A, Budoff MJ, Blumenthal RS. Screening patients for subclinical atherosclerosis with non-contrast cardiac CT. *Atherosclerosis*. 2007; 192:235–242. [PubMed: 17467714]
74. Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw L. Coronary artery calcium to predict all-cause mortality in elderly men and women. *J Am Coll Cardiol*. 2008; 52:17–23. [PubMed: 18582630]
75. O'Malley PG. A double take on serial measurement of coronary artery calcification. *Arch Intern Med*. 2009; 169:2051–2052. [PubMed: 20008686]
76. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology*. 1998; 51:S2–S17. [PubMed: 9674758]
77. Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid- β synthesis and clearance rates as measured in cerebrospinal fluid *in vivo*. *Nat Med*. 2006; 12:856–861. [PubMed: 16799555]
78. Storandt M, Mintun MA, Head D, Morris JC. Cognitive decline and brain volume loss as signatures of cerebral amyloid- β peptide deposition identified with Pittsburgh compound B. *Arch Neurol*. 2009; 66:1476–1481. [PubMed: 20008651]
79. The Australian Imaging Biomarkers and Lifestyle flagship study of ageing. Toronto, Canada: Australian ADNI; 2010.
80. Ikonomic MD, Uryu K, Abrahamson EE, Ciallella JR, Trojanowski JQ, Lee VM, et al. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. *Exp Neurol*. 2004; 190:192–203. [PubMed: 15473992]
81. DeKosky ST, Ikonomic MD, Gandy S. Traumatic brain injury—football, warfare, and long-term effects. *N Engl J Med*. 2010; 363:1293–1296. [PubMed: 20879875]
82. Gorelick PB, William M. Feinberg lecture: cognitive vitality and the role of stroke and cardiovascular risk factors. *Stroke*. 2005; 36:875–879. [PubMed: 15731466]
83. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Rotterdam Scan Study. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke*. 2003; 34:392–396. [PubMed: 12574548]
84. Salerno JA, Murphy DG, Horwitz B, DeCarli C, Haxby JV, Rapoport SI, Schapiro MB. Brain atrophy in hypertension: a volumetric magnetic resonance imaging study. *Hypertension*. 1992; 20:340–348. [PubMed: 1516953]
85. Lewis H, Behr D, Cookson N, Oakley A, Piggott M, Morris CM, et al. Quantification of Alzheimer pathology in ageing and dementia: age-related accumulation of amyloid- β (42) peptide in vascular dementia. *Neuropathol Appl Neurobiol*. 2006; 32:103–118. [PubMed: 16599940]
86. Pantoni L, Gorelick P. Advances in vascular cognitive impairment 2010. *Stroke*. 2011; 42:291–293. [PubMed: 21233478]
87. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003; 348:1215–1222. [PubMed: 12660385]
88. Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer Disease Neuroimaging Initiative. *Arch Neurol*. 2010; 67:1370–1378. [PubMed: 21060014]
89. Petrovitch H, White LR, Izmirlian G, Ross GW, Havlik RJ, Markesbery W, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol Aging*. 2000; 21:57–62. [PubMed: 10794849]
90. Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Med*. 2009; 6:e1000180. [PubMed: 19901977]
91. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre community-based population in England and Wales. *Lancet*. 2001; 357:169–175. [PubMed: 11213093]
92. Snowden DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer's disease: the Nun Study. *JAMA*. 1997; 277:813–817.

93. Pendlebury S, Rothwell PM. Prevalence, incidence, factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* 2009; 8:1006–1018. [PubMed: 19782001]
94. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol.* 2008; 105:1652–1660. [PubMed: 18772322]
95. Grinberg LT, Thal DR. Vascular pathology in the aged human brain. *Acta Neuropathol.* 2010; 119:277–290. [PubMed: 20155424]
96. Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes. The Three-City (3C)-Dijon Magnetic Resonance Imaging Study. *Circulation.* 2011; 123:266–273. [PubMed: 21220733]
97. Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, et al. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study. *Acta Psychiatr Scand.* 2010; 122:319–325. [PubMed: 20626720]
98. Ikejima C, Yasuno F, Mizukami K, Sasaki M, Tanimukai S, Asada T. Prevalence and causes of early-onset dementia in Japan: a population-based study. *Stroke.* 2009; 40:2709–2714. [PubMed: 19478230]
99. Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology.* 1995; 45:1161–1168. [PubMed: 7783883]
100. Sekikawa A, Kuller LH, Ueshima H, Park JE, Suh I, Jee SH, Lee HK, Pan WH. Coronary heart disease mortality trends in men in the post World War II birth cohorts aged 35–44 in Japan, South Korea and Taiwan compared with the United States. *Int J Epidemiol.* 1999; 28:1044–1049. [PubMed: 10661646]
101. Matsui Y, Tanizaki Y, Arima H, Yonemoto K, Doi Y, Ninomiya T, et al. Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama Study. *J Neurol Neurosurg Psychiatry.* 2009; 80:366–370. [PubMed: 18977814]
102. Hooijmans CR, Kiliaan AJ. Fatty acids, lipid lowering metabolism and Alzheimer pathology. *Eur J Pharmacol.* 2008; 585:176–196. [PubMed: 18378224]
103. Florent-Bechard S, Malaplate-Armand C, Koziel V, Kriem B, Olivier JL, Pillot T, et al. Towards a nutritional approach for prevention of Alzheimer's disease: biochemical and cellular aspects. *J Neurol Sci.* 2007; 262:27–36. [PubMed: 17681547]
104. He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens.* 2009; 23:363–384. [PubMed: 19110538]
105. D'elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease: a meta-analysis of prospective studies. *J Am Coll Cardiol.* 2011; 57:1210–1219. [PubMed: 21371638]
106. Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia. A systematic review and meta-analysis. *Neurology.* 2011; 76:914–922. [PubMed: 21383328]
107. Luchsinger JA. Type 2 diabetes and related conditions in relation to dementia: an opportunity for prevention? *J Alzheimers Dis.* 2010; 20:723–736. [PubMed: 20413862]
108. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol.* 2011; 68:51–57. [PubMed: 20837822]
109. Martin M, Doti CG, Ledesma MD. Brain cholesterol in normal and pathological aging. *Biochim Biophys Acta.* 2010; 1801:934–944. [PubMed: 20359547]
110. Merlo S, Spampinato S, Canonico PL, Copani A, Sortino MA. Alzheimer's disease: brain expression of a metabolic disorder? *Trends Endocrinol Metab.* 2010; 21:537–544. [PubMed: 20541952]
111. Donahue JE, Johanson CE. Apolipoproteins, amyloid- β , and blood-brain barrier permeability in Alzheimer disease. *J Neuropathol Exp Neurol.* 2008; 67:261–270. [PubMed: 18379441]

112. Marzolo MP, Bu G. Lipoprotein receptors and cholesterol in APP trafficking and proteolytic processing, implications for Alzheimer's disease. *Semin Cell Dev Biol.* 2009; 20:191–201. [PubMed: 19041409]
113. Kuller LH. Statins and dementia. *Curr Atheroscler Rep.* 2007; 9:154–161. [PubMed: 17877925]
114. Di Paolo G, Kim TW. Linking lipids to Alzheimer's disease: cholesterol and beyond. *Nat Rev Neurosci.* 2011; 12:284–296. [PubMed: 21448224]
115. Zipp F, Waiczies S, Aktas O, Neuhaus O, Hemmer B, Schraven B, et al. Impact of HMG-CoA reductase inhibition on brain pathology. *Trends Pharmacol Sci.* 2007; 28:342–349. [PubMed: 17573124]
116. Thambisetty M, Simmons A, Velayudhan L, Hye A, Campbell J, Zhang Y, et al. Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. *Arch Gen Psychiatry.* 2010; 67:739–748. [PubMed: 20603455]
117. Schrijvers EM, Koudstaal PJ, Hofman A, Breteler MM. Plasma clusterin and the risk of Alzheimer disease. *JAMA.* 2011; 305:1322–1326. [PubMed: 21467285]
118. Jones L, Harold D, Williams J. Genetic evidence for the involvement of lipid lowering metabolism in Alzheimer's disease. *Biochim Biophys Acta.* 2010; 1801:754–761. [PubMed: 20420935]
119. Deane R, Zlokovic BV. Role of the blood-brain barrier in the pathogenesis of Alzheimer's disease. *Curr Alzheimer Res.* 2007; 4:191–197. [PubMed: 17430246]
120. Chen, X.; Stern, D.; Yan, SD. Cellular targets of amyloid b peptide. In: Dawbarn, D.; Allen, SJ., editors. *Neurobiology of Alzheimer's Disease.* New York NY: Oxford University Press, Inc; 2007. p. 227–243.
121. Rossner S, Sastre M, Bourne K, Lichtenthaler SF. Transcriptional and translational regulation of BACE1 expression-implications for Alzheimer's disease. *Prog Neurobiol.* 2006; 79:95–111. [PubMed: 16904810]
122. Wyss-Coray T. Inflammation in Alzheimer disease: driving force by-stander or beneficial response? *Nat Med.* 2006; 12:1005–1015. [PubMed: 16960575]
123. In 't Veld BA, Launer LJ, Breteler MM, Hofman A, Stricker BH. Pharmacologic agents associated with preventive effect on Alzheimer's disease: a review of the epidemiologic evidence. *Epidemiol Rev.* 2002; 24:248–268. [PubMed: 12762096]
124. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. *Arthrit Care Res.* 2011; 63:522–529.
125. Deary IJ, Corely J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, et al. Age-associated cognitive decline. *Br Med Bull.* 2009; 92:135–152. [PubMed: 19776035]
126. Hedeem T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci.* 2004; 5:87–97. [PubMed: 14735112]
127. Salhouse TA. When does age-related cognitive decline begin? *Neurobiol Aging.* 2009; 30:507–514. [PubMed: 19231028]
128. Eshaghian S, Kaul S, Shah PK. Cardiac amyloidosis: new insights into diagnosis and management. *Rev Cardiovasc Med.* 2007; 8:189–199. [PubMed: 18192942]
129. Falk RH, Dubrey SW. Amyloid heart disease. *Prog Cardiovasc Dis.* 2010; 52:347–361. [PubMed: 20109604]
130. Bates KA, Verdile G, Li QX, Ames D, Hudson P, Masters CL, et al. Clearance mechanisms of Alzheimer's amyloid- β peptide: implications for therapeutic design and diagnostic tests. *Mol Psychiatry.* 2009; 14:469–486. [PubMed: 18794889]
131. Newman AB, Boudreau RM, Naydeck BL, Fried LF, Harris TB. A physiologic index of comorbidity: relationship to mortality and disability. *J Gerontol A Biol Sci Med Sci Am.* 2008; 63:603–609.
132. Fried LP, Xue Q, Cappola AR, Ferrucci L, Chaves P, Varadhan R, et al. Nonlinear multisystem physiologic dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci Am.* 2010; 64:1049–1057.

133. Kuller, LH.; Chang, Y.; Becker, JT.; Lopez, OL. Does Alzheimer's disease over 80 years old have a different etiology?. Abstract accepted for presentation at: Alzheimer's Association 2011 International Conference on Alzheimer's Disease; July 12–21, 2011; Paris, France.
134. Power C, Jefferis BJ, Manor O. Childhood cognition and risk factors for cardiovascular disease in mid-adulthood: the 1958 British Birth Cohort Study. *Am J Public Health*. 2010; 100:129–136. [PubMed: 19910352]
135. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev*. 2004; 3:369–382. [PubMed: 15541707]
136. Olive M, Harten I, Mitchell R, Beers JK, Djabali K, Cao K, et al. Cardiovascular pathology in Hutchinson-Gilford progeria: correlation with the vascular pathology of aging. *Arterioscler Thromb Vasc Biol*. 2010; 30:2301–2309. [PubMed: 20798379]
137. Sierra F, Hadley E, Suzman R, Hodes R. Prospects for life span extension. *Ann Rev Med*. 2009; 60:457–469. [PubMed: 18817460]
138. Rea SL, Ventura N, Johnson TE. Relationship between mitochondrial electron transport chain dysfunction, development, and life extension in *Caenorhabditis elegans*. *PLoS Biol*. 2007; 5:e259. [PubMed: 17914900]
139. Larbi A, Franceschi C, Mazzatti Solana R, Wikby A, Pawelec G. Aging of the immune system as a prognostic factor for human longevity. *Physiology*. 2008; 23:64–74. [PubMed: 18400689]
140. Willcox BJ, Donlon TA, He Q, Chen R, Grove JS, Yano K, et al. FOXO3A genotype is strongly associated with human longevity. *Proc Natl Acad Sci*. 2008; 105:13987–13992. [PubMed: 18765803]
141. Minamino T. Role of cellular senescence in lifestyle-related disease. *Circ J*. 2010; 74:2527–2533. [PubMed: 21084758]
142. Coman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*. 2009; 325:201–204. [PubMed: 19590001]
143. Zhang C, Browne A, Child D, Tanzi RE. Curcumin decreases amyloid- β peptide levels by attenuating the maturation of amyloid- β precursor protein. *J Biol Chem*. 2010; 285:28472–28480. [PubMed: 20622013]
144. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009; 374:1196–1208. [PubMed: 19801098]