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Causes and Patterns of Dementia: An Update in the Era of Redefining Alzheimer's Disease

Bryan D. James[1,2] and David A. Bennett[1,3]

[1]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois 60612, USA; email: Bryan_james@rush.edu

[2]Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois 60612, USA

[3]Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois 60612, USA

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Abstract

The burden of dementia continues to increase as the population ages, with no disease-modifying treatments available. However, dementia risk appears to be decreasing, and progress has been made in understanding its multifactorial etiology. The 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research framework for Alzheimer's disease (AD) defines AD as a biological process measured by brain pathology or biomarkers, spanning the cognitive spectrum from normality to dementia. This framework facilitates interventions in the asymptomatic space and accommodates knowledge that many additional pathologies (e.g., cerebrovascular) contribute to the Alzheimer's dementia syndrome. The framework has implications for how we think about risk factors for "AD": Many commonly accepted risk factors are not related to AD pathology and would no longer be considered risk factors for AD. They may instead be related to other pathologies or resilience to pathology. This review updates what is known about causes, risk factors, and changing patterns of dementia, addressing whether they are related to AD pathology/biomarkers, other pathologies, or resilience.

INTRODUCTION

The prevention of dementia is one of the prevailing public health crises today. The number of people suffering from dementia is substantial, with an estimated 5.5 million or more persons in the United States and 46 million globally (3, 4). These numbers will continue to rise owing to demographic shifts toward older ages and increases in health and longevity globally. These changes, coupled with declining fertility, forecast an ever-increasing percentage of the population with dementia. No disease-modifying treatments are currently available for the predominant form of dementia, Alzheimer's dementia, despite billions of dollars having been invested in this goal (40). For a public health problem of this magnitude, prevention is the only viable approach (79, 131). However, there is reason for optimism regarding the future of dementia research and prevention. First, evidence shows that the age-specific risk of dementia may be declining in the United States and other developed nations (43, 83). Thus, even though the number of persons with dementia will increase as more people reach older ages, the actual risk of developing dementia once an individual enters later life may be going down. Second, researchers have made significant progress in recent years toward understanding the multifactorial and overlapping causes of dementia, opening alternative avenues for intervention (17).

A major development reflecting this progress is the recently proposed National Institute on Aging–Alzheimer's Association (NIA-AA) framework for research on Alzheimer's disease (AD) (66). The framework defines AD as a biological process on the basis of the demonstration of brain pathology at autopsy or with in vivo biomarkers rather than on the basis of clinical signs. This framework is intended to put AD in line with other common chronic disease processes such as chronic kidney disease, chronic obstructive pulmonary disease, and cancer. It further recognizes a presymptomatic period in which researchers can target interventions before the clinical symptoms of dementia emerge, which is essential to developing a therapeutic for disease prevention. This framework accommodates the knowledge that many pathologies, such as cerebrovascular disease, in addition to AD contribute to the Alzheimer's dementia syndrome. It is also compatible with the widely recognized phenomenon that there is often discordance between AD pathologic severity and cognitive outcomes at the individual level, owing to the presence of other pathologies as well as protective factors that promote resilience or reserve capacity.

The framework has implications for how to consider the previous evidence regarding risk factors for, or the epidemiologic patterns of, "AD." Many commonly accepted risk factors for Alzheimer's dementia are not related to AD pathology. Some have been shown to be related to vascular or other pathologies, and some are independent of known pathologies. Furthermore, some risk factors may modify the relationship of pathology to cognitive outcomes. Similarly, the apparent declining risk of dementia may be due to decreases at the population level in vascular and other risk factors, or to increases in protective factors such as education, rather than to secular trends in AD pathology. Using evidence from in vivo biomarker studies and community-based clinical-pathologic studies, this review updates what is known about the causes, risk factors, and changing patterns of Alzheimer's dementia and summarizes the evidence in light of whether they are related to AD pathology, other pathologies, or resilience. Finally, we discuss how this framework and the modern understanding of what causes dementia can inform drug development and public policy.

CAUSES OF DEMENTIA

Redefining Alzheimer's Disease

For decades, AD has been defined as a clinical-pathological construct called "possible or probable AD" and has been confirmed during autopsy by the presence of neuritic plaques and neurofibrillary

tangles (97). As a consequence, the term AD has been used to describe both the neuropathological entity as well as the prototypical clinical syndrome of memory loss and other cognitive problems. Over the following quarter-century, problems with this conceptualization emerged. First, evidence increasingly indicated that persons with mild cognitive impairment (MCI), and indeed without any cognitive impairment, could meet pathologic criteria for AD (18, 19, 39, 78, 125). This was found to be true with in vivo biomarkers, as well (1, 114). Furthermore, industry was increasingly interested in enrolling patients into trials in the predementia space. The criteria were revised in 2011 to recognize the continuum of the Alzheimer's dementia phenotype and incorporate the emerging availability of in vivo biomarkers of AD (98). These criteria recognized "MCI due to AD" (2), but persons without cognitive impairment would receive the cumbersome designation of AD pathophysiologic process (133). Additionally, confusion was increasingly sown by use of the same word, "AD," to refer to two very different constructs: a dementia syndrome and a pathologic footprint. Other fields solved this problem with two different words; e.g., stroke is the clinical syndrome, and cerebrovascular disease is the underlying biology. Thus, in 2018, criteria for AD were again revised; the term is limited to the pathology—Aβ deposition (A), pathologic tau (T), and neurodegeneration (N)—regardless of its clinical consequences, which is the basis for the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework (66). Alzheimer's clinical syndrome, or Alzheimer's dementia here, refers to what was once called "possible or probable AD"; a syndrome does not define an etiology but rather a clinical outcome of one or more diseases. By contrast, we treat the underlying biology when it is known.

The framework views the disease as a continuum with a long preclinical phase (46), with cognitive decline occurring continuously over many years (102, 116) and with the accumulation of AD biomarkers beginning years or decades prior to the onset of clinical signs (13, 48, 71, 143). The cutting edge of biomarker research is constantly evolving; at the time of this publication, most biomarkers come from neuroimaging or cerebrospinal fluid (CSF). As laid out in the framework paper, biomarkers of amyloid deposition include cortical amyloid positron emission tomography (PET) ligand binding and low CSF $A\beta_{42}$; biomarkers of fibrillar tau include elevated CSF phosphorylated tau (P-tau) and cortical tau PET ligand binding; and evidence of neurodegeneration or neuronal injury includes CSF T-tau, fluorodeoxyglucose (FDG) PET hypometabolism, and atrophy on structural magnetic resonance imaging (66).

Mixed Pathologies and Alzheimer's Dementia

Although AD is the most common pathologic cause of dementia in old age, a number of other common pathologies are known to contribute as well. Just as the burden of AD pathology increases markedly with age, several other brain diseases that affect cognition accumulate as well, including cerebrovascular disease manifesting as infarctions, atherosclerosis, arteriolosclerosis, and white matter changes, as well as neocortical Lewy body disease (LBD) and increasingly recognized roles for TAR DNA-binding protein 43 (TDP-43) and hippocampal sclerosis (HS) (76). While each of these pathologies represents a separate dementia-related disease process, they are not mutually exclusive. In fact, studies show that a large proportion of older persons, both with and without dementia, have multiple pathologies, referred to as mixed pathologies, in the brain (125, 126, 150). Mixed pathologies are often found in the brains of persons who are diagnosed specifically with Alzheimer's dementia (44, 70, 127). While most persons diagnosed with Alzheimer's dementia are confirmed to have a pathologic diagnosis of AD at autopsy, these individuals are often also shown to have vascular and other pathologies present as well (70, 76, 127).

Each pathology coexisting with AD serves as an additional "hit" to the brain that increases the risk of dementia (8, 10, 70, 77, 125–128). As the likelihood of each pathology accumulates

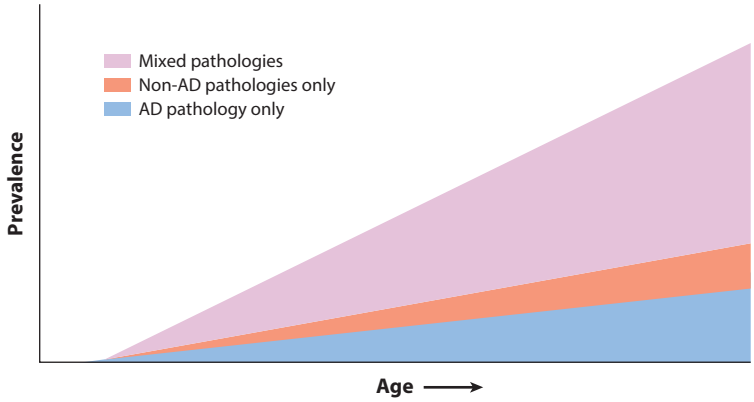

Figure 1

Schematic representation of accumulation of pathologies in the brain with age in a theoretical population. Over time, both Alzheimer's disease (AD) and non-AD pathologies accumulate in the brains of most older adults; the proportion of persons with mixed pathologies (i.e., both AD and non-AD pathologies) increases dramatically with age. At the oldest ages of life expectancy, most individuals will have some form of pathology in their brain. Persons with mixed pathologies are more likely to develop dementia than are persons with single pathologies, and each type of pathology serves as a "hit" to the system that increases the likelihood of dementia. However, the specific burden of pathologies that lead to the onset of dementia will differ across individuals owing to person-specific neural reserve capacity.

with age, the prevalence of mixed pathology increases at older age ranges, indicating that mixed pathologies may be the predominant cause of dementia in the oldest old, the age group at highest risk (68). In fact, some studies suggest that comorbid pathologies may account for an equal or higher proportion of the overall burden of dementia compared with AD pathology (96). **Figure 1** visualizes the accumulation of both AD and non-AD pathologies in an adult population as it ages: As each pathology accumulates, the proportion of mixed pathology increases as well, which correlates with increased risk for dementia with age in a population. The specific combinations of mixed pathologies are manyfold, and the relative contribution to loss of cognition due to specific pathologies can vary widely at the individual level (25).

Appreciating the role of mixed pathologies is important for understanding how risk factors lead to Alzheimer's dementia. However, mixed pathologies do not tell the whole story, as known brain pathologies do not fully explain age-related cognitive decline and the expression of dementia. Known pathologies appear to account for less than half of the person-specific variance in cognitive decline, leaving the majority unexplained (24). This gap may be partially explained by as-yet undiscovered pathologies much like the recent discovery of TDP-43, but it is unlikely to explain more than a fraction of the unexplained variance. Instead, the secret may lie in person-specific differences in the ability of the brain to protect itself from pathology (17).

Resilience to Pathology: Neural Reserve Capacity

The amount of AD and/or other known pathologies is only modestly correlated with cognitive impairment and decline. Given the same degree of pathology, certain individuals may show signs while others remain asymptomatic, as shown in numerous clinical-pathological studies (21, 78) and more recently using in vivo biomarkers (71). This finding implies that certain individuals possess resilience to pathology, which allows them to tolerate more pathology before reaching

the threshold for dementia, i.e., a cognitive or neural reserve capacity (17, 134). Reserve capacity is found in all human physiological systems as the organ system finds ways to maintain function despite damage from disease. In the case of the brain, reserve capacity may be developed through a number of structural or functional mechanisms that have been hypothesized for years (134) but are poorly understood. The biological basis for neural reserve is only now beginning to be elucidated and includes cellular, synaptic, and biochemical avenues (7), such as synaptic (60) and presynaptic proteins (15, 64), neuronal or nuclear hypertrophy (65, 117), neuronal density (157), and brain microstructure (6), among others.

The disconnect between pathological burden and cognitive function is not random; instead, many factors appear to be able to impart reserve because either they are related to cognitive function independent of pathology or they modify the relationship between pathology and cognition (142, 161). These include not only experiential and psychological factors, but also genetic and medical factors. Perhaps the most promising aspect of neural reserve is that it may be more modifiable relative to disease pathologies. In a recent paper, researchers proposed a schema distinguishing interventions or risk factors in preclinical studies of AD that impart resistance, i.e., the avoidance of accumulation of AD pathology, versus those that impart resilience, the ability to cope with AD pathology (5).

RISK FACTORS FOR DEMENTIA: RELATIONSHIPS TO ALZHEIMER'S DISEASE, OTHER PATHOLOGIES, OR RESILIENCE

The proposed research framework, along with accumulating knowledge of the roles of mixed pathologies and resilience, has important implications for how we think about risk factors for "AD." A schematic representation of how risk factors may be related to dementia is provided in **Figure 2**. Conceptually, a risk factor may (1) affect AD pathology, (2) affect vascular or other pathology, (3)

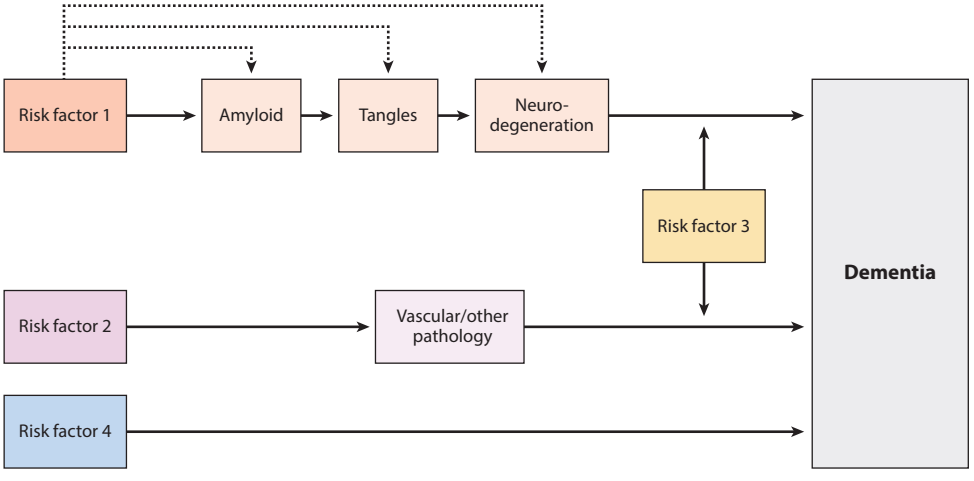

Figure 2

Schematic representation of various ways that risk factors may be related to dementia. Risk factor 1 is related to dementia directly through Alzheimer's disease (AD) pathology; the dotted lines indicate that such a risk factor may work through affecting one specific step on the cascade: amyloid, tau tangles, or neurodegeneration. Risk factor 2 is related to dementia through vascular or other known pathologies in the brain. Risk factor 3 is related to dementia by moderating the relationship of AD or other pathologies with dementia, i.e., increases or decreases the risk of dementia for a given level of pathology. Risk factor 4 is related to dementia independently of known pathology.

modify the relationship between pathology and dementia, or (4) be completely independent of known pathology.

Here, we review many commonly recognized risk factors for Alzheimer's dementia through this lens and summarize the evidence, to date, regarding which of these pathways appear to be at play for each risk factor. We focus on risk factors with the most evidence of a relationship with Alzheimer's dementia or dementia in general. Evidence comes from clinical-pathological studies as well as in vivo biomarker studies where available; because AD biomarker research is relatively new, some of these risk factors have not been studied in this context. Similarly, the relationship of many of these risk factors with non-AD pathologies is not fully explored, but we provide some of the evidence that is available. We limit the review to observational studies in humans.

Genetics

Family history of Alzheimer's dementia is an established risk factor for late-onset Alzheimer's dementia (4). Persons with first-degree relatives with Alzheimer's dementia will not definitely develop dementia, although they are at higher risk. There are also mutations in three genes, amyloid precursor protein (*APP*) and *presenilin 1* and *2*, which cause autosomal dominant Alzheimer's dementia. Cases occur mostly before the age of 65, but these mutations account for less than 0.5% of persons with Alzheimer's dementia.

The most firmly established genetic risk factor for late-onset Alzheimer's dementia is the *APOE* gene; the ε4 allele is associated with an approximately threefold increase in risk for Alzheimer's dementia compared with the more common ε3 allele, and the rare ε2 allele is associated with decreased risk (90, 109). The *APOE* gene regulates cholesterol transport in the bloodstream; however, the mechanisms through which it contributes to Alzheimer's disease remain poorly understood (80, 90). *APOE* plays a large role in β-amyloid metabolism, and the ε4 allele is related to more AD pathology in neuropathological studies (50, 81, 111) and amyloid accumulation in biomarker studies (67, 89); by comparison, the ε2 allele is related to less AD pathology (50). Evidence from some imaging studies also indicates that ε4 modifies the relationship between amyloid load and cognitive function (75, 103).

Whereas the *APOE* genotype appears closely linked to the biological hallmarks of AD, this finding has not been shown to be the case with other genes linked to clinical Alzheimer's dementia. In one study, 22 genomic variants in addition to *APOE* that have been associated with Alzheimer's dementia were tested for associations with pathologic diagnosis of AD, gross infarcts and microinfarcts, Lewy bodies, and hippocampal sclerosis (50). Aside from *APOE*, only 4 genomic variants were associated with AD pathology, and very few of the variants were associated with infarcts and hippocampal sclerosis. Prior to that study, a genome-wide association study (GWAS) meta-analysis of almost 5,000 autopsied participants found that 12 of 21 susceptibility variants for Alzheimer's dementia were associated with AD pathology (14). Both studies show that many genetic risk factors for Alzheimer's dementia do not work through AD pathology. Another approach has been to examine genetic markers associated with the expression of dementia among persons with AD pathology in the brain; certain genetic markers were identified and could provide insight into the biology of resilience to AD (101).

Understanding how genetic variants and other risk factors actually lead to cognitive decline is a daunting challenge because the molecular machinery linking them must be interrogated in brain tissue. Unlike cancer and infectious disease, which can be repeatedly studied under a microscope along with generating molecular genomic data, for the most part the human brain can be accessed only after death. We are just beginning to explore the links between the genome and the epigenome, transcriptome, proteome, and metabolome (41, 53, 107). Much of this work is being

performed as part of the Accelerating Medicines Partnership for AD (AMP-AD; **https://www.nia.nih.gov/research/amp-ad**). These linkages will be the roadmap to identifying new therapeutic targets that will be investigated for druggability in ex vivo and preclinical model systems.

Sociodemographic and Behavioral Factors

Education. The link between higher levels of education and lowered risk of Alzheimer's dementia is well established (135). Education has long been posited to build reserve capacity; a number of clinical-pathologic studies have shown that education is associated with cognitive decline or dementia regardless of AD pathology (26, 42, 49, 106, 121) or that education modifies the relationship between AD pathology and cognition (22, 120). None of these studies showed a direct relationship between education and AD pathology, though some have found direct relationships between education and infarcts (42) as well as modification effects for infarcts (49). Studies using in vivo CSF and imaging biomarkers have corroborated these findings of both independent (108, 118) and modification effects (42, 47, 100, 115, 119, 145). Therefore, the evidence supports the hypothesis that education, and the related construct of occupational complexity (55, 135), imparts resilience to pathology and a neural reserve capacity. Elucidating the mechanisms of neuronal and synaptic plasticity that underlie this resilience is an important goal for dementia research.

Physical, cognitive, and social activities. A wide variety of activity, including physical, cognitive, and social or leisure activities, has been linked to a reduction of risk for dementia (52, 124, 146, 156). These activity types overlap greatly and likely work through a wide variety of mechanisms, ranging from cardiovascular benefits of physical activity to the potential building of reserve capacity through cognitive stimulation.

Physical activity is not restricted to recreational exercise but includes walking, yard work, and house work. Because of the link between vascular health and Alzheimer's dementia, physical activity's relationship to AD pathology has been widely explored (31). Evidence has shown that physical activity does not work solely through cerebrovascular channels but may be directly related to AD pathology. Higher levels of physical activity have been associated with lower amyloid and tau burden on CSF (85) and PET measures (32, 33, 59, 86, 94, 110), although other studies have shown no direct relation between physical activity and AD pathology (34, 56, 141). Thus, there is evidence for both resistance and resilience to AD pathology, perhaps accounted for by wide varieties in measurement and methodologies. Some of the potential mechanisms for association with AD pathology will be explored below in the discussion of vascular risk factors.

Cognitively stimulating activities such as reading, puzzles, and games are associated with a lower risk for Alzheimer's dementia (138, 156) and are posited to build reserve capacity much like education. Studies have shown that early-life and late-life cognitive activities are independently associated with cognitive decline after adjustment for AD and other pathologies (153) and even that cognitive activities in adulthood are more strongly related to reserve (residual variance in cognition after adjusting for AD and other pathologies) than is education (113). In biomarker studies using both CSF and PET, cognitive activity was related to cognitive performance independent of AD biomarkers (56, 141), while another study showed that lifetime cognitive activity moderated the relationship between *APOE* genotype and amyloid deposition, indicating reserve that may protect against genetic risk (159). At least one study has shown a direct relationship between lifetime cognitive engagement and lower amyloid deposition on PET (82), but most studies report that the relationship with cognition is independent of AD and support the reserve hypothesis (139). Finally, one study found that brain microstructure partially mediated the association between cognitive activity and cognition (6).

Social or leisure activity is another lifestyle activity that has been linked to dementia (122, 124, 147), though, to date, the association has rarely been explored in the context of AD pathology. Many social activities have elements of physical and cognitive activity, such as dancing or visiting museums with friends, so it is difficult to tease apart underlying mechanisms; many researchers have collapsed the concepts into that of leisure activities (124, 146) or have made a composite of activities (138). However, socializing, specifically, does appear to confer benefits to the brain. Studies have shown that larger social networks modify the relationship between AD pathology and cognition (20), and a sense of loneliness is related to cognitive decline independent of AD pathology but not independent of infarcts (155). One PET study showed a cross-sectional association between loneliness and higher amyloid burden, but here loneliness was interpreted as a neuropsychiatric symptom of preclinical AD (45). Reciprocal effects and reverse causality still need to be clarified in examining the evidence linking activity, behavior, and experiential factors with dementia.

Diet and nutrition. The role of diet and nutrition in the development of Alzheimer's dementia has only recently begun to be studied in depth, owing mostly to the complexities of measuring nutrient intake, though consensus is emerging that saturated fats and *trans*–fatty acids may increase risk for dementia while leafy greens and certain vitamins and other nutrients may reduce risk (12). In the context of AD pathology, even less evidence exists, though studies have shown that seafood consumption is associated with less AD pathology among ε4 carriers (104), tocopherols in the brain are associated with less AD pathology (105), and Mediterranean diet is associated with lower amyloid load (94). Other studies report that high-intensity physical activity may modify the effect of diet on CSF amyloid levels (11). Much more research is needed, but diet may be one modifiable risk factor with direct impact on the accumulation of AD pathology.

Sleep and circadian rhythm. Evidence has shown that sleep is important to amyloid clearance, and sleep deprivation is therefore related to the accumulation of amyloid in the brain; the relationship appears to be bidirectional, though, as accumulation of amyloid pathology can disrupt sleep patterns (74). One study reported that better sleep consolidation modified the relationship of the *APOE* ε4 allele with incident Alzheimer's dementia and tau tangle pathology, indicating that it may provide both resistance and resilience for those at risk (88). Disruption of diurnal circadian and seasonal rhythms also appears to be linked to dementia and has been associated with AD pathology, although whether these disruptions are a cause or a consequence of pathology, or both, is less clear (87). Causality needs to be established to determine whether interventions to improve sleep can mitigate the risk of Alzheimer's dementia, but evidence does support a clear relationship between this disease and sleep and circadian rhythms.

Psychological Risk Factors

A number of psychological factors, including personality traits and affective states, are related to Alzheimer's dementia, and investigators have explored the relationships between these factors and pathology. Conscientiousness—the tendency to be self-disciplined, scrupulous, and purposeful—showed no direct relationship with AD or other pathologies but modified the relationship between tangle density and infarcts with cognition (158). Harm avoidance, a personality trait indicative of behavioral inhibition (e.g., pessimism and shyness), was associated with infarcts but not with AD pathology (151, 152). A sense of purpose in life has been strongly linked to a number of health outcomes in aging, including dementia, and it appears to modify the association between AD pathology and cognition, implying a source of reserve (23). Finally, depressive symptomology is

related to cognitive decline independent of pathology and does not appear to be the result of preclinical pathology, as some have posited (154). Altogether, it appears that psychological factors may provide a reserve to cope with AD pathology and that some of these factors work through vascular mechanisms, but none are direct risk factors for AD.

Medical Risk Factors

Cardiovascular risk factors. The link between heart health and brain health has been firmly established, and many cardiovascular risk factors are clearly related to risk for cerebrovascular disease and vascular dementia. Relationships with AD pathology are less clear. Diabetes, for one, is strongly associated with an increased risk for Alzheimer's dementia, but clinical-pathologic studies are conflicting. Most of these studies show no association of diabetes with AD (63), although recently one did show a relationship with less AD pathology (16) while another showed diabetes was related to cerebral infarcts but not AD pathology (9). In another study, glucose levels were not associated with amyloid PET (137). Blood pressure has a complicated relationship with Alzheimer's dementia. It appears that midlife blood pressure, but not late-life blood pressure, is associated with dementia (73). Evidence indicates that diastolic blood pressure is associated with amyloid PET (137). Similarly, while midlife high body mass index (BMI) may be a risk factor for dementia (51), high BMI in late life has been associated with a lower risk of Alzheimer's dementia (36). Further loss of BMI regardless of starting BMI was associated with elevated Alzheimer's dementia risk (35). In studies examining multiple vascular risk factors at once, obesity, smoking, diabetes, hypertension, and cardiac and metabolic conditions were related to neurodegeneration but not to amyloid PET, though dyslipidemia was related to amyloid and tau PET (139, 140), and persons with two or more vascular risk factors in midlife had nearly threefold higher odds of brain amyloid deposition in late life as measured by PET (58). Therefore, the link between cardiovascular risk factors and AD pathology is complicated, and some evidence indicates that they may be directly related to amyloid deposition or clearance, as well as to cerebrovascular pathology.

Head trauma. A vast literature has linked traumatic brain injury (TBI) to elevated risk of dementia (72), but whether AD is a direct pathologic outcome rather than other neurodegenerative disease processes, such as the recently characterized chronic traumatic encephalopathy, is under review. Despite evidence from retrospective autopsy reviews indicating a link between TBI and amyloid accumulation, examinations of this relationship using prospective study designs with comparison groups are less clear. In two recent cohort studies, TBI was not related to AD pathology in autopsy (38) or to AD imaging biomarkers (148). Another study found that among individuals with MCI, but not cognitively normal individuals, self-reported head trauma was associated with greater PET amyloid deposition (99). More research is necessary to determine if TBI is directly related to accumulation of AD pathology.

CHANGING PATTERNS OF DEMENTIA

The NIA-AA framework also has striking implications for determining how many people have AD as well as learning how we understand the reasons for the changing patterns of the disease.

Increasing Burden

As the population in the United States and globally experiences shifts to older ages due to increased longevity as well as demographic trends such as the aging of the baby boom generation,

the number of people with dementia continues to increase. In the United States, the most commonly cited number is >5.5 million people living with Alzheimer's dementia, which is projected to increase to nearly 14 million by 2050 (62). Estimates from other cohorts using different diagnostic methods are slightly lower but still project a dramatic increase in numbers by 2050 (29). The global burden is likewise predicted to grow dramatically, from an estimated 46 million living with dementia in 2015 to >130 million by 2050 (3); other estimates are lower but have the numbers quadrupling by 2050 (30). This projected increase is based on population aging, as age is the predominant risk factor for dementia, as well as the lack of effective AD-modifying agents.

Decreasing Risk

While the number of persons with dementia will continue to increase in the coming years owing to population aging, evidence indicates that the actual risk of developing dementia at any given age has been decreasing over time in the United States and other Western countries (112, 160). For example, in a population-based study, the prevalence of dementia decreased from 12.2% to 8.7% between 1993 and 2002 (84), while another large study in the United States showed a decrease from 5.7% to 2.9% between 1982 and 1999 (93). In terms of incidence, which is a more accurate measure of the actual risk of disease, the Framingham Heart Study reported a decrease in incidence from 2.8 per 100 persons in the late 1980s and early 1990s to 2.0 per 100 persons during the late 2000s and early 2010s (123), while another study showed a decrease in incidence of dementia in more recent years or when comparing younger to older birth cohorts (43). However, other studies have reported no change in incidence of dementia over time (61).

The reported declines in risk of dementia have been attributed largely to changes in risk factors over preceding decades, especially improved control of cardiovascular risk factors (37, 123, 129) and increasing levels of education (95). Therefore, these optimistic trends in the pattern of dementia incidence are almost certainly brought about through changes in the prevalence of cerebrovascular pathologies or increased neural reserve and not through changes in AD pathology at the population level.

Mortality

According to official reports based on death certificate reporting, Alzheimer's is the sixth leading cause of death in the United States, and both the number (94,000 in 2014 versus 45,000 in 1999) and rate (25.4 per 100,000 population in 2014 versus 16.5 per 100,000 in 1999) of Alzheimer's deaths have been increasing in recent years (136). A number of reasons can be cited for this observed increase, including an increase in the number of persons living with (and therefore dying with) Alzheimer's dementia due to population aging, although the age-specific mortality risk is increasing as well. However, other likely reasons do not reflect actual increases in numbers but rather changes in the reporting of deaths due to dementia. Underreporting of dementia on death certificates is well-documented (54); priority is given to more proximate causes of death such as pneumonia, which are often the end result of the cascade of insults to the brain brought on by dementia. Increases in reporting in recent years may thus reflect increased awareness of dementia as an underlying cause of death by physicians, coroners, and medical examiners who assign causes of death, as well as increases in premorbid dementia diagnosis for patients seeking earlier care for cognitive symptoms (136). Indeed, there is reason to believe that the number of deaths attributable to Alzheimer's and other dementias is likely much larger than what is reported on death certificates, perhaps in the range of half a million per year using risk estimation methods (69, 149). As these papers point out, death in the age of chronic diseases such as dementia has

multiple causes, and an attributable risk model rather than the assignment of a single cause of death may be more relevant to public health. Increased awareness of this contribution may be leading to more of these deaths being recorded with Alzheimer's and other dementias as an underlying cause, though more evidence needs to be gathered. Regardless, these trends reflect demographic or reporting trends rather than changes in the underlying AD process over time. It is unclear how increased recognition of preclinical AD could affect measurement of mortality; while mortality is usually thought of as the end stage of severe dementia, evidence indicates that preclinical AD is related to increased mortality risk (144).

Number of Persons Living with AD

As outlined by the framework, the number of persons living with Alzheimer's dementia is only a fraction of the number of persons who have AD. A recent analysis attempted to forecast the prevalence of preclinical AD in the United States with a forward calculation method utilizing a multistate model based on the framework and transition rates based on biomarker studies (28). This analysis resulted in an estimated 46.7 million Americans with AD, compared with 6.1 million with dementia or MCI due to AD. In an accompanying paper using these same methods, the authors calculated the lifetime risk of developing Alzheimer's dementia at a number of ages, and they determined that most persons with AD will not progress to the clinical stage because of the long preclinical period and the competing risk of death (27). However, this analysis did not account for the effect of mixed pathologies or reserve. More research is necessary, but this analysis is a telling first look at the significant number of people living with the disease while also showing how much of a disconnect there is between the disease and the clinical manifestation of it.

IMPLICATIONS FOR FUTURE RESEARCH

We have summarized the current understanding of the multifaceted causes of dementia shaped largely by a newly proposed conception of AD, as well as the concomitant roles of mixed pathologies and neural reserve. We have reviewed the evidence for the most well-established risk factors for Alzheimer's dementia, showing that most of them do not appear to affect AD pathology directly; instead, some may work through vascular or other pathologies, some may work through modifying the relationship of pathology with dementia, and many are independent of pathologies altogether. We have also summarized the changing patterns of dementia, including an increase in the numbers of persons living with and dying from Alzheimer's dementia despite an apparent decrease in the age-specific risk of the syndrome. This decrease in risk may be unrelated to changes in AD pathology, with which many millions of Americans are living without obvious signs, most of whom likely will not live long enough to develop symptoms. These findings, most coming from the last decade or two of research, have implications for how we approach the development of interventions or preventive measures for dementia. Given that there have been ~450 failed clinical trials since the last drug for AD was approved by the US Food and Drug Administration, new approaches are necessary (40).

The first implication is that we can lower the risk for dementia without directly altering AD. Given the failure rate of trials targeting β amyloid, this realization optimistically provides alternate avenues of prevention and drug discovery, be they further reductions in vascular risk or other disease processes or, perhaps more innovatively, the targeting of neural reserve capacity (17). Indeed, as part of the AMP-AD project, researchers have already identified therapeutic targets for resilience (107, 162). As outlined here, AD pathology appears to account for only a portion of the variance in cognitive decline, and addressing the full complexity of the pathologic

causes of disease may require drug cocktails that are unrealistic for many older adults who have aging kidneys and livers and who already take many medications. A hypothetical therapeutic agent that increases neural reserve could provide protection from any and all pathologies.

Second, the framework's new conception of AD and dementia has implications for how we define and communicate about AD, both within the scientific community and more generally. The answers to the questions "How many people have Alzheimer's disease?" and "What increases your risk of Alzheimer's disease?" are directly shaped by the framework. Forecasts of the numbers of people living with preclinical AD provide a foreboding picture of the tremendous proportion of the population at risk for dementia. However, most older persons with preclinical AD will not develop dementia in their lifetimes, so presenting the preclinical numbers as the "prevalence of Alzheimer's" will overstate the actual burden of the disease. Furthermore, presenting risk factors that are not related to AD pathology as "risk factors for AD" paints an inaccurate picture of the mechanisms at play because there is slim evidence that modifiable risk factors lead to an avoidance of AD and instead appear to aid in coping with the disease. Thus, there are downstream implications to study designs for preclinical model systems, which are needed for drug discovery. Is there value to examining risk factors such as cognitive activity or social isolation if they are not associated with β amyloid or tau tangles in a mouse model? These risk factors have major public health importance in their ability to reduce the risk of dementia until measures to directly resist AD are discovered. As the new research framework is adopted and revised, we hope it will lead to a greater precision in terminology and refinement in how findings are presented that is acceptable to scientists as well as advocates, policy makers, and the general public.

The framework has important policy implications regarding funding priorities as well as national and global strategies to combat this epidemic. While a disease-modifying treatment that halts or slows progression of AD remains the ultimate goal, the emergence of such a treatment could lead to an increase in the number of people living with the disease through a longer symptomatic phase, which would be accompanied by a dramatic swell in medical costs and debates about Medicare coverage and access (130). Furthermore, there is the question of whether our health care system infrastructure could handle this surge in demand for persons requiring screening, diagnosis, and treatment (91). Therefore, from a public health perspective, prevention of dementia through targeting modifiable risk factors and neural reserve capacity could be more cost-effective and efficacious (131). The simultaneous pursuit of clinical trials for disease-modifying treatment and research into population-based prevention strategies requires a great deal of funding, a call that the US Congress has largely answered in recent years by dramatically increasing funding for Alzheimer's research. A swell in funding increases avenues for the pursuit of alternate strategies to the amyloid hypothesis and hopefully bolsters the chances of a breakthrough. However, advocates argue that Alzheimer's is still underfunded compared with other major killers, including AIDS, a disease that has made major strides owing to massive funding support. Due to the even greater complexity of Alzheimer's disease and the human brain, as well as the higher prevalence of persons at risk, the same degree of progress in Alzheimer's research may require an even greater investment.

CONCLUSION

We are at a critical juncture in the field of Alzheimer's research. Drug trials targeting the underlying disease have failed repeatedly, despite accumulating evidence of successes in lowering risk at the population level through other means. The prevailing postulate is that AD trials have thus far intervened too late in the disease process after irreversible brain damage has accumulated, prompting the call for trials in the preclinical space created by this new research framework (132). Some

researchers believe, however, that this track record of failure instead indicates that the hallmark plaques and tangles of AD are merely markers of the dementia-inducing processes rather than causal (57, 92); ideally, the framework provides the means to test this assumption. In the meantime, recognition of the role of mixed pathologies and neural reserve provides important alternate targets to reduce dementia risk while the search for the first AD-modifying drug continues. In the end, all can agree that it is the prevention and treatment of the clinical symptoms of dementia—the deterioration of memory and other cognitive abilities and loss of independence—that should remain the primary focus of research in this field.

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